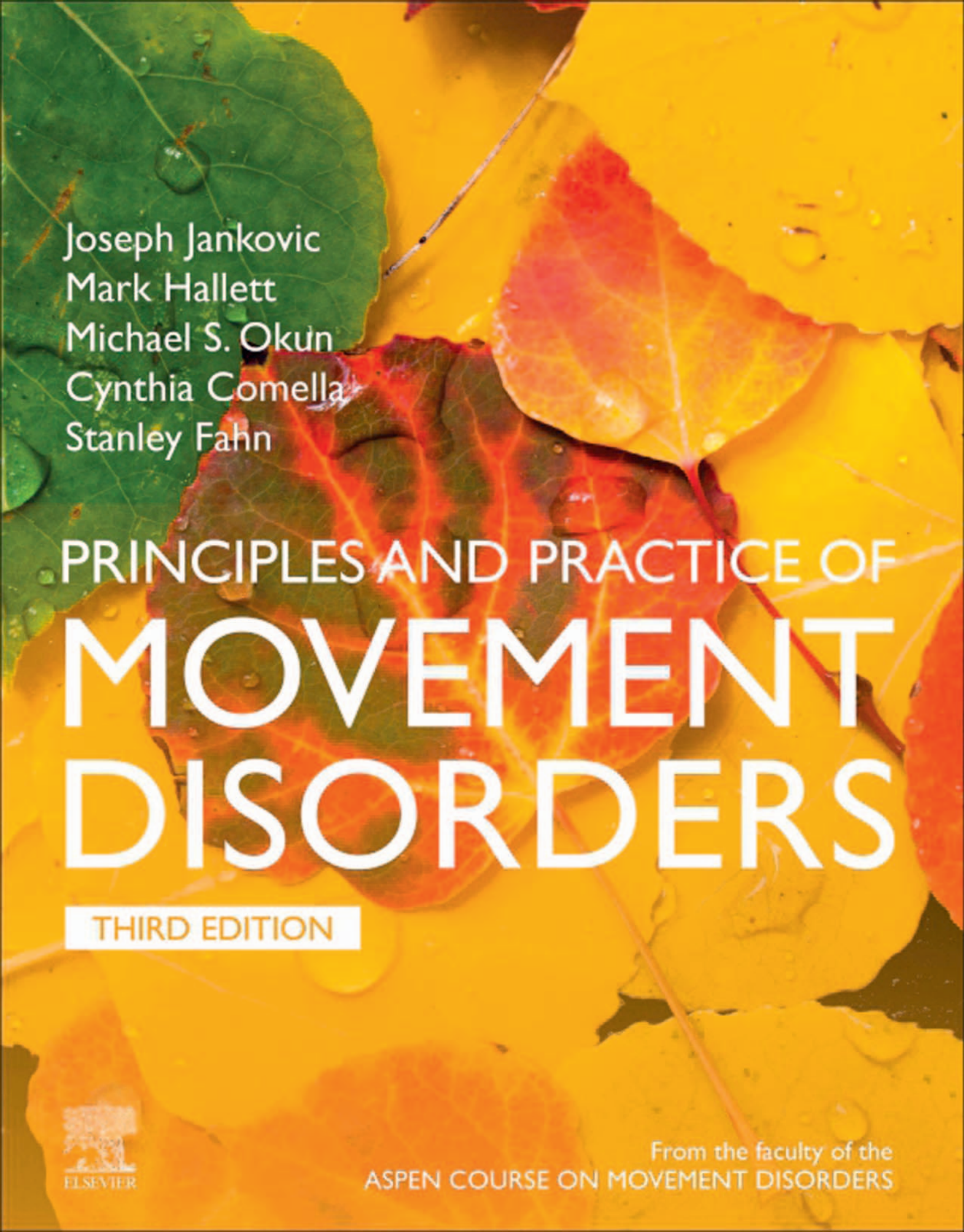




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Stanley Fahn

PRINCIPLES AND PRACTICE OF MOVEMENT DISORDERS

THIRD EDITION



From the faculty of the
ASPEN COURSE ON MOVEMENT DISORDERS

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PRINCIPLES AND PRACTICE OF
**MOVEMENT
DISORDERS**

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THIRD EDITION

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Dedication

We dedicate this book to our loving families in acknowledgment of their understanding and support. We also hope that the book will honor the memory of our close friend and colleague David Marsden.

Preface



C. David Marsden (1938–1998)

We are pleased to present the 3rd edition of *Principles and Practice of Movement Disorders*, commonly referred to as the “Aspen Book”. The first Aspen Course, titled “A Comprehensive Review of Movement Disorders for the Clinical Practitioner”, was held August 5-7, 1991, at the legendary Hotel Jerome, located in Aspen, Colorado. After several years the course grew in size and moved to the biggest venue in the city, the St. Regis Hotel. The COVID-19 pandemic forced the 30th anniversary course to be held virtually, but that allowed the attendance to swell to a record 1,787 neurologists, fellows, and other professionals drawn from 86 countries.

The original goal of the course was to provide a forum for a readily accessible, informative, and enjoyable educational program on Parkinson disease, other parkinsonian disorders and all hyperkinetic disorders including tremor, dystonia, chorea, athetosis, ballism, tics, myoclonus, stereotypies, drug-induced movement disorders, gait disorders, ataxias, functional (psychogenic) movement disorders, and other

disorders of movement. The course also featured the latest advances in medical and surgical treatments. The didactic lectures, which included introductory reviews of phenomenology and basal ganglia anatomy and physiology, were richly supplemented by videos. The emphasis was placed on visual recognition as well as classical and nuanced phenomenology. Anyone who has ever attended an “Aspen course” knows that the faculty are held to the highest possible standard and that every new advance is covered. Indeed, the tradition of the Aspen Course is that “*a rite of passage every movement disorder fellow must pass through the Aspen course.*” The legend of the Aspen course is that “*anyone serious about movement disorders has taken the Aspen course at least once.*”

Although this book cannot fully capture or replace the active and informal interactions between participants and faculty, it does provide the most current and comprehensive information on all movement disorders. In addition to updating all the chapters and adding a chapter on autoimmune movement disorders, a rapidly evolving field, this 3rd edition includes more than a hundred additional videos. This book provides an authoritative manual for movement disorders for all learners.

Over the past three decades the faculty of the course and the authorship of the book evolved. The original edition, published in 2007, was co-authored by Drs. Stan Fahn and Joe Jankovic and dedicated to the memory of our close friend and collaborator, David Marsden, with contributions from Drs. Mark Hallett and Peter Jenner who became the co-faculty of the Aspen course after David’s untimely death on September 29, 1998. Dr. Hallett was added as a co-author for the 2nd edition, published in 2011. Drs. Fahn, Jankovic, and Hallett were the faculty for the Aspen course between 2009 and 2015 after which time the CME credit provider transitioned from Columbia University to the International Parkinson and Movement Disorder Society. Drs. Michael Okun and Cynthia Comella, the new co-directors of the course, were added to this, the 3rd, edition of the book, with contributions from Dr. Jennifer Goldman.

We hope that this volume will build on the success of the prior two editions by providing an authoritative, evidence-based, but also clinically practical review of the rapidly growing field of movement disorders. The growth in the field has been stimulated not only by the recognition of the broad spectrum and rich phenomenology of hypokinetic, hyperkinetic, and other movement disorders, but also by advances in genetics, immunology, molecular biology, pharmacology, imaging, and surgery. Furthermore, experimental therapeutics will likely deliver not only more effective and novel symptomatic treatments but also potentially disease modifying therapies for Parkinson disease and other movement disorders. These advances have already resulted in robust improvements in patient outcomes. Movement disorders is an exciting field, which focuses on clinical phenomenology,

with critical advances in basic and translational science and innovative therapeutics. This book includes these latest advances and a rich library of video cases. This likely accounts for the large demand for the book. We invite you to share our passion for movement disorders by reading the entire book, viewing all the videos, or simply using the text as an authoritative reference.

We want to thank Melanie Tucker, Sharon Nash, Andrew Riley, and other members of Elsevier for their dedicated professionalism and their untiring support.

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For more information about the Aspen course, see the article commemorating the 30th anniversary: Jankovic J. 30 Years of "The Aspen Course": A Comprehensive Review of Movement Disorders for the Clinical Practitioner. *Moving Along* 2020;24 (4):17-20.

<https://www.movementdisorders.org/MDS-Files1/News/Moving-Along/2021/moving-along-2020-issue4-final.pdf>

Clinical overview and phenomenology of movement disorders

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To study the phenomenon of disease without books is to sail an uncharted sea, while to study books without patients is not to go to sea at all.

Sir William Osler

Fundamentals

The quotation from Sir William Osler in 1901 at the dedication ceremony for a new building of the Boston Medical Library (cited by [Cushing, 1940](#)) is an apt introduction to this chapter, which offers a description of the various phenomenologies of movement disorders. Movement disorders can be defined as neurologic syndromes in which there is either an excess of movement or a paucity of voluntary and automatic movements, unrelated to weakness or spasticity ([Table 1.1](#)). The former group is commonly referred to as *hyperkinesias* (excessive movements), *dyskinesias* (unnatural movements), and *abnormal involuntary movements* (commonly abbreviated as AIMS). In this text, the term *dyskinesias* is used most often, but all three terms are interchangeable. The six major categories of dyskinesias in alphabetical order are asynergia/ataxia, chorea, dystonia, myoclonus, tics and tremor. [Table 1.1](#) presents the complete list. Abnormal movements are usually caused by muscle contractions, but they also can be the result of motor inhibitions, as seen in asterixis (negative myoclonus), motor impersistence (negative chorea), and cataplexy (falling because of attacks of muscle paralysis as is common in narcolepsy).

The *paucity of movement* group (also in [Table 1.1](#)) can be referred to as *hypokinesia* (decreased amplitude of movement), but *bradykinesia* (slowness of movement), and *akinesia* (loss of movement) could be reasonable alternative names. Most clinicians refer to this group simply as bradykinetic disorders, and this term is typically equated with parkinsonian syndromes, because these syndromes are the

most common cause of such paucity of movement; other hypokinetic disorders represent only a small group of patients. Practically then, movement disorders can be conveniently divided into parkinsonism and all other types (i.e., dyskinesias); each of these two groups has about an equal number of patients. In the clinic, however, patients with parkinsonism are much more common because their natural history is to worsen over time and because there is treatment available to ameliorate the symptoms. Thus, parkinsonian patients return to the clinic at frequent intervals.

In evaluating patients with movement disorders, the approach to reaching a diagnosis differs from the classic approach for most neurologic disorders, for which the first question is “where is the lesion?” followed by “what is the lesion?”. For movement disorders, the first question usually is “what is the nature of the abnormal movements?”; that is, “what is the phenomenology?”. The next question is “what is the cause of these movements?”. This is often solved by recognizing syndromic patterns associated with that particular phenomenology. The syndromes for each type of dyskinetic phenomenology are recognized by an assortment of clinical features, including age at onset, family history, known antecedent events (e.g., trauma, infection, stroke, or cancer), progressive or stable or fluctuating course, type of onset (i.e., sudden or insidious), rate of worsening, and results of laboratory investigations, including neuroimaging and gene tests. Once the etiology is identified, appropriate specific treatment can be applied. If no specific treatments are available, symptomatic therapy is used. Medical research and observations have uncovered selective medications or surgery for specific dyskinesias and the bradykinesias, and these are discussed in the chapters of this book, which is largely organized according to phenomenology. A few etiologies of movement disorders have their individual chapters (tardive syndromes in [Chapter 17](#), Wilson disease in [Chapter 22](#), autoimmune disorders in [Chapter 23](#), and

Table 1.1 List of movement disorders**Hypokinesias**

Akinesia/bradykinesia (parkinsonism)
 Apraxia
 Blocking (holding) tics
 Cataplexy and drop attacks
 Catatonia, psychomotor depression, and obsessional slowness
 Freezing phenomenon
 Hesitant gaits
 Hypothyroid slowness
 Rigidity
 Stiff muscles

Hyperkinesias

Abdominal dyskinesias
 Akathitic movements
 Ataxia/asynergia/dysmetria
 Athetosis
 Ballism
 Chorea
 Dystonia
 Hemifacial spasm
 Hyperekplexia
 Hypnogenic dyskinesias
 Jumping disorders
 Jumpy stumps
 Moving toes and fingers
 Myoclonus
 Myokymia and synkinesis
 Myorhythmia
 Paroxysmal dyskinesias
 Periodic movements in sleep
 Rapid eye movement (REM) sleep behavior disorder
 Restless legs
 Stereotypy
 Tics
 Tremor

psychogenic (functional) movement disorders in [Chapter 27](#)). These four topics have multiple phenomenologies and special complex treatments that warrant their special individual chapters. Distinguishing between organic and psychogenic causation requires expertise in recognizing the various phenomenologies, a primary mission of this Overview chapter. Psychogenic (functional) movement disorders are covered in detail in [Chapter 27](#).

Those who are interested in keeping up to date in the field of movement disorders should refer to a number of journals dedicated to this field. The first such journal, *Movement Disorders*, is published by The International Parkinson and Movement Disorder Society (MDS) (<http://www.movementdisorders.org>). The journal is published 12 times per year with occasional extra issues on a specific theme. Some of the articles in the journal are accompanied by videos to demonstrate the phenomenology. The Society also publishes an online quarterly, *Movement Disorders Clinical Practice*. Both journals come with MDS membership, which is open to all interested medical professionals. Other specialty journals are *Parkinsonism and Related Disorders*, *Journal of Parkinson's Disease*, *Tremor and Other Hyperkinetic Movements* (an open access journal), and *Nature's Partner Journal*, *npj Parkinson's Disease* (an open access online journal).

Categories of movements

Movements can be categorized into one of four classes: *automatic*, *voluntary*, *semivoluntary* (also called involuntary) ([Lang, 1991](#); [Tourette Syndrome Classification Study Group, 1993](#); [Fahn, 2005](#)), and *involuntary* ([Jankovic, 1992](#)). *Automatic* movements are learned motor behaviors that are performed without conscious effort, for example, walking an accustomed route and tapping of the fingers when thinking about something else. *Voluntary* movements are intentional (planned or self-initiated) or externally triggered (in response to some external stimulus, such as turning the head toward a loud noise or withdrawing a hand from a hot plate). Intentional voluntary movements are preceded by the Bereitschaftspotential (or readiness potential), a slow negative potential recorded over the supplementary motor area and contralateral premotor and motor cortex appearing 1 to 1.5 seconds before the movement. The Bereitschaftspotential does not appear with other movements, including the externally triggered voluntary movements ([Papa et al., 1991](#)). In some cases, learned voluntary motor skills are incorporated within the repertoire of the movement disorder, such as camouflaging choreic movements or tics by immediately following them with voluntarily executed movements, so-called parakinesias. *Semivoluntary* (or *unvoluntary*) movements are induced by an inner sensory stimulus (e.g., need to “stretch” a body part or need to scratch an itch) or by an unwanted feeling or compulsion (e.g., compulsive touching or smelling). Many of the movements occurring as tics or as a response to various sensations (e.g., akathisia and restless legs syndrome) can be considered involuntary because the movements are usually the result of an action to nullify an unwanted, unpleasant sensation. Unvoluntary movements usually are suppressible. *Involuntary* movements are often nonsuppressible (e.g., most tremors and myoclonus), but some can be partially suppressible (e.g., some tremors, chorea, dystonia, stereotypies, and some tics) ([Koller and Biary, 1989](#)).

The origins of abnormal movements

Many movement disorders are associated with pathologic alterations in the basal ganglia or their connections. The basal ganglia are that group of gray matter nuclei lying deep within the cerebral hemispheres, that is, telencephalon (caudate, putamen, and pallidum), the diencephalon (subthalamic nucleus), the mesencephalon (substantia nigra), and the mesencephalic-pontine junction (pedunculopontine nucleus) (see [Chapter 3](#)). There are some exceptions to this general rule. Pathologic conditions of the cerebellum or its pathways typically result in impairment of coordination (asynergia, ataxia), misjudgement of distance (dysmetria), and intention tremor. Myoclonus and many forms of tremors do not appear to be related primarily to basal ganglia pathologic conditions, and often arise elsewhere in the central nervous system, including cerebral cortex (cortical reflex myoclonus), brainstem (cerebellar outflow tremor, reticular reflex myoclonus, hyperekplexia, and rhythmical brainstem myoclonus such as palatal myoclonus/tremor and ocular myoclonus), and spinal cord (rhythmic segmental myoclonus and nonrhythmic propriospinal myoclonus). Moreover, many myoclonic disorders are associated with diseases in which the cerebellum is involved, such as those causing the Ramsay Hunt syndrome of

progressive myoclonic ataxia (see [Chapter 18](#)). The peripheral nervous system also can give rise to abnormal movements, such as the painful legs–moving toes syndrome ([Marsden, 1994](#)). It is not known for certain which part of the brain is associated with tics, although the basal ganglia and the limbic structures have been implicated. Certain localizations within the basal ganglia are classically associated with specific movement disorders: substantia nigra with bradykinesia and rest tremor, subthalamic nucleus with ballism, caudate nucleus with chorea, and putamen with dystonia.

Movement disorders can be isolated (i.e., present and manifest only as a movement disorder) or can be combined with other neurologic abnormalities. They can be caused by endocrine disorders and disease of internal organs (see review by [Pedroso et al., 2019](#)), and, as uncovered in the last dozen years, and discussed later, they can be due to genetic mutations and immunologic dysfunction

Historical perspective

The neurologic literature contains a number of seminal papers, reviews, and books that emphasized and established movement disorders as associated with basal ganglia pathologic conditions ([Alzheimer, 1911](#); [Fischer, 1911](#); [Wilson, 1912](#); [Hunt, 1917](#); [Vogt and Vogt, 1920](#); [Jakob, 1923](#); [Putnam et al., 1940](#); [Denny-Brown, 1962](#); [Martin, 1967](#)). Before the term *movement disorders* was created, most of the conditions now included under that heading were commonly called *extrapyramidal disorders*, a label coined by [Wilson \(1912\)](#) to associate

these conditions with the basal ganglia. In his review on the classification of movement disorders, [Fahn \(2011\)](#) explains both the origin of the term *movement disorders* and the reasons why *extrapyramidal* is not an accurate label.

A historical perspective of movement disorders can be gained by listing the dates when the various clinical entities were first introduced ([Table 1.2](#)).

Epidemiology

Movement disorders are common neurologic problems, and epidemiologic studies are available for some of them ([Table 1.3](#)). There have been several studies for Parkinson disease (PD), and these have been carried out in several countries ([Tanner, 1994](#); [de Lau and Breteler, 2006](#)). [Table 1.3](#) lists the prevalence rates of some movement disorders. The frequency of different types of movement disorders seen in the two specialty clinics at Columbia University and Baylor College of Medicine is presented in [Table 1.4](#). More detailed information is provided in the relevant chapters for specific diseases.

Genetics

A large number of movement disorders are genetic in etiology; many of the diseases have now been mapped to specific regions of the genome, and a good proportion of them have been localized to a specific gene ([Table 1.5](#)). The number of new genes or gene loci found is growing at a rapid rate. For example, in the previous edition of this book, 16 genetic loci

Table 1.2 Some notable historical descriptions of movement disorders

Year	Source	Entity	Year	Source	Entity
	Bible	Reference to tremor in the aged	1871	Steinthal	Apraxia
	Bible	Trembling associated with fear and strong emotion	1872	Huntington	Huntington disease
1567	Paracelsus	Mercury-induced tremor (published posthumously)	1872	Mitchell	Jumpy stumps
16th century	Paracelsus	Chorea for dancing mania (published posthumously)	1874	Kahlbaum	Catatonia
1652	Tulpius	Spasmodic torticollis	1878	Beard	Jumpers
1685	Willis	Restless legs syndrome	1881	Friedreich	Myoclonus
1686	Sydenham	Sydenham chorea	1885	Gilles de la Tourette	Tourette syndrome
1786	Vicq-d'Azyr	Identification of substantia nigra	1885	Gowers	Paroxysmal kinesigenic choreoathetosis
1817	Parkinson	Parkinson disease	1886	Spencer	Palatal myoclonus
1825	Itard	Tourette syndrome	1887	Dana	Hereditary tremor
1830	Bell	Writer's cramp	1887	Wood	Cranial dystonia
1837	Couper	Manganese-induced parkinsonism	1889	Benedikt	Benedikt syndrome
1848	Grisolle	Primary writing tremor	1891	Unverricht	Progressive myoclonus epilepsy (Unverricht–Lundborg disease)
1864	Mitchell	Causalgia	1895	Schultze	Myokymia
1864	Solly	Writer's cramp	1895	Brissaud	Description of <i>geste antagoniste</i> , thought to be a sign of psychogenicity
1865	Luys	Identification of subthalamic nucleus	1900	Dejerine/Thomas	Olivopontocerebellar atrophy
1871	Hammond	Athetosis	1900	Liepmann	Apraxia
1871	Traube	Spastic dysphonia	1901	Haskovec	Akathisia

Continued

Table 1.2 Continued

Year	Source	Entity	Year	Source	Entity
1902	Meige and Feindel	Coined the term <i>geste antagoniste</i> , thought to be a sign of psychogenicity	1957	Schonecker	Tardive dyskinesia
1903	Batten	Neuronal ceroid lipofuscinosis	1958	Kirstein/Silfverskiöld	Startle disease (hyperekplexia)
1904	Holmes	Midbrain ("rubral") tremor	1958	Smith et al.	Dentatorubral-pallidoluysian degeneration
1908	Schwalbe	Familial dystonia	1958	Monrad-Krohn/Refsum	Myorhythmia
1910	Meige	Oromandibular dystonia	1959	Paulson	Acute dystonic reaction
1911	Oppenheim	Dystonia musculorum deformans	1960	Ekbom	Restless legs
1911	Lafora	Lafora disease	1960	Shy/Drager	Dysautonomia with parkinsonism (multiple system atrophy)
1912	Wilson	Wilson disease	1961	Hirano et al.	Parkinsonism-dementia complex of Guam
1912	Lewy	Lewy bodies in Parkinson disease	1961	Andermann et al.	Facial myokymia
1916	Henneberg	Cataplexy	1961	Isaacs	Neuromyotonia, Isaacs syndrome
1917	Hunt	Progressive pallidal atrophy	1962	Kinsbourne	Opsoclonus-myoclonus
1920	Creutzfeldt	Creutzfeldt-Jakob disease	1963	Lance/Adams	Posthypoxic action myoclonus
1921	Jakob	Creutzfeldt-Jakob disease	1964	Adams et al.	Striatonigral degeneration
1921	Hunt	Dyssynergia cerebellaris myoclonica (Ramsay Hunt syndrome)	1964	Steele et al.	Progressive supranuclear palsy
1922	Hallervorden/Spatz	Pantothenate kinase deficiency (neurodegenerative disorder with brain iron deposition-1)	1964	Levine	Neuroacanthocytosis
1923	Sicard	Akathisia	1964	Kinsbourne	Sandifer syndrome
1924	Fleischhacker	Striatonigral degeneration	1964	Lesch/Nyhan	Lesch-Nyhan syndrome
1926	Davidenkow	Myoclonic dystonia	1965	Hakim/Adams	Normal pressure hydrocephalus
1927	Goldsmith	Hereditary chin quivering	1965	Goldstein/Cogan	Apraxia of eyelid opening
1927	Orzechowski	Opsoclonus	1966	Suhren et al.	Hyperekplexia
1931	Herz	Myorhythmia	1966	Rett	Rett syndrome
1931	Guillain/Mollaret	Palato-pharyngo-laryngo-oculo-diaphragmatic myoclonus	1967	Haerer et al.	Hereditary nonprogressive chorea
1932	De Lisi	Hypnic jerks	1968	Rebeiz et al.	Corticobasal degeneration
1933	Spiller	Fear of falling	1968	Delay/Denniker	Neuroleptic malignant syndrome
1933	Scherer	Striatonigral degeneration	1969	Horner/Jackson	Hypnogenic paroxysmal dyskinesias
1940	Mount/Reback	Paroxysmal nonkinesigenic dyskinesia (paroxysmal dystonic choreoathetosis)	1969	Graham/Oppenheimer	Multiple system atrophy
1941	Louis-Bar	Ataxia-telangiectasia	1970	Spiro	Minipolymyoclonus
1943	Kanner	Autism	1970	Ritchie	Jumpy stump
1944	Asperger	Autism	1971	Spillane et al.	Painful legs and moving toes
1946	Titeca/van Bogaert	Dentatorubral-pallidoluysian degeneration	1973	Brait et al.	Parkinsonism with motor neuron disease
1946	Alexander	Alexander disease	1975	Perry et al.	Familial parkinsonism with hypoventilation and mental depression
1946	Evans	Reflex sympathetic dystrophy	1976	Segawa et al.	Dopa-responsive dystonia
1953	Adams/Foley	Asterixis	1976	Allen/Knopp	Dopa-responsive dystonia
1953	Symonds	Nocturnal myoclonus (periodic movements in sleep)	1976	Whitely et al.	Encephalomyelitis with rigidity
1954	Davison	Pallido-pyramidal syndrome (PARK15)	1977	Hallett et al.	Reticular myoclonus
1956	Moersch/Woltman	Stiff-person syndrome	1978	Satoyoshi	Satoyoshi syndrome
			1978	Fahn	Tardive akathisia

Table 1.2 Some notable historical descriptions of movement disorders—Continued

Year	Source	Entity	Year	Source	Entity
1979	Hallett et al.	Cortical myoclonus	1990	Ikeda et al.	Cortical tremor/myoclonus
1979	Rothwell et al.	Primary writing tremor	1991c	Brown et al.	Propriospinal myoclonus
1980	Fukuhara et al.	Myoclonus epilepsy associated with ragged red fibers (MERFF)	1991	Hymas et al.	Obsessional slowness
1980	Coleman et al.	Periodic movements in sleep	1991	De Vivo et al.	GLUT1 deficiency syndrome
1981	Fahn/Singh	Oscillatory myoclonus	1992	Stacy/Jankovic	Tardive tremor
1981	Lugaresi/Cirignotta	Hypnogenic paroxysmal dystonia	1993	Bhatia et al.	Causalgia-dystonia
1982	Burke et al.	Tardive dystonia	1993	Atchison et al.	Primary freezing gait
1983	Langston et al.	MPTP-induced parkinsonism	1993	Achiron et al.	Primary freezing gait
1984	Heilman	Orthostatic tremor	1994	Merskey and Bogduk	Complex regional pain syndrome
1985	Aronson	Breathy dysphonia	2001	Hagerman et al.	Fragile X-associated tremor/ataxia syndrome (FXTAS)
1986	Bressman et al.	Biotin-responsive myoclonus	2002	Namekawa et al.	Adult-onset Alexander disease
1986	Schenck et al.	REM sleep behavior disorder	2002	Okamoto et al.	Adult-onset Alexander disease
1986	Schwartz et al.	Oculomasticatory myorhythmia	2002	Parkinson Study Group	SWEDDs (scans without evidence of dopaminergic deficit)
1987	Tominaga et al.	Tardive myoclonus	2003	Whone et al.	SWEDDS
1987	Little/Jankovic	Tardive myoclonus	2007	Dalmau et al.	NMDA receptor antibody encephalitis
1989	Fahn	Paradoxical dystonia	2011	Irani et al.	Lgi1 antibody induced faciobrachial dystonic seizures
1990	Iliceto et al.	Abdominal dyskinesias			

Other important dates in the history of clinical aspects of movement disorders are 1912, the coining of the term “extrapyramidal” by Wilson (same year as the discovery of the Lewy body in Parkinson disease); 1968, the creation of the term “movement disorders” as explained in [Fahn \(2011\)](#); 1985, the founding of The Movement Disorder Society (subsequently renamed the International Parkinsonism and Movement Disorder Society; and 1986, the publication of the first issue of the journal *Movement Disorders*.

MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NMDA, N-methyl-D-aspartic acid; REM, rapid eye movement.

Table 1.3 Prevalence of movement disorders

Disorder	Rate per 100,000	Reference
Restless legs	9,800*	Rothdach et al., 2000
Essential tremor	415	Haerer et al., 1982
Parkinson disease	187	Kurland, 1958
Tourette syndrome	29–1052	Caine et al., 1988 ; Comings et al., 1990
	2,990	Mason et al., 1998
Primary torsion dystonia	33	Nutt et al., 1988
Hemifacial spasm	7.4–14.5	Auger et al., 1990
Blepharospasm	13.3	Defazio et al., 2001
Hereditary ataxia	6	Schoenberg, 1978
Multiple system atrophy	4.4	Schrage et al., 1999
Huntington disease	2–12	Harper, 1992 ; Kokmen et al., 1994
Wilson disease	3	Reilly and Hutchinson, 1993
Progressive supranuclear palsy	2	Golbe, 1994
	2.4	Nath et al., 2001
	6.4	Schrage et al., 1999

Rates are given per 100,000 population.

*For restless legs, the rate cited is in a population 65 to 83 years of age. For Parkinson disease, the rate is 347 per 100,000 for ages over 39 years ([Schoenberg et al., 1985](#)).

Table 1.4 The prevalence of movement disorders encountered in two large movement disorder clinics

Movement disorder	Number of patients	Percent	Movement disorder	Number of patients	Percent
Parkinsonism	15,107	36	Cerebellar	205	
Parkinson disease	10,182		Midbrain ("rubral")	88	
Progressive supranuclear palsy	750		Primary writing	114	
Multiple system atrophy	841		Orthostatic	82	
Corticobasal degeneration	291		Other	1,035	
Vascular	867		Tics (Tourette syndrome)	2,753	6.6
Drug-induced	327		Chorea	1,225	2.9
Hemiparkinsonism–hemiathrophy	116		Huntington disease	690	
Gait disorder	329		Hemiballism	123	
Other	1,308		Other	412	
Dystonia	10,394	24.9	Tardive syndromes	1,253	3.0
Primary dystonia	7,784		Myoclonus	1,020	2.4
Focal		59	Hemifacial spasm	693	1.7
Segmental		29	Ataxia	764	1.8
Generalized		12	Paroxysmal dyskinesias	474	1.1
Secondary dystonia	6,610		Stereotypies (other than TD)	246	0.6
Hemidystonia		279	Restless legs syndrome	807	1.9
Tardive	595		Stiff-person syndrome	70	0.2
Other	1,737		Psychogenic movement disorder	1,268	0.3
Tremor	6,754	13.8	Grand Total	41,738	100
Essential tremor	2,818				

These data were obtained from the combined databases of the Movement Disorder Clinics at Columbia University Medical Center (New York City) and Baylor College of Medicine (Houston) for patients encountered through April 2009. Because some patients might have more than one type of movement disorder (such as a combination of essential tremor and Parkinson disease), they would be listed more than once. Therefore, the figures in the table represent the types of movement disorder phenomenology encountered in two large clinics, rather than the exact number of patients.

had been identified with the PD label, coded as PARK. That number reached 23 at the time of finalizing this edition. Many other genetic mutations result in parkinsonism without the designation PARK (see [Chapter 5](#)). A comprehensive list of movement disorders whose genes have been mapped or identified are listed in [Table 1.5](#). Three detailed chapters ([Fahn and Goldman, 2015](#); [Goldman and Fahn, 2015, 2020](#)) have been published specifically related to movement disorder genetics. The MDS Task Force on nomenclature of genetic movement disorders made a recommendation ([Marras et al., 2016](#)) for a new naming scheme that markedly differs from the one proposed by molecular geneticists and used for several decades. This geneticist-created nomenclature system uses symbols to represent disease phenomenology (e.g., PARK for parkinsonism, DYT for dystonia) followed by sequential numerals that were assigned chronologically as new gene loci and gene identifications were made. The MDS Task Force pointed out problems with this scheme; a major one for the field of movement disorders is the inclusion of paroxysmal movement disorders into the DYT label.

The Task Force made a major contribution with its new nomenclature. It is more rigorous by including only

identified genes, not conditions with just chromosomal mapping. A major change was the naming of a gene by its major phenotype (e.g., PARK, DYT, CHOR, PxMD) followed by a *gene name*, not a numeral. A major problem, though, is that it is almost impossible for clinicians to recall the exact names of genes, and chromosomal loci without an identified gene are excluded in the Task Force classification. The old, original numeral nomenclature is much easier to recall and to pronounce. If a gene mutation causes more than one phenotype, both labels are used in the Task Force system, assigning more than one name to a gene (e.g., PARK/DYT). The Task Force also allows labels for distinctive imaging features (e.g., brain iron accumulations and brain calcifications). The Task Force system eliminates risk factor genes and allows only disease-causing genes. Finally, the Task Force requires confirmatory studies before a new gene locus can be labeled in the scheme. [Table 1.5](#) uses the older nomenclature, which includes both disease-causing and risk factor genes. There is a major advantage to being all inclusive for the clinician. In addition, [Table 1.5](#) includes genes with mapped loci, but not yet identified genes, because this inclusion also aids the clinician to identify specific etiologies.

Table 1.5 Gene localization of movement disorders

Category of disease	Pattern of inheritance	Chromosome region	Name of gene	Gene identified	Triplet repeat	Name of protein	Function of protein
Parkinson disease							
(1) Familial Parkinson disease (PARK1)	Autosomal dominant	4q22.1	<i>SNCA</i>	Yes	No	Alpha- synuclein	Synaptic protein
(2) Young-onset Parkinson disease (PARK2)	Autosomal recessive/ dominant	6q26	<i>PRKN</i>	Yes	No	Parkin	Ubiquitin-protein ligase
(3) PARK3	Autosomal Dominant	2p13	Susceptibility locus	N/I	N/I	N/I	—
(4) Familial Parkinson disease (PARK4)	Autosomal dominant	4q22.1	<i>SNCA</i>	Yes	No	Duplication or triplication of alpha-synuclein region of chromosome	Excess amount of normal alpha-synuclein
(5) Familial Parkinson (PARK5)	Autosomal recessive	4p13	<i>UCHL1</i>	Yes	No	Ubiquitin carboxy-terminal hydrolase L1	Splits conjugated ubiquitin into monomers
(6) Young-onset Parkinson disease (PARK6)	Autosomal recessive	1p36.12	<i>PINK1</i>	Yes	No	PTEN-induced putative kinase 1 (PINK1)	Mitochondrial, antistress-induced degeneration
(7) Young-onset Parkinson disease (PARK7)	Autosomal recessive	1p36.23	<i>DJ-1</i>	Yes	No	DJ-1	Oxidative stress sensor; supports antioxidation
(8) Familial Parkinson disease (PARK8)	Autosomal dominant	12q12	<i>LRRK2</i>	Yes	No	LRRK2, dardarin	Phosphorylates proteins
(9) Kufor-Rakeb syndrome (PARK9); also CNL12, see no. 354)	Autosomal Recessive	1p36.13	<i>ATP13A2</i>	Yes	No	ATP13A2	Maintain acid pH in lysosome
(10) Familial Parkinson disease (PARK10)	Autosomal recessive	1p32	Susceptibility gene (Iceland)	No	No	N/I	N/I
(11) Familial Parkinson disease (PARK11)	Autosomal dominant	2q37.1	GIGYF2 susceptibility gene	Yes	No	GRB10-Interacting GYF Protein 2	N/I
(12) Familial Parkinson disease (PARK12)	X-linked recessive	Xq21-q25	Susceptibility gene	No	No	N/I	N/I
(13) Familial Parkinson disease (PARK13)	Autosomal dominant	2p13.1	<i>HTRA2</i> susceptibility gene	Yes	No	High-temperature requirement protein A2 (HTRA2)	Serine protease in endoplasmic reticulum and mitochondria
(14) Familial parkinsonism-dystonia (PARK14) (also infantile neuroaxonal dystrophy) (NBIA2, PLAN, see no. 240) (also as adult-onset dystonia-parkinsonism without iron)	Autosomal recessive	22q13.1	<i>PLA2G6</i>	Yes	No	Phospho-lipase A2	Releases fatty acids from phospholipids

Continued

Table 1.5 Gene localization of movement disorders—Continued

Category of disease	Pattern of inheritance	Chromosome region	Name of gene	Gene identified	Triplet repeat	Name of protein	Function of protein
(15) Early-onset pallido (parkinsonian)-pyramidal syndrome (PARK15)	Autosomal recessive	22q12.3	FBXO7	Yes	No	Component of modular E3 ubiquitin protein ligases	Functions in phosphorylation-dependent ubiquitination
(16) Familial Parkinson disease (PARK16)	Unknown	1q32	Susceptibility gene	?	?	Discovered by genomewide association studies (GWAS) in Japan and Europe	?
(17) Familial Parkinson disease (PARK17)	Autosomal dominant	16q11.2	VPS35	Yes	No	Vesicle protein sorting 35	Vesicle protein sorting 35 mediates retrograde transport between endosomes and the trans-Golgi network
(18) Familial Parkinson disease (PARK18)	Autosomal dominant	3q27.1	EIF4G1	Yes	No	Eukaryotic initiation factor	Facilitates the recruitment of mRNA to the ribosome
(19) Juvenile Parkinson disease (PARK19)	Autosomal recessive	1p31.3	DNAJC6	Yes	No	Auxilin	Clathrin-mediated endocytosis
(20) Young-onset Parkinson disease (PARK20)	Autosomal recessive	1p31.3	DNAJC6	Yes	No	Auxilin	Clathrin-mediated endocytosis
(21) Young-onset Parkinson disease (PARK21)	Autosomal recessive	21q22.11	SYNJ1	Yes	No	Synaptojanin 1	Synaptic vesicle recycling
(22) Familial Parkinson disease (PARK22)	Autosomal dominant	20p13	B230	Yes	No	Transmembrane protein 230	Protein is in vesicles; involved with vesicle and endosomal trafficking
(23) Familial Parkinson disease (PARK28)	Autosomal dominant	7p11.2	CHCHD2	Yes	No	CHCHD2	Located in intermembrane space in mitochondria; respiratory chain
(24) Early-onset Parkinson disease (PARK29)	Autosomal recessive	15q22.2	VPS13C	Yes	No	Vacuolar protein sorting 13	Related to parkin and PINK1-mediated mitophagy
(25) Familial Parkinson disease with lipomatosis	Autosomal dominant	?	?	?	?	?	?
(26) X-linked Intellectual disability with Parkinson disease (Waisman syndrome)	X-linked recessive	Xq28	RAB39B	Yes	No	Rab GTPase	Regulate vesicular trafficking; synapse formation and maintenance
(27) Young-onset Parkinson disease with psychosis and mood disorders	Spontaneous mutation	22q11.2 deletion	?	No	No	?	?
(28) Parkinson disease (Gaucher disease)	Autosomal dominant (homozygous → Gaucher disease)	1q21	GBA susceptibility gene	Yes	No	Beta-glucocerebrosidase	Metabolizes membrane lipid glucosylceramide to ceramide and glucose in the lysosome

(29) Parkinson disease	Autosomal dominant	2q24.1	<i>NR4A2</i> susceptibility gene	Yes	No	Nurr1	Dopamine cell development; transcription activator
(30) Parkinson disease	GWAS study	18q12.3	<i>RIT2</i> locus susceptibility gene	Yes	No	N/I	GTPase and calmodulin binding
(31) Parkinson disease and dementia	Autosomal dominant	7p22.3	<i>PRKAR1B</i>	Yes	No	cAMP dependent protein kinase A	Essential enzyme in the signaling pathway of the second messenger cAMP
(32) Perry syndrome (familial parkinsonism with hypoventilation and depression)	Autosomal dominant	2p13	<i>DCTN1</i>	Yes	No	Dynactin 1	Cellular transport functions, including axonal transport
(33) Familial Parkinson disease susceptibility gene	Autosomal recessive	15q26.1	<i>POLG</i>	Yes	No	MtDNA Polymerase gamma-1	Synthesis, replication and of mtDNA
(34) Adult-onset nondopa responsive parkinsonism with striatal degeneration	Autosomal dominant	5q13.3	<i>PDE8B</i>	Yes	No	Cyclic nucleotide phosphodiesterase	Catabolizes cyclic nucleotides
(35) Infantile/ childhood Parkinson disease (see also DYT5b, no. 202)	Autosomal recessive	11p15.5	<i>TH</i>	Yes	No	Tyrosine hydroxylase	Converts tyrosine to levodopa
(36) Infantile/ childhood Parkinson disease	Autosomal recessive	1p12	<i>WARS2</i>	Yes	No	Mitochondrial tryptophanyl tRNA synthetase	Catalyze the aminoacylation of tRNA(trp) with tryptophan
(37) Nonprogressive young-onset Parkinson disease	Autosomal recessive	1p12	<i>DNAJC12</i>	Yes	No	Mitochondrial tryptophanyl tRNA synthetase	Catalyze the aminoacylation of tRNA(trp) with tryptophan
Parkinsonism in dopa-responsive dystonia (DRD) (DYT5a); see no. 201 in Dystonia section							
Parkinsonism in SCA2; see no. 125 in Ataxia section							
Parkinsonism in SCA17 (susceptibility factor); see no. 139 and 176 (ref: Kim et al., 2009)							
(38) Infantile parkinsonism-dystonia	Autosomal recessive	5p15.33	<i>SLC6A3</i>	Yes	No	Dopamine transporter	Reuptake dopamine from synapse
(39) Infantile parkinsonism with dysautonomia	Autosomal recessive	10q25.3	<i>SLC18A2</i>	Yes	No	Vesicular monoamine transporter 2 (VMAT2)	Transports cytosolic dopamine and 5HT into synaptic vesicles
(40) Familial Parkinson disease	Mitochondrial	Mitochondria	N/I	No	No	N/I	Complex I
(41) Familial Parkinson disease	Mitochondrial gene	Mitochondria	<i>MT-ND4</i>	Yes	No	N/I	Complex I
(42) Parkinson disease	Susceptibility gene	17q21.31	<i>MAPT</i>	Yes	No	Tau	Fibrils
(43) Parkinson disease (Niemann-Pick A and B in Ashkenazi Jews)	Susceptibility gene	11p15.4	<i>SMPD1</i> (p.L302Plocus)	Yes	No	Sphingomyelinase	Generates ceramide; lysosomal

Continued

Table 1.5 Gene localization of movement disorders—Continued

Category of disease	Pattern of inheritance	Chromosome region	Name of gene	Gene identified	Triplet repeat	Name of protein	Function of protein
(44) Familial Parkinson disease	Autosomal recessive	21q22.3	<i>PDXK</i>	Yes	No	Pyridoxal kinase	Converts vitamin B ₆ to pyridoxal-5-phosphate
(45) Parkinson-dystonia-hypermanganese	Autosomal recessive	1q41	<i>SLC30A10</i>	Yes	No	Mn transporter	Mn transporter; deficiency results in Mn accumulation
(46) Parkinson-dystonia-hypermanganese	Autosomal recessive	8p21.3	<i>SLC39A14</i>	Yes	No	Divalent metal transporter	Excess Mn accumulation
(47) Parkinson disease and DLB	Autosomal dominant	14q11.2	<i>LRP10</i>	Yes	No	Low-density lipoprotein receptor related protein 10	Trafficking between the transgolgi network, endosomes and plasma membrane
(48) Juvenile Parkinson disease	Autosomal recessive	7q32.3	<i>PODXL</i>	Yes	No	Podocalyxin-like protein	A sialomucin protein involved in adhesion and cell morphology
(49) Juvenile Parkinson disease with Intellectual disability	Autosomal recessive	2p23.3	<i>PTRHD1 (C2orf79)</i>	Yes	No	Peptidyl-tRNA hydrolase domain-containing 1	Recycles peptidyl-tRNA
(50) Familial Parkinson disease	Autosomal dominant	11p15.4	<i>RIC3</i>	Yes	No	Resistance to inhibitors of cholinesterase 3	Protein associated with nicotinic receptors
Parkinson-plus syndromes							
(51) Parkinsonism with ophthalmoplegia	Autosomal dominant	10q24.31	<i>PEO1</i>	Yes	No	Twinkle	Essential for mtDNA maintenance and regulates mtDNA copy number
(52) Juvenile parkinsonism with spasticity	Autosomal recessive	15q21.1	<i>SPG11</i>	Yes	No	Spatacsin	Neuronal axonal growth, function, and intracellular cargo trafficking; mediates lysosome reformation
(53) Juvenile parkinsonism with spasticity	Autosomal recessive	14q21.1	<i>SPG15</i>	Yes	No	Spastizin	Mediates lysosome reformation
(54) Parkinsonism with basal ganglia calcifications (IBGC1)	Autosomal dominant	8p11.21	<i>SLC20A2</i>	Yes	No	Sodium-dependent phosphate transporter 2	Cellular phosphate uptake
(55) Parkinsonism with basal ganglia calcifications (IBGC2)	Autosomal dominant	2q37	N/I	No	N/I	N/I	N/I
(56) Parkinsonism with basal ganglia calcifications (IBGC4)	Autosomal dominant	5q32	<i>PDGFRB</i>	Yes	No	Platelet-derived growth factor receptor beta	Modulates endothelial growth and angiogenesis
(57) Parkinsonism with basal ganglia calcifications (IBGC5)	Autosomal dominant	22q13.1	<i>PDGFB</i>	Yes	No	Platelet-derived growth factor subunit beta	Modulates endothelial growth and angiogenesis
(58) Parkinsonism with basal ganglia calcifications (IBGC6)	Autosomal dominant	1q25.3	<i>XPR1</i>	Yes	No	Xenotropic and polytropic retrovirus receptor 1	Phosphate transporter

(59) parkinsonism and ataxia with pontine calcifications	Autosomal recessive	9p13.3	<i>MYORG</i>	Yes	No	Myogenesis-regulating glycosidase	42B) parkinsonism and ataxia with pontine calcifications
(60) Diffuse Lewy body disease	Autosomal dominant	2q35-q36	N/I	No	N/I	N/I	N/I
(61) Frontotemporal dementia	Autosomal dominant	17q21.31	<i>MAPT</i>	Yes	No	Tau	Microtubules
(62) Frontotemporal dementia	Autosomal dominant	17q21.31	<i>PGRN</i>	Yes	No	Progranulin	Precursor to granulin
(63) Frontotemporal dementia (FTD-3) (FTLD-UPS)	Autosomal dominant	3p11.2	<i>CHMP2B</i>	Yes	No	Charged multivesicular body protein 2B	Endosome-lysosome fusion
(64) Frontotemporal dementia	Autosomal dominant	16p11.2	<i>FUS</i>	Yes	No	Fusion gene	Translocation of protein to nucleus
(65) Frontotemporal dementia ± ALS (see also HD phenocopy, no. 176)	Autosomal dominant	9p21.2	<i>C9orf72</i>	Yes	Expanded hexanucleotide repeat (GGGGCC)	Uncharacterized	N/I
(66) Pick disease	Autosomal dominant	17q21.31	<i>MAPT</i>	Yes	No	Tau	Microtubules
(67) Progressive supranuclear palsy (PSP) and corticobasal ganglionic degeneration (GBD)	Susceptibility locus	17q21.31	<i>MAPT</i>	Yes	No	Tau	Microtubules
(68) Multiple system atrophy (MSA)	Susceptibility locus	5q22.2	<i>SNCAIP</i>	Yes	No	Synphilin-1	linteracts with alpha-synuclein
(69) MSA	?	3p21.31	<i>BSN</i> (formerly <i>ZNF231</i>)	Yes	No	Bassoon presynaptic cytomatrix protein	A scaffolding protein involved in organizing the presynaptic cytoskeleton
(70) MSA	Susceptibility locus	4q21.23	<i>COQ2</i>	Yes	No	Parahydroxybenzoate-polyprenyltransferase	Biosynthesis of CoQ
(71) Parkinson-MELAS syndrome	Mitochondrial gene	Mitochondria	Cytochrome b	Yes	No	Cytochrome b	Complex III
(72) Guamanian PD-ALS-dementia	Autosomal dominant	15q21.2	<i>TRPM2</i>	Yes	No	Transient receptor potential melastatin 2	Calcium-permeable cation channel
(73) Familial Amyotrophic lateral sclerosis (ALS)	Autosomal dominant	21q22.11	<i>SOD1</i>	Yes	No	Cu/Zn superoxide dismutase	Convert superoxide to H ₂ O ₂
(74) Familial ALS	Autosomal dominant	1p36.22	<i>TARDP</i>	Yes	No	TAR DNA-binding protein 43 (<i>TDP-43</i>)	Regulation of gene expression and splicing
(75) Familial ALS	Autosomal dominant	16p11.2	<i>FUS</i>	Yes	No	Fusion gene	Translocation of protein to nucleus
(76) Parkinson disease and ALS	Autosomal dominant	14q11.2	<i>ANG</i>	Yes	No	Angiogenin	Induces neovascularization
Ataxia syndromes							
(77) Friedreich ataxia (FRDA1)	Autosomal recessive	9q21.11	<i>FXN</i>	Yes	GAA	Frataxin	Mitochondrial iron chaperone
(78) Friedreich ataxia (FRDA2)	Autosomal recessive	9p23-p11	<i>FRDA2</i>	No	N/I	N/I	N/I

Continued

Table 1.5 Gene localization of movement disorders—Continued

Category of disease	Pattern of inheritance	Chromosome region	Name of gene	Gene identified	Triplet repeat	Name of protein	Function of protein
(79) Ataxic cerebral palsy (CPAT1)	Autosomal recessive	9p12-q12	—	No	N/I	N/I	N/I
(80) Posterior column ataxia with retinitis pigmentosa (AXPC1)	Autosomal recessive	1q32.3	<i>FLVCR1</i>	Yes	No	Feline leukemia virus subgroup C receptor 1	Heme transporter
(81) Adult-onset ataxia with tocopherol deficiency	Autosomal recessive	8q12.3	<i>TTPA</i>	Yes	No	α -Tocopherol transfer protein	Transfers α -tocopherol from liposomes to mitochondrial membranes
(82) Ataxia- telangiectasia	Autosomal recessive	11q22.3	<i>ATM</i>	Yes	No	Phosphatidylinositol 3-kinase (PI3K)	DNA repair
(83) Cerebrotendinous xanthomatosis	Autosomal recessive	2q35	<i>CYP27A1</i>	Yes	No	Sterol 27-hydroxylase	Enzyme converts cholesterol to chenodeoxycholic acid. With enzyme deficiency, cholestanol accumulates (65)
(84) Early-onset cerebellar ataxia with oculomotor apraxia (AOA1)	Autosomal recessive	9p21.1	<i>APTX</i>	Yes	No	Aprataxin	Nucleotide-binding
(85) AOA2, also SCAR1	Autosomal recessive	9q34.13	<i>SETX</i>	Yes	No	Senataxin	DNA repair
(86) AOA3	Autosomal recessive	17p13.1	<i>PIK3R5</i>	Yes	No	PI3K regulator subunit 5	Phosphorylates PI3K
(87) AOA4	Autosomal recessive	19q12.33	<i>PNKP</i>	Yes	No	polynucleotide kinase 3'-phosphatase	DNA-damage repair
(88) SCAR2	Autosomal recessive	9q34-qter	—	No	N/I	N/I	N/I
(89) SCAR3	Autosomal recessive	6p23-p21	—	No	N/I	N/I	N/I
(90) SCAR4 ataxia with saccadic intrusions (formerly SCA24)	Autosomal recessive	1p36	—	No	N/I	N/I	N/I
(91) SCAR5 (congenital ataxia)	Autosomal recessive	15q25.3	<i>ZNF592</i>	Yes	No	Zinc finger protein 592	Transcriptional regulation
(92) SCAR6 nonprogressive infantile ataxia	Autosomal recessive	20q11-q13	—	No	N/I	N/I	N/I
(93) SCAR7 (see also CLN2, no. 343)	Autosomal recessive	11p15.4	<i>TPP1</i>	Yes	No	Tripeptidyl peptidase 1	Removes tripeptides from the N termini of proteins in lysosome
(94) SCAR8	Autosomal recessive	6q25.1-q25.2	<i>SYNE1</i>	Yes	No	Synaptic nuclear envelope protein 1	Nuclear envelope

(95) SCAR9 (primary coenzyme Q10 deficiency-4)	Autosomal recessive	1q42.13	<i>ADCK3</i>	Yes	No	Mitochondrial protein aarF domain containing kinase 3	Coenzyme Q10 synthesis
(96) SCAR10	Autosomal recessive	3p22.1	<i>ANO10</i>	Yes	No	Anoctamin 10	Calcium-activated chloride channel
(97) SCAR11	Autosomal recessive	1p32.2	<i>SYT14</i>	Yes	No	Synaptotagmin 14	Membrane-trafficking
(98) SCAR12 with Intellectual disability and epilepsy	Autosomal recessive	16q21.1-q23	<i>WWOX</i>	Yes	No	WW domain-containing oxidoreductase	Regulation of protein degradation, transcription, and RNA splicing
(99) SCAR13 (see also SCA44, no. 164)	Autosomal recessive	6q24.3	<i>GRM1</i>	Yes	No	Metabotropic glutamate receptor 1	Activates phospholipase C
(100) SCAR14 (also SCA5)	Autosomal recessive	11q13.2	<i>SPTBN2</i>	Yes	No	Spectrin, beta, nonerythrocytic 2	Structural components of membrane-cytoskeleton
(101) SCAR15	Autosomal recessive	3q29	<i>KIAA0226</i>	Yes	No	Rubicon	Vesicular trafficking and late endosome maturation
(102) SCAR16	Autosomal recessive	16p13.3	<i>STUB1</i>	Yes	No	STIP1 homology and U-Box containing protein 1	Ubiquitin ligase/ cochaperone
(103) SCAR17	Autosomal recessive	10q24.31	<i>CWF19L1</i>	Yes	No	C19L1 protein	mRNA processing
(104) SCAR18	Autosomal recessive	4q22.1-q22.2	<i>GRID2</i>	Yes	No	Glutamate receptor, ionotropic, delta 2	Protein located on Purkinje cells
(105) SCAR19; Lichtenstein– Knorr syndrome; deafness-ataxia	Autosomal recessive	1p36.11	<i>SLC9A1</i>	Yes	No	Sodium/hydrogen exchanger 1	Regulates pH homeostasis
(106) SCAR20; ataxia with poor speech	Autosomal recessive	6q14.3	<i>SNX14</i>	Yes	No	Sorting nexin14	Sorting of endosomes
(107) SCAR21; ataxia with hepatopathy	Autosomal recessive	11q13.1	<i>SCYL1</i>	Yes	No	SCY1-like 1 protein	Activates transcription of the telomerase reverse transcriptase and DNA polymerase beta genes
(108) SCAR22; adult-onset cerebellar ataxia	Autosomal recessive	2q11.2	<i>VWA3B</i>	Yes	No	von Willebrand factor A domain containing 3B	Transcription, DNA repair, and ribosomal and membrane transport
(109) SCAR23 ataxia with epilepsy	Autosomal recessive	6p22.3	<i>TDP2</i>	Yes	No	Tyrosyl DNA phosphodiesterase-2	Repairs “abortive” topoisomerase II–induced double-strand breaks
(110) SCAR24 ataxia	Autosomal recessive	3q22.1	<i>UBA5</i>	Yes	No	Ubiquitin-like modifier activating enzyme 5	Activates ubiquitin-fold modifier 1
(111) SCAR25 ataxia	Autosomal recessive	6q21	<i>ATG5</i>	Yes	No	Autophagy related 5 protein	Autophagic vesicle formation

Continued

Table 1.5 Gene localization of movement disorders—Continued

Category of disease	Pattern of inheritance	Chromosome region	Name of gene	Gene identified	Triplet repeat	Name of protein	Function of protein
(112) SCAR26 ataxia	Autosomal recessive	19p13.31	<i>XRCC1</i>	Yes	No	X-ray repair cross-complementing protein 1	Scaffold protein that assembles multiprotein complexes involved in DNA single-strand break repair
(113) SPAX1 hereditary spastic ataxia	Autosomal dominant (Newfoundland)	12p13.31	<i>VAMP1</i>	Yes	No	Vesicle-associated membrane protein-1, also known as synaptobrevin-1	Synaptic vesicle exocytosis
(114) SPAX2 hereditary spastic ataxia	Autosomal recessive (Morocco)	17p13.2	<i>KIF1C</i>	Yes	No	Kinesin-like protein	Microtubule-based protein
(115) SPAX3 hereditary spastic ataxia	Autosomal recessive (French Canada)	2q33.1	<i>MARS2</i>	Yes	No	Mitochondrial methionyl-tRNA synthetase	Covalently links methionine with tRNA
(116) SPAX4 hereditary spastic ataxia	Autosomal recessive (Amish)	10p11.23	<i>MTPAP</i>	Yes	No	Mitochondrial poly(A) polymerase	Synthesizes the 3' poly(A) tail of mitochondrial transcripts
(117) SPAX5 hereditary spastic ataxia (see also SCA28, no. 150)	Autosomal recessive (Colombia)	18p11.21	<i>AFG3L2</i>	Yes	No	Mitochondrial AFG3-like AAA ATPase 2	Degrades misfolded proteins and regulates ribosome assembly
(118) SPAX6 hereditary spastic ataxia Charlevoix–Saguenay type	Autosomal recessive	13q12.12	<i>SACS</i>	Yes	No	Sacsin	Integrates the ubiquitin-proteasome system and Hsp70 chaperone
(119) SPAX7 hereditary spastic ataxia with miosis	Autosomal dominant	N/I	N/I	N/I	N/I	N/I	N/I
(120) hereditary spastic ataxia with hypomyelinating leucodystrophy	Autosomal recessive	10q26.3	<i>NKX6-2</i>	Yes	No	Homeobox protein NKX6-2	Oligodendrocyte maturation
(121) Hereditary spastic ataxia 96A	Autosomal recessive	16q24.3	<i>SPG7</i>	Yes	No	Paraplegin	Proteolytic and chaperone-like activities at the inner mitochondrial membrane
(122) Recessive ataxia with Intellectual disability (dysequilibrium syndrome)	Autosomal recessive	9p24.2	<i>VLDLR</i>	No	N/I	Very-low-density lipoprotein receptor	Role in triglyceride metabolism
(123) Epilepsy, ataxia, sensorineural deafness, tubulopathy (EAST syndrome)	Autosomal recessive	1q23.2	<i>KCNJ10</i>	No	N/I	Inwardly rectifying potassium channel	Recycle potassium for the Na/K-ATPase
(124) SCA1	Autosomal dominant	6p22.3	<i>ATXN1</i>	Yes	CAG 40-83	ataxin-1	transcriptional repression
(125) SCA2	Autosomal dominant	12q24.12	<i>ATXN2</i>	Yes	CAG 34-59	Ataxin-2	Located in Golgi apparatus

(126) SCA3 (Machado–Joseph disease)	Autosomal dominant	14q32.12	<i>ATXN3</i>	Yes	CAG 56-86	Ataxin-3	Deubiquitinase, a component of the ubiquitin proteasome system
(127) SCA4	Autosomal dominant	16q22.1	—	No	N/I	N/I	N/I
(128) SCA5 (also SCAR14)	Autosomal dominant	11q13.2	<i>SPTBN2</i>	Yes	No	Spectrin, beta, nonerythrocytic 2	Structural components of membrane-cytoskeleton
(129) SCA6 (see also EA2, no. 286)	Autosomal dominant	19p13.2	<i>CACNA1A</i>	Yes	CAG 21-31	Alpha-1A calcium channel protein	Ca ⁺⁺ channel
(130) SCA7	Autosomal dominant	3p14.1	<i>ATXN7</i>	Yes	CAG 38-200	Ataxin-7	Transcription factor
(131) SCA8	Autosomal dominant	13q21	<i>ATXN8OS and ATXN</i>	Yes	CTG/CAG 100- 155	Ataxin-8 and ataxin8 opposite strand	N/I
(132) SCA10	Autosomal dominant	22q13.31	<i>ATXN10</i>	Yes	ATTC 800-3800	Ataxin-10	N/I
(133) SCA11	Autosomal dominant	15q15.2	<i>TTBK2</i>	No	No	Tau tubulin kinase-2	Phosphorylates tau and tubulin
(134) SCA12	Autosomal dominant	5q32	<i>PPP2R2B</i>	Yes	CAG 43-93	Regulatory subunit B of protein phosphatase 2	Regulatory processes
(135) SCA13	Autosomal dominant	19q13.33	<i>KCNC3</i>	Yes	No	Potassium channel subfamily	Voltage-gated potassium channel
(136) SCA14	Autosomal dominant	19q13.42	<i>PRKCG</i>	Yes	No	Protein kinase C, gamma	Phosphorylation of apataxin
(137) SCA15 (see also SCA29, no. 151)	Autosomal dominant	3p26.1	<i>ITPR1</i>	Yes	No	Type 1 inositol 1,4,5-triphosphate receptor	Release calcium ions from intracellular stores
(138) SCA16	Now recognized as identical to SCA15						
(139) SCA17 (also called HDL4) (see no. 175)	Autosomal dominant	6q27	<i>TBP</i>	Yes	CAG 45-63	TATA-binding protein (TBP)	Transcription initiation factor
(140) SCA18 with sensorimotor neuropathy	Autosomal dominant	7q22-q32	—	No	N/I	N/I	N/I
(141) SCA19 (same as SCA22)	Autosomal dominant	1p13.2	<i>KCND3</i>	Yes	No	Kv4.3, a subunit of a potassium channel	A-type voltage-gated potassium channel
(142) SCA20	Autosomal dominant	11p12	260-kb duplication in chromosome	N/I	N/I	N/I	N/I
(143) SCA21	Autosomal dominant	1p36.33	<i>TMEM240</i>	Yes	No	Transmembrane protein 240	Most likely transmembrane transport
(144) SCA22	Same as SCA19						
(145) SCA23 adult onset with neuropathy	Autosomal dominant	20p13	<i>PDYN</i>	Yes	No	Prodynorphin	Precursor protein for several opioid neuropeptides
(146) SCA24	Now called SCAR4; see no. 90)						

Continued

Table 1.5 Gene localization of movement disorders—Continued

Category of disease	Pattern of inheritance	Chromosome region	Name of gene	Gene identified	Triplet repeat	Name of protein	Function of protein
(147) SCA25 ataxia with sensory neuropathy	Autosomal dominant	2p21-p13	—	N/I	N/I	N/I	N/I
(148) SCA26	Autosomal dominant	19p13.3	<i>EEF2</i>	Yes	No	Eukaryotic translation elongation factor-2	Translocation step in protein synthesis
(149) SCA27	Autosomal dominant	13q33.1	<i>FGF14</i>	Yes	No	Fibroblast growth factor 14	Neuronal signaling and axonal trafficking
(150) SCA28 (see also SPAX5, no. 117)	Autosomal dominant	18p11.21	<i>AFG3L2</i>	Yes	No	Mitochondrial AFG3-like AAA ATPase 2	Degrades misfolded proteins and regulates ribosome assembly
(151) SCA29 Congenital, nonprogressive ataxia; see also SCA15, no. 137	Autosomal dominant	3p26.1	<i>ITPR1</i>	Yes	No	Type 1 inositol 1,4,5-triphosphate receptor	Release calcium ions from intracellular stores
(152) SCA30	Autosomal dominant	4q34.3-q35.1	SCA30	N/I	N/I	N/I	N/I
(153) SCA31	Autosomal dominant	16q21	<i>BEAN</i>	Yes	Pentanucleotide repeats of (TGGA) _n	Brain expressed, associated with Nedd4	Interacts with ubiquitin-protein ligases
(154) SCA32	Autosomal dominant	7q32-q33	GWAS study	No	N/I	N/I	N/I
(155) SCA34	Autosomal dominant	6q14.1	<i>ELOVL4</i>	Yes	No	Elongation of very-long-chain fatty acids-like 4	Synthesis of polyunsaturated fatty acids
(156) SCA35	Autosomal dominant	20p13	<i>TMG6</i>	Yes	No	Transglutaminase 6	Cross-links proteins
(157) SCA36	Autosomal dominant	20p13	<i>NOP56</i>	Yes	Expansion of an intronic GGCCTG hexanucleotide repeat	NOP56	Nucleolar ribonucleoprotein involved with rRNA processing
(158) SCA37	Autosomal dominant	1p32	N/I	No	N/I	N/I	N/I
(159) SCA38	Autosomal dominant	6p12.1	<i>ELOVL5</i>	Yes	No	Elongation of very-long-chain fatty acids-like 5	Synthesis of polyunsaturated fatty acids
(160) SCA40	Autosomal dominant	14q32	<i>CCDC88C</i>	Yes	No	Coiled-coil domain containing protein 88C	Promotes beta-catenin degradation
(161) SCA41	Autosomal dominant	4q27	<i>TRPC3</i>	Yes	No	Transient receptor potential cation channel, subfamily C, member 3	Cation channel linked to intracellular signaling pathways
(162) SCA42	Autosomal dominant	17q21.33	<i>CACNA1G</i>	Yes	No	Low voltage calcium channel A1G	Pacemaker activity
(163) SCA43 (cerebellar ataxia with neuropathy)	Autosomal dominant	3q25.2	<i>MME</i>	Yes	No	Neprilysin	Zinc-dependent metalloprotease

(164) SCA44 adult-onset cerebellar ataxia (see also SCAR13, no. 99)	Autosomal dominant	6q24.3	<i>GRM1</i>	Yes	No	Metabotropic glutamate receptor 1	Mutation causes gain of function hyperglutamatergic activity with increased calcium influx into Purkinje cells
(165) SCA45 late-onset cerebellar ataxia	Autosomal dominant	5q33.1	<i>FAT2</i>	Yes	No	Protocadherin fat 2	Cell adhesion for cerebellum development
(166) SCA46 Adult-onset cerebellar ataxia with sensory axonal neuropathy	Autosomal dominant	19q13.2	<i>PLD3</i>	Yes	No	phospholipase D member 3	Hydrolyze membrane phospholipids
(167) X-linked congenital ataxia (SCAX1)	X-linked Recessive	Xp11.21-q21.3	<i>ATP2B3</i>	Yes	No	Calcium-ATPase	Calcium transport
(168) X-linked congenital ataxia (SCAX5)	X-linked Recessive	Xq25-q27.1	—	No	N/I	N/I	N/I
(169) Adult-onset Alexander disease	Autosomal dominant	17q21.31	<i>GFAP</i>	Yes	No	Glial fibrillary acidic protein	Astrocytic protein
(170) Adult-onset cerebellar ataxia	Autosomal dominant	4q22.1-q22.2	<i>GRID2</i>	Yes	No	Glutamate receptor delta-2 (GluRD2)	Subfamily of ionotropic glutamate receptors in cerebellum
Choreic syndromes							
(171) Huntington disease (HD)	Autosomal dominant	4p16.3	<i>HTT</i>	Yes	CAG	Huntingtin	Regulates transcription
(172) Huntington-like disease-1 (HDL1)	Autosomal dominant	20p13	<i>PRNP</i>	Yes	Octapeptide repeats	Prion protein	N/I
(173) Huntington-like disease-2 (HDL2)	Autosomal dominant	16q24.2	<i>JPH3</i>	Yes	CTG/CAG	Juncto-philin-3	Links the plasma membrane and the endoplasmic reticulum
(174) Huntington-like disease-3 (HDL3)	Autosomal recessive	4p15.3	—	No	No	N/I	N/I
(175) Huntington-like disease-4 (HDL4) (same as SCA17) (see no. 139)	Autosomal dominant	6q27	<i>TBP</i>	Yes	CAG 45-63	TATA box-binding protein (TBP)	Transcription initiation factor
(176) Huntington-like phenocopy (see also FTD-ALS, no. 65)	Autosomal dominant	9p21.2	<i>C9orf72</i>	Yes	Expanded hexanucleotide repeat (GGGGCC)	Uncharacterized	N/I
(177) Huntington-like	Autosomal recessive	7p22.1	<i>RNF216</i>	Yes	No	Ring finger protein 216	E3 ubiquitin-protein ligase
(178) Neuroacanthocytosis	Autosomal recessive	9q21.2	<i>VPS13A</i>	Yes	No	Chorein	Protein sorting
(179) McLeod syndrome	X-linked recessive	Xp21.1	<i>XK</i>	Yes	No	XK	Kell blood group precursor
(180) Benign hereditary chorea	Autosomal dominant	14q13.3	<i>NKX2-1</i>	Yes	No	Thyroid transcription factor-1 (TTF-1)	Thyroid function

Continued

Table 1.5 Gene localization of movement disorders—Continued

Category of disease	Pattern of inheritance	Chromosome region	Name of gene	Gene identified	Triplet repeat	Name of protein	Function of protein
(181) Neonatal brain-thyroid-lung syndrome, a more severe manifestation than (180).	Autosomal dominant	14q13	<i>NKX2-1</i>	Yes	No	Thyroid transcription factor-1 (TTF-1)	Thyroid function
(182) Benign hereditary chorea	Autosomal dominant	8q21.3-q23.3	—	N/I	N/I	N/I	N/I
(183) Benign hereditary chorea (see also no. 186)	Autosomal dominant	3q21.1	<i>ADCY5</i>	Yes	No	Adenylate cyclase 5	Converts ATP to cAMP
(184) Dentatorubral-pallidoluysian atrophy (DRPLA)	Autosomal dominant	12p13.31	<i>ATN1</i>	Yes	CAG 53-88	Atrophin-1	N/I
Choreoathetosis							
(185) Choreoathetosis and Intellectual disability	X-linked recessive	Xp11	N/I	N/I	N/I	N/I	N/I
(186) Familial dyskinesias with hypotonia (originally called familial dyskinesias with facial myokymia)	Autosomal dominant	3q21.1	<i>ADCY5</i>	Yes	No	Adenylate cyclase 5	Converts ATP to cAMP
(187) Infantile epileptic encephalopathy with choreoathetosis and dystonia	Autosomal dominant (de novo mutations)	16q13	<i>GNAO1</i>	Yes	No	Alpha subunit of guanine nucleotide binding protein	Regulates G protein signaling
(188) Infantile and childhood-onset choreoathetosis	Autosomal recessive	6q27	<i>PDE10A</i>	Yes	No	Cyclic nucleotide phosphodiesterase	Regulation of cyclic nucleotide signaling
(189) Childhood-onset chorea with striatal degeneration	Autosomal dominant	6q27	<i>PDE10A</i>	Yes	No	Cyclic nucleotide phosphodiesterase	Regulation of cyclic nucleotide signaling
(190) Epileptic encephalopathy with dyskinesia	Autosomal recessive	9q31.3	<i>FRRS1L</i>	Yes	No	Ferric chelate reductase-1 like	A component of the outer core of AMPA receptor accessory proteins
(191) Glutaric academia 1	Autosomal recessive	19p13.13	<i>GCDH</i>	Yes	No	Glutaryl-CoA dehydrogenase	Dehydrogenates and decarboxylates glutaryl-CoA to crotonyl-CoA in the degradation of L-lysine, L-hydroxylysine, and L-tryptophan
(192) Alpha-methylacetoacetic aciduria	Autosomal recessive	11q22.3	<i>ACAT1</i>	Yes	No	Mitochondrial acetyl-CoA acetyltransferase-1	Forms acetoacetyl-CoA from two molecules of Acetyl-CoA; involved in many metabolic pathways

(193) GABA transaminase deficiency	Autosomal recessive	16p13.2	<i>ABAT</i>	Yes	No	GABA transaminase	Metabolizes GABA to succinic semialdehyde
(194) Complex movement disorder (ataxia, chorea, dystonia, tremor) ± spasticity	Autosomal recessive	1p36.22-p36.21	<i>VPS13D</i>	Yes	No	Vacuolar protein sorting 13D	Protein sorting
(195) Infantile epileptic encephalopathy with chorea	Autosomal dominant	4p12	<i>GABRA2</i>	Yes	No	Alpha2 subunit of the GABA _A receptor	GABA _A receptor
(196) Infantile encephalopathy with developmental delay, hypotonia, choreoathetosis, and optic atrophy	Autosomal recessive	13q12.13	<i>ATP8A2</i>	Yes	No	ATPase, type 8A, member 2	Transport of aminophospholipids
Dystonia							
(197) Oppenheim torsion dystonia (DYT1)	Autosomal dominant	9q34.11	<i>TOR1A</i>	Yes	No	torsin A	Chaperone, ATPase
(198) DYT2	Autosomal recessive	1p35.1	<i>HPCA</i>	Yes	No	Hippocalcin	Regulating voltage-dependent calcium channels
(199) Lubag (X-linked dystonia-parkinsonism) (XDP) (DYT3)	X-linked recessive	Xq13.1	<i>TAF1</i>	Yes	No	TATA-binding protein-associated factor-1	DNA-binding protein complex required for transcription
(200) DYT4	Autosomal dominant	19p13.3	<i>TUBB4</i>	Yes	No	Beta-tubbulin 4a	Globular protein in microtubules
(201) Dopa- responsive dystonia (DYT5a)	Autosomal dominant	14q22.2	<i>GCH1</i>	Yes	No	GTP cyclo- hydrolase 1	Synthesis of BH4
(202) Dopa- responsive dystonia (DYT5b) (see also no. 35)	Autosomal recessive	11p15.5	<i>TH</i>	Yes	No	Tyrosine hydroxylase	Converts tyrosine to levodopa
(203) Dopa- responsive dystonia and Parkinson (see also no. 35)	Autosomal recessive	10q21.3	<i>DNAJC12</i>	Yes	No	DnaJ/HSP40 subfamily C, member 12	Chaperone of amino-acid hydrolase interactions required for catecholamine synthesis
(204) DYT6 Mixed type dystonia	Autosomal Dominant	8p11.21	<i>THAP1</i>	Yes	No	THAP1	Regulates endothelial cell proliferation
(205) DYT7 Familial torticollis	Autosomal dominant	18p?	—	N/I	N/I	N/I	N/I
(206) Myoclonus-dystonia (DYT11)	Autosomal dominant	7q21.3	<i>SGCE</i>	Yes	No	Epsilon-sarcoglycan	Transmembrane protein
(207) Rapid-onset dystonia-parkinsonism (RDP) (DYT12) (see also Alternating hemiplegia of childhood, no. 225)	Autosomal dominant	19q13.2	<i>ATP1A3</i>	Yes	No	Na ⁺ /K ⁺ -ATPase alpha3 subunit (ATP1A3)	Sodium pump

Continued

Table 1.5 Gene localization of movement disorders—Continued

Category of disease	Pattern of inheritance	Chromosome region	Name of gene	Gene identified	Triplet repeat	Name of protein	Function of protein
(208) DYT13 Cervical-cranial-brachial dystonia	Autosomal dominant	1p36.32-p36.13	—	No	N/I	N/I	N/I
(209) DYT15 Myoclonus-dystonia	Autosomal dominant	18p11	—	N/I	N/I	N/I	N/I
(210) DYT16 Young-onset dystonia-parkinsonism	Autosomal recessive	2q31.2	<i>PRKRA</i>	Yes	No	Double-stranded RNA (dsRNA)-activated protein kinase	Mediator of the effects of interferon
(211) DYT17 Familial dystonia	Autosomal recessive	20p11.2-q13.12	—	No	N/I	N/I	N/I
(212) DYT21 Adult-onset mixed dystonia	Autosomal dominant	2q14.3-q21.3	—	No	N/I	N/I	N/I
(213) DYT23 Cervical dystonia	Autosomal dominant	9q34	<i>CIZ1</i>	Yes	No	CDKN1A interacting zinc finger protein 1	Regulates the cellular localization of p21(Cip1)
(214) DYT24 Cervical-cranial-brachial dystonia	Autosomal dominant	11p14.2	<i>ANO3</i>	Yes	No	Anoctamin 3	Ca-activated Cl channel
(215) DYT25 Cervical-cranial dystonia	Autosomal dominant	18p11.21	<i>GNAL</i>	Yes	No	Guanine nucleotide-binding protein G(olf) subunit alpha [G-alpha(olf)]	Couples D1 and A2a receptors to adenylyl cyclase in the striatum
(216) Myoclonus-dystonia (DYT26)	Autosomal dominant	22q12.3	<i>KCTD17</i>	Yes	No	Potassium channel tetramerization domain 17	Calcium homeostasis in endoplasmic reticulum
(217) Early-onset isolated dystonia (neck and arms) (DYT27)	Autosomal recessive	2q37.3	<i>COL6A3</i>	Yes	No	$\alpha 3$ (VI) Collagen	$\alpha 3$ -Subunit of the heterotrimeric type VI collagen, an extracellular matrix protein in microfibrillar networks
(218) Childhood-onset dystonia with optic atrophy and BG abnormalities (DYT29)	Autosomal recessive	1p35.3	<i>MECR</i>	Yes	No	Mitochondrial trans-2-enoyl-coenzyme A-reductase	Mitochondrial fatty acid synthesis
(219) Childhood-onset generalized dystonia (onset in legs) (DYT28)	Autosomal dominant	19q13.12	<i>KMT2B</i>	Yes	No	Histone lysine methyltransferase	Epigenetic histone methylation to induce gene activation
(220) Juvenile-onset dystonia	Autosomal recessive	20p13	<i>VPS16</i>	Yes	No	Vacuolar protein sorting 16	Vesicle-mediated protein trafficking to endosomes and lysosomes
(221) Juvenile-onset dystonia with Intellectual disability	Autosomal dominant	1p36.33	<i>GNB1</i>	Yes	No	Guanine nucleotide-binding protein, beta 1	Transduce extracellular signals to effector protein

(222) Childhood-onset dystonia with spasticity	Autosomal recessive [†]	2q33.1	<i>ALS2</i>	Yes	No	Alsin	Binds to a small GTPase RAB5 and functions as a guanine nucleotide exchange factor for RAB5 and has a role in intracellular endosomal trafficking
(223) Infantile encephalopathy with developmental delay, hypotonia, and dystonia	Autosomal dominant	1q25.3	<i>CACNA1E</i>	Yes	No	Alpha1 subunit of the voltage-gated Ca _v 2.3 channel	R-type calcium channel
(224) Alternating hemiplegia of childhood-1 (AHC1)	Autosomal dominant	1q23.2	<i>ATP1A2</i>	Yes	No	Na ⁺ /K ⁺ -ATPase alpha2 subunit (ATP1A2)	Sodium pump
(225) Alternating hemiplegia of childhood-2 (AHC2) (see also RDP, no. 207)	Autosomal dominant	19q13.2	<i>ATP1A3</i>	Yes	No	Na ⁺ /K ⁺ -ATPase alpha3 subunit (ATP1A3)	Sodium pump
(226) Aromatic amino acid decarboxylase deficiency	Autosomal recessive	7p12.1	Aromatic amino acid decarboxylase	Yes	No	Aromatic amino acid decarboxylase	Converts dopa to dopamine and 5-HTP to serotonin
(227) Sepiapterin reductase deficiency	Autosomal recessive	2p13.2	<i>SPR</i>	Yes	No	Sepiapterin reductase	Reduces 7,8-dihydro-biopterin to tetrahydrobiopterin
(228) Torticollis	Susceptibility gene	4p16.1	<i>DRD5</i>	Yes	No	Dopamine D5 receptor	Dopamine D5 receptor
(229) Blepharospasm	Susceptibility gene	4p16.1	<i>DRD5</i>	Yes	No	Dopamine D5 receptor	Dopamine D5 receptor
(230) Deafness-dystonia-optic atrophy	X-linked recessive	Xq22.1	<i>DDP</i>	Yes	No	DDP	Intermembrane protein transport in mitochondria
(231) Dystonic lipidosis (Niemann-Pick type C [NPC])	Autosomal recessive	18q11.2	<i>NPC1</i>	Yes	No	NPC intracellular cholesterol transporter 1	Regulation of intracellular cholesterol trafficking
(232) MEGDEL syndrome (dystonia and deafness)	Autosomal recessive	6q25.3	<i>SERAC1</i>	Yes	No	Serine active site-containing protein 1	Intracellular cholesterol trafficking
(233) Mohr-Tranebjaerg syndrome (deafness-dystonia)	X-recessive	Xq22.1	<i>TIMM8A</i>	Yes	No	Translocase of inner mitochondrial membrane 8	Imports hydrophobic proteins into mitochondrial inner membrane
(234) Dystonia-deafness syndrome	Autosomal dominant	7p22.1	<i>ACTB</i>	Yes	No	Beta actin	Cytoplasmic actin modulates cell migration
(235) Dystonia-ataxia	Autosomal recessive	1q44	<i>COX20</i>	Yes	No	Cytochrome C oxidase 20	Assembly of mitochondrial complex IV
(236) Dystonia with pallidal degeneration (see also no. 301)	Autosomal recessive	10q26.3	<i>ECHS1</i>	Yes	No	Enoyl-CoA hydratase short-chain 1	Mitochondrial enzyme involved in degrading amino acids and fatty acids

Continued

Table 1.5 Gene localization of movement disorders—Continued

Category of disease	Pattern of inheritance	Chromosome region	Name of gene	Gene identified	Triplet repeat	Name of protein	Function of protein
(237) Dystonia parkinsonism with GM1 gangliosidosis	Autosomal recessive	3p22.3	<i>GLB1</i>	Yes	No	Beta-galactosidase 1	Hydrolyzes β -galactosides
(238) Childhood-onset ataxia, dystonia gaze palsy, cognitive decline, and dysautonomia	Autosomal recessive	5q35.3	<i>SQSTM1</i>	Yes	No	Sequestosome 1	Autophagic removal of damaged mitochondria
(239) NBIA1 Neurodegeneration with brain iron accumulation 1 (PKAN)	Autosomal recessive	20p13	<i>PANK2</i>	N/I	N/I	Pantothenate kinase 2	CoA biosynthesis
(240) NBIA2 Infantile neuroaxonal dystrophy with parkinsonism dystonia and ataxia (PLAN), (also as adult-onset dystonia-parkinsonism without iron) (PARK14, no. 14)	Autosomal recessive	22q13.1	<i>PLA2G6</i>	Yes	No	Phospho-lipase A2	Releases fatty acids from phospholipids
(241) Neuroferritinopathy (NBIA3)	Autosomal dominant	19q13.33	<i>FTL1</i>	Yes	No	Ferritin light polypeptide	Iron binding
(242) NBIA4 (MPAN)	Autosomal recessive	19q12	<i>C19orf12</i>	Yes	No	Mitochondrial transmembrane protein	N/I
(243) NBIA5 (BPAN) (formerly called SENDA)	X-linked dominant	Xp11.23	<i>WDR45</i>	Yes	No	Beta-propeller protein	Form a beta-propeller platform for simultaneous and reversible protein-protein interactions
(244) NBIA6 (CoPAN)	Autosomal recessive	17q21.2	<i>COASY</i>	Yes	No	Coenzyme A synthase	CoA synthesis
(245) NBIA aceruloplasminemia	Autosomal recessive	3q24-q25	<i>CP</i>	Yes	No	Ceruloplasmin	Oxidizes ferrous ion
(246) NBIA fatty acid hydroxylase neurodegeneration (FAHN) (also known as SPG35)	Autosomal recessive	16q23.1	<i>FA2H</i>	Yes	No	Fatty acid 2-hydroxylase	Acetyl-CoA metabolism
(247) Striatal necrosis associated with Leber optic atrophy	Mitochondrial	Mitochondrial	ND6	Yes	No	NADH dehydrogenase, subunit 6	Decrease complex 1 activity
(248) Striatal necrosis (biotin-thiamine- responsive basal ganglia disease (BTBGD)	Autosomal recessive	2q36.3	<i>SLC19A3</i>	Yes	No	Thiamine transporter-2	Thiamine metabolism
(249) Striatal necrosis with dystonia and ataxia	Autosomal recessive	14q12	<i>NUBPL</i>	Yes	No	Nucleotide binding protein-like protein	Fe/S protein required for the assembly of mitochondrial Complex I
(250) Striatal necrosis with dystonia	Autosomal recessive	8q22.1	<i>NDUFA6</i>	Yes	No	NADH de-hydrogenase complex I assembly factor 6	Fe/S protein required for the assembly of mitochondrial Complex I
(251) Lesch–Nyhan syndrome	X-linked recessive	Xq26.2- q26.3	<i>HPRT</i>	Yes	No	Hypoxanthine-guanine-phosphoribosyl transferase	—

(252) Woodhouse Sakati syndrome	Autosomal recessive	2q31.1	<i>C2orf37 (DCAF17)</i>	Yes	No	DDB1 and CUL4 associated factor 17 (DCAF17)	Nucleolar transmembrane protein
(253) Spastic paraplegia with dystonia	Autosomal dominant	2q24-q31	N/I	N/I	N/I	N/I	N/I
(254) Dystonia and sleep episodes, dysautonomia, and oculogyria (AADC deficiency)	Autosomal recessive	7p12	<i>DDC</i>	Yes	No	Aromatic amino acid decarboxylase	Converts dopa to dopamine and 5-hydroxy-tryptophan to serotonin
(255) Dystonia parkinsonism and dysautonomia resulting from dihydropteridine reductase deficiency	Autosomal recessive	4p15.32	<i>QDPR</i>	Yes	No	Dihydropteridine reductase	Catalyzes the reduction of quinoid dihydrobiopterin to tetrahydrobiopterin
(256) Dystonia parkinsonism and dysautonomia resulting from 6-pyruvoyltetrahydropterin synthase deficiency	Autosomal recessive	11q23.1	<i>PTS</i>	Yes	No	6-Pyruvoyl-tetrahydro-pterin synthase	Catalyzes the conversion of 6-pyruvoyl-tetrahydro-pterin to tetrahydro-biopterin
(257) Mitochondrial depletion with encephalopathy and dystonia	Autosomal recessive	13q14.2	<i>SUCLA2</i>	Yes	No	Beta subunit of succinyl-CoA synthase	Mitochondrial matrix enzyme catalyzes the synthesis of succinyl-CoA
(258) Dystonia and ataxia from 3-hydroxy-isobutyryl-CoA hydrolase deficiency	Autosomal recessive	2q32.2	<i>HIBCH</i>	Yes	No	3-Hydroxy-isobutyryl-CoA hydrolase	Catalysis of valine and propionic acid pathways
(259) Dystonia, myoclonus and developmental delay	Autosomal recessive	2q21q22.13	<i>KCNJ6</i>	Yes	No	Potassium channel, inwardly rectifying subfamily J member 6	G protein-coupled inwardly directed K ⁺ channel
Hyperekplexia							
(260) Hereditary hyperekplexia (HKPX1)	Autosomal dominant	5q33.1	<i>GLRA1</i>	Yes	No	Alpha1 subunit of glycine receptor	Ligand-gated chloride channel
(261) Hereditary hyperekplexia (HKPX2)	Autosomal recessive	4q32.1	<i>GLRB</i>	Yes	No	Beta subunit of glycine receptor	Glycine receptor
(262) Hereditary hyperekplexia (HKPX3)	Autosomal recessive	11p15.1	<i>SLC6A5</i>	Yes	No	Presynaptic glycine transporter-2 (GLYT2)	Presynaptic glycine transporter
Myoclonus							
(263) Unverricht–Lundborg disease (EPM1)	Autosomal recessive	21q22.3	<i>CSTB</i>	Yes	Dodecamer repeat expansion	Cystatin B	Cysteine protease inhibitor
(264) Lafora body disease (EPM2A)	Autosomal recessive	6q24.3	<i>EPM2A</i>	Yes	No	Laforin	Tyrosine phosphatase
(265) Lafora body disease (EPM2B)	Autosomal recessive	6p22.3	<i>NHLRC1</i>	Yes	No	Malin	E3 ubiquitin ligase
(266) Progressive myoclonus epilepsy (EPM3) (see also CLN14, no. 355)	Autosomal recessive	7q11.21	<i>KCTD7</i>	Yes	No	Potassium channel	Potassium transport
(267) Progressive myoclonus epilepsy with or without renal failure (EPM4)	Autosomal recessive	4q21.1	<i>SCARB2</i>	Yes	No	Scavenger receptor class B member 2	Lysosomal integral membrane protein. Transports glucocerebrosidase (GCase) to the lysosome

Continued

Table 1.5 Gene localization of movement disorders—Continued

Category of disease	Pattern of inheritance	Chromosome region	Name of gene	Gene identified	Triplet repeat	Name of protein	Function of protein
(268) Progressive myoclonus epilepsy (EPM5)	Autosomal dominant	3p14.1	<i>PRICKLE2</i>	Yes	No	PRICKLE2	Unknown
(269) Progressive myoclonus epilepsy (EPM6) (North Sea PME)	Autosomal recessive	17q21.32	<i>GOSR2</i>	Yes	No	Golgi Snare-27kd	Trafficking membrane protein that transports proteins among the medial- and trans-Golgi compartments
(270) Progressive myoclonus epilepsy	Autosomal recessive	21q22.3	<i>COL6A2</i>	Yes	No	Alpha2 subunit of type VI collagen	Extracellular matrix
(271) Progressive myoclonus epilepsy (EPM7)	Autosomal dominant	11p15.1	<i>KCNC1</i>	Yes	No	KV3.1 subunit of the KV3 voltage-gated potassium ion channels	Potassium transporter
(272) Progressive myoclonus epilepsy (EPM8)	Autosomal recessive	19p13.11	<i>CERS1</i>	Yes	No	Ceramide synthase 1	Transmembrane protein of the endoplasmic reticulum, catalyzes the biosynthesis of C18-ceramides
(273) Progressive myoclonus epilepsy (EPM9)	Autosomal recessive	19p13.3	<i>LMNB2s PRDM8</i>	Yes	No	Lamin B2 protein	On inner nuclear envelope, involved in nuclear stability and chromatin structure
(274) Progressive myoclonus epilepsy (EPM10) (Lafora bodies)	Autosomal recessive	4q21.21	<i>PRDM8</i>	Yes	No	PR domain zinc finger protein 8	Interacts with laforin and malin and causes translocation of the two proteins to the nucleus
(275) Febrile-induced dyskineisas (myoclonus, myokymia, chorea) with neonatal epilepsy (AD)	Autosomal dominant	20q13.3	<i>KCNQ2</i>	Yes	No	Voltage-gated potassium channel, subfamily Q member 2 (Kv7.2)	M-current, a slowly activating, noninactivating current that regulates neuronal excitability
(276) Delayed development, hypomyelination, myoclonus, ataxia, seizures, tremor	Autosomal recessive	11q13.4	<i>FOLR1</i>	Yes	No	Folate receptor	Folate transport from blood into brain; treatable with folinic acid
(277) Adult familial myoclonus epilepsy (FAME1) (<i>FCMTE1</i>)	Autosomal dominant	8q24	<i>FCMTE1</i>	No	N/I	N/I	N/I
(278) FAME2 (<i>FCMTE2</i>)	Autosomal dominant	2p11.2	<i>ADRA2B</i>	Yes	No	Alpha2-adrenergic receptor subtype B	The mutant increases the epinephrine-stimulated calcium signaling
(279) FAME3 (<i>FCMTE3</i>)	Autosomal dominant	5p15.2	<i>CTNND2</i>	Yes	No	Delta-catenin	Expressed in dendrites and participates in modulating dendritic arborization, especially Purkinje cells

(280) FAME4 (<i>FCMTE4</i>)	Autosomal dominant	3q26.32-q28	<i>FCMTE4</i>	No	N/I	N/I	N/I
(281) FAME5 (<i>FCMTE5</i>)	Autosomal recessive t	1q32.1	<i>CNTN2</i>	Yes	No	Contactin-2	Maintains voltage-gated potassium channels at nodes of Ranvier
(282) Familial Creutzfeldt–Jakob disease	Autosomal dominant	20p13	<i>PRNP</i>	Yes	No	Prion protein	N/I
(283) Infantile spasms (also known as West syndrome; early infantile epileptic encephalopathy-1 (EIEE1))	X-linked recessive	Xp21.3	<i>ARX</i>	Yes	No	Aristaless-related homeobox	Cerebral development and patterning
(284) EIEE2	X-linked recessive	Xp22.13	<i>CDKL5</i>	Yes	No	Cyclin-dependent kinase-like 5	Kinase
(285) Neonatal intractable myoclonus, hypotonia, optic nerve, developmental arrest	De novo mutations	12q13.3	<i>KIF5A</i> (also causes <i>SPG10</i>)	Yes	No	Kinesin family member 5A	Mitochondrial transport
Paroxysmal dyskinesias							
(286) Episodic ataxia1 (EA1)/myokymia	Autosomal dominant	12p13.32	<i>KCNA1</i>	Yes	No	Kv1.1 voltage gated K channel	K ⁺ transport
(287) Episodic ataxia2 (EA2)/vestibular (see also SCA6; no. 129)	Autosomal dominant	19p13.2	<i>CACNA1A</i>	Yes	No	CaV2.1 voltage-gated Ca channel	Ca ⁺⁺ transport
(288) Episodic ataxia3 (EA3)/vertigo and tinnitus	Autosomal dominant	1q42	<i>EA3</i>	N/I	N/I	N/I	N/I
(289) Episodic ataxia4 (EA4)/diplopia	Autosomal dominant	?	<i>EA4</i>	N/I	N/I	N/I	N/I
(290) Episodic ataxia5 (EA5)/vertigo	Autosomal dominant	2q23.3	<i>CACNB4</i>	Yes	No	Calcium-channel beta4-subunit	Ca ⁺⁺ transport
(291) Episodic ataxia6 (EA6)	Autosomal dominant	5p13.2	<i>SLC1A3</i>	Yes	No	Excitatory amino acid transporter 1 (EAAT1)	Glial glutamate transporter
(292) Episodic ataxia 7 (EA7)	Autosomal dominant	19q13	<i>EA7</i>	N/I	N/I	N/I	N/I
(293) Late-onset episodic ataxia (EA8)	Autosomal dominant	1p36.13-p34.3	<i>EA8</i>	N/I	N/I	N/I	N/I
(294) Paroxysmal kinesigenic dyskinesia (PKD) with infantile convulsions (EKD1) (DYT10) (see also no. 302)	Autosomal dominant	16p11.2	<i>PRRT2</i>	Yes	No	Proline-rich transmembrane protein 2 (PRRT2)	Interacts with SNAP25
(295) Paroxysmal kinesigenic dyskinesia (PKD) (EKD2) (DYT19)	Autosomal dominant	16q13-16q21.1	<i>EKD2</i>	No	N/I	N/I	N/I

Continued

Table 1.5 Gene localization of movement disorders—Continued

Category of disease	Pattern of inheritance	Chromosome region	Name of gene	Gene identified	Triplet repeat	Name of protein	Function of protein
(296) Paroxysmal kinesigenic dyskinesia (PKD)	Autosomal dominant	3q28-291	<i>EKD3</i>	No	N/I	N/I	N/I
(297) Paroxysmal nonkinesigenic dyskinesia (PNKD) (Mount–Reback syndrome (DYT8))	Autosomal dominant	2q35	<i>PNKD</i>	Yes	No	PNKD, formerly called myofibrillogenesis regulator 1	Regulatory role in neurotransmitter release exocytosis
(298) PNKD2 (DYT20)	Autosomal dominant	2q31	—	No	N/I	N/I	N/I
(299) Paroxysmal dyskinesia and spasticity	Previously labeled as DYT9. Now recognized as GLUT1 deficiency, see DYT18, no. 303						
(300) Paroxysmal dyskinesia and epilepsy, either PKD or PNKD	Autosomal dominant	10q22.3	<i>KCNMA1</i>	Yes	No	Alpha subunit of the Ca-activated potassium channel	Potassium transport
(301) Exercise-induced dystonia (see also no. 236)	Autosomal recessive	10q26.3	<i>ECHS1</i>	Yes	No	Enoyl-CoA hydratase short-chain 1	Mitochondrial enzyme involved in degrading amino acids and fatty acids
(302) Rolandic epilepsy with childhood exercise-induced dyskinesia and writer's cramp (see also EKD1, no. 294)	Autosomal recessive	16p11.2	<i>PRRT2</i>	Yes	No	Proline-rich transmembrane protein 2 (<i>PRRT2</i>)	Interacts with SNAP25
(303) Paroxysmal exertional dyskinesia (PED) (DYT18)	Autosomal dominant	1p34.2	<i>SLC2A1</i>	Yes	No	Glucose transporter 1 (GLUT1)	Transport of glucose into red blood cells and brain
(304) Familial hypnogenic seizures/dystonia (ENFL1)	Autosomal dominant	20q13.33	<i>CHRNA4</i>	Yes	No	Nicotinic acetylcholine receptor alpha4 subunit	Nicotinic ACh receptor
(305) Familial hypnogenic seizures/dystonia (ENFL2)	Autosomal dominant	15q24	N/I	N/I	N/I	N/I	N/I
(306) Familial hypnogenic seizures/dystonia (ENFL3)	Autosomal dominant	1q21.3	<i>CHRNA2</i>	Yes	No	Beta2 nicotinic acetylcholine receptor subunit	Nicotinic ACh receptor
(307) ENFL4 ; Epilepsy, nocturnal frontal lobe, 4	Autosomal dominant	8p21.2	<i>CHRNA2</i>	Yes	No	Nicotinic cholinergic receptor alpha2 subunit	Nicotinic ACh receptor
(308) ENFL5; epilepsy, nocturnal frontal lobe, 5	Autosomal dominant	9q34	<i>KCNT1</i>	Yes	No	Sodium-gated potassium channel subfamily T member 1	Potassium channel
(309) Allan-Herndon-Dudley syndrome with paroxysmal dyskinesia, spasticity and Intellectual disability	X-linked recessive	Xq13.2	<i>MCT8</i>	Yes	No	Monocarboxylate transporter 8	Active transporter of thyroid hormones

(310) Benign paroxysmal tonic upgaze and torticollis (see also EA2, no. 287)	Autosomal dominant	19p13.2	<i>CACNL1A4</i>	Yes	No	CaV2.1 voltage-gated Ca channel	Ca ⁺⁺ transport
(311) Pyruvate dehydrogenase deficiency with episodic dyskinesias	X-dominant	Xp22.12	<i>PDHA1</i>	Yes	No	Pyruvate dehydrogenase	Converts pyruvate into acetyl-CoA
Restless legs syndrome							
(312) Restless legs syndrome RLS1	Autosomal recessive	12q12-q21	Susceptibility locus	N/I	N/I	N/I	N/I
(313) Restless legs syndrome RLS2	Autosomal dominant	14q13-q21	Susceptibility locus	N/I	N/I	N/I	N/I
(314) Restless legs syndrome RLS3	Autosomal dominant	9p24-p22	<i>PTPRD</i> (susceptibility locus)	Yes	No	Protein tyrosine phosphatase receptor type delta	Axonal guidance during development
(315) Restless legs syndrome RLS4	Autosomal dominant	2q33	(Susceptibility locus)	N/I	N/I	N/I	N/I
(316) Restless legs syndrome RLS5	Autosomal dominant	20p13	(Susceptibility locus)	N/I	N/I	N/I	N/I
(317) Restless legs syndrome RLS6	GWAS study	6p21	<i>BTBD9</i> (susceptibility locus)	Yes	No	BTB/POZ domain containing protein 9	Synaptic plasticity
(318) Restless legs syndrome RLS7	GWAS study	2p14-p13	<i>MEIS1</i> (susceptibility locus)	Yes	No	Homeobox protein Meis1	Normal development
(319) Restless legs syndrome RLS8	Autosomal dominant	5q31	<i>PCDHA3</i> (susceptibility locus)	Yes	No	Protocadherin alpha-3	Integral plasma membrane proteins
Stereotypies							
(320) Rett syndrome	X-linked dominant	Xq28	<i>MECP2</i>	Yes	No	Methyl-CpG-Binding protein	Chromatin binding protein
(321) Congenital variant Rett syndrome (also dystonia and chorea)	Autosomal dominant	14q12	<i>FOXP1</i>	Yes	No	Forkhead box G1B	Development of the fetal telencephalon; primarily involved in promoting neural precursor proliferation and cerebral cortical expansion
(322) Head bobbing	Autosomal recessive	6p22.3	<i>ALDH5A1</i>	Yes	No	Succinic semialdehyde dehydrogenase	Catabolism of GABA
Tics							
(323) [†] Tourette syndrome	Autosomal dominant	2p16.3	<i>NRXN-1</i>	Yes	No	Neurexin-1	Cell-surface receptors that bind neuroligins at CNS synapses

Continued

Table 1.5 Gene localization of movement disorders—Continued

Category of disease	Pattern of inheritance	Chromosome region	Name of gene	Gene identified	Triplet repeat	Name of protein	Function of protein
(324) [†] Tourette syndrome	Autosomal dominant	3p26.3	<i>CNTN6</i>	Yes	No	Contactin-6	Adhesion molecule in the immunoglobulin superfamily.
(325) Tourette syndrome	Autosomal dominant	15q21.2	<i>HDC</i>	Yes	No	L-histidine decarboxylase	Rate-limiting enzyme in histamine biosynthesis
(326) Tourette syndrome	Autosomal dominant	11q23	—	No	N/I	N/I	N/I
(327) Tourette syndrome	Susceptibility loci	7q31; 2p11; 8q22	—	No	N/I	N/I	N/I
(328) Tourette syndrome, OCD, chronic tics	Candidate gene	18q22	—	No	N/I	N/I	N/I
(329) Tourette syndrome	Candidate gene	13q31.1	<i>SLITRK1</i>	Yes	No	SLITRK1	Transmembrane protein controlling neurite outgrowth
(330) Tourette syndrome	GWAS study	9q32	<i>COL27A1</i>	Yes	No	Alpha1 subunit of type XXVII collagen	Extracellular matrix
Tremor							
(331) Familial essential tremor (ETM1)	Autosomal dominant	3q13.31	—	N/I	N/I	N/I	N/I
(332) Familial essential tremor (ETM2)	Autosomal dominant	2p25-p22	—	N/I	N/I	N/I	N/I
(333) Familial essential tremor (ETM3)	Autosomal dominant	6p23	—	N/I	N/I	N/I	N/I
(334) Familial essential tremor (ETM4)	Autosomal dominant	16p11.2	<i>FUS</i>	Yes	No	Fusion gene	Translocation of protein to nucleus
(335) Familial essential tremor (ETM5)	Autosomal dominant	11q14.1	<i>TENM4</i>	Yes	No	Teneurin transmembrane protein 4	Regulator of oligodendrocyte differentiation and myelination of small diameter axons
NOTE: ETM4 being mapped to the <i>FUS</i> gene has been challenged by Parmalee et al., 2013.							
(336) Familial essential tremor	Autosomal dominant (risk factor)	15q24.3	<i>LINGO1</i>	Yes	No	Leucine-rich repeat neuronal protein 1	Axon regeneration and oligodendrocyte maturation
(337) Familial essential tremor	Autosomal dominant (risk factor)	17q24.3	<i>SCN4A</i>	—	—	Sodium channel	—
(338) Hereditary geniospasm (chin quivering)	Autosomal dominant	9q13-q21	—	N/I	N/I	N/I	N/I

(339) Roussy–Lévy syndrome	Autosomal dominant	1q23.3	<i>CMT1B</i>	Yes	No	Myelin protein zero	Myelin
(340) Fragile X-associated tremor-ataxia syndrome (FXTAS)	X-linked recessive	Xq27.3	<i>FMR1</i>	Yes	CGG repeats 55-200	FMRP	Synaptic structure development; nucleocytoplasmic shuffling
A variety of movements							
(341) Wilson disease	Autosomal recessive	13q14.3	<i>ATP7B</i>	Yes	No	Cu-ATPase	Copper transport
Neuronal ceroid lipofuscinoses (Batten disease)							
(342) CLN1 Infantile, late-infantile, juvenile, adult forms	Autosomal recessive	1p34.2	<i>PPT1</i>	Yes	No	Palmitoyl protein thioesterase	Lysosomal Proteolysis
(343) CLN2 (see also SCAR7, no. 93)	Autosomal recessive	11p15.4	<i>TPP1</i>	Yes	No	Tripeptidyl-peptidase 1	Lysosomal peptidase
(344) CLN3	Autosomal recessive	16p11.2	—	No	N/I	Battenin	N/I
(345) CLN4A	Autosomal recessive	15q23	<i>CLN4A = Mutations in CLN6</i>	Yes	No	N/I	N/I
(346) CLN4B	Autosomal dominant	20q13.33	<i>DNAJC5</i>	Yes	No	Cysteine string protein	ATP-dependent chaperone
(347) CLN5	Autosomal recessive	13q22.3	<i>CLN5</i>	Yes	No	Unnamed membrane protein	Lysosomal proteolysis
(348) CLN6	Autosomal recessive	15q23	<i>CLN6</i>	Yes	No	N/I	N/I
(349) CLN7	Autosomal recessive	4q28.2	<i>MFSD8</i>	Yes	No	Major facilitator superfamily domain-containing protein-8	Lysosomal
(350) CLN8	Autosomal recessive	8p23.3	<i>CLN8</i>	Yes	No	Transmembrane protein	Lysosomal
(351) CLN9	Autosomal recessive	?	<i>CLN9</i>	No	N/I	N/I	N/I
(352) CLN10	Autosomal recessive	11p15.5	<i>CTSD</i>	Yes	No	Cathepsin D	Proteolysis
(353) CLN11	Autosomal recessive	17q21.31	<i>GRN</i>	Yes	No	Progranulin	Granulin precursor
(354) CLN12 (see also Kufor–Rakeb, no. 9)	Autosomal recessive	1p36.13	<i>ATP13A2</i>	Yes	No	Same gene and protein as Kufor–Rakeb (see no. 9)	—
(355) CLN13	Autosomal recessive	11q13.2	<i>CTSF</i>	Yes	No	Cathepsin F	Proteolysis
(356) CLN14 (see also EPM3, no. 266)	Autosomal recessive	7q11.21	<i>KCTD7</i>	Yes	No	Potassium channel	Potassium transport

*Organized by phenotype (starting with the parkinsonian disorders), this table lists the names of the disease entities, their pattern of hereditary transmission, and their identified gene mutations, chromosomal locations, names of the coded protein and the normal function of the protein. A reference citation for each entity is provided, linked by the identity's number in the table.

†ACh, acetylcholine; ALS, amyotrophic lateral sclerosis; AMP, adenosine monophosphate; AMPA, α -amino-3-hydroxyl-5-methyl-4-isoxazole-propionate; ATP, adenosine triphosphate; BH4, tetrahydrobiopterin; CAG, cytosine-adenosine-guanosine trinucleotide; guanosine-adenosine-adenosine; cAMP, cyclic adenosine monophosphate; CGG, cytosine-guanosine-guanosine; CNS, central nervous system; CoA, coenzyme A; DA, dopamine; DLB, Lewy body disorder; GAA, guanidinoacetate; GABA, gamma-aminobutyric acid; GBD, corticobasal degeneration; GTG, guanosine-thymidine-guanosine; GWAS, genome-wide association study; 5HT, 5-hydroxytryptamine; Hsp70, heat shock protein 70; MEGDEL, 3-methylglutaconic aciduria, deafness, encephalopathy, and Leigh-like disease; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes; N/I, not yet identified; OCD, obsessive-compulsive disorder; SENDA, static encephalopathy with neurodegeneration in adulthood.

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Table 1.5 Gene localization of movement disorders—Continued

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Atasu et al, 2018; (199) Wilhelmsen et al, 1991; Müller et al, 1994; Nolte et al, 2003; Fabbrini et al, 2005; Makino et al, 2007; (200) Parker, 1985; Hersheson et al, 2013; Lohmann et al, 2013; (201) Nygaard et al, 1993; Ichinose et al, 1994; (202) see ref for 28; (203) Anikster et al, 2017; Straniero et al, 2017; (204) Almasy et al, 1997; Saunders-Pullman et al, 2007; Fuchs et al, 2009; (205) Leube et al, 1996; (206) Nygard et al, 1999; Klein et al, 2000; Zimprich et al, 2001; (207) Kramer et al, 1999; Pittcock et al, 2000; de Carvalho Aguiar et al, 2004; (208) Valente et al, 2001a; (209) Grimes et al, 2002; (210) Camargos et al, 2008; Seibler et al, 2008; (211) Chouery et al, 2008; (212) Holmgren et al, 1995; Norgren et al, 2011; (213) Xiao et al, 2012; (214) Charlesworth et al, 2012; (215) Bressman et al, 1994; Fuchs et al, 2013; (216) Mencacci et al, 2015b; (217) Zech et al, 2015; (218) Heimer et al, 2016; (219) Zech et al, 2016; Meyer et al, 2017; (220) Cai et al, 2016; (221) Steinrück et al, 2016; (222) Sheerin et al, 2014; (223) Helbig et al, 2018; (224) Swoboda et al, 2004; Bassi et al, 2004; (225) Heinzen et al, 2012; Yang et al, 2014; (226) Hyland et al, 1992; Chang et al, 2004; (227) Friedman et al, 2006; (228) Placzek et al, 2001; (229) Misbahuddin et al, 2002; (230) Koehler et al, 1999; Jin et al, 1999; Tranebjærg et al, 2000; Rothbauer et al, 2001; Swerdlow and Wooten, 2001; Ujike et al, 2001; (231) Carstea et al, 1993; Lossos A et al, 1997; (232) Wortmann et al, 2012; Maas et al, 2013; (233) Jin et al, 1996; (234) Gearing et al, 2002; Eggink et al, 2017; Skogseid et al, 2018; Maas et al, 2017; (235) Doss et al, 2014; (236) Olgiati et al, 2016b; (237) Muthane et al, 2004; Roze et al, 2005; (238) Haack et al, 2016; Muto et al, 2018; Zúñiga-Ramírez et al, 2019; (239) Taylor et al, 1996; Zhou et al, 2001; Hayflick et al, 2003; (240) see ref for 14; (241) Curtis et al, 2001; Mir et al, 2005; (242) Hartig et al, 2011; Hogarth et al, 2013; (243) Haack et al, 2012; (244) Dusi et al, 2014; (245) Fasano et al, 2008; (246) Edvardson et al, 2018; Dick et al, 2010; Kruer et al, 2010; (247) Solano et al, 2003; (248) Zeng et al, 2005; Debs et al, 2010; Eichler et al, 2017; (251) Sege-Peterson et al, 1993; Jinnah et al, 2006; (252) Schneider and Bhatia, 2008; Alazami et al, 2008; (253) Gilbert et al, 2009; (254) Hyland et al, 1992; Pons et al, 2004; (255) Sedel et al, 2006; (256) Thöny and Blau, 1997; (257) Ostergaard et al, 2007; Carrozzo et al, 2007; (258) Schottmann et al, 2016; (259) Horvath et al, 2018; (260) Shiang et al, 2018; (263) Paucar et al, 2018; (261) Rees et al, 2002; Al-Owain et al, 2012; (262) Rees et al, 2006; (263) Lehesjoki et al, 1993, 1998; (264) Maddox et al, 1997; Minassian et al, 1998; Serratosa et al, 1999; Minassian et al, 2001; (265) Chan et al, 2003a, 2003b; (266) Van Bogaert et al, 2007; (267) Andermann et al, 1986; Badhwar et al, 2004; Dibbens et al, 2009; (268) Tao et al, 2011; (269) Corbett et al, 2011; (270) Karkheiran et al, 2014; (271) Muona et al, 2015; (272) Vanni et al, 2014; (273) Damiano et al, 2015; (274) Turnbull et al, 2012; (275) Dhamija et al, 2017; (276) Steinfeld et al, 2009; Grapp et al, 2012; Tabassum et al, 2019; (277) Mikami et al, 1999; Plaster et al, 1999; (278) Guerini et al, 2001; Madia et al, 2008; De Fusco et al, 2014; (279) Depienne et al, 2010; van Rootselaar et al, 2017; (280) Yeetong et al, 2013; (281) Stogmann et al, 2013; (282) Prusiner, 1993; (283) Stromme et al, 2002; Turner et al, 2002; (284) Weaving et al, 2004; (285) Duis et al, 2016; (286) Browne et al, 1994; Litt et al, 1994; (287) Vahedi et al, 1994; von Brederlow et al, 1995; (288) Steckley et al, 2001; Cader et al, 2005; (289) Damji et al, 1996; (290) Escayg et al, 2000; (291) Jen et al, 2005; de Vries et al, 2009; (292) Kerber et al, 2007; (293) Damak et al, 2009; Conroy et al, 2014; (294) Tomita et al, 1999; Bennett et al, 2000; Lee et al, 2012; (295) Valente et al, 2000; (296) Liu et al, 2016; (297) Fouad et al, 1996; Fink et al, 1996, 1997; Hofele et al, 1997; Jarman et al, 1997a; Raskind et al, 1998; Lee et al, 2004; (298) Spacey et al, 2006; (299) Auburger et al, 1996; (300) Du et al, 2005; Yin et al, 2018; (301) Olgiati et al, 2016; (302) Szeppetowski et al, 1997; Lee et al, 1998; Carelli et al, 1999; Guerrini et al, 1999; Roll et al, 2002; (303) Weber et al, 2008; Suls et al, 2008; Schneider et al, 2009; Pons et al, 2010; (304) Oldani et al, 1998; Nakken et al, 1999; (305) Gambardella et al, 2000; (306) Phillips et al, 1998, 2001; (307) Aridon et al, 2006; (308) Heron et al, 2012; (309) Fuchs et al, 2009; (310) Roubertie et al, 2008; (311) McWilliam et al, 2010; (312) Desautels et al, 2001; Winkelman et al, 2006; (313) Bonati et al, 2003; Levchenko et al, 2004; (314) Liebetanz et al, 2006; Lohmann-Hedrich et al, 2008; Schormair et al, 2008; (315) Pichler et al, 2006; (316) Levchenko et al, 2006; (317) Stefansson et al, 2007; Winkelman et al, 2007; (318) Winkelman et al, 2007; (319) Weissbach et al, 2012; (320) Sirianni et al, 1998; Amir et al, 1999; Auranen et al, 2001; Ben-Zeev et al, 2002; (321) Kortüm et al, 2011; Papandreou et al, 2016; (322) O'Rourke et al, 2010; (323, 324) Huang et al, 2017; (325) Ercan-Sencicek et al, 2010; Karagiannidis et al, 2013; (326) Merette et al, 2000; (327) Petek et al, 2001; Simonic 2001; (328) Cuker et al, 2004; (329) Abelson et al, 2005; (330) Scharf et al, 2013; (331) Gulcher et al, 1997; (332) Higgins et al, 1997; (333) Deng et al, 2007; (334) Merner et al, 2012; (335) Hor et al, 2015; (336) Stefansson et al, 2009; Tan et al, 2009; Clark et al, 2010; (338) Jarman et al, 1997b; (339) Planté-Bordeneuve et al, 1999; (340) Hagerman et al, 2001; Jacquemont et al, 2003, 2004; Hagerman et al, 2004; (341) Bull et al, 1993; Tanzi et al, 1993; (342) Jarvela et al, 1991; Vesa et al, 1995; Das et al, 1998; (343) Sharp et al, 1997; (344) Jarvela et al, 1997; Michalewski et al, 1998; Mole, 1998; Narayan et al, 2006; (345) Berkovic et al, 1988; Arsov et al, 2011; (346) Nasková et al, 2011; (347) Savukoski et al, 1998; (348) Sharp et al, 1997; Gao et al, 2002; (349) Mole, 1998; Kousi et al, 2009; (350) Ranta et al, 1999; (351) Schulz et al, 2004; (352) Steinfeld et al, 2006; (353) Smith KR et al, 2012; (354) De Volder et al, 1990; (355) Smith et al, 2013; (356) Staropoli et al, 2012.

Jinnah (2016) points out that the Task Force nomenclature emphasizes the predominant phenotype of a given genotype, but the phenotypes can vary with the same genotype. A mutant gene with many phenotypes is more difficult and cumbersome to label in this new nomenclature.

Several inherited movement disorders are due to expanded repeats of the trinucleotide cytosine-adenine-guanine (CAG), and other expanded trinucleotide repeats (e.g., Friedreich ataxia is due to repeats of guanine-adenine-adenine (GAA)). Normal individuals contain an acceptable number of these trinucleotide repeats in their genes, but these triplicate repeats are unstable and when expanded lead to disease (Table 1.6). Neurogenetics is one of the fastest moving research areas in neurology, so the list in Table 1.5 keeps expanding rapidly.

Many of the inherited diseases listed in Table 1.5 are rare. An MDS task force reported that more than 30 rare inherited movement disorders are treatable (Jinnah et al., 2018). Some of these are designated as *inborn errors of metabolism*. This term has been applied to inherited diseases with an alteration in some enzymatic metabolic process. Often such genetic defects result in an accumulation of a metabolic substrate that failed to be degraded. In other entities the failure to produce an essential compound leads to a functional deficit. Hundreds of rare inborn errors of metabolism have been described, especially with the development of next-generation sequencing. Most of these disorders begin in childhood, but adult onset is not uncommon. Ebrahimi-Fakhari and colleagues (2019) reviewed the inborn errors of metabolism that can manifest with a movement disorder. This review is particularly valuable because it caters to the clinician by classifying these disorders by the movement phenomenology. Furthermore, the authors

present 10 of the treatable ones so that the clinician will be able to single these out and hopefully not miss them. These 10 conditions in rank order are Wilson disease, hypermanganesemia, dopa-responsive dystonia, Niemann-Pick type C, glutaric aciduria type 1, glut1 deficiency syndrome, cerebrotendinous xanthomatosis, cerebral folate deficiency, biotin- and thiamine-responsive basal ganglia disease, and ataxia with vitamin E deficiency. Each of these disorders can manifest with different phenomenologies, the most common being dystonia and ataxia. Other abnormal movements, such as parkinsonism, tremor, and myoclonus, are often incorporated into the clinical presentation.

Autoimmune disorders as a cause of movement disorders

Symptoms and signs of disease in medicine can have a wide range of etiologies, including genetic, infectious, traumatic, vascular, and psychogenic, among others. In the chapters in this book covering the various phenomenologies and syndromes, possible etiologies of each phenomenology are listed. Autoimmune etiologies have become more recognized in recent years as inducing a wide variety of neurologic disorders, including movement disorders. Some, such as lupus erythematosus and antiphospholipid antibody syndrome, may induce their neurologic symptoms secondarily through vascular involvement. Others directly affect the neurons or glia to induce symptoms. Stiff-person syndrome is one of the early recognized autoimmune movement disorders (see Chapter 21). The first antibody recognized in stiff-person syndrome was against the enzyme glutamic acid decarboxylase. Since then, antibodies against amphiphysin, dipeptidyl-peptidase-like protein-6 (DPPX), gamma-aminobutyric acid type A receptor (GABAAR), glycine receptor (GlyR), and glycine transporter 2 (GlyT2) have been reported (Balint and Bhatia, 2016). Thus, despite different etiologic triggers, the resulting motor phenomenology is the same.

Antibodies derived in response to a variety of tumors can result in the autoimmune disorders known as paraneoplastic syndromes. There have been numerous case reports of a variety of movement disorders being caused by a variety of cancers. Published reviews of these paraneoplastic movement disorders have helped organize our understanding of them (Grant and Graus, 2009; Mehta et al., 2009; Panzer and Dalmau, 2011; Vigliani et al., 2011; Dalmau and Rosenfeld, 2014). Most affected individuals are adults over the age of 50 years. One of the most striking dyskinesias predominantly affecting the oral area (but also limbs) with stereotypic, nonceasing movements is the encephalitis caused by the antibody to the N-methyl-D-aspartate receptor (anti-NMDAR), initially reported by Dalmau and colleagues (2007). All ages have been affected, and although ovarian cancer is the most common source, boys with teratomas also have been reported. Video 1.1 is an example of the characteristic anti-NMDAR-induced encephalitis with stereotypies, particularly affecting the oral region. ▶

As a group, paraneoplastic movement disorders have a subacute onset with rapid evolution. There is often a mixture of more than one phenotype. One type of cancer can cause different neurologic phenotypes, and one phenotype can be caused by different types of cancers. Many paraneoplastic movement disorders can be treated by removing the tumor and instigating pharmacotherapy against the autoimmunity. Therefore, early diagnosis by recognizing the different phenotypes is important. A fairly common paraneoplastic movement disorder is opsoclonus-myoclonus.

Table 1.6 Size of trinucleotide repeats in movement disorders

Disease	Type of nucleotide	In normal persons	In disease
Huntington	CAG	6–35	>36
		Incompletely penetrant	36–40
		Fully penetrant	>40
HDL2	CAG/CTG	6–28	>41
SCA-1	CAG	6–35	>48
SCA-2	CAG	14–32	>31
SCA-3 (Machado–Joseph)	CAG	12–40	>54
SCA-6	CAG	4–18	>19
SCA-7	CAG	7–17	>36
SCA-12	CAG	7–28	>109
SCA-17	CAG	25–42	>46
DRPLA	CAG	6–35	>45
Friedreich ataxia	GAA	7–34	>100
FXTAS	CGG	6–53	>54

DRPLA, dentatorubral-pallidoluysian atrophy; FXTAS, fragile X-associated tremor/ataxia syndrome; HDL2, Huntington disease like 2; SCA, spinocerebellar degeneration. Data in part from Den Dunnen, 2017; and OMIM (<http://www.ncbi.nlm.nih.gov/omim>).

Many other autoimmune causes of movement disorders besides neoplasms have been identified. These are the ones that can cause the chorea in Sydenham disease, the ataxia of celiac disease, and the parkinsonism/dystonia in Sjögren syndrome. Baizabal-Carvallo and Jankovic (2012) reviewed these and paraneoplastic causes of movement disorders. Celiac disease as a cause of ataxia is discussed in Chapter 20. Cortical myoclonus associated with celiac disease is less common (Tison et al., 1989; Bhatia et al., 1995; Tijssen et al, 2000). Despite the cerebral cortex being electrophysiologically associated with the myoclonus, autopsies have reported pathologic findings only in the cerebellum in these cases. One feature emphasized by Bhatia and colleagues (1995) is a characteristic myoclonus affecting just the legs in celiac disease. An example of such a case in which there are correlates of electrical discharges in the electroencephalogram (EEG) involving the leg area of the cerebral cortex is presented in Video 1.2 in the discussion of myoclonus. Faciobrachial dystonic seizures are due to an autoimmune encephalitis caused by the Lgi1 antibody against the voltage-gated potassium channel (Irani et al., 2011) (Video 1.3) and is discussed within the dystonia section in this chapter. Technically, faciobrachial dystonic seizures are categorized as a seizure disorder and not a true movement disorder, but they mimic dystonic movements in some fashion and hence the name of the phenomenology is appropriate. A thorough review covering immune disorders resulting in abnormal movement was published by Balint and Bhatia (2016)]. Some patients with multiple system atrophy (MSA) have been found to have neuropathology changes consistent with Sjögren disease, an autoimmune disorder (Conway et al., 2020). ●

Quantitative assessments

The assessment of severity of disease is a process that is carried out by all clinicians when evaluating a patient. Quantifying the severity provides the means to monitor the progression of the disorder and the effect of intervention by pharmacologic or surgical approaches. Many mechanical and electronic devices, including accelerometers, can quantitate specific signs, such as tremor, rigidity, and bradykinesia. These have been developed by physicians and engineers over at least 90 years (Lewy, 1923; Carmichael and Green, 1928), and newer computerized devices continue to be conceived and developed (Larsen et al., 1983; Tryon, 1984; Potvin and Tourtelotte, 1985; Pullman, 1998; Cohen et al., 2003; Beckmann et al., 2018). New wrist-wearing devices are being tested, and applications have been developed for smartphones to help electronically quantify abnormal movements and severity of PD (Trister et al., 2016; Prince et al., 2018), and in time these may become useful tools.

The advantages of mechanical and electronic measurements are objectivity, consistency, uniformity among different investigators, and rapidity of database storage and analysis. However, these measurements might not be as sensitive than more subjective clinical measurements. In one study comparing objective measurements of reaction and movement times with clinical evaluations, Ward and colleagues (1983) found the latter to be more sensitive. Small wearable devices and smartphone applications are being developed to quantify movement patterns (Battista et al., 2021; Channa et al., 2021; Daneault et al., 2021; Su et al., 2021; Vergara-Diaz et al., 2021), and these may become useful tools someday.

The mechanical and electronic methods of measurement have other disadvantages. Instrumentation can usually

measure only a single part of the body, measure only a single sign, and measure at a single point in time. Data-stored computerized devices, however, have an advantage of obtaining measurements over a long period. Disorders such as parkinsonism encompass a wide range of motor abnormalities and behavioral features. Clinical measurements can cover a wider range of the parkinsonian spectrum of impairments and have the advantage of being performed at the bedside or in the office or clinic at the time the patient is being examined by the physician. Equally important, clinical assessment can evaluate disability in terms of activities of daily living (ADLs), and the one developed by England and Schwab (1956) and modified slightly (Fahn and Elton, 1987) has proven highly useful.

A number of clinical rating scales have been proposed (e.g., see Marsden and Schachter, 1981). Several that are now considered standards and are in wide use can be recommended: the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn and Elton, 1987) is the standard scale for rating severity of signs and symptoms of PD; a videotaped demonstration of the assigned ratings has been published (Goetz et al., 1995). A modification of the UPDRS by the MDS has been completed (Goetz et al., 2008a) and is known as the MDS-UPDRS. It has several advantages, namely assessing milder signs, better written definitions, and expanding the assessment of tremor and nonmotor symptoms in PD. A videotaped demonstration of the assigned ratings for the component of MDS-UPDRS also has been published (Goetz et al., 2010). A mathematical correlation of scores between the UPDRS and MDS-UPDRS has been calibrated (Goetz et al., 2012). The nonmotor component of the MDS-UPDRS has been found to correlate well with a specific Non-Motor Symptoms Scale for Parkinson Disease (Martinez-Martin et al., 2015). Other standard scales for PD and its complications are the Schwab and England Activities of Daily Living Scale for parkinsonism (Schwab and England, 1969) as modified (Fahn and Elton, 1987); the Hoehn and Yahr Parkinson Disease Staging Scale (Hoehn and Yahr, 1967) as modified (Fahn and Elton, 1987); the Unified Dyskinesia Rating Scale (Goetz et al., 2008b), which, compared with other dyskinesia rating scales, was found to be superior in detecting change in a controlled clinical trial testing a drug for dopa-induced dyskinesias (Goetz et al., 2013); the Parkinson Psychosis Rating Scale (Friedberg et al., 1998); the daily diary to record fluctuations and dyskinesias (Hauser et al., 2004); the Core Assessment Program for Intracerebral Transplantation (Langston et al., 1992); the Progressive Supranuclear Palsy Rating Scale (Golbe and Ohman-Strickland, 2007), the Fahn-Marsden Dystonia Rating Scale (Burke et al., 1985); the Unified Dystonia Rating Scale (Comella et al., 2003); the Toronto Western Spasmodic Torticollis Rating Scale (TWSTERS) for cervical dystonia (Comella et al., 1997); the Fahn-Tolosa-Marin clinical rating scale for tremor (Fahn et al., 1993); the Bain tremor scale (Bain et al., 1993); the Essential Tremor Rating Assessment Scale (TETRAS) (Elble et al., 2012); and the Unified Huntington's Disease Rating Scale, which also has a published videotaped demonstration of assigned ratings (Huntington Study Group, 1995).

Differential diagnosis of hypokinesias

For a list of hypokinesias, refer to Table 1.1.

Akinesia/bradykinesia

Akinesia, bradykinesia, and hypokinesia literally mean “absence,” “slowness,” and “decreased amplitude” of movement, respectively. The three terms are commonly grouped together for convenience and usually referred to under the term *bradykinesia*. These phenomena are a prominent and most important feature of parkinsonism and are often considered a *sine qua non* for parkinsonism. In fact, the presence of bradykinesia is a necessary sign for the diagnosis of PD according to the UK Parkinson Disease Society’s Brain Bank criteria (Hughes et al., 1992). Although akinesia means “lack of movement,” the label is often used to indicate a very severe form of bradykinesia (Video 1.4). Bradykinesia is mild in early PD and becomes more severe as the disease worsens; a similar pattern is seen in other forms of parkinsonism. A discussion of the phenomenology of akinesia/bradykinesia requires a brief description of the clinical features of parkinsonism, presented here. A fuller discussion is presented in Chapter 4. ▶

Parkinsonism is a neurologic syndrome manifested by any combination of six independent, nonoverlapping cardinal motor features: tremor-at-rest, bradykinesia, rigidity, flexed posture, freezing, and loss of postural reflexes (Table 1.7). At least two of these six cardinal features should be present before the diagnosis of parkinsonism is made, one of them being bradykinesia, as mentioned previously. There are many causes of parkinsonism; they can be divided into five major categories: primary, secondary, parkinsonism-plus disorders, hereditary degenerative disorders, and benign parkinsonism (Table 1.8). Primary parkinsonism (PD) is a progressive disorder of unknown etiology or of a known gene mutation, and the diagnosis is usually made by excluding other known causes of parkinsonism (Fahn, 1992). The complete classification of parkinsonian disorders is presented in Chapter 4. The specific diagnosis of the type of parkinsonism depends on details of the clinical history, the neurologic examination, and laboratory tests.

The primary parkinsonism disorder known as Parkinson disease (PD), often referred to as idiopathic parkinsonism,

Table 1.7 Cardinal features of parkinsonism

Tremor-at-rest
Bradykinesia/hypokinesia/akinesia
Rigidity
Flexed posture of neck, trunk and limbs
Loss of postural reflexes
Freezing

Table 1.8 Categories of parkinsonism

- | |
|--|
| A. Primary (Parkinson disease) |
| B. Secondary parkinsonism (environmental and acquired etiology) |
| C. Parkinsonism-plus syndromes (progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration, Parkinsonism-dementia disorders) |
| D. Hereditary degenerative disorders (e.g., Wilson disease, neurodegenerations with brain iron accumulation) |
| E. Benign parkinsonism (dopa-responsive dystonia) |

is the most common type of parkinsonism encountered by the neurologist. But drug-induced parkinsonism (a secondary parkinsonism) is probably the most common form of parkinsonism (Video 1.5) because neuroleptic drugs (dopamine receptor–blocking agents), which cause drug-induced parkinsonism, are widely prescribed for treating psychosis (see Chapter 17). Here, some of the motor phenomenology of parkinsonism is discussed as part of the overview of the differential diagnosis of movement disorders based on phenomenology. ▶

PD begins insidiously. Tremor is usually the first symptom recognized by the patient. However, the disorder can begin with slowness of movement, shuffling gait, painful stiffness of a shoulder, micrographia, or even depression or rapid eye movement (REM) sleep behavior disorder. In the early stages, the motoric symptoms and signs tend to remain on one side of the body (Video 1.6), but with time the other side slowly becomes involved as well. ▶

Tremor is present in the distal parts of the extremities and the lips while the involved body part is “at rest.” “Pill-rolling” tremor of the fingers and flexion–extension or pronation–supination tremor of the hands are the most typical (see Video 1.6). The tremor ceases on active movement of the limb but can reemerge when the limb remains in a posture against gravity. Resting tremor must be differentiated from postural and kinetic tremors, in which tremor appears only when the arm is being used. These tremors are typically caused by other disorders, namely essential tremor and cerebellar disorders. An occasional patient with PD will have an action tremor of the hand instead of or in addition to tremor-at-rest (Video 1.7). In the cranial structures, the lips, chin, and tongue are the predominant sites for tremor (Video 1.8, whereas head (neck) tremor, although it can occur in PD, is more typical of essential tremor, cerebellar tremor, and dystonic tremor. ▶

Akinesia/bradykinesia/hypokinesia manifests cranially by masked facies (hypomimia), decreased frequency of blinking, impaired upgaze, impaired ocular convergence, soft speech (hypophonia), loss of inflection (aprosody), and drooling of saliva because of decreased spontaneous swallowing (Video 1.9). When examining cranial structures, one should look for other signs of PD or Parkinson-plus syndromes. Repetitive tapping the glabella often reveals non-suppression of blinking (Myerson sign) in patients with PD (Brodsky et al., 2004) (Video 1.10), whereas blinking is normally suppressed after two or three blinks (Brodsky et al., 2004). Eyelid opening after the eyelids were forcefully closed is usually normal in PD but may be markedly impaired in progressive supranuclear palsy (PSP); this has been called “apraxia of eyelid opening” (Video 1.11) even though the term apraxia is a misnomer. The eyes looking straight ahead are typically quiet in PD, but in some Parkinson-plus syndromes, square wave jerks may be seen, especially in PSP (Video 1.12). Ocular movements are usually normal in PD, except for impaired upgaze and convergence. When saccadic eye movements are impaired, and especially when downgaze is impaired, a Parkinson-plus syndrome such as PSP or corticobasal degeneration (CBD) is usually indicated (Xie et al. 2015) (Video 1.13). ▶

In the arms, bradykinesia is manifested by slowness in shrugging or relaxing the shoulder (Video 1.14); slowness in raising the arm; loss of spontaneous movement such as gesturing;

Video 1.1 Anti-NMDA Receptor encephalitis.

Video 1.2 Leg myoclonus.

Video 1.3 Faciobrachial dystonic seizures.

Video 1.4 Akinesia/bradykinesia/hypokinesia.

Video 1.5 Drug-induced parkinsonism.

Video 1.6 Unilateral PD.

Video 1.7 Postural and action tremor in a patient with PD.

Video 1.8 Jaw tremor as well as hand tremor in a patient with PD.

Video 1.9 Masked face and drooling of saliva.

smallness and slowness of handwriting (micrographia); slowness and decrementing amplitude of repetitively opening and closing the hands, tapping a finger, and twisting the hand back and forth; difficulty with hand dexterity for shaving, brushing teeth, and putting on makeup; and decreased arm swing when walking. In the legs, bradykinesia is manifested by slowness and decrementing amplitude in repetitively stomping the foot or tapping the toes; by slowness in making the number 8 with the foot; and by a slow, short-stride, shuffling gait with reduced heel strike when stepping forward. Typically in PD, there is a narrow base, that is, the feet are close together when the patient walks. In the trunk, bradykinesia is manifested by difficulty arising from a chair, getting out of automobiles, and turning in bed. ►

Bradykinesia encompasses a loss of automatic movements and slowness in initiating movement on command and reduction in amplitude of the voluntary movement. An early feature of reduction of amplitude is the decrementing of the amplitude with repetitive finger tapping or foot tapping (see Video 1.14), which also manifests by impaired rhythm of the tapping. Decreased rapid successive movements both in amplitude and speed are characteristic of bradykinesia regardless of the etiology of parkinsonism (Video 1.15). Carrying out two activities simultaneously is impaired (Schwab et al., 1954), and this difficulty may be a manifestation of bradykinesia (Fahn, 1990). With the stimulation of a sufficient sensory input, bradykinesia, hypokinesia, and akinesia can be temporarily overcome (kinesia paradoxa) (Video 1.16). ►

Rigidity (described later) is another cardinal feature of parkinsonism. Rigidity usually manifests in the distal limbs by a ratchety “give” when a joint is passively moved throughout its range of motion, so-called cogwheel rigidity. Rigidity of proximal joints is easily appreciated by the examiner swinging the shoulders (Wartenberg sign) (Video 1.17), flexing and extending the elbows, or rotating the hips. The patient often complains of stiffness of the neck, which is due to rigidity; the neck is a common location for rigidity. In patients with atremulous PD and in whom the disease remains manifest unilaterally for several years, a pseudohemiplegic gait pattern can be seen because of the combination of rigidity and akinesia. The patient has dragging of the affected leg and does not swing the affected arm, which is flexed at the elbow (Video 1.18).

As the disease advances, the patient begins to assume a *flexed posture*, particularly of the neck, thorax, elbows, hips, and knees. The patient begins to walk with decreased arm swing and then with the arms flexed at the elbows and the forearms placed in front of the body. With the knees slightly flexed, the patient tends to shuffle the feet, which stay close to the ground and are not lifted up as high as they would be in normal persons; with time there is loss of heel strike, which would normally occur when the foot moving forward is placed on the ground. Eventually, the flexion can become extreme (Video 1.19), leading to camptocormia (Azher and Jankovic, 2005) or pronounced kyphoscoliosis with truncal tilting. ►

Loss of postural reflexes occurs later in the disease. The patient has difficulty righting himself or herself after being pulled or tilted off balance (Martin, 1967). A simple test (the “pull test”) for the righting reflex is for the examiner to stand behind the patient and give a firm tug on the patient’s shoulders toward the examiner, explaining the procedure in advance and directing that the patient should try

to maintain balance by taking a step backward (Munhoz et al., 2004; Hunt and Sethi, 2006). Typically, after a practice pull, a normal person can recover within two steps (Video 1.20). A mild loss of postural reflexes can be detected if the patient requires several steps to recover balance. A moderate loss is manifested by a greater degree of retropulsion. With a more severe loss the patient would fall if not caught by the examiner (Video 1.21), who must always be prepared for such a possibility. With a marked loss of postural reflexes, a patient cannot withstand even a gentle tug on the shoulders or cannot stand unassisted without falling. To avoid having the patient fall to the ground, the examiner must always be prepared to catch the patient (Video 1.22). It is wise to have a wall behind the examiner when the pull test is being performed. This is essential if the patient is a large or bulky individual (Video 1.23); with this insurance against falling, one can perform a pull test on any individual. ►

A combination of loss of postural reflexes and stooped posture can lead to *festination*, in which the patient walks faster and faster, eventually running, trying to catch up with his or her center of gravity to prevent falling (Video 1.24). ►

Akinesia needs to be distinguished from the freezing phenomenon, both of which are features of parkinsonism. The *freezing phenomenon* (Nutt et al., 2011) affects gait more than other parts of the body and begins either with start-hesitation—that is, the feet take short, sticking, shuffling steps when the patient initiates walking—or when turning while walking (Videos 1.25 and 1.26). With progression, the feet become “glued to the ground” when the patient walks through a crowded space (e.g., a row of seats in a theater or a revolving door) or is trying to move in the presence of a time restriction (e.g., crossing the street at the green light or entering an elevator before the door closes). Often, patients develop destination-freezing—that is, stopping before reaching the final destination. For example, the patient might stop too soon when reaching a chair in which he or she intends to sit down (Video 1.27). With further progression, sudden transient freezing can occur when the patient is walking in an open space or when the patient perceives an obstacle in the walking path. The freezing phenomenon can also affect arms and speech and is discussed in more detail under “Freezing” later in this chapter.

Sometimes severe orthostatic hypotension can mimic freezing of gait because the patient feels faint, the legs become wobbly and shaky, and the patient is unable to move because of the feeling of not being able to maintain an erect posture (Video 1.28). *Fear of falling* is a type of gait disorder that needs to be differentiated from slowness of walking because of PD. Most people have fear of falling because they have fallen in the past and have subsequently become exceedingly cautious (Video 1.29). Fear of falling can develop in people who have not fallen (Video 1.30). Extreme cases of fear of falling can be due to agoraphobia, which is fear of being in an open space, a psychiatric anxiety disorder (Video 1.31).

In addition to these motor signs, most patients with PD have behavioral signs. *Bradyphrenia* is mental slowness, analogous to the motor slowness of bradykinesia. Bradyphrenia is manifested by slowness in thinking or in responding to questions. It occurs even when PD begins at a young age and is more common than dementia. The “tip-of-the-tongue” phenomenon (Matison et al., 1982), in which a patient cannot immediately come up with the correct answer but knows what it is, may be a feature of

Video 1.10-6 Myerson sign.

Video 1.11 Apraxia of eyelid opening.

Video 1.12 Square wave jerks.

Video 1.13 Impaired ocular movements.

Video 1.14 Decreased shouldershrug, decrementing rapid successive movements, and decreased armswing due to bradykinesia.

Video 1.15 1 Decreased rapid successive movements in juvenile Huntington disease.

Video 1.16 Overcoming akinesia.

Video 1.17 Shoulder rigidity manifested by decreased armswing with passive movement of the shoulders.

bradyphrenia. With time, the parkinsonian patient gradually becomes more passive, indecisive, dependent, and fearful. The spouse gradually makes more of the decisions and becomes the dominant voice. Eventually, the patient would sit much of the day unless encouraged to do activities. Passivity and lack of motivation also are expressed by the patient not desiring to attend social events. The term *abulia* is used to describe such severe apathy, loss of mental and motor drive, and blunting of emotional, social, and motor expression. Abulia encompasses loss of spontaneous and responsive motor activity and loss of spontaneous affective expression, thought, and initiative.

Depression is a frequent feature in patients with PD, being obvious in around 30% of cases. The prevalence of *dementia* in PD is about 40%, but the proportion increases with age. Below the age of 60 years, the proportion with dementia is about 8%; older than 80 years, it is 69% (Mayeux et al., 1992). Following PD patients over time, about 80% develop dementia (Aarsland et al., 2003; Buter et al., 2008). The risk for death is markedly increased when a PD patient becomes demented (Marder et al., 1991).

The age at onset of PD is usually above the age of 40, but younger patients can be affected. Onset between ages 20 and 40 is called young-onset Parkinson disease (YOPD); but the trend today is to label onset below age 50 as YOPD. People with YOPD usually develop pronounced levodopa-induced dyskinesias and motor fluctuations (Videos 1.32A,B). Onset before age 20 is called juvenile parkinsonism. Juvenile parkinsonism does not preclude a diagnosis of PD (Video 1.33), but it raises questions of other etiologies, even with dopa-responsive parkinsonism, such as neurodegenerations with brain iron accumulation (Video 1.34), and other degenerations. Non-dopa-responsive cases of juvenile parkinsonism include (see Video 1.9), the Westphal variant of Huntington disease (HD) (see Video 1.15), and neuroleptic-induced parkinsonism (Video 1.36). In addition, familial and sporadic primary juvenile PD often do not show the typical pathologic hallmark of Lewy bodies (Dwork et al., 1993). A number of autosomal recessive genes such as *PRKN*, *PINK1*, and *DJ1* (see Chapter 5) can cause juvenile PD without the presence of Lewy bodies. One needs to be aware when reading the literature that in Japan onset before age 40 is called juvenile parkinsonism. Juvenile parkinsonism with spasticity can occur in the hereditary spastic paraplegias known as SPG11 (Anheim et al., 2009; Paisán-Ruiz et al., 2010; Guidubaldi et al., 2011) and SPG15 (Schicks et al., 2011; Mallaret et al., 2014a). ▶

PD is more common in men, with a male-to-female ratio of 3:2. The incidence in the United States is 20 new cases per 100,000 population per year (Schoenberg, 1987), with a prevalence of 187 cases per 100,000 population (Kurland, 1958). For the population over 40 years of age, the prevalence rate is 347 per 100,000 (Schoenberg et al., 1985). With the introduction of levodopa the mortality rate dropped from 3-fold to 1.5-fold above normal. But after the first wave of impaired patients becoming improved with this new and effective treatment, the mortality rate for PD gradually climbed back to the pre-levodopa rate (Clarke, 1995).

Apraxia

Apraxia is a cerebral cortex, not a basal ganglia, dysfunction. Apraxia is traditionally defined as a disorder of voluntary

movement that cannot be explained by weakness, spasticity, rigidity, akinesia, sensory loss, or cognitive impairment. It can exist and be tested for in the presence of a movement disorder provided that akinesia, rigidity, or dystonia is not so severe that voluntary movement cannot be executed. The classic work of Liepmann (1920) defined three categories of apraxia.

1. In *ideational apraxia* the concept or plan of movement cannot be formulated by the patient. Some examiners test for ideational apraxia by asking the patient to perform a series of sequential movements such as pretending to fill a pipe, lighting it, and then smoking, or putting a letter into an envelope, sealing it, and then affixing a stamp. Ideational apraxia is due to parietal lesions, most often diffuse and degenerative.
2. In *ideomotor apraxia* the concept or plan of movement is intact, but the individual motor engrams or programs are defective. Ideomotor apraxia is commonly tested for by asking patients to undertake specific motor acts to verbal or written commands, such as waving goodbye, saluting like a soldier, combing their hair, or using a hammer to fix a nail, etc. The patients with ideomotor apraxia often improve their performance if asked to mimic the action when the examiner shows them what to do or when given the object or tool to use. Ideomotor apraxia usually does not interfere with normal spontaneous motor actions but requires specific testing for its demonstration. It usually, but not always, is associated with aphasia and is due mainly to lesions in the dominant hemisphere, particularly in the parietotemporal regions, the arcuate fasciculus, or the frontal lobe; such ideomotor apraxia is bilateral, provided there is not a hemiplegia. Lesions of the corpus callosum can cause apraxia of the nondominant hand.
3. *Limb-kinetic apraxia* is the least understood type. It refers to a higher order motor deficit in executing motor acts that cannot be explained by simple motor impairments. It has been attributed to lesions of premotor regions in the frontal lobe, such as the supplementary motor area.

The concepts of apraxia are being refined into more discrete identifiable syndromes as knowledge of the functions of the cortical systems controlling voluntary movement advances (for reviews, see Pramstaller and Marsden, 1996; Zadikoff and Lang, 2005). A quick, convenient method for testing for apraxia at the bedside is to ask the patients to copy a series of hand postures shown to them by the examiner.

Ideomotor and limb-kinetic apraxias are found in a number of movement disorders, for example, CBD (Videos 1.37, 1.38) and PSP (see Chapter 9). A number of other phenomena reflecting cerebral cortex dysfunction may be seen in such patients. Patients with CBD frequently have signs of cortical myoclonus (Video 1.39) or cortical sensory deficit. The alien limb phenomenon, also seen in CBD, consists of involuntary, spontaneous movements of an arm or leg (Video 1.40), which curiously and spontaneously moves to adopt odd postures quite beyond the control or understanding of the patient. Intermanual conflict is another such phenomenon; one hand irresistibly and uncontrollably begins to interfere with voluntary action of the other. The abnormally behaving limb may also show forced grasping of objects, such as blankets or clothing. Such patients often exhibit other frontal lobe signs, such as a grasp reflex or utilization behavior, in

Video 1.18 Pseudohemiplegic gait in young-onset PD.

which they compulsively pick up objects presented to them and begin to use them. For example, if a pen is presented with no instructions, they pick it up and write. If a pair of glasses is proffered, they place the glasses on the nose; if further pairs of glasses are then shown, the patient may end up with three or more spectacles on the nose! 🕒

Patients presenting with features of CBD may actually have other pathologic conditions, such as PSP and Alzheimer disease, instead of CBD. For this reason, until an autopsy can confirm the pathologic findings of CBD, the clinical presentation is now called corticobasal syndrome (CBS).

Blocking (holding) tics

Blocking (or holding) is a motor phenomenon that is seen occasionally in patients with tics and is characterized as a brief interference of social discourse and contact. There is no loss of consciousness, and, although the patient does not speak during these episodes, he or she is fully aware of what has been spoken. These *blocking tics* appear in two situations: (1) as an accompanying feature of some prolonged tics, such as during a protracted dystonic tic (Video 1.41) or during tic status and (2) as a specific tic phenomenon in the absence of an accompanying obvious motor or vocal tic. The latter occurrences have the abruptness and duration of a dystonic tic or a series of clonic tics, but they do not occur during an episode of an obvious motor tic. 🕒

Although both types can be called blocking tics, the first type can be considered “intrusions” because the interruption of activity is due to a positive motor phenomenon (i.e., severe, somewhat prolonged motor tics) that interferes with other motor activities. An example would be a burst of tics that is severe enough to interrupt ongoing motor acts, including speech, as seen in Video 1.41. 🕒

The second type (i.e., inhibition of ongoing motor activity without an obvious “active” tic) can be considered a negative motor phenomenon, that is, a “negative” tic. The negative type of *blocking tics* should be differentiated from absence seizures or other paroxysmal episodes of loss of awareness. There is never loss of awareness with blocking tics. Individuals with intrusions and negative blocking recognize that they have these interruptions of normal activity and are fully aware of the environment during them, even if they are unable to speak at that time.

Cataplexy and drop attacks

Drop attacks can be defined as sudden falls with or without loss of consciousness, as a result of either collapse of postural muscle tone or abnormal muscle contractions in the legs (Video 1.42). About two-thirds of cases are of unknown etiology (Meissner et al., 1986). Symptomatic drop attacks have many neurologic and nonneurologic causes. Neurologic disorders include leg weakness; sudden falls in parkinsonian syndromes, including those caused by freezing and orthostatic hypotension (Video 1.28); transient ischemic attacks; epilepsy; myoclonus; startle reactions (hyperekplexia); paroxysmal dyskinesias; structural central nervous system lesions; and hydrocephalus. In some of these, there is loss of muscle tone in the legs, in others there is excessive muscle stiffness with immobility, such as in hyperekplexia. Syncope and cardiovascular disease account for nonneurologic causes.

Idiopathic drop attacks usually appear between the ages of 40 and 59 years, the prevalence increasing with advancing age (Stevens and Matthews, 1973), and are a common cause of falls and fractures in the elderly (Sheldon, 1960; Nickens, 1985). A review of drop attacks has been provided by Lee and Marsden (1995). 🕒

Cataplexy is another cause of symptomatic drop attacks that does not fit the categories listed previously. Patients with cataplexy fall suddenly without loss of consciousness but with inability to speak during an attack. There is a precipitating trigger, usually laughter or a sudden emotional stimulus. The patient’s muscle tone is flaccid and remains this way for many seconds. Cataplexy is usually just one feature of the narcolepsy syndrome; other features include sleep paralysis and hypnagogic hallucinations, in addition to the characteristic feature of sudden, uncontrollable falling asleep. A review of cataplexy has been provided by Guilleminault and Gelb (1995).

Catatonia, psychomotor depression, and obsessional slowness

In 1874, Karl Ludwig Kahlbaum wrote the following description: “the patient remains entirely motionless, without speaking, and with a rigid, mask-like facies, the eyes focused at a distance; he seems devoid of any will to move or react to any stimuli; there may be fully developed ‘waxen’ flexibility, as in cataleptic states, or only indications, distinct, nevertheless, of this striking phenomenon. The general impression conveyed by such patients is one of profound mental anguish . . .” (from Bush et al., 1996).

Gelenberg (1976) defined *catatonia* as a syndrome characterized by catalepsy (abnormal maintenance of posture or physical attitudes), waxy flexibility (retention of the limbs for an indefinite period in the positions in which they are placed), negativism, mutism, and bizarre mannerisms. Patients with catatonia can remain in one position for hours and move exceedingly slowly to commands, usually requiring the examiner to push them along (Videos 1.43 and 1.44A,B). However, when moving spontaneously, they move quickly, such as when scratching themselves. In contrast to patients with parkinsonism, there is no concomitant cogwheel rigidity, freezing, or loss of postural reflexes. Classically, catatonia is a feature of schizophrenia, but it can also occur with severe depression. Gelenberg also stated that catatonia can appear with conversion hysteria, dissociative states, and organic brain disease. However, we think that the organic syndromes of akinetic mutism, abulia, encephalitis, and so forth should be distinguished from catatonia and catatonia should preferably be considered a psychiatric disorder. 🕒

Depression is commonly associated with a general slowness of movement and of thought, so-called psychomotor retardation; catatonia can be considered an extreme case of this problem. Although depressed patients are widely recognized to manifest slowness in movement, some—particularly children—might not have the more classic symptoms of low mood, dysphoria, anorexia, insomnia, somatizations, and tearfulness. In this situation, slowness as a result of depression can be difficult to distinguish from the bradykinesia of parkinsonism. As in catatonia, lack of rigidity and preservation of postural reflexes may help differentiate psychomotor slowness from parkinsonism. However, there can

Video 1.19 Flexed posture.

Video 1.20 Normal pull test.

Video 1.21 Examples of abnormal (positive) pull tests.

Video 1.22 Always be prepared to catch a patient when performing the Pull Test:

Video 1.23 Performing the Pull Test on very large patients:

Video 1.24 Festinating gait.

be loss of facial expression and decreased blinking in both catatonia and depression. Lack of Myerson sign, snout reflex, and palmomental reflexes are the rule, all of which are usually present in parkinsonism. In children with psychomotor depression and motor slowness (Video 1.45), the differential diagnosis is that of juvenile parkinsonism, including Wilson disease and the akinetic form of HD. ►

Some patients with obsessive-compulsive disorder (OCD) may present with extreme slowness of movement, so-called *obsessional slowness* (Video 1.46). Hymas and colleagues (1991) evaluated 17 such patients out of 59 admitted to hospital with OCD. These patients had difficulty initiating goal-directed action and had many suppressive interruptions and perseverative behavior. Besides slowness, some patients had cogwheel rigidity, decreased arm swing when walking, decreased spontaneous movement, hypomimia, and flexed posture. However, there was no decrementing of either amplitude or speed with repetitive movements, no tremor, and no micrographia. In addition, there was no freezing or loss of postural reflexes. Like other cases of OCD, this is a chronic illness. Fluorodopa positron emission tomography scans revealed no abnormality of dopa uptake, thereby clearly distinguishing this disorder from PD (Sawle et al., 1991). However, there is hypermetabolism in orbital, frontal, premotor, and midfrontal cortex, suggesting excessive neural activity in these regions.

Freezing

Freezing refers to transient periods, usually lasting several seconds, in which the motor act is halted, being stuck in place. It commonly develops in parkinsonism (see Chapter 4), both primary and atypical parkinsonism (Giladi et al., 1997), and it is one of its six cardinal signs. The freezing phenomenon also has been called motor blocks (Giladi et al., 1992). The terms *pure akinesia* (Narabayashi et al., 1976 and 1986; Imai et al., 1986) and *gait ignition failure* (Atchison et al., 1993; Nutt et al., 1993) refer to syndromes in which freezing is the predominant clinical feature with only a few other features of parkinsonism.

In freezing there can be several different phenomena. One is that there is no apparent attempt to move. Another is that the voluntary motor activity being attempted is halted because agonists and antagonist muscles are simultaneously and isometrically contracting (Andrews, 1973), preventing normal execution of voluntary movement. The motor blockage in this circumstance, therefore, is not one of lack of muscle activity, but rather is analogous to being glued to a position so that the patient exerts increased effort to overcome being “stuck.” The stuck body part attempts to move to overcome the block, and muscle force (isometric) is being exerted. In some instances of freezing of gait, there is trembling of the legs as the patient attempts to move (Nutt et al., 2011). So, with freezing of gait, by far the most common form of the freezing phenomenon, as the patient attempts to move the feet, short and incomplete steps are attempted, but the feet tend to remain in the same place (“glued to the ground”). After a few seconds, the freezing clears spontaneously, and the patient is able to move at his or her normal pace again until the next freezing episode develops. Often, the patient has learned some trick maneuver to terminate the freezing episode sooner (Videos 1.47, 1.48). Stepping

Table 1.9 Types of freezing phenomena

Start-hesitation (freezing when gait is initiated)
Turning-hesitation (freezing when turning)
Destination-hesitation (freezing when approaching the target)
Freezing when a physical or a temporal “obstacle” is encountered
Freezing when movement is time-dependent (e.g., entering or leaving elevator before door closes)
Spontaneous sudden transient freezing
Palilalia or freezing of speech
“Apraxia” of eyelid opening or levator inhibition
Freezing of limbs

over someone’s foot or an inverted cane when the legs begin to freeze is one method by which patients can manage to ambulate (Video 1.49). ►

Although freezing most often affects walking, it can manifest in other ways (Table 1.9). Speech can be arrested with the patient repeating a sound until it finally becomes unstuck and speech then continues (Video 1.50). Freezing of speech can be considered a severe form of parkinsonian palilalia, which usually refers to a repetition of the first syllable of the word the patient is trying to verbally express. Parkinsonian palilalia differs from the palilalia seen in patients with Gilles de la Tourette syndrome, in which there is repetition of entire words or a string of words (see Video 1.41). Stuttering of speech is a fairly common problem starting in childhood and may lessen with speech therapy. Some patients with PD who had stuttering in childhood may develop a return of the stuttering after the onset of PD. A rare patient with PD may develop stuttering de novo (Video 1.51). There is a similarity between stuttering and severe palilalia. ►

Freezing of the arms, such as during handwriting or teeth-brushing, has also been reported (Narabayashi et al., 1976). Difficulty opening the eyes can be another example of freezing (see Video 1.11). This eyelid freezing was originally called *apraxia of eyelid opening*, which is a misnomer because the problem is not an apraxia. Eyelid freezing has also been called “levator palpebrae inhibition” (Lepore and Duvoisin, 1985) and even a form of dystonia. Although previously unrecognized as a freezing phenomenon and usually considered a form of body bradykinesia, difficulty in arising from a chair may be due to freezing in some patients (see Video 1.47). Patients use many tricks to overcome freezing, but these might not always be successful. A discourse on the freezing phenomenon is provided in a review by Fahn (1995). ►

As was discussed previously, the freezing phenomenon occurs in parkinsonism, whether it be primary (PD), secondary (such as vascular parkinsonism), or parkinsonism-plus syndromes, such as PSP and multiple system atrophy (MSA) (Giladi et al., 1992). It can also appear as an idiopathic freezing gait disorder without other features of parkinsonism, except for loss of postural reflexes and mild bradykinesia (Achiron et al., 1993; Atchison et al., 1993) (Video 1.52). In many patients, it is an early sign of impending PSP (Riley et al., 1994) (Video 1.53) but has also been reported in nigropallidal degeneration (Katayama et al., 1998) or in primary pallidal degeneration. Necrosis of the globus pallidus from a variety of causes, including carbon monoxide poisoning, can be associated with freezing of gait (Video 1.54). ►

Video 1.25 Freezing when turning and when starting to walk.

Video 1.26 Freezing while turning.

Video 1.27 Destination-freezing.

Video 1.28 Shaky legs when standing with onset of orthostatic hypotension.

Video 1.29 Fear of falling.

Video 1.30 Fear of Falling in a person who had not fallen.

Hesitant gaits

Hesitant gaits or uncertain gaits are seen in a number of syndromes (see [Chapter 19](#)). The *cautious gait* that is seen in some elderly people is slow on a wide base with short steps and superficially may resemble that of parkinsonism except that there are no other parkinsonian features. *Fear of falling* (discussed earlier), because of either perceived postural instability or realistic loss of postural righting reflexes, produces an inability to walk independently without holding onto people or objects (see Video 1.29). Because this abnormal gait disappears when the person walks holding onto someone, it is often considered to be a psychiatric disorder, a phobia of open spaces (i.e., agoraphobia), or a psychogenic disorder. However, a history of previous falls usually plays a role in patients developing this disorder; in this situation it is a true fear of falling, which should be distinguished from agoraphobia, a psychiatric condition. Fear of falling from having actually fallen, from loss of postural reflexes, from gait ataxia, or from some other gait disorder is usually due to anxiety and should be distinguished from a conversion disorder, the major cause of psychogenic (functional) movement disorders (see [Chapter 27](#)). A *cautious gait*, such as from fear of falling, may be superimposed on any other gait disorder.

The opposite of fear of falling is a complete disregard despite the likelihood of falling, a recklessness that is often seen in patients with PSP. These patients may have fallen many times, and still they often get up, aware they may fall, and start to walk or turn without use of a walker or someone to support them.

The *senile gait disorder* (or *gait disorder of the elderly*) is a poorly understood condition that comprises a number of different syndromes ([Nutt et al., 1993](#)). In *gait ignition failure* ([Atchison et al., 1993](#)), also called *primary freezing gait* ([Achiron et al., 1993](#)), the problem is one of getting started. Once underway, such patients walk fairly briskly (see Video 1.52), and equilibrium is preserved. In *frontal gait disorders*, there is also start-hesitation, and walking is with slow, small, shuffling steps, similar to that in PD. However, there are few other signs of parkinsonism, and equilibrium is preserved. Such a gait can occur with frontal lobe tumors, cerebrovascular disease, and hydrocephalus, all causing frontal lobe damage. This pattern has been incorrectly called frontal ataxia or gait apraxia in the older literature. A true gait apraxia resulting from parietal lobe lesions is much less common. The most common movement disorder causing gait apraxia is corticobasal syndrome (Videos 1.55, 1.56).

Other hesitant gaits are those resulting from *severe dysequilibrium*. These types of gait have been associated with frontal cortex and deep white matter lesions (*frontal dysequilibrium*) or thalamic and midbrain lesions (*subcortical dysequilibrium*) ([Nutt et al., 1993](#)). Hesitant gaits syndromes are covered in more depth in [Chapter 19](#).

Hypothyroid slowness

Along with decreased metabolic rate, cool body temperature, bradycardia, myxedema, loss of hair, hoarseness, and myotonia, severe hypothyroidism can feature motor slowness, weakness, and lethargy. These signs could be mistaken for the bradykinesia of parkinsonism, but the combination of the other signs of hypothyroidism, along with lack of

rigidity and loss of postural reflexes should point to the correct diagnosis.

Rigidity

Rigidity is characterized as increased muscle tone to passive motion. It is distinguished from spasticity in that it is present equally in all directions of the passive movement, equally in flexors and extensors and throughout the range of motion, and it does not exhibit the clasp-knife phenomenon or increased tendon reflexes, both of which are classic signs of spasticity. Rigidity can be smooth (lead-pipe) or jerky (cogwheel). Cogwheeling occurs in the same range of frequencies as action and resting tremor ([Lance et al., 1963](#)) and appears to be due to superimposition of a tremor rhythm ([Denny-Brown, 1962](#)). In parkinsonism (nigral lesion), cogwheel rigidity is more common than the lead-pipe variety; lead-pipe rigidity can be caused by a number of other central nervous system lesions ([Fahn, 1987a](#)), including those involving corpus striatum (hypoxia, vascular, neuroleptic malignant syndrome [NMS], CBD) (Video 1.57), midbrain (decorticate rigidity), medulla (decerebrate rigidity), and spinal cord (tetanus). When a patient does not thoroughly relax to allow passive manipulation of his or her joints, but tends to actively resist, the result is increased muscle tone, so-called *Gegenhalten* or *paratonia*. *Gegenhalten* is commonly seen in patients with impaired cognition or in those who are anxious and are unable to relax. Often, with *Gegenhalten*, more force applied by the examiner is met with more resistance by the patient. ▶

An increase in passive muscle tone can sometimes lead to impaired motor performance or even immobility. Before there was a clear understanding of bradykinesia, rigidity was considered to be responsible for the paucity of movement in parkinsonism. But rigidity is clearly distinct from bradykinesia; the former is more easily treated by levodopa therapy or by stereotactic thalamotomy or stimulation of the subthalamic nucleus and can be relieved, whereas bradykinesia with residual paucity of movement persists. When rigidity is extremely severe, such that the examiner can barely move the limbs, as in patients with NMS, the patient is virtually unable to move. The extended neck that is occasionally seen in PSP (Steele-Richardson-Olszewski syndrome) may be due to rigidity (versus dystonia); the neck can be immobile in this disorder, and other axial muscles are also rigid.

Rigidity is one feature of NMS (see [Chapter 17](#)), which is an idiosyncratic adverse effect of dopamine receptor-blocking agents, usually antipsychotic drugs ([Smego and Durack, 1982](#); [Kurlan et al., 1984](#)), but it also has been reported to occur on sudden discontinuation of levodopa therapy ([Friedman et al., 1985](#); [Keyser and Rodnitzky, 1991](#)) (Video 1.58). The clinical features of the syndrome are the abrupt onset of a combination of rigidity/dystonia, fever with other autonomic dysfunctions such as diaphoresis and dyspnea, and an altered mental state, including confusion, stupor, or coma. The level of serum creatine kinase activity is usually elevated. NMS can occur when the dopamine receptor-blocking agents were administered at therapeutic, not toxic, dosages. There does not seem to be any relationship with the duration of therapy. It can develop soon after the first dose or any time after prolonged treatment. This is a potentially lethal disorder unless treated; up to 25% of cases died in one report ([Henderson and](#)

Video 1.31 Gait disorder due to agoraphobia.

Wooten, 1981). NMS is sometimes called malignant catatonia (Boeve et al., 1994) and needs to be distinguished from malignant hyperthermia and serotonin syndrome (Video 1.59). ▶

Stiff muscles

Stiff muscles are defined as being the result of continuous muscle firing without muscle disease and not rigidity or spasticity. These are reviewed in detail in [Chapter 21](#). Briefly, there are four major clinical categories of stiff-muscle syndromes: continuous muscle fiber activity or neuromyotonia, encephalomyelitis with rigidity, stiff-limb syndrome, and stiff-person syndrome (Thompson, 1994), with the last three being variations of the same disorder. *Neuromyotonia* is a syndrome of myotonic failure of muscle relaxation plus myokymia and fasciculations. Clinically it manifests as continuous muscle activity causing stiffness and cramps. The best known neuromyotonic disorder is Isaacs syndrome (Isaacs, 1961) (Video 1.60).

Encephalomyelitis with rigidity (Whiteley et al., 1976), initially called spinal interneuronitis (Brown et al., 1997), manifests with marked rigidity and muscle irritability, with increased response to tapping the muscles, and myoclonus (Video 1.61). It is now recognized as a severe manifestation of stiff-person syndrome and may respond to corticosteroid therapy. ▶

Stiff-person syndrome refers to a disorder (Spehlmann and Norcross, 1979) in which many somatic muscles are continuously contracting isometrically, resembling “chronic tetanus,” in contrast to dystonic movements, which produce abnormal twisting and patterned movements and postures. The contractions of stiff-person syndrome are usually forceful and painful and most frequently involve the trunk and neck musculature (Video 1.62). The proximal limb muscles also can be involved, but rarely does the disorder first affect the distal limbs. Benzodiazepines and valproate are usually somewhat effective. Withdrawal of these agents results in an increase of painful spasms. This disorder has now been recognized to be an autoimmune disease, with circulating antibodies against the GABA-synthesizing enzyme, glutamic acid decarboxylase, and also other types of antibodies, including antibodies against insulin (Solimena et al., 1988, 1990; Blum and Jankovic, 1991]. Diabetes is a common accompanying disorder. The diagnosis can now be aided by laboratory testing for these antibodies. The syndrome of spinal neuronitis, also called encephalomyelitis with rigidity and myoclonus, is a more acute variant of the stiff-person syndrome. The so-called stiff-baby syndrome (Video 1.63) is not part of the stiff-person syndrome but is actually due to infantile hyperekplexia, in which the muscles continue to fire repeatedly and so frequently that the muscles appear to contract continuously. ▶

Evaluation of a dyskinesia

The traditional approach in neurology when evaluating a patient is to first ask where the lesion is, then what the lesion is, and finally how the problem is to be treated. Essentially, the first question, then, is about localization within the nervous system. This traditional approach is not ordinarily followed when confronting a patient with a movement disorder. The first question related to a patient with a

movement disorder is what the phenomenology is, that is, what type of dyskinesia we are witnessing. The next question is what is the cause, and the third question is how do we treat it. In other words, localization, although important in many situations, is not as important as in recognizing the phenomenology. We can expand on the three questions with a prior one, namely, whether the excess movement is a dyskinesia or a variation of normal motor control.

The first question to be answered in seeing a person with extraneous movements is whether abnormal involuntary movements are actually present. One must consider whether the suspected movements might be purposeful voluntary movements, such as exaggerated gestures, mannerisms, or compulsive movements, or whether sustained contracted muscles might be physiologic reflex muscle tightness to reduce pain, so-called guarding. It should also be noted that as a general rule, abnormal involuntary movements are exaggerated with anxiety and most diminish or disappear during sleep. They may or may not lessen with amobarbital or with hypnosis.

Once it has been decided that abnormal movements are present, the next question is to determine the category of the involuntary movement, such as chorea, dystonia, myoclonus, tics, or tremor. In other words, determine the nature of the involuntary movements. To do so, one evaluates features such as rhythmicity, speed, duration, pattern (e.g., repetitive, flowing, continual, paroxysmal, diurnal), induction (i.e., stimuli-induced, action-induced, exercise-induced), complexity of the movements (complex versus simple), suppressibility by volitional attention or by sensory tricks, and whether the movements are accompanied by sensations such as restlessness or the urge to make a movement that can release a built-up tension. In addition, the examiner must determine which body parts are involved. The evaluation for the type of dyskinesia is the major subject of the next section in this chapter.

The third question is to determine the etiology of the abnormal involuntary movements. Is the disorder hereditary, sporadic, or secondary to some known neurologic disorder? The etiology and workup for the various dyskinesias are discussed in each chapter dealing with specific types of movement disorders in this textbook. As a general rule, the etiology can be ascertained on the basis of the history and judiciously selected laboratory tests.

The final question is how best to treat the movement disorder. Treatments of the various movement disorders are covered in the appropriate chapters of this book.

Differential diagnosis of the hyperkinesias (dyskinesias)

The differential diagnosis of movement disorders depends primarily on their clinical features. It is important to observe and describe the nature of the involuntary movements as mentioned previously. In addition, one examines for postural changes, alteration of muscle tone, loss of postural reflexes, motor impersistence, and any other neurologic abnormalities on the general neurologic examination.

A list of abnormal involuntary movements is presented alphabetically in [Table 1.1](#) under Hyperkinesias. A brief description of each of these is now presented along with its

Video 1.32A Young-onset Parkinson disease (YOPD) with levodopa-induced peak-dose dystonia:

Video 1.32B Young-onset Parkinson disease (YOPD) with Super OFFs at the beginning and end of a levodopa response

Video 1.33 Juvenile Parkinson disease.

Video 1.34 Juvenile onset akinetic-rigid-dystonic syndrome in a child with neuronal degeneration with brain iron accumulation (NBIA).

major recognizable and differentiating features. [Tables 1.10 to 1.18](#) (later in chapter) list the ordinary processes of distinguishing one type of dyskinesia from another by major stepwise deciphering based on a practical approach.

Table 1.10 The clinical approaches to recognizing the various dyskinesias

Level A: immediate impressions

1. Rhythmic versus arrhythmic (see [Table 1.11](#))
2. Sustained versus nonsustained (see [Table 1.12](#))
3. Paroxysmal versus continual versus continuous* (see [Table 1.13](#))
4. Sleep versus awake (see [Table 1.14](#))

Level B: more prolonged observations

At rest versus with action versus overflow (see [Table 1.15](#))

Patterned versus nonpatterned (see [Table 1.16](#))

Combinations of varieties of movements (see [Table 1.17](#))

Level C: features requiring longer observation (see [Table 1.18](#))

Speed: slow versus fast

Amplitude: ballistic versus not ballistic

Force: powerful (painful) versus easy-to-overcome

Suppressibility

Vocalizations

Self-mutilation

Complexity of movements

Sensory component

Ocular movements

*Continual means over and over again; continuous means without stopping or unbroken.

Abdominal dyskinesias

Abdominal dyskinesias are continuous movements of the abdominal muscles; involuntary movements of the diaphragm can also manifest as abdominal dyskinesias. The movements persist, and their sinuous, rhythmic nature has led to their being called belly dancer's dyskinesia ([Iliceto et al., 1990](#)). They may be associated with abdominal trauma in some cases, and a common result is segmental abdominal myoclonus

Table 1.12 Differential diagnosis of sustained hyperkinesias

Sustained contractions or postures	Nonsustained contractions
Stiff person syndrome	All others
Rigidity	
Dystonia	
Oculogyric crisis	
Paroxysmal dystonia	
Dystonic tics	
Pseudodystonias (e.g., Sandifer syndrome)	
Neuromyotonia	
Congenital torticollis	
Orthopedic torticollis	

Table 1.11 Differential diagnosis of rhythmic and arrhythmic hyperkinesias

Rhythmic	Irregular	Arrhythmic
Tremor	Cortical myoclonus	Akathitic movements
Resting	Minipolymyoclonus	Athetosis
Postural	Dystonic tremor*	Ballism
Action	Epilepsia partialis continua	Chorea
Intention	Moving toes/fingers	Dystonia*
Orthostatic tremor		Hemifacial spasm
Dystonic tremor*		Hyperekplexia
Dystonic myorhythmia*		Arrhythmic myoclonus
Myoclonus, segmental*		Some stereotypies*
Myoclonus, oscillatory		Tics
Myorhythmia*		
Periodic limb movements in sleep		
Some stereotypies		
Classic tardive dyskinesia (tardive stereotypy)*		

*Any apparent incongruity of some dyskinesias appearing in both columns has been explained in the definitions of the different dyskinesias. Dystonia often, but not always, has repetitive movements, which were coined as myorhythmia by [Herz \(1931, 1944\)](#) and now labeled as dystonic tremor and also patterned movements. Today, myorhythmia refers to the slow, rhythmic movements, most classically seen in Whipple disease. Segmental myoclonus (e.g., palatal myoclonus/tremor) is typically rhythmic, whereas other forms of myoclonus are arrhythmic. Some stereotypies can occur as repetitive, rhythmic movements (e.g., flapping arm movements) and some manifest at irregular intervals, and these are in the left and right columns, respectively. In contrast, classic tardive dyskinesia movements (e.g., oral-buccal-lingual dyskinesias) are continuous and relatively rhythmic, and these have been called tardive stereotypies and are placed in the left column.

Table 1.13 Differential diagnosis of paroxysmal and nonparoxysmal hyperkinesias

Paroxysmal	Continual	Continuous
Tics	Ballism	Abdominal dyskinesias
Paroxysmal kinesigenic dyskinesia	Chorea	Athetosis
Paroxysmal nonkinesigenic dyskinesia	Dystonic movements	Tremors
Paroxysmal exertional dyskinesia	Myoclonus, arrhythmic	Dystonic postures
Episodic ataxia	Some stereotypies	Minipolymyoclonus
Episodic tremor	Akathitic moaning	Myoclonus, rhythmic
Hypnogenic dystonia		Tardive stereotypy*
Paroxysmal dystonia in infancy		Myokymia
Self-stimulatory behavior		Tic status*
Some stereotypies		Some jumpy stumps
Akathitic movements		Moving toes/fingers
Some jumpy stumps		Myorhythmia

*Tic status refers to the rare episodes in which tics become so severe that they do not stop. Stereotypies, including tardive stereotypy (classic tardive dyskinesia), was explained in Table 1.11.

Continual means over and over again; *continuous* means without stopping or unbroken.

Table 1.14 Differential diagnosis of hyperkinesias present while asleep or awake

Appears during sleep and disappears when awakened	Present while awake and persists during sleep	Diminishes during sleep
Hypnogenic dyskinesias	Secondary palatal myoclonus	Primary palatal myoclonus
Periodic limb movements in sleep	Ocular myoclonus	All others
Rapid eye movement sleep behavior disorder	Spinal myoclonus	
	Oculofaciomasticatory myorhythmia	
	Severe dystonia	
	Severe tics	
	Peripheral movement disorders	
	Moving toes/fingers	
	Myokymia	
	Neuromyotonia (Isaacs syndrome)	

Table 1.15 Differential diagnosis of hyperkinesias present at rest or with action**At rest only (disappears with action)**

Akathitic movements
 Paradoxical dystonia*
 Resting tremor, but can reemerge with posture holding
 Restless legs
 Orthostatic tremor (only on standing)
 Posture-specific tremors

With action only

Ataxia
 Action dystonia
 Action myoclonus
 Tremor: postural, action, intention
 Task-specific tremor
 Task-specific dystonia

At rest and continues with action

Abdominal dyskinesias
 Athetosis
 Ballism
 Chorea
 Dystonia*
 Jumpy stumps
 Minipolymyoclonus
 Moving toes/fingers
 Myoclonus*
 Myokymia
 Pseudodystonias*
 Tics

*Paradoxical dystonia refers to dystonia that is present only at rest and disappears with action (Fahn, 1989); orthostatic tremor is tremor of the thighs and legs (spreading to the trunk) that occurs only on prolonged standing and disappears with walking or sitting; most dystonias and myoclonias that are present at rest are also present and often worse with action; pseudodystonias refer to neuromyotonia and other causes of stiff muscles or postures that are not the result of dystonia (common causes are orthopedic deformities and pain); discussed in Chapter 11.

Table 1.16 Patterned and nonpatterned movements

Patterned (i.e., same muscle groups)	Nonpatterned
Abdominal dyskinesias	All others
Dystonia	
Hemifacial spasm	
Moving toes/fingers	
Segmental myoclonus	
Myorhythmia	
Myokymia	
Most stereotypies	
Tardive dyskinesia movements	
Tremor	

Table 1.17 Combinations of varieties of movements

Psychogenic movement disorders
Tardive syndromes
Neuroacanthocytosis
Wilson disease
Huntington disease
Lesch–Nyhan syndrome
Dentatorubral–pallidoluysian atrophy (DRPLA)
Ataxia–telangiectasia (A-T)
Dystonia*
Neurodegenerations with brain iron accumulation (NBIA)
Cerebellar–parkinsonian syndromes
Cerebellar–dystonia syndromes
Fragile X-associated tremor–ataxia syndrome (FXTAS)
Multiple system atrophy (MSA)
Spinocerebellar ataxia-3 (SCA3)
Progressive supranuclear palsy (PSP)
Spasticity–cerebellar syndromes
Multiple system atrophy (MSA)
Hereditary spastic paraplegias

*Patients with dystonia can have additional dyskinesias that are part of the spectrum of classic torsion dystonia (see [Chapter 11](#)). These include tremor, myoclonus, and choreic-like movements. Dystonia-plus syndromes can have features of parkinsonism or myoclonus in addition to dystonia. Degenerative dystonia syndromes, including NBIA, often have parkinsonism.

([Kono et al., 1994](#)) (Video 1.64). Another common cause is tardive dyskinesia (Video 1.65). *Hiccups*, which are regularly recurring diaphragmatic myoclonus, do not move the abdomen and umbilicus in a sinewy fashion but with sharp jerks and typically with noises as air is expelled by the contractions, so they should not present a diagnostic problem. Abdominal dyskinesias are discussed in [Chapter 26](#). ▶

Akathitic movements

Akathisia (from the Greek, meaning “unable to sit still”) refers to a feeling of inner, general restlessness that is reduced or relieved by moving about. The typical akathitic patient, when seated, may caress his or her scalp, cross and uncross the legs, rock the trunk, squirm, get out of the chair often to pace back and forth (Video 1.66), and even make noises such as moaning (Video 1.67). Carrying out these motor acts brings relief from the sensations of akathisia. Akathitic movements are complex and usually stereotyped; the same type of movements are employed over and over. Other movement disorders that show complex movements are tics, compulsions, mannerisms, and the stereotypies associated with intellectual disability, autism, psychosis, and some encephalitides, such as the NMDA receptor antibody encephalitis. Akathisia does not necessarily affect the whole body; an isolated body part can be affected. Focal akathisia often produces a sensation of burning or pain, again relieved by moving that body part (Video 1.68). Common sites for focal akathisia/pain are the mouth and vagina ([Ford et al., 1994](#)). ▶

Akathisia may be expressed by vocalizations, such as continual moaning, groaning, or humming. Other movement disorders associated with moaning sounds or humming are tics, oromandibular dystonia, HD, parkinsonian disorders ([Micheli et al., 1991](#); [Friedman, 1993](#)), and those induced by levodopa ([Fahn et al., 1996](#)).

The patient can transiently suppress akathitic movements and vocalizations if he or she is asked to do so. Typically, relief of the movements occur when the patient carries out voluntary movement (Video 1.69). The entity of paradoxical dystonia (dystonia appears at rest and clears when the patient purposefully moves) ([Fahn, 1989](#)) (Video 1.70); it can be mistaken for akathisia.

The most common cause of akathisia is iatrogenic. It is a frequent complication of antidopaminergic drugs, including those that block dopamine receptors (such as antipsychotic drugs and certain antiemetics) and those that deplete dopamine (such as reserpine and tetrabenazine). Akathisia can occur when drug therapy is initiated (acute akathisia), subsequently with the emergence of drug-induced parkinsonism, or after chronic treatment (tardive akathisia). Acute akathisia is eliminated on withdrawal of the medication. Tardive akathisia usually is associated with the syndrome of tardive dyskinesia (see [Chapter 17](#)). Like tardive dyskinesia, tardive akathisia is aggravated by discontinuing the neuroleptic agent, and it is usually relieved by increasing the dose of the offending drug, which masks the movement disorder. When associated with tardive dyskinesia, the akathitic movements can be rhythmic, such as body rocking or marching in place. In this situation, it is difficult to be certain whether such rhythmic movements are due to akathisia or to tardive dyskinesia.

The exact mechanism of akathisia is not known, but it seems that the dopamine systems are involved, possibly in the limbic system or frontal cortex. It is of interest that akathisia, both generalized and regional, can be present in patients with PD. It can occur as part of PD (in the absence of drug therapy) and can sometimes occur with levodopa or anticholinergics (Video 1.71). Akathisia can be a feature of nonmotor “offs” (see [Chapter 6](#)).

Ataxia/asynergia/dysmetria

Ataxia, *asynergia*, and *dysynergia* are interchangeable terms that refer to decomposition of movement as a result of breakdown of normal coordinated execution of a voluntary movement. Ataxia is one of the cardinal clinical features of cerebellar disease or of lesions involving the pathways to or from the cerebellum (Video 1.72). Instead of a smooth, continuous movement; the limb wanders off its trajectory attempting to a reach a target, with corrective maneuvers that resemble oscillations of the limb. The limb usually misses the target (*dysmetria*); the ataxia worsens when the limb approaches the target. Common tests for ataxia and dysmetria are the finger-to-nose-to-finger maneuver and the maneuver of heel-to-knee and then the heel sliding down the shin. A useful test to see upper limb ataxia is to ask the patient to follow the examiner’s finger with the patient’s finger (finger-chasing task); the examiner moves his or her finger quickly after instructing the patient to follow that finger, keeping about 2 cm away from touching the examiner’s finger. Limb ataxia is also manifested by *dysdiadochokinesia* which refers to the breakup and irregularity that occurs when the limb is attempting to carry out rapid alternating movements. The dysmetria with cerebellar dysfunction is due to overshooting (hypermetria) and undershooting (hypometria) of the target. There may be an associated intention (or terminal) tremor (see under “Tremor” later in this chapter). Ataxia is usually associated with hypotonia, loss of check (when a fast

Video 1.35 Juvenile onset tremulous parkinsonism that progressed to become akinetic, rigid, dystonic syndrome with speech involvement and eventually dementia and bed-ridden.

Video 1.36 Oculogyric crisis and parkinsonism due to neuroleptic treatment.

Video 1.37 Apraxia.

Table 1.18 Clinical features requiring longer observation time

Speed: fast versus slow			Vocalizations
Fastest	Intermediate	Slowest	Phonic tics: simple or complex
Minipolymyoclonus	Chorea	Athetosis	Akathitic moaning
Myoclonus	Ballism	Moving toes/fingers	Huntington disease Neuroacanthocytosis
Hyperekplexia	Jumpy stumps	Myorhythmia	Cranial dystonia
Startle	Tremors	Akathitic movements	Self mutilation
Hemifacial spasm (HFS) (myoclonic form)	Tardive stereotypy	HFS (tonic form)	Lesch–Nyhan syndrome Neuroacanthocytosis
<i>COMMENT:</i> HFS can be either myoclonic (fastest) or tonic (slowest) <i>NOTE:</i> tics and dystonic movements can be of all speeds			Tourette syndrome
Amplitude			Psychogenic movement disorders
Large	Medium	Very small	Complex movements
Ballism	Chorea and all others	Minipolymyoclonus	Tics
<i>NOTE:</i> Jumpy stumps would be large if the involved limb were not amputated, but the short stump keeps the amplitude at a medium level			Akathitic movements
Force			Compulsions
Powerful	Intermediate	Mild	Stereotypies
Stiff person	Dystonia	All others	Psychogenic movements (<i>NOTE:</i> Each of the above can also consist of simple movements)
Jumpy stumps			Sensory component
Fixed postures of dystonia			Akathisia
Suppressibility			Moving digits, painful limbs
Stereotypies > tics, akathitic movements > chorea > ballism > dystonia > tremor			Restless legs
Not suppressible: hemifacial spasm, minipolymyoclonus, myoclonus, hyperekplexia, myorhythmia, moving toes			Tics
			Ocular movements
			Ocular tics
			Oculogyric crises
			Opsoclonus
			Ocular myoclonus
			Ocular myorhythmia
			Ocular dysmetria
			Nystagmus
			Square wave jerks

voluntary movement is unable to stop precisely on target when the limb reaches its destination), and rebound (when sudden displacement of a limb results in excessive overcorrection to return to the baseline position). Ataxia is seen only during voluntary movement and is not a feature of a limb at rest. Ataxia of gait is typified by unsteadiness on walking with a wide base, the body swaying, and an inability to walk on tandem (heel-to-toe). Details on ataxia, including anatomic, clinical, and etiologies are provided in [Chapter 20](#).) The ataxias are a common neurologic problem because they result from any involvement of the cerebellum and all neural

pathways leading to and away from the cerebellum. As an example, in an analysis of the most common movement disorder resulting from lysosomal storage diseases, ataxia was the most common, followed by rest tremor, dystonia, and myoclonus ([Ebrahimi-Fakhari et al., 2018](#)). ▶

Athetosis

Athetosis has been used in two senses: to describe a class of slow, writhing, continuous, involuntary movements and to describe the syndrome of athetoid cerebral palsy. The latter

Video 1.38 Other examples of apraxia.

Video 1.39 Cortical myoclonus.

commonly occurs as a result of injury to the basal ganglia in the prenatal or perinatal period or during infancy. Athetotic movements affect the limbs, especially distally, but can also involve axial musculature, including neck, face, and tongue (Video 1.73). When not present in certain body parts at rest, it can often be brought out by having the patient carry out voluntary motor activity elsewhere in the body; this phenomenon is known as *overflow*. For example, speaking can induce increased athetosis in the limbs, neck, trunk, face, and tongue. Athetosis often is associated with sustained contractions producing abnormal posturing. In this regard, athetosis blends with dystonia. Although the speed of athetosis is usually slow, sometimes it is fast enough to blend in with the speed of chorea, and the term *choreoathetosis* is used. Athetosis resembles “slow” chorea in that the direction of movement changes randomly and in a flowing pattern (see Chapter 14). Athetotic movements of the tongue are a common feature of classic tardive dyskinesia, known as oral-buccal-lingual dyskinesias (Video 1.75). ●

Pseudoathetosis refers to distal athetoid movements of the fingers and toes as a result of loss of proprioception, which can be due to sensory deafferentation (sensory athetosis) or to central loss of proprioception (Sharp et al., 1994) (Video 1.76).

Ballism

Ballism refers to very-large-amplitude choreic movements of the proximal parts of the limbs, causing flinging and flailing limb movements (see Chapter 14). Ballism is most frequently unilateral, in which case it is referred to as *hemi-ballism*. This is often the result of a lesion in the contralateral subthalamic nucleus or its connections or of multiple small infarcts (lacunes) in the contralateral striatum (Video 1.77). Any structural damage in this area of the brain can result in hemiballism, including infections and trauma (Video 1.78). In rare instances, ballism occurs bilaterally (*biballism*) and is due to bilateral lacunes in the basal ganglia (Sethi et al., 1987). Like chorea, ballism can sometimes occur as a result of overdosage of levodopa. ●

Chorea

Chorea refers to involuntary, irregular, purposeless, nonrhythmic, abrupt, rapid, unsustained movements that seem to flow from one body part to another. A characteristic feature of chorea is that the movements are unpredictable in timing, direction, and distribution (i.e., random). Although some neurologists erroneously label almost all nonrhythmic, rapid involuntary movements as choreic, many in fact are not. Nonchoreic rapid movements can be tics, myoclonus, and dystonia (see chapters for each of these disorders); in these other conditions, the movements repeat themselves in a set distribution of the body (i.e., are patterned) and do not have the changing, flowing nature of choreic movements, which travel around the body. In rapid dystonic movements, there is a recognizable repetitive recurrence to the movements in the affected body parts, unlike the random nature of chorea. The prototypical choreic movements are those seen in HD (Video 1.79), in which the brief and rapid movements are irregular and occur randomly as a function of time. In Sydenham chorea and in the withdrawal emergent syndrome (Chapter 17), the flowing choreic movements have a restless

appearance (Videos 1.80 and 1.81). HD is an autosomal dominant disorder with increased triplet repeats in the *HTT* gene (see Table 1.5). There are several HD look-alikes caused by different gene mutations, the most common involving the C9orf72 gene. Mutations in this gene are a common cause of amyotrophic lateral sclerosis and frontotemporal degeneration and are sometimes associated with atypical parkinsonisms and PD (Bourinaris and Houlden, 2018). ●

When choreic movements are infrequent, they appear as isolated, small-amplitude, brief movements, somewhat slower than myoclonus but sometimes difficult to distinguish from it. When chorea is more pronounced, the movements occur almost continually, presenting as involuntary movements flowing from one site of the body to another.

Choreic movements can be partially suppressed, and the patient can often camouflage some of the movements by incorporating them into semipurposeful movements, known as *parakinesia*. Chorea is usually accompanied by *motor impersistence* (“negative chorea”), the inability to maintain a sustained contraction. A common symptom of motor impersistence is the dropping of objects from a closed hand. Motor impersistence is detected by examining for the inability to keep the tongue protruded and by the presence of the “milk-maid” grip because of the inability to keep the fist in a sustained tight grip. For details on choreic disorders, see Chapter 14. The chapter discusses the wide range of etiologies, including nonketotic hyperglycemic chorea (Video 1.82), lupus erythematosus (Video 1.83), and various genetic causes besides HD. Today, with levodopa therapy for PD so commonly used around the world, probably the most common cause of chorea is dopa-induced dyskinesia (Video 1.84, 1.85, 1.86). New gene mutations causing chorea are being found (Mencacci and Carecchio, 2016).

Dystonia

Dystonia refers to movements that tend to be sustained at the peak of the movement, are usually twisting and frequently repetitive, and often progress to prolonged abnormal postures (see Chapter 11). In contrast to chorea, dystonic movements repeatedly involve the same group of muscles—that is, they are patterned. Agonist and antagonist muscles contract simultaneously (cocontraction) to produce the sustained quality of dystonic movements. The speed of the movement varies widely from slow (athetotic dystonia) to shock-like (myoclonic dystonia). When the contractions are very brief (e.g., less than a second), they are referred to as dystonic spasms. When they are sustained for several seconds, they are called dystonic movements. When they last minutes to hours, they are known as *dystonic postures*. When present for weeks or longer, the postures can lead to permanent fixed contractures.

When dystonia first appears, the movements typically occur when the affected body part is carrying out a voluntary action (*action dystonia*) and are not present when that body part is at rest. With progression of the disorder, dystonic movements can appear at distant sites (*overflow*) when other parts of the body are voluntarily moving, such as occurs also in athetosis and in dopa-induced dyskinesias. With further progression, dystonic movements become present when the body is “at rest.” Even at this stage, dystonic movements are usually made more severe with voluntary activity. Whereas primary dystonia often begins

Video 1.40 Alien limb.

Video 1.41 Blocking tics.

Video 1.42 Drop attack due to hyperekplexia (excessive startle):

as action dystonia and may persist as the kinetic (clonic) form, secondary dystonia often begins as sustained postures (tonic form).

One of the characteristic and almost unique features of dystonic movements is that they can often be diminished by tactile or proprioceptive “sensory tricks” (*gestes antagoniste*). Thus, touching the involved body part or an adjacent body part can often reduce the muscle contractions. When first described in patients with torticollis, this maneuver was thought to indicate that the torticollis was psychogenic in origin (Brissaud, 1895; Meige and Feindel, 1902; Broussolle et al., 2015). For decades afterward, inexperienced clinicians assumed that this sign indicates that the abnormal movements are psychogenic, but the opposite conclusion should be reached, namely that the presence of sensory tricks strongly suggests an organic etiology (Fahn and Williams, 1988; Broussolle et al., 2015). If the dystonia becomes more severe, sensory tricks tend to be lost.

When a single body part is affected, the condition is referred to as *focal dystonia*. Common forms of focal dystonia are spasmodic torticollis (cervical dystonia), blepharospasm (upper facial dystonia), spasmodic dysphonia (vocal cord dystonia), and writer’s cramp (hand dystonia). Involvement of two or more contiguous regions of the body is referred to as *segmental dystonia*. *Generalized dystonia* indicates involvement of the trunk and some other part of the body. *Multifocal dystonia* involves two or more regions, not conforming to segmental or generalized dystonia. *Hemidystonia* refers to involvement of the arm and leg on the same side. A variety of these types of dystonia are shown in Videos 1.87 to 1.95. ▶

One type of focal dystonia requires special mention, namely sustained contractions of ocular muscles, resulting in tonic ocular deviation, usually upward gaze (see Videos 1.34, 1.36). This is referred to as *oculogyric crisis*. This sustained ocular deviation was encountered in victims of encephalitis lethargica and later in those survivors who developed postencephalitic parkinsonism. Primary torsion dystonia does *not* involve the ocular muscles; thus oculogyria is not truly a feature of dystonia syndromes. Oculogyria is more common today as a complication of dopamine receptor-blocking agents (Paulson, 1960) (see Video 1.36) as in drug-induced parkinsonism, in the juvenile parkinsonism associated with the degenerative disease known as neuronal intranuclear inclusion disease (Kilroy et al., 1972; Funata et al., 1990), and with the biochemical deficiency of the monoamines in the metabolic disorders of aromatic amino acid decarboxylase deficiency (Hyland et al., 1992; Chang et al., 2004) and pterin deficiencies (Hyland et al., 1998). There has been a case report of oculogyric crises in a patient with dopa-responsive dystonia (Lamberti et al., 1993) and its phenocopy, tyrosine hydroxylase deficiency. We have seen oculogyria induced by levodopa therapy in children with neuronal degeneration with brain iron accumulation (NBIA) (Video 1.34). *Paroxysmal tonic upgaze* also has been seen in infants and children and often eventually subsides (Ouvrier and Billson, 1988), but it may be a forerunner of developmental delay, intellectual disability, or language delay, indicating impaired corticomesencephalic control of vertical eye movements (Hayman et al., 1998).

Another specific type of action dystonia should be mentioned, namely lingual feeding dystonia, because it is virtually pathognomonic of the disorder *neuroacanthocytosis*.

When a person with this type of dystonia is eating, the tongue is uncontrollably pushed out of the mouth, often resulting in biting the tongue and dropping food from the mouth (Video 1.95). ▶

Although classic torsion dystonia may appear initially only as an action dystonia, it usually progresses to manifest as continual contractions. A rarer presentation is when primary dystonia appears initially at rest and would clear when the affected body part or some other part of the body is voluntarily active; this type has been called *paradoxical dystonia* (Fahn, 1989) (Video 1.96; see also Video 1.70). In contrast to this continual type of classic torsion dystonia, a variant of dystonia also exists in which the movements occur in attacks, with a sudden onset and limited duration known as *paroxysmal dyskinesias* (see later in this chapter and also Chapter 24). These are categorized among the paroxysmal disorders. Among the other disorders to be differentiated from dystonia are conditions appearing as sustained contractions; these are tonic tics (also called dystonic tics) (see Chapter 15) and conditions referred to as *pseudodystonias* (see Chapter 11). Faciobrachial dystonic seizures could be mistaken for segmental dystonia. These are stereotypic bursts of dystonic postures of the face and one arm resulting from an autoimmune encephalitis caused by the Lgi1 antibody against the voltage-gated potassium channel. Lgi1 is the label for leucine-rich glioma inactivated 1 protein, which is part of the voltage-gated potassium channel complex (Irani et al., 2011) (see Video 1.3). They have an excellent response to corticosteroids. Rarely, a similar phenomenology can occur as a psychogenic movement disorder (Video 1.97). ▶

Hemifacial Spasm

Hemifacial spasm (HFS), as the name indicates, refers to unilateral facial muscle contractions. Generally, these are continual rapid, brief, repetitive spasms (clonic form of HFS) (Video 1.98), but they also can be more prolonged sustained tonic spasms (tonic form) mixed with periods of quiescence (Video 1.99). Often the movements can be brought out when the patient voluntarily and forcefully contracts the facial muscles; when the patient then relaxes the face, the involuntary movements appear (Video 1.100). HFS usually affects both upper and lower parts of the face ipsilaterally, but patients are commonly more concerned about closure of the eyelid than about the contractions of the cheek or at the corner of the mouth. HFS involves the facial nerve, and often it is due to compression of the nerve by an aberrant blood vessel (Jannetta, 1982). HFS is an example of a peripherally induced movement disorder (see Chapter 26). ▶

HFS can usually be easily distinguished from blepharospasm, because the latter involves the face bilaterally and the dystonic contractions often spread to contiguous structures, such as oromandibular and nuchal muscles. Rarely is blepharospasm the result of unilateral dystonia. In such a circumstance, it can be difficult clinically to distinguish it from HFS. In the rare occasions when HFS develops bilaterally, one side usually precedes the other, and when the facial muscles contract in HFS, they would be asynchronous between the two sides. Blepharospasm tends to pull the eyebrow down because of contraction of the procerus muscle in addition to the orbicularis oculi. In contrast, HFS tends to elevate the eyebrow owing to its being pulled upward by the forehead muscles. This upward pulling of the eyebrow is

Video 1.43 Catatonia.

Video 1.44A Another examples of catatonia.

Video 1.44B An example of a milder case of catatonia.

Video 1.45 Psychomotor slowness.

Video 1.46 Obsessional Slowness.

Video 1.47 Freezing when trying to rise from a chair.

Video 1.48 Freezing when trying to go through a doorway.

Video 1.49 Stepping over an inverted cane to overcome freezing of gait.

Video 1.50 Freezing of speech (severe palilalia).

Video 1.51 Stuttering/palilalia in the progression of Parkinson disease.

Video 1.52 Primary freezing gait syndrome.

Video 1.53 Freezing on turning in early PSP.

known as *the other Babinski sign* (Devoize, 2001) (Videos 1.101 and 102). Sometimes facial tics (Video 1.103) and psychogenic facial movements (Video 1.104) can mimic HFS. The absence of “the other Babinski sign” can be a clinical clue. ►

Another condition that has been confused with HFS is repetitive facial myoclonus seen with Whipple disease. In this disorder the myoclonic jerks in the face tend to be fairly rhythmic; the contractions usually involve the other side of the face to some extent, and the movements are not sustained (Video 1.105) in myorhythmia. Electromyography (EMG) may be of use because HFS is associated with high-frequency, repetitive discharges and sometimes with ephaptic transmission. The contractions in both HFS and blepharospasm are intermittent, but both can be sustained. ►

Hyperekplexia and jumping disorders

Hyperekplexia (“startle disease”) is an excessive startle reaction to a sudden, unexpected stimulus (Andermann and Andermann, 1986; Brown et al., 1991b; Matsumoto and Hallett, 1994). The startle response can be either a short “jump” or a more prolonged series of repetitive jerks resembling a tonic spasm, that can result in falls (see Video 1.42). This condition can be familial or sporadic. Startle can occur in neurodegenerative diseases and can lead to falls, as seen in video 1.42. If patients have a delayed reaction to sudden noise or threat, a psychogenic problem should be considered (Thompson et al., 1992) (Videos 1.06 and 1.107).

Startle syndromes may encompass *jumping disorders* and other similar conditions, with names like Jumping Frenchmen of Maine (Video 1.108), latah, myriachit, and Ragin’ Cajun, but all of these appear to be influenced by social and group behavior. These different names were coined for ethnic groups in different parts of the world, although their clinical features are similar. In jumping disorders, after the initial jump to the unexpected stimulus, there is automatic speech or behavior, such as striking out. In some of these, there is automatic obedience to words such as “jump” or “throw” (Matsumoto and Hallett, 1994). Such automatic behaviors are not seen in hyperekplexia. The startle disorders are discussed in more detail in Chapter 18.

Hypnogenic dyskinesias: periodic movements in sleep and REM sleep behavior disorder

Most dyskinesias disappear during deep sleep, although they may emerge during light sleep. The major exceptions are symptomatic rhythmic *oculopalatal myoclonus* that persists during sleep, in addition to being present while the patient is awake (Deuschl et al., 1990), and the moving toes disorder. There are, however, a few movement disorders that are present only when the patient is asleep. The most common hypnogenic dyskinesia is the condition known as *periodic movements in sleep* (Coleman et al., 1980; Lugaresi et al., 1983, 1986; Hening et al., 1986), initially referred to as *nocturnal myoclonus* (Symonds, 1953). The latter term is unacceptable because the movements are not shock-like, but, in fact, are rather slow. They appear as flexor contractions of one or both legs, with dorsiflexion of the big toe and the foot and flexion of the knee and hip (Video 1.109). They occur in intervals, approximately every 20 seconds, and hence have been given its new, more acceptable name (Coleman et al., 1980). Periodic movements in sleep are

a frequent component of the restless legs syndrome (see Chapter 25). In addition to periodic movements in sleep, this syndrome also is associated with myoclonic-like and dystonic-like movements during sleep and while the patient is drowsy (Hening et al., 1986).

REM sleep is the stage of sleep in which dreaming occurs. Along with the ocular movements, there is atonia of the other somatic muscles in the body; this permits people to remain free of body movements when they dream. *REM sleep behavior disorder (RBD)*, originally described by Schenck and colleagues (1986), is a condition in which there is lack of somatic muscle atonia, thus enabling such individuals to move while they dream (acting out their dreams). The affected individual is unaware of these movements unless awakened by falling out of bed or by the bed partner who might have been struck or kicked by the abnormal movements and then awakens the person to stop the movements. RBD may precede by several years the development of a subsequent synucleinopathy (PD or MSA) (Tan et al., 1996; Postuma et al., 2006; Claassen et al., 2010; Boeve et al., 2013. Schenck et al., 2013; Berg and Postuma, 2018; Yao et al., 2018b). RBD may instead develop after the onset of the synucleinopathy, and not all individuals with RBD will develop a synucleinopathy (Postuma et al., 2009).

Another rare nocturnal dyskinesia is hypnogenic paroxysmal dystonia or other dyskinesias that occur only during sleep (Video 1.110) (see Chapter 24). Hypnogenic dystonia can be complex and cause sustained contractions, similar to those occurring in torsion dystonia. As its name suggests, such movements occur as a paroxysm during sleep and last only a few minutes. They might or might not awaken the patient. Most are due to frontal lobe seizures (Fish and Marsden, 1994). ►

Jumpy stumps

Jumpy stumps are uncontrollable and sometimes exhausting chaotic movements of the stump remaining from an amputated limb (Video 1.111). When they occur, it is after a delayed period after the amputation (Marion et al., 1989). ►

Moving toes and fingers

The painful legs, moving toes syndrome (see Chapter 26) refers to a disorder in which the toes of one foot or both feet are in continual flexion–extension with some lateral motion, associated with a deep pain in the ipsilateral leg (Spillane et al., 1971). The constant movement has a sinusoidal quality (Videos 1.112–1.114). The movements and pain are continuous, and both occur even during sleep, though they may be reduced and the normal sleep pattern may be altered (Montagna et al., 1983). The leg pain is much more troublesome to the patient than are the constant movements. In most patients with this disorder, there is evidence for a lesion in the lumbar roots or in the peripheral nerves (Nathan, 1978; Montagna et al., 1983; Dressler et al., 1994). An analogous disorder, “painful arm/hand, moving fingers,” has been described (Verhagen et al., 1985) (Video 1.115). Some patients have moving digits without pain. Some patients have moving digits without pain. It is possible to have moving lips and painful (or painless) face (Video 1.116). ►

Video 1.54 Freezing associated with pallidal necrosis.

Video 1.55 Tachyphemia, arm dystonia and rigidity and apraxia of limbs and gait.

Video 1.56 Leg and gait apraxia.

Video 1.57 Unilateral rigidity in corticobasal syndrome.

Video 1.58 Neuroleptic malignant syndrome (NMS).

Video 1.59 Serotonin syndrome.

Myoclonus

Myoclonic jerks are sudden, brief, shock-like involuntary movements caused by muscular contractions (positive myoclonus) or inhibitions (negative myoclonus) (see [Chapter 18](#)). The most common form of negative myoclonus is *asterixis*, which frequently accompanies various metabolic encephalopathies. In *asterixis*, the brief flapping of the outstretched limbs is due to transient inhibition of the muscles that maintain posture of those extremities (Video 1.117). Unilateral *asterixis* has been described with focal lesions of the contralateral medial frontal cortex, parietal cortex, internal capsule, and ventrolateral thalamus ([Obeso et al., 1995](#)). ▶

Myoclonus can appear when the affected body part is at rest or when it is performing a voluntary motor act, so-called action myoclonus (Video 1.118). Myoclonic jerks are usually irregular (arrhythmic) but can be rhythmic (such as in *palatal myoclonus* (Videos 1.119 and 1.120) or in *ocular myoclonus* (Video 1.121), with a rate of approximately 2 Hz). Palatal myoclonus is also known as palatal tremor. Rhythmic ocular myoclonus secondary to a lesion in the dentato-olivary pathway needs to be distinguished from arrhythmic and chaotic *opsoclonus* or dancing eyes (Video 1.122). Rhythmic myoclonus is typically due to a structural lesion of the brainstem or spinal cord (therefore, also called segmental myoclonus), but not all cases of segmental myoclonus are rhythmic and some types of cortical epilepsy partialis continua can be rhythmic (Video 1.2). Oscillatory myoclonus is depicted as rhythmic jerks that occur in a burst and then fade ([Fahn and Singh, 1981](#)). Spinal myoclonus, in addition to manifesting as segmental and rhythmic (Video 1.223), can also manifest as flexion axial jerks triggered by a distant stimulus that travels via a slow-conducting spinal pathway, a type that is called *propriospinal myoclonus* ([Brown et al., 1991c](#)). Many patients with the phenomenology of propriospinal myoclonus have been proposed to have a psychogenic etiology (Video 1.124) based on electrophysiologic findings that show that trained volunteers could mimic both the rhythmic jerks and the pattern and timing of polymyographic spread; in many patients a Bereitschaftspotential is seen ([Kang and Sohn, 2006](#); [Erro et al., 2013](#); [Esposito et al., 2014](#); [van der Salm et al., 2014](#)). Respiratory myoclonus can be variable and has been called diaphragmatic flutter and diaphragmatic tremor ([Espay et al., 2007](#)). ▶

Myoclonic jerks occurring in different body parts are often synchronized, a feature that may be specific for myoclonus. The jerks often can be triggered by sudden stimuli such as sound, light, visual threat, or movement (reflex myoclonus). Some types of myoclonus have a relationship to seizures in that both seem to be the result of hyperexcitable neurons.

Cortical reflex myoclonus usually manifests as a focal myoclonus and is triggered by active or passive muscle movements of the affected body part (see Video 1.39). It is associated with high-amplitude ("giant") somatosensory evoked potentials and with cortical spikes that are observed by computerized back averaging, time-locked to the stimulus ([Obeso et al., 1985](#)). An example of cortical myoclonus affecting the legs in a patient with celiac disease is seen in Video 1.2. Spread of cortical activity within the hemisphere and via the corpus callosum can produce generalized cortical myoclonus or multifocal cortical myoclonus ([Brown et al., 1991a](#)). Reticular reflex

myoclonus ([Hallett et al., 1977](#)) is more often generalized or spreads along the body away from the source in the brainstem in a timed-related sequential fashion. ▶

The fact that rhythmic myoclonus consists of synchronous contractions of agonist muscles rather than alternating agonist–antagonists contractions and the fact that those in one body part are time-relatedly synchronized with contractions elsewhere are strong arguments for categorizing rhythmic myoclonus as a myoclonic disorder and not a type of tremor. Furthermore, rhythmic myoclonias tend to persist during sleep, whereas tremors usually disappear during sleep.

Action or intention myoclonus is often encountered after cerebral hypoxia–ischemia (Lance–Adams syndrome) and with certain degenerative disorders such as progressive myoclonus epilepsy (Unverricht–Lundborg disease) and progressive myoclonic ataxia (Ramsay Hunt syndrome). The myoclonic ataxia syndromes are often associated with more easily controlled epilepsy; a more useful definition has been proposed ([van der Veen et al., 2018](#)). Usually action myoclonus is more disabling than is rest myoclonus. Negative myoclonus also occurs in the Lance–Adams syndrome, and when it occurs in the thigh muscles when the patient is standing, it manifests as bouncy legs (Video 1.125). In the *opsoclonus-myoclonus* syndrome, originally described by [Kinsbourne \(1962\)](#) and subsequently called both "dancing eyes, dancing feet" and "polymyoclonia" by [Dyken and Kolar \(1968\)](#), the amplitude of the myoclonus is usually very tiny, resembling irregular tremors. Because of the small amplitudes of the continuous, generalized myoclonus, it is preferable to use the term *minipolymyoclonus* (see Video 1.121), a term that was first used by [Spiro \(1970\)](#) to describe small-amplitude movements in childhood spinal muscular atrophy and subsequently used by Wilkins and colleagues (1985) for the type of myoclonus that is seen in primary generalized epileptic myoclonus. Opsoclonus-myoclonus is often associated with neuroblastomas in children and can represent a paraneoplastic disorder associated with other cancers in children and adults. It can be associated with acute postinfectious cerebellitis (see Video 1.121). It is rare to find opsoclonus outside the paraneoplastic and parainfectious etiologies. There has been a report of opsoclonus in an adult with sphenoid sinusitis ([Turner et al., 2018](#)). ▶

Myokymia and synkinesis

Myokymia is a fine persistent quivering or rippling of muscles (sometimes called live flesh by patients). The term has evolved since first used ([Schultze, 1895](#)), when it described benign fasciculations. Although some may still refer to the benign fasciculations that frequently occur in orbicularis oculi as *myokymia*, [Denny-Brown and Foley \(1948\)](#) distinguished between myokymia and benign fasciculations on the basis of EMG. In myokymia, the EMG reveals regular groups of motor unit discharges, especially doublets and triplets, occurring with a regular rhythmic discharge. Myokymia occurs most commonly in facial muscles. Most facial myokymias are due to pontine lesions, particularly multiple sclerosis ([Andermann et al., 1961](#); [Matthews, 1966](#)), and less often to pontine glioma. When caused by multiple sclerosis, facial myokymia tends to abate after weeks or months. When caused by a pontine glioma, facial myokymia may persist indefinitely and can be associated with facial contracture (Video 1.126). Myokymia is also a feature of neuromyotonia (see under "Stiff Muscles,"

Video 1.60 Isaacs syndrome (neuromyotonia).

Video 1.61 Subacute rigidity, rash, fever, and myoclonus.

Video 1.62 Stiff-person syndrome.

Video 1.63 Stiff-baby syndrome.

Video 1.64 Abdominal dyskinesias from spinal myoclonus.

Video 1.65 Abdominal dyskinesias as part of tardive dyskinesia.

Video 1.66 Akathitic movements.

Video 1.67 Akathitic movements and moaning associated with tardive dyskinesia.

earlier in this chapter). Myokymia can persist during sleep. Continuous facial myokymia in multiple sclerosis has been found by magnetic resonance imaging to be caused by a pontine tegmental lesion involving the postnuclear, postgenu portion of the facial nerve (Jacobs et al., 1994). An autosomal dominant form, in which choreic and dystonic movements are also present, has been described (Fernandez 2001b). It begins as a paroxysmal dyskinesia and then becomes continuous. The mutation was found in the gene for adenylyl cyclase 5 (Chen et al., 2012). ●

Aberrant reinnervation of the facial nerve after denervation, such as from Bell palsy, is manifested by *synkinesis*, which is the occurrence of involuntary movements in one part of the face accompanying voluntary contraction of another part. For example, moving the mouth in a smile may cause the eyelid to close or closing the eyelid may cause contraction of the ipsilateral lower facial muscles (Videos 1.127, 1.128). ●

For the sake of completeness, it is important to mention fasciculations, the small-amplitude contractions of muscles innervated by a motor unit (Video 1.129). This is seen predominantly with disease of the anterior horn cells and presents as low-amplitude intermittent twitching of muscles as a result of motor unit discharges, which are usually not strong enough to move a joint, although this can occur, particularly in children.

Myorhythmia

The term *myorhythmia* has been used in different ways over time. Herz (1931, 1944) used it to refer to the somewhat rhythmic movements that are sometimes seen in patients with torsion dystonia. Today, these are simply called dystonic movements and do not distinguish between the movements that are repetitive and those that are not. Dystonic myorhythmia should not be confused with dystonic tremor, which strongly resembles other tremors but is due to dystonia. Monrad-Krohn and Refsum (1958) used the term *myorhythmia* to label what is today called palatal myoclonus (also known as palatal tremor) or other rhythmic myoclonias. This meaning of the term *myorhythmia* also has been adopted by Masucci and colleagues (1984). *Myorhythmia* could be used to represent a somewhat slow frequency (<3 Hz) and a prolonged, rhythmic or repetitive movement in which the movement does not have the sharp square wave appearance of a myoclonic jerk. Therefore, it would not be applied to palatal myoclonus. Myorhythmia also would not apply to the sinusoidal cycles of most tremors (parkinsonian, essential, cerebellar) because the frequency of these tremors is faster than what is defined for myorhythmia.

The most typical disorder in which the term *myorhythmia* is applied is in Whipple disease, first applied to this disorder by van Bogaert and colleagues in 1963. Since then others used the term in Whipple disease to describe slow-moving, repetitive, synchronous, rhythmic contractions in ocular, facial, masticatory, and other muscles, so-called *oculofaciomasticatory myorhythmia* (Schwartz et al., 1986; Hausser; Hauw et al., 1988; Tison et al., 1992). Vertical supranuclear ophthalmoplegia also often occurs. Ocular myorhythmia manifests as continuous, horizontal, pendular, vergence oscillations of the eyes, usually of small amplitude, occurring about every second (Video 1.130). They may be asymmetric and may

continue in sleep. They never diverge beyond the primary position. Divergence and convergence are at the same speed. They are not accompanied by pupillary miosis. Thus the term *myorhythmia* is used in more than one way, that is, the slow ocular oscillations and both the slow and fast rhythmic slow contractions in the face, jaw, and skeletal muscles in Whipple disease. The fast movements seem to be better described as a rhythmic myoclonus (see Video 1.105). The abnormal movements of facial and masticatory muscles can also persist in sleep, as is seen with secondary palatal myoclonus. Bally and colleagues (2018) reviewed the abnormal movements, including myorhythmia in Whipple disease. ●

Sometimes the term *myorhythmia* may be applied to slow, undulating, rhythmic movements of muscles, unrelated to Whipple disease. Perhaps some of these types of movements are part of the spectrum of complex tics, whereas in others they may represent psychogenic movements. In this book, the myorhythmias are discussed in Chapter 10.

Paroxysmal dyskinesias

The paroxysmal dyskinesias represent various types of dyskinetic movements, particularly choreoathetosis and dystonia, that occur out of the blue and then disappear after being present for seconds, minutes, or hours (see Chapter 24). The patient can remain normal for months between attacks, or there can be many attacks per day. Paroxysmal attacks of ataxia or tremor also occur, and they have been called *episodic ataxias and tremors*. They are usually familial and may include vestibular signs and symptoms. The gene mutations causing the paroxysmal dyskinesias and episodic ataxias are discussed in Chapter 24, and Ero and Bhatia (2018) have reviewed these disorders.

Paroxysmal kinesigenic dyskinesia is the best described and easiest to diagnose because it is characteristically triggered by a sudden movement, and the abnormal movements last only seconds to a few minutes. Paroxysmal kinesigenic dyskinesia can be hereditary or symptomatic and usually is very successfully treated with anticonvulsants. The abnormal movements easily habituate; that is, they fail to recur if the sudden movement is immediately repeated. These movements can be dystonic, ballistic, and choreic (Videos 1.131, 1.132). Many brief paroxysmal bursts of movements may occur each day. ●

Paroxysmal nonkinesigenic dyskinesia can be hereditary or symptomatic; is triggered by stress, fatigue, caffeine, or alcohol; and can last minutes to hours (Video 1.133). It is more difficult to treat than the kinesigenic variety, but it sometimes responds to clonazepam or other benzodiazepines and sometimes to acetazolamide. Paroxysmal nonkinesigenic dyskinesia can be familial or sporadic. Sporadic paroxysmal nonkinesigenic dyskinesia in our experience is more often a psychogenic movement disorder (see Chapter 27), particularly if it is a combination of both paroxysmal and continual dystonias. *Paroxysmal exertional dyskinesia* can be due to glucose transporter 1 deficiency or be sporadic. The attacks of dyskinesias occur after sustained exercising and last about 30 minutes. There are other causes of exercise-induced dystonia such as a deficiency of the metabolic enzyme, enoyl-CoA hydratase short-chain 1, which is a mitochondrial enzyme involved in degrading amino acids and fatty acids (Olgiati et al., 2016b). ●

Video 1.68 Focal tardive akathisia and tardive dyskinesia affecting the legs.

Video 1.69 Suppression of akathitic movements by carrying out active voluntary movements.

Video 1.70 Dystonia at rest that disappears with action (paradoxical dystonia).

Video 1.71 Restlessness and increased tremulousness following a dose of levodopa in a person with PD.

Restless legs

The term *restless legs syndrome* (RLS) refers to more than just the phenomenon of restless legs, in which the patient has unpleasant crawling sensations in the legs, particularly when sitting and relaxing in the evening, which then disappear on walking (Ekblom, 1945; 1960). The complete syndrome consists of several parts, in which one or more may be present in any individual. Although the unpleasant dysesthesias in the legs are the most common symptom, as was mentioned previously in the discussion on nocturnal dyskinesias, the clinical spectrum may also include periodic movements in sleep (see Video 1.109), and myoclonic jerks, more sustained dystonic movements, or stereotypic movements that occur while the patient is awake, particularly in the late evening (Walters et al., 1991). Other movement disorders associated with a sensory phenomenon are akathisia (feeling of inner restlessness) and tics (feeling of tension or sensory urges that are relieved on producing a tic). A consensus statement on the criteria for RLS has been published (Allen et al., 2014). RLS is covered in Chapter 25. ●

Stereotypy

A *stereotypy* is a non-goal-directed movement or vocalization pattern that is repeated continually for a period of time in the same form and on multiple occasions and is typically distractible (Edwards et al., 2012). There may be long periods of minutes between movements, or the movements may be very frequent. When they occur at irregular intervals, stereotypies may not always be easily distinguished from motor tics, compulsions, gestures, and mannerisms. They can also appear as paroxysmal movements when a child is excited (Tan et al., 1997). In their classic monograph on tics, Meige and Feindel (1902) distinguished between stereotypies and motor tics by describing the latter as acts that are impelling but not impossible to resist, whereas the former, although illogical, are without an irresistible urge. Tics almost always occur intermittently and not continuously; that is, they occur paroxysmally out of a background of normal motor behavior. Although stereotypies also can be bursts of repetitive movements emerging out of a background of normal motor activity, they often repeat themselves in a uniform repetitive fashion for long periods (Lees, 1985). Stereotypies typically occur in patients with tardive dyskinesia (Video 1.134) and with schizophrenia, Intellectual disability (especially Rett syndrome) (Video 1.135), and autism (Videos 1.36 and 1.37), characteristics that assist in separating these from motor tics (Shapiro et al., 1988). Stereotypies apparently occur in Asperger syndrome, a form of mild autism. They have been seen in patients with the Klüver-Bucy syndrome (Video 1.138). They can also be seen in normal children left alone and when not in contact with other people (Video 1.139). ●

Although motor tics are often considered to be stereotypic, when a tic bursts out, it is not necessarily a repetition of the previous tic movement. Thus, tics are usually not repetitive from one burst to the next. However, the same type of tic movement will usually recur after some period of time passes, which provides their stereotypic nature. The diversity of motor tics is one feature that sets their phenomenology apart from that of stereotypies. Tics are rarely continuously

repetitive, and when this occurs, the term *tic status* can be applied. As is pointed out in the next section, tics have many other features that aid in their diagnosis, such as their suppressibility, their accompaniment by an underlying urge or compulsion to make the movement, their variability, their migration from one body part to another part, their abruptness, their brevity, and the repetitiveness, rather than randomness, of the particular body part affected by the movements (Fahn, 2005). Therefore, although tics have an element of stereotypy, this type of stereotypy, which can be considered paroxysmal, intermittent, or at most continual (meaning with interruptions), needs to be distinguished from continuous (uninterrupted) involuntary movements that repeat unceasingly. The latter type of continuous stereotypy is what distinguishes the disorders known as stereotypies and is the hallmark of abnormal movements in patients with classic tardive dyskinesia, which is called tardive stereotypy (Jankovic, 2005), the most common type of stereotypy seen in movement disorder clinics.

Compulsions are repetitive, purposeless, usually complex movements seen in patients with OCD. They are associated with an irresistible urge to make the movement. Patients realize that they are making the movements in response to this “need to do so.” In this respect, compulsions resemble tics and not stereotypies, which are not accompanied by any urge. In fact, some patients with Gilles de la Tourette syndrome also have OCD, and in this situation it might be impossible to distinguish between tics and compulsions (Jankovic, 2001). Like stereotypies, compulsions could be carried out in a uniform repetitive fashion for long periods but at the expense of all other activities because compulsions may be impossible to stop. In contrast, stereotypies usually can be stopped on command, and the patient will have normal motor behavior until they start up again, usually as soon as the patient is no longer paying attention to the command.

Gestures are culturally developed, expressive, voluntary movements that are calculated to indicate a particular state of mind and that also may be used as a means of adding emphasis to oratory (Lees, 1985). *Mannerisms* are sets of movements that include gestures plus more peculiar and individualistic movements that are not considered bothersome. Mannerisms can be considered to represent a type of motor signature that individualizes a person. Sometimes mannerisms can be bizarre, and these could be considered tics or on the borderline with tics. Because gestures and mannerisms rarely continually repeat themselves, they would not likely be confused with stereotypies, but there may be problems at times distinguishing them from tics.

From this description, stereotypies can be divided into two phenomenologically distinct groups. One type is that in which the stereotypy, though repetitive for prolonged periods, occurs intermittently, with normal motor activity being the general background. It is this type that can be difficult to distinguish from tics and compulsions. The second type is that in which the repetitive movements are virtually always there, with less time spent without them. The most common of this type of continuous stereotypy is that of classic *tardive dyskinesia* (TD). The movements that are seen in classic tardive dyskinesia are rhythmic and continuously repetitive complex chewing movements (oral-buccal-lingual dyskinesia) (see Video 1.134). Often, this tardive stereotypy will appear together in the same patient with different motor

Video 1.72 Cerebellar ataxia and asynergia.

Video 1.73 Athetoid cerebral palsy.

Video 1.74 Athetoid cerebral palsy.

Video 1.75 Athetosis of the tongue.

Video 1.76 Pseudoathetosis of fingers and toes.

Video 1.77 Hemiballism.

phenomena that make up the tardive dyskinesia syndromes (see [Chapter 17](#)), namely dystonia (tardive dystonia), and akathisia (tardive akathisia). All are secondary to exposure to dopamine receptor–blocking drugs. Another disorder with continuous stereotypies is the encephalitis related to NMDA receptor antibodies ([Dalmau et al., 2007](#); [Dale et al., 2009](#); [Zandi et al., 2009](#); [Ferlioli et al. 2010](#); [Irani et al., 2010](#)) in which a pattern of repetitive mouthing movements and limb movements occurs (Video 1.1). In this book, [Chapter 17](#) is devoted to stereotypies. ▶

Tics

Tics consist of abnormal movements (motor tics) or abnormal sounds (phonic tics). When both types of tics are present, the designation of *Gilles de la Tourette syndrome* or *Tourette syndrome* is commonly applied (see [Chapter 15](#)). Tics frequently vary in severity over time and can have remissions and exacerbations.

Motor and phonic tics can be simple or complex and occur abruptly for brief moments from a background of normal motor activity. Thus, they are paroxysmal in occurrence unless they are so severe as to be continual. A single simple motor tic may be impossible to distinguish from a myoclonic or choreic jerk; each of these would be an abrupt, sudden, isolated movement. Examples include a shoulder shrug, head jerk, blink, dart of the eyes, and twitch of the nose. Most of the time, such simple tics are repetitive, such as a run of eye blinking or a sequence of several simple tics in a row. In this more complex pattern, tics can be easily distinguished from the other hyperkinesias. Even when tics are simple jerks, more complex forms of tics also may be present in the same patient, allowing one to establish the diagnosis by “the company it keeps.” One type of simple tic, an ocular tic, is quite distinct (Video 1.140). A single ocular movement is not a feature of chorea or myoclonus but is common in tics ([Frankel and Cummings, 1984](#)). ▶

Complex motor tics are very distinct, consisting of coordinated patterns of sequential movements that can appear in different parts of the body (Video 1.141) and are not necessarily identical from occurrence to occurrence in the same body part. Examples of complex tics include such acts as touching other people, head shaking with shoulder shrugging, kicking of legs, and jumping. Obscene gesturing (copropraxia) is another example. Complex tics can produce bizarre combinations of paroxysmal repetitive motor and phonic behaviors (Video 1.142), including spitting (Video 1.143) and knee-cap tics (Video 1.144). ▶

Like akathitic movements, tics are usually preceded by an uncomfortable feeling or sensory urge that is relieved by carrying out the movement, like “scratching an itch.” Thus, the movements and sounds can be considered “unvoluntary.” Unless very severe, tics can be voluntarily suppressed for various periods of time. But when they are suppressed, inner tension builds up and is relieved only by an increased burst of more tics (Video 1.145). ▶

Motor tics can vary in speed, from being as rapid as myoclonic jerks to being slow and sustained contractions, resembling dystonic movements (Video 1.146). The complex sequential pattern of muscular contractions in dystonic tics makes the diagnosis obvious in most cases. Moreover,

torsion dystonia is a continual hyperkinesia, whereas tics are paroxysmal bursts of varying duration. When a motor tic remains in one focal area of the body and develops with specific movements, the differential diagnosis of a task-specific dystonia has to be considered. ▶

Involuntary ocular movements can be an important feature for differentiation of tics from other dyskinesias. Whether a brief jerk of the eyes or more sustained eye deviation, ocular movements can occur as a manifestation of tics (see Video 1.140). Very few other dyskinesias involve ocular movements (see [Table 1.18](#)). The exceptions are opsoclonus (dancing eyes) (see Video 1.122), which is a form of myoclonus; ocular myoclonus (rhythmic vertical oscillations at a rate of 2 Hz) (see Video 1.121) that often accompanies palatal myoclonus; ocular myorhythmia, a slow horizontal oscillation (see Video 1.130); and oculogyric crisis (a sustained deviation of the eyes [see Videos 1.34 and 1.36 thus a dystonia) associated with dopamine receptor–blocking drugs or as a consequence of encephalitis lethargica or other parkinsonian disorders such as neuronal intranuclear hyaline inclusion disease and aromatic amino acid decarboxylase deficiency. See the discussion of oculogyric crises under “Dystonia,” earlier in this chapter. ▶

Phonic tics can range from simple throat-clearing sounds or grunts to complex verbalizations and the utterance of obscenities (coprolalia). Sniffing can be a phonic tic, involving nasal passages rather than the vocal apparatus. Like motor tics, phonic tics can be divided into simple and complex. Throat-clearing and sniffing represent simple phonic tics, whereas verbalizations are considered complex phonic tics. Shouting/screaming phonic tics can be very distressful (Video 1.147) and not just to the person with the tics, but all the people listening to them. Groaning tics (Video 1.148) are not as serious. Treatment with botulinum toxin into the vocal cords may be helpful ([Scott et al., 1996](#)). ▶

Involuntary phonations occur in only a few other neurologic disorders besides tics (see [Table 1.18](#)). These include the moaning in akathisia and in parkinsonism; the brief sounds in oromandibular dystonia and HD; and the sniffing, spitting, groaning, or singing that is occasionally encountered in HD and neuroacanthocytosis.

In severe situations, tics can persist with one tic after another without much of a pause between them. This situation, known as tic status (Video 1.149, 1.150), becomes an urgent problem requiring strong efforts of treatment. Although most cases of tics are idiopathic without a known cause or familial, there are cases of secondary tics from brain insults; cocaine use is not an uncommon cause of secondary tics (Video 1.151). Psychogenic tics are very uncommon but can occur (Video 1.152) (see [Chapter 27](#)).

Tremor

Tremor is an oscillatory, typically rhythmic and regular, movement that affects one or more body parts, such as the limbs, neck, tongue, chin, or vocal cords. Jerky, irregular “tremor” is usually a manifestation of myoclonus or dystonia. Tremor is produced by rhythmic alternating or simultaneous contractions of agonists and antagonist muscles. The rate, location, amplitude, and constancy vary depending on the specific type of tremor and its severity. It is helpful to determine whether the tremor is present at rest (with the patient sitting or lying in repose) (Video 1.53), with posture-holding (with the arms or legs extended in front of

Video 1.78 Hemiballism from an ipsilateral lesion.
Video 1.79 Huntington disease.

Video 1.80 Sydenham disease.

the body) (Video 1.154), with action (such as writing or pouring water) (see Video 1.154), or with intention maneuvers (such as bringing the finger to touch the nose) (Video 1.155). Tremors can, thus, be classified as tremor-at-rest, postural tremor, action tremor, or intention tremor, respectively. Some tremors may be present only during a specific task (such as writing) or with a specific posture, such as standing as in orthostatic tremor (Video 1.156). These are called task-specific and position-specific tremors, respectively, and may overlap with task-specific and position-specific action dystonias, which may also appear as tremors (dystonic tremor) (Video 1.157). ●

The MDS Task Force on Tremor developed a classification scheme for tremor (Bhatia et al., 2018). Tremor is classified along two axes: axis 1 contains the clinical characteristics, including historical features (age at onset, family history, and temporal evolution), tremor characteristics (body distribution, activation condition), associated signs (systemic, neurologic), and laboratory tests (electrophysiology, imaging); axis 2 lists the etiology as acquired, genetic, or idiopathic. The new tremor classification has been utilized to segregate genetic causes of tremor into isolated and combined forms (Magrinelli et al., 2020). There has been some criticism of the new MDS classification scheme of dividing essential tremor (ET) into pure ET and ET Plus (Louis et al., 2020).

Relating to phenomenology, the most common cause of a rest tremor is parkinsonism, particularly PD. The most common cause of postural and action tremor is the condition known as essential tremor (heavily discussed in the consensus statement mentioned earlier). The most common cause of intention tremor is a lesion in the cerebellar outflow pathway. A combination of rest tremor and a worse action and intention tremor is often a manifestation of a lesion in the midbrain (Video 1.158), commonly mislabeled as “rubral” tremor, but is more appropriately called midbrain tremor or Holmes tremor because of involvement of both the nigrostriatal and dentato-rubro-thalamic pathways. It is important to realize that any tremor, especially wing beating and other unusual tremors, can be a manifestation of Wilson disease (see Chapter 22) (Videos 1.159, 1.160). ●

The clinical approach to differentiate the dyskinesias

The process by which one distinguishes one type of dyskinesia from the others is by characterizing the type of abnormal movements that are present and then determining which dyskinesia definition most appropriately encompasses the overall picture and, at the same time, eliminating the dyskinesias that fail to fit. One performs this process in a hierarchic manner, first considering the immediately obvious clinical features (Level A) and proceeding to the next two lower levels in order, each taking longer periods of observation (Table 1.10).

Level A has four equal factors, and each has its own table dividing movement disorders into those that fit these factors: rhythmicity (Table 1.11), duration of the contractions (Table 1.12), continuity of the contractions (Table 1.13), and their appearance with sleep or when awake (Table 1.14). The second level (Level B), taking a slightly longer period of

observation, has three factors. The first is evaluating whether the movements occur when the affected body part is at rest, in a voluntary action, or both (Table 1.15). This table lists those movement disorders that are present when the affected body part is at rest and disappear with action, appear only with action, or are present both at rest and continue with action. By “action,” we refer to the presence of the movements when the affected body part is performing a voluntary movement. In the action category are task-specific and posture-specific dyskinesias. Table 1.16 considers whether the movements keep involving the same set of muscles recurring in a repetitive manner (patterned) rather than randomly to involve different muscle groups. Table 1.17 lists disorders in which there are commonly combinations of various dyskinesias,

The third level (Level C), taking still longer periods of observation, evaluates many factors: speed, amplitude, force, suppressibility, presence of vocalizations, presence of self-mutilation, complexity of the movements, and whether there are associated sensory symptoms (Table 1.18).

Tables 1.10 to 1.18 are intended to assist the clinician in studying phenomenology and establishing the correct label for the dyskinesia or syndrome. Once this has been accomplished, it is then the clinician’s task to determine the etiology that has produced this dyskinesia. The chapters describing the details of each motor phenomenology also describe our approach for evaluating patients to determine the etiologies and treatments.

Conclusions

Working definitions and clinical characteristics of the movement disorders have been presented. Electrophysiologic recordings are adding to our definitions, but they must be compatible with the clinical definitions that have been in use for decades. There are eight predominant movement disorders: (1) akinesia/bradykinesia; (2) rhythmic tremor and other rhythmic movements; (3) the sustained contractions of dystonia/athetosis; (4) three types of usually fast movements—myoclonus, chorea/ballism, and tics; (5) stereotypies/compulsions; (6) paroxysmal dyskinesias; (7) ataxia/asynnergia; and (8) hypnogenic dyskinesias. The others are less common. The pathophysiology of movement disorders is beginning to be understood. Many appear to involve the dopamine system and the basal ganglia, such as too little dopaminergic activity (parkinsonian rigidity and bradykinesia) or too much (chorea, ballism, and tardive dyskinesia). It is hoped that much more knowledge will be gained to provide a better understanding of these disorders, but the first task of the clinician is to recognize the characteristics of the movement disorder to decide on the clinical syndrome that the patient presents. The next task is to unravel the etiologic diagnosis to provide information on genetics, prognosis, and treatment.

References available on Expert Consult:
www.expertconsult.com.

Video 1.81 Sydenham chorea.

Video 1.82 Nonketotic hyperglycemic chorea.

Video 1.83 Chorea in systemic lupus erythematosus (SLE).

Video 1.84 Levodopa-induced choreic dyskinesias.

Video 1.85 Levodopa-induced “disco-nesias”.

Video 1.86 Levodopa-induced dyskinesias controlled by a pallidotomy.

Video 1.87 Blepharospasm.

Video 1.88 Cranial segmental dystonia (Meige syndrome).

Video 1.89 Spasmodic dysphonia (dystonic adductor dysphonia).

Video 1.90 Jerky torticollis (cervical dystonia).

Video 1.91 Writer’s cramp (arm and hand dystonia).

Video 1.92 Truncal dystonia.

Video 1.93 Segmental axial.

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Motor control: Physiology of voluntary and involuntary movements

Chapter contents

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Movement, whether voluntary or involuntary, is produced by the contraction of muscle. Muscle, in turn, is normally controlled entirely by the anterior horn cells or alpha motoneurons. An anterior horn cell with its innervated muscle fibers is called the motor unit. Some involuntary movement disorders arise from muscle, the alpha motoneuron axon, or the alpha motoneuron itself. Although this territory might be considered neuromuscular disease, the border to movement disorders can be fuzzy and patients may present to the office of the movement disorder specialist for diagnosis and management. Examples of involuntary movement arising from neuromuscular disorders that will be discussed in subsequent chapters are listed in [Table 2.1](#).

As the sole controller of muscle, the alpha motoneuron is clearly important in understanding the genesis of movement. The influences on the alpha motoneuron are many and complex but have been extensively studied. Here only the basics will be reviewed ([Hallett, 2003b](#); [Pierrot-Deseilligny and Burke, 2012](#)). Inputs onto the alpha motoneuron can be divided into the segmental inputs and the supraspinal inputs.

Segmental inputs onto the alpha motoneuron

Fig. 2.1 depicts some of the reflex connections onto the alpha motoneuron.

Renshaw cell. The alpha motoneuron axon has a recurrent collateral in the spinal cord that synapses onto the Renshaw cell. Similar to the neuromuscular junction, the neurotransmitter onto the Renshaw cell is acetylcholine. The Renshaw cell then directly inhibits the alpha motoneuron using glycine as the neurotransmitter. This is termed recurrent

inhibition. It provides inhibitory feedback to the pool of alpha motoneurons to prevent excessive output.

Ia afferent. The Ia afferent comes from the muscle spindle and provides a sensitive measure of muscle stretch. It synapses monosynaptically with excitation onto the alpha motoneuron using glutamate as the neurotransmitter and is the substrate of the tendon reflex. Electrical stimulation of the Ia afferents proximal to the muscle spindle produces the H reflex.

Ib afferent. The Ib afferent comes from the Golgi tendon organ and responds to tension of the muscle tendon. It excites the Ib inhibitory interneuron, which in turn inhibits the alpha motoneuron in a disynaptic chain.

Ia afferent from an antagonist muscle. Ia afferents from antagonist muscles excite interneurons in the spinal cord called the Ia inhibitory interneurons. This interneuron provides direct inhibition of the alpha motoneuron disynaptically. Glycine is the neurotransmitter. This is called reciprocal inhibition.

Flexor reflex afferents. Fibers, largely small myelinated and unmyelinated, carrying nociceptive information provide polysynaptic excitation onto the alpha motoneuron. These are the substrate for the flexor reflex.

Presynaptic inhibition. The inhibitory influences described so far are direct on the alpha motoneuron and are largely mediated by the neurotransmitter glycine. Some inhibitory influences, however, are presynaptic on excitatory synapses, such as the Ia afferent synapse. Presynaptic inhibition is commonly mediated by gamma-aminobutyric acid (GABA). Some presynaptic inhibition of the Ia afferent synapse is produced by oligosynaptic input from the antagonist Ia afferent. This effect will cause a “second phase” of reciprocal inhibition slightly later than the disynaptic reciprocal inhibition described earlier.

All of these mechanisms can be studied in humans, although often limited to only certain muscles (Pierrot-Deseilligny and Burke, 2012). Such studies have illuminated the pathophysiology of both segmental and suprasegmental movement disorders. The reason that suprasegmental movement disorders can be evaluated with these tests is that supraspinal influences can affect segmental function.

Examples of movement disorders arising from segmental dysfunction that will be discussed in subsequent chapters are listed in Table 2.2.

Supraspinal control of the alpha motoneuron

The main supraspinal control comes from the corticospinal tract. Approximately 30% of the corticospinal tract arises

from the primary motor cortex, and other significant contributions come from the premotor and sensory cortices. The fibers largely cross in the pyramid, but some remain uncrossed. Some terminate as monosynaptic projections onto alpha motoneurons, and others terminate on interneurons, including those in the dorsal horn. Other cortical neurons project to the basal ganglia, cerebellum, and brainstem, and these structures can also originate spinal projections. Particularly important is the reticular formation that originates several reticulospinal tracts with different functions (Nathan et al., 1996; Baker, 2011; Takakusaki et al., 2011, 2016). The nucleus reticularis gigantocellularis mediates some long-loop reflexes and is hyperactive in a form of myoclonus. The nucleus reticularis pontis caudalis mediates the startle reflex. The inhibitory dorsal reticulospinal tract may have particular

Table 2.1 Examples of involuntary movements arising from neuromuscular conditions

Muscle

Rippling muscle disease

Alpha motoneuron axon

Hemifacial spasm
Peripheral myoclonus
Fasciculation
Neuromyotonia

Anterior horn cell

Fasciculation
Spinal alpha rigidity

Table 2.2 Examples of movement disorders arising from segmental dysfunction

Disorder	Mechanism
Tetanus	Tetanus toxin blocks the release of GABA and glycine at spinal synapses
Stiff-person syndrome	Mainly a disorder of GABA and presynaptic inhibition in the spinal cord
Hereditary hyperekplexia	A disorder of glycine receptors with deficient inhibition at multiple synapses, including that from the Ia inhibitory interneuron

GABA, Gamma-aminobutyric acid.

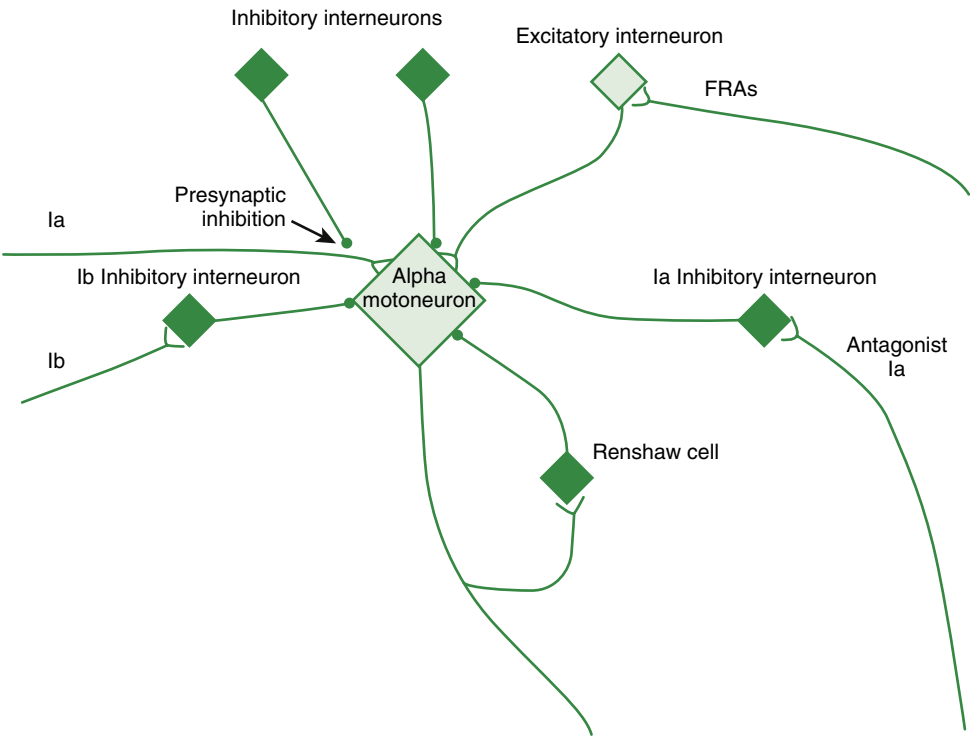


Fig. 2.1 Diagram of reflex connections onto the alpha motoneuron. Inhibitory neurons are dark green and excitatory neurons light green. Excitatory synapses are Y-shaped; inhibitory synapses are balls. FRAs, Flexor reflex afferents.

relevance for spasticity (Takakusaki et al., 2001; Li, 2017). In conceptualizing the cortical innervation of the reticular formation, it is possible to use the term corticoreticulospinal tract. The rubrospinal tract, originating in the magnocellular division of the red nucleus, although important in lower primates, is absent in humans because the magnocellular red nucleus has almost completely disappeared.

Both the basal ganglia circuitry and cerebellar circuitry can be considered as subcortical loops that largely receive information from the cortex and return a majority of the output back to the cortex via the thalamus (Fig. 2.2). As a generality the basal ganglia support movement by facilitating what movements to make, and what not to make, whereas the cerebellum contributes to the timing of movement. Both also have smaller directly descending projections. Although both loops use the thalamus, the relay nuclei are separate, and the loops had been considered to be largely separate. Subsequent data, however, show that the cerebellum and basal ganglia do communicate subcortically (Fig. 2.3) (Bostan and Strick, 2010; Bostan et al., 2010; Bostan and Strick, 2018; Bostan et al., 2018). The function of these connections is not yet clear, but they do indicate some coordination between these important subcortical loops.

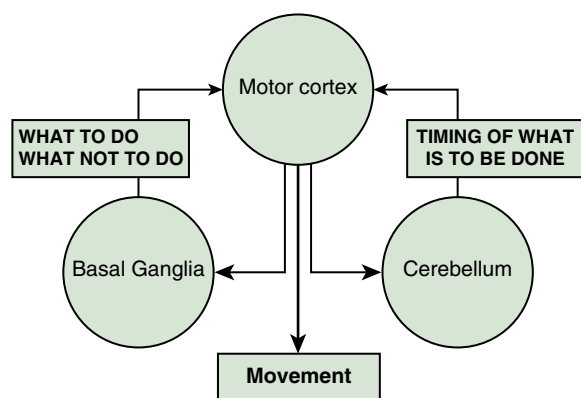


Fig. 2.2 The general anatomic pattern for the basal ganglia and cerebellar loops. Both structures receive input from the cortex and feedback via the thalamus. The basal ganglia facilitate movement selection, and the cerebellum aids movement timing.

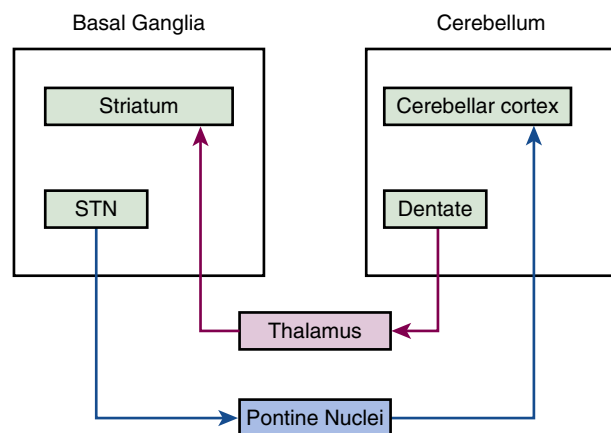


Fig. 2.3 Interconnections between cerebellum and basal ganglia. Output from the dentate goes via the thalamus to the striatum. Output from the subthalamic nucleus (STN) goes via the pons to the cerebellar cortex.

The basal ganglia

The basal ganglia are of critical importance to many movement disorders, and details of their anatomy are presented in Chapter 3.

The basal ganglia loop anatomy is complex with many connections, but an old simple model is still popular and does have some heuristic value (Bar-Gad et al., 2003; Wichmann and DeLong, 2003a, 2003b; DeLong and Wichmann, 2007) (Fig. 2.4A). In this model there are two pathways that go from the cortex and then back to the cortex. The direct pathway is the putamen, internal division of the globus pallidus (GPi), and thalamus (mainly the Vop nucleus). The indirect pathway is the putamen, external division of the globus pallidus (GPe), subthalamic nucleus (STN), GPi, and thalamus. The substantia nigra pars compacta (SNc) is the source of the important nigrostriatal dopamine pathway and appears to modulate the loop, although not being in the loop itself. The substantia nigra pars reticulata (SNr) has connections similar to those of the GPi, and its function is also similar. The putamen neurons of the direct pathway have dopamine D2 receptors and are facilitated by dopamine, whereas the putamen neurons of the indirect pathway have dopamine D1 receptors and are inhibited.

Fig. 2.4B shows a more complete diagram indicating more connections and some of the complexity. An important addition is the hyperdirect pathway directly from the cortex to the STN. There are also more reciprocal connections and much more connectivity of the GPe (Pamukcu et al., 2020). What is not in this diagram are some additional small nuclei such as the pedunculopontine nucleus (PPN), an elongated nucleus in the lateral mesencephalon and pons (Benarroch, 2013; Vitale et al., 2018; Garcia-Rill et al., 2019), and more will be said of it in Chapter 3. This nucleus receives output from the STN and GPi and may be important in balance, gait, and sleep regulation.

What do the basal ganglia contribute to movement? There are likely many contributions, to be considered in Chapter 3, but the topic remains somewhat controversial.

The basal ganglia are anatomically organized to work in a center-surround mechanism. This idea of center-surround organization was one of the possible functions of the basal ganglia circuitry suggested by Alexander and Crutcher (1990). This was followed up nicely by Mink (1996, 2003, 2006), who detailed the possible anatomy (Fig. 2.5). The direct pathway has a focused inhibition in the globus pallidus, whereas the STN has divergent excitation. The direct pathway (with two inhibitory synapses) is a net excitatory pathway and the indirect pathway (with three inhibitory synapses) and hyperdirect pathway (with one inhibitory synapse) are net inhibitory pathways. Hence, the direct pathway can be the center and the indirect and hyperdirect pathways the surround of a center-surround mechanism. Such a mechanism should make a movement more selective, similar to how a center-surround mechanism sharpens boundaries in sensory processing (Beck and Hallett, 2011).

Whether or not the basal ganglia work in a center-surround fashion, there is evidence that the direct pathway does indeed facilitate movement and the indirect pathway inhibits movement. DA excites the direct pathway striatal neurons via the D1 receptors and should facilitate movement, whereas DA inhibits the indirect pathway striatal neurons mediated by the D2 receptors and should reduce movement. D1 and D2 receptors have

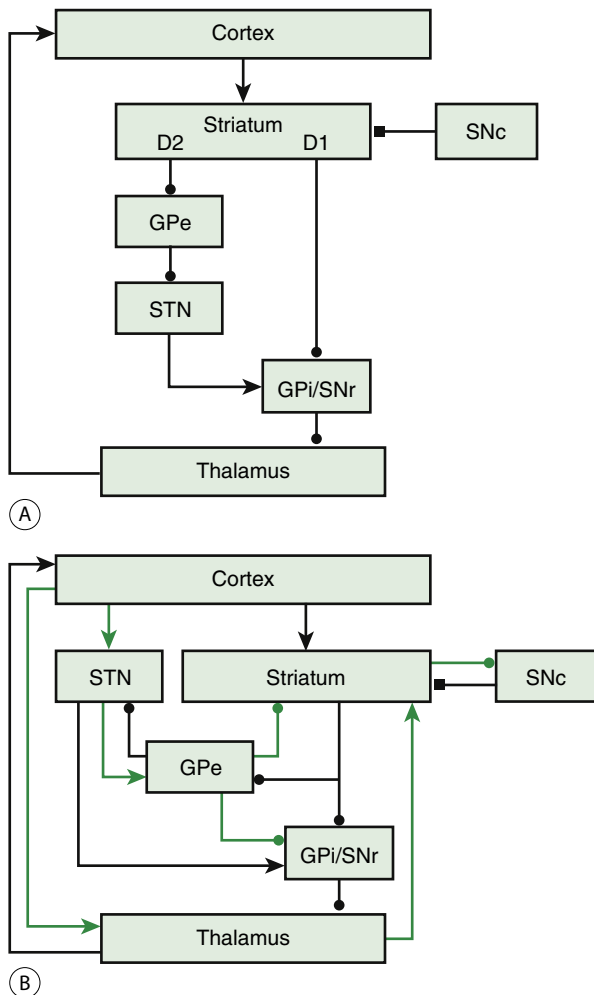


Fig. 2.4 The corticobasal ganglia network. The box and arrow network of the different pathways of the basal ganglia. (A) The early network model based on the work of Albin, DeLong, and Crossman. (B) A more advanced network. Note that what is missing from these diagrams is that the dopaminergic influence is excitatory on the D1 receptors of the direct pathway and inhibitory on the D2 receptors of the indirect pathway. The early model network is in black, and later additions are in green. Glutamatergic synapses are denoted by arrows, GABAergic synapses by circles, and dopaminergic synapses by squares. GPe, Division of the globus pallidus; GPi, internal division of the globus pallidus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus. (From Bar-Gad I, Morris G, Bergman H. Information processing, dimensionality reduction and reinforcement learning in the basal ganglia. *Prog Neurobiol.* 2003;71[6]:439–473, with permission.)

been activated separately using optogenetic techniques in the mouse and have produced the expected effects on spontaneous movements in the cage (Kravitz et al., 2010). Again, using optogenetic methods, stimulating projection neurons of the direct pathway generally produce opposite effects in the motor cortex to stimulating projection neurons of the indirect pathway (Oldenburg and Sabatini, 2015; Bakhurin et al., 2020).

Basal ganglia disorders are characterized by a wide variety of movement signs and symptoms. Often they are divided into hypokinetic and hyperkinetic varieties, implying too little movement on the one hand and too much movement on the other. A full listing of these disorders is in Chapter 1. Here, the pathophysiology of Parkinson disease (PD) and dystonia will be emphasized. We try to explain the abnormalities with reference to the known circuitry, but this is not always easy to do (Hallett and Obeso, 2015).

Parkinson disease

PD is classically characterized by bradykinesia, rigidity, and tremor-at-rest. Bradykinesia and rigidity seem mainly to result from the degeneration of the nigrostriatal pathway, whereas tremor is only partly the result of this and has other influences that are not well understood. Because of the multiplicity of degenerations, it has not been possible to find a single underlying pathophysiologic mechanism that explains everything. Nevertheless, considerable data are available that give separate understanding to each of the three classic features (Hallett, 2003a; Rodriguez-Oroz et al., 2009; Hess and Hallett, 2017; Obeso et al., 2017).

Bradykinesia

The most important functional disturbance in patients with PD is a disorder of voluntary movement prominently characterized by slowness. This phenomenon is generally called bradykinesia, although it has at least two components, which can be designated as bradykinesia and akinesia (Berardelli et al., 2001; Hallett, 2011; Hess and Hallett, 2017; Bologna et al., 2020). Bradykinesia refers to ongoing slowness of movement. Akinesia refers to failure of willed movement to occur. There are two possible reasons for the absence of expected movement. One is that the movement is so slow (and small) that it cannot be seen. A second is that the time needed to initiate the movement becomes excessively long.

Although self-paced movements can give information about bradykinesia, the study of reaction time movements can yield information about both akinesia and bradykinesia. In the reaction time situation, a stimulus is presented to a subject, and the subject must make a movement as rapidly as possible. The time between the stimulus and the start of movement is the *reaction time*; the time from initiation to completion of movement is the *movement time*. Using this logic, prolongation of reaction time is akinesia, and prolongation of movement time is bradykinesia. Studies of patients with PD confirm that both reaction time and movement time are prolonged. However, the extent of abnormality of one does not necessarily correlate with the extent of abnormality of the other (Evarts et al., 1981). This suggests that they may be impaired by separable physiologic mechanisms. In general, prolongation of movement time (bradykinesia) is better correlated with the clinical impression of slowness than is prolongation of reaction time (akinesia).

Some contributing features of bradykinesia are established. One is that there is a failure to energize muscles up to the level necessary to complete a movement in a standard amount of time. This has been demonstrated clearly with attempted rapid, monophasic movements at a single joint (Hallett and Khoshbin, 1980). In this circumstance, movements of different angular distances are accomplished in approximately the same time by making longer movements faster. The electromyographic (EMG) activity underlying the movement begins with a burst of activity in the agonist muscle of 50 to 100 ms, followed by a burst of activity in the antagonist muscle of 50 to 100 ms, followed variably by a third burst of activity in the agonist. This “triphasic” pattern has relatively fixed timing with movements of different distance, correlating with the fact of similar total time for movements of different distance. Different distances are

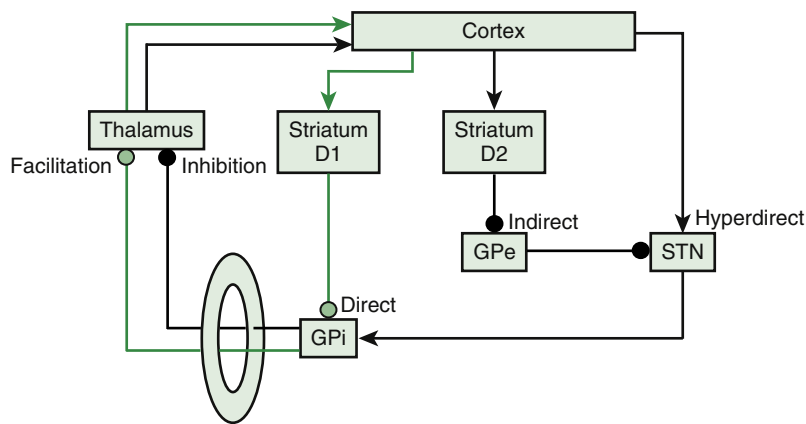


Fig. 2.5 The figure illustrates how the organization of the basal ganglia can support a center-surround mechanism of motor control. Excitatory synaptic connections are arrows, and inhibitory synaptic connections are circles. The “center” loop (green), including the direct pathway, facilitates movement. Note that in the entire loop, there are two inhibitory neurons, so the net action is facilitation. The “surround” loop (black), including both the indirect and hyperdirect pathways, inhibits movement. The indirect pathway has three inhibitory neurons, and the hyperdirect pathway has one inhibitory neuron, so the net action of both is inhibition. The center loop works by reducing inhibitory influence on the thalamus; the surround loop works by increasing inhibitory influence on the thalamus. GPe, Division of the globus pallidus; GPi, internal division of the globus pallidus; STN, subthalamic nucleus.

accomplished by altering the magnitude of the EMG within the fixed duration burst. The pattern is correct in PD patients, but there is insufficient EMG activity in the burst to accomplish the movement. These patients often must go through two or more cycles of the triphasic pattern to accomplish the movement. Interestingly, such activity looks virtually identical to the tremor-at-rest seen in these patients. The longer the desired movement, the more likely it is to require additional cycles. These findings have been reproduced, including by Baroni and colleagues (Baroni et al., 1984), who also showed that levodopa normalized the pattern and reduced the number of bursts.

Berardelli and colleagues (1986) showed that PD patients could vary the size and duration of the first agonist EMG burst with movement size and added load in the normal way. However, there was a failure to match these parameters appropriately to the size of movement required. This suggests an additional problem in scaling of actual movement to the required movement. A problem in sensory scaling of kinesthesia was demonstrated by Demirci and colleagues (1997). PD patients used kinesthetic perception to estimate the amplitude of passive angular displacements of the index finger about the metacarpophalangeal joint and to scale them as a percentage of a reference stimulus. The reference stimulus was either a standard kinesthetic stimulus preceding each test stimulus (task K) or a visual representation of the standard kinesthetic stimulus (task V). The PD patients' underestimation of the amplitudes of finger perturbations was significantly greater in task V than in task K. Thus, when kinesthesia is used to match a visual target, distances are perceived to be shorter by the PD patients. Assuming that visual perception is normal, kinesthesia must be “reduced” in PD patients. This reduced kinesthesia, when combined with the well-known reduced motor output and probably reduced corollary discharges, implies that the sensorimotor apparatus is “set” smaller in PD patients than in normal subjects.

In a slower, multijoint movement task, PD patients show a reduced rate of rise of muscle activity that also implies deficient activation (Godaux et al., 1992). On the other hand, Jordan and colleagues (1992) showed that release of force was just as slowed as increase of force, suggesting that slowness to change and not deficient energization was the main problem. If termination of activity is an active process, this finding really does not argue against deficient energization.

A second physiologic mechanism of bradykinesia is that there is difficulty with simultaneous and sequential

movements (Benecke et al., 1987). That PD patients have more difficulty with simultaneous movements than with isolated movements was first pointed out by Schwab and colleagues (1954). Quantitative studies show that slowness in accomplishing simultaneous or sequential movements is more than would be predicted from the slowness of each individual movement. With sequential movements, there is another parameter of interest, the time between the two movements designated the interonset latency (IOL) by Benecke and colleagues (Benecke et al., 1987). The IOL is also prolonged in patients with PD. This problem, similar to the problem with simple movements, also can be interpreted as insufficient motor energy.

Akinesia would seem to be multifactorial, and a number of contributing factors are already known. As noted earlier, one type of akinesia is the limit of bradykinesia from the point of view of energizing muscles. If the muscle is selected but not energized, then there will be no movement. Such phenomena can be recognized on some occasions with EMG studies in which EMG activity will be initiated but will be insufficient to move the body part. Another type of akinesia, again as noted previously, is prolongation of reaction time; the patient is preparing to move, but the movement has not yet occurred. Considerable attention has been paid to mechanisms of prolongation of reaction time. One factor is easily demonstrable in patients with rest tremor, who appear to have to wait to initiate the movement together with a beat of tremor in the agonist muscle of the willed movement (Hallett et al., 1977; Staude et al., 1995).

Another mechanism of prolongation of reaction time can be seen in those circumstances in which eye movement must be coordinated with limb movement (Warabi et al., 1988). In this situation, there is a visual target that moves into the periphery of the visual field. Normally, there is a coordinated movement of eyes and limb, the eyes beginning slightly earlier. In PD, some patients do not begin to move the limb until the eye movement is completed. This might be due to a problem with simultaneous movements, as noted earlier. Alternatively, it might be that PD patients need to foveate a target before they are able to move to it.

Many studies have evaluated reaction time quantitatively with neuropsychological methods (Hallett, 1990; Arroyo et al., 2021). The goal of these studies is to determine the abnormalities in the motor processes that must occur before a movement can be initiated. To understand reaction time studies, it is useful to consider from a theoretical point of view the tasks that the brain must accomplish. The starting

point is the “set” for the movement. This includes the environmental conditions, initial positions of body parts, understanding the nature of the experiment, and, in particular, some understanding of the expected movement. In some circumstances, the expected movement is described completely, without ambiguity. This is the “simple reaction time” condition. The movement can be fully planned. It then needs to be held in store until the stimulus comes to initiate the execution of the movement. In other circumstances, the set does not include a complete description of the required movement. It is intended that the description be completed at the time of the stimulus that calls for the movement initiation. This is the “choice reaction time” condition. In this circumstance, the programming of the movement occurs between the stimulus and the response. Choice reaction time is always longer than simple reaction, and the time difference is due to this movement programming.

In most studies, simple reaction time is significantly prolonged in patients compared with normal subjects (Hallett, 1990). On the other hand, patients appear to have near-normal choice reaction times or the increase of choice reaction time over simple reaction time is similar in patients and normal subjects. The study of choice reaction times was extended by considering three different choice reaction time tasks that required the same simple movement but differed in the difficulty of the decision of which movement to make (Brown et al., 1993). Comparing PD patients to normal subjects, the patients had a longer reaction time in all three conditions, but the difference was largest when the task was the easiest and smallest when the task was the most difficult. Thus, the greater the proportion of time there is in the reaction time devoted to motor program selection, the closer to normal are the PD results. Assuming that the motor programming and motor execution proceed in parallel, the difficulty must be in execution. This result is also compatible with the result from some studies that patients do not have much slowness of thinking, called bradyphrenia (Arroyo et al., 2021). However, careful studies have shown that even nondemented PD patients may have some bradyphrenia (Sawamoto et al., 2007; Hanakawa et al., 2017).

Transcranial magnetic stimulation (TMS) can be used to study the initiation of execution. With low levels of TMS, it is possible to find a level that will not produce any motor evoked potentials (MEPs) at rest but will produce an MEP when there is voluntary activation. Using such a stimulus in a reaction time situation between the stimulus to move and the response, Starr and associates (1988) showed that stimulation close to movement onset would produce a response even though there was still no voluntary EMG activity. A small response first appeared about 80 ms before EMG onset and grew in magnitude closer to onset. This method divides the reaction time into two periods. In the first period, the motor cortex remains “unexcitable”; in the second, the cortex becomes increasingly “excitable” as it prepares to trigger the movement. Most of the prolongation of the reaction time appeared because of prolongation of the later period of rising excitability (Pascual-Leone et al., 1994; Chen et al., 2001). The finding of prolonged initiation time in PD patients is supported by studies of motor cortex neuronal activity in reaction time movements in monkeys rendered parkinsonian with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Watts and Mandir, 1992). In these

investigations, there was a prolonged time between initial activation of motor cortex neurons and movement onset.

Thus, an important component of akinesia is the difficulty in initiating a planned movement. This statement would not be a surprise to PD patients, who often say that they know what they want to do, but they just cannot do it. A major problem in bradykinesia is a deficiency in activation of muscles, whereas the problem in akinesia seems to be a deficiency in activation of motor cortex. The dopaminergic system apparently provides energy to many different motor tasks, and the deficiency of this system in PD leads to both bradykinesia and akinesia.

Another factor that should be kept in mind is that patients appear to have much more difficulty initiating internally triggered movements than externally triggered movements. This is clear clinically in that external cues are often helpful in movement initiation. Examples include improving walking by providing an object to step over or playing march music. This also can be demonstrated in the laboratory with a variety of paradigms (Georgiou et al., 1993; Curra et al., 1997; Majsak et al., 1998; Hallett, 2008).

There are other interesting features of bradykinesia. The sequence effect is the gradual reduction in size of repetitive movements (Bologna et al., 2020). An example is in handwriting, which is not only small (micrographia) but often reduces in size. Another example is progressive shortening of steps in gait that precede a freeze. The sequence effect can be present early in patients with PD, and it does not seem to be responsive to dopamine (Kang et al., 2010, 2011) and may have to do with the cumulative energetic cost of movement (Tinaz et al., 2016). Another feature is the loss of automaticity; patients cannot carry out tasks automatically, but rather they have to continue to think about them (Wu et al., 2015). There is evidence that the sequence effect is due to problems with a cerebellar-cortical circuit (Wu et al., 2016).

How does bradykinesia arise from dysfunction of the nigrostriatal pathway? Thinking about the simple basal ganglia diagram, dopamine facilitates the direct pathway and inhibits the indirect pathway. Loss of dopamine will lead to lack of facilitation of movement in both pathways. This could certainly be represented by bradykinesia. This has been referred to as a loss of “motor motivation” (Mazzoni et al., 2007). The origin of rigidity and tremor is less understandable, but also less directly linked to dopamine deficiency clinically (Rodriguez-Oroz et al., 2009; Hess and Hallett, 2017; Bologna et al., 2020).

Rigidity

Tone is defined as the resistance to passive stretch. Rigidity is one form of increased tone that is seen in disorders of the basal ganglia (“extrapyramidal disorders”) and is particularly prominent in PD. Increased tone can result from changes in (1) muscle properties or joint characteristics, (2) amount of background contraction of the muscle, and (3) magnitude of stretch reflexes. There is evidence for all three of these aspects contributing to rigidity. For quantitative purposes, responses can be measured to controlled stretches delivered by devices that contain torque motors. The stretch can be produced by altering the torque of the motor or by altering the position of the shaft of the motor. The perturbation can be a single step or more complex, such as a sinusoid. The mechanical

response of the limb can be measured: the positional change if the motor alters force or the force change if the motor alters position. Such mechanical measurements can directly mimic and quantify the clinical impression (Hallett et al., 1994; Hallett, 2012a,b).

Patients with PD do not relax well and often have slight contraction at rest. This is a standard clinical and electrophysiologic observation, and it is clear that this mechanism plays an important part in rigidity.

There are increases in long-latency reflexes in PD patients. Generally, this is neurophysiologically distinct from the increases in the short-latency reflexes seen in spasticity, the increase in tone of the “pyramidal” type. The short-latency reflex is the monosynaptic reflex. Reflexes occurring at a longer latency than this are designated long latency. When a relaxed muscle is stretched, in general only a short-latency reflex is produced. When a muscle is stretched while it is active, one or more distinct long-latency reflexes are produced after the short-latency reflex and before the time needed to produce a voluntary response to the stretch. These reflexes are recognized as separate because of brief time gaps between them, giving rise to the appearance of distinct “humps” on a rectified EMG trace. Each component reflex, either short or long in latency, has about the same duration, approximately 20 to 40 ms. They appear to be true reflexes in that their appearance and magnitude depend primarily on the amount of background force that the muscle was exerting at the time of the stretch and the mechanical parameters of the stretch; they do not vary much with whatever the patient might want to do after experiencing the muscle stretch. By contrast, the voluntary response that occurs after a reaction time from the stretch stimulus depends strongly on the will of the individual.

Long-latency reflexes are best brought out with controlled stretches with a device such as a torque motor. Although long-latency reflexes are normally absent at rest, they are prominent in PD patients (Hallett et al., 1994; Hallett, 2012a,b). Long-latency reflexes are also enhanced in PD with background contraction. Because some long-latency stretch reflexes appear to be mediated by a loop through the sensory and motor cortices, the enhancement of long-latency reflexes has been generally thought to indicate increased excitability of this central loop.

There is some evidence that at least one component of the increased long-latency stretch reflex in PD is a group II-mediated reflex. This suggestion was first made by Berardelli and associates (1983) on the basis of physiologic features, including insensitivity to vibration. It was subsequently supported by the observation that an enhanced late stretch reflex response could not be duplicated with a vibration stimulus (Cody et al., 1986). Some studies show a correlation between clinically measured increased tone and the magnitude of long-latency reflexes (Berardelli et al., 1983), whereas others do not (Bergui et al., 1992; Meara and Cody, 1993). Long-latency reflexes contribute significantly to rigidity but are apparently not completely responsible for it.

Classic Parkinson tremor

The classic tremor of PD is often called tremor-at-rest; it also can be seen in other parkinsonian states such as those produced by neuroleptics or other dopamine-blocking agents (Hallett, 2012a,b; Helmich et al., 2012; Hallett, 2014;

Helmich, 2018). It is present at rest, disappears with action (pause), but may resume with static posture, when it is called reemergent tremor (Wilken et al., 2018). That the tremor may also be present during postural maintenance is a significant point of confusion in regard to naming this tremor a tremor-at-rest. It can involve all parts of the body and can be markedly asymmetrical, but it is most typical with a flexion-extension movement at the elbow, pronation and supination of the forearm, and movements of the thumb across the fingers (“pill-rolling”). Its frequency is 3 to 7 Hz but is most commonly 4 or 5 Hz; EMG studies show alternating activity in antagonist muscles.

The anatomic basis of the tremor-at-rest may well differ from the classic neuropathologic finding of PD, that of degeneration of the nigrostriatal pathway. For example, 18F-dopa uptake in the caudate and putamen declines with bradykinesia and rigidity but is unassociated with degree of tremor (Otsuka et al., 1996). However, there might be a relationship to dopamine innervation of the globus pallidus, as shown with dopamine single-photon emission computed tomography (SPECT) (Helmich et al., 2011; Helmich et al., 2012). Evidence from positron emission tomography (PET) studies suggests that tremor may be associated with a serotonergic deficiency (Doder et al., 2003; Loane et al., 2013). Another point in favor of this idea is that the tremor may be successfully treated with a stereotactic lesion or deep brain stimulation of the ventral intermediate (VIM) nucleus of the thalamus, a cerebellar relay nucleus. Interestingly, tremors can be divided into two groups, one group is at least somewhat dopamine responsive, the other is not (Zach et al., 2020).

Although cells in the globus pallidus may have oscillatory activity, they are not as strongly related to the tremor as the cells in the VIM of the thalamus (Hayase et al., 1998; Hurtado et al., 1999). Zirh and colleagues studied the physiologic properties of cells in the VIM in relation to tremor production (Zirh et al., 1998). They have tried to see if the pattern of spike activity is consistent with specific hypotheses. They examined whether parkinsonian tremor might be produced by the activity of an intrinsic thalamic pacemaker or by the oscillation of an unstable long-loop reflex arc. In one study of 42 cells, 11 with a sensory feedback pattern, 1 with a pacemaker pattern, 21 with a completely random pattern, and 9 that did not fit any pattern were found (Zirh et al., 1998). Using sophisticated analytical techniques, it can be demonstrated that oscillations both in the VIM and the STN play an efferent role in tremor generation, but that the tremor itself feeds back to these same structures to influence the oscillation (Tass et al., 2010). This does suggest that in some sense the whole loop is responsible for the tremor, and it is possible to see evidence for that with PET scanning (Mure et al., 2011) and magnetoencephalography (MEG) (Timmermann et al., 2003). The basal ganglia loop may well trigger the cerebellar loop to produce the tremor (Helmich et al., 2011, 2012).

Wherever the pacemaker for the tremor, it is important to note that whereas the tremor is synchronous within a limb, it is not synchronous between limbs (Hurtado et al., 2000). Hence, a single pacemaker does not influence the whole body.

There are other types of tremor in PD, including an action tremor that resembles essential tremor (Dirkx et al., 2018). The latter has a faster frequency than the classic tremor-at-rest and is not dopa-responsive.

Dystonia

Dystonia is characterized by abnormal muscle spasms producing distorted motor control and undesired postures (Breakefield et al., 2008; Albanese et al., 2013; Quartarone and Hallett, 2013; Balint et al., 2018a,b; Bruggemann, 2021). Early on, dystonia is produced only by action, but then it can occur spontaneously. There are presently three general lines of work that may indicate the physiologic substrate for dystonia.

Loss of inhibition

A principal finding in focal dystonia is loss of inhibition (Beck and Hallett, 2011; Hallett, 2011a,b; Quartarone and Hallett, 2013). Loss of inhibition is likely responsible for the excessive movement seen in dystonia patients. Excessive movement includes abnormally long bursts of EMG activity, co-contraction of antagonist muscles, and overflow of activity into muscles not intended for the task. Loss of inhibition can be demonstrated in spinal and brainstem reflexes. Examples are the loss of reciprocal inhibition in the arm in patients with focal hand dystonia and abnormalities of blink reflex recovery in blepharospasm. Loss of reciprocal inhibition can be partly responsible for the presence of co-contraction of antagonist muscles that characterizes voluntary movement in dystonia.

Loss of inhibition also can be demonstrated for motor cortical function, including the TMS techniques of short intracortical inhibition (SICI), long intracortical inhibition (LICI), and the silent period (SP) (Hallett, 2011a,b; Quartarone and Hallett, 2013).

SICI is obtained with paired pulse methods and reflects interneuron influences in the cortex (Hallett, 2007a,b; Thirugnanasambandam et al., 2015). In such studies, an initial conditioning stimulus is given, enough to activate cortical neurons but small enough that no descending influence on the spinal cord can be detected. A second test stimulus, at suprathreshold level, follows at a short interval. Intracortical influences initiated by the conditioning stimulus modulate the amplitude of the MEP produced by the test stimulus. At short intervals, less than 5 ms, there is inhibition that is likely largely a GABAergic effect, specifically GABA-A (Di Lazzaro et al., 2000). (At intervals between 8 and 30 ms, there is facilitation, called intracortical facilitation). There is a loss of intracortical inhibition in patients with focal hand dystonia (Ridding et al., 2000; Berardelli et al., 2008). Inhibition was less in both hemispheres of patients with focal hand dystonia, and this indicates that this abnormality is more consistent as a substrate for dystonia.

The SP is a pause in ongoing voluntary EMG activity produced by TMS. The first part of the SP is due in part to spinal cord refractoriness, and the latter part is entirely due to cortical inhibition (Fuhr et al., 1991). This type of inhibition is likely mediated by GABA-B receptors (Werhahn et al., 1999). SICI and the SP show different modulation in different circumstances and clearly reflect different aspects of cortical inhibition. The SP is shortened in focal dystonia.

Intracortical inhibition also can be assessed with paired suprathreshold TMS pulses at intervals from 50 to 200 ms. This is called LICI, to differentiate it from SICI, as noted previously. LICI and SICI differ as demonstrated by the facts that

with increasing test pulse strength, LICI decreases but SICI tends to increase and that there is no correlation between the degree of SICI and LICI in different individuals (Sanger et al., 2001). The mechanisms of LICI and the SP may be similar in that both seem to depend on GABA-B receptors. Chen and colleagues (1997) investigated long intracortical inhibition in patients with writer's cramp and found a deficiency only in the symptomatic hand and only with background contraction. This abnormality is particularly interesting because it is restricted to the symptomatic setting, and therefore might be a correlate of the development of the dystonia.

There is also neuroimaging evidence consistent with a loss of inhibition. Dopamine D2 receptors are deficient in focal dystonias (Perlmutter et al., 1997; Simonyan et al., 2013). There is weak evidence for reduced GABA concentration both in basal ganglia and motor cortex using magnetic resonance spectroscopy (Levy and Hallett, 2002; Herath et al., 2010), but PET scanning with flumazenil, which binds to the GABA receptor, is decreased in several regions in patients with dystonia (Garibotto et al., 2011; Gallea et al., 2018).

Loss of cortical inhibition in the motor cortex can give rise to dystonic-like movements in primates. Matsumura and colleagues (1991) showed that local application of bicuculline, a GABA antagonist, onto the motor cortex led to disordered movement and changed the movement pattern from reciprocal inhibition of antagonist muscles to co-contraction. In a second study, they showed that bicuculline caused cells to lose their crisp directionality, converted unidirectional cells to bidirectional cells, and increased firing rates of most cells, including making silent cells into active ones (Matsumura et al., 1992).

There is a valuable animal model for blepharospasm that supports the idea of a combination of genetics and environment, and, specifically, that the background for the development of dystonia could be a loss of inhibition (Schicatano et al., 1997). In this model, rats were lesioned to cause a depletion of dopamine, which reduces inhibition. Then the orbicularis oculi muscle was weakened. This causes an increase in the blink reflex drive to produce an adequate blink. Together, but not separately, these two interventions produced spasms of eyelid closure, similar to blepharospasm. Shortly after the animal model was presented, several patients with blepharospasm after Bell palsy were reported (Chuke et al., 1996; Baker et al., 1997). This could be a human analog of the animal experiments. The idea is that those patients who developed blepharospasm were in some way predisposed. A gold weight implanted into the weak lid of one patient, aiding lid closure, improved the condition, suggesting that when the abnormal increase in reflex drive was removed, the dystonia could be ameliorated (Chuke et al., 1996).

Loss of surround inhibition, a functional consequence of loss of inhibition

A principle for function of the motor system may be "surround inhibition" (Beck and Hallett, 2011; Hallett, 2011a,b). Surround inhibition is a concept well accepted in sensory physiology to sharpen visual perception. When making a movement, the brain must activate the desired movement, and it appears that, simultaneously, other possible movements are suppressed. The suppression of unwanted movements would be surround inhibition, and this should produce

a more precise movement. For dystonia, a failure of surround inhibition may be particularly important because overflow movement is often seen and is a principal abnormality.

There is good evidence for surround inhibition in human movement. Sohn and associates (2003) demonstrated that with movement of one finger there is widespread inhibition of muscles in the contralateral limb. Sohn and associates have shown that there is some inhibition of muscles in the ipsilateral limb when those muscles are not involved in any way in the movement (Sohn and Hallett, 2004b). MEPs from abductor digiti minimi were slightly suppressed during the movement of the index finger in the face of increased F-wave amplitude and persistence, indicating that cortical excitability is reduced. There appears to be a role for the parietal area in producing surround inhibition (Thirugnanasambandam et al., 2020).

Surround inhibition was studied similarly in patients with focal hand dystonia (Sohn and Hallett, 2004a). The MEPs were enhanced similarly in the flexor digitorum superficialis and abductor digiti minimi, indicating a failure of surround inhibition. Using other experimental paradigms, a similar loss of surround inhibition in the hand has been found (Stinear and Byblow, 2004; Beck et al., 2008; Belvisi et al., 2014; Kassavetis et al., 2014). Making a long term depression-like plastic change to dorsal inferior parietal lobule, an area playing a role in surround inhibition, ameliorates some of the physiological abnormalities in writer's cramp (Merchant et al., 2020).

How can the abnormalities of dystonia be related to the basal ganglia? This is not completely clear, but, as pointed out earlier, the organization of the basal ganglia should be able to support surround inhibition in motor control. Some investigators think there is an imbalance in the direct and indirect pathways so that the direct pathway is relatively overactive or that the indirect pathway is relatively underactive. Indeed, there is evidence for this with a decrease of D2 receptors and an increase of D1 receptors in the putamen in patients with focal dystonia (Berman et al., 2013; Simonyan et al., 2017). This should lead to excessive movement and, in particular, a loss of surround inhibition.

Abnormal plasticity

There is abnormal plasticity of the motor cortex in patients with focal hand dystonia (Quartarone, Siebner, and Rothwell, 2006; Weise et al., 2006; Quartarone and Hallett, 2013). This has been demonstrated using the technique of paired associative stimulation (PAS) (Stefan et al., 2000). In PAS, a median nerve shock is paired with a TMS pulse to the sensorimotor cortex timed to be immediately after the arrival of the sensory volley. This intervention increases the amplitude of the MEP produced by TMS to the motor cortex. It has been demonstrated that the process of PAS produces motor learning similar to that of long-term potentiation. In patients with dystonia, PAS produces a larger increase in the MEP than that seen in normal individuals. There is also an abnormality in homeostatic plasticity. Homeostatic plasticity is the phenomenon by which plasticity remains within limits; this can be exceeded in dystonia (Kang et al., 2011).

Increased plasticity may arise from decreased inhibition so the inhibitory problem may well be more fundamental. This abnormality may be an important link in demonstrating

how environmental influences can trigger dystonia. Abnormal plasticity can arise, at least in part, from abnormal synaptic processes in the basal ganglia (Peterson et al., 2010; Sciamanna et al., 2012; Maltese et al., 2018).

The possibility of increased plasticity in dystonia had been suspected for some time given that repetitive activity over long periods seems to be a trigger for its development. An animal model supported this idea (Byl et al., 1996). Monkeys were trained to hold a vibrating manipulandum for long periods. After some time, they became unable to do so, and this motor control abnormality was interpreted as a possible dystonia. The sensory cortex of these animals was studied, and sensory receptive fields were found to be large. The interpretation of these results was that the synchronous sensory input caused the receptive field enlargement and that the abnormal sensory function led to abnormal motor function. The results suggested that the same thing might be happening in human focal dystonia: repetitive activity caused sensory receptive field changes and led to the motor disorder.

Abnormal sensory function

Stimulated by the findings of sensory dysfunction in the primate model, investigators began examining sensory function in patients with focal hand dystonia and found it to be abnormal. Although there is no apparent sensory loss on a clinical level, detailed testing of spatial and temporal discrimination revealed subtle impairments (Molloy et al., 2003; Scontrini et al., 2009; Conte et al., 2019). The abnormality is present on both hands of patients with unilateral hand dystonia and also on hands of patients with cervical dystonia and blepharospasm. The identification of abnormality of sensation beyond the symptomatic body parts indicated that the sensory abnormality could not be a consequence of abnormal learning but is more likely a preexisting physiologic state.

Sensory dysfunction also can be demonstrated with somatosensory evoked potential (SEP) testing (Bara-Jimenez et al., 1998). The dipoles of the N20 from stimulation of individual fingers show disordered representation in the primary sensory cortex (Bara-Jimenez et al., 1998), and these abnormalities are present on both hands of patients with focal hand dystonia (Meunier et al., 2001). The bilateral SEP abnormality was the first indication in the literature that the sensory abnormality was more likely endophenotypic than a consequence of repetitive activity. PET studies show that the sensory cortex is more activated than normal with writing and is more activated when patients are experiencing more dystonia (Lerner et al., 2004). Voxel-based morphometry studies in patients with focal hand dystonia show an increase in gray matter in the primary sensory cortex (Garraux et al., 2004). Such observations indicate that dystonia is both a sensory disorder and a motor disorder.

There are data from sensory function that are compatible with loss of surround inhibition. Tinazzi and colleagues (2000) studied median and ulnar nerve SEPs in patients who had dystonia involving at least one upper limb. They compared the amplitude of SEP components obtained by stimulating the median and ulnar nerves (MU) simultaneously with the amplitude value being obtained from the arithmetic sum of the SEPs elicited by stimulating the same nerves separately ($M + U$). The ratio of MU to ($M + U$) indicates the interaction

between afferent inputs from the two peripheral nerves. No significant difference was found between SEP amplitudes and latencies for individually stimulated median and ulnar nerves in dystonic patients and normal subjects, but recordings in patients yielded a significantly higher percentage ratio for spinal N13, brainstem P14, and cortical N20, P27, and N30 components. The authors state that “these findings suggest that the inhibitory integration of afferent inputs, mainly proprioceptive inputs, coming from adjacent body parts is abnormal in dystonia. This inefficient integration, which is probably the result of altered surrounding inhibition, could give rise to an abnormal motor output and might therefore contribute to the motor impairment present in dystonia.”

Another demonstration of loss of surround inhibition in sensory function is in the temporal domain. Patients have difficulty recognizing two stimuli when they are close together. The loss of temporal discrimination seems particularly sensitive for dystonia and has been seen even in asymptomatic relatives of dystonic patients (Hutchinson et al., 2013). This abnormality seems to be the result of a loss of a short latency inhibition, identified using SEP recovery curves (Tamura et al., 2008).

Dyskinesias

The dyskinesias include the choreas such as Huntington disease (HD), hemiballismus, and dopa-induced dyskinesia.

These are characterized by involuntary movements that generally appear randomly. These might arise because of a substantial failure of the indirect pathway of the basal ganglia loop (Loonen and Ivanova, 2013); however, the pathophysiology is difficult to fully explain (Hallett and Obeso, 2015). This circumstance would result in a failure of the inhibitory role of the basal ganglia, and involuntary movement would manifest. Evidence for this circumstance exists in HD, in which the initial degeneration of the putamen targets those neurons bearing dopamine D2 receptors (Starr et al., 2008).

Cerebellum

The anatomy of the cerebellar pathways, like the basal ganglia pathways, is complex, but there are simplified models that aid thinking (Schmahmann, 1994; Schmahmann and Pandya, 1997; D’Angelo, 2018; Diedrichsen et al., 2019) (Fig. 2.6). The main cortico-cerebellar-cortical loop is frontal lobe, pontine nuclei, cerebellar cortex (via the middle cerebellar peduncle), deep cerebellar nuclei (pass by the red nucleus), and ventral lateral nucleus of the thalamus (via the superior cerebellar peduncle), and motor cortex (Haubenberger and Hallett, 2018). The input fibers to the cerebellar cortex are the mossy fibers that synapse onto granule cells, which in turn synapse onto Purkinje cells. There is also extensive sensory input via spinocerebellar tracts, largely carried in the inferior cerebellar peduncle. A critical modulatory

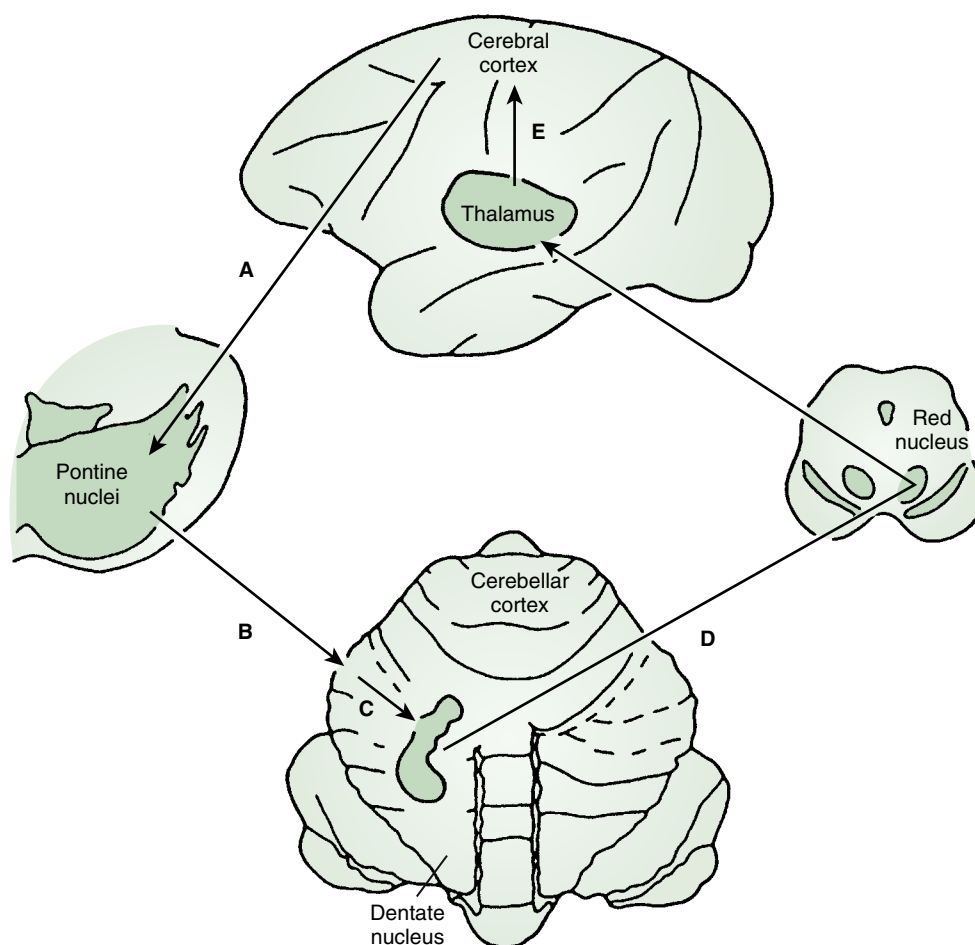


Fig. 2.6 Diagram of the cerebrocerebellar circuit. Note that the path from the cortex to cerebellum is crossed (path B) and the return path is also crossed (path D); hence, the cortical and cerebellar hemispheres are on opposite sides; although the motor cortex is contralateral to movement, the cerebellar activity is ipsilateral. (From Schmahmann JD. *The cerebellum in autism: Clinical and anatomical perspectives*. In: Bauman ML, Kemper TL, eds. *The Neurobiology of Autism*. Baltimore, MD: Johns Hopkins University Press; 1994, pp. 195–226, with permission.)

loop involves the inferior olivary nucleus. The inferior olive innervates both the cerebellar cortex and deep nuclei via the inferior cerebellar peduncle and the climbing fibers that synapse directly onto Purkinje cells. Feedback returns to the inferior olive by a dentate-olivary pathway that travels in the superior cerebellar peduncle, goes around the red nucleus (and some neurons synapse there), and descends in the central tegmental tract.

The cerebellum is connected with much of the brain and is clearly involved with many brain functions (Manto et al., 2012; Bodranghien et al., 2016). The uniform anatomy of the cerebellum suggests that there is a general process that takes place in the cerebellum, but what that is has not been identified (Diedrichsen et al., 2019). An examination of clinical deficits after cerebellar injury gives some idea about the role of the cerebellum in movement.

Ataxia

The term *ataxia*, literally meaning *without order*, refers to disorganized, poorly coordinated, or clumsy movement (Massaquoi and Hallett, 2002; Massaquoi, 2012; Bodranghien et al., 2016). Since the time of Holmes (1939), it has been applied more specifically to clumsiness that is due to lesions of the cerebellum and its immediate connecting pathways, of proprioceptive sensory pathways, or sometimes of the vestibular system. To identify the presence of ataxia, it should not be explained by any abnormality in (maximal isometric) strength, segmental reflexes, muscular tone, ability to isolate movement of individual body parts, or gross motor sequencing or spatial planning. The clumsiness is also not due to spontaneous involuntary movements. Ataxia may be associated with any voluntary movement and with many reflex movements. It commonly affects upright balance, gait, manual coordination, and speech, yielding stagger, clumsy manipulation, and slurring dysarthria that appear drunken. Indeed, the motor coordination-impairing effects of ethanol are attributed to its specific interference with cerebellar function.

Tonic force control abnormalities: hypotonia and asthenia

Normal individuals have very low, barely perceptible muscle tone when fully relaxed. Holmes thought, however, that acutely injured soldiers with penetrating wounds to the cerebellum had further reduced resistance to passive movement. He viewed hypotonia as a fundamental abnormality that underlies many cerebellar motor deficits (Holmes, 1939). This hypotonia tended to be characteristic especially of the upper extremities and to normalize gradually over weeks to months depending on the severity of the injury. Gilman and associates (1981) demonstrated that in primates this change parallels the recovery of muscle spindle sensitivity that was acutely depressed by loss of cerebellar fusimotor facilitation.

In humans, Holmes clearly distinguished the weakness that followed acute massive damage to the cerebellar hemispheres, asthenia, from that associated with corticospinal tract lesions, paresis. The former did not affect specific muscle groups more than others and was not necessarily associated with changes in tendon reflex sensitivity. Weakness is

actually an inconstant complaint in cerebellar patients, and the problem may be easy fatigability or a lack of coordination or stability, not of peak strength. Holmes also drew attention to the inability of some patients to maintain steady force levels (*astasia*, after Luciani). Patients sometimes complain of sudden losses of strength, such as a leg “giving out” or the tendency of an item to drop suddenly from the hand. Holmes attributed these episodes to hypotonia, but their nature remains unclear.

Easy fatigability is a prominent complaint of many patients with cerebellar ataxia. The fatigue may affect an individual body part but may also be sensed more globally. Most patients report that all of the aspects of their ataxia worsen when they are fatigued. A poor night’s sleep or a particularly busy previous day predisposes to a day of especially poor motor control. Patients frequently take naps during the day which provide benefit. Electrophysiologic studies of fatigue in nondepressed patients with cerebellar ataxia by Samii and colleagues (Samii et al., 1997) showed decreased postexercise facilitation of motor potentials evoked from TMS. This is a central activation defect, similar to that seen in patients with depression and chronic fatigue syndrome. Ultimately, the general fatigue in cerebellar disease and other movement disorders may be related to the increased mental concentration needed to compensate for degraded automatic motor control.

Force-rate and movement amplitude scaling deficits: dysmetria, impaired check, and past-pointing

Classic descriptions of cerebellar ataxia include various clinical signs such as dysmetria, dyssynergia (asynergia, decomposition of movement), dysdiadochokinesia, dysrhythmia, and kinetic (intention) and postural tremors. Characteristically, ataxic individuals have particular difficulty in properly generating, guiding, and terminating high-speed movements. Movements accelerate somewhat slowly and are relatively late in onset if executed in reaction to a cue. Movements may then either partially arrest before reaching their targets or gradually accelerate to excessive speed and overshoot their targets to an abnormal degree. These two types of errors are examples of dysmetria and hypometria and hypermetria, respectively. Two distinct motor control abnormalities appear to underlie dysmetria: force-rate inadequacy and step amplitude mis-scaling (Massaquoi and Hallett, 2002). The former causes brief, more consistent velocity-sensitive inaccuracies and the latter more variable protracted errors.

At a fundamental level, the patient with cerebellar ataxia has difficulty changing voluntary force levels abruptly. Both acceleration and braking are impaired. In point-to-point movements, for example, this voluntary force-rate deficit is generally corroborated by a slowness in the build-up of agonist EMG and a prolonged agonist action with delayed onset of antagonist EMG (Hallett et al., 1991; Hallett and Massaquoi, 1993). In patients attempting rapid, single-joint movement, the first agonist burst is frequently prolonged regardless of the distance and speed of the movement, and the most striking kinematic abnormality is prolonged acceleration time. The pattern of acceleration time exceeding deceleration time is common in patients but uncommon in normal persons. The duration of the first agonist burst

correlates with, and is largely responsible for, acceleration time. Altered production of appropriate acceleration for rapid voluntary movements may therefore be the primary abnormality in cerebellar dysfunction for attempted rapid voluntary movements. Hypermetria would be the expected resultant movement error unless there is compensation. Hypometria has been attributed to overcompensation, to asthenia in the acute setting, to tremor, or to failure of timely relaxation of the antagonist during movement initiation (Manto et al., 1998). Any of these mechanisms may be contributory in a given movement, and the topography of the lesion might correlate with the type of deficit (Manto et al., 1998).

For point-to-point movements of any given duration, ataxic movements generally exhibit overshoot. Whenever there is no observable overshoot, the movements of ataxic individuals are usually abnormally slow or hypometric. From the point of view of the Fitts speed–accuracy trade-off, slow movements will lead to greater accuracy. Generally, therefore, in the assessment of ataxia it is important to note both the degree of overshoot and the movement time. Appropriate abnormality of either may be consistent with ataxia. Because, however, there may be alternative explanations for increased movement time, slowness is a much less specific finding than overshoot. Patients often slow down intentionally to maintain error levels that are acceptable to them. Therefore, it is important for an examiner to urge the patient to use maximal speed.

In spinocerebellar atrophy type 6 (SCA6), there is an abnormality of a voltage-sensitive calcium channel. Hyperventilation enhances the defective function of the channel and increases the behavioral dysfunction. In addition to modifying nystagmus, hypermetria in single-joint movements is exaggerated with hyperventilation (Manto, 2001). This may be a useful clinical provocative test.

Patients with cerebellar deficits also have abnormalities in termination of movement. This problem has been explicitly studied in a task in which subjects were asked to make a rapid elbow flexion on the background of tonic elbow extension needed to hold a position against a background force (Hallett et al., 1975). In this circumstance, the tonic triceps activity typically stops before the phasic biceps activity occurs (the “Hufschmidt phenomenon”). Patients with cerebellar dysfunction have a delay in terminating the triceps activity so that it overlaps the beginning of the biceps activity. This delay in stopping leads to overlap of the end of one movement with the beginning of the next.

The practical consequence of sluggishness in termination can be seen at the bedside with the sign called *impaired check*. If a patient’s elbow that was flexed strongly against the grasp of the examiner is suddenly released, it is difficult for the patient to avoid striking himself or herself with the hand. Impaired check also can be attributed to delay in the triggering of the antagonist muscle (Terzuolo et al., 1973). The distinction between sluggish reduction and delayed changes in force is partially artificial.

In addition to transient overshoot, some patients may show movements that come to rest briefly, or nearly come to rest, at locations that are different from that of the target, most often beyond it (*past-pointing*). Unlike dynamic overshoot, which is always speed-dependent, this effective mis-scaling of the overall movement amplitude is less

consistently related to the movement velocity and often improves with repetition. The sign can be elicited using the Barany pointing test, in which the patient is asked to extend an arm forward, holding it parallel to the floor, and to note its position carefully (Gilman et al., 1981). Next, the patient closes the eyes and points the arm toward the ceiling. The arm is then rapidly brought down to a level as close to its original horizontal position as possible. The ataxic patient without demonstrable proprioceptive deficits may return at least briefly to a steady position beyond (lower than) the original, as if there is an error in the calculation of the distance moved or to have been moved. Among ataxic patients, past-pointing is less consistently observed than is dynamic overshoot, and it is not known whether past-pointing is as closely linked to movement acceleration as is dynamic overshoot. If the patient is allowed to practice and view the error a few times, he or she may become able correct the final position using a second movement while maintaining the eyes closed. It is as if a more precise proprioceptive measurement system can be employed after movement completion. Eventually, the patient may learn to produce a normally scaled movement. That the initial mis-scaling is often correctable may be related to residual cerebellar function, to a retained ability to increase dependence on proprioceptive information, or to rescaling movement at extracerebellar sites.

Exaggerated postural reactions: rebound

When the cerebellar patient is asked to maintain a steady outstretched arm position and the examiner applies a gentle downward tap, there typically follows a rapid, excessive upward displacement termed *rebound* (note that the term currently has a meaning slightly different from the original). Rebound often occurs transiently in normal individuals and is usually quickly attenuated with reperturbation as the normal subject adapts to the amplitude or force of the disturbance. Because of the excessive rate and magnitude of the response, the patient initially yields less than normal to the perturbation, but overshoots in the opposite direction. Rebound may be partially due to sluggish braking as occurs with *impaired check*. However, an excess force-rate abnormality is at least contributory.

Abnormal control of simple multijoint movements: dyssynergia

In ataxic simple multijoint movements, such as intended straight point-to-point hand movements, there is a breakdown in the normal coordination of joint rotations. This has been termed *dyssynergia* or *asynergia* and is described as a type of *movement decomposition*. This typically causes abnormal movement path deviations. As the movements of normal subjects usually display some natural deviation from perfect linearity, abnormality in path is a matter of degree of curvature and of specific pattern. Evidence is now accumulating that ataxic multijoint movements exhibit characteristic trajectory abnormalities (Massaquoi and Hallett, 1996). Thach and colleagues (Thach et al., 1993) attributed the pronounced ataxia seen in multijoint movements to a hypothetically preferential role for the cerebellum in the coordination of multijoint movement. Although

the neuroanatomic organization of the cerebellum makes it particularly well suited for coordinating muscle actions of different body parts, the function of the cerebellum in both single and multijoint control may be fundamentally similar.

Analysis of simple, horizontal planar two-joint arm movements suggests that the deficits in acceleration and braking observed at single joints may account, at least in part, for the dysssynergia observed (Hallett and Massaquoi, 1993; Massaquoi and Hallett, 1996). It appears that the force-rate deficit may be accentuated at the joint having the greatest torque-rate demand, which causes an imbalance in the joint accelerations leading to hand movement curvature. This suspected mechanism is consistent with the marked worsening of dysssynergia with increases in intended acceleration. In addition to the need for forces to launch and stop, there is a requirement for rapid compensation for the disturbing effects of multiple interaction torques between body segments and the need to coordinate more muscles having different individual actions. Indeed, several groups have specifically related multijoint trajectory errors in cerebellar ataxia to deficits in interaction torque compensation (Topka et al., 1998; Bastian et al., 2000).

Several investigators have suggested other mechanisms for asynergia. Multijoint movements sometimes may be decomposed into multistep single-joint movement components as a voluntary strategy to simplify programming by minimizing interaction torques between the joints (Bastian et al., 1996). Dysssynergy may be due to the general difficulties cerebellar patients have with timing tasks (Keele and Ivry, 1990). From this perspective, dysmetria and dysssynergy within simple (single intended velocity peak) single and multijoint movements may have a mechanism similar to that which underlies *dysdiadochokinesia*, a disruption of compound movements involving more than one intended velocity peak (see later).

Abnormalities in timing and coupling movements and other processes: dysrhythmia, dysdiadochokinesia, delayed reaction time, and impaired time interval assessment

Ataxia also includes disruption of the normally smooth concatenation and coordination of compound movement subcomponents. This gives rise to a particular degradation of the rhythm of repetitively alternating single movements (*dysrhythmia*) and of the synchronization of single-joint movement components within repetitively alternating multijoint movements yielding *dysdiadochokinesia* (*adiadochokinesia*), a second type of movement decomposition. Although clinical testing for dysrhythmia and dysdiadochokinesia typically employs rapidly alternating oppositely directed movements that maximize the sensitivity for detecting errors in the timing of movement onsets and offsets, timing difficulties may be noted in a variety of tasks that involve sequential movements. Bedside testing for dysrhythmia can be done by asking the patient to tap out a rhythm with a single-joint movement. Tests for dysdiadochokinesia include alternately slapping the palmar and dorsal surfaces of the hand on the thigh or making rapid pincer movements of the index finger tip to the opposing midthumb crease. Accurate slapping

or tapping requires precise synchronization of rotations of more than one joint (the elbow and radioulnar joints in the first case, the interphalangeal and metacarpophalangeal joints in the latter). In these two tasks, ataxic patients display both an irregular underlying rhythm and inaccurately placed contacts owing to failed multijoint coordination. Dysdiadochokinesia can therefore be seen as a combination of dysrhythmia and dyssynergia.

In addition to timing aberrations that are associated with, and may result from, clumsy movement execution, there appears to be a separate timing abnormality that results from failure of a cerebellum-dependent "central clock" (Keele and Ivry, 1990). Theoretically, this clock assists in the timely launching of movements with respect to preceding movements (Grill et al., 1997). The same system may generally help launch movements with respect to other events, both external and internal. In all types of reaction tasks, not only does agonist EMG build up more slowly in cerebellar patients, but the EMG onset itself is significantly delayed with respect to the time of the stimulus, as if a triggering system is defective (Grill et al., 1997).

Abnormalities in motion assessment and prediction: impairment of tracking

Probably closely related to their problems with assessment of time intervals and movement amplitude scaling is cerebellar patients' basic difficulty in using sensory information to assess and predict motion characteristics. This applies both to body parts, as shown by Grill and associates (1994) and as exhibited in past-pointing tests, and to external objects. Especially in rapid multicomponent movements, a certain amount of motion prediction ability is important for effective performance. Because of the delays in the transmission of neural signals, initiation of movement subcomponents may need to take place well in advance of completion of the preceding subcomponent (Grill et al., 1997). Often, however, details of the plan for the second motion may depend on the progress of the first motion. For example, in throwing a ball, timing of release must be coordinated with the movement of the arm to produce a properly directed trajectory. Similarly, for any control system having non-trivial feedback delays, high-precision tracking of a moving target requires a certain amount of predictive control. This may take the form of additional open-loop (feed-forward) predictive signals or the processing of higher derivatives of error information (e.g., velocity error information for position control) which inherently includes some predictive information.

The cerebellum appears to be involved in both predictive feedforward and velocity feedback control. Motion prediction deficits often can be identified at the bedside by asking the patient to track, with his or her finger, the examiner's finger as it moves slowly back and forth in a smooth motion. A motion should be used that normally would be easy to predict and at a speed that would not engender overshoot in a simple point-to-point movement. Cerebellar patients will nevertheless frequently lag the examiner during the motion and/or overshoot at the direction reversals, presumably because they fail to assess properly the examiner's rate of acceleration and deceleration or the rhythm of the examiner's overall movement (Morris et al., 1990).

Increased movement variability

Ataxic motor performance is frequently described as being more variable than normal (Hallett and Massaquoi, 1993; Palliyath et al., 1998). Ataxic variability may arise more as a consequence of enhanced susceptibility to perturbation and of the sequential compounding of errors, than inherent noise. Most natural tasks involve multijoint movements, which inherently have many degrees of movement freedom, and ongoing efforts to guide motion. Elemental trajectory errors may, therefore, interact, propagate, and become compounded, a process that effectively produces motor control noise.

Cerebellar tremors

Two types of action cerebellar tremor are commonly identified: kinetic and postural tremor. Lesions of the dentate, of the interpositus and of the cerebellar outflow via the brachium conjunctivum appear to be the most frequently associated with action tremors. Both manifest alternating EMG bursting in agonist and antagonist muscles (Hallett, 1987). All types of cerebellar action tremors may be exacerbated near a point of attempted fixation, such as the endpoint, if greater effort is made to maintain position precisely. Tremor frequency may differ between limbs, and the oscillations are generally not synchronous in nonadjacent body parts. However, as are most tremors, cerebellar action tremors are worsened by fatigue. Cerebellar action tremors are often improved and sometimes eliminated by eye closure (Sanes et al., 1988). Propranolol has no substantial effect, and alcohol tends to worsen cerebellar action tremors.

Basic mechanisms that have been suggested to underlie cerebellar tremor have included (1) serial voluntary corrections for positioning error (serial dysmetria) (Hallett, 1987), (2) abnormality of transcortical and segmental proprioceptive feedback loops (Hore and Flament, 1986), and (3) action of central oscillators (Ito, 1984). Sufficient evidence has accumulated to indicate that each of these mechanisms is likely to be important to some component of body oscillations in ataxic patients under various circumstances.

Increased postural sway and titubation

Ataxic patients exhibit increased irregular sway when standing and sometimes a more regular tremor (titubation). The characteristics of these involuntary movements vary according to the site of the cerebellar system lesion. Diener and Dichgans performed extensive studies of postural balance in patients with cerebellar system disease (Diener et al., 1984; Diener and Dichgans, 1992). Common to all ataxic patients, except those with lesions restricted to the hemispheres, is the tendency to have abnormally large-amplitude sway when the eyes are closed. Patients with anterior lobe atrophy as a result of chronic alcohol intake and malnutrition and patients with Friedreich ataxia have a high Romberg quotient, meaning that they sway considerably more with eyes closed. In general, the eyes-closed instability is greater in Friedreich ataxia patients, who typically have significant proprioceptive loss and may fall without vision. By contrast, the anterior lobe lesion patients tend to oscillate markedly without falling when their eyes are closed. Patients with anterior lobe

damage also tend to move much more in an anteroposterior direction, whereas those with Friedreich ataxia have an abnormal degree of lateral sway.

Patients with vestibulocerebellar lesions display increased, omnidirectional, low-frequency (~1 Hz) sway and may fall with eyes both open and closed and therefore have a normal Romberg quotient. Patients who have hemispheric lesions may exhibit slightly increased sway relative to normal persons, but balance instability is not prominent. Those with diffuse cerebellar damage exhibit a mixture of characteristics. They may be differentiated from normal persons but not from each other on the basis of posturography.

In addition to low-frequency (~1 Hz) sway, a characteristic 2- to 3-Hz body tremor is seen exclusively in patients with anterior lobe dysfunction when the eyes are closed. Unlike the irregular head and trunk titubation that may be seen with various other cerebellar lesions, the anterior lobe tremor consists of regular anteroposterior oscillation at the head, hip, and ankle.

Dysarthria

When ataxia affects speech, it manifests as clumsy, slurring, and poorly modulated. No disruption of language usage, structure, or content is attributable to the cerebellar dysfunction. As noted by Gilman and associates (1981), adjectives commonly used to describe cerebellar speech include scanning, slurring, staccato, explosive, hesitant, slow, altered accent, and garbled. These investigators have identified 10 elemental speech abnormalities that are present to varying degrees in different cerebellar patients: (1) imprecise consonants, a feature basic to all dysarthrias; (2) excess and equal stress, the inappropriate allocation of emphasis and accent; (3) irregular articulatory breakdown, the elision of syllables or phonemes; (4) distorted vowels; (5) harshness; (6) prolonged phonemes; (7) prolonged intervals; (8) monopitch; (9) monoloudness; and (10) slow rate. Cerebellar speech also may be tremulous and may trail off to a whisper. However, it should again be noted that many patients are intentionally slow and perhaps regularize their speech, that is, voluntarily generate "scanning" speech to increase its intelligibility.

Gait ataxia

A deterioration in the stability of ambulation is the chief complaint of the majority of patients afflicted with cerebellar dysfunction. This is apparently due to two factors. First, the vermis of the cerebellum appears to be preferentially or initially affected in many degenerative conditions. This is especially the case for alcoholic and nutritional degeneration but also for cases of multiple system atrophy. Second, walking, which consists of carefully managing a series of controlled collisions with the environment, is very demanding dynamically. Unlike the vocal tract and the arms, which are mechanically stable and will come to rest on relaxation, the upright body, virtually an inverted pendulum, is unstable. Thus, the body does not automatically return to a consistent initial condition after each step. Rather, each successive step depends sensitively on the manner in which the preceding step was completed. This aspect of bipedal locomotion probably contributes significantly to the variability of foot placement in ataxic gait.

Despite the variability in ataxic locomotion there are still consistent kinematic patterns (Palliyath et al., 1998). As in upper extremity multijoint movement tasks, lower extremity multijoint coordination is characteristically abnormal. In particular, when walking, patients show a relatively greater delay of plantar flexion at the ankle than in flexion at the knee and a relatively sluggish dorsiflexion of the ankle at the onset of swing. In walking, the largest and fastest required force transients are the forceful ankle plantar flexion at the end of stance and the rapid ankle dorsiflexion that follows immediately at the onset of swing. Therefore, as argued with respect to the shoulder in upper extremity multijoint coordination failure, each of these two lower extremity coordination abnormalities is consistent with a force-rate deficit (or perhaps force-delay) at the joint, in this case the ankle, that has the greatest force-rate demand. The situation is not completely clear, however, because a similar ankle-knee relationship may be seen in elderly patients without ataxia. Further quantitative studies are needed. In any case, owing at least in part to the sluggishness of dorsiflexion, there is a tendency for ataxic patients to trip as their toes fail to clear the ground during swing. That no significant abnormality was noted in the height of toe lift during swing phase by Palliyath and associates (1998) may well be because trials in which stumbles occurred were excluded from analysis.

Ataxic gait, when under control, tends to be slower than normal and to have shortened strides. As argued by Palliyath and associates (1998), this is at least partially a voluntary compensation for the loss of control that occurs at higher speeds. Because walking involves controlled falling, both forward and laterally onto the next foot placement, walking with too slow a cadence demands prolonged balancing on each leg, which is difficult for the ataxic patient. Therefore, as patients slow down, they will tend to adopt a much shorter stride to maintain their cadence or a wider base to stabilize themselves laterally. Possibly because of the resulting waddle, patients sometimes report that they walk “better” when they move at a moderate speed rather than very slowly, even though they may become more prone to veer or to trip than when they waddle.

Impaired motor learning

The consideration that ataxic patients should have difficulty with motor learning follows from the apparent logic that if they could learn, why would they still be clumsy. Motor learning itself is a complex phenomenon with a number of different components (Hallett et al., 1996; Hallett and Grafman, 1997; Krakauer and Mazzoni, 2011). One aspect can be defined as a change in motor performance with practice. Other aspects would include increasing the repertoire of motor behavior and maintenance of a new behavior over a period of time. Even considering only a change in motor performance, there are likely to be several different phenomena. Adaptation and skill learning can be distinguished. Adaptation is simply a change in the nature of the motor output, whereas skill learning is the development of a new capability. There has been considerable work at a basic level relating learning to cerebellar function (De Zeeuw and Ten Brinke, 2015).

Adaptation learning clearly involves the cerebellum. Adaptation to lateral displacement of vision as produced by prism

glasses is a method for assessing learning of a visual-motor task. When prism glasses are used, there is at first a mismatch between where an object is seen and where the pointing is directed. With experience, normal humans adjust to this and begin to point correctly. This correct pointing can be a product of both a true change in the visual-motor coordination or an intellectual decision to point in a different direction than where the object appears to be so that the correct movement is made. When the glasses are removed, typically the patient initially points in the direction opposite to that when the glasses were worn. In the naive patient, this is an excellent measure of true change in the visual-motor task because there is no reason for making any intellectual decision to point other than in the direction that the object appears to be. With additional experience, the patients return to correct performance again. Patients with cerebellar damage show poor or no adaptation (Weiner et al., 1983; Martin et al., 1996). Another paradigm that can test adaptation learning is a task with a change in the visual-motor gain. An example is making movements of the elbow by matching targets on a computer screen. If the gain of the elbow with respect to the display on the computer screen is changed, the amount of movement to match the targets will change. In the normal circumstance after a gain change, there would be an error that gradually would be reduced with continued practice. Deuschl and colleagues (1996) found that ataxic patients showed much slower learning than the normal controls.

Conditioning, such as eye blink conditioning, is recognized as a form of motor learning. In nonhuman animal studies, eye blink conditioning seems to require the cerebellum, at least for the expression and timing of the response. A number of groups have studied eye blink conditioning in patients with cerebellar lesions and found them to be markedly deficient (Daum et al., 1993; Topka et al., 1993).

For motor skill learning, Topka and associates (1998) evaluated the ability of patients to learn a multijoint two-dimensional trajectory with the upper extremity. Although the performance of the patients was clearly impaired, they improved their performance as much as the normal subjects as long as the task was done slowly. With rapid movements, learning did slow down abnormally in the patients. Skill learning has many components, including features such as the sequencing of the different components. Other parts of the brain play important roles in these other functions and can be responsible for the learning in the ataxic patients. Functional imaging studies, for example, show increased activation with learning in motor cortex, premotor cortex, and parietal areas (Hallett et al., 1996; Hallett and Grafman, 1997; Wu et al., 2004). Early skill learning involves the motor cortex (Muellbacher et al., 2002), and as the skill becomes better learned and more stable, a network of parietal and premotor cortices becomes more active. The cortical network becomes more tightly connected as the task becomes automated (Wu et al., 2008). This will become more relevant with the discussion of apraxia.

Clinical localization

Virtually any lesion of the cerebellar parenchyma can be associated with ataxia. Presumably because of the considerable redundancy, complex interconnectedness, plasticity of cerebellar circuits, and interindividual physiologic

differences, attempts at precisely localizing cerebellar function on the basis of experimental and natural lesions have yielded inconsistent results. Similarly, it is usually not possible to predict lesion site within the cerebellum with great accuracy from the clinical examination. The clinicoanatomic correlations described later should therefore be viewed only as predominant patterns. See [Timmann and associates \(2008\)](#) for a review.

The cerebellum is often considered to be functionally divided into four parts on the basis of its output nuclei. Three sagittal zones—midline, intermediate, and lateral—project, respectively, to the fastigius, interpositus (globose and emboliform nuclei in combination), and dentate nuclei, and the vestibulocerebellum (flocculonodular lobe) projects to the lateral vestibular nucleus, which effectively functions as a fourth cerebellar deep nucleus. From a clinical point of view, however, partitioning into simply midline, lateral (or vermis and hemispheres), and vestibular cerebellum is usually sufficient. The vestibulocerebellum, owing to its large involvement in head, eye, and balance control, can be considered part of the midline region. At least for tasks used in bedside examination, the functions of the intermediate and lateral zones of the hemispheres are not readily distinguished. In addition, it is also useful to keep in mind that tremor appears to be seldom the result of lesions of the cerebellar cortex alone and that the superior/anterior portion of the vermis, in particular, is affected in relative isolation by vitamin deficiency (often secondary to chronic alcohol intoxication) and tumors (especially in children), which produce a fairly pure ataxia of upright stance and gait with minimal, if any, limb ataxia, dysarthria, or nystagmus.

In general, signs that involve only the limbs unilaterally are most often due to lesions of the ipsilateral cerebellar hemispheres. However, this is not uniformly the case. In a series of 106 patients having unilateral or predominantly unilateral hemispheric injury (most postsurgical cases) studied by Lechtenberg and Gilman (1981), predominantly right limb dysmetria was associated with right hemisphere damage in 22 of 26 (85%) cases and left limb dysmetria with left hemispheric damage in 37 of 42 (88%) cases. For dysdiadochokinesia, ipsilateral hemispheric lesions were seen in 11 of 12 (91%) right predominant cases and 25 of 32 (78%) left predominant cases. The mechanism of strictly contralateral hemispheric effects on limb movement is not known. The handedness of the subjects was not reported. However, assuming the usual prevalence, the findings for dysdiadochokinesia are consistent with a mild additional impairment of the nondominant hand. This is consistent with the apparent importance of cerebrocerebellar interaction with rapid alternating movements (see earlier). When vermal lesions affected the limbs, the deficits were usually seen bilaterally, and when there was asymmetry of deficit, the left limbs tended to be more severely affected. Overall, tremor was found less often than dysmetria or dysdiadochokinesia, but it occurred with similar rates in vermal and unilateral hemispheric disease.

Deficits involving the head, trunk, balance, and gait in isolation tend to be related preferentially to vermal lesions. However, other sites are possible. As discussed earlier, dysarthria, deficits involving the mouth, though midline, may be due to vermal or hemispheric dysfunction.

Cortical control mechanisms

As noted earlier, the primary motor cortex provides the principal output to the corticospinal tract. Thus, its inputs determine the brain's contribution to movement. The main inputs come from the premotor cortices, including the lateral premotor cortex, the supplementary motor area, and the caudal parts of the cingulate motor area. These areas in turn receive their input from wide areas of brain, including the presupplementary motor area, rostral parts of the cingulate motor area, dorsolateral prefrontal cortex, and parietal areas. Considerable attention has been given to the parietal-premotor connections, which are highly specific and appear to provide important links between sensory and motor function ([Rizzolatti et al., 1998](#); [Rizzolatti and Luppino, 2001](#); [Schaffelhofer and Scherberger, 2016](#); [Vijayakumar et al., 2018](#)) (Fig. 2.7). As noted earlier, in the discussion of motor skill learning, the parietal-premotor connections become more active and more tightly connected with motor skill. Different sets of connections relate to different tasks. For example, different parietal-premotor connections relate to the reach and grasp of a reach-to-grasp movement ([Konen et al., 2013](#)).

Apraxia

The apraxias are disorders of motor control, characterized by a loss of the motor program, not explicable by more elemental motor, sensory, coordination, or language impairments ([Gross and Grossman, 2008](#); [Foundas, 2013](#); [Buxbaum and Randerath, 2018](#); [Foundas and Duncan, 2019](#)). Ideomotor apraxia is present when there is knowledge of the task, but there are temporal and spatial errors in performance ([Wheaton and Hallett, 2007](#)). It has long been suspected to be due to a lesion of, or a disconnection between, parietal and premotor areas. Apraxias are seen with left hemisphere strokes involving parietal and/or premotor areas. Because motor skills seem to be stored in these areas, it is not surprising that they are lost with lesions in this region. [Table 2.3](#) lists the types of apraxias.

A highly specific abnormality of praxis function is the task-specific deficit in focal hand dystonia such as writer's cramp or musician's cramp. This disorder appears to be an abnormality of a parietal-ventral premotor pathway ([Gallea et al., 2016](#)).

Voluntary movement

Although clearly much is known about the anatomy and physiology of the motor system, there is still considerable difficulty with the concept of voluntariness ([Hallett, 2007a,b, 2009, 2016](#)). Many movements are triggered by sensory stimuli ("externally triggered"), and the physiology of this mechanism is relatively clear. However, there are certainly movements that appear to be "internally triggered" and humans have the sense that they have willed the movement. The self-initiation of movement appears to involve mesial motor structures such as the supplementary motor area and the dorsolateral prefrontal cortex ([Deiber et al., 1999](#)). As pointed out by Paus (2001), the mesial motor structures, including the anterior cingulate cortex, in particular, is a place of convergence for homeostatic drive, emotion, and

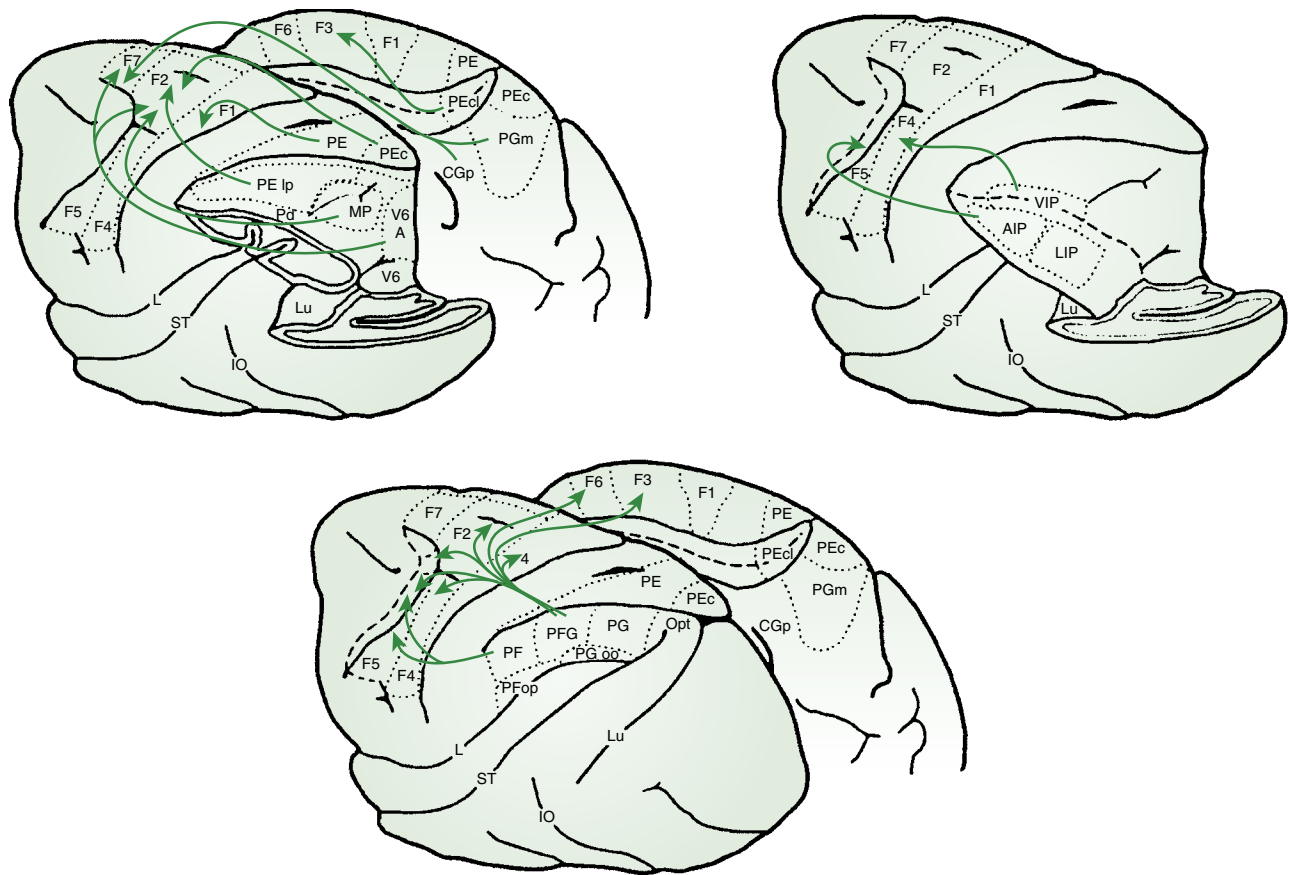


Fig. 2.7 Diagram of the multiple parieto-frontal connections as identified in the primate. The critical concept is that there are multiple parietal areas and multiple frontal areas and that there are highly specific parietal-frontal connections between them; each connection has a specific motor function. For abbreviations, see original reference. (From Rizzolatti G, Luppino G, Matelli M. *The organization of the cortical motor system: new concepts. Electroencephalogr Clin Neurophysiol* 1998;106(4):283–296, with permission.)

cognition that can then strongly influence what movements will be made. This is how internally triggered movements are generated; persons drink when they are thirsty, seek happiness, and repeat activities that previously generated a reward. The external drivers and internal drivers of movement interact in the premotor cortex, which in turn strongly influences the motor cortex in generating the motor command (Fig. 2.8). In the mouse, experience-dependent medial prefrontal cortex ensembles can drive distinct behaviors (Ye et al., 2016).

The sense of volitariness does not appear to drive movement itself (although this is argued) but is a perception or element of consciousness. The components of consciousness are called qualia and the sense of volitariness is a quale. Volitariness has two elements, the sense of willing and the sense of agency. Agency is the perception of control, and self-agency would be the quale that “you made the movement that just occurred.” There can be willing without agency (if a movement does not actually happen), but agency generally needs the sense of willing and the appreciation that a movement actually happened. Agency likely needs the combination of a feedforward signal from the movement generation process and a feedback signal from the movement (Nahab et al., 2011; Kranick and Hallett, 2013). Because there is virtually no understanding of the nature of consciousness itself, it is not completely clear how the qualia of willing and agency actually occur. ; however, there are neuroimaging studies that give clues (Darby et al., 2018; Zito et al., 2020).

Table 2.3 Types of apraxia

Limb kinetic apraxia	Loss of hand and finger dexterity; significantly affecting manipulative movements
Ideomotor apraxia	Deficit in pantomiming tool use and gestures with temporal and spatial errors. Knowledge of tasks is still present
Ideational apraxia	Failure to carry out a series of tasks using multiple objects for an intended purpose; problem in the sequencing of actions. Tools are identifiable
Conceptual apraxia	Loss of tool knowledge; inappropriate use of tools and objects; inability to solve mechanical problems
(Verbal-motor) dissociation apraxia	Failure to respond to verbal commands, but use of objects is appropriate
Conduction apraxia	Problems with imitating, but not with responding to verbal commands

Modified from Wheaton LA, Hallett M. Ideomotor apraxia: A review. *J Neurol Sci.* 2007;260:1–10.

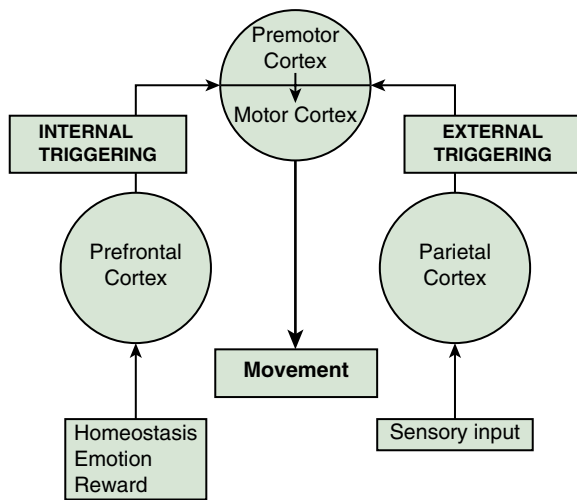


Fig. 2.8 Diagram showing the interaction of internal and external influences to the premotor and motor cortex.

Disorders of willed movement

In neurology, there are many disorders in which the issue of will arises (Hallett, 2007a,b, 2009; Kranick and Hallett, 2013).

There are patients who have movements that are commonly held as being involuntary. Myoclonus is such an example. The brain makes the movement, yet the patient interprets the movement as involuntary. Early in the course of HD, patients with chorea often do not recognize that there are any involuntary movements. It is not clear why this happens or why it changes later.

Although tics are generally considered involuntary, patients with tics often cannot verbalize whether their movements are voluntary or involuntary. This may not be a relevant distinction in their minds. It is perhaps a better description to say that they can suppress their movements or they just let them happen (Cavanna and Nani, 2013). Tics look like

voluntary movements in all respects from the point of view of EMG and kinesiology (Hallett, 2000). Interestingly, they are often not preceded by the normal brain potential, the Bereitschaftspotential, and hence the brain mechanisms for their production clearly differs from ordinary voluntary movement (Obeso et al., 1981; Karp et al., 1996; van der Salm et al., 2012).

The symptom of loss of voluntary movement is often called abulia or, in the extreme, akinetic mutism (Fisher, 1983). The classic lesion is in the midline frontal region affecting areas including the supplementary motor area and cingulate motor areas. The bradykinesia and akinesia of PD are related.

The alien hand phenomenon is characterized by unwanted movements that arise without any sense of their being willed. In addition to simple, unskilled, quasireflex movements (e.g., grasping), there also can be complex, skilled movements such as intermanual conflict or interference (Fisher, 2000; Hallett, 2007a,b; Kranick and Hallett, 2013). There appears to be difficulty in self-initiating movement and excessive ease in the production of involuntary and triggered movements. In cases with discrete lesions, this seems to have its anatomic correlation in the territory of the anterior cerebral artery.

Functional (psychogenic or conversion disorder) movements are movements interpreted by the patient as involuntary. Their cause is actually obscure because the physiology of conversion is really unknown (Edwards et al., 2012; Edwards, 2013; Kranick and Hallett, 2013). Electroencephalographic investigation of these movements shows a normal-appearing Bereitschaftspotential preceding them (Toro and Torres, 1986; Terada et al., 1995). The normal brain potential, however, indicates that there must be substantial sharing of brain voluntary movement mechanisms (Hallett, 2010). The pathophysiology is beginning to be better understood (Demartini et al., 2020; Drane et al., 2020).

References available on Expert Consult:
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Functional neuroanatomy of the basal ganglia

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Introduction

The basal ganglia comprise a collection of nuclear structures deep in the brain and have been defined anatomically and functionally. Anatomically, the basal ganglia are the deep nuclei in the telencephalon. Functionally, three closely associated structures, the subthalamic nucleus (STN) (in the diencephalon), the substantia nigra (SN), and pedunculo-pontine nucleus (PPN) (both in the mesencephalon), are also included as part of the motor part of the basal ganglia. The definition of which structures are included has varied over the years and depends also in part on a preconceived notion of their function. Most of the time, and for the purposes of the study of movement disorders, the basal ganglia are viewed as having primarily a motor function. Indeed, the early movement disorders included in the concept, such as Parkinson disease (PD) (see [Table 3.1](#) for all abbreviations in this chapter) and Huntington disease (HD), were primarily basal ganglia related, and interested neuroscientists would meet at “basal ganglia clubs.” It is now clear, however, that the basal ganglia also play a role in cognitive, behavioral, and emotional functions. For example, the limbic system interacts extensively with the basal ganglia, and some components of the basal ganglia, such as the amygdala (archistriatum), nucleus accumbens, and ventral pallidum, serve these functions ([Haber and Knutson, 2010](#); [Tremblay et al., 2015](#)).

The core motor structures of the basal ganglia include the caudate and putamen, collectively called the neostriatum (commonly abbreviated as the striatum), the globus pallidus (GP) (paleostriatum), the STN, the SN, and the PPN ([Figs. 3.1–3.3](#)). The putamen and GP together are sometimes called the lenticular nucleus. The main informational processing loop of the basal ganglia, as described in [Chapter 2](#), comes from the cortex and goes back to the cortex via the thalamus. The substantia nigra pars compacta (SNc) is largely a modulator of this main loop, with dopamine as its

neurotransmitter. Other modulators are the locus coeruleus (LC), with norepinephrine (NE) as neurotransmitter, and the median raphe nucleus (MRN), which uses serotonin as neurotransmitter. The notion that the basal ganglia provide an “extrapyramidal” control of movement separate from the cortical-pyramidal control is not correct because the main output of the basal ganglia projects to the cortex. Therefore, the term *extrapyramidal disorders* for disorders arising from dysfunction of the basal ganglia is a misnomer.

In this chapter, we will first consider the neurotransmitters and their receptors that are involved in basal ganglia circuitry ([Table 3.2](#)). Next, we will consider the main components of the basal ganglia and the way that they interact with each other. At the end, we will review some features of the physiologic activity and consider what the main functions of the basal ganglia might be. As an introductory comment to the section on neurotransmitters, it is important to note that although we generally discuss neurons as if they had a single neurotransmitter, typically neurons may have more than one. For example, dopaminergic neurons may also contain glutamate ([El Mestikawy et al., 2011](#)) and striatal medium spiny neurons contain protein neurotransmitters in addition to gamma-aminobutyric acid (GABA).

Neurotransmitters

Dopamine

It is appropriate to start out the discussion of neurotransmitters with a consideration of dopamine, the most “prominent” neurotransmitter because it is depleted in PD and because we have the means to manipulate this transmitter in therapeutics. The main sources of dopamine are the lateral SNc (A9), the medial ventral tegmental area (VTA, A10), and the retrorubral area (A8) (see [Fig. 3.2](#)). The SNc innervates the striatum via the nigrostriatal pathway, and the VTA and retrorubral areas give rise to the mesolimbic innervation of the

Table 3.1 Abbreviations

AAADC	Aromatic L-amino acid decarboxylase	L-dopa	Levodopa
ACh	Acetylcholine	LFP	Local field potential
AChE	Acetylcholinesterase	M1	Primary motor cortex
ADP	Adenosine diphosphate	MAO	Monoamine oxidase
2-AG	2-Arachidonoylglycerol	mAChR	Muscarinic acetylcholine receptor
AMPA	α -Amino-3-hydroxyl-5-methyl-4-isoxazole-propionate	mGluR	Metabotropic glutamate receptor
ATP	Adenosine triphosphate	MEA	Midbrain extrapyramidal area
BuChE	Butyrylcholinesterase (pseudocholinesterase)	MPTP	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
cAMP	Cyclic adenosine monophosphate	MRN	Median raphe nucleus
ChAT	Choline acetyltransferase	MSN	Medium spiny neuron
CM	Centrum medianum nucleus of the thalamus	3-MT	3-Methoxytyramine (3-O-methyldopamine)
CoA	Coenzyme A	nAChR	Nicotinic acetylcholine receptor
COMT	Catechol-O-methyltransferase	NE	Norepinephrine
DA	Dopamine	NMDA	N-methyl-D-aspartic acid
DAG	Diacylglycerol	PD	Parkinson disease
DAT	Dopamine transporter	Pf	Parafascicular nucleus of the thalamus
DBH	Dopamine beta-hydroxylase	PMv	Premotor cortex, ventral division
DBS	Deep brain stimulation	PPN	Pedunculopontine nucleus
DOPAC	3,4-Dihydroxyphenylacetic acid	PPNc	Pedunculopontine nucleus, pars compacta
EAAT	Excitatory amino acid transporter	PPNd	Pedunculopontine nucleus, pars dissipatus
GABA	Gamma-amino butyric acid	SERT	Serotonin transporter
GABA-T	GABA-transaminase	SMA	Supplementary motor area
GAD	Glutamic acid decarboxylase	SN	Substantia nigra
GAT	GABA transporter	SNC	Substantia nigra, pars compacta
Glu	Glutamate	SNr	Substantia nigra, pars reticulata
GP	Globus pallidus	STN	Subthalamic nucleus
GPe	Globus pallidus externa	TANs	Tonically active neurons
GPI	Globus pallidus interna	TH	Tyrosine hydroxylase
HD	Huntington disease	TRVP ₁	Transient receptor potential vanilloid type1
5-HT	5-Hydroxytryptamine, serotonin	VA	Ventral anterior nucleus of thalamus
5-HTP	5-Hydroxytryptophan	VACHT	Vesicular ACh transporter
HVA	Homovanillic acid	VL	Ventral lateral nucleus of thalamus
IP3	Inositol triphosphate	VMAT2	Vesicular monoamine transporter 2
KA	Kainate	VTA	Ventral tegmental area
LC	Locus coeruleus	ZI	Zona incerta

ventral striatum (nucleus accumbens) and the mesocortical innervation of the dorsolateral and ventromedial prefrontal cortex regions (Fig. 3.4) (Van den Heuvel and Pasterkamp, 2008). Less appreciated is that the SNc also innervates the globus pallidus and subthalamic nucleus (Smith and Kieval, 2000), and that the thalamus also received dopamine input from a variety of sources (Sanchez-Gonzalez et al., 2005).

Dopamine is formed from levodopa (L-dopa) by the enzyme aromatic L-amino acid decarboxylase (AADC),

which has been commonly called dopa decarboxylase (Fig. 3.5) (Stahl, 2013). Once synthesized, dopamine is taken up into synaptic vesicles by the vesicular monoamine transporter 2 (VMAT2). In vivo, levodopa is synthesized from L-tyrosine by the enzyme tyrosine hydroxylase (TH). L-tyrosine is an essential amino acid in the brain, because it cannot be synthesized from L-phenylalanine, as it can in the rest of the body. Dopamine can be metabolized by monoamine oxidase (MAO) to 3,4-dihydroxyphenylacetic

Fig. 3.1 Anatomy of the basal ganglia. A coronal section of the brain showing most of the basal ganglia nuclei. A, Anterior nucleus; DM, dorsomedial nucleus; LP, lateral posterior nucleus; VPL, ventral posterior lateral nucleus. (From Woolsey TA, Hanaway J, Gado MH. *The Brain Atlas: A Visual Guide to the Human Central Nervous System*. 3rd ed. Hoboken, NJ: John Wiley & Sons; 2008.)

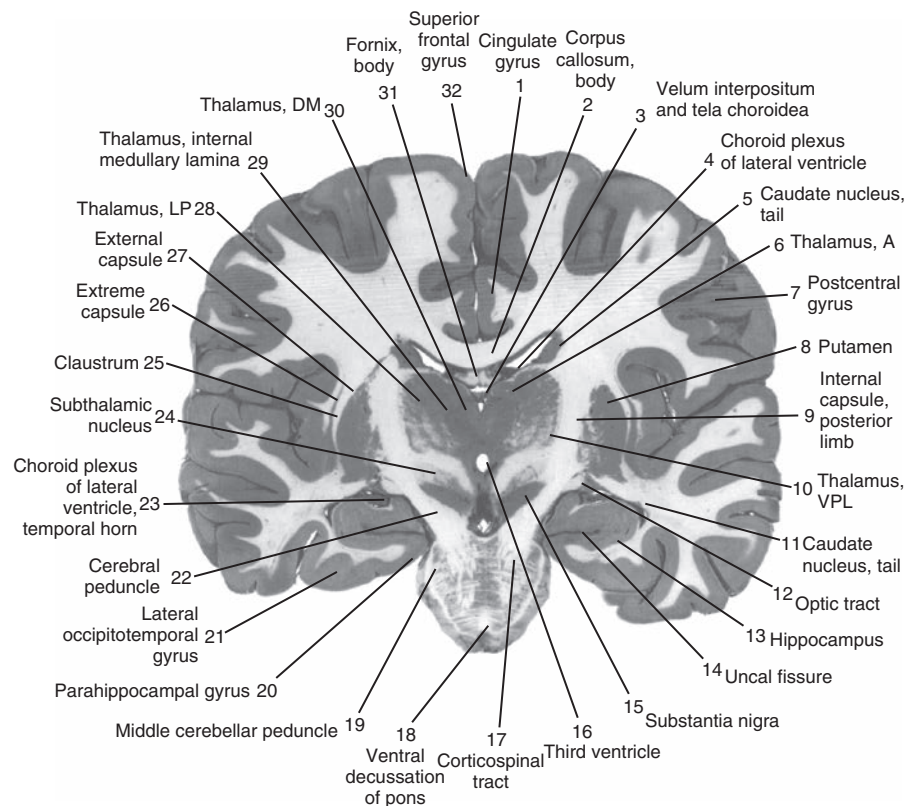
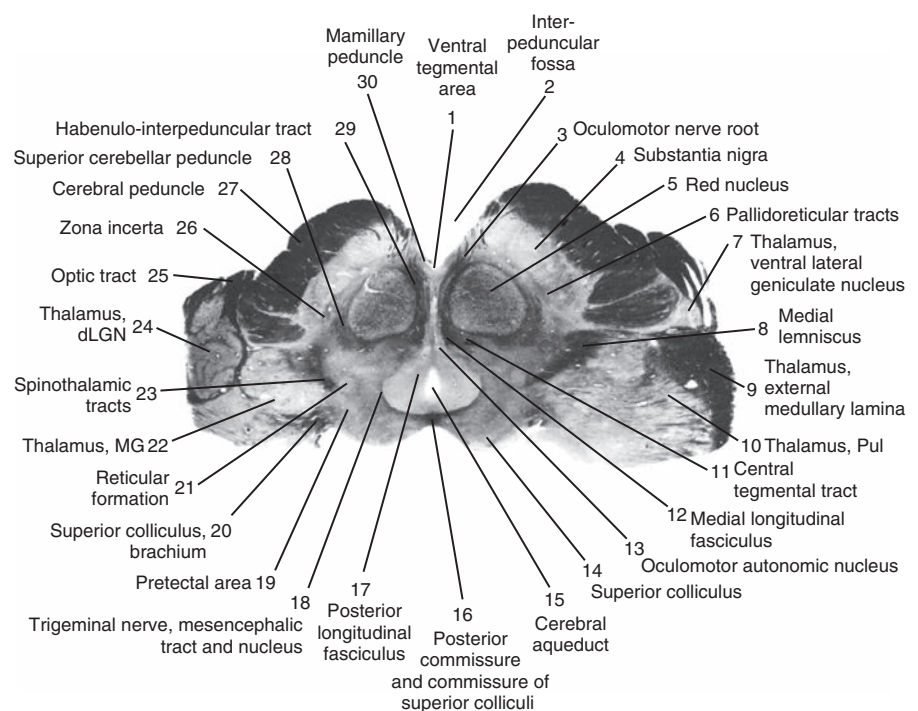


Fig. 3.2 An axial section at the midbrain level showing the principal nuclei for the origin of dopamine projections, the substantia nigra, and the ventral tegmental area. dLGN, Dorsal lateral geniculate nucleus; MG, medial geniculate nucleus; Pul, pulvinar. (From Woolsey TA, Hanaway J, Gado MH. *The Brain Atlas: A Visual Guide to the Human Central Nervous System*. 3rd ed. Hoboken, NJ: John Wiley & Sons; 2008.)



acid (DOPAC), by catechol-O-methyltransferase (COMT) to 3-methoxytyramine (3-MT) (also called 3-O-methyldopamine), and by both enzymes serially to homovanillic acid (HVA). MAO exists in two forms, MAO-A and MAO-B, both found in the mitochondria of neurons and glia (Bortolato et al., 2008). COMT is a membrane-bound enzyme (Bonifacio et al., 2007). Physiologically, dopamine action is terminated by reuptake into the

dopaminergic nerve terminal by action of the dopamine transporter (DAT). Once in the cytosol, it can be taken back up into synaptic vesicles by VMAT2. Dopamine neurons have MAO-A (not MAO-B) (Demarest et al., 1980), but virtually no COMT. Dopamine not taken up into vesicles will therefore be metabolized to DOPAC. If dopamine remains nonmetabolized in the cytosol, it might contribute to oxidative stress, as discussed in Chapter 5.

DOPAC can diffuse out of the presynaptic terminal, where it might confront COMT on the postsynaptic neuron, endothelial cells, or possibly glial cells and be converted to HVA. MAO-B is prominent in the basal ganglia and is largely in glial cells. Any dopamine not taken up in the presynaptic terminal might diffuse into glial cells (DAT is not necessary in nondopaminergic cells), where it would be converted to HVA. HVA and DOPAC eventually will diffuse out of cells and either into the circulation or into the cerebrospinal fluid via the choroid plexus.

The exact biology of dopamine differs in different parts of the body and even different parts of the brain. For example, in the cerebral cortex there is not much DAT so that after dopamine release, COMT is much more important in terminating dopamine action (Matsumoto et al., 2003).

There are five subtypes of dopamine receptors, D1 to D5, in two families, D1-like and D2-like (Missale et al., 1998; Beaulieu and Gainetdinov, 2011; Klein et al., 2019). The D1-like family, composed of D1 and D5, activates adenylyl cyclase and causes conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). Raising the concentration of cAMP is typically excitatory. The D2-like family, composed of D2, D3, and D4, inhibits adenylyl cyclase and reduces the concentration of cAMP. Lowering cAMP is typically inhibitory. Some D2 receptors, called autoreceptors, are on the presynaptic side of dopamine synapses, regulating release by negative feedback. The dopamine receptors are G protein coupled and give rise to downstream effects in the postsynaptic cell in addition to modulating adenylyl cyclase (Klein et al., 2019).

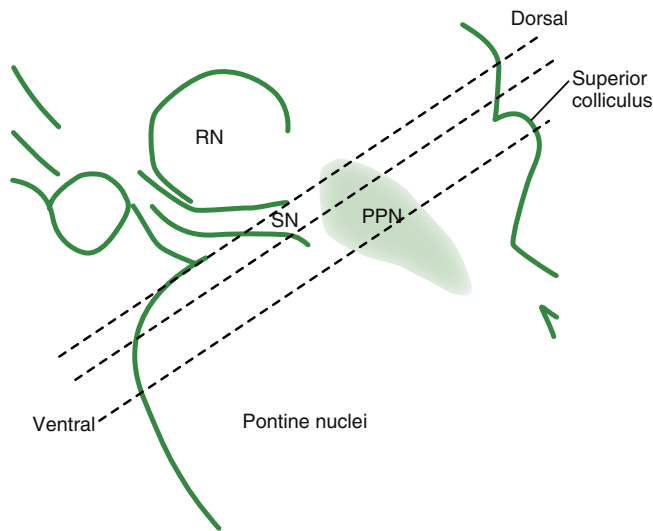


Fig. 3.3 Location of the pedunculopontine nucleus (PPN) with respect to the red nucleus (RN) and the substantia nigra (SN). (From Jenkinson N, Nandi D, Muthusamy K, et al. *Anatomy, physiology, and pathophysiology of the pedunculopontine nucleus*. *Mov Disord*. 2009;24[3]:319–328.)

Acetylcholine

Cholinergic neurons have two different types of roles (Pisani et al., 2007; Eskow Jaunarajs et al., 2015). One is as an interneuron, and the “giant aspiny interneuron” of the striatum is cholinergic (Girasole and Nelson, 2015). A second role is as a projection neuron. There are two prominent cholinergic projection systems in the brain. The best known are the neurons of the basal forebrain, such as the nucleus basalis of Meynert, which innervate wide areas of cortex, are involved with

Table 3.2 Neurotransmitters relevant to basal ganglia function

Dopamine
Acetylcholine
Glutamate
Gamma-aminobutyric acid (GABA)
Norepinephrine
Serotonin
Adenosine
Endogenous opioids
Neuropeptides
Endocannabinoids

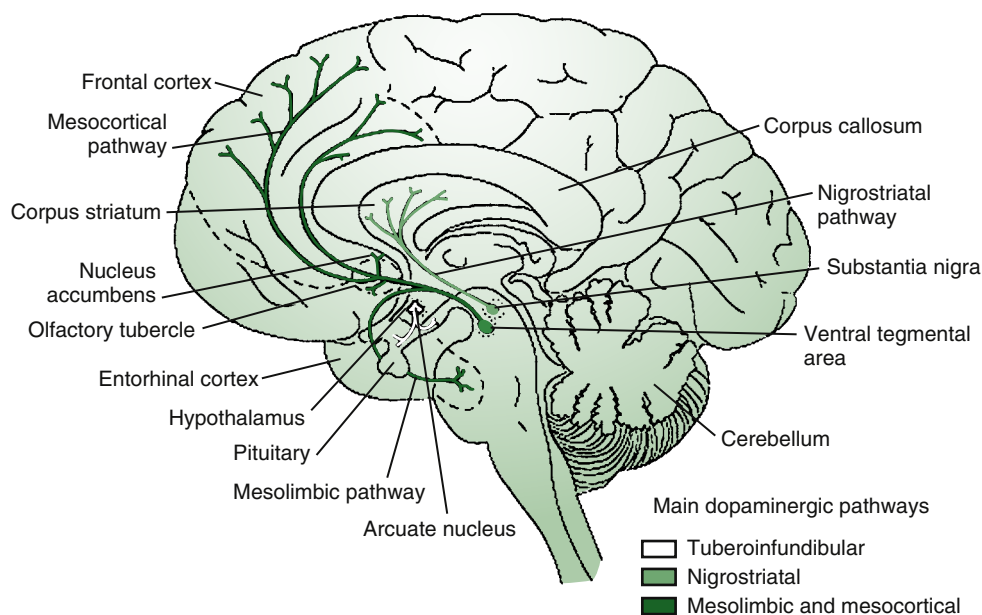
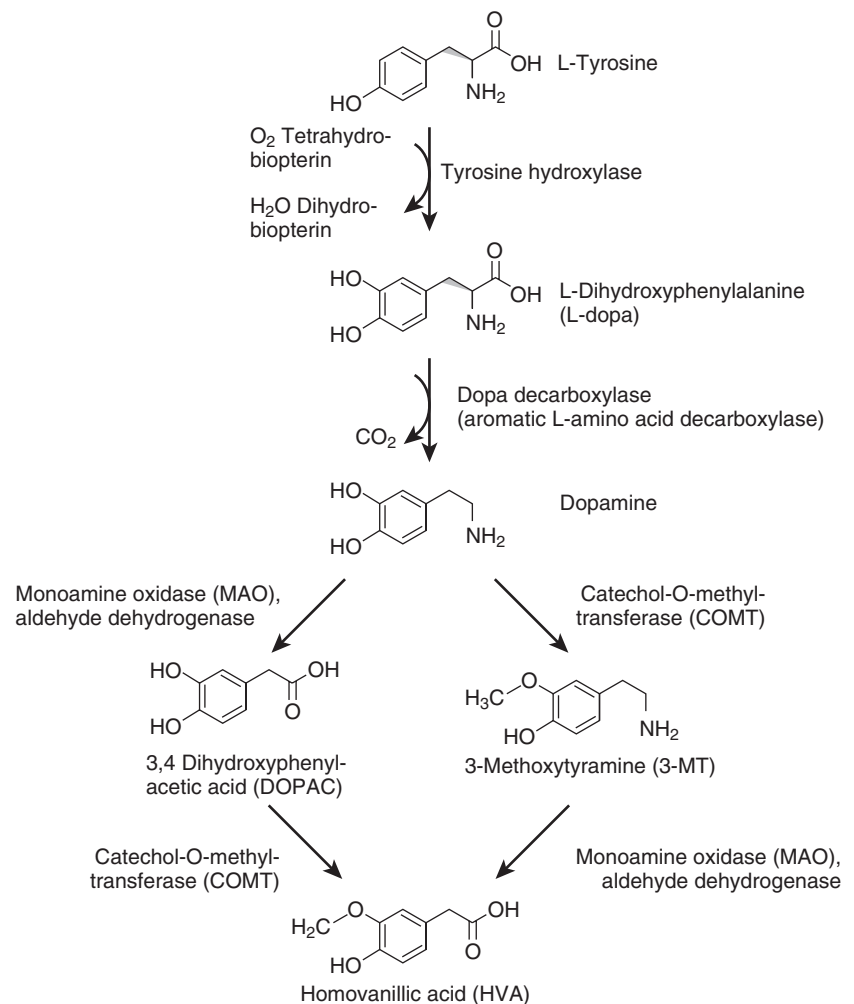


Fig. 3.4 The dopamine projection systems in the brain. The nigrostriatal pathway begins in the substantia nigra (light green), the mesolimbic and mesocortical pathways begin in the ventral tegmental area (dark green), and the tuberoinfundibular pathway begins in the arcuate nucleus (white). (From <http://www.austrianprescriber.com>.)

Fig. 3.5 Metabolism of dopamine. (From <http://en.wikipedia.org/wiki/Dopamine>.)



functions such as memory, and are deficient in Alzheimer disease. The other is the set of projections from the mesopontine tegmental complex, which includes the PPN. These are importantly involved in the basal ganglia motor system.

Acetylcholine (ACh) is synthesized in neurons from choline and acetyl-coenzyme A (acetyl-CoA) by the enzyme choline acetyltransferase (ChAT). After synthesis it is collected into vesicles by the enzyme vesicular ACh transporter (VACHT). Once released from the nerve terminals it is broken down by acetylcholinesterase (AChE), which is both presynaptic and postsynaptic, and butyrylcholinesterase (BuChE), also called pseudocholinesterase, that resides in glia (Cooper et al., 2003; Siegel et al., 2006). The resultant choline is taken back up into the presynaptic cell by a choline transporter (Stahl, 2013).

The two broad classes of ACh receptors are nicotinic and muscarinic. Nicotinic receptors (nAChR) are ionotropic and are prominent outside the brain at the neuromuscular junction and autonomic ganglia, but are also in the brain (Albuquerque et al., 2009). Activation at an nAChR will open a nonselective cation channel allowing flow of sodium, potassium, and sometimes calcium. Muscarinic receptors (mAChR) are metabotropic and also found both inside and outside the brain. Activation at an mAChR couples to a variety of types of G proteins (Eglen, 2005, 2006). There are many types of nAChR, and these are generally described by their subunit composition (Liu and Su, 2018). Designations

of M_1 to M_5 are given to the mAChRs. Both nAChR and mAChR are found in the basal ganglia, and there are both excitatory and inhibitory effects.

Glutamate

Glutamate (Glu) is the primary excitatory neurotransmitter in the brain, and as such it has a prominent role in the excitatory cortical-striatal input and in the excitatory projection from the STN to the globus pallidus interna (GPi). Glu is a central molecule in many cellular processes and is also the precursor for the most important inhibitory neurotransmitter in the brain, GABA. Glu is made from glutamine in mitochondria by glutaminase. It is then taken up into synaptic vesicles by the vesicular glutamate transporter. On release, its action is terminated by its being taken up into glial cells via an excitatory amino acid transporter (EAAT) and then converted to glutamine by glutamine synthetase. Glutamine transporters then move the glutamine from the glial cell into the neuron (Siegel et al., 2006; Stahl, 2013).

Glu receptor biology is very complex, and the details are well beyond this chapter (Willard and Koochekpour, 2013; Reiner and Levitz, 2018). There are three groups of metabotropic glutamate receptors (mGluR), groups I, II, and III, depending on mGluR composition. There are also three classes of ionotropic receptors, α -amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA), N-methyl-D-aspartic acid (NMDA)

(Hansen et al., 2017), and the kainate (KA) receptors. Hence, glutamate not only transmits an excitatory signal by opening calcium channels, but also sets many metabolic processes in action, such as creating short- and long-term changes in synaptic excitability. Such changes are thought to be fundamental in brain plasticity (Lovinger, 2010; Reiner and Levitz, 2018).

Gamma-amino butyric acid

GABA is the main inhibitory neurotransmitter in the brain, and this includes the major inhibitory connections in the basal ganglia. It is synthesized by glutamic acid decarboxylase (GAD) from glutamate. Once synthesized, it is collected into synaptic vesicles by vesicular inhibitory amino acid transporters. After release, its action is terminated by its being taken back into the presynaptic cell by the GABA transporter (GAT). If the nerve ending has too much GABA in it, it can be broken down by GABA transaminase (GABA-T).

There are three classes of GABA receptors: A, B, and C (Stahl, 2013; Siucinska, 2019). GABA-A and GABA-C are ionotropic and have inhibitory action by opening chloride and potassium channels. Much is known about GABA-A, but only little about GABA-C. GABA-A channels have many subclasses depending on the subunit makeup. An important distinction between subclasses is whether they are sensitive to benzodiazepines, depending on whether the benzodiazepines bind to them. In the sensitive channels, benzodiazepines can increase the inhibitory action of a GABA-A synapse. GABA-B is a metabotropic receptor (Filip and Frankowska, 2008) and produces a longer duration inhibition than GABA-A by promoting potassium channels and inhibiting calcium channels.

Norepinephrine

NE influence on the basal ganglia comes from the strong projection to it from the LC (Sasaki et al., 2008). NE is made from dopamine (in noradrenergic neurons) by the action of dopamine beta-hydroxylase (DBH). After synthesis, it is stored in vesicles by action of VMAT2 (similar to dopamine). After release, it is taken back up presynaptically by the NE transporter. Like dopamine, it can be metabolized by MAO-A, MAO-B, or COMT, but similar to dopamine, the main enzyme in the presynaptic terminal is MAO-A.

There are a large number of NE receptors; the different classes are alpha 1A, 1B, 1D, alpha 2A, 2B, 2C, and beta 1, 2, and 3 (Stahl, 2013). All can be postsynaptic, and the alpha 2 receptors also can be presynaptic. Activation of the presynaptic receptors inhibits further NE release. The alpha 1 receptors are G protein coupled, and increase levels of phospholipase C, inositol trisphosphate (IP3), and calcium. The alpha 2 receptors are G protein coupled, with an action to inactivate adenylate cyclase and reduce concentrations of cAMP. The beta receptors couple to G proteins that activate adenylate cyclase and increase cAMP.

Serotonin (5-hydroxytryptamine)

Serotonin (5-HT) influence on the basal ganglia comes from the MRN (Sasaki et al., 2008). 5-HT is synthesized from the amino acid tryptophan. Tryptophan is converted to

5-hydroxytryptophan (5-HTP) by tryptophan hydroxylase, and then 5-HTP is converted to 5-HT by aromatic amino acid decarboxylase (AADC). As with dopamine and NE, after synthesis, 5-HT is taken up into vesicles by the action of VMAT2. After release, it is metabolized by MAO-A or taken back up into the serotonergic neuron by the serotonin transporter (SERT). Serotonergic neurons contain both MAO-A and MAO-B.

There are many subtypes of 5-HT receptors (Sarkar et al., 2020), categorized into seven families, 5-HT₁ to 5-HT₇. 5-HT₃ is a ligand-gated sodium (Na⁺) and potassium (K⁺) channel that depolarizes membranes. The other family members are G protein coupled. 5-HT₁ and 5-HT_{5A} decrease cAMP; 5-HT₄, 5-HT₆, and 5-HT₇ increase cAMP; 5-HT₂ increases IP3 and diacylglycerol (DAG). 5-HT_{1A} and 5-HT_{1B/D} receptors are presynaptic and act to reduce 5-HT release, a negative feedback influence. Postsynaptic receptors include 5-HT_{1A}, 5-HT_{1B/D}, 5-HT_{2A}, 5-HT_{2C}, 5-HT₃, 5-HT₄, 5-HT₅, 5-HT₆, and 5-HT₇. Serotonin actions are complex. Activation of the 5-HT_{1A} receptor is generally inhibitory but also increases dopamine release. Activation of the 5-HT_{2A} receptor is generally excitatory but also inhibits dopamine release (Stahl, 2013). Monoamine interactions in general are very complex; for example, NE can influence 5-HT release and 5-HT can influence NE release.

Adenosine

Adenosine is a purine nucleoside and is an endogenous molecule in the brain (Benarroch, 2008a). Part of ATP, adenosine diphosphate (ADP), and cAMP, adenosine is a critical molecule in cellular energy metabolism, but it also plays a role as a neurotransmitter. Adenosine is found both intracellularly and extracellularly, and the concentration in the synaptic area is regulated by adenosine transporters (Hasko et al., 2008). There are four subtypes of adenosine receptors, A1, A2A, A2B, and A3, all G protein coupled. Caffeine is an important antagonist at the adenosine receptors. The A1 receptor is generally inhibitory, and the A2 receptors are excitatory, increasing levels of cAMP. Adenosine A2A receptors are colocalized with striatal dopamine D2 receptors on GABAergic medium spiny neurons (MSNs) that project via the "indirect" striatopallidal pathway to the globus pallidus externa (GPe) (Fuxe et al., 2007; Mori, 2020). Adenosine at the A2A receptor reduces binding of dopamine to the D2 receptor, and an antagonist of adenosine, such as caffeine, therefore enhances dopamine binding (Simola et al., 2008; Stahl, 2013).

Endogenous opioids

There are a variety of subclasses of these neurotransmitters, including dynorphins, enkephalins, endorphins, endomorphins, and nociceptin. Although these neurotransmitters play an important role in pain, they also have a direct influence on other functions in the basal ganglia, importantly in the limbic part of the circuitry. They act on the G protein-coupled opioid receptors (Faouzi et al., 2020); delta, kappa, mu, and the nociceptin receptor; delta and kappa are the most prominent in the basal ganglia (Benarroch, 2012). Opioids facilitate dopamine release. GABA receptors on the presynaptic dopamine terminal act to inhibit dopamine release. Opioids act to inhibit GABA release, which will then in turn reduce the amount of inhibition on dopamine release.

Neuropeptides

The opioids are examples of neuropeptide neurotransmitters, but there are approximately 100 of them. Typically, they are coreleased with other neurotransmitters. A neuropeptide important in the basal ganglia that is not an opioid is substance P. The MSNs in the striatum that have D1 receptors have the cotransmitters substance P and dynorphin, and those with D2 receptors have enkephalin.

Endocannabinoids

Although much of the interest in cannabinoids originated with exogenous substances, there is an endogenous system (Morera-Herreras et al., 2012). The principal receptor in the central nervous system and abundant in the basal ganglia is the CB1 receptor (Davis et al., 2018). Transient receptor potential vanilloid type1 (TRVP₁) receptors also respond to cannabinoids. Natural ligands for the receptor are anandamide and 2-arachidonoylglycerol (2-AG). The evidence is that the cannabinoids modulate dopaminergic effects (Garcia et al., 2016; Covey et al., 2017; Behl et al., 2020) and in many circumstances diminish dopamine release and slow behavior (Kluger et al., 2015). The data are limited, however, and more work is needed.

Components of the basal ganglia

Striatum

The striatum is composed of the caudate, putamen, and ventral striatum. As will be discussed later, when dealing with circuitry, the different parts of the striatum have different functions related to different patterns of connectivity with the rest of the brain. In general, the putamen is the motor part; the caudate is the associative or cognitive part; and the ventral striatum, which includes the nucleus accumbens, is the limbic part.

A large majority of cells in the striatum (80%–95%) are MSNs, primarily affected in HD (Reiner and Deng, 2018). These are GABAergic cells that project out of the striatum to the GP. They receive glutamatergic input from the cortex and the thalamus. The centrum medianum (CM) nucleus of the thalamus projects to the putamen and the parafascicular (Pf) nucleus to the caudate. These cells also receive important dopaminergic input from the SNc. Additional input from the LC is noradrenergic and from the MRN is serotonergic. The glutamatergic input comes to the dendritic spines on these cells, and the dopaminergic input comes to the neck of these spines (Fig. 3.6). It certainly appears that dopamine regulates the glutamatergic influence on these cells. There are two types of MSNs that are differentiated by the dopamine receptors on their surface. Those that have D1 receptors, in addition to GABA, also contain the polypeptide neurotransmitters substance P and dynorphin. These cells project to the GPi in what is called the direct pathway. Those that have D2 receptors, in addition to GABA, also contain the polypeptide neurotransmitter enkephalin. These cells project to the GPe, as the first step of the circuit to the GPi, known as the indirect pathway.

The striatum also contains interneurons, which are aspiny and do not project outside the striatum. There are at least

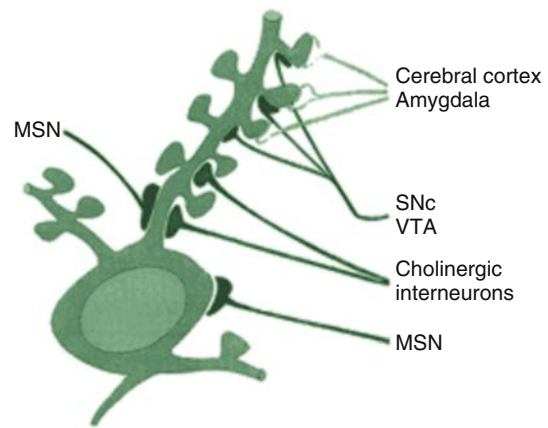


Fig. 3.6 Sites of synaptic input onto medium spiny neurons (MSNs) in the striatum. Note in particular that the cortical input is on the head of the spine and the dopaminergic input, from both substantia nigra pars compacta (SNc) and ventral tegmental area (VTA), are on the neck of the spine. (From Groenewegen HJ. *The basal ganglia and motor control*. *Neural Plast.* 2003;10[1–2]:107–120.)

four classes of these cells. One of these neurons is the giant aspiny cholinergic cell that has axons with large terminal fields (Pisani et al., 2007; Eskow Jaunarajs et al., 2015). These cells receive their principal input from the cortex (glutamate) and the SNc (dopamine). The cortical input activates the cells and the nigral input inhibits them. The cells have autonomous spontaneous activity and are also known as the tonically active neurons (TANs). This spontaneous action means that there is a tonic release of ACh in the striatum. The extracellular level of ACh will be modulated by AChE and by negative feedback mediated by presynaptic mAChRs. These interneurons are also influenced by adenosine, GABA, NE, and 5-HT (Pisani et al., 2007). The cells play a role in reward processing and modulation of dopamine-dependent neuroplasticity (Deffains and Bergman, 2015).

There are three classes of GABAergic interneurons in the striatum. These are identified by their containing parvalbumin, calretin, or somatostatin/nitric oxide/neuropeptide Y. All these cells are obviously inhibitory in nature. More detailed studies have been identifying more interneuron types, making the situation rather complex (Silberberg and Bolam, 2015).

Staining of the striatum for AChE revealed an interesting organization of the cells, which had not been anticipated by simple histology. There are regions called striosomes or patches that are AChE-poor, embedded in a matrix that is AChE-rich (Prager and Plotkin, 2019) (Fig. 3.7). This organization presumably comes from segregated influences of the cholinergic interneurons or the cholinergic projection neurons from the PPN. The matrix appears to receive more sensorimotor and associative input, and the striosomes receive more limbic input (Eblen and Graybiel, 1995; Crittenden and Graybiel, 2011). Interneurons span the two compartments, perhaps allowing for limbic influence on other functions. The output of the two compartments also differs (Crittenden and Graybiel, 2011; Fujiyama et al., 2011). The matrix projects mainly to the GP, and the striosomes provide the only projection to the SNc and a smaller contribution to the GP (Crittenden and Graybiel, 2011). Neurons in the striosomes also provide the major input to the pallidum (lateral) habenular circuit (Hong et al., 2019).

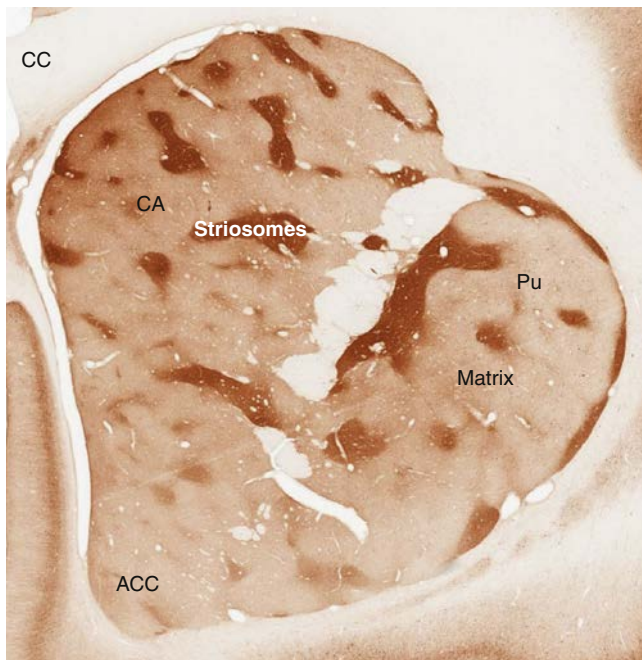


Fig. 3.7 Striosomes in the striatum of *Macaca fascicularis*. The striosomes are stained against potassium voltage-gated channel-interacting protein 1. ACC, Nucleus accumbens; CA, caudate; CC, corpus callosum; Pu, putamen. (From <http://www.BrainMaps.org>, copyright UC Regents, Davis.)

Globus pallidus

The GP is divided into the dorsal part and the ventral part (ventral striatum) and into the internal and external divisions, GPi and GPe, respectively, which are separated by the medial medullary lamina. There are only a few interneurons because most neurons are large, parvalbumin-positive, GABAergic neurons with large arbors of dendrites. The cells are shaped as flat disks that are parallel to each other (Yelnik et al., 1984). The GP gets input from all parts of the striatum, and the motor part is posterolateral (Nambu, 2011; Iwamuro et al., 2017). The pars reticulata of the SN (SNr) is similar in histology and connectivity to the GPi, from which it is separated by the internal capsule.

Subthalamic nucleus

The main neurons of the STN are glutamatergic with long dendrites (Yelnik and Percheron, 1979; Hamani et al., 2004). There are about 7.5% GABAergic interneurons (Levesque and Parent, 2005). The dorsolateral part of STN is motor (Nambu, 2011; Iwamuro et al., 2017), whereas the ventral part is associative and the medial part projects to limbic areas (Benarroch, 2008a).

Substantia nigra

The two parts of the SN are rather different from each other and will be described separately.

Substantia nigra pars compacta

The majority of the neurons of the SNc are dopaminergic and are the cells of origin of the nigrostriatal projection.

It is clear that the SNc facilitates movement, and there is good evidence as well for a role of dopamine in facilitating specific reward behaviors. Indeed, it is possible to identify rapid signaling of dopaminergic neurons for specific movements (da Silva et al., 2018) and for indicating reward (Howe and Dombeck, 2016). These neurons also have tonic release of dopamine and phasic release. The cells contain neuromelanin, which makes them dark, giving rise to the name of the nucleus ("nigra"). Because the death of these cells gives rise to the motor symptoms in PD, their cell biology has been studied extensively. Neuromelanin is derived from conjugation of dopamine-quinone, an oxyradical, thereby protecting the dopaminergic neurons from oxidative stress (Sulzer et al., 2000). Neuromelanin can chelate iron and can bind a variety of toxins (Zecca et al., 2001). Some of the dendrites of the dopaminergic cells extend into the SNr, where they have GABAergic receptors. About 15% of cells are interneurons, at least some of which are GABAergic (Hebb and Robertson, 2000).

Substantia nigra pars reticulata

The SNr is similar to the GPi in its histology, connectivity, and even pattern of degeneration in neurologic disorders. Hence, it is often considered a part of the GPi that has been separated by anatomic accident. In addition to connectivity similar to that of the GPi, it has an important output to the superior colliculus, which plays an important role in the control of saccadic eye movements.

Pedunculopontine nucleus

The PPN has important reciprocal connections with other parts of the basal ganglia, and it is crucial to understand its role. It appears to be a critical component in the midbrain locomotor area, among other functional activities. The PPN region is rather complex and is composed of a number of subregions that are not always completely distinct from each other. Many of the details of the subregions, their exact localization in humans, their connectivities, and their neurotransmitters are still being worked out (Karachi et al., 2012; Fournier-Gosselin et al., 2013; Hamani et al., 2016; Snijders et al., 2016; Garcia-Rill et al., 2019). The PPN can be divided into the compacta (PPNc) and dissipatus (PPNd) (Pahapill and Lozano, 2000; Hamani et al., 2007; Zrinzo et al., 2008; Jenkinson et al., 2009; Benarroch, 2013). Other nuclei in the vicinity include the midbrain extrapyramidal area (MEA) (Steininger et al., 1992), the peripeduncular nucleus (Zrinzo and Hariz, 2007), the laterodorsal tegmental nucleus (Benarroch, 2013), and the cuneiform and subcuneiform nuclei (Piallat et al., 2009).

The PPNc is composed mainly of cholinergic cells. The PPNd may be mostly glutamatergic cells but has also cholinergic cells.

Lateral habenula

As we learn more about the basal ganglia, it becomes apparent that there are many structures with important influence on their function. There has been increasing interest in the lateral habenula (Hikosaka et al., 2008; Nair et al., 2013; Yang et al., 2018). The habenula is located above the

posterior thalamus near the midline. The cells have a mixture of neurotransmitters. The lateral part of the habenula has a strong inhibitory influence on the SNc (via the rostromedial tegmental nucleus) (Haber, 2014) and the MRN. There are also reciprocal connections with the VTA (Stamatakis et al., 2013). It appears to exert its inhibition when there is a negative result from action, thus inhibiting a possible favorable effect of dopamine in facilitating rewarded behavior (Bromberg-Martin et al., 2010) or directly promoting aversion (Lammel et al., 2012). It is also implicated in depression (Hu et al., 2020). The main inputs to the lateral habenula come from forebrain areas, the lateral hypothalamus and the perifornical area, and from the GPi (Haber, 2014).

Zona incerta

The zona incerta (ZI) is a distinct nucleus, which appears to be an extension of the reticular nucleus of the thalamus, sitting ventral to the thalamus and between the fields of Forel, the fiber tracts conveying the pallidal output to the thalamus (Plaha et al., 2008; Chou et al., 2018; Lau et al., 2020). It receives input from the GPi and SNr, the ascending reticular activating system, the cerebellum, and different regions of the cerebral cortex. Its output cells are GABAergic and go to the centrum medianum/parafascicular (CM/Pf) and the ventral anterior nucleus of thalamus (VA)/VL thalamic nuclei, MEA, medial reticular formation, and reciprocal connections to the cerebellum, GPi/SNr, and cerebral cortex. The ZI may act to help synchronize activity across the many regions that it contacts (Plaha et al., 2008) and function as an integrative node for behavior and physiological state (Wang et al., 2020).

Other nuclei

The LC is the source of noradrenergic input to the basal ganglia (Fig. 3.8). The MRN is the source of serotonergic input. The thalamus, although not part of the basal ganglia itself, is a main relay station for output from the GPi and SNr to the cortex. There are two important nuclear target regions, the VA/VL nuclei, which are the classic relay nuclei, and the CM/Pf nuclei, which are midline thalamic nuclei and serve as internal feedback to the basal ganglia. These thalamic neurons are all glutamatergic.

Circuitry of the basal ganglia

General circuitry

The connectivity of the basal ganglia is clearly crucial in carrying out its functions. The connections are complex, and it is necessary to have some general model for how they are organized. Such a model was proposed about two decades ago independently by three groups of investigators, each using a different technique: Crossman (1987); Albin Young, and Penney (1989); and DeLong (1990). This model has been extremely helpful in organizing thinking, planning pharmaceutical strategies for basal ganglia disorders, and even developing surgical approaches to patients. However, there were always difficulties with the model, and in more recent years it has become apparent that this model is not sufficient to explain what we now know. Hence, a new model is emerging that takes into account many more of the known connections and basal ganglia functions. It is worthwhile to present the older, “classic” model first, because it does form a foundation for the new model and much current thinking is still based on it.

The classic model is shown in Chapter 2, Fig. 2.2A, and is a part of the model shown in Fig. 3.9. In this model, described also in Chapter 2, there are two parallel loops from the cortex through the basal ganglia and back to the cortex and the direct and indirect pathway. The direct pathway starts with cortical glutamatergic input to the striatal cells bearing D1 receptors. These GABAergic neurons project directly to the GPi. The GABAergic neurons of the GPi project to the VA/VL nuclei of the thalamus, and the thalamic cells return glutamatergic input to the cortex. This four-neuron circuit has two inhibitory neurons and would be net excitatory. The indirect pathway starts with cortical glutamatergic input to the striatal cells bearing D2 receptors. These GABAergic cells project to the GPe, which has a GABAergic projection to the STN, which has a glutamatergic projection to the GPi. The final part of the path from GPi through thalamus to cortex is the same as the direct pathway. This is a six-neuron pathway with three inhibitory neurons, and therefore this would be net inhibitory. The SNc is a modulator of both direct and indirect pathways. By its influence on D1 and D2 receptors, it will facilitate those striatal neurons of the direct pathway

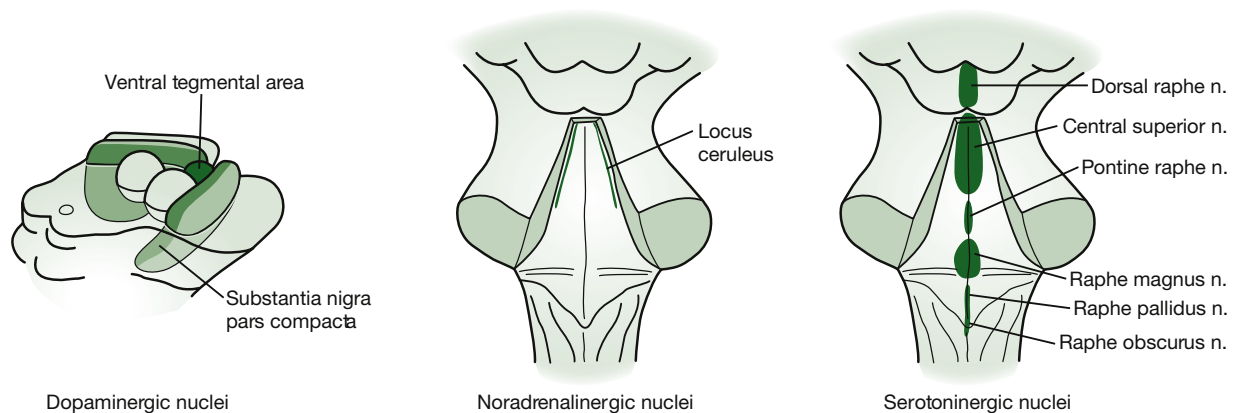
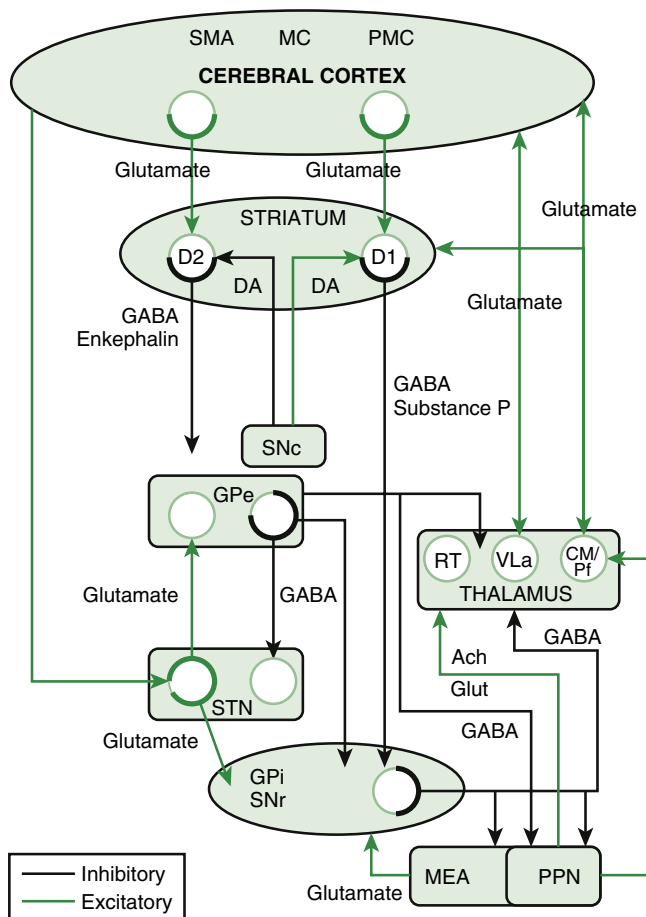


Fig. 3.8 Anatomy of the dopaminergic, noradrenergic, and serotonergic nuclei in the brainstem. Dopamine comes from the substantia nigra pars compacta and ventral tegmental areas, noradrenaline from the locus ceruleus, and serotonin from the median raphe nuclei. (From Sasaki M, Shibata E, Tohyama K, Kudo K, Endoh J, Otsuka K, Sakai A. Monoamine neurons in the human brain stem: Anatomy, magnetic resonance imaging findings, and clinical implications. *NeuroReport*. 2008;19:1649–1654.)

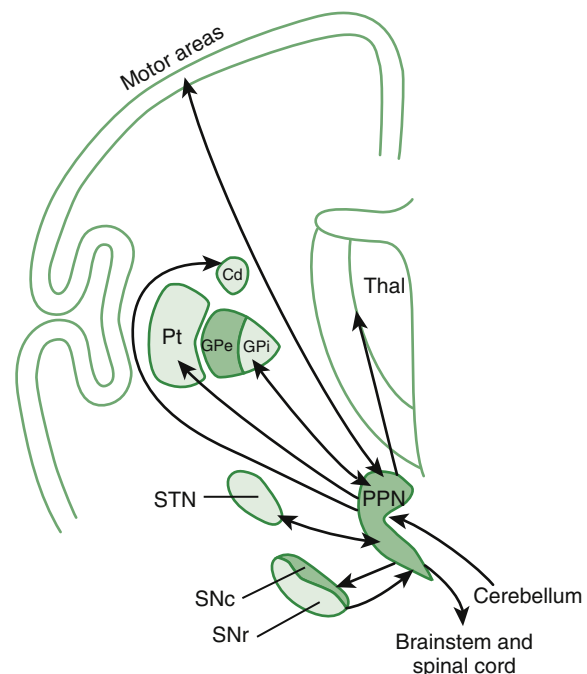
Many connections are left out of the classic model, and it appears that many of them are rather important. Fig. 3.9 (and Chapter 2, Fig. 2.4B) shows the connections of a more complete model. This model does not dispute any of the old connection; it adds new, apparently important connections. There is a strong connection from the cortex directly to the STN; this is called the hyperdirect pathway and appears to be a very important component (Pan et al., 2014; Coude et al., 2018; Miocinovic et al., 2018). Like the indirect pathway, its influence should be net inhibition. The cortex also has a strong projection directly to the thalamus (Crandall et al., 2015). A missing node in the older network is the CM/Pf nucleus of the thalamus. The GPI projects to it and to VA/VL, and the CM/Pf in turn projects back both to striatum and STN. CM projects mainly to the putamen and Pf to caudate and ventral pallidum. CM/Pf also has reciprocal connections to the cortex.



Additionally, the SNc projects to STN and the STN projects back to the GPe as a reciprocal connection to what was in the classic model. The GPe itself plays a more critical role, now not only getting input from the striatum, but also from STN and SNc. The major new aspects are increased importance of STN and GPe as integrative nodes, and more widespread direct influence of SNc (Obeso et al., 2008; Gittis et al., 2014).

Increasingly more connections are being described. Some may be quite important, and new physiologic schemes will have to be developed to take all this new information into account. Bridging collaterals connect the direct and indirect pathways (Cazorla et al., 2015). The direct pathway neuron from striatum to GPi has a collateral to GPe, and the indirect pathway neuron from GPe to STN has a collateral back to the striatum. There might even be a direct cortico-pallidal pathway as suggested by human magnetic resonance imaging studies (Milardi et al., 2015) and physiologic studies (Ni et al., 2018); however, there is also physiologic evidence against such a pathway (Miocinovic et al., 2018).

Even these newer models, discussed in the last paragraphs, do not include the brainstem influences. These come from the LC (NE), the MRN (5-HT), the ZI, the lateral habenula, and the PPN. The lateral habenula and the PPN have several different neurotransmitters, but the PPN is the main source of cholinergic input to the basal ganglia. The PPN has reciprocal connections with virtually every part of the basal ganglia circuitry (Fig. 3.10). The most important inputs come from GPi and STN, and the most important outputs go to STN, GPi, SNc, thalamus, and brainstem. The latter output to the brainstem is now thought to be the major directly



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descending motor influence from the basal ganglia. The PPN is also reciprocally connected directly to the cortex.

Parallel pathways

Another important principle of basal ganglia circuitry is its parallel organization (Alexander et al., 1986; Rodriguez-Oroz et al., 2009). Each part of the cortex has a separate pathway through the whole circuit (Fig. 3.11). In broad brush, the motor loop would run from motor cortex, to putamen, to lateral GPi, to VL, and back to cortex. An executive or cognitive loop would run from dorsolateral prefrontal cortex, to dorsolateral caudate, to medial GPi, to medial dorsal and VA nuclei of the thalamus, and back to cortex. A limbic loop, which plays an important part in reward (Haber and Knutson, 2010) and emotion, would run from anterior cingulate cortex, to ventral striatum, to ventral pallidum, to medial dorsal nucleus of thalamus, and back to cortex. These loops are generally separate, but there is some overlap allowing integration (Haynes and Haber, 2013; Averbeck et al., 2014; Jarbo and Verstynen, 2015). The loops are even more fine-grained, so that, for example, in the motor system, different parts of the motor system have different loops and somatotopy of different body parts is maintained throughout the loop (Middleton and Strick, 2000). For example, the primary motor area (M1), the supplementary motor area (SMA), and the ventral premotor area (PMv) will have separate loops. The cerebellum has similar isolated loops, and whereas it had been thought that the cerebellar and basal ganglia loops did not interact, it is now clear that there are important reciprocal connections (Bostan and Strick, 2010, 2018; Bostan et al., 2010, 2018).

Physiology

Cellular activity

Most information about normal cellular activity comes from recordings in animals. There are considerable data from primates. Human information comes largely from recordings when placing electrodes for deep brain stimulation (DBS) surgery and thus is pathologic rather than normal.

By comparing human pathologic data with animal models, such as the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) monkey model of PD, it has been generally concluded that primate information is likely quite similar to that of humans (Wichmann et al., 2018).

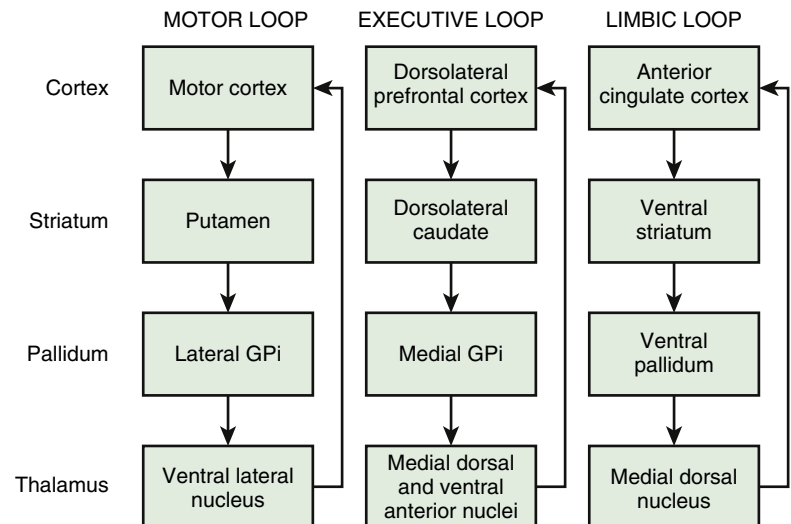
The MSNs in the striatum have a low firing rate, on average 0.5 to 2 Hz (van Albada and Robinson, 2009). Cells are often in a hyperpolarized, or down, state because of an intrinsic inwardly rectifying K⁺ current (Hammond et al., 2007). Cells will fire largely only when there is a convergence of inputs onto the cell. Excitatory inputs come mainly from cortex and thalamus. The excitatory input will be modulated by the striatal interneurons and the nigrostriatal dopamine neurons that have input at the base of the dendritic spine and on the shaft of the dendrite itself (see Fig. 3.6). The cholinergic interneurons, the TANs, appear to be the most spontaneously active neurons in the striatum. They fire at 2 to 10 Hz and are modulated to some extent during learning (Aosaki et al., 1995).

Cellular activity in the GPi is the opposite of the striatum; cells are tonically active at 60 to 90 Hz (van Albada and Robinson, 2009). Activity in the GPe shows two types of behavior. Approximately 85% of cells have high-frequency bursts together with long intervals of silence for up to several seconds and an average firing rate of 55 Hz. The other 15% have a slower average rate of about 10 Hz, with occasional bursts (van Albada and Robinson, 2009). Cells in the STN also show spontaneous activity, at about 20 to 30 Hz, and spikes may be in pairs or triplets (van Albada and Robinson, 2009). Cells in the VA/VL of the thalamus fire at about 18 to 19 Hz (van Albada and Robinson, 2009).

Circuit physiology

Exactly what the basal ganglia ordinarily contribute to brain processing is not certain. However, the cellular processing should give some insight into this. Inputs from cortex (and thalamus) come to the striatum, and, as noted previously, only a strong, convergent input will activate neurons. Activity of MSNs of the direct pathway will then suppress the tonically rapid firing cells in the GPi, which will release a

Fig. 3.11 Segregated loops through the basal ganglia. (Redrawn from Purves D, Augustine GJ, Fitzpatrick D, et al. *Neuroscience*. 2nd ed. Sunderland, MA: Sinauer Associates; 2001.)



region of the thalamus from tonic inhibition. This should be a net facilitation back to the cortex. At the same time that the GPi is inhibited by the direct pathway, there are a number of sources of excitation (or lessened inhibition). The GPe delivers less inhibition. Other inputs arrive via the STN, which gets less inhibition via the classic indirect pathway and excitation via the hyperdirect pathway. Thus, the output of the STN on the GPi is to excite it. The GPi therefore has to integrate its opposing inputs for a properly balanced output. This notion of how the direct and indirect pathways influence GPi cellular activity has been verified in mice using optogenetic techniques (in mice the SNr is used as the analog of the GPi in humans) (Freeze et al., 2013). As noted in Chapter 2, one possible function of the facilitation and inhibition is movement focusing and selection with a surround inhibition mechanism.

The basal ganglia clearly provide important signal processing, but there is strong evidence that they are also involved in motor learning (Obeso et al., 2017). The basal ganglia show significant plasticity of synaptic connections. Dopamine plays an important role in this plasticity, conveying reward signals that indicate the importance of what should be learned (Schultz, 2010; Steinberg et al., 2013; Kim and Hikosaka, 2015).

Another measure of cellular activity is called a local field potential (LFP). LFPs summate large numbers of neurons and synaptic activity, similar to the electroencephalograph (EEG). Like the EEG, LFPs can sometimes show rhythmic behavior in different frequency ranges (if cellular activity is analyzed, similar rhythmic activity can be appreciated [Du et al., 2018]). Cellular activity in the basal ganglia nuclei is not typically synchronized, and LFPs do not show prominent oscillations. In PD, there is synchronization and oscillations in both STN and GPi in the 10- to 30-Hz (beta) range (Brown, 2007; Galvan and Wichmann, 2008; Israel and Bergman, 2008; Alavi et al., 2013; Stein and Bar-Gad, 2013; Wichmann, 2018). The origin of this beta rhythm is not completely clear, but it appears to correlate with bradykinesia (Chen et al., 2010; Tass et al., 2010; Little et al., 2012). There is evidence that the beta oscillations may be more in the striatal neurons of the indirect pathway than the direct pathway, and that might be part of the explanation of why the oscillations are antikinetic (Sharott et al., 2017). The beta rhythm also may be coupled to even higher frequency oscillations

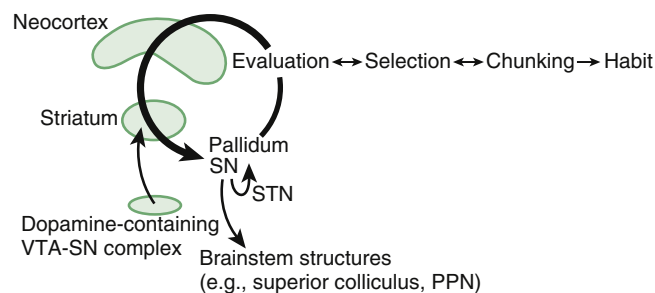


Fig. 3.12 Proposed basal ganglia function of making movements automatic and habitual by iterative cycling through the basal ganglia. PPN, Pedunculopontine nucleus; SN, substantia nigra; STN, subthalamic nucleus; VTA, ventral tegmental area. (From Graybiel AM. *Habits, rituals, and the evaluative brain*. *Annu Rev Neurosci*. 2008;31:359–387.)

(Lopez-Azcarate et al., 2010). There are also oscillations in alpha frequency range that correlate with tremor.

There are a number of theories as to what the basal ganglia contribute to movement processing, and by analogy to processing of cognitive and limbic information. One such theory is movement selection, wherein the direct pathway selects a movement to be facilitated, and the indirect and hyperdirect pathways inhibit undesired movements. Other concepts include the automatic running of motor programs (Marsden, 1982) and learning and release of habits (Graybiel, 2008). The latter idea is that certain behaviors that get rewarded and get repeated, eventually become automatic (Fig. 3.12). It also appears that the basal ganglia help speed up brain processes, both motor and nonmotor (Hanakawa et al., 2017). As is abundantly clear in this book, considering all the hyperkinetic and hypokinetic disorders that derive from basal ganglia dysfunction, the basal ganglia must have something to do with the regulation of amount of motor output. It seems also to be the case that the function of the basal ganglia must be to some extent a parallel pathway of brain function, because a large stroke destroying most of the basal ganglia or an ablative lesion of the GPi, such as performed with pallidotomy in PD, results in a patient performing reasonably well on most tasks.

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Parkinsonism: Clinical features and differential diagnosis

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Introduction

Parkinsonism is a syndrome manifested by a combination of the following six cardinal motor features: tremor-at-rest, rigidity, bradykinesia, loss of postural reflexes, flexed posture, and freezing (motor blocks). A combination of these signs is used to clinically define definite, probable, and possible parkinsonism (Table 4.1). The most common form of parkinsonism is the idiopathic variety known as Parkinson disease (PD), first recognized as a unique clinical entity by James Parkinson in 1817, who in his “Essay on the Shaking Palsy” identified six patients, three of whom he personally examined and the others he observed on the streets of London (Parkinson, 1817; Obeso et al., 2017). With the condition previously referred to as “paralysis agitans,” Charcot later in the nineteenth century gave credit to Parkinson by referring to the disease as “maladie de Parkinson” and pointed out that slowness of movement should be distinguished from weakness; he also recognized nontremulous forms of PD (Kempster et al., 2007). With the recognition of marked clinicopathologic heterogeneity of parkinsonism as a result of a single mutation and some uncertainty whether PD should be defined clinically, pathologically or genetically, a variety of other names have been proposed for this neurodegenerative disorder, including “Parkinson complex” and “Parkinson Lewy disease” (Langston, 2006), but it is unlikely that these names will replace the traditional name “Parkinson disease.” Some have argued that PD is not a single entity, but more of a syndrome, a notion supported by genetic forms of parkinsonism with variable clinical and pathologic features (Weiner, 2008; Stern et al., 2012). Although the diagnosis of PD is still largely based on clinical criteria, an increasing number of

tests and investigations are available to clinicians to confirm the diagnosis and possibly even identify the presymptomatic phase of the disease (Wu et al., 2011; Berardelli et al., 2013; Noyce et al., 2016). With increasing recognition of the presymptomatic or prodromal clinical features of PD, the proposed definitions of PD for clinical diagnosis and research utility have evolved (Berg et al., 2015; Postuma et al., 2015, 2017; Fereshtehnejad et al., 2017).

It was not until almost 100 years after Parkinson’s landmark paper when in 1912 Fritz Heinrich Lewy, a Berlin-born neuropathologist, described neuronal inclusions in the brain of patients with PD (Rodrigues e Silva et al., 2010; Shulman et al., 2011; Jellinger, 2012). Loss of cells in the substantia nigra (SN) was recognized in 1919 by Tretiakoff and colleagues (1919). In 1960 Ehringer and Hornykiewicz (1960) first noted that striatum of patients with PD was deficient in dopamine, and the following year, Birkmayer and Hornykiewicz (1961) injected levodopa in 20 patients with PD and postencephalitic parkinsonism and noted marked improvement in akinesia but not in rigidity. Later in the same decade, Cotzias and colleagues (1967, 1969) were credited with making levodopa clinically useful in patients with PD. Disclosure of the diagnosis of PD in several public figures has contributed over the years to increased awareness, education, and research about the disease.

With the increased recognition of the prodromal, premotor, and nonmotor clinical features of PD and associated biomarkers, and the expanding knowledge about the clinical heterogeneity of PD, overlap with other parkinsonian disorders, and growing appreciation of genetic etiologies, new classifications are necessary to take into account the clinical, syndromic, etiologic, and pathogenic aspects of parkinsonism (see Chapter 5).

Table 4.1 Parkinsonism motor features

1. Tremor at rest
2. Bradykinesia
3. Rigidity
4. Loss of postural reflexes
5. Flexed posture
6. Freezing (motor blocks)

Clinical features

Motor parkinsonism

The term *parkinsonism* is used to describe a syndrome manifested by a combination of the following six cardinal features: (1) tremor-at-rest, (2) bradykinesia, (3) rigidity, (4) loss of postural reflexes, (5) flexed posture, and (6) freezing (motor blocks). A combination of these signs is used to clinically define definite, probable, and possible parkinsonism. Diagnosis of definite parkinsonism requires that at least two of these features must be present, with one of them being resting tremor or bradykinesia; probable parkinsonism consists of resting tremor or bradykinesia alone; and possible parkinsonism includes at least two of the remaining four features. The four major characteristics of parkinsonism—tremor, rigidity, akinesia, and postural disturbances (forming the acronym TRAP)—account for most of the clinical abnormalities. The initial feature of many basal ganglia diseases is slowness of movement (*bradykinesia*), which also constitutes a primary feature in the United Kingdom Brain Bank diagnostic criteria for PD (Hughes et al., 1992b), but also paucity or absence of movement (*akinesias*), often associated with rigidity and tremor (Jankovic, 2007a). Some authors have used the term *hypokinesia* to describe a reduction in amplitude of movement. Many parkinsonian symptoms are explained by the combination of slowness and poverty of movement and increase in muscle tone (rigidity). These clinical features of parkinsonism will be discussed individually.

Parkinsonism, as a clinically defined feature, may reflect different underlying etiologies, such as PD, atypical parkinsonian syndromes (discussed in other chapters), and similarly appearing age-related features. Many parkinsonian symptoms and signs that could be associated with PD may be mistakenly attributed to “frailty” of the elderly because the disease is age-related (Clegg et al., 2013). It is worth noting that one hallmark of age-related frailty is sarcopenia, defined as gait speed slower than 1 m/s and measured appendicular muscle mass of 2 standard deviations (SDs) below the muscle mass of a 20- to 30-year-old individual, which occurs in 5% to 13% of adults between the ages 60 and 70 years (Tung et al., 2013). Longitudinal studies of older adults from the Religious Orders Study and Memory and Aging Project (n = 791, mean of 6.4 years until death, mean age 88.5 years) followed with annual clinical evaluations and documented physical frailty demonstrate high rates of mixed neuropathologic findings at autopsy, including macroinfarcts, Alzheimer disease (AD), Lewy body pathologic findings, and nigral neuronal loss, all of which probably contributed to the progressive physical frailty (Buchman et al., 2013). From the same cohort, 964 of 2001 (48.2%) individuals developed parkinsonism during a 5-year follow-up (Buchman et al., 2016),

which was related to age (hazard ratio [HR], 1.09; 95% confidence interval [CI], 1.08–1.10), but not to gender (HR, 1.06; 95% CI, 0.91–1.23) or education (HR, 0.99; 95% CI, 0.97–1.01). The incidence of parkinsonism increased with age: for adults younger than 75 years, the incidence of parkinsonism was 36 per 1000 person-years for adults younger than 75 years, 94.8 per 1000 person-years for those aged 75 to 84 years, and 160.5 per 1000 person-years for those 85 years and older. Most individuals exhibited 2 parkinsonism signs (83%; n = 800)—most commonly parkinsonian gait (n = 843; 87.4%). Incident parkinsonism was associated with depressive symptoms, neuroticism, urinary incontinence, sleep complaints, and chronic illness. Although walking tends to slow with normal aging, slow walking speed correlates with white matter changes only in individuals with low education level (Elbaz et al., 2013). The progression of parkinsonism in older adults relates to the burden of mixed brain pathologic conditions. In a cohort of 1430 individuals followed for a mean of 8.5 years, 53.9% developed parkinsonism proximate to death; those with more rapid progression of parkinsonism had PD pathologic findings at autopsy and the independent presence of AD and cerebrovascular pathologic findings (Buchman et al., 2019). Interestingly, the association between a higher person-specific weighted pathologic score and more rapidly progressive did not differ between those with or without a clinical diagnosis of PD but related to the underlying pathologic burden.

Bradykinesia

Bradykinesia translates as slowness in movement but is considered the slowness of movement and reduction in frequency and amplitude of repeated movements in the context of PD examination. Bradykinesia is the most characteristic clinical hallmark for the diagnosis of PD. It may be initially manifested by slowness in activities of daily living (ADLs), movements of limbs and/or whole body, and reaction times (Cooper et al., 1994; Touge et al., 1995; Giovannoni et al., 1999; Jankovic et al., 1999; Rodriguez-Oroz et al., 2009; Hallett, 2011; Maetzler et al., 2013; Schilder et al., 2017). On examination, bradykinesia manifests as slowness of movements but with a decrement in the amplitude and speed of the movement, such as when examined with the motor items in the International Parkinson and Movement Disorder Society and Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) for fine motor movement or rapid alternating movements. Although speed and amplitude are usually assessed together on the MDS-UPDRS, there is some evidence that amplitude is disproportionately more affected than speed in PD and may be due to different motor mechanisms. Thus, some have proposed that amplitude should probably be assessed separately (Espay et al., 2009). Other manifestations of bradykinesia include reduced arm swing when walking (loss of automatic movement) and gesturing when talking, loss of facial expression (hypomimia) (Ricciardi et al., 2015), reduced blinking, drooling because of failure to swallow saliva (Bagheri et al., 1999; Lal and Hotaling, 2006), and monotonic and hypophonic dysarthria. Micrographia may be represent a form of bradykinesia, although it may reflect an abnormal response from reduced motor output or weakness of agonist force coupled to distortions in visual feedback (Teulings et al., 2002; Inzelberg et al., 2016). Micrographia has been further

Table 4.2 Frequency of different movement disorders in a referral movement disorders clinic

Primary movement disorder	Total number		Percentage total	
Parkinsonism	10,952	—	31.86	—
Parkinson's disease (PD)	—	6,975	—	20.29
Dystonia	6,446	—	18.75	—
Tremor (other than PD)	4,862	—	14.14	—
Tics (including Tourette syndrome)	2,341	—	6.81	—
Chorea	1,445	—	4.20	—
Huntington disease	617	—	1.79	—
Ballism	68	—	0.20	—
Athetosis	13	—	0.04	—
Myoclonus	676	—	1.97	—
Other	6,960	—	—	—
Restless legs syndrome	—	—	—	2.41
Stereotypies (including tardive dyskinesia)	—	899	—	2.61
Akathisia	—	78	—	0.23
Ataxia	—	414	—	1.20
Psychogenic	—	1,752	—	5.10
All other	—	2,990	—	8.70
TOTAL	34,380	—	100.00%	—

These figures represent the number of reported disorders in each patient. Patients may have more than one disorder.
Courtesy Parkinson's Disease Center and Movement Disorders Clinic, Baylor College of Medicine, Houston, Texas.

characterized as consistent (small handwriting throughout) or progressive (progressive reduction in size); both types were associated with decreased activity and connectivity in the basal ganglia motor circuit, but in the persistent type, with additional disconnections between the rostral supplementary motor area, rostral cingulate motor area, and cerebellum on functional magnetic resonance imaging (fMRI), but levodopa only improved consistent micrographia (Wu et al., 2016). Bradykinesia, like other parkinsonian symptoms, is dependent on the emotional state of the patient. With a sudden surge of emotional energy, the immobile patient may catch a ball or make other fast movements. This curious phenomenon, called *kinesia paradoxa*, demonstrates that the motor programs are intact in PD, but that patients have difficulty using or accessing the programs without the help of an external trigger. Therefore, parkinsonian patients can use prior information to perform an automatic or preprogrammed movement, but not to initiate or select a movement. Although PD represents the most common form of parkinsonism, there are many other causes of bradykinesia, the parkinsonian clinical hallmark (Table 4.2).

The pathophysiology of bradykinesia is not well understood, but it is thought to relate to disruptions in basal ganglia circuitry and dopaminergic function. Bradykinesia may result from failure of basal ganglia output to reinforce the cortical mechanisms that prepare and execute the commands to move (Jankovic, 2007). Bradykinesia manifests as

slowness of self-paced movements and prolongation of reaction and movement time. Reaction and movement times are independently impaired in PD (Evarts et al., 1981). Reaction time is influenced not only by the degree of motor impairment but also the interaction between cognitive processing and the motor response. Patients with bradykinetic PD have more specific impairment in choice reaction time, which involves stimulus categorization and response selection, thereby reflecting more complex levels of cognitive processing, which can be affected in basal ganglia disorders, including PD. Of the various objective assessments of bradykinesia, movement time correlates best with the total clinical score, but it is not as sensitive an indicator of the overall motor deficit as is the clinical rating (Ward et al., 1983). The pre-movement electroencephalographic (EEG) potential (Bereitschaftspotential) is reduced in PD, probably reflecting inadequate basal ganglia activation of the supplementary motor area (Dick et al., 1989). On the basis of electromyographic (EMG) recordings in the antagonistic muscles of parkinsonian patients during a brief ballistic elbow flexion, Hallett and Khoshbin (1980) concluded that the most characteristic feature of bradykinesia was the inability to energize the appropriate muscles to provide a sufficient rate of force required for the initiation and maintenance of a large, fast (ballistic) movement. PD patients need a series of multiple agonist bursts to accomplish a larger movement. Thus, the amount of EMG activity in PD is underscaled (Berardelli et al., 2001). Although many patients with PD complain of "weakness," this subjective symptom is probably due to a large number of factors, including bradykinesia, rigidity, fatigue, and reduced power as a result of muscle weakness, particularly when lifting heavy objects (Allen et al., 2009).

Reduced dopaminergic function has been hypothesized to disrupt normal motor cortex activity, thereby leading to bradykinesia. Decreases in firing rates from single cortical neuronal recordings in free-moving rats correlated with haloperidol-induced bradykinesia, demonstrating that reduced dopamine action impairs the ability to generate movement and causes bradykinesia (Parr-Brownlie and Hyland, 2005). Of the various parkinsonian signs, bradykinesia correlates best with a reduction in the striatal fluorodopa uptake measured by positron emission tomography (PET) scans and in turn with nigral damage (Vingerhoets et al., 1997). This is consistent with the findings that decreased density of SN neurons correlates with parkinsonism in the elderly, even without PD (Ross et al., 2004). PET scans in PD patients have demonstrated decreased ^{18}F -fluorodeoxyglucose uptake in the striatum and accumbens-caudate complex roughly proportional to the degree of bradykinesia (Playford and Brooks, 1992). Nonhuman primate studies with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) monkeys provide evidence that bradykinesia results from excessive activity in the subthalamic nucleus (STN) and the internal segment of globus pallidus (GPI) (Bergman et al., 1990), a finding that has been identified in PD patients and may contribute to mechanisms underlying deep brain stimulation (DBS) (Dostrovsky et al., 2002). Thus, there is both functional and biochemical evidence of increased activity in the outflow nuclei, particularly STN and GPI, in PD. Increased iron accumulation in the substantia nigra, putamen, and GPI has been demonstrated in high-pass filtered phase MRI in PD patients compared with controls. The iron deposition in the deep brain nuclei in the

SN correlated with motor and bradykinesia-rigidity scores, but not with tremor scores, suggesting an *in vivo* reflection of dopaminergic neurodegeneration (Martin-Bastida et al., 2017). Although bradykinesia correlates well with dopaminergic deficit, slow gait correlates better with cholinergic degeneration as demonstrated by [(11)C]dihydrotetrabenazine dopaminergic and [(11)C]methyl-4-piperidiny propionate acetylcholinesterase (AChE) PET imaging (Bohnen et al., 2013); the cholinergic system may be implicated in gait at the level of the brainstem with the pedunculopontine nucleus and the prefrontal areas, which may be involved in gait, attention, and cognition (Yarnall et al., 2011).

Tremor

By using the term *shaking palsy*, James Parkinson in his *An Essay on the Shaking Palsy* (1817) drew attention to tremor as a characteristic feature of the disease later known as PD. Typical rest tremor has a frequency between 4 and 6 Hz and is almost always most prominent in the distal part of an extremity. In the hand, the tremor has been called a “pill-rolling tremor.” In the head region, tremor occurs most commonly in the lips, chin and jaw. Head tremor, a common manifestation of essential tremor (ET), is rare in PD (Roze et al., 2006; Gan et al., 2009). Some patients with PD complain of an inner, not visible, tremor, sometimes called “internal tremor” (Cochrane et al., 2015). Rest tremor of PD is often exacerbated during potential provocations, such as walking or mental tasks such as counting backward (Raethjen et al., 2008).

Some PD patients may have a postural tremor that is more prominent and disabling than the classic rest tremor. Postural tremor without parkinsonian features and without any other known etiology is often diagnosed as ET, but isolated postural tremor may be the initial presentation of PD, and it may be found with higher-than-expected frequency in relatives of patients with PD (Brooks, et al., 1992b; Jankovic et al., 1995; Jankovic, 2002; Louis et al., 2003). Relatives of patients with tremor-dominant PD have a significantly higher risk for action tremor than do relatives of patients with the postural instability gait disorder (PIGD) form of PD, but it is not yet clear whether the isolated tremor in the relatives is truly ET or whether it represents an isolated manifestation of PD (Jankovic et al., 1995; Louis et al., 2003). The two forms of postural tremor, ET and PD, can be differentiated by a delay in the onset of tremor when arms assume an outstretched position. Most patients with PD tremor have a latency of a few seconds (up to a minute) before the tremor reemerges during postural holding, hence the term *reemergent* tremor (Jankovic et al., 1999a,b; Jankovic, 2016) (Video 4.1). In contrast, the postural tremor of ET usually appears immediately after arms assume an outstretched posture. Because the reemergent tremor has a frequency similar to that of rest tremor and both tremors generally respond to dopaminergic drugs, reemergent tremor most likely represents a variant of the more typical rest tremor in PD. Some PD patients will also have a kinetic tremor, possibly related to enhanced physiologic tremor, that may also impair normal reach-to-grasp movement (Wenzelburger et al., 2000). ▶

Whereas Rajput and colleagues (1991) noted that 100% of 30 patients with pathologically proven PD experienced some degree of rest tremor at some time during the course of their disease, other studies demonstrate that not all PD patients have rest

tremor, with estimates about 35%. In another clinicopathologic study, only 76% of pathologically proven cases of PD had tremor (Hughes et al., 1992a) and in an expanded series of 100 pathologically proven cases of PD, tremor was present at onset in 69% and in 75% at some time during the course of PD (Hughes et al., 1993). In some, such as 9% of those studied by Hughes et al (1993), tremor may lessen as disease progresses and some may have more prominent postural or action tremors.

Presence of tremor as the initial symptom, or “tremor-predominant” PD, in contrast to the PIGD subtype of PD, often confers a favorable prognosis with slower progression of the disease. This is supported by a large number of studies. Indeed, one study addressing long-term course showed that the presence of tremor at onset was associated with much lower hazard for both motor and axial complications (Prange et al., 2019). Some have suggested the term “benign tremulous parkinsonism” for a subset of patients with minimal progression, frequent family history of tremor, and poor response to levodopa (Josephs et al., 2006; O’Suilleabhain et al., 2006; Deuschl, 2013; Selikhova et al., 2013). In 16 pathologically studied cases, those with benign tremulous parkinsonism had significantly less severe neuronal loss in the SN than controls (Selikhova et al., 2013). Of these, 12 had been correctly diagnosed with PD at their first neurologic evaluation, whereas the other 4 were originally thought to have another tremor disorder. Among the five cases that did not have PD pathologic conditions, none developed bradykinesia within the first 10 years, and the likely clinical diagnoses were ET with associated rest tremor or dystonic tremor. Others have argued against the term “benign tremulous parkinsonism” and proposed the term “monosymptomatic tremor at rest” because some symptoms are not experienced as “benign” and may still affect functioning (Deuschl, 2013). Furthermore, imaging documents evidence of dopaminergic deficits associated with PD and parkinsonism.

The pathophysiology of PD rest tremor is complex and most likely results from dysfunction of both the striato-pallidal-thalamocortical and the cerebello-dentato-thalamocortical circuits (Boecker and Brooks, 2011). The pallidum, in particular, appears to play a fundamental role in generation of tremor as suggested by a 4 to 8 Hz GPi neuronal firing in primate models of parkinsonism, correlation of tremor severity with pallidal (but not striatal) dopamine depletion, and complete abolition or a marked improvement of tremor with GPi ablation or DBS (Helmich et al., 2011). As a result of the abnormal neuronal activity at the level of the GPi, the muscle discharge in patients with PD changes from the normal high (40 Hz) to pulsatile (10 Hz) contractions. These muscle discharges, which may be viewed as another form of PD-associated tremor, can be auscultated with a stethoscope (Brown, 1997). Evidence from functional neurosurgical interventions for PD tremor also suggests contributions from excessive inhibitory output to the thalamus and altered firing patterns, leading to rhythmic burst activity in thalamic cells and role for cerebellar modulation of tremor (Duval et al., 2016). These authors propose a model such that the basal ganglia activity induces tremor, the thalamus generates PD tremor oscillations, and the cerebellum modulates tremor as if it were similar to a voluntary movement; in this model the role of the cerebellum is not its participation in the cerebello-thalamic circuit generating tremor (Helmich et al., 2011) but rather a modulator that compares an efferent copy

Video 4.1 Reemergent tremor.

of a voluntary alternating movement (i.e., tremor) to incoming peripheral sensory information.

Rigidity

Rigidity refers to the resistance detected when passively moving a joint throughout the range of movement. In contrast to spasticity, rigidity is velocity-independent and often called “lead-pipe” in quality. Cogwheeling is often encountered, particularly if there is associated tremor or an underlying, not yet visible, tremor. Historical references to parkinsonian rigidity include the observation of enhanced resistance to passive movement of a limb about a joint detected during voluntary movement of a contralateral limb (“Froment’s maneuver”), which was based on a series initially published by Froment and Gardere in 1926 (Broussolle et al., 2007). Rigidity may occur proximally (e.g., neck, shoulders, and hips) and distally (e.g., wrists and ankles). At times, it can cause discomfort and pain. Painful shoulder, possibly as a result of rigidity but frequently misdiagnosed as arthritis, bursitis, or rotator cuff, is a frequent initial manifestation of PD (Riley et al., 1989; Stamey et al., 2008). Subjective complaints of stiffness and imbalance can occur prior before overt parkinsonian signs and symptoms; those with these features in a longitudinal study ($n = 6038$, mean age 68.5 years) had an increased risk for developing PD with a HR of 2.11, 2.09, and 3.47, respectively (de Lau et al., 2006).

Dystonia

Although dystonia is not considered one of the cardinal signs of PD, it is often present in patients with PD (Jankovic and Tintner, 2001; Shetty et al., 2019). Dystonia is present in over 30% of PD patients and precedes the onset of other parkinsonian motor features. Foot dystonia associated with flexion of the toes and inversion of the foot may be the initial manifestation of PD. Furthermore, dystonia may be a feature of levodopa-related motor complications and may include wearing off dystonia or cervical, truncal, or hand dystonia as part of peak dose dyskinesia (Jankovic 2010; Wijemanne and Jankovic, 2019). Other examples of dystonia-parkinsonism overlap is in some patients with genetic dystonia and tardive dystonia coupled with drug-induced parkinsonism. Furthermore, DBS used in the treatment of PD can cause dystonia such as blepharospasm (Baizabal-Carvallo and Jankovic, 2016).

Flexed posture and other skeletal abnormalities

Although rigidity is often associated with postural deformity resulting in flexed neck and trunk posture and flexed elbows and knees, flexed posture and other skeletal abnormalities can occur independently. Some patients develop “striatal hand” deformity, characterized by ulnar deviation of hands, flexion of the metacarpophalangeal joints, and extension of the interphalangeal joints (Ashour et al., 2005; Ashour and Jankovic, 2006; Jankovic, 2007, 2010; Wijemanne and Jankovic, 2019) (Fig. 4.1). Striatal changes in the feet can also occur with extension of the big toe (“striatal toe”) or flexion of the other toes, which can be confused with arthritis. Striatal toe was present in 13 of 62 (21%) of patients with clinically diagnosed PD (Winkler et al., 2002). This phenomenon can be seen not



Fig. 4.1 Striatal hand deformity associated with Parkinson disease. (Courtesy J. Jankovic.)

only in PD but also in other parkinsonian disorders. Moreover, it should be differentiated from psychogenic toe, which usually manifests by increased resistance to passive manipulation, pain, and spontaneous toe plantar flexion with forced extension of the second to fifth toes (Espay and Lang, 2011).

Other skeletal abnormalities can occur in the neck and spine. These can be considered by body region (neck and spine) but also in the sagittal plane (e.g., antecollis and camptocormia) or coronal plane (scoliosis and Pisa syndrome). The prevalence of scoliosis, defined as lateral flexion not relieved by voluntary or passive movement and lateral curvature of the spine of at least 10 degrees, is reported in 9% to 91% of PD, whereas the prevalence of antecollis is about 5% to 6%; camptocormia, about 3% to 18%; and Pisa syndrome, about 2% (Michel et al., 2015; Tinazzi et al., 2015). Extreme neck flexion (“dropped head”) has been found in PD but also other parkinsonian disorders such as multiple system atrophy (MSA) (Oerlemans and de Visser, 1998; Askmark et al., 2001; Ashour et al., 2006; Kashiwara et al., 2006; Gdynia et al., 2009; Oyama et al., 2009; Jankovic 2010; Wijemanne and Jankovic, 2019). When neck flexion posture is present, neck extensor weakness should be differentiated from dystonic anterocollis in which muscle spasms or pulling of anterior neck muscles may be seen. Besides in parkinsonian disorders, head drop or neck flexion can be seen as an isolated syndrome such as neck extension weakness or in neuromuscular disorders with myopathic changes (Oyama et al., 2009; Savica et al., 2012). Some parkinsonian patients with dropped head syndrome also can have these features and evidence of myopathy on EMG, blood tests, or imaging (Savica et al., 2012). In 7 of 459 patients with parkinsonism with dropped head syndrome because of neck extensor weakness, myopathic changes on EMG were noted in all, with 2 of 5 undergoing muscle biopsy with mitochondrial abnormalities (Askmark et al., 2001); other studies find variable rates of EMG changes. Isolated neck and trunk extensor myopathy has been reported in other patients with anterocollis and camptocormia associated with parkinsonism (Lava and Factor, 2001; van de Warrenburg et al., 2008; Gdynia et al., 2009; Margraf et al., 2010; Spuler et al., 2010; Doherty et al., 2011; Jankovic, 2011). Other series have identified various



Fig. 4.2 Camptocormia associated with Parkinson disease. (Courtesy J. Jankovic.)

etiologies in patients with head drop: dystonia, disproportionately increased tone in the anterior neck muscles resulting in fibrotic and myopathic changes, amyotrophic lateral sclerosis, focal myopathy, inclusion body myositis, polymyositis, nemaline myopathy, facioscapulohumeral dystrophy, myasthenia gravis, encephalitis, dopamine agonists (Uzawa et al., 2009), and valproate toxicity (Umapathi et al., 2002; Gourie-Devi et al., 2003; Schabitz et al., 2003; Azher and Jankovic, 2005; van de Warrenburg et al., 2008). Evaluation may include EMG, laboratory tests for muscle damage or inflammation, and cervical spine MRI in which the muscle tissue may appear to have inflammatory changes. Treatments may involve increased dopaminergic medications but also frequently engage physical therapy and bracing support.

Postural abnormalities affecting the trunk can involve anteroposterior and/or lateral trunk flexion. Lateral trunk flexion or scoliosis can be frequently seen in PD, sometimes occurring as part of the disease, in addition to a prior scoliosis, or as a subacute phenomenon associated with medication adjustments (Michel et al., 2015; Tinazzi et al., 2015). Camptocormia is characterized by extreme flexion of the thoracolumbar spine that has a minimum of 45 degrees flexion in the thoracolumbar region and increases during walking but resolves in supine position (Videos 4.2-4.4) (Fig. 4.2) (Djaldetti et al., 1999; Umapathi et al., 2002; Azher and Jankovic, 2005; Tiple et al., 2009; Sako et al., 2009; Jankovic, 2010; Doherty et al., 2011; Ponfick et al., 2011; Seki et al., 2011; Michel et al., 2015; Nakane et al., 2015; Tinazzi et al., 2015).

Camptocormia appears to be more common in patients with more severe PD symptoms and prior vertebral surgery (Tiple et al., 2009). The term was coined during World War I when young soldiers who were apparently attempting to escape the stress of battle developed this peculiar posture, perhaps promoted by a stooped posture when walking in



Fig. 4.3 Scoliosis associated with Parkinson disease.

the trenches. Hypothesized mechanisms for camptocormia include dystonia resulting from a central disorder and extensor truncal muscle myopathy (Bloch et al., 2006; Djaldetti and Melamed, 2006; Lepoutre et al., 2006; Gdynia et al., 2009; Jankovic, 2010). Although myopathy may cause camptocormia, this is probably a very rare pathogenic mechanism of abnormal axial posture in PD because there is usually no demonstrable weakness but instead there is often increased muscle tone and activity, and the reported EMG, imaging, and histologic changes are relatively nonspecific (Jankovic, 2010; Doherty et al., 2011).

Pisa syndrome refers to lateral flexion with a minimum of 15 degrees alleviated by passive mobilization or supine positioning (Villarejo et al., 2003; Tassorelli et al., 2012; Michel et al., 2015; Tinazzi et al., 2015) (Fig. 4.3). In most patients, the tilt is away from the original symptom onset and is accompanied by greater EMG activity of the paravertebral thoracic muscles, but at the lumbar level there can be more atrophy, ipsilateral to the deviation, possibly because of muscle misuse (Tassorelli et al., 2012). The pathophysiology of Pisa syndrome is not well understood but may relate to features underlying the other described postural abnormalities and cholinergic-dopaminergic imbalance. Postural deformities such as striatal hand and foot deformities, antecollis, Pisa syndrome, scoliosis, and camptocormia are most likely of multifactorial pathophysiology that includes rigidity, dystonia, weakness caused by myopathy, body scheme defects resulting from centrally impaired proprioception, and structural changes in the spine (Jankovic, 2010; Doherty et al., 2011). In one study, in which Pisa syndrome was detected in 143 patients (8/8%), it was associated with older age, lower body mass index, longer PD duration, worse disease stage, and poorer quality of life (Tinazzi et al., 2015).

Treatments for these spinal deformities include adjustments of dopaminergic medications, botulinum toxin

Video 4.2 Camptocormia.

Video 4.3 Camptocormia.

Video 4.4 Camptocormia.

injections in some cases, DBS, and physical therapy. The axial dystonias resulting in scoliosis and camptocormia may improve with botulinum toxin injections into the paraspinal or rectus abdominus muscles (Azher and Jankovic, 2005; Bonnani et al., 2007). Other treatments include physical therapy, orthopedic procedures (Wadia et al., 2011), and even DBS (Sako et al., 2009). In a study of 78 PD patients with camptocormia and 78 PD patients without camptocormia, the camptocormia group had significantly higher prevalence of compression fractures, more severe parkinsonian symptoms, greater incidence of dementia, and higher serum creatine kinase than those without camptocormia (Nakane et al., 2015).

Gait disorder and freezing

Parkinsonian gaits are characterized chiefly by the combination of shuffling steps, start-hesitation, and freezing (as if the feet were glued to the floor) associated with stooped posture, flexed knees, narrow base, and turning en bloc (Mirelman et al., 2019). In early PD, common features include shortened stride length, asymmetry of stride length, decreased heel strike, decreased toe clearance, and reduced arm swing. PD patients may also have festination of gait in which their center of gravity is shifted forward or ahead of their feet, which leads to propulsion or forward acceleration. Some PD patients exhibit greater PIGD subtypes, in which gait and balance may be particularly affected. As PD advances, gait abnormalities may further affect balance and risk for falls. In the assessment of gait and posture, the examiner should observe the pattern of movement of the whole body when the patient walks and turns, etc. Although arm swing is not a separate item on the UPDRS, arm swing asymmetry may be the earliest feature of PD and has been found to be a potential prodromal marker in otherwise asymptomatic *LRRK2* mutation carriers (Mirelman et al., 2016).

One of the most disabling symptoms of PD is freezing of gait, also referred as motor blocks, considered by some as a form of akinesia (loss of movement) (Giladi et al., 1997; Giladi et al., 2001; Giladi and Nieuwboer, 2008; Morris et al., 2008; Nutt et al., 2011; Okuma 2014; Vandenbossche et al., 2013) (Videos 4.5 and 4.6). Although it most often affects the legs when walking, it can also involve upper limbs and the eyelids (apraxia of eyelid opening or eyelid closure) (Boghen et al., 1997). Freezing consists of sudden, transient (a few seconds) inability to move. It typically causes start-hesitation when initiating walking and the sudden inability to move feet (as if glued to the ground) when turning or walking through narrow passages (e.g., the door or the elevator) (Almeida and Lebold, 2010), when crossing streets with heavy traffic, or when approaching a destination (target hesitation). One study showed that the most efficient way to objectively ascertain freezing of gait is to ask patients to repeatedly make rapid 360-degree narrow turns from standstill, on the spot and in both directions (Snijders et al., 2012). Freezing is a common cause of falls in patients with PD that can result in injuries, including hip fractures. Recognition of freezing is important because it denotes poor prognosis; most patients become wheelchair bound within 5 years after onset of freezing (Jankovic, 2015). Based on responses by 6620 patients to a questionnaire sent to 12,000 members of the German Parkinson Association, 47% of patients reported

freezing, present more frequently in men than women and less frequently in patients who considered tremor as their main symptom (Macht et al., 2007). ●

Freezing of gait can have multiple components to it, such as motor control, medication effects, certain situations, and cognitive and emotional aspects. Situational freezing of gait tends to occur with gait initiation, turning, navigating environmental obstacles, or when dual tasking (or multitasking). Freezing may be a manifestation of the “off” phenomenon in PD patients who fluctuate but may also occur during “on” time (on freezing), independent of bradykinesia and tremor (Bartels et al., 2003; Espay et al., 2012). Off gait freezing correlates with dopa-responsive abnormal discriminatory processing as determined by abnormally increased temporal discrimination threshold (Lee et al., 2005). On gait freezing can have several different characteristics: (1) a trembling freezing of gate that worsened with increasing levodopa doses; (2) new on FOG without predating “off” freezing of gait; (3) concurrent worsening (freezing) of repetitive alternating hand movements in the on state; (4) good levodopa responsiveness of other parkinsonian features; and (5) preserved cognition, unlike the frontal cognitive impairment associated with “off” freezing of gate (Espay et al., 2012). The timing of motor state or certain situations associated with freezing of gate should be considered in the examination and management of freezing.

When freezing occurs early in the course of the disease or is the predominant symptom, a diagnosis other than PD should be considered. Disorders associated with prominent freezing include progressive supranuclear palsy (PSP), MSA, and vascular (lower body) parkinsonism (FitzGerald and Jankovic, 1989; Elble et al., 1996; Winikates and Jankovic, 1999; Jankovic et al., 2001; Kalra et al., 2010). Freezing often correlates with frontal executive deficits and atrophy in the dorsolateral prefrontal, medial, and lateral temporal, inferior parietal, and occipital cortices (Kostic et al., 2012). Isolated freezing usually suggests a diagnosis other than PD and may be present in atypical forms of parkinsonism or brainstem strokes (Kuo et al., 2008). The pathologic involvement of brainstem in patients with pure akinesia and gait freezing is suggested by decreased glucose metabolism on PET scans in the midbrain of such patients, similar to the findings in patients with PSP (Park et al., 2009).

The pathophysiology of freezing of gait may relate to neurodegeneration in certain brain areas, disconnection between brain regions involved in motor and cognitive control, and possibly peripheral muscle abnormalities (Gilat et al., 2018). Gait freezing in PD may relate to noradrenergic deficiency as a result of locus coeruleus (LC) degeneration (Zarow et al., 2003) and possible response to noradrenergic agents such as l-threo-dihydroxy-phenylserine, or DOPS (Narabayashi, 1999). Neurophysiologic studies in monkeys treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine found that dopamine depletion is associated with impaired selection of proprioceptive inputs in the supplementary motor area, which could interfere with motor planning and may be related to motor freezing (Escola et al., 2002). Integrating EMG signals over real time while recording EMG activity from lower extremities before and during freezing, Nieuwboer and colleagues (2004) showed significantly abnormal timing in the tibialis anterior and gastrocnemius muscles, although reciprocity is preserved. Thus, before freezing, the tibialis anterior

Video 4.5 Freezing.
Video 4.6 Freezing.

and gastrocnemius contract prematurely, and the duration of contraction is shortened in the tibialis anterior, but the amplitude of the EMG burst is increased (probably a compensatory strategy pulling the leg into swing), whereas the contraction is prolonged in the gastrocnemius during the actual swing phase. Other studies suggest transient overactivation in the inhibitory striatal output nuclei projecting to the motor thalamus and brainstem regions (Lewis and Shine 2014).

Gait freezing has been associated with reduced functional connectivity in the opercular parietal cortex and other brain areas (Lenka et al., 2016), abnormalities within both “executive-attention” and visual networks (Tessitore et al., 2012), and increased corticopontine projections crossing at the pons are associated with freezing of gait (Schweder et al., 2010). In a clinicopathologic study of 58 patients with pathologically confirmed PD and clinical evidence of freezing, greater severity of gait freezing correlated with the density of cortical Lewy body-containing neurons (Virmani et al., 2015). Using a virtual reality paradigm to elicit freezing of gait behavior in PD participants during fMRI, alterations in functional networks that capture different associated elements of gait freezing (cognitive, motor, and affective function) have been detected in PD freezers (Ehgoetz Martens et al., 2018). Coupling between the cognitive and limbic networks was associated with “worse freezing severity”, whereas anticoupling between the putamen and the cognitive and limbic networks was related to “increased compensation.” Additionally, anticoupling between cognitive cortical regions and the caudate nucleus were “independent of freezing severity” and thus may represent common neural underpinnings of freezing that are unaffected by heterogeneous factors.

Various therapeutic strategies have been studied for freezing of gait, including medical, surgical, and rehabilitative management. If gait freezing is related to the off state or suboptimal motor states, dopaminergic medications may be used. However, gait freezing may relate to nondopaminergic systems, and, thus, studies have focused on these systems as targets. Medical treatments with DOPS, selegiline, idazoxan, atomoxetine, and duloxetine (Cymbalta) (Giladi, 2008; Jankovic, 2009; Morgante and Fasano, 2010) and surgical approaches (Ferraye et al., 2008; Nashatiazedh et al., 2008) rarely provide satisfactory control of freezing. Other studies have included rivastigmine (negative results) (Henderson et al., 2016), amantadine (inconclusive results) (Macht et al., 2007; Lee et al., 2013), methyphenidate (no improvement and on one study, reduced gait freezing only in those with PD with STN-DBS) (Espay et al., 2011; Moreau et al., 2012), caffeine (insufficient results) (Kitagawa et al., 2007), and istradefylline (reduction in small open label study) (Matsuura et al., 2018). Other surgical interventions that have generated interest include electrical spinal cord stimulation, with open label case reports to date; one study found a 56% improvement in subjective freezing of gait along with improved objective gait measures after high-frequency (300 Hz) spinal cord stimulation at the upper thoracic (T2-T4) level in four PD patients with prior bilateral STN-DBS but gait freezing; beneficial effects of spinal cord stimulation on freezing remained for the 6 months duration of the study (Pinto de Souza et al., 2017). Patients often adopt a variety of cues or tricks to overcome the freezing attacks: marching to command (“left, right, left, right”), stepping over objects (the end of a walking stick, a pavement stone, cracks in the

floor, etc.), walking to music or a metronome, shifting body weight, rocking movements, and others (Dietz et al., 1990; Fahn, 1995; Marchese et al., 2001; Rubinstein et al., 2002; Suteerawattananon et al., 2004; Nieuwboer, 2008).

Loss of postural reflexes

Loss of postural reflexes is a characteristic feature in PD patients more typically in advanced disease stages but also those who exhibit the PIGD phenotype. Loss of postural reflexes and also of protective reactions can lead to falls and fall-related injuries in PD. Several studies have examined clinical features or risk factors associated with falls in PD. Compared with controls, those PD patients with falls (“PD fallers”) have a tendency to overestimate balance performance on functional reach testing, particularly with worsened disease, are willing to sacrifice motor performance to complete tasks, and make significantly more motor errors when performing a complex motor-cognitive task (e.g., carrying a tray and performing mental arithmetic) (Bloem et al., 2006). Abnormal axial posture, cognitive impairment, and freezing of gait were independent risk factors for falls and predicted 38 of 51 fallers (75%) and 45 of 62 nonfallers (73%) (Latt et al., 2009). Some studies suggest that frontal impairment, poor leaning balance, and leg weakness contribute to falls in PD, whereas other studies cite female gender, symmetric onset, and postural and autonomic instability as the most reliable predictors of falls in PD (Williams et al., 2006). Predictors of falls with high sensitivity (78%) and specificity (84%) include UPDRS total score, total gait freezing score, symptomatic postural orthostasis, Tinetti total score, and extent of postural sway in the antero-posterior direction.

The average period from symptom onset to first fall in PD is 108 months, which is longer than reported for PSP (16.8 months), vascular parkinsonism (40.8 months), MSA (42 months), and dementia with Lewy bodies (DLB) (54 months). Using a battery of neurologic and functional tests in 101 patients with early PD and in an optimally medicated state, 48% reported a fall and 24% more than one fall in a prospective follow-up over 6 months (Kerr et al., 2010). Many PD patients with postural instability, particularly when associated with flexed truncal posture (camptocormia), have festination of gait, which can contribute to falls. The pull test (pulling the patient by the shoulders) is commonly used to determine the degree of patient’s retropulsion or propulsion and is part of the UPDRS and MDS-UPDRS assessment (Visser et al., 2003; Hunt and Sethu, 2006; Valkovic et al., 2008).

Balance impairment and falls in PD may be related to cholinergic system alterations to a greater extent than dopaminergic neurotransmission (Thevathasan and Aziz, 2010; Yarnall et al., 2012; Bohnen et al., 2018). Evidence supports involvement of the cholinergic system-mediated higher level cortical and subcortical processing, including pedunculopontine nucleus function, in gait control. In a study of 44 nondemented patients with PD and 15 controls who underwent a clinical assessment and [(11)C]methyl-4-piperidiny propionate (PMP) AChE and [(11)C]dihydrotetrabenazine (DTBZ) vesicular monoamine transporter type 2 (VMAT2) brain PET imaging, PD fallers compared with PD nonfallers and controls had significantly reduced cortical AChE

hydrolysis rates (−12.3% versus −6.6%) (Bohnen et al., 2009). Although subcortical and brainstem cholinergic changes have been found in PD, they are greater in those with atypical parkinsonian syndromes; for example, a [(11)C]PMP PET study in PD (n = 12), MSA-parkinsonian type (MSA-P, n = 13), PSP (n = 4), and controls (n = 22) demonstrated a significant decrease in AChE activity in most cerebral cortical regions in PD and MSA-P, but a nonsignificant decrease in PSP, whereas there were greater decreases in subcortical cholinergic activity in MSA-P and PSP than in PD (Gilman et al., 2010). Greater decreases in subcortical AChE in MSA-P and PSP, such as in the pedunculopontine nucleus, may account for the earlier and more prominent gait disturbances in these two disorders compared with PD (Gilman et al., 2010). Using conditioning motor evoked responses elicited by transcranial magnetic stimulation of the motor cortex, significant reduction was found in short latency afferent inhibition, a surrogate measure of cholinergic activity, in patients with PD (Rochester et al., 2012).

Treatment of falls should include prevention and assessment of fall risk, home safety, and medical comorbidities that may contribute to fall risk (Fasano et al., 2017). A meta-analysis including five short-term studies (n = 620 participants) and six long-term studies (n = 590) showed that exercise-based interventions can provide benefit in both the short term and long term (Shen et al., 2016). Exercise interventions in trials demonstrating reduction in fall risk include tai chi and other movement and strengthening strategies. Medication interventions may include adjustments of PD medications. Given the relationship between the cholinergic system and falls, rivastigmine was studied in a controlled trial and demonstrated reduced falls in PD fallers by 45% compared with the placebo group (Henderson et al., 2016); however, there was no effect on gait freezing, cognition, or executive function. Droxidopa demonstrated reduced fall risk in PD patients with orthostatic hypotension compared with placebo (Hauser et al., 2016). Thus, the role of orthostatic hypotension in leading to falls, or unexplained falls, in PD should be considered.

Other motor features

PD-associated speech and voice impairment, often referred to as hypokinetic dysarthria, is characterized by low volume (hypophonia), uniform (monotonous) loudness and pitch (aprosody), imprecise consonants, hesitation, and short rushes of speech (tachyphemia). As a result of more sensitive and valid measures, speech abnormalities are now being increasingly detected in early stages of the disease and as many as 89% of people with PD develop speech disorders (Ramig and Fox, 2012; Ramig et al., 2018). Other speech characteristics include a variable (abnormally slow or increased) speech rate, palilalia, and stuttering. PD patients have been found to have higher speech acceleration than controls and a significant reduction in the number of pauses, indicating abnormal speech rate and rhythm (Skodda and Schlegel, 2008). Based on recordings of lip and jaw movements and acoustic data in 16 patients with PD and 16 age- and sex-matched neurologically healthy older adults, there was evidence of decreased amplitude and velocity of lower lip and jaw movements, decreased vocal intensity, and reduced second formant slopes without abnormalities

in speech rate (Walsh and Smith, 2012). A history of childhood stuttering that had remitted can subsequently recur with onset of PD, suggesting an involvement of the dopaminergic system in this speech disorder (Shahed and Jankovic, 2001). When speech therapy designed to stimulate increased vocal fold adduction with instructions to “think loud, think shout,” the Lee Silverman Voice Treatment (LSVT) (Ramig et al., 2001), was compared with “speak loud and low,” the Pitch Limiting Voice Treatment (de Swart et al., 2003), the two methods produced the same increase in loudness, but the latter method was found to prevent strained voicing. In a randomized controlled trial, Ramig et al (2018) examined two speech treatments matched in intensive dosage and high-effort mode of delivery but differing in their target subsystems, with one targeting voice (respiratory-laryngeal) and the other targeting articulation (orofacial-articulatory). PD participants were randomized to voice, speech, and untreated groups. At 7 months, PD participants in both LSVT groups showed significantly greater improvements compared with the untreated group. Although both LSVT groups improved the participant-reported Modified Communication Effectiveness Index at 1 month, only the LOUD group maintained this benefit at 7 months. Other treatment strategies for PD-related dysarthria include the use of various verbal cues to regulate speech volume (Ho et al., 1999), but DBS has a variable effect (Pinto et al., 2004). The low-volume voice in PD has been attributed in part to vocal fold bowing as a result of loss of muscle mass and control (Schulz et al., 1999), and augmentation of vocal folds with collagen injections provides improvement in voice quality and has a significantly beneficial impact on quality of life (Hill et al., 2003). Bulbar symptoms (dysarthria, hypophonia, dysphagia, and sialorrhea) are thought to result from orofacial-laryngeal bradykinesia and rigidity (Hunker et al., 1982).

Respiratory difficulties have been associated with PD, even from its earliest descriptions in the “Shaking Palsy.” These issues result from a variety of mechanisms, including a restrictive component caused by rigid respiratory muscles, upper airway obstruction, abnormal ventilatory drive, and levodopa-induced respiratory dyskinesias (Rice et al., 2002; Mehanna and Jankovic, 2010; Torsney and Forsyth, 2017). Expiratory muscle strength training may play a role in increasing maximum expiratory pressure and speech breathing patterns in PD, as suggested by a small study of 12 PD patients undergoing 8 weeks of training (Darling-White and Huber, 2017). Presence of inspiratory stridor is a red flag for PD but can be seen in MSA.

Dysphagia is a frequent symptom in PD and can greatly affect quality of life, morbidity, and mortality (Simons, 2017). Dysphagia is more common in advanced disease, but mild oropharyngeal symptoms can occur in early-stage PD. Swallowing mechanisms are complex, requiring coordination across the central and peripheral nervous system and musculature to complete the four swallowing phases (preoral, oral, pharyngeal, or esophageal). In PD, dysfunction may represent slowing of movements, decreased range of motion, reduced physical strength, changes in saliva production and chewing, and impaired perception. Assessment may include PD-specific screening tools (Swallowing Disturbance Questionnaire, Munich Dysphagia Test), other nonmotor symptom scales, or swallow studies, in the clinic or under fluoroscopic

guidance. Management may include modifications to diet and food or liquid consistency, rehabilitative techniques, expiratory muscle training, visual cuing techniques, chewing gum, and thermal-tactile stimulation techniques. When PD patients were compared with healthy controls, those with PD were found to swallow significantly more often during inhalation, at low tidal volumes, and exhibited significantly more postswallow inhalation (Gross et al., 2008). Impaired coordination of breathing and swallowing may contribute to the high frequency of aspiration pneumonia in PD. Drooling (sialorrhea) is one of the most embarrassing symptoms of PD (Chou et al., 2007). Although some studies have shown that PD patients actually have less saliva production (Proulx et al., 2005) than normal controls, others have suggested that the excessive drooling is due to a difficulty with swallowing (Bagheri et al., 1999). Salivary sympathetic denervation, however, could not be demonstrated by 6-[18F]-fluorodopamine scanning (Goldstein et al., 2002).

Some patients exhibit the reemergence of primitive reflexes attributed to a breakdown of the frontal lobe inhibitory mechanisms that are normally manifest in infancy and early childhood, hence the term *release signs* (Vreeling et al., 1993; Thomas, 1994; Rao et al., 2003; Borroni et al., 2006). The glabellar tap reflex, also known as Meyerson sign, often has been associated with PD. However, its diagnostic accuracy has not been subjected to rigorous studies. The glabellar tap reflex is elicited through repeated stimuli to the glabellar region of the forehead, inducing concomitant blinking with each tap. In the normal person, the reflex blinking habituates or the subject stops blinking with each stimulus tap after the second to fifth tap. Although relatively sensitive signs of parkinsonian disorders, particularly PD compared with controls, these primitive reflexes lack specificity because they do not differentiate among the three most common parkinsonian disorders (Brodsky et al., 2004). Abnormal spontaneous blinking, particularly the longer pauses between closing and opening phases, compared with normal controls suggests that the decreased blinking in PD reflects underlying bradykinesia (Agostino et al., 2008). In addition to these primitive reflexes, there are other “frontal” and “cortical disinhibition” signs, such as the applause sign (Wu et al., 2008), but none of them are specific for PD.

Examination of motor parkinsonism

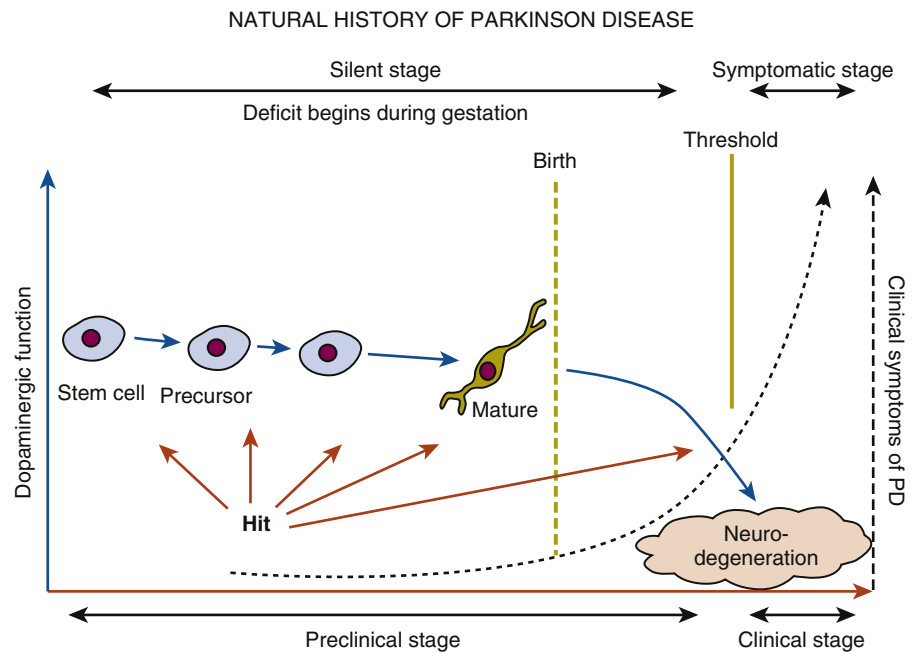
Clinicians must have the knowledge and skills to elicit the appropriate histories and target the neurologic examination in a way that will elicit the various neurologic signs that will differentiate between age-related frailty and parkinsonism (Tolosa et al., 2006; Jankovic, 2007, 2008; Jankovic and Lang, 2008; Morris and Jankovic, 2012). The initial presentation of PD varies, though tremor is the most commonly reported motor symptom in those who have autopsy confirmed PD (Hughes et al., 1993). However, it is recognized that rest tremor may not occur in all with PD. In a community study of 358 patients, tremor was the initial symptom in about half but about 40% had akinetic-rigid phenotype and less than 10% had gait disturbances (Wickremaratchi et al., 2011). Longitudinal follow-up and clinicopathologic correlates, however, may be important in determining whether these cases represent PD or early manifestations of other parkinsonian syndromes.

Early symptoms of PD may be nonspecific, such as those in an earlier retrospective study finding generalized stiffness, pain or paresthesia of the limbs, constipation, sleeplessness, and reduction in volume of the voice (Przuntek, 1992). More specific complaints that were elicited in a detailed history as the disease progressed included problems with fine motor skills, decreased sense of smell, loss of appetite, and a tremor occurring with anxiety. Family members retrospectively reported decreased arm swing on the affected side, decreased emotional expression, and personality changes, including more introversion and inflexibility. Other early symptoms may include foot dystonia, especially with younger onset, or shoulder pain, likely related to the decreased arm swing on the affected side. In one study of 25 PD patients and 25 controls, PD patients had 21 times the odds of having shoulder pain compared with those without PD (Madden et al., 2010). During the period before diagnosis, PD patients, compared with normal controls, had a higher frequency of mood disorder, fibromyalgia, and various pains (Defazio et al., 2008), particularly shoulder pain (Stamey et al., 2008; Madden et al., 2010; Yucel and Kusbeci, 2010; Ha et al., 2012).

Although the asymmetry of PD is well recognized, the relationship, if any, with handedness has not been fully elucidated but is a common question encountered in clinic visits. Using strict criteria for asymmetry, 46% of patients with PD had characteristic asymmetrical presentation that correlated with handedness (Uitti et al., 2005). Handedness, however, did not predict the onset of PD motor symptoms in another study (Stochl et al., 2009). Of 254 right-handed PD patients, 158 (62%) had right-hand dominance of PD symptoms, but it is not clear whether this is simply an expected lateralization (Van der Hoorn et al., 2011). In a study of right-handed PD patients, most had lower dopamine transporter (DAT) uptake in the left posterior putamen, but there was a subgroup of right-handed patients with more severe and predominant ipsilateral putaminal DAT decline (Scherfler et al., 2012). The authors concluded that “asymmetry of dopaminergic denervation and motor dysfunction in PD cannot be fully explained by hemispheric dominance alone, but that other factors must be involved.” Further studies are needed to better understand the mechanisms of asymmetry in neurodegenerative diseases (Melamed and Poewe, 2011). It is possible that the side of predominant involvement may be stochastically determined, similar to other complex diseases such as cancer (Djaldetti et al., 2006). The notion that the side of predominant involvement is merely coincidental and determined by chance alone is supported by seemingly random right and left distribution without correlation to hand-dominance, lack of concordance for the affected side within family members of genetically determined PD, and the frequent presence of asymmetrical involvement in drug-induced parkinsonism. In some cases, unintended movements accompanying voluntary activity in homologous muscles on the opposite side of the body, the so-called mirror movements, may occur even in early, asymmetric PD (Espay et al., 2005; Li et al., 2007), although one study showed that mirror movements actually occur less frequently in PD patients than in healthy controls (29% versus 71%, $P < 0.0001$) (Ottaviani et al., 2008).

In some cases, parkinsonism remains confined to one side and may be associated with hemiatrophy. In one study, the mean age at onset of the 30 patients who satisfied the criteria

Fig. 4.4 Developmental progression of neurodegeneration.



hemiparkinsonism-hemiatrophy was 44.2 (15–63) years with a mean duration of symptoms for 9.7 (2–20) years (Wijemanne and Jankovic, 2007) (see Table 4.2). Half of all patients had dystonia at onset and dystonia was present in 21 (70%) patients during the course of the syndrome. A majority of the patients were responsive to levodopa, and perinatal and early childhood cerebral injury appeared to play an important role in about half of the cases. Although there are no perinatal events that have been identified consistently as risk factors for PD (Gardner et al., 2010), the syndrome of hemiparkinsonism-hemiatrophy also suggests that some cases of PD may start prenatally, and, as a result of low number of dopaminergic neurons from birth and subsequent age-related attrition, develop PD symptoms in middle age (Le et al., 2009) (Fig. 4.4). The asymmetric lateral ventricular enlargement, which is associated with PD motor asymmetry (Lewis et al., 2009), may represent a nonspecific marker of underlying neurodegeneration or may suggest an early insult, similar to what has been postulated in hemiparkinsonism-hemiatrophy (Wijemanne and Jankovic, 2007).

Nonmotor features

Nonmotor symptoms of PD have increased in their recognition regarding their presence, impact on patient outcomes and quality of life, and treatment strategies. Nonmotor features, which can occur in 88% of all patients, are as troublesome if not more, than the classic motor features (Simuni and Sethi, 2008). The nonmotor manifestations and fluctuations in nonmotor symptoms have been found to be more disabling than the motor symptoms in 28% of PD patients (Witjas et al., 2002). Nonmotor symptoms can affect PD patients early in their course (Duncan et al., 2014) as well as in more advanced stages of the disease (Lang and Obeso, 2004; Chaudhuri et al., 2006a, b, 2007, 2011; Ahlskog, 2007; Martinez-Martin et al., 2007; Pfeiffer, 2007; Lim et al., 2009; Politis et al., 2010). The Sydney Multicenter Study found that after 15 years of disease PD patients had frequent nonmotor symptoms, some

of which had substantial effect on independence and quality of life: 84% experiencing cognitive decline, with 48% meeting diagnostic criteria for dementia; 58% were unable to live alone; and 40% were in long-term care facilities (Hely et al., 2005). After 20 years of follow-up, only 36 (26%) survived and the standardized mortality ratio (SMR) reached 3.1 (Hely et al., 2008). Of the 30 included in this longitudinal study, 100% had levodopa-induced dyskinesia and end-of-dose failure, 83% had dementia, and 48% were in nursing homes. Other problems included excessive daytime sleepiness in 70%, falls in 87%, freezing in 81%, fractures in 35%, symptomatic postural hypotension in 48%, urinary incontinence in 71%, moderate dysarthria in 81%, choking in 48%, and hallucinations in 74%. Of the 87 patients followed prospectively in the Sydney study whose brain was examined at autopsy, the final diagnosis was PD ($n = 29$), PD dementia ($N = 52$), and DLB ($n = 6$) (Halliday et al., 2008). The clinicopathologic correlations suggested that there were three groups of patients: (1) younger onset patients with a typical PD clinical course, brainstem Lewy bodies in those surviving to 5 years but by 13 years, 50% of cases have a limbic distribution of Lewy bodies; (2) older onset PD cases with shorter survival and higher Lewy body loads and additional plaque pathologic conditions; and (3) early malignant, dementia-dominant syndrome and severe neocortical disease, consistent with DLB.

In a multicenter study of 1072 consecutive patients with PD in 55 Italian centers, the PRIAMO study, 98.6% of patients reported a mean of 7.8 (range 0–32) nonmotor symptoms, such as fatigue (58%), anxiety (56%), leg pain (38%), insomnia (37%), urgency and nocturia (35%), drooling of saliva (31%), and difficulties in maintaining concentration (31%) (Barone et al., 2009). Apathy was the symptom associated with worse 39-item Parkinson's Disease Quality of Life Questionnaire (PDQ-39) score, but presence of fatigue, attention/memory, and psychiatric symptoms also had a negative impact on quality of life. Using validated questionnaires and clinimetric measures, the health-related quality (HRQL) of life of measures

correlated most strongly with the following nonmotor symptoms: autonomic dysfunction, sleep disturbance, and psychosis (Gallagher et al., 2010). In motor fluctuators, essentially all nonmotor symptoms, except dysphagia, excessive sweating, and bladder urgency, are more frequent and more severe in the off state compared with the on state (Storch et al., 2013). The nonmotor features associated with PD are presumably related to involvement of the nondopaminergic systems and even pathologic conditions outside the CNS (Djaldetti et al., 2009). Although typically observed in more advanced stages of the disease, nonmotor symptoms can be encountered even in early stages of the disease. In one study, within a mean duration of symptoms of 4.4 months, the most commonly experienced nonmotor symptoms were excessive saliva, forgetfulness, urinary urgency, hyposmia, and constipation (Khoo et al., 2013). In the UK Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation (ICICLE) in PD study (n = 158 newly diagnosed PD and n = 99 healthy controls), PD patients reported greater numbers of nonmotor symptoms as recorded on the Non-Motor Symptom Questionnaire and worse quality of life as measured on the PDQ-39 (Duncan et al., 2014). Motor and nonmotor symptoms negatively affected HRQL scores, particularly for those PD with PIGD motor subtype compared with those with tremor-dominant disease. Depression, incomplete bowel emptying, anxiety, impaired concentration, memory complaints, and insomnia had the greatest negative impact on HRQL. Thus, screening and management of these nonmotor symptoms should be part of early, as well as later, stage PD clinical care.

Cognitive and neuropsychiatric features

Cognitive and neuropsychiatric symptoms can have as much impact on the quality of life of a patient with PD as the motor symptoms (Aarsland et al., 2009 a-c; Svenningsson et al., 2012; Goldman 2016). Although the neuropsychiatric symptoms encountered in PD are diverse, they typically encompass mood, cognitive, and behavioral issues, specifically depression and anxiety; mild cognitive impairment and dementia; and apathy, impulse control disorders (ICDs), and psychosis.

In 537 patients with dementia associated with PD (PDD), 58% had associated depression, 54% apathy, 49% anxiety, and 44% had hallucinations (Aarsland et al., 2007). Many patients, for example, exhibit neurobehavioral disturbances, such as depression, dementia, tip-of-the-tongue phenomenon and other word finding difficulties (Matison et al., 1982), various psychiatric symptoms, and sleep disorders (van Hilten et al., 1994; Aarsland et al., 1999, 2011; Pal et al., 1999; Tandberg et al., 1999; Olanow et al., 2000; Wetter et al., 2000; Ondo et al., 2001; Emre, 2003; Granda and Iranzo, 2004; Adler and Thorpy, 2005; Goetz et al., 2008). Cognitive impairment is a frequent complication of PD, ranging from mild dysfunction such as slowing of thinking, to mild cognitive impairment, to a marked dementia. Mild cognitive impairment in PD (PD-MCI) has been increasingly recognized as a distinct entity or potential precursor stage to dementia, with an estimated prevalence of 19% to 38% (mean 27%) (Litvan et al., 2011, 2012; Goldman et al., 2014). PD dementia is a frequent complication

of long-standing PD, with cross-sectional estimates of about 40% and longitudinal studies revealing that 80% of patients with PD develop dementia after 8 or more years of disease (Hely et al., 2005; Emre et al., 2007; Aarsland et al., 2010).

Clinical features of PD cognitive impairment, whether PD-MCI or PD dementia, affect a broad range of cognitive domains and vary in severity. Common cognitive symptoms reflect dysfunction in attention, working memory, executive function, memory, and visuospatial function. Symptoms of PD cognitive impairment include slowed thinking, trouble with attention and concentration, problems with multitasking or planning, difficulty switching tasks or starting new ones, forgetfulness or short-term memory problems, or difficulty with sense of direction. Although language (i.e., confrontational naming) is generally less affected, patients with PD often report difficulty finding the “right words.” Cognitive deficits in PD-MCI may occur in isolation (single domain) or in combination, with multiple cognitive domains impaired. Dementia occurs when more than one cognitive domain is impaired and there is significant impact on daily function.

Aarsland and colleagues (2001) found in a community-based, prospective study that patients with PD have an almost sixfold increased risk for dementia. In an 8-year prospective study of 224 patients with PD, they found that 78.2% fulfilled the *Diagnostic and Statistical Manual of Mental Disorders*, third edition (DSM-III) criteria for dementia (Aarsland et al., 2003). The mean annual decline on Mini-Mental State Examination (MMSE) in patients with PD is 1 point, in patients with PD and dementia, it is 2.3 points (Aarsland et al., 2004). A long-term follow-up study of 233 subjects in Norway found that 60.1% of subjects by 12 years into the course of the disease had evidence of dementia (Buter et al., 2008). Based on this study, a 70-year-old man with PD but without dementia has a life expectancy of 8 years, three of which will be marked by coexistent dementia. Several studies demonstrate greater sensitivity for detecting early cognitive deficits the Montreal Cognitive Assessment (MoCA), for MCI-PD (Gill et al., 2008; Chou et al., 2010) and differentiating PD dementia from PD patients with mild cognitive impairment (Dalrymple-Alford et al., 2010). In a study designed to compare the two scales in 88 patients with PD, the percentage of subjects scoring below a cutoff of 26 of 30 (used by others to detect mild cognitive impairment) was significantly higher on the MoCA (32%) than on the MMSE (11%), suggesting that the MoCA may be a more sensitive tool to identify early cognitive impairment in PD (Zadikoff et al., 2007). Of the various scales specifically designed to assess cognitive impairment in PD the Scales for Outcomes of Parkinson's Disease-Cognition (SCOPA-COG), which mainly assesses “frontal-subcortical” cognitive defects, and the Parkinson's Disease Cognitive Rating Scale (PD-CRS), which assesses “instrumental-cortical” functions, have been most rigorously validated (Kulisevsky and Pagonabarraga, 2009). The SCOPA-COG also assesses greater attention, working memory, executive, and visuospatial functions (Marinus et al., 2003). Several reviews discuss the clinimetric properties of scales of global cognition in PD and choices in cognitive tests (Chou et al., 2010; Lee et al., 2012; Skorvanek et al., 2018).

Cognitive deficits have been found in 30% of patients with early PD (Elgh et al., 2009) and in other studies of de novo PD, between 19% and 42% (Foltynie et al., 2004; Aarsland

et al., 2009a-c; Yarnall et al., 2014; Weintraub et al., 2015). In the DATATOP study of patients with early PD, cognitive impairment, defined as scoring 2 SD below age- and education-adjusted MMSE norms, was 2.4% (95% CI, 1.2%–3.5%) at 2 years and 5.8% (3.7%–7.7%) at 5 years (Uc et al., 2009a-c). Risk factors for cognitive impairment in this population of patients (N = 740) were older age, hallucinations, male gender, increased symmetry of parkinsonism, increased severity of motor impairment (except for tremor), speech and swallowing impairments, dexterity loss, and presence of gastroenterologic/urologic disorders at baseline.

Patients with PD have nearly twice the risk for developing dementia as controls, and siblings of demented PD patients have an increased risk for AD (Marder et al., 1999). A prospective study, following patients with PD over 5 years, found that the presence of a marker of amyloid in the brain, seen with PET scanning, was associated with worsening cognition over time, also suggesting a contribution of AD pathologic conditions in patients with PD (Gomperts et al., 2013). In addition to the MMSE, other tests (e.g., the Frontal Assessment Battery) have been developed and validated to assess the cognitive and frontal lobe function (Dubois et al., 2000) in patients with dementia with or without parkinsonism. In agreement with basal forebrain cholinergic denervation even in early PD, prominent and widespread reduction in cortical, particularly the medial occipital secondary visual cortex (Brodmann area 18), AChE can be demonstrated using N-[11-C]methyl-4-piperidyl acetate PET (Shimada et al., 2009). These changes were more pronounced but similar in patients with PDD and DLB. Carrying at least one apolipoprotein E4 (APOE4) allele is associated with more rapid cognitive decline (Morley et al., 2012), though studies regarding APOE4 and PDD have yielded conflicting results. Some studies suggest two different PD cognitive phenotypes, one with frontostriatal-based deficits on attention and executive function tasks and the other with posterior cortical deficits on semantic fluency, memory, and visuospatial tasks (Williams-Gray et al., 2009); the latter phenotype may have a greater risk for developing PDD and associations with genotypes of glucocerebrosidase (GBA), *MAPT*, and APOE4. Cognitive impairment in PD can relate to the underlying dopaminergic deficit, but there is evidence that cholinergic and other non-dopaminergic deficits may also play a role (Kehagia et al., 2010). Regarding dopaminergic contributions to cognition, one hypothesis suggests that dopamine levels are initially increasing in the frontal cortex of PD brain as a response to decreased dopamine levels in basal ganglia, which may impair cognition, the so-called U-shaped effect linking impaired cognition to either underactivation or overactivation of dopamine systems (Kehagia et al., 2013). In addition to frontostriatal dopamine deficiency, parkinsonian dementia may develop later in the course or with age and may arise at least in part from Lewy body or amyloid deposition in posterior cortical regions such as the parietal and temporal lobes. In contrast to the frontostriatal dopamine-sensitive syndrome, PDD is characterized by visuospatial constructional deficits and recognition, semantic and episodic memory loss, not usually ameliorated by dopaminergic drugs, but possibly improved with cholinesterase inhibitors such as rivastigmine, similar to AD. Thus, PDD may arise from a potentially wide spectrum of neuropathologic and neurochemical changes and represents a different syndrome from

that produced by dopamine loss in the basal ganglia, both of which frequently occur together.

Imaging studies across different modalities (structural MRI, fMRI, PET, and single-photon emission computed tomography [SPECT]) demonstrate changes associated with cognitive dysfunction in PD (Duncan et al., 2013, 2016). Functional imaging also has been used to study risk factors for cognitive decline in PD. Temporoparietal cortical hypometabolism is present in patients with PD and may be a useful predictor of future cognitive impairment (Hu et al., 2000). Another predictor of cognitive dysfunction appears to be reduced 18F-fluorodopa uptake in the caudate nucleus and frontal cortex (Rinne et al., 2000) and in the mesolimbic pathways (Ito et al., 2002). Using event-related fMRI to compare groups of cognitively impaired and unimpaired patients, Lewis and colleagues (2003) showed a significant signal intensity reduction during a working-memory paradigm in specific striatal and frontal lobe sites in PD patients with cognitive impairment. These studies indicate that cognitive impairments in early PD are related to reductions in activity of frontostriatal neural circuitry. Studies using PET to study brain activation during frontal tasks, such as trial-and-error learning, Mentis and colleagues (2003) found that even in early PD when learning is still relatively preserved, PD patients had to activate four times as much neural tissue as the controls to achieve learning performance equal to controls. Although the sequence learning is impaired even in early PD, this learning deficit does not appear to reflect impairments in motor execution or bradykinesia and may be related to reduced attention (Ghilardi et al., 2003).

Pathologically, dementia correlates with cortical pathologic conditions, including Lewy bodies (Hughes et al., 1993; Hurtig et al., 2000; Irwin et al., 2012), especially in the cingulate and entorhinal cortex (Kovari et al., 2003). But the significance of cortical Lewy bodies is not clear, because most patients with PD have some detectable Lewy bodies in the cerebral cortex, and patients with PD with no dementia during life have been found to have neuropathologic findings diagnostic of Lewy body dementia (Colosimo et al., 2003). In contrast to earlier studies showing relatively low frequency of dementia in PD, more recent studies suggest that the cumulative prevalence may be as high as 78%, correlating best with cortical and limbic Lewy bodies (Emre, 2004). In one of the largest clinicopathologic studies involving 140 patients with a clinical diagnosis of PD either without cognitive impairment (N = 48) or dementia (PDD) (N = 92) 2 or more years after onset of motor symptoms, severity of cortical Lewy bodies and Lewy neurite pathologic conditions was positively associated with dementia ($P < 0.001$), with an odds ratio (OR) of 4.06 (95% CI, 1.87–8.81), as was APOE4 genotype ($P = 0.018$; OR, 4.19; 95% CI, 1.28–13.75) (Irwin et al., 2012). In addition, 28.6% of all PD cases had sufficient pathologic findings for comorbid AD.

Regarding management of cognitive impairment in PD, if acute or new onset, evaluation of acute changes in medical conditions, infections, medications for PD and non-PD symptoms, centrally acting medications, or other reasons should be considered. Management also includes addressing safety and driving issues. To date, only rivastigmine has been approved by the US Food and Drug Administration (FDA) for the treatment of PDD based on a randomized

double-blind, placebo-controlled 24-week trial of over 500 subjects with mild to moderate PDD and a modest but statistically significant improvement on the Alzheimer's Disease Assessment Scale Cognitive Subscale (Emre et al., 2004). Studies with memantine and PDD revealed mixed results (Aarsland et al., 2009a-c; Emre et al., 2009). Trials for PD-MCI with cholinesterase inhibitors and other agents with noradrenergic or dopaminergic mechanisms (e.g., atomoxetine and monoamine oxidase B inhibitors) have been negative for primary cognitive outcomes in PD-MCI (Goldman et al., 2015; Mamikonyan et al., 2015; Hinson et al., 2016; Weintraub et al., 2016).

Mood and behavioral disorders

Depression is a common comorbid condition in patients with PD; clinically significant depression is present in about a third of all PD patients (Pankratz et al., 2008; Reijnders et al., 2008; Stella et al., 2008; Aarsland et al., 2011) and may precede other symptoms or signs of PD (Alonso et al., 2009). Thirty-four percent of subjects met the DSM IV criteria for at least one anxiety disorder; 11.8% met criteria for multiple anxiety disorders; and 11.4% had clinically relevant anxiety symptoms (Leentjens et al., 2011). Depression is the most frequently identified determinant of HRQL (Soh et al., 2011). Death or suicidal ideation has been reported in 28% and 11%, respectively, and 4% of PD patients have a lifetime suicide attempt, correlated with severity of depression, ICD, and psychosis (Nazem et al., 2008; Weintraub, 2008).

The severity and impact of depression in PD may be assessed by several instruments, but the Hamilton Depression Scale (HAM-D), Beck Depression Inventory (BDI), Hospital Anxiety and Depression Scale (HADS), Montgomery-Asperg Depression Rating Scale (MADRS), and Geriatric Depression Scale (GDS) have been found particularly useful for screening purposes and HAM-D, MADRS, BDI, and the Zung Self-Rating Depression Scale (SDS) have been recommended for assessment of severity (Schrag et al., 2007a,b). Because of brevity, excellent psychometric properties and lack of copyright protection the 30-item GDS (GDS-30) is considered the most efficient screening tool in PD (Williams et al., 2012). Although the HADS and the GDS may be particularly useful in measuring severity of depression, these scales apparently are not sensitive enough to detect a change in patients with severe depression. In addition to instruments used to assess depression, scales for apathy and anhedonia (Leentjens et al., 2008a) and for anxiety (Leentjens et al., 2008b) associated with PD also have been developed and validated. Even without these tools, using DSM-IV-TR and a diagnostic examination by psychiatrists found a 49% lifetime prevalence of anxiety in a physician-based sample of 127 patients with PD (Pontone et al., 2009). Ultimately, clinicians have to choose the tool that is most suited for their practice or research (Goodarzi et al., 2016).

Stage of illness, motor impairment, and functional disability clearly correlate with depressive symptoms (Pankratz et al., 2008). A community-based study showed that 7.7% of PD patients met the criteria for major depression, 5.1% met those for moderate to severe depression, and another 45.5% had mild depressive symptoms (Tandberg et al., 1996). Depression in PD has a major impact on quality of life (Schrag, 2006). In 139 patients with PD,

Aarsland and colleagues (1999) found at least one psychiatric symptom in 61% of the patients. These included depression (38%), hallucinations (27%), and a variety of other behavioral and cognitive changes. In a study of 114 PD patients, 27.6% screened positive for depression during the average 14.6 months of follow-up; 40% were neither treated with antidepressants nor referred for further psychiatric evaluation (Ravina et al., 2007a). Furthermore, depression, as assessed by the GDS-15, correlated with impairment in ADLs ($P < 0.0001$). Subsequent analysis showed that increasing severity of depressive symptoms, older age, and longer PD duration predicted a lower likelihood of symptom resolution (Ravina et al., 2009). Patients with depression may be three times more likely to later develop PD (Schoorman et al., 2002). In one study, depression was found in 15% of patients with PD, and it had more impact on the ADLs than on the motor subscale of UPDRS (Holroyd et al., 2005).

Using (^{11}C)RTI-32 PET as a marker of both dopamine and norepinephrine transporter binding in 8 PD patients with and 12 without depression, Remy and colleagues (2005) showed significantly lower binding of this ligand in the LC and various limbic regions in depressed and anxious patients compared with those without these psychiatric symptoms. In a group of 94 patients with primary depression, Starkstein and colleagues (2001) found that 20% of patients had parkinsonism that was reversible on treatment of the depression. Blunted reactivity to aversive (pleasant and unpleasant) stimuli has been found in a group of nondemented PD patients (Bowers et al., 2006). Some investigators have attributed the various nonmotor symptoms associated with PD, such as depression, anxiety, lack of energy, and sexual dysfunction, to comorbid testosterone deficiency (found in 35% of PD patients) and suggested that testosterone treatment may be the appropriate therapy for these patients (Okun et al., 2002) and may also improve apathy associated with PD (Ready et al., 2004; Kirsch-Darrow et al., 2006). However, in a subsequent control clinical trial, testosterone was not found to be beneficial in men with PD (Okun et al., 2006).

Treatment of PD depression involves both pharmacologic and nonpharmacologic approaches. The evidence base, however, is limited for antidepressants in PD because few large randomized double-blind placebo-controlled studies have been conducted. In the Study of Antidepressants in PD (SAD-PD) trial comparing paroxetine, venlafaxine, and placebo, both drug treatment groups showed similar improvement in HAM-D scores at 12 weeks (Richard et al., 2012). In a randomized controlled study, nonpharmacologic therapies, such as cognitive-behavioral therapy, demonstrated greater improvement in HAM-D scores than clinical monitoring and modest gains in verbal memory and executive function scores (Dobkin et al., 2011).

Anxiety is a common neuropsychiatric issue in PD, occurring in 20% to 50% of patients with PD and is likely under-recognized and undertreated (Dissanayaka et al., 2011). Anxiety in PD may occur within the context of depression. However, anxiety can occur as part of generalized anxiety disorder, panic disorder, or other phobias or in certain situations such as freezing, fear of falling, or discomfort in social situations. Moreover, anxiety can manifest as a nonmotor fluctuation during off periods. Symptoms of off-period anxiety can mimic panic attacks with marked anxiety, shortness

of breath, diaphoresis, and autonomic and gastrointestinal symptoms. This can even lead to emergency department visits and evaluations for cardiopulmonary reasons. To date, no controlled trials have been specifically conducted in PD for anxiety. Medications used to treat anxiety disorders in PD are similar to those used in the non-PD population, such as selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), buspirone in some, and benzodiazepines used cautiously. If anxiety relates to nonmotor fluctuations, then dopaminergic medications may require adjustments to minimize off periods.

Apathy is the primary loss of motivation and decreased goal-directed behavior. Apathy represents a syndrome that encompasses behavioral, cognitive, and emotional aspects, although it can be distinct from depression (Pagonabarraga et al., 2015). It appears to be related to the underlying disease process rather than being a psychological reaction to disability or to depression (Kirsch-Darrow et al., 2006) and is closely associated with cognitive impairment (Pluck and Brown, 2002). Prevalence rates of apathy range from 15% to 75% depending on the population studied, with lower rates in early PD (20%–36%) and higher rates (over 60%) in more advanced PD (Aarsland et al., 2007, 2009a-c; Dujardin et al., 2007; Starkstein et al., 2009). Although depression and dementia are the most frequent comorbidities associated with apathy, about 13% of patients with PD exhibit apathy alone (Starkstein et al., 2009). Whether these symptoms represent a continuum of bradykinesia–bradyphrenia or different disorders is not easy to answer with the current rudimentary knowledge of these disorders (Muquit et al., 2001). Apathy is also associated with poor outcomes, decreased quality of life, and increased caregiver burden. Apathy has a major impact on HRQL even in patients with newly diagnosed PD (Benito-Leon et al., 2012). The care partner may appear to be more bothered by symptoms of apathy than the person with PD. Four different, but related, subdomains have been proposed to reflect behavioral, cognitive, and affective components and underlying subcortical and cortical brain regions affected (e.g., anterior cingulate, amygdala, ventral striatum, frontal cortex). Apathy encompasses a reward deficiency syndrome, depression, dysexecutive syndrome, and an autoactivation deficit in which patients lack spontaneous activation of mental processes without external stimulation. Pharmacologic treatment of apathy has used medications used for depression, dementia, or PD symptoms, but with limited evidence base. Although psychotherapy and occupational therapy may be helpful, pharmacologic or surgical treatment (e.g., subthalamic DBS) usually do not significantly ameliorate apathy (Starkstein et al., 2012). However, in a 12-week, randomized, double-blind, placebo-controlled study evaluating the effect of piribedil, a D2/D3 receptor agonist, in 37 PD patients with apathy after STN DBS, there was a significant improvement in the primary endpoint, the Starkstein Apathy Scale (the score was reduced by 34.6% in the piribedil group compared with 3.2% with placebo) (Thibois et al., 2013). Because of high drop-out rate, this study provides Class II evidence supporting the efficacy of piribedil for the treatment of postoperative apathy in PD patients. Rivastigmine was studied in a double-blind, placebo-controlled randomized trial for apathy in PD over 6 months; of the 101 patients screened, only 31 were eligible and randomized. Those treated with rivastigmine had improved symptoms on

the Lille Apathy Rating Scale, compared with placebo ($P = 0.03$) (Devos et al., 2014).

Psychosis can affect more than one-third of patients with PD treated with chronic dopaminergic therapy and over 50% in longitudinal studies of 10 years or more (Fernandez et al., 2008; Friedman, 2010; Goldman et al., 2016). Psychosis encompasses illusions, hallucinations, and delusions, though delusions are present in about 5% to 10% of PD patients. PD psychosis contributes to poor outcomes, with increased mortality, nursing home placement, and caregiver stress. Diagnostic criteria for psychosis in PD emphasize primarily the presences of paranoid delusions, visual hallucination, illusions, and false sense of presence in contrast to auditory hallucinations and thought disorder typically seen in patients with schizophrenia (Ravina et al., 2007b). Several studies have shown that the occurrence of psychosis is frequently associated with other psychiatric comorbidities, especially depression, anxiety, and apathy (Marsh et al., 2004), and with dementia (Factor et al., 2003). Visual hallucinations, although usually attributed to dopaminergic therapy, may be part of PD, particularly when there is coexistent dementia and depression (Fénelon et al., 2006; Marsh et al., 2006), and their presence strongly suggests underlying synuclein pathologic processes (Betram and Williams, 2012). One study concluded that the presence of hallucinations is the strongest predictor of nursing home placement and death (Aarsland et al., 2000). The prognosis of PD-associated psychosis, however, has improved with the advent of atypical neuroleptics in that the incidence of death within 2 years of nursing home placement decreased from 100% to 28%. Minor hallucinations may occur in as many as 40% of patients with PD, illusions in 25%, formed visual hallucinations in 22%, and auditory hallucinations in 10% (Fénelon et al., 2000). A feeling of presence, the vivid sensation that somebody (distinct from oneself) is present nearby, has been experienced by about half of patients with PD (Fénelon et al., 2011). Risk factors for hallucinations include older age, duration of illness, depression, cognitive disorder, daytime somnolence, poor visual acuity, family history of dementia (Paleacu et al., 2005), and dopaminergic drugs (Barnes and David, 2001; Goetz et al., 2001; Holroyd et al., 2001). Hallucinations seem to correlate with daytime episodes of rapid eye movement (REM) sleep and daytime non-REM and nocturnal REM sleep, suggesting that hallucinations and psychosis may represent a variant of narcolepsy-like REM sleep disorder (Arnulf et al., 2000) and that dream imagery plays an important role in visual hallucinations (Manni et al., 2002). Other studies, however, have found no correlation between hallucinations and abnormal sleep patterns (Goetz et al., 2005). Longitudinal follow-up of patients show that both hallucinations and REM sleep behavior disorder (RBD) increase over time, but sleep fragmentation and other sleep problems at baseline did not necessarily correlate with future development of hallucinations (Goetz et al., 2010a,b). The sleep abnormalities observed in patients with PD may possibly be related to a 50% loss of hypocretin (orexin) neurons (Fronczek et al., 2007; Thannickal et al., 2007). The presence of visual hallucinations usually indicates an underlying synuclein pathologic condition (Betram and Williams, 2012). In a prospective study of 104 patients with PD, 52 of whom were diagnosed with psychosis under National Institute of Neurological Disorders and Stroke (NINDS) criteria, the diagnosis

of PD psychosis was made with 94% sensitivity and 91% specificity (Gordon et al., 2016). Hallucinations in nonvisual modalities are frequently accompanied by visual hallucinations and occur in more advanced PD (Goetz et al., 2011). Compared with PD patients without hallucinations, those PD hallucinators exhibit greater cognitive deficits, particularly in attention, executive function, and visuospatial abilities. The pathophysiology of PD psychosis has focused on three primary neuroanatomical areas, the visual system, brainstem, cortex, and accompanying neurochemical and neuropathologic changes in these areas. PD psychosis may result from interactions between behavioral and cognitive phenomena and abnormalities in “top-down” or “bottom-up” processing, which have been found to have imaging correlates with gray matter atrophy in occipital, parietal, and other brain regions and altered connectivity across cortical and subcortical brain areas (Lenka et al., 2016). Treatments for PD psychosis include pharmacologic and nonpharmacologic strategies. If acute, evaluation for medical and neurologic conditions other than PD and a review of the patient’s medication regimen are important. Management may include decreasing or stopping dopaminergic medications in PD. To date, the only FDA-approved medication for PD psychosis is pimavanserin, a serotonergic receptor inverse agonists and antagonist, which in a randomized, controlled trial of 199 PD patients demonstrated significantly reduced symptoms of psychosis on the Scale for Assessment of Positive Symptoms for PD compared with placebo (Cummings et al., 2014).

In addition to these behavioral problems, many patients with PD develop obsessive-compulsive behavior, addictive personality, and ICD, particularly exemplified by compulsive gambling and shopping, hypersexuality, hoarding, and other compulsive behaviors (Molina et al., 2000; Alegret et al., 2001; Geschwandtner et al., 2001; Driver-Dunckley et al., 2003; Ferrara and Stacy, 2008; Mamikonyan et al., 2008; Stamey and Jankovic, 2008; Robert et al., 2009; O’Sullivan et al., 2010; Antonini et al., 2011; Voon et al., 2011). The Questionnaire for Impulsive-Compulsive Disorders in Parkinson’s Disease (QUIP) (Weintraub et al., 2009) assesses ICDs (involving gambling, sexual, buying, and eating behaviors), compulsive behaviors (punding, hobbyism, and walkabout), and compulsive medication use, and the Questionnaire for Impulsive-Compulsive Disorders in Parkinson’s Disease-Rating Scale (QUIP-RS) also appears to be a useful and valid instrument in diagnosing and assessing ICD (Weintraub et al., 2012). Although ICD in patients with PD is usually attributed to dopaminergic drugs, 17.5% of PD patients naive to dopaminergic drugs screened positive for at least one ICD symptom, although the frequency is similar to that with age-matched healthy controls, it rarely meets the DSM-IV criteria and appears to correlate with underlying depression (Antonini et al., 2011). In another study of naive (de novo) patients with PD, any impulse control or related behavior symptom was found in 20% of patients with newly diagnosed PD, but this was not different from the frequency of such behaviors in healthy controls, again confirming that ICD symptoms in patients with PD are usually drug-induced (Weintraub et al., 2013). Long-term follow-up, however, is needed to determine whether PD patients with ICD symptoms at onset have an increased risk for developing ICD once they are placed on dopaminergic medications. In one study at Baylor College of Medicine, of 300 consecutive patients

taking dopamine agonists for PD (N = 207), restless legs syndrome (N = 89), or both (N = 4), 19.7% reported increased impulsivity: 30 gambling, 26 spending, 11 sexual activities, and 1 wanton traveling, but only 11 of 59 (18.6%) thought the change was deleterious (Ondo and Lai, 2008). Younger age at PD onset, higher novelty-seeking traits, and a personal or family history of alcohol use disorders have been found to be associated with a greater risk for pathologic gambling with dopamine agonists (Voon et al., 2007). Gambling disorders affect 0.2% to 5.3% of adults worldwide and are often associated with other behavioral comorbidities (Hodgins et al., 2011). Pathologic gambling affects about 3% to 8% of PD patients and includes slot machines (33%), instant scratch cards, and lottery (20%), activities that require much shorter latencies than card playing or sports betting, suggesting that seeking immediate reward (reinforcement learning) rather than games that require decision making is contributing to the pathologic gambling in patients with PD (Piacentini, 2010). In a cross-sectional study of 3090 patients with idiopathic PD treated at 46 movement disorder centers in the United States and Canada (the DOMINION study, the following measures were used to assess ICD: Massachusetts Gambling Screen score for current problem/pathologic gambling, the Minnesota Impulsive Disorders Interview score for compulsive sexual behavior and buying, and DSM research (Weintraub et al., 2010). An ICD was identified in 13.6% of patients (gambling in 5.0%, compulsive sexual behavior in 3.5%, compulsive buying in 5.7%, and binge-eating disorder in 4.3%), and 3.9% had two or more ICDs. These disorders were more common in patients treated with a dopamine agonist than in patients not taking a dopamine agonist (17.1% versus 6.9%; OR, 2.72; 95% CI, 2.08–3.54; $P < 0.001$), but there was no difference in frequency of ICD in patients taking pramipexole or ropinirole. Increased risk for ICDs were associated with levodopa use, living in the United States, younger age, being unmarried, current cigarette smoking, and a family history of gambling problems. In another study, the following risk factors for ICD were identified: cigarette smoking, caffeine use, motor complications, and higher peak dopamine agonist dosage (Bastianes et al., 2013). Thus dopamine agonist treatment was associated with 2- to 3.5-fold increased odds of having an ICD. In a systematic review of the literature on pathologic gambling in PD the following were found to be significant risk factors: male sex, younger age or younger age at PD onset, personal or family history of substance abuse or ICD, a personality profile characterized by impulsiveness, and treatment with dopamine agonists more than with levodopa (Santangelo et al., 2013). Except for gradual discontinuation or tapering of the dopaminergic drugs there is no effective treatment of this form of ICD. Using perfusion technetium-99 SPECT scan to study brain activity, PD patients with pathologic gambling have been found to have resting state dysfunction of the mesocorticolimbic network involved in addictive behavior (Cilia et al., 2008). Thus, it is postulated that in such patients there is lack of the usual reduction in cortical perfusion typically associated with neurodegenerative process and that pathologic gambling results from abnormal drug-induced overstimulation of relatively spared mesocorticolimbic dopamine system. Increased striatal dopamine release has been postulated in PD patients with pathologic gambling, based on findings from raclopride PET scans (Steeves et al., 2009).

Various intrusive cognitive events with associated repetitive behaviors, representing the spectrum of obsessive-compulsive disorder (OCD) in PD, include the following domains: (1) checking, religious, and sexual obsessions; (2) symmetry and ordering; (3) washing and cleaning; and (4) punding. Punding is characterized by intense fascination with repetitive handling, examining, sorting, and arranging of objects, inordinate writing, doodling, painting, collecting things, shuffling through personal papers, journaling/blogging, Internet play, excessive cleaning or gardening or sorting household objects, humming or singing, and reciting long, meaningless soliloquies without an audience (Evans et al., 2004; Voon, 2004; Silveira-Moriyama et al., 2006). The behavior may be based on one's experiences and hobbies or may be more related to OCD features such as gambling, which in turn may be exacerbated by dopaminergic drugs (Kurlan, 2004). In a survey of 373 consecutive patients with PD, only 1.4% exhibited punding behavior (Miyasaki et al., 2007). Compulsive singing may be another variant of punding (Bonvin et al., 2007). Pathologic gambling has been attributed most frequently to the use of dopamine agonists (Kurlan, 2004; Dodd et al., 2005; Stamey and Jankovic, 2008), but levodopa and even STN DBS also have been reported to cause pathologic gambling. The OCD that is associated with PD has been reported to improve with high-frequency stimulation of the STN (Mallett et al., 2002).

Another behavioral abnormality, possibly related to underlying OCD, is "hedonistic homeostatic dysregulation." This behavior is seen particularly in males with early-onset Parkinson's disease (EOPD) who misuse and abuse dopaminergic drugs and develop cyclic mood disorder with hypomania or manic psychosis (Giovannoni et al., 2000; Pezzella et al., 2005). Other behavioral symptoms associated with dopamine dysregulation syndrome include compulsive dopaminergic replacement (Lawrence et al., 2003), craving, binge eating, compulsive foraging, euphoria, dysphoria, hypersexuality, pathologic gambling, compulsive shopping, aggression, insulting gestures, paranoia, jealousy, phobias, impulsivity, and other behaviors (Evans and Lees, 2004; Isaias et al., 2008; Mamikonyan et al., 2008; Stamey and Jankovic, 2008; Weintraub et al., 2008). Dopaminergic drugs, particularly dopamine agonists, have been demonstrated to precipitate or exacerbate behavioral symptoms of ICD, and the symptoms usually improve with reduction of dosage or cessation of the offending drug (Mamikonyan et al., 2008).

Many cognitive and behavioral symptoms associated with PD, such as depression, sleep disorders, and fatigue, can adversely influence the overall quality of life in patients with PD (Karlsen et al., 1999). In one study, 50% of patients with PD had significant fatigue that had a major impact on HRQL (Herlofson et al., 2012). PD-related fatigue contributes to poor functional capacity and physical function (Garber and Friedman, 2003; Chaudhuri and Behan, 2004; Friedman et al., 2007). A 16-item self-report instrument designed to measure fatigue associated with PD has been developed (Brown et al., 2005). One study showed that depression, postural instability, and cognitive impairment have the greatest influence of quality of life (Schrag et al., 2000). In a prospective longitudinal study of 111 patients followed for 4 years, Karlsen (2000) showed significantly increased distress, based on HRQL, not only because of motor symptoms

but also because of pain, social isolation, and emotional reactions. Other neurobehavioral features that have been noted in PD include variants of bradyphrenia (slowness of thought), such as abulia (severe apathy and lack of initiative and spontaneity) and akinetic mutism and catatonia (immobility, mutism, refusal to eat or drink, staring, rigidity, posturing, grimacing, negativism, waxy flexibility, echophenomenon, and stereotypy), have been recognized in patients with parkinsonism. Alexithymia also includes the inability to symbolize or mentalize emotions and also interferes significantly with the recognition of facial expressions of emotions.

There have been several studies attempting to address the question of "premorbid parkinsonian personality." Twin and other studies have suggested that since childhood PD patients tend to be more introverted, cautious, socially alert, tense, nervous, and rigid compared with controls (Ishihara and Brayne, 2006). Some have found PD patients, even before onset of motor symptoms, to often avoid risk-seeking behavior, such as smoking (Ward et al., 1983), and to exhibit lower impulsive and less novelty seeking behavior (Menza et al., 1993; Fujii et al., 2000; Evans et al., 2004). Because dopamine is involved in the reward system, presymptomatic dopamine deficiency may predispose some individuals to exhibit a "nonsmoking personality," thus accounting for the lower frequency of smokers among PD patients (Wirdfeldt et al., 2005). Many studies have demonstrated that even before they first develop any motor symptoms PD patients tend to have relatively characteristic personality traits, such as industriousness, seriousness, and inflexibility and they tend to be "honest" (Przuntek, 1992; Macias et al., 2008; Abe et al., 2009). One study of 32 patients, using F-fluorodeoxyglucose PET scans, showed that persons with PD are indeed "honest" and have difficulties making deceptive responses and that this personality trait might be derived from dysfunction of the prefrontal cortex (Abe et al., 2009). Anhedonia is another frequent symptom of PD, which may be independent from depression or motor deficits (Isella et al., 2003) but may be linked to depression, apathy, and frontal lobe dysfunction (Assogna et al., 2011). Despite the high frequency of depression, patients with PD appear to have higher levels of anger control, consistent with the recognized stoic personality trait (Macias et al., 2008). This "PD-related personality" may also explain why patients with PD appeared to have a decreased sense of humor, which depends on intact mesolimbic dopaminergic-reward system (Thaler et al., 2012).

Sleep disorders

Sleep disorders are being increasingly recognized as a feature of PD. An instrument consisting of 15 questions for assessing sleep and nocturnal disability has been described (Chaudhuri et al., 2002). Although most studies have attributed the excessive daytime drowsiness and irresistible sleep episodes (sleep attacks) to anti-PD medications (Ondo et al., 2001), some authors think that these sleep disturbances are an integral part of PD and are age-related (Gjerstad et al., 2006). Increasing the nighttime sleep with antidepressants or benzodiazepines may not necessarily alleviate daytime drowsiness (Arnulf et al., 2002). In a study of 303 PD patients, 63 (21%) had symptoms of restless legs syndrome, possibly

associated with low ferritin levels, but there was no evidence that restless legs syndrome leads to PD (Ondo et al., 2002). These results are nearly identical to another study that found restless legs syndrome in 22% of 114 patients with PD (Gomez-Esteban et al., 2007). In another study, 10 of 126 (7.9%) patients with PD and 1 of 129 (0.8%) controls had symptoms of restless legs syndrome (Krishnan et al., 2003). Tan and colleagues (2002) found motor restlessness in 15.2% of their patients with PD, but the prevalence of restless legs syndrome, based on diagnostic criteria proposed by the International Restless Legs Syndrome Study Group, in the PD population was the same as that in the general or clinic population. Degeneration of the diencephalospinal dopaminergic pathway has been postulated to be the mechanism of restless legs syndrome in patients with PD (Nomura et al., 2006). Other studies have concluded that leg motor restlessness, rather than true restless legs syndrome, is increased in early PD (Gjerstad et al., 2011).

Several studies have provided evidence that up to 50% of patients presenting with idiopathic RBD (IRBD) eventually developed parkinsonism, IRBD is now considered to represent a preparkinsonian state (Schenk et al., 1996; Plazzi et al., 1997; Comella et al., 1998; Ferini-Strambi and Zucconi, 2000; Wetter et al., 2000; Matheson and Saper, 2003; Gagnon et al., 2006; Iranzo et al., 2006, 2010, 2011, 2013; Postuma et al., 2006; Boeve et al., 2007; Britton and Chaudhuri, 2009; Postuma et al., 2009a, 2010; Classen et al., 2010; Goetz et al., 2010a,b; Sixel-Doring et al., 2011; Arnulf, 2012; Boeve, 2013). The following one question was found to have 94% sensitivity and 87% specificity in detecting RBD: "Have you ever been told, or suspected yourself, that you seem to 'act out your dreams' while asleep (e.g., punching, flailing your arms in the air, making running movements, etc.)?" (Postuma et al., 2012). Based on a study of 457 unselected sleep-disturbed patients with PD who underwent video-supported polysomnography, the overall frequency of RBD was found to be 46% (Sixel-Doring et al., 2011). The occurrence of RBD did not correlate with gender or PD subtype, but was associated with older age, longer disease duration, greater severity (higher Hoehn and Yahr stages, more falls, more fluctuations, more psychiatric comorbidity, and a higher dose of levodopa), higher amount of REM sleep, and more periodic leg movements during sleep. In one prospective study of patients with RBD who were being evaluated annually with several quantitative motor measures, including the UPDRS, Purdue Pegboard, alternate-tap test, and timed up-and-go, a prodromal interval of about 4.5 years was found based on data from 20 out of 78 patients with RBD who developed parkinsonism during the follow-up period (Postuma et al., 2012). In some cases, evidence of RBD was recorded up to 50 years before the onset of the initial symptoms of a neurodegenerative disorder, such as PD, PDD, DLB, or MSA (Claassen et al., 2010). RBD seems to be predictive of PD-associated dysautonomia, particularly orthostatic hypotension (Postuma et al., 2009b). The RBD Screening Questionnaire (RBDSQ) is a relatively sensitive instrument that captures most of the characteristics of RBD and may be useful as a screening tool (Stiasny-Kolster et al., 2007). In one study, 86% of patients with RBD had associated parkinsonism (PD 47%, MSA 26%, PSP 2%) (Olson et al., 2000). RBD was found in 11 of 33 (33%) patients with PD, and 19 of 33 (58%) had REM sleep without atonia

(Gagnon et al., 2002). In another study, RBD preceded the onset of parkinsonism in 52% of patients with PD (Olson et al., 2000). The strong male preponderance that is seen in patients with RBD is much less evident in patients who eventually develop MSA. The presence of RBD is probably the most useful marker for the development of DLB (Ferman et al., 2011; Dugger et al., 2012; Postuma, 2012). In one study of PD patients with RBD documented by baseline polysomnograph, 48% developed dementia within 4 years (Postuma et al., 2012). Using the Mayo Sleep Questionnaire to screen for RBD, 44 cognitively normal subjects with positive status for RBD and 607 RBD-negative subjects, aged 70 to 89 years, were followed prospectively for a median of 3.8 years. Although 14 subjects developed mild cognitive impairment, only 1 (2%) developed PD (Boot et al., 2012). It is likely, however, that if younger subjects were included in this prospective study the risk for developing PD in the RBD population would be much greater.

Although considered a parkinsonian symptom, RBD is probably related to cholinergic rather than dopaminergic deficit (Kotagal et al., 2012). This is supported by decreased [(11)C]methylpiperidyl propionate AChE binding on PET scans, indicative of decreased neocortical, limbic cortical, and thalamic cholinergic denervation (Kotagal et al., 2012). Furthermore, RBD is often exacerbated by dopaminergic therapy (Gjerstad et al., 2008). [¹¹C]-Dihydrotetrabenazine PET (Albin et al., 2000) and [¹²³I]-iodobenzamide SPECT (Eisensehr et al., 2000) found evidence of significantly reduced dopaminergic terminals and striatal D2 receptor density, respectively, in patients with RBD, though not to the same degree as in patients with PD. Patients with RBD are significantly less likely to have a tremor-dominant form of PD, have higher frequency of falls, and are less responsive to medications than PD patients without RBD (Postuma et al., 2008). Furthermore, patients with RBD have been found to have high incidence of mild cognitive impairment (Gagnon et al., 2009), impaired color discrimination, olfactory dysfunction, and dysautonomia, in addition to motor impairment (Postuma et al., 2006). RBD also has been found to predict cognitive impairment in PD patients without dementia (Vandette et al., 2007). Sleep walking has been demonstrated in PD patients with RBD (Poryazova et al., 2007). Only two cases with RBD have been examined at autopsy that showed evidence of Lewy body disease associated with degenerative changes in the SN and LC in one case, but not in the other case (Boeve et al., 2007). Thus, individuals with symptoms of RBD have a significantly increased risk for developing parkinsonism, particularly if functional imaging shows decreased nigrostriatal dopaminergic activity over the next decade, but progression to neurodegenerative disease is not inevitable (Britton and Chaudhuri, 2009; Postuma et al., 2009). In one study, patients with IRBD underwent (123I-FP-CIT) SPECT and transcranial sonography (TCS) before parkinsonism is clinically evident at baseline and after follow-up of 2.5 years (Iranzo et al., 2010). Of the 43 individuals with IRBD, reduced ¹²³I-FP-CIT binding in the striatum (putamen > caudate) was found in 17 (40%) ($P = 0.045$) compared with 18 (12%) controls. SN hyperechogenicity was found in 14 (36%) of 39 participants with IRBD, compared with 16 (11%) of 149 controls ($P = 0.0002$). Of these participants, 8 (30%) developed a neurodegenerative disorder: 5 with PD, 2 with DLB, and 1 MSA. Sensitivity of combined ¹²³I-FP-CIT

SPECT and TCS to predict conversion to synucleinopathy after 2.5 years was 100% and specificity was 55%.

There is a growing body of evidence supporting the notion that dopamine activity is normally influenced by circadian factors (Rye and Jankovic, 2002). For example, tyrosine hydroxylase falls several hours before the person wakes, and its increase correlates with motor activity. It has been postulated that low doses of dopaminomimetic drugs stimulate D2 inhibitory autoreceptors located on cell bodies of neurons in the ventral tegmental area resulting in sedation. This is consistent with the findings that local (ventral tegmental area) application of D2 antagonists causes sedation and administration of amphetamines initiates and maintains wakefulness. Although the cerebrospinal fluid (CSF) levels of hypocretin (Sutcliffe and de Lecea, 2002) have been reported to be normal in three PD patients with excessive daytime drowsiness, further studies are needed to explore the relationship between hypocretin and sleep disorders associated with PD (Overeem et al., 2002). Because the loss of dopamine in PD generally progresses from the putamen to the caudate and eventually to the limbic areas, it has been postulated that it is loss of dopamine in these latter circuits, most characteristic of advanced disease, that is a potential factor in the expression of excessive daytime drowsiness and sleep-onset REM in PD (Rye and Jankovic, 2002). It is not clear whether these circadian changes explain “sleep benefit” experienced by some patients upon awakening (van Gilst et al., 2013).

Autonomic dysfunction

Autonomic failure is typically associated with MSA and may be the presenting feature of that disease, but it may also herald the onset of PD (Kaufmann et al., 2004; Mostile and Jankovic, 2009; Jain, 2011; Pavy-Le Traon et al., 2011; Palma and Koufmann, 2014). In contrast to PD associated with dysautonomia, which is due to predominantly peripheral (ganglionic and postganglionic) involvement, in MSA the primary lesion is preganglionic; also, dysautonomic symptoms are more severe at baseline and become more global in MSA compared with PD (Lipp et al., 2009). Rating scales for dysautonomia associated with PD have been developed (Evatt et al., 2009). Dysautonomia, such as orthostatic hypotension, sweating dysfunction, sphincter dysfunction, and sexual impotence, occurs frequently in patients with PD (Senard et al., 1997; Swinn et al., 2003). In one study, 7 of 51 (14%) patients with early, untreated PD had decrease of more than 20 mm Hg in systolic blood pressure (Bonuccelli et al., 2003). Another community-based study of a cohort of PD patients showed that 42 of 89 (47%) met the diagnostic criteria for orthostatic hypotension (Allcock et al., 2004). Orthostatic hypotension, however, is not always detected in the clinic. Although the symptom of orthostatic lightheadedness has a relatively high specificity, it seems to have low sensitivity in predicting orthostatic hypotension, partly because it is more likely to occur after tilting than on standing and is often delayed by longer than the recommended 3 minutes (Jamnadas-Khoda et al., 2009). Autonomic symptoms, particularly orthostatic hypotension, seem to be more common in the PIGD form of PD (Allcock et al., 2006). Based on a review of medical records of 1318 patients

diagnosed with PD or atypical parkinsonism at the Parkinson's Disease Center and Movement Disorders Clinic, Baylor College of Medicine, the frequency of symptomatic orthostatic hypotension was 81% (21/26) in patients with MSA, 18% (198/1125) of PD patients, and 19% (31/167) of patients with non-MSA atypical parkinsonism (Ha et al., 2011). In a systematic review and meta-analysis of 25 published studies, the pooled estimate of prevalence of orthostatic hypotension, determined by blood pressure measurements rather than symptoms, in patients with PD was 30% (range 9.6%–64.9%) (Velseboer et al., 2011). Autonomic symptom severity was associated with more motor dysfunction, depressive symptoms, cognitive dysfunction, psychiatric complications, nighttime sleep disturbances, and excessive daytime sleepiness ($P < 0.01$) (Verbaan et al., 2007a). Although dysautonomia is typically associated with MSA, it also may be prominent in PD, although autonomic testing might not always differentiate between PD and MSA (Riley and Chelimsky, 2003).

Orthostatic hypotension in patients with PD has been traditionally attributed to dopaminergic therapy, but studies have provided evidence that orthostatic hypotension in PD is due to failure of reflexive sympathetically mediated cardiovascular stimulation from sympathetic denervation, as demonstrated by markedly decreased 6- $[^{18}\text{F}]$ -fluorodopamine-derived radioactivity in the septal and ventricular myocardium (Goldstein et al., 2002). This sympathetic nervous system deficit involved postganglionic catecholaminergic, not cholinergic, nerves (Sharabi et al., 2003).

Sweating dysfunction, hyperhidrosis, and to a lesser extent hypohidrosis, were reported by 64% of patients with PD compared with 12.5% of controls ($P < 0.005$) (Swinn et al., 2003). These symptoms did not correlate with the severity of the disease but occurred most frequently during the “off” periods and during “on with dyskinesia” periods. Because sudomotor skin response was reduced in the palms, the axial hyperhidrosis has been suggested to be a compensatory phenomenon for reduced sympathetic function in the extremities (Schestatsky et al., 2006). Sweating may be a particularly troublesome symptom during wearing off (Pursiainen et al., 2007). The presence of alpha-synuclein deposits in the dermis of a patient with pure autonomic failure provides evidence that this disorder and other disorders associated with autonomic failure (e.g., PD, DLB, and MSA) should be viewed as variant synucleinopathies (Kaufmann and Goldstein, 2010; Shishido et al., 2010).

Bladder and other urologic symptoms are frequent in PD and are among the most common complaints requiring medical attention (Blackett et al., 2009; Sakakibara et al., 2010). One survey found that over one-fourth of men with PD had urinary difficulty, most often causing urinary urgency (Araki and Kuno, 2000). In one study, urge episodes and urge incontinence were observed in 53% and 27% of the patients with PD, respectively, and detrusor overactivity in 46% of the patients with PD, which was less prevalent than in patients with DLB and AD, and mean voided volume, free flow, cystometric bladder capacity, and detrusor pressor were similar in the groups (Ransmayr et al., 2008).

Despite the possibility of hypersexuality, usually related to dopaminergic drugs, many patients with PD have sexual dysfunction (Celikel et al., 2008; Meco et al., 2008; Hand et al., 2010). In a review of sexual functioning of 32 women

and 43 men with PD, women reported difficulties with arousal (87.5%), reaching orgasm (75.0%), and sexual dissatisfaction (37.5%) (Bronner et al., 2004). Men reported erectile dysfunction (68.4%), sexual dissatisfaction (65.1%), premature ejaculation (40.6%), and difficulties reaching orgasm (39.5%). Reduced sexual drive and dissatisfaction with orgasm was particularly common in female PD patients (Celikel et al., 2008). Among 90 patients with PD, loss of libido was reported by 65.6%, and 42.6% of men also complained of erectile dysfunction (Kummer et al., 2009). Aging, female gender, lower education, and depression were significantly associated with decreased sexual desire. Premorbid sexual dysfunction may contribute to cessation of sexual activity during the course of the disease (among 23.3% men and 21.9% women). Associated illnesses, use of medications, motor difficulties, depression, anxiety, and advanced stage of PD contributed to sexual dysfunction. In one study of women with PD, sexual dysfunction was present in 86.9% of patients and 79.0% of controls, according to the Female Sexual Function Index ($P < 0.01$), and in 57.4% of patients and 22.6% of controls, according to the Sexual Dysfunction Inventory ($P < 0.001$) (Varanda et al., 2016).

Gastrointestinal dysfunction in PD has been attributed to many mechanisms such as involvement, including neurodegeneration and the presence of Lewy bodies, of the dorsal motor nucleus of the vagus, paravertebral sympathetic ganglia, intrinsic neurons of the enteric nervous system (Cersosimo and Benarroch, 2008; Derkindren et al., 2011; Pfeiffer, 2011). Dysphagia (Hunter et al., 1997; Kalf et al., 2012) along with delayed gastric emptying or gastroparesis (Hardoff et al., 2001) and constipation (Ashraf et al., 1997; Bassotti et al., 2000; Winge et al., 2003; Cersosimo and Benarroch, 2008; Ondo et al., 2012) represent the most frequent gastrointestinal manifestations of PD. In addition to constipation, about 60% of PD patients have evidence of delayed gastric emptying (Krygowska-Wajs et al., 2009). The mechanism of delayed gastric emptying (gastroparesis) is multifactorial and may be partly related to central and peripheral (enteric) synuclein pathologic conditions and involvement of the gastric-derived hormone ghrelin (Marin et al., 2013). Many of the gastrointestinal symptoms of PD have been documented in transgenic mice expressing mutant alpha-synuclein (either A53T or A30P) from insertions of an entire human SNCA gene, including synuclein-immunoreactive aggregates, accompanied by abnormal motor behavior but no cardiac autonomic abnormalities, olfactory dysfunction, dopaminergic neurotransmitter deficits, Lewy body inclusions, or neurodegeneration (Kuo et al., 2010). Dopaminergic neurons are abundant in the two plexuses that constitute the enteric nervous system: the myenteric or Aurbach plexus and the submucosal plexus. Enteric Lewy inclusions have been demonstrated in the esophagus of 14 of 15 patients with PD (Beach et al., 2009). Furthermore, enteric Lewy pathologic condition was found to correlate with axial PD symptoms, which has been postulated to reflect spread of the pathologic condition to nondopaminergic structures of the autonomic nervous system, brainstem, and cortex (Derkindren et al., 2011). On the basis of information on the frequency of bowel movements in 6790 men in the Honolulu Heart Program, Abbott and colleagues (2001) concluded that infrequent bowel movements are associated with increased risk for future PD. Based on the observation

from the Honolulu-Asia Aging Study that bowel frequency was lower in subjects who were found to have incidental Lewy bodies in their brains at postmortem examination than in controls, the investigators suggested that constipation was one of the earliest symptoms of PD (Abbott et al., 2007). In addition, constipation was associated with low SN neuron density (Petrovich et al., 2009). Based on a review of Mayo Clinic medical records of 196 case-control pairs ($N = 392$), constipation preceding PD was more common in cases than in controls (OR 2.48; $P = 0.0005$); the association remained significant for constipation documented 20 or less before the onset of motor symptoms of PD (Savica et al., 2009). Constipation in patients with PD is associated with slow colonic transit, weak abdominal strain, decreased phasic rectal contraction, and paradoxical sphincter contraction on defecation (Sakakibara et al., 2003). Several studies have demonstrated alpha-synuclein accumulation in colonic neurons and suggested that demonstration of synuclein pathologic findings in colonic biopsy samples might be a useful biomarker of PD. In one study, synuclein pathologic findings in submucosal nerve fibers was demonstrated in biopsy samples obtained through flexible sigmoidoscopy in 9 of 9 PD subjects, but in none of 23 healthy controls or 23 subjects with inflammatory bowel disease (Shannon et al., 2012a). In the second report, the same authors described synuclein pathologic findings in neurites and perikarya of submucosal neurons that also stained for substance P in three PD patients who had undergone colonic biopsy 2 to 5 years before the diagnosis of PD (Shannon et al., 2012b). Immunohistochemical staining for Lewy-type alpha-synucleinopathy in the submandibular gland was positive in all 28 PD subjects examined at autopsy and in 17 of 19 PD patients in whom biopsy with an 18-gauge needle was performed of the submandibular glands (Beach et al., 2013). In a study of 20 patients with PD and 14 age- and sex-matched controls, patients with PD had greater alpha-synuclein deposition and higher alpha-synuclein ratios in cutaneous sympathetic adrenergic and sympathetic cholinergic fibers but not sensory fibers compared with controls, suggesting that measures of alpha-synuclein deposition in cutaneous autonomic nerves may be a useful biomarker for PD (Wang et al., 2013). In another study, involving 10 patients with PD, 10 patients with MSA, and 6 control subjects with ET, phosphorylated alpha-synuclein deposits were found in sympathetic skin nerve fibers of all patients with PD, but not in any of the patients with MSA or ET (Zange et al., 2015).

Dermatologic changes such as seborrhea, hair loss, and leg edema may represent evidence of peripheral involvement in PD, although some of these changes may be exacerbated by anti-PD drugs (Tabamo and DiRicco, 2002; Tan and Ondo, 2002). There have been numerous reports of skin biopsies in patients with PD revealing synuclein pathologic findings and possibly serving as a diagnostic biomarker (Donadio et al., 2016; Gibbons et al., 2016). Further studies, however, are needed to determine whether this technique improves diagnostic accuracy and whether it can reliably differentiate between PD patients with and without autonomic dysfunction. Several reports (Jansson and Jankovic, 1985; Gorell et al., 1994; Vanacore et al., 1999; Guttman et al., 2004; Inzelberg and Jankovic, 2007) have shown that cancer might be less common in patients with PD, with the major exception being malignant melanoma with an almost 2-fold

increased risk (Olsen et al., 2005; Pan et al., 2011, 2012; Kareus et al., 2012) and a higher risk for family history of melanoma (Gao et al., 2009) and possibly prostate cancer (Kareus et al., 2012).

Sensory abnormalities

In addition to motor and behavioral symptoms, PD patients often exhibit a variety of sensory deficits. Sensory complaints, such as paresthesias, akathisia, and oral and genital pain (Comella and Goetz, 1994; Ford et al., 1996; Djaldetti et al., 2004; Tinazzi et al., 2006; Defazio et al., 2008, 2013; Ha and Jankovic, 2012, are frequently not recognized as parkinsonian symptoms and result in an inappropriate and exhaustive diagnostic evaluation. In addition, growing evidence indicates that haptics, one's ability to determine the shape, orientation, and texture of an object by actively touching its surface and exploring it with the hands, is clearly impaired in PD (Konzak et al., 2012).

Olfactory function is impaired in 90% of PD cases, but hyposmia may be present in 25% of controls because of head trauma, rhinitis, and other causes. Several studies have demonstrated that hyposmia may be present even in very early stages of PD (Stern et al., 1994; Katzenschlager and Lees, 2004; Lee et al., 2006; Silveira-Moriyama et al., 2009a) and may predate other clinical symptoms of PD by at least 4 years (Ross et al., 2008). One study showed that idiopathic olfactory dysfunction (hyposmia) may be associated with a 10% increased risk for developing PD (Ponsen et al., 2004). Camicioli and colleagues (2001) found that a combination of finger tapping, olfaction ability (assessed by the University of Pennsylvania Smell Identification Test, or UPSIT), and visual contrast sensitivity, or Paired Associates Learning, discriminated between PD patients and controls with 90% accuracy. A color-coded probability scale has been developed to interpret UPSIT in patients with suspected parkinsonism (Silveira-Moriyama et al., 2009b). In addition to UPSIT, there are many other ways to evaluate olfactory dysfunction in neurodegenerative disorders (Barresi et al., 2012).

In one study, after 5 years of prospective follow-up 5 of 40 (12.5%) hyposmic first-degree relatives of patients with PD fulfilled clinical diagnostic criteria for PD; none of the other 349 relatives available for follow-up developed PD (Ponsen et al., 2010). All hyposmic individuals developing PD had an abnormal baseline beta-CIT SPECT scan. Thus a two-step approach using olfactory testing followed by DAT SPECT scanning in hyposmic individuals appears to have a high sensitivity and specificity in detecting PD. The mechanism of olfactory loss in PD is not well understood, but it does not appear to be due to damage to the olfactory epithelium but rather results from abnormalities in central regions involved in odor perception (Witt et al., 2009). In fact, recent studies indicate that cholinergic denervation of the limbic archicortex is a more important determinant of hyposmia than nigrostriatal dopaminergic denervation in patients with PD and that deficits in odor identification are associated with greater cognitive impairment (Bohnen et al., 2010; Baba et al., 2012). These findings are based on a study of 58 patients with PD who underwent PET scans using [(11)C]methyl-4-piperidinyl propionate AChE as a cholinergic ligand. The investigators

found that odor identification test scores correlated positively with AChE activity in the hippocampal formation ($r = 0.56$, $P < 0.0001$), amygdala ($r = 0.50$, $P < 0.0001$), and neocortex ($r = 0.46$, $P = 0.0003$) and with cognitive measures such as episodic verbal learning ($r = 0.30$, $P < 0.05$). Although probably unrelated to olfactory loss (or motor deficits), patients with PD have been found to have a higher frequency of rhinorrhea compared with normal controls (Chou et al., 2011).

To determine which signs in very early, presymptomatic or prodromal phase of the disease predicts the subsequent development of PD, Montgomery and colleagues (1999) studied 80 first-degree relatives of patients with PD and 100 normal controls using a battery of tests of motor function, mood, and olfaction (Tissinigh et al., 2001; Double et al., 2003). They found that 22.5% of the relatives and only 9% of the normal controls had abnormal scores. It is, of course, not known how many of the relatives with abnormal scores will develop PD; therefore, the specificity and sensitivity of the test battery in predicting PD cannot be determined. UPSIT administered to 62 twin pairs who were discordant for PD showed that smell identification was reduced in the twins affected with PD in comparison to those without symptoms (Marras et al., 2005). After a mean interval of 7.3 years, 19 of the twins were retested. Neither of two twins who developed new PD had had impaired smell identification at baseline, although their UPSIT scores declined more than those of the other 17 twins. The authors concluded that "smell identification ability may not be a sensitive indicator of future PD 7 or more years before the development of motor signs." In another study of 295 PD patients and 150 controls, olfactory impairment was found to be an independent feature of PD, unrelated to other PD symptoms (Verbaan et al., 2008). Furthermore, *Parkin* and *DJ-1* mutation carriers had normal olfaction. Impaired olfaction, which often precedes the onset of motor symptoms of PD, correlates well with decreased beta-CIT uptake and (Berendse et al., 2002; Siderowf et al., 2005) and with decreased ¹²³I-metaiodobenzylguanidine (MIBG) cardiac uptake (Lee et al., 2006). Indeed, cardiac sympathetic denervation correlates well with olfactory dysfunction (Iijima et al., 2010). Reduced olfaction in PD may be related to a neuronal loss in the corticomedial amygdala (Harding et al., 2002) or to an increase of dopaminergic neurons in the olfactory bulb (dopamine inhibits olfactory transmission), as determined by increased tyrosine hydroxylase-reactive neurons (Huisman et al., 2008). It is important to point out, however, that olfaction is impaired in the elderly population. Using the San Diego Odor Identification Test and self-report, Murphy (2002) found that 24.5% of people between the ages of 53 and 97 have impaired olfaction and the incidence is 62.5% in people over age 80. Loss of smell is characteristic of PD and AD but is usually not present in ET, PSP, corticobasal degeneration, vascular parkinsonism (Katzenschlager et al., 2004), or parkinsonism resulting in *parkin* mutation (Khan et al., 2004). Within PD, patients with the tremor-dominant form with family history were found to have less olfaction loss than those without family history, suggesting that the familial tremor-dominant form of PD might be a different disease from sporadic PD (Ondo and Lai, 2005). In 19 patients with PARK8 (*LRRK2* G2019S mutations), the mean UPSIT scores were significantly lower than in healthy controls ($P < 0.001$).

and similar to that of patients with PD, but the score was normal in two asymptomatic carriers (Silveira-Moriyama et al., 2008). Alpha-synuclein pathologic findings, including Lewy bodies, were identified in the rhinencephalon of four brains of the *LRRK2* patients who had hyposmia. Biopsy of olfactory nasal neurons does not aid in differentiating PD and AD from the other neurodegenerative disorders (Hawkes, 2003). Some investigators think that olfactory testing is comparable to other diagnostic tests, such as MRI, SPECT, and neuropsychologic testing, in differentiating PD from other parkinsonian disorders and in early detection of PD (Katzen-schlager and Lees, 2004). Olfactory impairment early in the course of PD has led to the hypothesis for the pathogenesis of PD suggesting that some infectious, prion-like process, or environmental agent enters the brain by the olfactory route (Doty, 2008; Lerner and Bagic, 2008) (see also Chapter 5). The prodromal phase, often associated with olfactory deficit, dysautonomia, and sleep disorder, lasts months or years before the onset of typical motor features of PD (Hawkes, 2008). Although several studies have demonstrated relatively high specificity and sensitivity of alpha-synucleinopathy in the olfactory bulb with Lewy body disorders (Beach et al., 2009), there is no decrease of the size of the olfactory bulb in patients with PD (Muller et al., 2005), and some studies have even provided evidence of increased, rather than decreased, number of dopaminergic neurons in the olfactory bulb of female PD patients (Huisman et al., 2008).

There is some evidence that although the visual acuity in PD is usually spared, restriction of ocular movements, manifested chiefly by impaired saccadic and smooth pursuit and limitation of upward gaze and convergence, coupled with difficulties in rapidly following a track and detecting moving objects in their lateral visual field and erroneously think that there are moving objects in their lateral visual field ("sensation de passage"), contribute to the visual deficit noted in many patients with PD (Diederich et al., 2002). Using modern eye movement tracking, oscillatory fixation instability, also referred to as ocular tremor (mean frequency of 5.7 Hz; range 4.3–10.9 Hz), was found to be present in all 112 patients with PD tested (Gitchel et al., 2012). Although somewhat similar to pendular nystagmus, ocular tremor differs in that it is of smaller amplitude and more chaotic, with multiple sinusoidal frequencies. In contrast to other neurodegenerative disorders such as HD (Patel et al., 2012), reflexive saccades are normal and there are no square wave jerks in PD. The generator for ocular tremor is probably different from that of the typical limb or face tremor. Some patients with PD also experience progressive impairment of color discrimination, contrast sensitivity (especially in the blue-green axis), visual speed, visual construction, and visual memory (Bodis-Wollner, 2002; Diederich et al., 2002; Uc et al., 2005). A review of 81 PD patients found nonmotor tasks were affected by visual or visuospatial impairment (Davidsdottir et al., 2005). Motor disturbances were directly attributed to visual hallucinations, double vision, and estimating spatial relations, and most often produced freezing of gait. Although color visual discrimination, as measured by the Farnsworth-Munsell 100-hue test, has been found to be abnormal in some patients with PD, this does not appear to be an early marker for PD (Vesela et al., 2001). It is not known whether this visual dysfunction is due to retinal or postretinal abnormality. In their review of ophthalmologic features of PD, Bioussé and colleagues (2004) noted that

any of the following may contribute to the ocular and visual complaints in patients with PD: decreased blink rate, ocular surface irritation, altered tear film, visual hallucinations, blepharospasm, decreased blink rate, and decreased convergence. Electrophysiologic testing has revealed prolonged visual evoked potential latencies and abnormal electroretinographic patterns, suggesting retinal ganglion cell impairment playing a role in the loss of acuity in PD subjects (Sartucci et al., 2003). Disturbances in the visual pathway from the retina to the occipital cortex have been demonstrated and may account for a large variety of visual disturbances experienced by patients with PD (Archibald et al., 2009). In one study, levodopa was found to significantly increase response time for reflexive (stimulus driven) prosaccades and reduced error rate for voluntary (internally guided) antisaccades, suggesting that medicated patients are better able to plan and execute voluntary eye movements, mediated by the frontostriatal system (Hood et al., 2007).

There are other sensory abnormalities in patients with PD. For example, age-dependent, high-frequency hearing loss has been found in patients with PD compared with healthy controls (Vitale et al., 2012). One study showed that patients with PD who experience pain have increased sensitivity to painful stimuli (Djaldetti et al., 2004). Using quantitative sensory testing with thermal probes, laser-evoked potentials (LEPs), and laser-induced sudomotor skin responses (1-SSRs) in "off" and "on" conditions, Schestatsky et al. (2007) found lower heat pain and laser pinprick thresholds, higher LEP amplitudes, and less habituation of sympathetic sudomotor responses to repetitive pain stimuli in patients with PD who complained of primary central pain compared with PD patients without pain and control subjects, suggesting an abnormal control of the effects of pain inputs on autonomic centers. Joint position has been found to be impaired in some patients with PD (Zia et al., 2000). Peripheral neuropathy usually is not a feature of PD, although evidence based on hospitalized PD cases suggests a higher than expected incidence of peripheral neuropathy, possibly related to levodopa treatment and elevated methylmalonic acid levels (Toth et al., 2010). Some studies have suggested that the PD-related neuropathy is linked to elevated plasma levels of homocysteine and methylmalonic acid and reduced vitamin B₁₂ levels (Rajabally and Martey, 2011).

Other nonmotor symptoms in PD can involve appetite, sweet cravings, and weight loss (Hillen and Sage, 1996). Weight loss is another, though poorly understood, manifestation of PD (Jankovic et al., 1992; Ondo et al., 2000; Chen et al., 2003; Lorefalt et al., 2004; Bachmann and Trenkwalder, 2006; Uc et al., 2006a,b; Barichella et al., 2009). In one study, PD patients lost $7.7\% \pm 1.5\%$ of body weight over a mean of 7.2 years of follow-up, compared with only $0.2\% \pm 0.7\%$ over a mean of 10 years in controls (55.6% of PD patients versus 20.5% of controls lost more than 5% of weight, $P < 0.001$) (Uc et al., 2006a,b). Weight loss correlated with worsening of parkinsonism, age at diagnosis, visual hallucinations, and possibly dementia. In HD, weight loss has been attributed to higher sedentary energy expenditure (Pratley et al., 2000), but the mechanism of weight loss in PD is not well understood, though it is not thought to be due to reduced energy intake (Chen et al., 2003). It is important to note that these nonmotor symptoms may be as disabling as the classic motor symptoms or even more so (Lang and Obeso, 2004). Although most animal models of

PD have focused on the motor symptoms, there is growing interest in developing models with both motor and nonmotor features to better simulate the human condition. Mice genetically engineered to have VMAT2 deficiency, in addition to progressive loss of striatal dopamine, L-dopa-responsive motor deficits, alpha-synuclein accumulation, and nigral dopaminergic cell loss, also display progressive deficits in olfactory discrimination, delayed gastric emptying, altered sleep latency, anxiety-like behavior, and age-dependent depressive behavior (Taylor et al., 2009). Restoring monoamine function in these animals (and patients with PD) may be beneficial in treating the disease.

Clinical rating scales and other assessments

To assess the severity of motor and nonmotor symptoms and signs of PD, several clinical rating scales have been developed over the years. The gold standard is the UPDRS, which was subsequently modified by the MDS (Goetz et al., 2008). Although a variety of neurophysiologic and computer-based methods have been proposed to quantitate the severity of the various parkinsonian symptoms and signs (Maetzler et al., 2013), studies primarily rely on clinical rating scales, particularly the UPDRS and also the MDS-UPDRS, Hoehn and Yahr Staging Scale (Goetz et al., 2004), and Schwab-England Scale of ADLs (Fahn et al., 1987; Goetz et al., 1994, 1995, 2008; Bennett et al., 1997; Stebbins et al., 1999; Ramaker et al., 2002). To address some of the limitations of the original UPDRS scale, a revised scale, MDS-UPDRS, was developed (Goetz et al., 2007, 2008, 2010a,b). The MDS-UPDRS retains the original UPDRS structure of four parts with a total summed score, but the parts have been modified to provide a section that integrates nonmotor elements of PD: I: Nonmotor Experiences of Daily Living; II: Motor Experiences of Daily Living; III: Motor Examination; IV: Motor Complications. All items have five response options with uniform anchors of 0 = normal, 1 = slight, 2 = mild, 3 = moderate, 4 = severe. The MDS-UPDRS has been translated into 19 languages. A short (0–3) Parkinson's Evaluation Scale (SPES) and Scale for Outcomes in Parkinson's Disease (SCOPA) also are short, reliable scales that can be used in both research and practice (Marinus et al., 2004). In some studies, the UPDRS has been supplemented by more objective timed tests, such as the Purdue Pegboard test and movement and reaction times (Jankovic, 2007). In addition to clinical rating scales there are a variety of computer-based techniques that use wearable sensors to objectively assess and quantitate tremor and other parkinsonian features (Maetzler et al., 2013).

In a systematic review of the studies published between 2005 and 2015 evaluating technologies objectively measuring clinical signs of PD, axial features and bradykinesia were most frequently studied with these devices, whereas rigidity and nonmotor features were underrepresented (Sánchez-Ferro et al., 2016). The most common devices studied were accelerometers and gyroscopes, such as DynaPort, and most studies were conducted in clinical or laboratory settings (Rovini et al., 2017; Van Uem et al., 2018). Only 6% of the systems showed some promise in being included in clinical assessments in a useful time period. In another study by some of the same authors, 73 devices were evaluated, but only 9 were classified as "recommended" (Godinho et al.,

2016). Further studies with a larger number of patients, a broader spectrum disease, and in real-life settings are needed to further develop these tools.

When a particular aspect of parkinsonism requires more detailed study, separate scales should be employed, such as certain tremor scales or the Gait and Balance Scale (GABS) (Thomas et al., 2004). In addition, it is important that in performing the UPDRS and the MDS-UPDRS, the instructions are followed exactly. For example, one study of a pull test, a measure of postural instability (Hunt and Sethi, 2006), in 66 subjects, performed by 25 examiners showed marked variability in the technique among the examiners, and only 9% of the examinations were rated as error-free (Munhoz et al., 2004). Another study showed that the "push and release test" predicts which PD patients will be fallers better than the pull test (Valkovic et al., 2008). The standard pull test consists of a sudden, firm, and quick shoulder pull without prior warning, but with prior explanation, and executed only once (Visser et al., 2003). If the patient takes more than two steps backward, this is considered abnormal. When performing the push and release test, subjects are instructed to stand in a comfortable stance with their eyes open while the examiners stand behind them. The subjects are then instructed to push backward against the palms of the examiner's hands placed on the subjects' scapulae while the examiners flex their elbows to allow slight backward movement of the trunk just behind their heels. The examiners then suddenly remove their hands, requiring the subjects to take a backward step to regain balance.

Several instruments have been developed using questionnaires, such as questions about the nonmotor symptoms of PD, including the nonmotor questionnaire or NMSQuest (Barone et al., 2009) and the nonmotor scale or the NMS Scale (Chaudhuri et al., 2006b), or on life satisfaction; "general life satisfaction" (QLSM-A) and "satisfaction with health" (QLSM-G), in which each item is weighted according to its relative importance to the individual. The 30-item NMSQuest contains nine dimensions: cardiovascular, sleep/fatigue, mood/cognition, perceptual problems, attention/memory, gastrointestinal, urinary, sexual function, and miscellany (Chaudhuri et al., 2007). In 242 patients, mean age 67.2 years and mean duration of symptoms of 6.4 years, the mean score was 56.5 ± 40.7 (range: 0–243), the following symptoms were "flagged" by the NMSQuest: nocturia (61.9%), urgency (55.8%), constipation (52.5%), sad/blues (50.1%), insomnia (45.7%), concentrating (45.7%), anxiety (45.3%), forgetfulness (44.8%), dribbling (41.5%), restless legs (41.7%), and others (Martinez-Martin et al., 2007). In one study these instruments were validated against the 36-item short form health survey (SF-36) and the EuroQol (EQ-5D) (Kuehler et al., 2003). When the initial questionnaires were reduced to 12 items for a "movement disorder module" (QLSM-MD), and five items for a "deep brain stimulation module" (QLSM-DBS), psychometric analysis revealed Cronbach (alpha) values of 0.87 and 0.73, and satisfactory correlation coefficients for convergent validity with SF-36 and EQ-5D. Other quality-of-life instruments have been used in assessing the response to therapies, particularly surgery because this treatment intervention is especially susceptible to a placebo effect (Kuehler et al., 2006; Martinez-Martin and Deuschl, 2007; Diamond and Jankovic, 2013). Moreover, there are individual scales that assess global cognitive

function, depression, anxiety, apathy, psychosis, autonomic features, and sleep, among others that have either been applied to PD or developed specifically and clinimetrically for PD. For further information, many scales covering these topics have been reviewed by the MDS Rating Scales Task Force with related publications.

Measuring the quality of health care is critical for assessing the overall impact of a disease on the individual and family, to track the progression of the disease, and to develop standards of care. The American Academy of Neurology Quality Measurement and Reporting Subcommittee proposed 10 quality measures for PD, such as an annual PD review, assessments of psychiatric and cognitive impairment, querying about autonomic dysfunction, sleep disturbances, falls, and medication-related motor complications, discussing rehabilitative and surgical options, and counseling regarding safety issues (Cheng et al., 2010). There have been other reviews of PD-related HRQL scales (Martinez-Martin, 2011). There are also many scales, such as the PDQ-39 (Hagell and Nygren, 2007) and the Parkinson's Disease Quality-of-Life Questionnaire (PDQL) (deBoer et al., 1996), that attempt to assess the overall health-related or preference-based quality of life (Marinus et al., 2002; Siderowf et al., 2002; Den Oudsten et al., 2007) and the impact of the disease on the performance of ADLs (Lindeboom et al., 2003). The Parkinson's Disease Quality of Life Scale (PDQUALIF), developed by the Parkinson Study Group, is being used in clinical trials designed to assess the impact of PD on quality of life (Welsh et al., 2003). The briefer version of PDQ-39, the PDQ-8, has been found to be a longitudinally reliable and responsive measure of HRQL and to estimate the minimally important difference or minimal clinically important change in response to therapeutic intervention (Schrag et al., 2006; Luo et al., 2009). In addition to these quantitative measures of PD-related disability, screening tools have been developed and validated to enhance early recognition of parkinsonism. One such instrument uses nine questions that were found to reliably differentiate patients with early PD from those without parkinsonism (Hoglinger et al., 2004). The generic 15D instrument has been found to be valid for measuring HRQL in PD (Haapaniemi et al., 2004). In a study of 227 patients, 82 of whom were followed for up to 8 years, HRQL measured by the Nottingham Health Profile found that the steepest progression was in the physical mobility, followed by social isolation and emotional reactions (Forsaa et al., 2008). A variety of disability rating scales have been developed over the years and the following were recommended by the MDS Task Force for Rating Scales: Functional Status Questionnaire, Lawton-Brody Activities of Daily Living, Nottingham Activities of Daily Living, Schwab and England Activities of Daily Living, Self-Assessment PD Disability, Short Parkinson's Evaluation Scale/Scales for Outcomes in PD, Unified PD Rating Scale-II: Activities of Daily Living, Movement Disorders Society UPDRS Motor Experiences of Daily Living, PROMIS, and Neuro-QoL Physical Function (Shulman et al., 2016). One of the most important factors contributing to quality of life is the ability to drive (Crizzle et al., 2012). Using a standardized open-route method of assigning driving abilities and safety, Wood (2005) found that patients with PD are

significantly less safe than are controls and, more important, that the driver's perception of his or her ability to drive correlated poorly with the examiner's assessment. Distractibility, impaired cognition, visual perception, and motor function, associated with sleepiness, are among the major factors in driving safety errors committed by PD patients (Newman, 2006; Uc et al., 2006a,b, 2009a-c, 2011; Singh et al., 2007). One study found the following most common errors committed by PD patients while driving: indecisiveness in T-junctions and reduced usage of rear view and side mirrors (Cordell et al., 2008). Driving simulation under low-contrast visibility conditions, such as fog or twilight, showed that a larger proportion of drivers with PD crashed (76.1% versus 37.3%, $P < 0.0001$) and the time to first reaction in response to incursion was longer (median 2.5 versus 2.0 seconds, $P < 0.0001$) compared with controls (Uc et al., 2009a-c). The strongest predictors of poor driving outcomes among the PD cases were worse scores on measures of visual processing speed and attention, motion perception, contrast sensitivity, visuospatial construction, motor speed, and ADLs score.

Clinical-pathophysiologic-pathologic correlations of motor parkinsonian features

The pathophysiologic processes of the various parkinsonian symptoms are not well understood. A current, albeit simplified, model of the basal ganglia suggests that two distinct loops regulate basal ganglia activity: a direct pathway connecting the striatum with GPe $\rightarrow$ STN $\rightarrow$ GPi and an indirect pathway between the striatum and GPi, the main outflow nucleus, which projects to the brainstem and thalamus, thereby modulating thalamocortical interactions. Two different frequencies of pathologic activity are associated with the main clinical symptoms of PD: an approximately 20-Hz β -band activity, which seems to be closely related to bradykinesia and rigidity, and an approximately 10-Hz activity, which appears to be related to tremor (Timmerman and Fink, 2011). Using combined magnetoencephalographic and subthalamic local field potential recordings in 13 patients with PD at rest, Litvak and colleagues (2011) found a temporoparietal-brainstem network coherent with the STN in the alpha (7–13 Hz) band and a predominantly frontal network coherent in the beta (15–35 Hz) band. They found that "Dopaminergic medication modulated the resting beta network, by increasing beta coherence between the subthalamic region and prefrontal cortex." Using diffusion-weighted MRI (DW-MRI) and resting state connectivity using resting state fMRI (rsfMRI), several investigators have found connectivity deficits in the cortico-subcortical sensory motor networks between the striatum and other subcortical structures (brainstem, thalamus, and cerebellum) but increased striatal correlations with certain portions of the cerebral cortex (Hacker et al., 2012; Sharman et al., 2013). Although little is known about the cerebellum in PD, there are some PD-related pathologic changes in the cerebellum and the cerebellum may play a compensatory role and may be involved in both motor and nonmotor symptoms (Wu and Hallett, 2013).

Clinicopathologic studies have provided insights into the clinical heterogeneity in parkinsonian patients and

implications in not only dopaminergic but also other neurotransmitter systems. By using statistical cluster analysis of 120 patients with early PD, four main subgroups were identified: (1) young-onset, (2) tremor-dominant, (3) nontremor-dominant with cognitive impairment and mild depression, and (4) rapid disease progression but no cognitive impairment (Lewis et al., 2005). A systematic review of 242 pathologically verified cases of PD showed that the cases were segregated into earlier disease onset (25%), tremor dominant (31%), nontremor dominant (36%), and rapid disease progression without dementia (8%) subgroups (Selikhova et al., 2009). The nontremor cases were more likely to have a phenotype associated with cognitive disability, the earlier disease onset group had the longest duration to death and greatest delay to the onset of falls and cognitive decline, and the rapid disease progression group was associated with older age, early depression, and early midline motor symptoms. The nontremor-dominant subgroup had significantly more cortical Lewy bodies, amyloid-beta plaque load, and cerebral amyloid angiopathy than the early disease onset and tremor-dominant groups. Other clinicopathologic correlates may help elucidate gait freezing in parkinsonian patients, with involvement of pathways among the pons, diencephalon, and areas in the motor cortex. Indeed, presence of freezing has been associated with atrophy in the left inferior, precentral, and inferior parietal gyrus, frontal and parietal atrophy (Kostic et al., 2011), and increased amyloid in the cortex (Müller et al., 2012). Strokes in the pedunculo-pontine nucleus can manifest with a freezing gait disorder (Kuo et al., 2008), and stimulation of this area can improve freezing (Mazzone et al., 2005; Thevathasan et al., 2011). The PIGD motor subtype of PD may have distinct neuropathologic changes on autopsy.

Only 27% of patients with the PIGD form of idiopathic parkinsonism were found to have Lewy bodies at autopsy (Rajput et al., 1993). Several studies also show that white matter changes (leukoaraiosis) significantly contribute to the PIGD phenotype (Bohnen et al., 2011). In the London brain bank series, only 11% of the 100 pathologically proven cases of PD had tremor-dominant disease and 23% had “akinetic/rigid” disease; the rest (64%) were diagnosed as having a “mixed pattern” (Hughes et al., 1993). In contrast to the 76% to 100% occurrence of tremor in PD, only 31% of those with atypical parkinsonism (PSP; striatonigral degeneration [SND]; Shy-Drager syndrome (SDS); and the combination of SND and olivopontocerebellar atrophy had rest tremor (Rajput et al., 1991), and 50% of the 24 cases with non-PD parkinsonism in the London series had tremor, type not specified (Hughes et al., 1992b).

Regarding tremor-dominant motor subtypes, in a clinicopathologic study, Hirsch and colleagues (1992) demonstrated that patients with PD and prominent tremor have degeneration of a subgroup of midbrain (A8) neurons, whereas this area is spared in PD patients without tremor. Other clinicopathologic studies have confirmed that the tremor-dominant type of PD shows more damage to the retrorubral field A8, containing mainly calretinin-staining cells but only a few tyrosine hydroxylase and DAT immunoreactive neurons (Jellinger, 1999). In addition, tremor-dominant PD appears to be associated with more severe neuron loss in medial than in the lateral zona compacta of the SN (SNzc). The ventral (rostral and caudal) GPi seems to be relatively

spared in tremor-dominant PD because the dopamine levels in this area are essentially normal but are markedly decreased in the other pallidal regions (Rajput et al., 2008). In contrast, A8 is rather preserved in the PIGD, rigid-akinetic PD, possibly owing to the protective role of calcium-binding protein. Using voxel-based morphometry of 3-tesla, T1-weighted MRI in 14 patients with tremor-dominant PD and 10 PD patients without rest tremor, decreased gray matter volume in the cerebellum was associated with parkinsonian rest tremor (Benninger et al., 2009). These findings support the hypothesis that differential damage of subpopulations of neuronal systems is responsible for the diversity of phenotypes seen in PD and other parkinsonian disorders. Detailed clinicopathologic-biochemical studies will be required to prove or disprove this hypothesis.

Patients with the tremor-dominant PD have increased metabolic activity in the pons, thalamus, and motor association cortices (Antonini et al., 1998). In contrast, bradykinesia may correlate best with nigrostriatal deficiency on ¹⁸F-6-fluorodopa PET studies (Vingerhoets et al., 1997). Tremor in PD also seems to correlate with serotonergic dysfunction as suggested by a 27% reduction in the midbrain raphe 5-HT_{1A} binding demonstrated by ¹¹C-WAY 100635 PET scans (Doder et al., 2003). In contrast to dopamine, which is reduced by more than 80% in the caudate and more than 98% in the putamen of brains of patients with PD, serotonin markers are reduced by 30% to 66% (Kish et al., 2008). Although the reduction of serotonin in the caudate nucleus has been suggested to be associated with “associative-cognitive problems,” the clinical significance of relative serotonin preservation in the putamen is not known. The role of serotonin in motor dysfunction, levodopa-induced dyskinesias, mood, and psychosis associated with PD has been reviewed, but because of lack of data no definite conclusions can be made (Fox et al., 2009).

The notion of PD has evolved from the traditional view of a single clinicopathologic entity to “Parkinson diseases” with different etiologies and clinical presentations as evidenced by the genetic heterogeneity of PD (Tan and Jankovic, 2006). The autosomal recessive juvenile parkinsonism (AR-JP) resulting from mutation in the *parkin* gene on chromosome 6q25.2–27 (PARK2) may present with a dystonic gait or camptocormia during adolescence or early adulthood (or even in the sixth or seventh decade) and with levodopa-responsive dystonia and may be characterized by symmetrical onset, marked sleep benefit, early levodopa-induced dyskinesias, hemiparkinsonism–hemiatrophy, hyperreflexia, and “slow” orthostatic tremor. Patients with *parkin* mutation seem to have a slower disease course (Lücking et al., 2000; Rawal et al., 2003; Schrag and Schott, 2006). Furthermore, similar to EOPD, patients with *parkin* mutations show marked decrease in striatal 6-[¹⁸F]-fluoro-L-dopa (F-dopa) PET, but in contrast to PD, *parkin* patients show additional reductions in caudate and midbrain and significantly decreased raclopride binding in striatal, thalamic, and cortical areas (Scherfner et al., 2004). PARK2 (resulting from *parkin* mutations) is the most common cause of EOPD, followed by *DJ-1*, and *PINK1* mutations, although these genetic causes accounted for only 9% of all cases of EOPD (Macedo et al., 2009). Other causes of levodopa-responsive juvenile parkinsonism or EOPD include dopa-responsive dystonia, spinocerebellar ataxia 2 (SCA2), and SCA3 (Paviour et al., 2004).

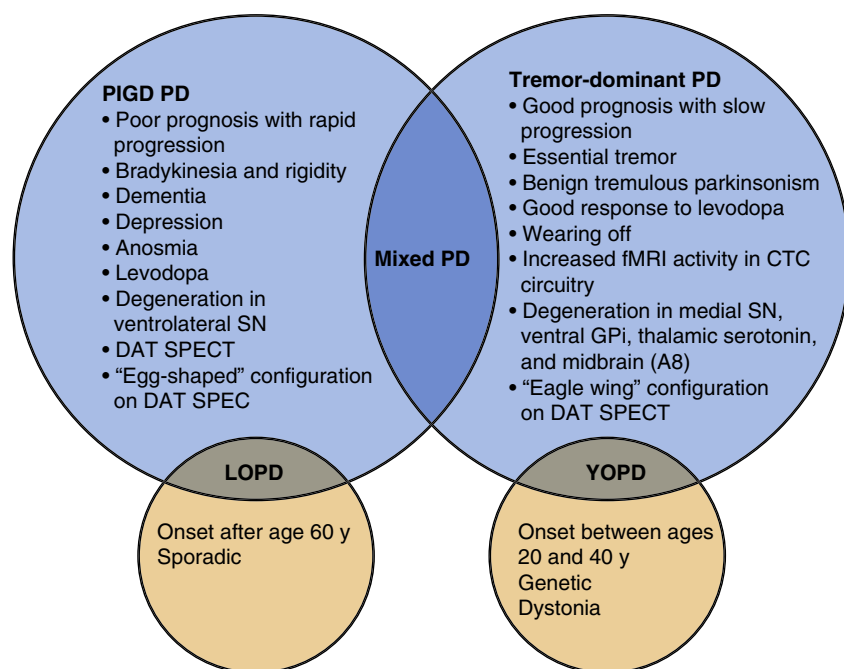


Fig. 4.5 Two major subtypes of Parkinson disease (PD): Tremor-dominant and postural instability gait disorder (PIGD). CTC, Cerebello-thalamo-cortical; DAT, dopamine transporter; fMRI, functional magnetic resonance imaging; GPi, internal division of the globus pallidus; SN, substantia nigra; SPECT, single-photon emission computed tomography; LOPD, late onset PD; YOPD, young onset PD. (Thenganatt MA, Jankovic J: 2014. *Parkinson disease subtypes*. JAMA Neurol. 2014;71[4]:499; and Jankovic J, Kapadia AS: Functional decline in Parkinson disease. Arch Neurol 2001;58:1611–1615.)

Mutations in the *GBA* gene, which encodes a lysosomal enzyme involved in sphingolipid degradation, are recognized to be the single largest risk factor for development of PD (O'Regan et al., 2017). Although pathologic studies to date are limited, clinically, on imaging and pharmacologically, *GBA* PD is almost identical to idiopathic PD, although *GBA* PD may have greater neuropsychiatric features. From experimental models, key pathologic pathways of interest in the context of *GBA* mutations include alpha-synuclein aggregation, lysosomal-autophagy axis changes, and endoplasmic reticulum stress and may provide targets for drug development.

Clinical heterogeneity of Parkinson disease

The clinical heterogeneity of PD is well recognized, and various subtypes have been identified. Clinical subtypes of PD have been grouped, particularly by age or motor phenotype (Marras and Lang, 2013; Thenganatt and Jankovic, 2014) (Fig. 4.5), though cognitive subtypes are also recognized (Williams-Gray et al., 2009). These subtypes may confer not only different clinicopathologic correlates, but different rates of progression (Jankovic, 2005; Le et al., 2009, Williams-Gray et al., 2009). Two major motor subtypes have been studied: one characterized by tremor as the dominant parkinsonian feature and the other dominated by PIGD (Zetuský et al., 1985; Jankovic et al., 1990; McDermott et al., 1995; Thenganatt and Jankovic, 2014; Konno et al., 2018) (see Fig. 4.5). The mean tremor score was defined as the mean of the sum of the baseline tremor (UPDRS part II) and tremor scores (UPDRS part III) for face, right and left hand, right and left foot, and right and left hand action tremor. The mean PIGD score was defined as the sum of an individual's baseline falling, freezing, walking, gait, and postural stability UPDRS scores divided by five. Patients were categorized as having tremor-dominant PD if the ratio of the mean tremor score to the mean PIGD score was 1.50

or greater and as PIGD dominant if the ratio was 1.00 or less (Jankovic et al., 1990). Tremor/PIGD scores were later calculated in 877 patients with PD using the UPDRS formula and the new MDS-UPDRS tremor-to-PIGD ratios showed optimal sensitivity and specificity at cutoff scores of 1.15 or greater for tremor-dominant classification, and if the ratio is 0.90 or less, the patient is classified as PIGD; the ratio between the two defines the “intermediate” group (Stebbins et al., 2013).

The tremor-dominant form of PD seems to be associated with a relatively preserved mental status, earlier age at onset, and slower progression of the disease than the PIGD subtype, which is characterized by more severe bradykinesia and a more rapidly progressive course (Post et al., 2007). Several studies have demonstrated that patients with the tremor-dominant form have less cognitive impairment (Verbaan et al., 2007b) and less susceptibility to acting on motor impulses compared with patients with the PIGD form of PD (Wylie et al., 2012). PD patients who are young and have tremor at the onset of their disease seem to have a slower progression and a more favorable prognosis than those with bradykinesia and the PIGD. In one study, the relative risk for death in patients with the tremor-dominant form of PD was significantly lower than in PD patients without rest tremor (1.52 versus 2.04, $P < 0.01$) (Elbaz et al., 2003). The more favorable course of the tremor-dominant form of PD is supported by the finding that the reduction in F-dopa uptake, as measured by PET and expressed as K_i , was 12.8% over a 2-year period in PD patients with severe tremor compared with a 19.4% reduction in the mild or no tremor group ($P = 0.04$) (Whone et al., 2002). Patients with the tremor-dominant form of PD progressed at a slower rate than did patients with the other PD subtypes (Jankovic and Kapadia, 2001, Hilker et al., 2005) (Fig. 4.6). Furthermore, tremor-predominant PD for whom rest tremor is the initial manifestation seem to have a lower probability of levodopa-induced dyskinesia (Kipfer et al., 2011). A clinicopathologic study of 166 patients with PD followed for over 39 years (1968



Fig. 4.6 Young-onset Parkinson disease (PD) progresses at a slower rate than late-onset PD. UPDRS, Unified Parkinson's Disease Rating Scale. (Jankovic J, Kapadia AS: Functional decline in Parkinson disease. *Arch Neurol*. 2001;8[10]:1611; and Jankovic J, Kapadia AS: Functional decline in Parkinson disease. *Arch Neurol* 2001;58:1611–1615.)

to 2006) showed that the age at onset was significantly younger, progression to Hoehn and Yahr stage 4 was slower, and dementia was least common in the tremor-dominant cases (Rajput et al., 2009). In addition, the tremor-dominant form of PD is associated with a more frequent family history of tremor, and it is more likely to have coexistent ET (Jankovic et al., 1995; Shahed and Jankovic, 2007; Hedera et al., 2009).

In contrast, those with PD with predominantly axial symptoms, such as dysarthria (Ho et al., 1999), dysphagia, loss of equilibrium, and freezing of gait, may have greater impairment in their disease than those who have predominantly limb manifestations (Jankovic et al., 1990; Muslimovic et al., 2008; Hariz and Forsgren, 2011). Axial impairment, probably mediated predominantly by nondopaminergic systems, is associated with incident dementia (Levy et al., 2000). Even at their first visit to a neurologist, PIGD patients had worse status with respect to ADLs and HRQL measures than those with tremor-dominant PD (Hariz and Forsgren, 2011). The poor prognosis associated with PIGD forms is also partly due to a lack of response of these symptoms to dopaminergic drugs (Jankovic et al., 1990; Kompoliti et al., 2000) (Fig. 4.7). In this regard, one study suggested that an abnormal tandem gait (the “ten steps” test) is much more common in patients with atypical parkinsonism than in those with typical PD and this test seems to differentiate the two groups with 82% sensitivity and 92% specificity (Abdo et al., 2006). In a study of 490 PD subjects followed by the NeuroGenetics Research Consortium, logistic regression analysis concluded that postural instability and freezing of gait are demographically and genetically distinct subtypes of PIGD (Factor et al., 2011). In other classifications of PD subtypes, the differences are largely driven by the severity of “nondopaminergic” features and levodopa-related motor complications (Van Rooden et al., 2011). Using a grip task paradigm with

fMRI and voxel-based morphometry, reduced brain activity was found in the prefrontal cortex and GPi of patients with nontremor-dominant PD compared with both patients with tremor-dominant PD and healthy controls (Prodoehl et al., 2013). Overnight polysomnography studies showed that increased activity during REM sleep is a predictor of gait freezing in patients with PD (Videnovic et al., 2013). In one study, higher patient age, higher UPDRS motor examination axial score, and a lower animal fluency score were all associated with a higher probability of an unfavorable outcome (Velseboer et al., 2016).

Other criteria have been used to define PD subtypes. Using the SPES/SCOPA rating scale (Marinus et al., 2004) in 399 PD patients, four distinct motor patterns were identified: tremor-dominant, bradykinetic-rigid, and two types of axial patterns: (1) rise, gait, postural instability (similar to PIGD) and (2) freezing, speech, and swallowing, the latter related to complications of dopaminergic therapy (van Rooden et al., 2009). In a random sample of 173 patients, four different subtypes were identified: rapid disease progression subtype, young-onset subtype, nontremor-dominant subtype (associated with hypokinesia, rigidity, postural instability, and gait disorder, cognitive deterioration, depressive and apathetic symptoms, and hallucinations), and a tremor-dominant subtype (Reijnders et al., 2009). The AAN “Practice Parameter on Diagnosis and Prognosis of New Onset Parkinson Disease” made the following conclusions. (1) Early falls, poor response to levodopa, symmetry of motor manifestations, lack of tremor, and early autonomic dysfunction are probably useful in distinguishing other parkinsonian syndromes from PD. (2) Levodopa or apomorphine challenge and olfactory testing are probably useful in distinguishing PD from other parkinsonian syndromes. (3) Predictive factors for more rapid motor progression, nursing home placement, and shorter survival time include older age at onset of PD, associated comorbidities, presentation with rigidity and bradykinesia, and decreased dopamine responsiveness (Suchowersky et al., 2006). Using a cluster analysis, a systematic review of the literature confirmed the following disease subtypes: (1) young age at onset and slow disease progression, (2) old age at onset and rapid disease progression, (3) tremor-dominant, and (4) PIGD (Jankovic et al., 1990; Factor et al., 2011) dominated by bradykinesia and rigidity (Van Rooden et al., 2009).

Using data from de novo PD patients enrolled in the Parkinson's Progression Markers Initiative ($n = 421$), Fereshtehnejad and colleagues (2017) identified distinct subgroups by cluster analysis. Key classifiers in cluster analysis were a motor summary score and three nonmotor features (cognitive impairment, RBD disorder, and dysautonomia), which were used to define three distinct subtypes. Of the PD patients, 223 were classified as “mild motor-predominant,” 52 as “diffuse malignant,” and 146 as “intermediate.” Those with diffuse malignant PD had significantly lower levels of CSF amyloid-beta and ratio of amyloid-beta to total tau, greater brain atrophy on MRI, and a faster progression, with greater decline in cognition and in dopamine functional neuroimaging after an average of 2.7 years.

To determine whether age at onset predicts future course and response to levodopa, 48 patients with EOPD (onset between 20 and 40 years of age) were compared with 123

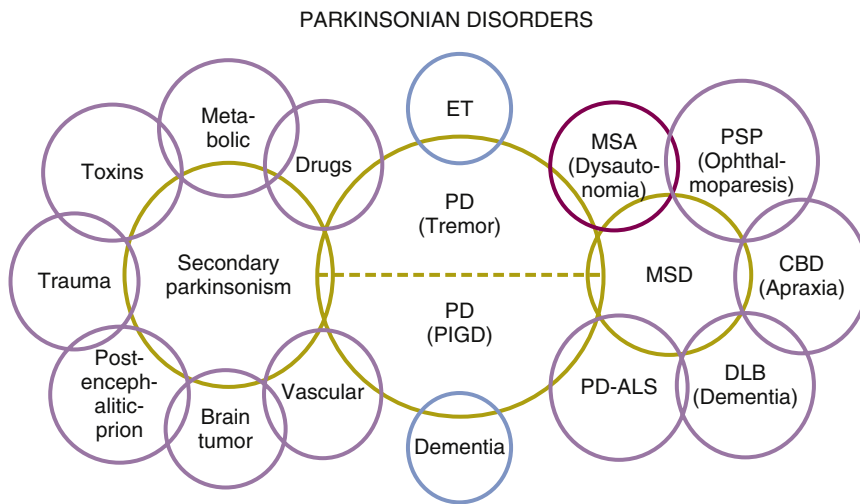


Fig. 4.7 Differential diagnosis of Parkinson disease (PD). CBD, Corticobasal degeneration; DLB, dementia with Lewy bodies; ET, essential tremor; MDS, multiple system degeneration; MSA, multiple system atrophy; P-D-ALS, parkinsonism-dementia-amyotrophic lateral sclerosis; PI-GD, postural instability gait disorder; PSP, progressive supranuclear palsy.

late-onset PD (LOPD) patients (onset at 60 years of age or older) (Jankovic et al., 1997). EOPD patients presented more frequently with rigidity, whereas those with LOPD presented more frequently with PI-GD; there was no difference in the occurrence of tremor at onset. In one longitudinal study, patients older than 70 years at diagnosis had a high hazard rate for PI-GD type of PD but slower progression compared with younger patients (Prange et al., 2019). EOPD patients generally respond to levodopa better but are more likely to develop dyskinesias and “wearing-off” (Quinn et al., 1987; Jankovic et al., 1997; Schrag et al., 1998; Kumar et al., 2005; Schrag and Schott, 2006; Wickremaratchi et al., 2011). The EOPD subtype is characterized by slower progression of disease, increased rate of dystonia and levodopa-induced dyskinesia, and less motor and cognitive disability (Graham and Sagar, 1999; Diederich et al., 2003; Wickremaratchi et al., 2011). PD seems to have a much greater psychosocial impact on EOPD patients in terms of loss of employment, disruption of family life, perceived stigmatization, and depression than on LOPD patients (Schrag et al., 2003). Many EOPD patients have been found to have parkin mutations (PARK 2) or other mutations in other gene loci (PARK 6 and PARK 7), but their clinical characteristics and ^{18}F -dopa uptake are similar to those in other EOPD patients without mutations (Thobois et al., 2003). To investigate nigrostriatal dopamine dysfunction in EOPD versus LOPD, 78 patients and 35 healthy control subjects underwent longitudinal DTBZ PET scans to estimate the density of the vesicular monoamine transporter type 2, [(11) C]d-threo-methylphenidate PET scans to estimate the density of the presynaptic DAT, and 6-[(18) F]-fluoro-L-dopa PET scans to estimate the activity of the enzyme dopa-decarboxylase (de la Fuente-Fernandez et al., 2011). Whereas at symptom onset the loss of putamen DTBZ binding was substantially greater in younger compared with older PD patients ($P = 0.015$), the rate of progression of DTBZ binding loss was significantly slower in younger patients ($P < 0.05$). The estimated presymptomatic phase of the disease spanned more than two decades in younger patients, compared with one decade in older patients. Thus, younger PD patients seem to have more severe nigrostriatal damage at onset of motor symptoms, but progress more slowly, suggesting more efficient compensatory mechanisms.

Natural history and progression

The natural history of PD appears to be influenced not only by the age at onset and the clinical presentation, but also by a number of other factors, such as stress (Tanner and Goldman, 1996), pregnancy (Shulman et al., 2000), intercurrent illness (Onofrj and Thomas, 2005), and therapy. Infection, gastrointestinal disorder, and surgery are among the most common causes of the syndrome of acute akinesia, a sudden deterioration in motor performance that usually lasts 4 to 26 days and represents a life-threatening complication of PD, usually requiring hospitalization (Onofrj and Thomas, 2005). Although therapeutic advances have had a positive impact on the quality of life, epidemiologic studies have not been able to demonstrate that levodopa significantly prolongs life (Clarke, 1995). Several studies, however, have concluded that PD patients have a nearly normal life expectancy (Lilienfeld et al., 1990; Clarke, 1995; Parkinson Study Group, 1998). In a prospective study of 800 patients who were followed longitudinally from the early stages of their disease for an average of 8.2 years, the overall death rate was 2.1% per year, which was similar to that of an age- and gender-matched U.S. population without PD (Parkinson Study Group, 1998). In a 10-year Sydney multicenter follow-up of 149 patients with PD initially enrolled in a double-blind study of levodopa/carbidopa versus bromocriptine, the SMR was 1.58, which was significantly higher than that of the Australian population ($P < 0.001$) (Hely et al., 1999). In a subsequent report, based on a population-based study, Morgante and colleagues (2000) showed a relative risk for death in patients with PD of 2.3 (95% CI, 1.60–3.39). In another study of 170 elderly patients with PD, with a mean age at death of 82 years, who were followed for a median of 9.4 years, the relative risk for death compared with referent subjects was 1.60 (95% CI, 1.30–1.8), and the mean duration of illness was 12.8 years (Fall et al., 2003). Pneumonia was the most frequent cause of death in both studies. The SMR was reported to be 1.52 in a community-based study of a Norwegian population (Herlofson et al., 2004). The HR for mortality was 1.64 for patients with PD compared with controls, but the mortality increased if there was associated dementia, depression, or both (Hughes et al., 2004). In a 15-year follow-up of patients who were originally enrolled

in the Sydney Multicenter Study of PD comparing levodopa with low-dose bromocriptine, the SMR was 1.86. In a comprehensive review of the literature, SMR has been reported to range between 1 and 3.4 (Ishihara et al., 2007). On the basis of 296 deaths in a cohort of patients who were originally enrolled in the DATATOP study and followed for 13 years, survival was found to be strongly related to response to levodopa (Marras et al., 2005). SMR based on a cohort analysis of 22,071 participants in the Physicians' Health Study, with 560 incident cases of PD, was found to be 2.32 (95% CI, 1.85–2.92) (Driver et al., 2008). Age-specific life expectancy was found to be reduced in patients with PD, particularly those with young-onset PD (Ishihara et al., 2007). In a 20-year follow-up study of 238 consecutive patients with PD, the SMR was 0.9 by 10 years and 1.3 by 20 to 30 years (Diem-Zangerl et al., 2009). The authors concluded that when PD patients are "Under regular specialist care using all currently available therapies life expectancy in PD does not appear seriously compromised, but male gender, gait disorder, and absent rest tremor at presentation are associated with poorer long-term survival." In a community-based sample of 230 patients with PD from southwestern Norway, followed prospectively with repetitive assessments of motor and nonmotor symptoms from 1993 to 2005, 211 (92%) died during the study period with a median survival time from motor onset of 15.8 years (range 2.2–36.6) (Forsaa et al., 2010). Although there is a marked variability in time of death, the following factors were associated with higher mortality: older at onset, chronologic age, male sex, more severe impairment, and the presence of psychotic symptoms and dementia (Forsaa et al., 2010). Another factor that appears to influence survival is whether the patient is followed by a neurologist or primary care physician. In one study, based on 138,000 incident PD cases, only 58% of whom were cared for by neurologists, showed that PD patients seen by a neurologist were 20% less likely to die over a 6-year period than those seen by a primary care physician (Willis et al., 2011). They were also 20% less likely to be placed in a nursing home and 14% less likely to have a broken hip. Women were 22% less likely to see a neurologist than men, and minorities were 17% less likely to see a neurologist than Whites.

There is growing evidence that the progression of PD is not linear and that the rate of deterioration is much more rapid in the early phase of the disease (Fearnley and Lees, 1991; Jankovic, 2005; Schapira and Obeso, 2006; Lang, 2007; Maetzler et al., 2009; Stoessl et al., 2011a,b; Prange et al., 2019). This is also supported by functional imaging (F-dopa PET) (Bruck et al., 2009) and postmortem pathologic studies (Fearnley and Lees, 1991) (see later). Indeed, observational clinical studies have shown that UPDRS motor scores decline by 5.1% per annum in early disease compared with 0.4% in later stages of PD (Schrage et al., 2007a,b). In a prospective study of 145 clinic-based patients followed for 1 year and 124 community-based patients followed for 4 years, the annual mean rate of deterioration in motor and disability scores ranged between 2.4% and 7.4% (Schrage et al., 2007a,b). These findings, based on longitudinal follow-up data, provide evidence for a variable course of progression of the different PD symptoms, thus implying different biochemical or degenerative mechanisms for the various clinical features associated with PD. Although the deterioration in motor scores seem to flatten in more advanced stages of the disease,

disability scores continued to progress, probably because of emergence of nonmotor symptoms. The study by Greffard and colleagues (2006) has also suggested that the rate of progression might not be linear and that the disease might progress more rapidly initially (about 8–10 UPDRS points in the first year) and the rate of deterioration slows in more advanced stages of the disease. This is supported by the findings in moderately advanced cases of PD requiring levodopa treatment compared with patients in early stages of the disease such as those enrolled in the DATATOP study (Parkinson Study Group, 1998). In that study of early, previously untreated patients, the rate of annual decline in the total UPDRS score was 14.02 ± 12.32 (mean $\pm$ SD) in the placebo-treated group. This is nearly identical to the one UPDRS unit of decline per month in the ELLDOPA study (Fahn et al., 2004). In contrast, in a group of 238 patients treated with levodopa, bromocriptine, or both in whom progression was estimated on the basis of a retrospectively determined duration of the symptoms, the annual rate of decline in bradykinesia score was 3.5% during the first year but was estimated to be only 1.5% in the 10th year (Lee et al., 1994). More rapid progression in the early stages than in more advanced stages of the disease is also suggested by the finding of mean of 0.5 annual decline in F-dopa influx constant in the contralateral putamen in the first 2 years and only 0.2 during the subsequent 3 years (Bruck et al., 2009).

To study the overall rate of functional decline and to assess the progression of different signs of PD, 297 patients (181 males) with clinically diagnosed PD for at least 3 years were prospectively followed (Jankovic and Kapadia, 2001) (see Figs. 4.5 and 4.6). Data from 1731 visits over a period of an average of 6.36 years (range 3–17) were analyzed. The annual rate of decline in the total UPDRS scores was 1.34 units when assessed during "on" and 1.58 when assessed during "off." Patients with older age at onset had a more rapid progression of disease than did those with younger age at onset. Furthermore, the older onset group had significantly more progression in mentation, freezing, and parts I and II UPDRS subscores. Handwriting was the only component of UPDRS that did not significantly deteriorate during the observation period. Regression analysis of 108 patients, whose symptoms were rated during their "off" state, showed a faster rate of cognitive decline as the age at onset increased. The slopes of progression in UPDRS scores, when adjusted for age at initial visit, were steeper for the PIGD group of patients than in the tremor-dominant group. In a study of 573 patients with newly diagnosed PD, PIGD, cognitive impairment, and hallucinations were among the most reliable predictors of high mortality (Lo et al., 2009). More rapid progression of axial (gait and postural) symptoms than other motor features has been also supported by other studies (Evans et al., 2011). These findings are consistent with those of a retrospective cohort study of 138,000 Medicare beneficiaries with incident PD, 35% of whom survived the 6-year follow-up period (Willis et al., 2012). Dementia, diagnosed in 70% of cases, most often in African American patients (78.2%), was associated with a significantly higher mortality. Thus, assessments of the efficacy of putative modifying therapies should focus on measuring their effects on delaying postural instability and dementia, the two symptoms that the greatest impact on patients' quality of life, because delaying their onset or progression may be most meaningful to the patients. These

results are similar to the 1.5-point annual decline, based on longitudinal assessments using the motor function (part III) portion of the UPDRS, reported by [Louis and colleagues \(1999\)](#) in a community-based study of 237 patients with PD who were followed prospectively for a mean of 3.30 years. Another prospective study, involving 232 patients with PD, showed annual decline in UPDRS motor score of 3.3 points (range 0–108; 3.1%) and 0.16 points in Hoehn and Yahr stage (range 0–5; 3.2%), with slower and more restricted decline in EOPD cases ([Alves et al, 2005](#)).

Interestingly, in a study of 787 older (mean age at baseline: 75.4 years) Catholic clergy without clinically diagnosed PD who were prospectively followed up to 7 years, the average decline in UPDRS units was 0.69 per year ([Wilson et al., 2002](#)). In those subjects who had some worsening of their global UPDRS score (79% of all subjects), the risk for death was 2.93 times the rate in those without progression (21%). The risk for death was associated with worsening of gait and posture but not with rigidity or postural reflex impairment, even though the latter two signs (but not bradykinesia or tremor) also worsened. The average reported rate of decline in total UPDRS is about 8 units per year. A systematic review of 13 studies investigating predictors of prognosis concluded that greater baseline impairment, early cognitive disturbance, older age, and lack of tremor at onset are relatively predictive of a poor prognosis ([Marras et al., 2002](#)). The aging process has been found to contribute particularly to the axial (gait and postural) impairment in PD ([Levy et al., 2005](#)) and advancing age, rather than duration of the disease, seems to be the most important determinant of clinical progression ([Levy, 2007](#)).

Epidemiology

The frequency of PD varies depending on the diagnostic criteria, study population, and epidemiologic methods used, although the prevalence is generally thought to be about 0.3% in the general population and 1% in people over the age 60 years; the reported incidence figures have ranged from 8 to 18 per 100,000 person years ([Twelves et al., 2003](#); [de Lau et al., 2006](#)); 13.4 in one well-conducted study ([Van Den Eeden et al., 2003](#)). In a study of 364 incident cases of parkinsonism among residents of Olmsted County, Minnesota, for the period from 1976 through 1990, 154 with PD (42%), 72 with drug-induced parkinsonism (20%), 61 unspecified (17%), 51 with parkinsonism in dementia (14%), and 26 with other causes (7%) were identified ([Bower et al., 1999](#)). In another Mayo Clinic study, the lifetime risk for developing PD has been estimated to be 2.0% for men and 1.3% for women (ratio = 1.5) ([Elbaz et al., 2002](#)). The average annual incidence rate of parkinsonism (per 100,000 person-years) in the age group 50 to 99 years was 114.7 and the incidence increased exponentially with age from 0.8 in the age group 0 to 29 years to 304.8 in the age group 80 to 99 years. The cumulative incidence of parkinsonism was 7.5% to age 90 years. Men had a higher incidence than women at all ages for all types of parkinsonism except drug-induced. In another Mayo Clinic study based on 542 incidence cases of parkinsonism, the incidence rate of synucleinopathies was 21.0 per 100,000 person-years and for tauopathies it was 1.1 ([Savica et al., 2013](#)). In a follow-up study from Mayo Clinic

of 464 patients with PD, 275 were men and the median age at onset was 73 years, the overall incidence rates increased significantly over 30 years in men (RR, 1.24 per decade; 95% CI, 1.08–1.43), particularly for men 70 years or older ([Savica et al., 2016](#)). In the U.S. studies, African Americans have been found to be half as likely to be diagnosed with PD as Whites; these differences could not be explained by differences in age, sex, income, insurance, or access to health care ([Dahodwala et al., 2009](#)). Based on a meta-analysis of 29 studies reporting familial aggregation, the relative risk for PD in a first-degree relative is 2.9 and 4.4 in siblings, and 2.7 for a child–parent pair ([Thacker and Ascherio, 2008](#)). Estimates of the prevalence of PD in North America have been defined by combining data from a multistudy sampling strategy in diverse geographic regions and/or data sources from five separate cohort studies in California, Minnesota, and Hawaii in the United States and Ontario, Canada ([Marras et al., 2018](#)). Using age- and sex-specific metaestimates from these areas and the U.S. population structure from 2010, the overall prevalence of PD among those aged 45 years or older was estimated to be 572 per 100,000 (95% CI, 537–614) and with 680,000 individuals in the United States aged 45 years or older with PD in 2010. Projected estimates are an increase to approximately 930,000 people with PD in 2020 and 1,238,000 in 2030.

Nearly all epidemiologic studies of PD show that both incidence and prevalence of PD are 1.5 to 2 times higher in men than in women ([Haaxma et al., 2007](#)). Although there is no obvious explanation for this observed male preponderance, exposure to toxins, head trauma, neuroprotection by estrogen in women, mitochondrial dysfunction, or X-linked genetic factors have been suggested ([Wooten et al., 2004](#); [Haaxma et al., 2007](#)). The most plausible explanation is that symptoms of PD may be delayed in women by higher striatal dopamine levels, possibly because of the effects of estrogen ([Haaxma et al., 2007](#); [Taylor et al., 2007](#)), but this would not explain the lack of female preponderance in the Asian, particularly Chinese, population ([de Lau et al., 2006](#)).

Diagnostic criteria for Parkinson disease

Several diagnostic criteria have been developed for PD, including the UK PD Society Brain Bank criteria used in various clinicopathologic studies ([Hughes et al., 1992a,b](#)) ([Table 4.3](#)). During a workshop sponsored by the NINDS, a set of diagnostic criteria for PD was proposed, based on a review of the literature regarding the sensitivity and specificity of the characteristic clinical features ([Gelb et al., 1999](#); [Jankovic, 2008](#)) ([Table 4.4](#)). The reliability of the different diagnostic criteria, however, has not been vigorously tested by an autopsy examination, which is commonly considered the gold standard ([de Rijk et al., 1997](#)). Early clinicopathologic series concluded that only 76% of patients with a clinical diagnosis of PD actually met the pathologic criteria; the remaining 24% had evidence of other causes of parkinsonism ([Hughes et al., 1992a,b](#)). This study was based on autopsied brains collected from 100 patients who had been clinically diagnosed with PD by the UK PD Society Brain Bank ([Hughes, 1992a,b](#)). Similar findings were reported in another study, which was based on autopsy examinations of brains from 41 patients who were followed prospectively by the same neurologist over a 22-year period

Table 4.3 U.K. Parkinson's Disease Society Brain Bank's clinical criteria for the diagnosis of probable Parkinson disease*Step 1*

1. Bradykinesia
2. At least one of the following criteria:
 - A. Rigidity
 - B. 4- to 6-Hz rest tremor
 - C. Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

*Step 2: Exclude other causes of parkinsonism**Step 3: At least three of the following supportive (prospective) criteria:*

1. Unilateral onset
2. Rest tremor present
3. Progressive disorder
4. Persistent asymmetry affecting side of onset most
5. Excellent response (70%–100%) to levodopa
6. Severe levodopa-induced chorea (dyskinesia)
7. Levodopa response for 5 years or more
8. Clinical course of 10 years or more

Data from Hughes AJ, Daniel SE, Kilford L, Lees AJ: Accuracy of clinical diagnosis of idiopathic Parkinson's disease: A clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry*. 1992;55:181–184; and Hughes AJ, Ben-Shlomo Y, Daniel SE, Lees AJ: What features improve the accuracy of clinical diagnosis in Parkinson's disease: A clinical pathological study. *Neurology* 1992;42:1142–1146.

(Rajput et al., 1991). When Hughes and associates (2001) examined the brains of patients diagnosed with PD by neurologists, the diagnostic accuracy increased to 90%; 6% had MSA, 2% had PSP, 1% had neurofibrillary tangles, and 1% had evidence of vascular parkinsonism. In a study of 143 cases of parkinsonism that came to autopsy and had a clinical diagnosis made by neurologists, the positive predictive value of the clinical diagnosis was 98.6% for PD and 71.4% for the other parkinsonian syndromes (Hughes et al., 2002). In the DATATOP study, 800 patients were prospectively followed by trained PD specialists from early, untreated stages of clinically diagnosed PD for a mean of 7.6 years (Jankovic et al., 2000). An analysis of autopsy data, imaging studies, response to levodopa, and atypical clinical features indicated an 8.1% inaccuracy of initial diagnosis of PD by PD experts, but the final diagnosis was not based on pathologic confirmation in all cases. In a study of 89 incident patients initially diagnosed with parkinsonism by experienced clinicians, the diagnosis was subsequently changed in 22 (33%) during the median follow up of 29 months (Caslake et al., 2008). In this cohort, 38% of those initially diagnosed with PD had their diagnosis changed to DLB; other common misdiagnosis was ET in patients initially thought to have PD and vice versa. This and other studies underscore the need for valid diagnostic criteria to be used in assessing patients with initial manifestations of parkinsonism. In a community-based study of 402 patients taking antiparkinsonian medications, parkinsonism was confirmed in 74% and clinically probable PD in 53%. The most common causes of misdiagnosis were ET, AD, and vascular parkinsonism. Over one-quarter of subjects did not benefit from antiparkinsonian medication (Meara et al., 1999). Parkinsonian signs, including rigidity, gait disturbance, and bradykinesia, may also occur as a consequence of normal aging, although comorbid medical conditions, such as diabetes, may significantly increase the

Table 4.4 National Institute of Neurological Disorders and Stroke diagnostic criteria for Parkinson disease (PD)**Group A features: Characteristic of PD**

1. Resting tremor
2. Bradykinesia
3. Rigidity
4. Asymmetric onset

Group B features: Suggestive of alternative diagnoses

1. Features unusual early in the clinical course
 - a. Prominent postural instability in the first 3 years after symptom onset
 - b. Freezing phenomenon in the first 3 years
 - c. Hallucinations unrelated to medications in the first 3 years
 - d. Dementia preceding motor symptoms or in the first year
2. Supranuclear gaze palsy (other than restriction of upward gaze) or slowing of vertical saccades
3. Severe, symptomatic dysautonomia unrelated to medications
4. Documentation of condition known to produce parkinsonism and plausibly connected to the patient's symptoms (e.g., suitably located focal brain lesions or neuroleptic use within the past 6 months)

I. Criteria for definite PD

- A. All criteria for *possible* PD are met *and*
- B. Histopathologic confirmation of the diagnosis is obtained at autopsy

II. Criteria for probable PD

- A. At least three of the four features in Group A are present
- B. None of the features in Group B is present (*NOTE: Symptom duration of at least 3 years is necessary to meet this requirement*)
- C. Substantial and sustained response to levodopa or a dopamine agonist has been documented

III. Criteria for possible PD

- A. At least two of the four features in Group A are present; at least one of these is tremor or bradykinesia
- B. Either (1) none of the features in Group B is present or (2) symptoms have been present for less than 3 years and none of the features in Group B is present to date
- C. Either (1) substantial and sustained response to levodopa or a dopamine agonist has been documented or (2) patient has not had adequate trial of levodopa or a dopamine agonist

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risk for these motor signs (Arvanitakis et al., 2004). Historically, there has been debate whether levodopa responsiveness should be included among diagnostic criteria for PD. Although nearly all patients with PD do respond, a small minority with “documented” PD have a poor or no response, although levodopa responsiveness has not been well defined in the literature (Constantinescu et al., 2007).

The International Parkinson Disease and Movement Disorders Society introduced new diagnostic criteria for PD, on the basis that there have been advances in our understanding of PD-related nonmotor features, prodromal symptoms, synucleinopathies, genetic causes, and novel hypotheses about spread of disease, among others (Berg et al., 2014; Postuma et al., 2014, 2015; Postuma and Berg 2017). The new criteria proposed categories for “clinico-genetic PD” as a subtype, defined early stages of PD (preclinical, prodromal, and

clinical disease), and eliminated DLB as an exclusion criterion but recognizing that dementia could occur at any stage in PD. In addition, supportive criteria included levodopa response, levodopa-induced dyskinesia, rest tremor of a limb, and biomarkers demonstrating olfactory loss and abnormal cardiac MIBG scintigraphy. In one study examining the utility of these new criteria applied retrospectively in a large cohort of newly diagnosed PD (less than 3.5 years), the authors found that 1835 of 2000 cases (91.7%) met MDS criteria for PD, either clinically established ($n = 1261$, 63.1%) or clinically probable ($n = 574$, 28.7%), leaving 165 (8.3%) not fulfilling criteria (Malek et al., 2017). Clinically established cases were significantly more likely to have limb rest tremor (89.3%), a good levodopa response (79.5%), and olfactory loss (71.1%) than clinically probable cases (60.6%, 44.4%, and 34.5%, respectively). After follow-up of 30 months, 89.5% of clinically established cases at baseline remained as PD (established/probable), and 86.9% of those categorized as clinically probable at baseline remained as PD (established/probable). Those cases not fulfilling PD criteria had more severe parkinsonism, especially PIGD features and cognitive impairment.

Genetics

Advances in genetics have markedly increased our knowledge of molecular pathogenesis of neurodegeneration and the genetic heterogeneity of the various parkinsonian disorders (Ferreira et al., 2017; Obeso et al., 2017) (see also Chapter 5). There are many other genetic forms of parkinsonism that overlap phenomenologically with idiopathic PD. Several genes have been associated with autosomal dominant (*SNCA/PARK1*, *LRRK2*, *EIF4G1*, *VPS35*) (Deng et al., 2013) or recessive (*parkin/PARK2*, *PINK1*, *DJ1/PARK7*) parkinsonism that resembles PD. Mutations in multiple other genes may cause parkinsonism, including genes for hereditary ataxias (*ATXN2*, *ATXN3*, *FMR1*), frontotemporal dementia (*C9ORF72*, *GRN*, *MAPT*, *TARDBP*), *DYT5* (*GCH1*, *TH*, *SPR*), and others (*ATP13A2*, *CSF1R*, *DNAJC6*, *FBXO*, *GIGYF2*, *HTRA2*, *PLA2G6*, *POLG*, *SPG11*, *UCHL1*) (Pushmann, 2013). Clinical genetic testing is available for many of the autosomal dominant and autosomal recessive forms, but, because of variable penetrance, the predictability of these mutations causing the disease is difficult to assess making genetic counseling challenging.

Although classified as forms of PD, many of the genetic forms of PD have an atypical clinical phenotype. For example, mutations in the first PD-related gene identified, the alpha-synuclein gene (*SNCA*), *PARK1*, are often associated with cognitive or psychiatric symptoms, dysautonomia, and myoclonus with widespread alpha-synuclein pathologic findings in the central and peripheral nervous system. Thus, patients with *PRKN* mutations (*PARK2*), who account for nearly a third of patients with EOPD, tend to present with hand or leg tremor and dystonia and develop freezing, postural deformity, levodopa-induced dyskinesias and hallucinations relatively early in the course of the disease (Doherty et al., 2013). They also may present with dystonic gait, cervical dystonia, dopa-responsive dystonia, hemiparkinsonism–hemiatrophy, festination, retropulsion, leg tremor at rest and on standing, marked sleep benefit,

hyperreflexia, ataxia, peripheral neuropathy, and dysautonomia (Klein and Lohmann, 2009). Pathologically, *PARK2* is characterized by predominantly ventral nigral degeneration and absence of or rare Lewy bodies (Doherty et al., 2013). *PARK-DJ1* has a clinical phenotype that is similar to that of parkin- and *PINK1*-related parkinsonism, with age of onset around the mid-30s, good levodopa response, slow progression, and focal dystonia. Carriers of the *LRRK2* G2019S mutation are more likely to manifest the PIGD subtype of PD rather than the tremor-dominant phenotype, although in contrast to the PIGD in patients with sporadic PD, *LRRK2* patients tend to have a much slower, less aggressive course (Alcalay et al., 2009; Dächsel and Farrer, 2010). Other studies have confirmed that in comparison with genetically undefined patients, *LRRK2* mutation carriers had more severe motor symptoms, a higher rate of dyskinesia, and less postural tremor, whereas *PINK1* mutation carriers have younger age at onset and slower progression. However, similar to *LRRK2* PD patients, *PINK1* PD patients have an increased rate of drug-induced dyskinesia and a lower rate of postural tremor (Nishioka et al., 2010). In one study of unaffected *LRRK2* G2019S mutation carriers, 85% showed pathologic SN hyperechogenicity, a similar frequency found in idiopathic PD, but reduced striatal uptake in DaT-SPECT was observed in only 43.7% (Sierra et al., 2013). Of genetic risk factors for PD, *GBA* mutations are recognized as the most common (De Paolo et al., 2009). Findings suggest a differential effect of mild versus severe *GBA* mutations on the risk and age of onset of PD; carriers with severe *GBA* mutations have a higher risk for younger age of onset. Some *GBA* mutation carriers may exhibit greater cognitive and behavioral changes with a meta-analysis revealing a 2.4-fold increased risk for cognitive impairment, 1.8-fold increased risk for psychosis, and a 2.2-fold increased risk for depression (Creese et al., 2018).

Pathologic findings

The neuropathologic findings in PD consist of multifocal degeneration involving the central, peripheral, and autonomic nervous system and other organs associated with widespread occurrence of Lewy bodies and dystrophic Lewy neurites (Jellinger, 2012; Goedert et al., 2013). In the absence of a specific biologic marker or a diagnostic test, the diagnosis of PD can be made with certainty only at autopsy. PD is pathologically defined as a neurodegenerative disorder characterized chiefly by (1) depigmentation of the SN associated with degeneration of melanin- and dopamine-containing neurons, particularly in the SNzc and in the norepinephrine-containing neurons in the LC, and (2) the presence of Lewy bodies (eosinophilic cytoplasmic inclusions) in the SNzc and other brain regions, including the LC and some cortical areas. In fact, some studies have found that, despite the universally accepted notion that the SN is the site of the brunt of the pathologic processes in PD, neuronal loss in the LC is more severe (Zarow et al., 2003). These criteria are open to question, however, because typical cases of levodopa-responsive parkinsonism have been reported without Lewy bodies and with or without neurofibrillary tangles in the SN (Rajput et al., 1991). In contrast, the pathologically typical form of Lewy body parkinsonism has been described with

atypical clinical features such as poor response to levodopa (Mark et al., 1992). Both the Canadian (Rajput et al., 1991) and the London's Parkinson's Disease Society Brain Bank studies (Hughes et al., 1992b) showed that 24% of patients in each series had a pathologic diagnosis other than PD. Furthermore, in patients with pathologically documented PD, other disorders may be present that can cloud the clinical picture. For example, in 100 cases of pathologically proven PD, Hughes and colleagues (1993) found 34 with coexistent pathologic findings in the striatum and 28 outside the nigrostriatal system; vascular changes involving the striatum were found in 24 patients, AD changes in 20 (3 had striatal plaques), and diffuse Lewy body disease or DLB in 4. As was noted previously, in a subsequent study, the diagnostic accuracy had improved markedly (Hughes et al., 2002). Until parkinsonian disorders can be differentiated by disease-specific biologic or etiologic markers, neuroimaging, or other laboratory tests, the separation of the different parkinsonian disorders still depends largely on clinicopathologic correlations.

Although the emphasis in PD research has been on dopaminergic deficiency underlying motor dysfunction, there is a growing body of evidence that the caudal brainstem nuclei (e.g., dorsal motor nucleus of the glossopharyngeal and vagal nerves), anterior olfactory nucleus, and other nondopaminergic neurons might be affected long before the classic loss of dopaminergic neurons in the SN, based on accumulation of Lewy neurites detected by staining for alpha-synuclein (Braak et al., 2003, 2004; Braak and Del Tredici, 2008; Hawkes et al., 2010; Jellinger, 2012). According to the Braak staging, in presymptomatic stage 1, the Lewy neurite pathologic findings remain confined to the medulla oblongata and olfactory bulb. In stage 2, it has spread to involve the pons. In stages 3 and 4, the SN and other nuclear groups of the midbrain and basal forebrain are the focus of initially subtle and then more pronounced changes, at which time the illness reaches its symptomatic phase. In end stages 5 and 6, the pathologic process encroaches on the telencephalic cortex. A clinicopathologic study of 129 brains in the UK Brain Bank focusing on the late phase of PD indicates that although it takes longer for young-onset patients to reach the end stage of the disease, their disease course is marked by more rapid physical and cognitive decline, however, their terminal stage is rather similar irrespective of age at onset (Kempster et al., 2010). The data suggest a pattern to the order that they take place in and their proximity to death. For example, visual hallucinations occurred on average 5.1 years before death, regular falls 4.1 years, dementia 3.3 years, and need for residential care 3.3 years. This progression, according to the authors, supports "a staging system based on the rostral extent and severity of Lewy body pathology, although other pathologies may play a synergistic role in causing cognitive disability," consistent with the Braak hypothesis.

Although some studies have provided support for the caudal-rostral Braak staging hypothesis (Kingsbury et al., 2010), many authors have challenged it for several reasons, including (1) lack of cell counts to correlate with the described synuclein pathologic findings; (2) no immunohistochemistry findings to identify neuronal types; (3) no observed asymmetry in the pathologic findings that would correlate with the well-recognized asymmetry of clinical findings; (4) bulbar symptoms are late, not early, features of PD despite the suggested early involvement of the dorsal motor

nucleus of the vagal nerve; (5) exclusion of cases of DLB, which Braak viewed as part of stage 6, but others suggest that it is a separate entity; (6) the idiopathic Lewy body cases were preselected for the presence of alpha-synuclein deposition; (7) cases with well-documented alpha-synuclein inclusions at higher levels in the neuraxis without involvement of caudal brainstem have been reported; (8) the pathologic examination did not include the spinal cord and peripheral autonomic nervous system; and (9) brain synucleinopathy consistent with Braak stages 4 and 6 has been found in individuals without any neurologic signs (Burke et al., 2008). Finally, it is not uniformly accepted that aggregates of alpha-synuclein are pathogenetic in themselves, because some have argued that they actually represent compensatory, beneficial survival mechanisms used by the neurons (Dickson et al., 2009; Shulman et al., 2011).

Ancillary tests

Neuroimaging

Although there is no blood or CSF test that can diagnose PD to date, certain neuroimaging techniques may be helpful in differentiating PD from other parkinsonian disorders (Stoessl et al., 2011a,b). Furthermore, neuroimaging, together with clinical ratings, have been used to assess progression of PD (Antonini and DeNotaris, 2004; Jankovic, 2005; Brooks, 2007; Martin et al., 2008; Nadhagopal et al., 2008; Stoessl et al., 2011 a,b; Ziegler et al., 2013). MRI in patients with typical PD is usually normal; but a high-field-strength (1.5 T) heavily T2-weighted MRI may show a wider area of lucency in the SN that is probably indicative of increased accumulation of iron (Olanow, 1992). Diffusion-weighted imaging provides information on neuronal integrity by quantitating motion of water molecules, which is impaired in axonal cell membranes damaged by a neurodegenerative disease, such as PD. When this technique was applied to 17 patients with PD, 16 (94%) were correctly discriminated with a sensitivity of 100% and a specificity of 88% (Scherfner et al., 2006). These patients showed significant increases of diffusivity in the region of both olfactory tracts. Abnormal proton transverse relaxation rate ($R2^*$) measured by 3-tesla MRI, consistent with iron deposition in the lateral SN pars compacta (SNpc), seems to correlate with progression of motor symptoms and as such may have potential utility as a biomarker for disease progression (Martin et al., 2008). Using the Spin-Lattice Distribution Index (SI), a measure of MRI signal in the SNpc, provides a "highly sensitive" marker for PD (Hutchinson and Raff, 2008). In a study of 14 patients with early, untreated PD and 14 age- and gender-matched controls using a 3-tesla MRI and high-resolution diffusion tensor imaging (DTI) protocol, fractional anisotropy (FA) was reduced in the SN of subjects with PD compared with controls ($P < 0.001$), particularly in the caudal SN compared with the rostral region of interest, with 100% sensitivity and specificity for distinguishing patients with PD from healthy subjects (Vaillancourt et al., 2009), though other studies have not fully replicated these findings. Although there is a high correlation between DTI findings and number of SN compacta (SNpc) dopaminergic neurons lost with MPTP intoxication in a murine model of PD, there is no apparent correlation between the FA values

and UPDRS motor scores. In one study of 13 patients with Hoehn and Yahr stage 1 PD, SNc volumes were found to be significantly decreased, providing further evidence that SNc degenerated before the basal forebrain (Ziegler et al., 2013). The imaging methods used in this study, including 3-tesla MRI, multiecho magnetization-prepared rapid gradient-echo with T1-weighting, three-dimensional T2-weighted turbo spin-echo, multiecho fast low-angle shot with proton density weighting, and three-dimensional T2-weighted FLAIR turbo spin-echo, coupled with some even newer methods, such as MR sequences sensitive to neuromelanin and segmented inversion-recovery ratio imaging, it is likely that imaging biomarkers will become even more sensitive to early changes than ever before. Other techniques to differentiate PD from atypical parkinsonian syndromes have focused on free water diffusion imaging (Planetta et al., 2016). Whereas PD, MSA, and PSP, compared with controls, had increased free water measurements in the anterior and posterior part of the SN, only the atypical parkinsonian disorders had additional elevated free water and altered free water corrected FA in the basal ganglia, thalamus, and cerebellum.

Using [^{18}F]-fluorodopa PET scans to assess the integrity of the striatal dopaminergic terminals, characteristic reduction of the [^{18}F]-fluorodopa uptake, particularly in the putamen, can be demonstrated in virtually all patients with PD, even in the early stages (Brooks, 1991). In addition to reduced density of the dopamine receptors, patients with atypical parkinsonism have decreased striatal metabolism as demonstrated by PET scans (Eidelberg et al., 1993), and of presynaptic vesicles with DTBZ. VMAT2 brain PET imaging also may be helpful in differentiating PD from atypical parkinsonism (Gilman et al., 1996; Marek et al., 1996; Booij et al., 1997; Bohnen et al., 2009). Imaging-neuropathologic correlative studies have shown that F-dopa, DTBZ, and other ligand studies in MPTP primates showed that tracer uptake studies correlated with striatal dopamine levels but not with nigral neurons except when the nigral counts are less than 50% of normal (Karimi et al., 2013). Other ligands used in the assessment of parkinsonian disorders include PMP AChE (Stoessl et al., 2011a). Using [^{11}C]-raclopride to image dopamine D2 receptors, Brooks and colleagues (1992a) showed that in patients with untreated PD, the striatal D2 receptors are well preserved, whereas patients with atypical parkinsonism have a decrease in the density of dopamine receptors.

DAT imaging using DAT-SPECT has been found to be a useful tool in reliably differentiating between PD, ET, dystonic tremor, drug-induced, psychogenic and vascular parkinsonism (Schwarz et al., 1992; Catafau et al., 2004; Kagi et al., 2009; Jankovic, 2011). DAT imaging, however, does not seem to differentiate between PD and atypical parkinsonian disorders such as MSA (Perju-Dumbrava et al., 2012). Even within PD cases, the pattern of abnormal SPECT has been proposed to help identify particular subtypes. The tremor-dominant type of PD is characterized more by an eagle wing-shaped, or comma, configuration of dopaminergic uptake, consistent with a more severe neuronal loss in medial than in the lateral SNzc (which projects to the caudate nucleus and anterior putamen) plus the retrorubral field (with projections to the dorsolateral striatum and ventromedial thalamus). More pronounced loss of dopamine terminals in the caudate nucleus and the lateral putamen is seen, whereas

the egg-shaped configuration of FP-CIT SPECT scans is more suggestive of akinetic-rigid patients, consistent with the neuropathologic findings of more severe cell loss in the ventrolateral part of the SNzc that projects to the dorsal putamen (Eggers et al., 2011). Striatal dopaminergic deficit in ET has been demonstrated in some, but not all SPECT studies using ligands for DAT, such as [^{123}I](N)-(3-iodopropene-2-yl)-2beta-carbomethoxy-3beta-(4-chlorophenyl) tropane (IPT) SPECT, [^{123}I] β -carbomethoxy-3- β -(4-iodophenyl)-tropane (β -CIT) SPECT or [^{123}I]-ioflupane SPECT (DaTscan). DaTscan was approved by FDA in 2011 to assist in the evaluation of adult patients with suspected parkinsonian syndromes. At baseline, DaTscan shows 93% sensitivity and 46% specificity with respect to diagnosing degenerative parkinsonism versus nondegenerative tremor disorders; the figures are 78% and 97%, respectively, at 3 years (Cummings et al., 2011). Similar high sensitivity and specificity have been reported by other studies but may not be any higher than a clinical diagnosis (de la Fuente-Fernandez, 2012).

Neuroimaging techniques can be used not only in diagnosis but also in following the progression of the disease (Cummings et al., 2011; Wu et al., 2011; Agarwal and Stoessl, 2013). Several studies have shown that the annualized rate of reduction in striatal dopaminergic markers, such as uptake of ^{18}F -dopa or DAT binding, to range from 4% to 13% for patients with PD and 0% to 2.5% in healthy controls (Parkinson Study Group, 2002; Stoessl et al., 2011a). In one study using 6-[^{18}F]-fluoro-l-dopa (FDOPA) PET, Nurmi and colleagues (2001) showed a $10.3\% \pm 4.8\%$ decline in the uptake in the putamen over a 5-year period. Using serial FDOPA PET in a prospective, longitudinal study of 31 patients with PD followed for more than 5 years (mean follow-up: 64.5 ± 22.6 months), Hilker and colleagues (2005) found an annual decline in striatal FDOPA ranging from 4.4% (caudate) to 6.3% (putamen), consistent with most other similar studies (Morrish et al., 1998). They concluded that “the neurodegenerative process in PD follows a negative exponential course,” and in contrast to the long-latency hypothesis, they estimated that the preclinical disease period is relatively short: only about 6 years. In a PET follow-up brain graft study of patients with advanced PD, Nakamura and colleagues (2001) found a 4.4% annual decline in the sham-operated patients. Jennings and colleagues (2001) found, on the basis of sequential [2beta-carboxymethoxy-3-beta-(4[^{123}I]iodophenyl)tropane] (β -CIT) and SPECT imaging at intervals ranging from 9 to 24 months, the annual rate of loss of striatal β -CIT uptake to be 7.1% in subjects having a diagnosis of PD for fewer than 2 years compared with a 3.7% rate in those having a diagnosis of PD for longer than 4.5 years. Other longitudinal studies of PD progression, imaging ligands targeting dopamine metabolism (^{18}F -dopa) and DAT density using PET and SPECT, respectively, have demonstrated an annualized rate of reduction in striatal [^{18}F]-dopa or [^{123}I] β -CIT uptake of about 11.2% (6%–13%) in PD patients compared with 0.8% (0%–2.5%) change in healthy controls (Marek et al., 2001). Using free water diffusion analyses, Ofori et al (2015) found elevated free water in the posterior SN in PD, which increased with progression over a year follow-up and, furthermore, predicted changes in bradykinesia and cognitive status over 1 year (Ofori et al., 2015).

These imaging studies are consistent with pathology studies showing that the rate of nigral degeneration in PD patients is 8-fold to 10-fold higher than that of healthy age-matched controls. The several studies, including the one by [Hilker and colleagues \(2005\)](#), that suggest that the rate of progression of PD is not linear over time, being more rapid initially and slowing in more advanced stages of the disease, argues against the long-latency hypothesis for presymptomatic period in PD ([Jankovic, 2005](#)). Finally, on the basis of clinicopathologic correlation, [Fearnley and Lees \(1991\)](#) suggested that there is a 30% age-related nigral cell loss at disease onset, again indicating rapid decline in nigral dopaminergic cells in the early stages of the disease. This has been confirmed by longitudinal imaging studies ([Soessl et al., 2011](#)). Genetic studies have found that the age at onset of PD (and AD) is strongly influenced by a gene on chromosome 10q ([Li et al., 2002](#)).

Increased echogenicity on brain parenchyma TCS is an ultrasound sign that has been found to be relatively specific for PD and that has been used to differentiate PD from atypical parkinsonism, mostly MSA ([Walter et al., 2003](#); [Berg et al., 2008](#)). The investigators found that 24 of 25 (96%) patients with PD exhibited hyperechogenicity, whereas only 2 of 23 (9%) patients with atypical parkinsonism showed a similar pattern. They concluded that brain parenchyma sonography may be highly specific in differentiating between PD and atypical parkinsonism. In another study the sensitivity of TCS was 90.7% and the specificity was 82.4%; the positive predictive value was 92.9% ([Gaenslen et al., 2008](#)). In this study, however, tremor-dominant PD patients were excluded. Furthermore, in about 10% of patients, SN cannot be imaged because of an inadequate temporal bone window. Because the hyperechogenicity seems to be constant over time, TCS possibly may be used to detect this sign as a marker for PD before the onset of neurologic symptoms. Indeed, the combination of motor asymmetry, loss of smell, and midbrain hyperechogenicity was found to be associated with high predictive value for the diagnosis of PD ([Busse et al., 2012](#)).

Presymptomatic diagnosis and biomarkers

One of the most important challenges in PD research is to identify individuals who are at risk for PD and diagnose the disease even before the initial appearance of symptoms ([Sherer et al., 2012](#); [Agarwal and Stoessl, 2013](#); [Berardelli et al., 2013](#); [Salat et al., 2016](#)). It has been proposed that there are four preclinical stages of the disease: (1) prephysiologic (patients with a genetic risk of disease), (2) preclinical (imaging or biomarker abnormalities without symptoms), (3) premotor (nonmotor features present), and (4) prediagnostic (subtle motor features present) ([Stern et al., 2012](#)). In addition, MDS research criteria for prodromal PD have been published with calculations for the probability of prodromal PD based on background risk taking into account environmental and genetic risk factors and results of diagnostic marker testing ([Berg et al., 2015](#)).

Although some studies suggest that the pathologic processes in the SN begin 4 to 7 years before the onset of symptoms ([Fearnley and Lees, 1991](#); [Hilker et al., 2005](#); [Hawkes, 2008](#)), some evidence suggests that the disease may start

even prenatally ([Le et al., 2009](#)). The Parkinson's Associated Risk Study (PARS) evaluated 7500 first-degree relatives of individuals with PD with olfactory testing and a subset with DAT SPECT scanning to identify those most likely to develop PD ([Berg et al., 2012](#)). The Prospective Evaluation of Risk Factors for Idiopathic Parkinson's Syndrome (PRIPS) study enrolled 1847 individuals free of PD and followed them longitudinally ([Berg et al., 2013](#)). After 3 years of follow-up, 11 subjects had developed PD. Using inclusion criteria based on combination of age, positive family history and/or hyposmia, and SN hyperechogenicity 1 in 16 individuals meeting all three criteria developed PD. The Honolulu Asia Aging Study has followed 8006 Japanese American men and identified several clinical features that were associated with increased incidence of PD ([Ross et al., 2012](#)). When impaired olfaction, excessive daytime sleepiness, low frequency of bowel movements, and slow reaction time were assessed in combination, the presence of all four signs was associated with an incidence of PD of 215 per 10,000 person-years compared with an incidence of 16 per 10,000 person-years in those with none of the signs. Thus, it would be necessary to apply a preventive strategy to 100 such high-risk individuals for an average of 10 years to prevent 21 new cases of PD.

Biomarkers can provide information on the presence (trait) and severity (state) of the disease. Some have even suggested that biomarkers rather than clinical definitions are used to define disease phenotypes ([Espay et al., 2017](#)). Searching for sensitive biomarkers, such as clinical, motor, physiologic, and olfactory testing, CSF proteomics, genetic testing, sleep and autonomic studies, and neuroimaging, that detect evidence of PD even before clinical symptoms first appear, has been the primary focus in many research centers around the world and in multicenter programs such as the Parkinson's Progressive Marker Initiative ([Michell et al., 2004](#); [Hawkes, 2008](#); [Marek et al., 2008, 2011](#); [Halperin et al., 2009](#); [Mollenhauser and Trenkwalder, 2009](#); [Wu et al., 2011](#)) (Fig. 4.8). These biomarkers, if found to be useful, should reliably predict risk (clinical, genetic, blood/CSF test, imaging), diagnosis, progression (prognosis), and response to treatment. Several cross-sectional and longitudinal biomarker studies are currently being conducted in various centers around the world using the most advanced clinical, neurophysiologic, and imaging techniques coupled with refinements in genomics, proteomics, lipidomics, and metabolomics applied to blood, CSF, and other tissues, in hope to identify markers that are both sensitive and specific for the diagnosis of PD and also predictive of long-term prognosis ([Aarsland and Ravina, 2010](#); [Ballard and Jones, 2010](#); [Hong et al., 2010](#); [Siderowf et al., 2010](#); [Tokuda et al., 2010](#); [Wu et al., 2011](#); [Shi et al., 2011](#); [Hatano et al., 2016](#)). One study, using a combination of three independent platforms: ultra-high-performance liquid chromatography/tandem mass spectrometry (UPLC/MS/MS) optimized for basic species, UPLC/MS/MS optimized for acidic species and gas chromatography/MS (GC/MS), showed that metabolomic profiles of PD were clearly different from normal controls ([Hatano et al., 2016](#)). Patients with PD had significantly lower levels of tryptophan, caffeine and its metabolites, bilirubin, and ergothioneine, and significantly higher levels of levodopa metabolites and biliverdin than those of normal controls. These findings, however, should be validated and replicated in independent cohorts using different platforms.

PARKINSON DISEASE

Symptomatic

Presymptomatic

- Gene mutations
- Essential tremor
- Anosmia
- Constipation
- REM behavioral disorder
- Shoulder pain
- Red or blond hair color
- Slow reaction time
- Lower impulsiveness
- Low uric acid
- Low LDL
- Nurr1 in lymphocytes
- Blood/CSF proteomics
- Imaging: MRI-DTI, PET, SPECT, sonography



Fig. 4.8 Premotor markers of Parkinson disease. CSF, Cerebrospinal fluid; LDL, low-density lipoprotein; MRI-DTI, magnetic resonance imaging–diffusion tensor imaging; PET, positron emission tomography; REM, rapid eye movement; SPECT, single-photon emission computed tomography.

Change to Data on blood and CSF markers correlate with motor or nonmotor symptoms associated with PD. For example, low plasma levels of epidermal growth factor (EGF) have been found to correlate with baseline cognitive impairment in patients with PD (Chen-Plotkin et al., 2011). Besides loss of olfaction, constipation, shoulder pain, RBD, and imaging studies, other symptoms, signs, and tests are being explored as potential biomarkers for early detection of PD. For example, mRNA expression of Nurr1 on peripheral lymphocytes has been found to be decreased in patients with PD compared with other dopaminergic disorders (Le et al., 2008). Furthermore, mRNA expression of cochaperone ST13 in peripheral blood, which stabilizes heat shock protein 70, a modifier of alpha-synuclein misfolding, has been found to be lower in patients with PD than in controls ($P = 0.002$) in two independent populations (Scherzer et al., 2007). Another potential biomarker, N8-acetyl spermidine was found to be significantly elevated in the blood of PD patients with rapidly progressive disease compared with both control subjects and slow progressors (Roede et al., 2013). Many studies have investigated the role of CSF markers in detecting early PD and in following the progression of the disease. In one study, CSF was assayed in 146 subjects, 108 of whom had synucleinopathy (34 PD, 54 MSA, 20 pure autonomic failure) and 38 controls, and low dihydroxyphenylacetic acid (DOPAC) was found to be 100% sensitive and 89% specific in separating patients with PD from controls (but did not differentiate patients with PD from those with MSA) (Goldstein et al., 2012). Thus, low CSF DOPAC, the immediate metabolite of dopamine, appears to be much more predictive of PD than CSF homovanillic acid (HVA). Using an enzyme-linked immunosorbent assay (ELISA) method that detects only oligomeric “soluble aggregates” of alpha-synuclein in plasma from 34 PD patients compared with 27 controls, significantly elevated levels were detected in 52% of the PD patients compared with only 14.8% of controls, indicating a specificity of 0.852, sensitivity of 0.529, and a positive predictive value of 0.818 (El-Agnaf et al., 2006).

Mean CSF alpha-synuclein concentrations as measured by ELISA have been found to be significantly lower in PD, DLB, and MSA than in other neurologic diseases with high positive predictive value (Mollenhauer et al., 2013). Using ELISA, western blot, and Biacore surface plasmon resonance, one study found significantly higher antibody titers against monomeric alpha-synuclein in the blood sera of PD patients compared with controls, though the responses decreased with PD progression ($P < 0.0001$) (Yanamandra et al., 2011). The authors suggested that this finding indicates a potential protective role of autoimmunity in maintaining the body homeostasis and clearing protein species whose disbalance may lead to amyloid assembly. Using highly sensitive and quantitative Luminex assays, the following proteins were measured in the CSF of patients with various neurodegenerative disorders: total tau, phosphorylated tau, amyloid beta peptide 1 to 42 ($A\beta(1-42)$), Flt3 ligand, and fractalkine levels, in addition to DJ-1 and alpha-synuclein (Shi et al., 2011). The combinations of these biomarkers could differentiate PD patients not only from normal controls but also from patients with AD and MSA with excellent sensitivity (99%) and specificity (95%). In addition, CSF fractalkine/ $A\beta(1-42)$ positively correlated with PD severity in cross-sectional samples as well as with PD progression in longitudinal samples. Thus, this panel of seven CSF proteins could aid in PD diagnosis, differential diagnosis, and correlation with disease severity and progression. In a study examining several CSF biomarkers, CSF levels of alpha-synuclein were decreased in patients with PD, PDD, DLB, and MSA but increased in patients with AD; furthermore, CSF levels of neurofilament light chain were substantially increased in atypical parkinsonian disorders (i.e., PSP, MSA, and CBD) (Hall et al., 2012; Marques et al., 2019). In one study, using ELISA, relatively high levels of alpha-synuclein and ratio of oligomeric to total alpha-synuclein in the CSF differentiated with high sensitivity and specificity patients with PD from healthy and diseased controls (Tokuda et al., 2010). In contrast, using a combination of western blotting, gel filtration, mass spectrometry, and Luminex assays, Hong et al (2010) found alpha-synuclein (and DJ-1) levels to be decreased in PD patients versus controls or AD patients when there was control for blood contamination. Other studies found that low CSF alpha-synuclein levels alone have relatively low sensitivity and specificity, but low ratio of total tau/alpha-synuclein and phosphorylated tau/alpha-synuclein discriminated well among PD, DLB, and AD (Parnetti et al., 2011). The following values have been shown to be low in the CSF of patients with PD compared with healthy or disease controls: total alpha-synuclein, ratio of alpha-synuclein to tau, and lysosomal enzyme beta-glucocerebrosidase activity; low $A\beta42$ correlated with cognitive impairment. In contrast, levels of alpha-synuclein oligomers are increased. The reported variations in results are in part the result of differences in assay techniques, antibodies directed to different epitopes, limited numbers of patients, inadequate controls, contamination by blood products, and many other factors. It is not yet clear whether and how the CSF biomarkers will be used in future clinical trials (Perrin, 2012).

Neuroimaging of the presynaptic nigrostriatal terminals has been suggested as a potential biomarker for diagnosis of early PD and for early differentiation between PD and other parkinsonian disorders. Presymptomatic carriers of *LRRK2*

mutation have been shown to have decreased dopaminergic activity and a greater rate of decline in dopaminergic imaging markers, particularly DAT binding compared with healthy controls, suggesting that functional neuroimaging may provide sensitive signal for subclinical dopaminergic deficiency (Nandhagopal et al., 2008; Stoessl et al., 2011a,b). To evaluate the diagnostic accuracy of DAT imaging using (^{123}I)beta-CIT, Jennings and colleagues (2004) evaluated 35 patients referred by community neurologists with suspected early PD. The clinical diagnosis was “confirmed” by two movement disorder experts, which represented the diagnostic gold standard. A disagreement between the gold standard diagnosis and imaging diagnosis occurred in only 8.6% of cases, giving the imaging sensitivity of 0.92 and specificity of 1.00). They concluded that (^{123}I)beta-CIT and SPECT imaging is a useful diagnostic tool to differentiate between patients with early PD and those with other parkinsonian disorders. Using PET tracers 6-[(18)F]-fluorodopa (FD), [(11)C]-2 β -methoxy-3 β -4-fluorophenyltropane (CFT), and DTBZ to measure specific uptake in SN MPTP of macaques, the investigators found a strong correlation between reduced uptake of both CFT and DTBZ in the SN and dopaminergic cell counts in the SN, and a linear relationship with motor impairment (Brown et al., 2013). Thus, this imaging technique may be a highly relevant biomarker of nigrostriatal function. In a cross-sectional study of 40 patients with MCI-PD, dynamic A β -amyloid PET imaging using [(11)C] Pittsburgh compound B (PiB) showed only 6 in 40 (15%) had increased cerebral PiB binding at levels seen in patients with AD (Petrou et al., 2012).

Many studies provide evidence suggesting that the latency between the onset of neuronal degeneration (or onset of the disease process) and clinical symptoms might not be as long as was initially postulated (Morrish, 1996). On the basis of a study of 36 control and 20 PD brains, Fearnley and Lees (1991) suggested that the presymptomatic phase of PD from the onset of neuronal loss to the onset of symptoms might be only 5 years, thus arguing against aging as an important cause of PD. With advancing age, there is 4.7% per decade rate of loss of pigmented neurons from the SNpc, whereas in PD, there is 45% loss in the first decade. Because the rate of progression is so highly variable, it is perhaps not surprising that the estimates of presymptomatic period vary between 40 years and 3.1 years, depending on the method used (Morrish et al., 1996). The shorter presymptomatic period has been suggested by longitudinal ^{18}F -dopa PET studies (Morrish et al., 1996).

One of the benefits of longitudinal imaging studies, often despite their challenges, such as a study by Hilker and colleagues (2005; see also Jankovic, 2005), is that they can be used to estimate duration of the presymptomatic period. Assuming that the threshold at which symptoms are first manifested is at 69% of the normal putaminal FDOPA uptake, Hilker and colleagues (2005) concluded that the preclinical disease period must be relatively short: only about 6 years. This is consistent with other imaging and with autopsy data (Fearnley and Lees, 1991). The 31% loss of striatal dopaminergic terminals needed before onset of symptoms, demonstrated by Hilker and colleagues (2005), is substantially lower than the 60% to 80% loss of dopaminergic neurons in the SN that is traditionally cited as being required before symptoms of PD first become evident. The

difference may be explained by compensatory changes in response to presynaptic dopaminergic loss, such as enhanced synthesis of dopamine in surviving dopaminergic neurons, upregulation of striatal dopa-decarboxylase activity, and increased dopaminergic innervation of the striatum (Jankovic, 2005). Furthermore, there may be functional compensatory changes, as suggested by the finding of increased FDOPA uptake in the GPi internus, in early PD. This enhanced function of the nigropallidal dopaminergic projection maintains a more normal pattern of pallidal output in early stages of the disease, but these compensatory mechanisms eventually fail, and the disease starts to progress. Thus, because of the compensatory changes, FDOPA PET more accurately reflects dopaminergic function at the striatal terminal rather a cell loss in the SN. These compensatory mechanisms may also explain why, despite age-related loss of nigral neurons, there is little or no change in FDOPA uptake with normal aging (Sawle et al., 1990) and why up to 15% of patients with signs of PD, as determined by experienced parkinsonologists, have normal FDOPA or β -CIT scans without evidence of dopaminergic deficit (SWEDDs) (see Table 4.3) (Marek et al., 2003, 2011, 2014; Whone et al., 2003; Clarke, 2004; Fahn et al., 2004; Jankovic, 2005; Scherfler et al., 2007; Bajaj et al., 2010; Schwingsenschuh et al., 2010). These SWEDDs might represent patients with PD and compensatory striatal changes or with other disorders. They might also represent false-negative results and therefore highlight the relative lack of sensitivity of these functional neuroimaging studies as potential biomarkers for detection of PD, particularly at early stages of the disease (Michell et al., 2004). Because individuals with SWEDDs fail to develop dopaminergic deficit and fail to show clinical worsening, it is likely that these individuals were incorrectly diagnosed. This is supported by normal olfaction in SWEDD individuals (Silveira-Moriyama et al., 2009). One possible condition misdiagnosed as PD, but with SWEDD, is adult-onset dystonic tremor, which may manifest as unilateral or asymmetric rest tremor and decreased arm swing (Schneider et al., 2007; Stamelou et al., 2013). In one study, two movement disorder specialists evaluated patients with tremor-dominant PD from SWEDDs patients with atypical tremor and dystonic tremor, and found relatively high false positive (17.4%–26.1%) and negative (6.7%–20%) rates, indicating that patients with atypical tremor, monosymptomatic rest tremor and dystonic tremor are frequently wrongly diagnosed as PD (Bajaj et al., 2010). In another study of 25 tremulous SWEDD patients, the investigators found that despite clinical overlap, lack of true bradykinesia, presence of dystonia, and head tremor favored a diagnosis of SWEDDs, whereas reemergent tremor, true fatiguing or decrement, good response to dopaminergic drugs, and presence of nonmotor symptoms favored PD (Schwingsenschuh et al., 2010). Although most SWEDD cases are due to a clinical misdiagnosis of PD, there exists a small proportion of patients with SWEDD who may have PD on the basis of a positive levodopa response, clinical progression, or imaging and/or genetic evidence (Erro et al., 2016). Furthermore, some patients with PD symptoms may fulfill the diagnostic criteria for SWEDD initially, but then they progress to PD with dopaminergic deficit (Wile et al., 2016).

To the extent that future protective therapies may prevent or even halt the neurodegenerative process, it is essential that

Table 4.5 Classification of parkinsonism**I. Primary (idiopathic) parkinsonism**

- Parkinson disease
- Juvenile parkinsonism

II. Multisystem degenerations (parkinsonism-plus)

- Progressive supranuclear palsy (PSP), Steele-Richardson-Olszewski disease (SRO)
- Multiple-system atrophy (MSA)
- Striatonigral degeneration (SND or MSA-P)
- Olivopontocerebellar atrophy (OPCA or MSA-C)
- Shy-Drager syndrome (SDS)
- LYTICO-Bodig or parkinsonism-dementia-ALS complex of Guam (PDACG)
- Cortical-basal ganglionic degeneration (CBGD)
- Progressive pallidal atrophy
- Parkinsonism-dementia complex
- Pallidopyramidal disease

III. Heredodegenerative parkinsonism

- Hereditary juvenile dystonia-parkinsonism
- Autosomal dominant Lewy body disease Huntington disease
- Wilson disease
- Hereditary ceruloplasmin deficiency
- Hallervorden-Spatz disease
- Olivopontocerebellar and spinocerebellar degenerations
- Machado-Joseph disease
- Familial amyotrophy-dementia-parkinsonism
- Disinhibition-dementia-parkinsonism-amyotrophy complex

- Gerstmann-Strausler-Scheinker disease
- Familial progressive subcortical gliosis
- Lubag (X-linked dystonia-parkinsonism)
- Familial basal ganglia calcification
- Mitochondrial cytopathies with striatal necrosis
- Ceroid lipofuscinosis
- Familial parkinsonism with peripheral neuropathy
- Parkinsonian-pyramidal syndrome
- Neuroacanthocytosis
- Hereditary hemochromatosis

IV. Secondary (acquired, symptomatic) parkinsonism

- Infectious: Postencephalitic, AIDS, SSPE, Creutzfeldt-Jakob disease, prion diseases
- Drugs: Dopamine receptor-blocking drugs (antipsychotic, antiemetic drugs), reserpine, tetrabenazine, alpha-methyl-dopa, lithium, flunarizine, cinnarizine
- Toxins: 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine, CO, Mn, Hg, CS₂, cyanide, methanol, ethanol
- Vascular: Multi-infarct, Binswanger disease
- Trauma: Pugilistic encephalopathy
- Other: Parathyroid abnormalities, hypothyroidism, hepatocerebral degeneration, brain tumor, paraneoplastic, normal pressure hydrocephalus, noncommunicating hydrocephalus, syringomyelia, hemiatrophy-hemiparkinsonism, peripherally induced tremor and parkinsonism, and psychogenic

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they be implemented early in the course of the disease. Therefore clinical and basic studies have focused on a search for presymptomatic biomarkers of PD (Michell et al., 2004). An identification of a disease-specific diagnostic test would be immensely helpful not only in defining the various PD subtypes and in differentiating PD from atypical parkinsonian syndromes but also, more importantly, in identifying populations that are at increased risk for developing PD. Such potentially vulnerable populations could then be targeted for protective therapy. Novel imaging techniques are being developed not only to monitor the progression of the disease but also as diagnostic tools to be used in clinically uncertain cases. Using the DAT ligand IPT and SPECT, Schwarz and colleagues (2000) showed a reduction of DAT binding in patients with early PD, suggesting that this technique has potential to detect preclinical disease. Comparing inversion recovery MRI and ¹⁸F-dopa PET in 10 patients with Hoehn and Yahr stage 2 and 4 PD and 8 normal controls, Hu and colleagues (2001) found that discriminant function analysis of the quantified MRI nigral signal correctly classified the combined PD patient/control group, but three patients with PD were incorrectly classified as “normal,” whereas with PET, 100% of PD patients and controls were correctly classified. In a study of 118 patients with clinically uncertain parkinsonian syndromes, all patients with presynaptic parkinsonism had abnormal ¹²³I-ioflupane SPECT (DaTSCAN, Amersham Health), whereas 94% with “nonpresynaptic” parkinsonism had a normal scan (Catafau et al., 2004). Abnormal echogenicity on TCS may be detected in early, and possibly even in presymptomatic, PD (Weise et al., 2009). Decreased cardiac MIBG uptake was found even in de novo patients with

PD, suggesting that this test could be used to detect early or even presymptomatic PD (Oka et al., 2006; Lee et al., 2006). Reduction in myocardial MIBG uptake seems to correlate with presynaptic nigrostriatal dopaminergic deficit as measured by putaminal [¹²³]FP-CIT SPECT, suggesting that brain and extracranial neurodegeneration in PD are coupled (Spiegel et al., 2007). Cardiac sympathetic degeneration and Lewy body pathologic findings, even in the presymptomatic phase of PD, are likely responsible for these abnormalities, although PD-related clinically evident heart disease has not been demonstrated (Fujishiro et al., 2008).

Differential diagnosis

Causes of parkinsonism other than PD can be classified as secondary, multiple-system degeneration or the parkinsonism-plus syndromes and heredodegenerative disorders (Stacy and Jankovic, 1992) (Table 4.5). Features that are found to be particularly useful in differentiating PD from other parkinsonian disorders include absence or paucity of tremor, early gait abnormality (such as freezing), postural instability, pyramidal tract findings, and poor response to levodopa (Tables 4.1 and 4.6). Although good response to levodopa is often used as an index of well-preserved postsynaptic receptors, supporting the diagnosis of PD, only 77% of pathologically proven cases had “good” or “excellent” initial levodopa response in the London series (Hughes et al., 1993). Furthermore, two patients with pathologically proven Lewy body parkinsonism but without response to levodopa have been reported (Mark et al., 1992). Therefore

Table 4.6 Motor and nonmotor symptoms associated with Parkinson disease

Motor	Nonmotor
Tremor, bradykinesia, rigidity, postural instability	Behavioral: Depression, apathy, anhedonia, pseudobulbar effect, cautious personality, fatigue
Hypomimia, dysarthria, dysphagia, sialorrhea	Cognitive: Bradyphrenia, tip-of-the-tongue, dementia
Microphagia, difficulties cutting food, feeding, dressing, hygiene; slow activities of daily living	Sensory: Anosmia, ageusia, impaired visual acuity, contrast, and color sensitivity, paresthesias, pain (shoulder)
Decreased arm swing, shuffling gait, freezing, festination, difficulty rising from chair, turning in bed	Dysautonomia: Orthostatic hypotension, constipation, urinary and sexual dysfunction, abnormal swelling, seborrhea, rhinorrhea, weight loss
Glabellar reflex, blepharospasm, dystonia, skeletal deformities, striatal hand/foot	Sleep disorders: RBD, vivid dreams, daytime drowsiness, sleep fragmentation, restless legs syndrome?

RBD, Rapid eye movement sleep behavior disorder.

although improvement with levodopa supports the diagnosis of PD, response to levodopa cannot be used to reliably differentiate PD from other parkinsonian disorders (Parati et al., 1993). Subcutaneous injection of apomorphine, a rapidly active dopamine agonist, has been used to predict

response to levodopa and thus to differentiate between PD and other parkinsonian disorders (Hughes et al., 1990; D'Costa et al., 1991; Bonuccelli et al., 1993). Although PD patients are much more likely to improve with apomorphine, this test is cumbersome, and it does not reliably differentiate PD from the atypical parkinsonian disorders. Furthermore, response to apomorphine test is not superior to chronic levodopa therapy in diagnosis of PD; therefore this test adds little or nothing to the diagnostic evaluation (Clarke and Davies, 2000). The differences in response to dopaminergic drugs may be partly explained by differences in the density of postsynaptic dopamine receptors. These receptors are preserved in PD, in which the brunt of the pathologic process is in the SN, whereas they are usually decreased in other parkinsonian disorders in which the striatum is additionally affected. Perhaps expression analysis of genes in brains of patients with various neurodegenerative diseases and recognizing disease-specific patterns will in the future assist in differentiating PD from other parkinsonian disorders. For example, using microarray technology in SN samples from six patients with PD, two with PSP, one with frontotemporal dementia-parkinsonism (FTDP), and five controls, Hauser and colleagues (2005) found 142 genes that were differentially expressed in PD cases and controls, 96 in the combination of PSP-FTDP, and 12 that were common to all three disorders. Further studies are needed to confirm this intriguing finding.

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Etiology and pathogenesis of Parkinson disease

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Anatomical and biochemical pathologic processes of PD

Historical introduction

Parkinson disease (PD) was first described in 1817 with the publication by James Parkinson of a small book entitled *An Essay on the Shaking Palsy* (Parkinson, 1817). In it, he described six individuals with the clinical features that have come to be recognized as a disease entity. One of the people was followed in detail over a long period; the other five consisted of brief descriptions, including two of whom he had met walking in the street and another whom he had observed at a distance. Such distant observations without a medical examination demonstrates how readily distinguishable the condition is. The physical appearance of flexed posture, resting tremor, and shuffling gait are easily recognizable. Parkinson’s opening description has the key essentials: “Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured.” In his small monograph, Parkinson provided a detailed description of the symptoms and also discussed the progressive worsening of the disorder, which he called “the shaking palsy” and also its Latin term “paralysis agitans.” On the 200th anniversary of Parkinson’s publication, a group of scholars summarized many aspects of current knowledge of PD, including a brief description of James Parkinson, the person, and of the clinical features of the disorder that he described and also some features, particularly nonmotor features, that he missed (Obeso et al., 2017).

After the publication of Parkinson’s *Essay*, the disease was widely accepted in the medical community. It took 70 years for the disorder to be referred to as “Parkinson’s disease,” as recommended by the French neurologist Charcot (1879), who argued against the term “paralysis agitans” (see Goetz, 1987, for English translation) and recommended the disorder be named after James Parkinson. Charcot argued that there is no true paralysis but rather “lessened muscular power” that is today called akinesia, hypokinesia, or bradykinesia; all three terms are often used interchangeably by clinicians, although these three terms specifically refer to lack of movement, small movement, and slow movement, respectively. These terms represent a paucity of movement not resulting from weakness or paralysis. Similarly, Charcot emphasized that tremor need not be present in the disorder, so “agitans” and “shaking” are not appropriate as part of the name of the disorder.

The clinical features of PD and its differential diagnosis are presented in a separate chapter, Chapter 4.

Incidence, prevalence, and mortality

Although PD can develop at any age, it begins most commonly in older adults, with a peak age at onset of around 60 years. The likelihood of developing PD increases with age, with a lifetime risk currently of 1 in 15 (Dorsey et al., 2018). A positive family history doubles the risk for developing PD to about 4%. A summation from seven population-based studies in various European countries found the overall prevalence of PD in people aged over 65 to be 1.8%, with an increase from 0.6% for persons aged 65 to 69 years to 2.6% for people aged 85 to 89 years (de Rijk et al., 2000).

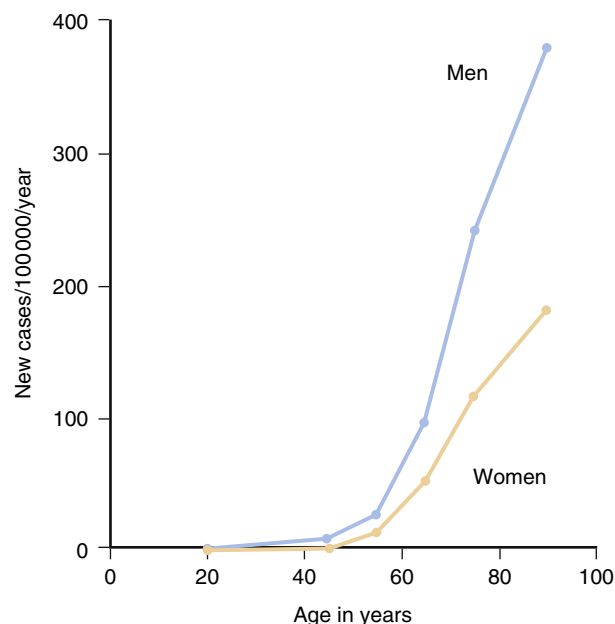


Fig. 5.1 Age- and gender-specific incidence rates (new cases per 100,000 person-years) of PD in Olmstead County, MN, 1996–1990. (From Bower JH, Maraganore DM, McDonnell SK, Rocca, WA: Influence of strict, intermediate, and broad diagnostic criteria on the age- and sex-specific incidence of Parkinson's disease. *Mov Disord.* 2000;15[5]:819–825.)

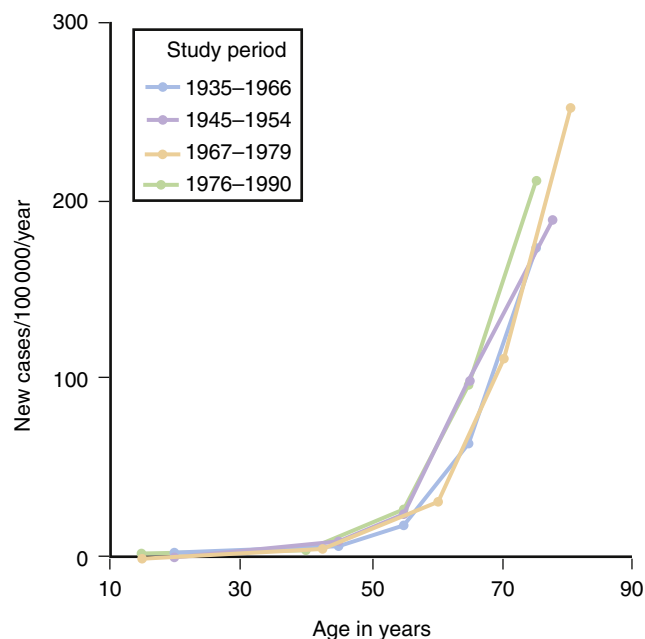


Fig. 5.2 Comparison of age-specific incidence rates of parkinsonism in Olmstead County, MN, over decades. (From Rocca WA, Bower JH, McDonnell SK, Peterson BJ, Maraganore DM: Time trends in the incidence of parkinsonism in Olmstead County, Minnesota. *Neurology.* 2001;57[3]:462–467.)

Twin studies indicate that PD with an onset under the age of 50 years is more likely to have a genetic relationship than for patients with an older age at onset (Tanner et al., 1999). Males have higher prevalence (male-to-female ratio of 3:2) and incidence rates than females (Fig. 5.1) (Bower et al., 2000), but the age-specific incidence rates have not varied over the last seven decades (Fig. 5.2) (Rocca et al., 2001). The incidence rates vary among studies, but average between 11.0 and 13.9 per 100,000 population per year (Van Den Eeden et al., 2003). In a Northern California study, the incidence rates varied among ethnic groups, being highest in Hispanics, then non-Hispanic whites, then Asians, and lowest in blacks (Van Den Eeden et al., 2003). Most of the speculation of the lower prevalence and incidence rates in females centered on hormonal differences between the genders. But an X-chromosome-wide association study has found two gene loci on the X-chromosome may contribute to PD genetic risk (Le Guen et al., 2021).

The prevalence rates of PD have varied in different studies and in different countries (Pringsheim et al., 2014). The figure of 187 per 100,000 population given by Kurland (1958) is a reasonable estimate in the United States. However, if the population is restricted to adults older than 39 years of age, the prevalence rate is 347 per 100,000 (Schoenberg et al., 1985) because both prevalence and incidence rates increase with age. At age 70, the prevalence is approximately 550 per 100,000, and the incidence is 120 per 100,000 per year. At the present time, approximately 850,000 individuals in the United States have PD, although one estimate is less than this (Hirtz et al., 2007). The number is expected to grow as the population ages (Dorsey et al., 2007). Advancing age is the single greatest risk factor for developing sporadic PD. The world-wide prevalence of PD is growing at an exponential rate, and it is the fastest growing of all neurologic diseases (Dorsey and Bloem, 2018; Dorsey et al., 2018). The

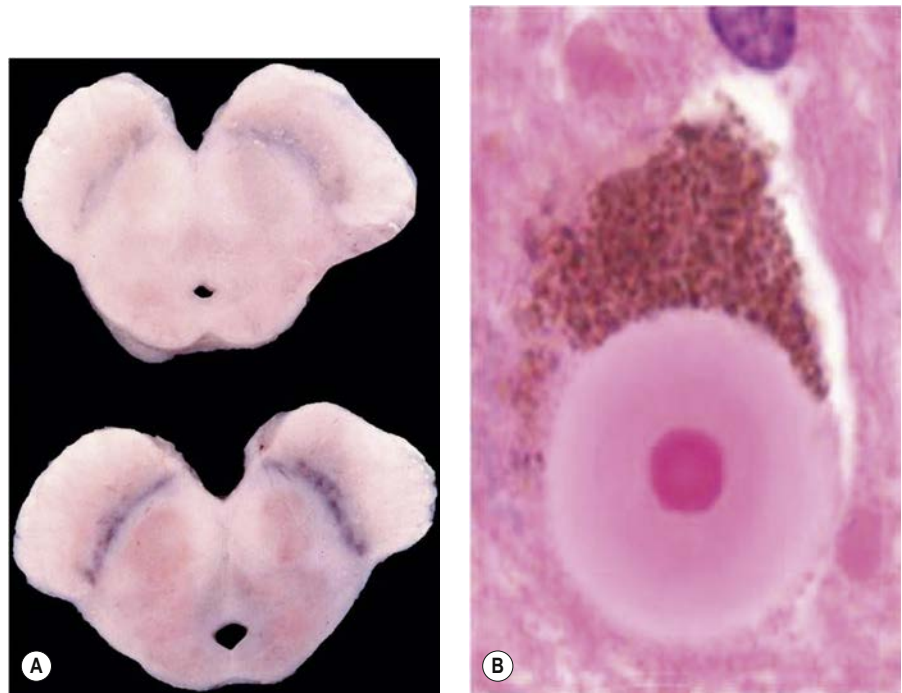
incidence rate is particularly increasing in men over 70 years of age (Savica et al., 2016). A younger age at onset of PD is associated with a slower rate of progression and a greater compensatory capacity (de la Fuente-Fernández et al., 2011).

In the pre-levodopa era, mortality was reported to be 3-fold greater in patients with PD (Hoehn and Yahr, 1967). The mortality rate was reduced to 1.6-fold greater than age-matched non-PD individuals after the introduction of levodopa (Yahr, 1976; Elbaz et al., 2003). Today, patients with PD can live 20 or more years, depending on the age at onset (Kempster et al., 2007). Death in PD is usually the result of some concurrent unrelated illness or the effects of decreased mobility, aspiration, or increased falling with subsequent physical injury. The Parkinson-plus syndromes typically progress at a faster rate and often cause death within 9 years. Thus, the diagnosis of PD versus other forms of parkinsonism is of prognostic importance and therapeutic significance because it almost always responds to at least a moderate degree with levodopa therapy, whereas the Parkinson-plus disorders usually do not.

Anatomic pathology of PD and Lewy bodies

It was many years after Parkinson's original description before the basal ganglia were recognized by Meynert in 1871 as being involved in disorders of abnormal movements. It was not until 1895 that the substantia nigra (SN) was suggested to be affected in PD. Brissaud (1895) suggested this on the basis of a report by Blocq and Marinesco (1893) of a tuberculoma in that site that was associated with a contralateral hemiparkinsonian tremor. These authors were careful to point out that the pyramidal tract and the brachium conjunctivum above and below the level of the lesion contained no degenerating fibers. The importance of the SN was emphasized by Tretiakoff in his doctoral thesis in 1919 (Tretiakoff, 1919; Lees et al., 2008). He studied the SN in 54

Fig. 5.3 Pathologic findings of PD. Left panel: Cross-section of a midbrain from a patient with PD (upper figure) and from an individual without PD (lower figure). This demonstrates depigmentation of the substantia nigra in PD. Right panel: A high-powered view of a pigmented nigral neuron containing an intracytoplasmic eosinophilic inclusion, the Lewy body. (Courtesy Jean-Paul Vonsattel, MD.)



brains, including nine cases of PD, one case of hemiparkinsonism, and three cases of postencephalitic parkinsonism, finding neuronal loss in this nucleus in all 13 cases. With the hemiparkinsonian case, Tretiakoff found a lesion in the nigra on the opposite side, concluding that the nucleus served the motor activity on the contralateral side of the body. The SN, so named because of its normally high content of neuromelanin pigment, was noted to show depigmentation, loss of nerve cells, and gliosis. These findings remain the principal and essential histopathologic features of the disease. In his study, Tretiakoff also found Lewy bodies in the SN, expanding the earlier observation of [Lewy \(1912, 1914\)](#), who had discovered the presence of these cytoplasmic inclusions in the substantia innominata and the dorsal vagus nucleus in PD. Lewy bodies are located in the neuronal cytoplasm and have an eosinophilic core surrounded by a clear halo ([Fig. 5.3](#)). They are now widely recognized as a major pathologic hallmark of the disorder. Lewy bodies have since been seen in autonomic ganglia, the peripheral nervous system ([Del Tredici et al., 2010](#)), and other regions of the central nervous system (CNS), including the cerebral cortex ([Jellinger, 2009a](#)) and olfactory cells ([Saito et al., 2016](#)). Biopsies of peripheral tissue, such as the gastrointestinal tract and submandibular gland, can reveal Lewy pathologic findings, and this approach has been proposed as a potential biomarker for PD ([Adler et al., 2016](#); [Stokholm et al., 2016](#); [Campo et al., 2018](#); [Shin et al., 2019](#)).

[Foix and Nicolesco \(1925\)](#) made a detailed study of the pathologic findings of PD in 1925 and found that the most constant and severe lesions are in the SN. Since then many workers, including [Hassler \(1938\)](#) and [Greenfield and Bosanquet \(1953\)](#), have confirmed these findings and added other observations, including involvement of other brainstem nuclei such as the locus ceruleus (LC) and the raphe nuclei. The pigmented cells of the LC contain neuromelanin; these cells are also lost in PD, with many of those remaining containing Lewy bodies. The asymmetry of clinical signs in PD is

reflected by the asymmetrical and more severe contralateral loss of substantia nigra pars compacta (SNc) neurons. Neuronal loss extends beyond loss in SNc, LC, and raphe, with loss of neurons in the dorsal motor vagal nucleus, hypothalamus, nucleus basalis of Meynert, and sympathetic ganglia ([Forno, 1982](#); [Jellinger, 1987](#)). There is also neurodegeneration of glutamatergic projection neurons from thalamus to the basal ganglia ([Henderson et al., 2000](#)) and glutamatergic projection neurons from the presupplementary motor cortex to the premotor cortices ([Halliday et al., 2005](#)).

PD and the Parkinson-plus syndromes have in common a degeneration of SNc dopaminergic neurons, with a resulting deficiency of striatal dopamine as a result of loss of these nigrostriatal neurons. The average number of pigmented (dopamine-containing) neurons in an 80-year-old human is 550,000; in those with PD, there is a reduction by 66% ([Pakkenberg et al., 1991](#)). The average total number of non-pigmented neurons is 260,000 in controls and reduced by 24% in the patients. Accompanying this neuronal loss is an increase in glial cells in the nigra and a loss of the neuromelanin normally contained in the dopaminergic neurons. There is also a reduction of nigral neurons and striatal dopamine with aging ([Carlsson and Winblad, 1976](#); [McGeer et al., 1977](#); [Fearnley and Lees, 1991](#)) ([Fig. 5.4](#)), and although PD is associated with increasing age, the greater rate ([Fig. 5.5](#)) and the pattern of cell loss in the SN differ between those in aging and those in PD ([Figs. 5.6 and 5.7](#)) ([Fearnley and Lees, 1991](#); [Kish et al., 1992](#)). Still, a case has been made that aging plays a primary role as a risk factor for PD, based on studies in nonhuman primates ([Collier et al., 2011](#)). Moreover, there is an inverted U-shape curve of neuromelanin content in the human SN over the life span ([Fig. 5.8](#)) ([Xing et al., 2018](#)), supporting the loss of dopaminergic neurons with age. Clinical features begin to emerge when approximately 80% of striatal dopamine content (or 60% of nigral dopaminergic neurons) is lost ([Bernheimer et al., 1973](#)). The course of clinical decline is associated with the progressive reduction

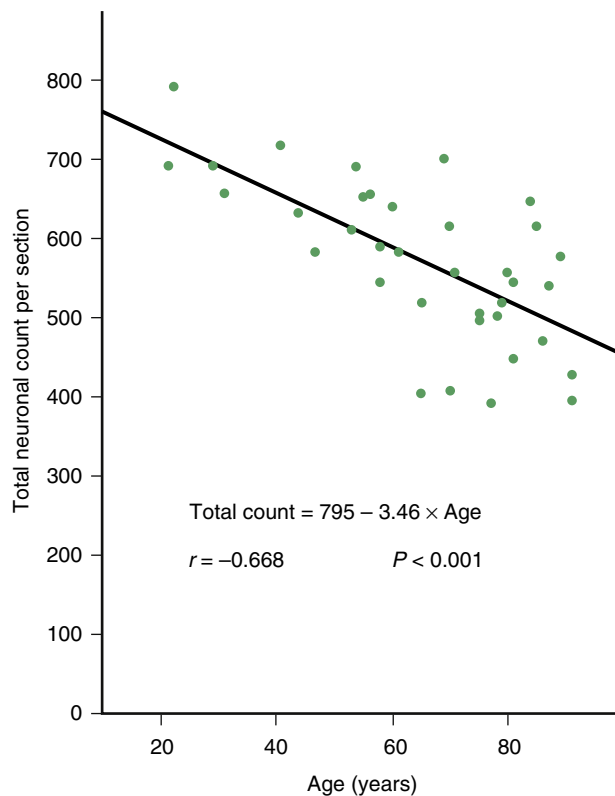


Fig. 5.4 Loss of pigmented nigral neurons with age. The total neuronal count equals the number of pigmented cell bodies in one section of the caudal substantia nigra. (From Fearnley JM, Lees AJ: Ageing and Parkinson's disease: Substantia nigra regional selectivity. *Brain*. 1991;114:2283–2301.)

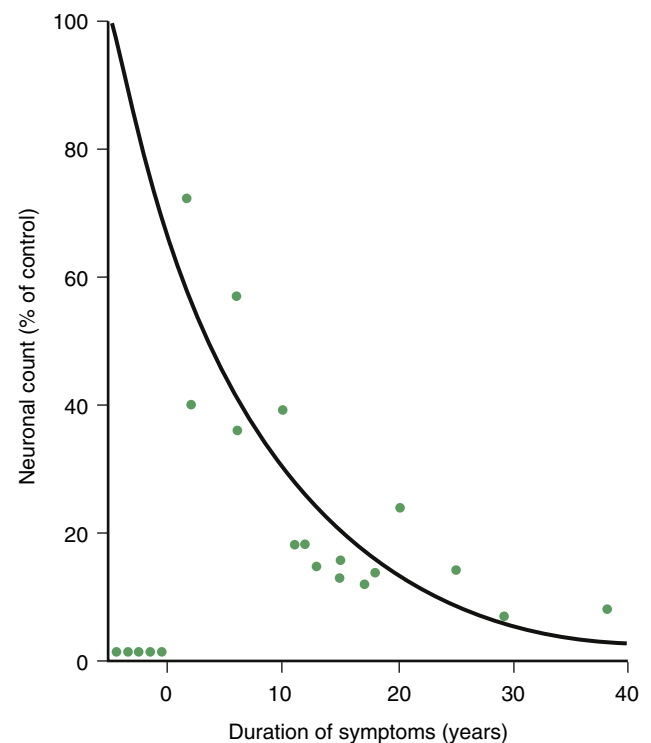


Fig. 5.5 Total pigmented nigral neurons with disease duration. (From Fearnley JM, Lees AJ: Ageing and Parkinson's disease: Substantia nigra regional selectivity. *Brain*. 1991;114:2283–2301.)

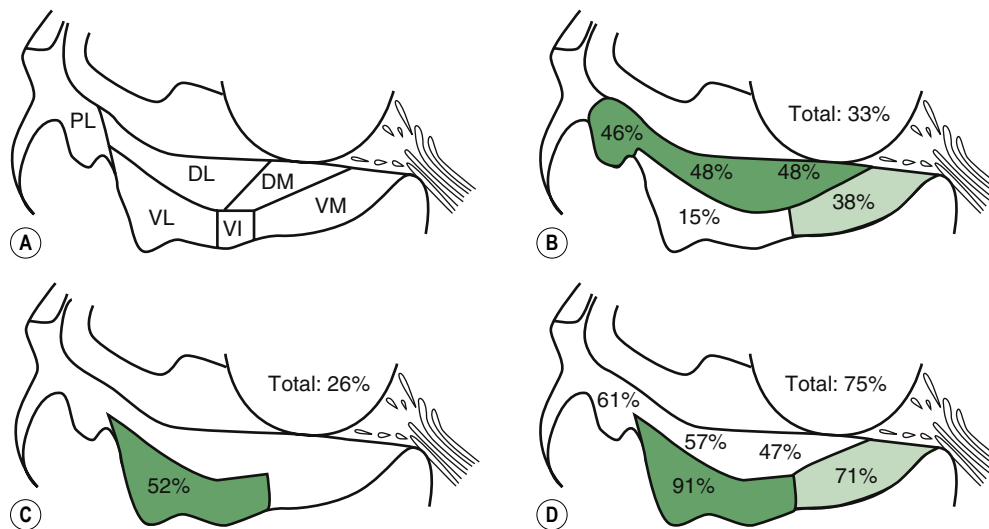


Fig. 5.6 Regional pigmented neuronal loss in aging and in Parkinson disease. (A) Normal anatomy. (B) Aging. Numbers indicate percentage of neurons lost between ages 20 and 90. (C) Incidental Lewy body disease. (D) Parkinson disease. In C and D, numbers indicate average percentage loss compared with normals. Dorsal tier: DL, lateral; DM, medial; PL, pars lateralis. Ventral tier: VI, intermediate; VL, lateral; VM, medial. (From Fearnley JM, Lees AJ: Ageing and Parkinson's disease: Substantia nigra regional selectivity. *Brain*. 1991;114:2283–2301.)

of striatal dopamine (Riederer and Wuketich, 1976). There is mounting evidence that the loss of the dopaminergic nigrostriatal neurons starts at the nerve terminals in the striatum and then dies back to involve the axons and cell bodies in the SN (Cheng et al., 2010; Burke and O'Malley, 2013; Kurowska et al., 2016; Tagliaferro and Burke, 2016; O'Keefe and Sullivan, 2018; Padmanabhan and Burke, 2018). With special magnetic resonance imaging (MRI) techniques, neuromelanin can now be assessed (Sulzer et al., 2018), and these MRI studies show reduced neuromelanin in the SN (Wang et al., 2019) and LC (Sommerauer et al., 2018).

Pathologically, almost all patients with PD have Lewy bodies in the SN and LC. Juvenile PD (Dwork et al., 1993; Hattori et al., 2000), now recognized as being the result mainly of homozygous and compound heterozygous *PRKN* mutations, is a major exception. In addition, only about two-thirds of PD patients with the LRRK2 G2019S mutation have Lewy bodies (Kalia et al., 2015). Other gene mutations in the LRRK2 gene, including the R1441G mutation (Martí-Massó et al., 2009), are less likely to have Lewy bodies (Poulopoulos et al., 2012). In one case of young-onset PD with *PINK1* mutation, the autopsy showed the presence of Lewy bodies

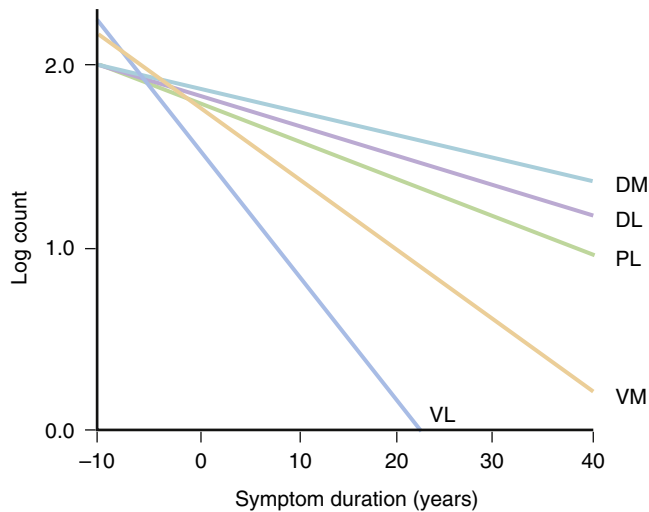


Fig. 5.7 Logarithm of regional age-adjusted neurons with PD duration. DL, Dorsal tier lateral; DM, dorsal tier medial; PL, dorsal tier pars lateralis; VL, Ventral tier lateral; VM, Ventral tier medial. (From Fearnley JM, Lees AJ: Ageing and Parkinson's disease: Substantia nigra regional selectivity. *Brain*. 1991;114:2283–2301.)

(Samaranch et al., 2010). The pathologic processes have not yet been described in juvenile PD patients with homozygous mutations in *DJ-1* genes, but there is one case of heterozygotic *DJ-1* mutation with rapid, young-onset PD developing dementia and not responding to levodopa, and who had widespread Lewy bodies (Taipa et al., 2016). Clinically, this is not similar to the juvenile onset, slowly progressive form of homozygous recessive *DJ-1* PD. There are no Lewy bodies in the Parkinson-plus syndromes or in postencephalitic parkinsonism (Jellinger, 2009b). In drug-induced parkinsonism, Lewy bodies are not seen except in some individuals with incidental Lewy bodies (Shuaib et al., 2016). In PD patients who develop dementia, Lewy bodies are seen in the cerebral cortex and in the hippocampus (Hall et al., 2014).

The presence of Lewy bodies in the SNc and the LC plus the clinical features of PD (without the characteristic clinical features of some other form of parkinsonism) are usually used to make the pathologic diagnosis of PD, but there is no complete agreement among neuropathologists about the pathologic criteria for the diagnosis of PD (Forno, 1982, 1996). Some patients with clinical PD die with nigral degeneration without Lewy bodies (Rajput et al., 1991, Hughes et al., 1992, 2002). In fact, as mentioned previously, patients with juvenile PD usually do not have Lewy bodies (Dwork et al., 1993), especially those with homozygous or compound heterozygous *PRKN* mutations (Hattori et al., 2000). Thus, Lewy bodies are a critical pathologic marker confirming the diagnosis of PD, but they are not necessarily present in all cases of PD, and their presence is not pathognomonic for PD (Forno 1982).

Lewy bodies are found in 4% to 6% of routine autopsies (Forno, 1982), the incidence rate increases with age as does PD (Fearnley and Lees, 1991) (Table 5.1), and people dying with such incidental Lewy bodies are considered to have a presymptomatic state of PD (DelleDonne et al., 2008; Dickson et al., 2008; Frigerio et al., 2011). The site of regional nigral neuronal loss in incidental Lewy body disease is the lateral region in the ventral tier, the same as for PD (see Fig. 5.6) (Fearnley and Lees, 1991). These brains show a reduction in striatal dopaminergic markers (e.g., tyrosine hydroxylase

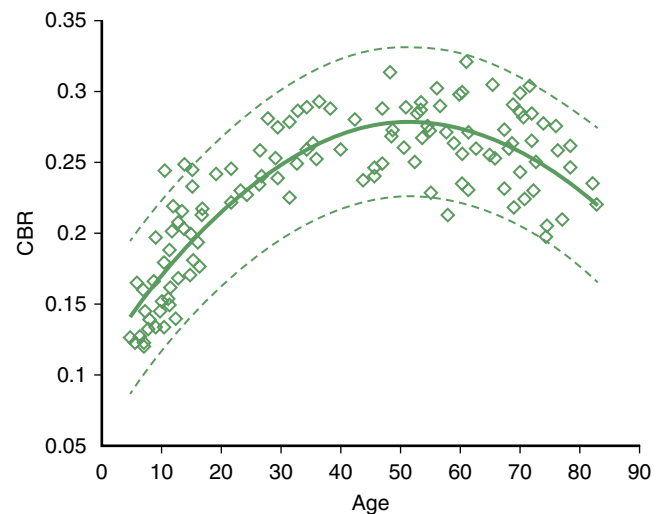


Fig. 5.8 Inverted U-shaped age effect on pigmented substantia nigra (neuromelanin). There is a rapid increase in the contrast-to-background (CBR) noise ratio up to age 20 years, with a slower increase after that, followed by a plateau around age 45 to 53 years, followed by a decline after that. (From Xing Y, Sapuan A, Dineen RA, Auer DP: Life span pigmentation changes of the substantia nigra detected by neuromelanin-sensitive MRI. *Mov Disord*. 2018;33[11]:1792–1799.)

Table 5.1 Age-specific prevalence of incidental Lewy bodies

Age	N	Percent
<20	0/2	
20–29	0/6	
30–39	0/6	
40–49	1/7	3.7
50–59	0/20	
60–69	2/51	3.9
70–79	3/56	5.4
80–89	6/49	12.2
90–99	1/8	12.5

Data from Fearnley JM, Lees AJ: Ageing and Parkinson's disease: Substantia nigra regional selectivity. *Brain*. 1991;114:2283–2301.

and vesicular monoamine transporter 2) but not as severe as those with clinical PD (DelleDonne et al., 2008; Dickson et al., 2008). Cortical Lewy bodies in patients with dementia and no parkinsonism could be a separate disease or a variant in the presentation of the same disorder that causes PD.

Lewy bodies consist of a dense granular inner core surrounded by a radiating filamentous outer zone (Fig. 5.9) and without a clear demarcating membrane separating them from the cytoplasm (Duffy and Tennyson, 1965; Forno and Dourville, 1976); they consist of a crowded aggregated protein-lipid complex (Shahmoradian et al., 2019).

The outer zone contains the protein, alpha-synuclein (Hishikawa et al., 2003), and antibodies to this protein are commonly used by neuropathologists to locate and identify Lewy bodies in brain and other tissues. Other proteins are also found in Lewy bodies, including ubiquitin and heat shock proteins (Chartier and Duyckaerts, 2018). However, the process of Lewy Body formation, rather than simply α -synuclein fibrillization, has now been directly implicated as one of the major drivers of neurodegeneration (Mahul-Mellier et al., 2020). Lewy neurites are aggregates of alpha-synuclein localized in neuronal processes. Although alpha-synuclein oligomers and fibrils are clearly

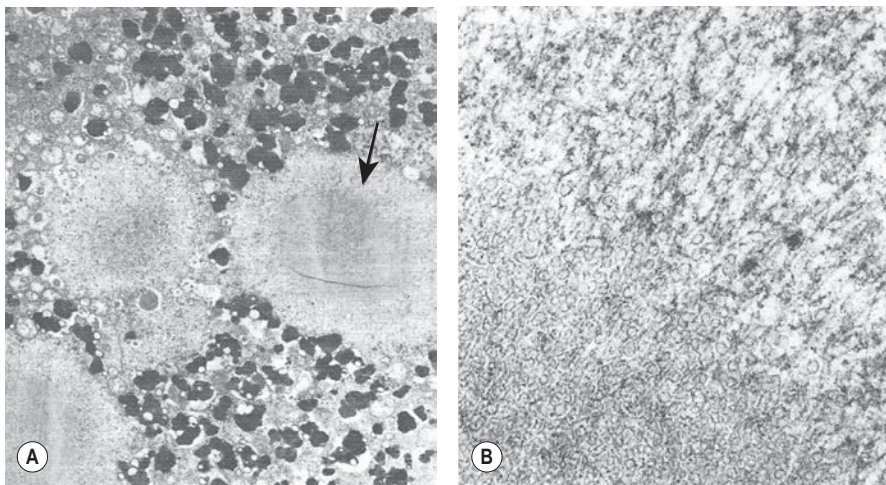


Fig. 5.9 Electron microscopic appearance of the Lewy body. There is a dense central core surrounded by radiating filamentous material. The higher density micrograph is on the right. (From Fahn S, Duffy P: *Parkinson's disease*. In Goldensohn ES, Appel SH (eds): *Scientific Approaches to Clinical Neurology*. Philadelphia, Lea & Febiger, 1977, pp. 1119–1158.)

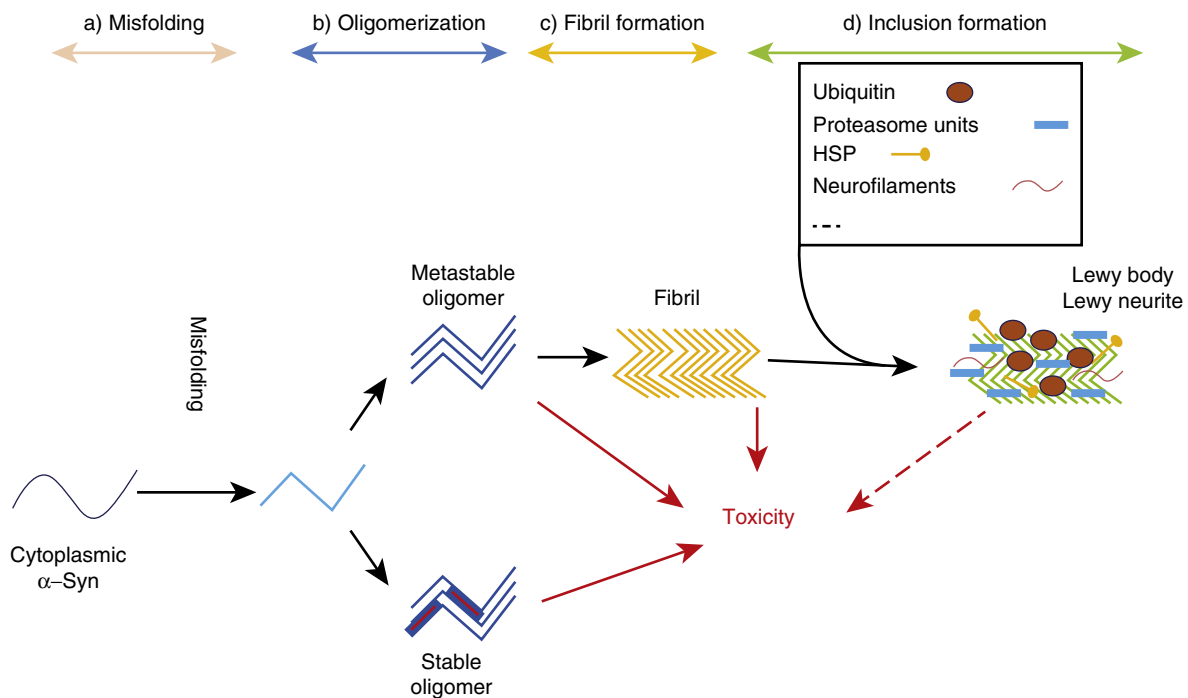


Fig. 5.10 Proposed stages in the development of Lewy bodies. The four stages are (a) misfolding of soluble monomeric alpha-synuclein (α -syn), (b) oligomerization, (c) formation of fibrils, and (d) development of cytoplasmic inclusion, the Lewy body. Oligomers can be stable or unstable, both of which can be toxic to the cell. Unstable oligomers can form fibrils, which are thought to be even more toxic than oligomers. In the formation of Lewy bodies, fibrils are joined with other proteins (ubiquitin, proteasome units, heat shock proteins [HSPs] and neurofilaments) to become incorporated into Lewy bodies and Lewy neurites, whose toxicity is uncertain. (From Chartier S, Duyckaerts C: *Is Lewy pathology in the human nervous system chiefly an indicator of neuronal protection or of toxicity?* *Cell Tissue Res*. 2018;373[1]:149–160.)

toxic (discussed in more detail later in the section of the rogue protein hypothesis), there is debate and uncertainty as to whether the Lewy body is also toxic or is a means of protection by the neuron against the toxic fibrils (Chartier and Duyckaerts, 2018). A diagram describing the relationship of natural alpha-synuclein, mostly a soluble protein in the nerve terminal cytosol, alpha-synuclein oligomers and fibrils, and Lewy bodies is presented in Fig. 5.10.

Biochemical pathologic processes of PD

The pigmented neurons of both the SNc and the ventral tegmental area (VTA) (medial to the SN in the midbrain) contain dopamine. The former neurons project to the neostriatum, the latter to the limbic system and the neocortex. In

PD, the mesolimbic and mesocortical neurons are relatively spared, whereas the nigrostriatal neurons are progressively lost. As a result, there is a corresponding decrease of dopamine content in both the nigra and the striatum, with the innervation of the posterior putamen affected first and most severely, as can be detected in 6- ^{18}F -fluoro-L-dopa (FDOPA) positron emission tomography (PET) scans (Fig. 5.11) and in dopamine transporter (DAT) single-photon emission computed tomography (SPECT) scans. Whereas dopamine is reduced initially in the posterior striatum in PD, over time, as the disease progresses, all striatal subregions are affected to a similar extent (Nandhagopal et al., 2009).

The pigmented neurons of the LC contain norepinephrine, and these neurons project widely in the CNS. A third set of monoaminergic neurons are those containing serotonin

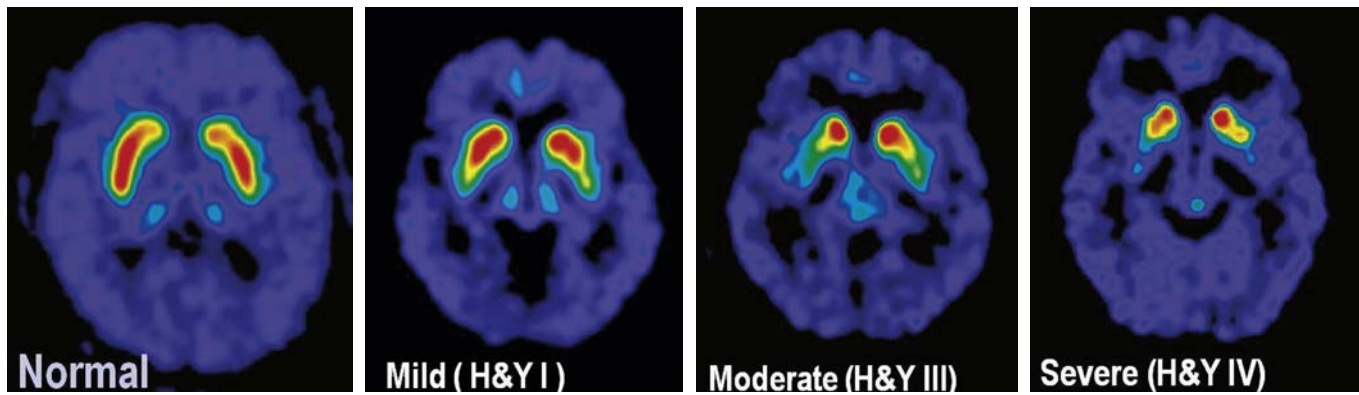


Fig. 5.11 Examples of FDOPA PET scans with clinical progression of PD. FDOPA uptake is reduced in a progressive pattern, first and most severely in the posterior putamen, then the anterior putamen, and finally the caudate nucleus. In the most severe state shown here, there is still FDOPA uptake in the caudate nucleus. H&Y, Hoehn and Yahr stage. (Courtesy David Eidelberg, MD.)

Table 5.2 Concentration of neurotransmitters, their metabolites, and synthesizing enzymes in selected regions of brain of controls and PD

Brain Region	DA	HVA	NE	5-HT	GAD	CAT
Putamen						
Controls	5.06	4.92	0.10	0.32	622	1656
PD	0.14	0.54	0.05	0.14	292	780
Caudate						
Controls	4.06	2.92	0.09	0.33	659	1460
PD	0.20	1.19	0.04	0.12	321	694
Globus pallidus						
Controls	0.5	2.92	0.06	0.23	553	231
PD	0.2	0.72	0.05	0.13	388	39
Substantia nigra						
Controls	0.46	2.32	0.23	0.55	637	63
PD	0.07	0.41	0.11	0.26	263	12
Nucleus accumbens						
Controls	3.79	4.38	1.29	—	—	—
PD	1.61	3.13	0.52	—	—	—

All results are mean values. Results of the monoamines and HVA are means expressed as $\mu\text{g/g}$ wet tissue. Results of GAD activity are expressed as $\text{nmol}/\text{CO}_2/\text{h}/\text{mg}$ protein. Results of CAT activity are expressed as $\text{pmol}/\text{min}/\text{mg}$ protein.

CAT, Cholineacetyltransferase; DA, dopamine; HVA, homovanillic acid, a metabolite of DA; NE, norepinephrine; 5-HT, serotonin; GAD, glutamic acid decarboxylase.

Data from Hornykiewicz O: Brain neurotransmitter changes in Parkinson's disease. In Marsden CD, Fahn S (eds): Movement Disorders. London, Butterworth Scientific, 1982, pp. 41–58).

(5-hydroxytryptamine [5-HT]), located in the raphe of the pons and medulla. In PD a progressive loss of all three types of monoaminergic cells occurs, most severely in the dopaminergic cells. So, in addition to a depletion of striatal dopamine, there is also a reduction in brain norepinephrine and 5-HT (Ehringer and Hornykiewicz, 1960; Hornykiewicz, 1966) (Table 5.2). There is also reduction in other neurotransmitters (Agid et al., 1987) and enzyme activities for the synthesis of other neurotransmitters (see Table 5.2), indicating the biochemical changes in PD extends beyond the loss of only the monoamines.

In addition to the cardinal motor features of PD, such as rest tremor, bradykinesia, rigidity, and postural instability that define the clinical diagnosis, there are also a host of non-motor symptoms, some occurring before the motor symptoms and some occurring after (see Chapter 8). The early motor symptoms of bradykinesia and rigidity and tremor are associated with monoaminergic cell and neurotransmitter loss. The later motor symptoms of flexed posture, loss of postural reflexes, and the freezing phenomenon appear

to correlate poorly with dopaminergic deficit, and are likely associated with involvement of other brain structures. For example, the pedunculopontine nucleus has been suggested to play a role in freezing of gait (Kuo et al., 2008). The non-motor symptoms probably are the result of loss of neuronal function other than dopamine. Catecholamine reduction in PD is seen in the autonomic nervous system and accounts for the reduction in ^{123}I -metaiodobenzylguanidine (MIBG) SPECT scan labeling in the heart in PD because of loss of postganglionic myocardial sympathetic nerve fibers (Rascol and Schelosky, 2009). Other imaging techniques to detect impairment of the autonomic nervous system have also been studied (Knudsen and Borghammer, 2018). A noradrenergic transporter PET ligand showed reduced uptake in PD and even more so in patients who also had rapid eye movement (REM) sleep behavior disorder (RBD) (Sommerauer et al., 2018). A neuropathological study combined with good clinical data found no correlation of clinical orthostatic hypotension in people with PD and the degree of neuronal loss in the SN or LC (Tong and Chen, 2021).

Among the neurotransmitter changes is the reduction of brain acetylcholine (Bohnen and Albin, 2010). Acetylcholinesterase (AChE), which serves as a marker for cholinergic neurons, can be measured by PET scanning (Shimada et al., 2009). A reduction of AChE begins early in PD (Bohnen and Albin, 2009). Reduced thalamic AChE activity correlates with falling in PD (Bohnen et al., 2009), and in part represents decreased cholinergic output of the pedunculo-pontine nucleus (PPN), which appears to be important for gait. Cortical loss of acetylcholine probably contributes to the dementia seen in PD (Shimada et al., 2009; Bohnen and Albin, 2010; Nahimi 2015). Overall, reduced AChE is more widespread and profound in both PD with dementia and in dementia with Lewy bodies (Shimada et al., 2009).

With the loss of striatal dopamine, there are compensatory changes, such as supersensitivity of dopamine receptors, so that symptoms of PD are first encountered only when there is about an 80% reduction of dopamine concentration in the putamen (or a loss of 60% of nigral dopaminergic neurons) (Bernheimer et al., 1973). Another compensatory mechanism is an increase in neurotransmitter turnover, as detected by an increased ratio of homovanillic acid (HVA) to dopamine. In a major review, Hornykiewicz (1966) correlated loss of dopamine concentration in the striatum with severity of bradykinesia and rigidity in PD. With further loss of dopamine concentration, parkinsonian bradykinesia becomes more severe. The progressive loss of the dopaminergic nigrostriatal pathway can be detected during life using PET and SPECT scanning (see Fig. 5.9); these show a continuing reduction of FDOPA and DAT ligand binding in the striatum that correlates with the bradykinesia score in the Unified Parkinson's Disease Rating Scale (UPDRS) (Brooks et al., 1990; Snow et al., 1994; Seibyl et al., 1995; Morrish et al., 1996; Vingerhoets et al., 1997; Broussolle et al., 1999; Benamer et al., 2000). Using special statistical techniques, fluorodeoxyglucose (FDG) PET also shows a correlation between worsening bradykinesia and increase of lentiform metabolism (Eidelberg et al., 1995). In fact, using FDG PET demonstrates a metabolic network characteristic of PD compared with other forms of parkinsonism (Hirano et al., 2009; Tang et al., 2010).

Interconnected pathogenic mechanisms of PD

The best correlation of symptoms with progressive loss of striatal dopamine are those of bradykinesia and rigidity, which relate to striatal dopamine deficiency and loss of SNc dopaminergic neurons and can be correlated with a progressive decrease of dopaminergic imaging by PET or SPECT (see earlier discussion). These symptoms are two of the cardinal features of the disease; therefore, research efforts have concentrated on the pathogenic mechanisms that cause loss of the nigrostriatal dopamine system, and this will be reflected in this review. Similar mechanisms might involve the other monoaminergic systems (noradrenergic and serotonergic). It seems likely that loss of these other monoamines might be instrumental in the high rate of depression (Mayeux et al., 1984) and anxiety in patients with PD. There is little knowledge of the pathogenesis of neuronal loss of nonaminergic neurons, except that toxic forms of alpha-synuclein, referred to here as a rogue protein, can spread from cell to cell and eventually cause cell death, mostly by a death process called

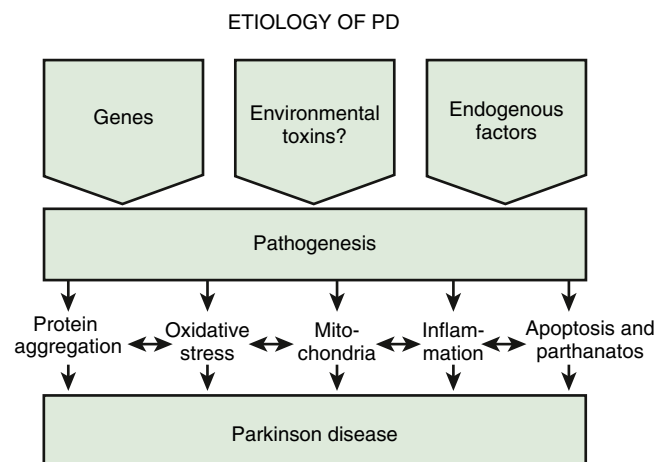


Fig. 5.12 Pattern of etiologic and pathogenic factors leading to dopamine neuron loss and the clinical motor features of PD.

parthanatos (described later). In addition, little is known about the anatomic or biochemical associations for most clinical features of the disease, including motoric features of tremor, freezing, flexed posture, loss of postural reflexes, and the multitude of nonmotor features.

A variety of pathogenic mechanisms have been uncovered for the loss of dopamine neurons, and probably more will be uncovered. The reader is referred to reviews on this topic for details (Dauer and Przedborski, 2003; Jenner and Olanow, 2006; Gupta et al., 2008; Sulzer and Surmeier, 2013; Obeso et al., 2017; Poewe et al., 2017; Surmeier et al., 2017). With the development of genetic causes of PD, a multiple-hit hypothesis was proposed by Sulzer (2007) and is discussed later in this chapter. Evidence has accumulated over decades from pathologic and biochemical findings that implicate oxidative stress, mitochondrial dysfunction, excitotoxicity, inflammation, and apoptosis as taking place in the SNc (Fig. 5.12).

More recently, alpha-synuclein aggregation has taken center stage both in the progressive worsening of PD spreading from the SN to involve other parts of the brain and in the mechanism of cell death (Wong and Krainc, 2017). The mechanism of cell death in PD was previously considered to be by the process of apoptosis, but is currently considered to be mainly by parthanatos (David et al., 2009), which is discussed later. Alpha-synuclein can convert from a soluble monomer to form toxic oligomers and fibrils, and then Lewy bodies and Lewy neurites. New research on alpha-synuclein has placed a major emphasis on the accumulation of toxic protein as perhaps the most important pathogenic factor. The spread of the toxic fibrils of alpha-synuclein likely contributes to the worsening of PD, with more symptoms developing over time as more neurons are affected and die. Alpha-synuclein fibrils has become a rogue protein, or prion-like, in that when it leaves one neuron and enters an adjacent one, the rogue protein can convert natural alpha-synuclein of the newly invaded cell into a toxic form, hence considered prion-like. Each of the factors in Fig. 5.12 cross-interacts with the others to add to the pathogenesis of cell death. The understanding of alpha-synuclein becoming a rogue protein has led to the development of potential disease-modifying strategies (Jankovic, 2019).

How are the toxic forms of alpha-synuclein initially generated? One mechanism is by the mutated gene (*SNCA*) that generates a form of alpha-synuclein that cannot be autophagotized, so it accumulates (Cuervo et al., 2004). Other mechanisms are by excessive synthesis (by duplication and triplication of the *SNCA* gene) (Singleton et al., 2003). Excessive monomeric alpha-synuclein can oligomerize starting the process to generate the toxic forms of the protein. There could be a deficit of insufficient degradation (i.e., inadequate autophagy) of alpha-synuclein (Wong and Krainc, 2017). There is also much interest that alpha-synuclein enters the brain through the olfactory system or the gut via the vagus nerve terminals there. This chapter will provide more details on these processes of pathogenesis.

Of all the etiologic and pathogenic factors discussed so far and others to be discussed later, why is the nigrostriatal dopaminergic neuron particularly affected in PD, so-called selective vulnerability? There are a number of unique factors with these neurons, a leading one being high exposure to oxidative stress due to the enzymatic and auto-oxidation of dopamine.

These neurons are autonomously paced around 2 Hz, so they are continuously using a high amount of energy. These neurons are extremely highly branched with huge numbers of nerve terminals for each neuron, and the neuron is unmyelinated, which may make it more susceptible. These factors are discussed in the next section.

Oxidative stress

Why is the nigrostriatal dopaminergic neuron particularly affected in PD? A common source of oxidative stress in all cells is via normal mitochondrial function. A key source of additional oxidative stress in monoaminergic neurons is via monoamine metabolism and auto-oxidation (discussed in more detail later in the Endogenous Factors section). Because most research in PD neurodegeneration has been applied to dopaminergic neurons, we will focus on dopamine. Another factor leading to increased oxidative stress in SNc dopaminergic neurons is the influx of calcium into the cytosol because of the opening of L-type calcium channels during autonomous pacemaking, resulting in greater production of reactive oxygen species by the mitochondria (Surmeier et al., 2011) (discussed in more detail later in the Endogenous Factors section). An important element of the nigrostriatal dopamine neuron, making it quite susceptible to oxidative damage, is the neuron's unique anatomic features of being poorly myelinated and with very long, highly branched axons and terminals (Fig. 5.13) (Matsuda et al., 2009).

Antioxidant defenses protect cells, and one of the leading antioxidants is reduced glutathione (GSH), and this is diminished in the SNc of PD patients at postmortem (Perry et al., 1982; Sian et al., 1994). This reduction of GSH is specific to PD brains and is not seen in atypical parkinsonisms with nigral degeneration. The reduction of GSH likely reflects an excess usage of this reducing agent, implying a high degree of oxidative stress taking place there. The decrease in GSH in the SNc occurs in incidental Lewy bodies and in PD, suggesting that oxidative stress has occurred before nerve cell loss. Some evidence suggests that GSH depletion itself may play an active role in PD pathogenesis

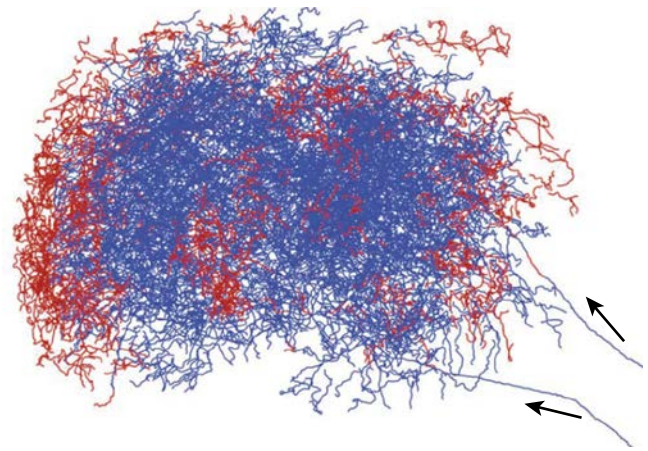


Fig. 5.13 The widespread arborization of two nigrostriatal neurons (one red, the other blue) in the rat. (From Matsuda W, Furuta T, Nakamura KC, Hioki H, Fujiyama F, Arai R, et al: Single nigrostriatal dopaminergic neurons form widely spread and highly dense axonal arborizations in the neostriatum. *J Neurosci*. 2009;29[2]:444–453.)

(Martin and Teismann, 2009). It should be mentioned that intranasal but not intravenous GSH administration can enter the brain, but a small clinical trial showed no clinical benefit (Mischley et al., 2015). Iron accumulation in the nigra also contributes to oxidative stress (Dexter et al., 1989a). Oxidized products of lipids, DNA, and protein are seen in PD nigra (Dexter et al., 1989b; Sanchez Ramos et al., 1994), providing postmortem evidence of oxidative stress. Neuromelanin in dopamine neurons is derived mainly from the condensation of oxidized dopamine products and thus represents a protective mechanism by the cell to defend against oxidative stress (Sulzer et al., 2004). One of the mutant genes that can cause PD, *DJ-1*, functions normally to protect against oxidative stress and is discussed later in the section on Genetics.

It is of interest that an endogenous substance, uric acid, which has antioxidant properties, has been correlated with a reduction in developing PD (Weisskopf et al., 2007). Subsequent studies evaluating urate levels in plasma in the PRECEPT (Schwarzschild et al., 2008) and cerebrospinal fluid (CSF) in the DATATOP (Ascherio et al., 2009) clinical trials found that higher urate levels in men were associated with a slower rate of progression of PD. Treatment with urate's precursor, inosine, was tested in a controlled clinical trial as a therapeutic agent for PD. Unfortunately, as announced in a press release, inosine did not slow the progression of PD (<https://www.michaeljfox.org/foundation/news-detail.php?parkinson-inosine-trial-ending-early>). Furthermore, the De Novo Parkinson Cohort (DeNoPa) study showed that elevated uric acid, in addition to other factors, was associated with faster disease progression in PD (Mollenhauer et al., 2019). Other antioxidants have been studied, but most have been ineffective, including high-dosage tocopherol (vitamin E) (Parkinson Study Group, 1993) and high-dosage coenzyme Q10 (Parkinson Study Group QE3 Investigators, 2014).

Of all the antioxidant type drugs tested, only the type B monoamine inhibitors, such as selegiline and rasagiline, have shown the ability to reduce PD signs and symptoms, and this topic is covered in Chapter 6.

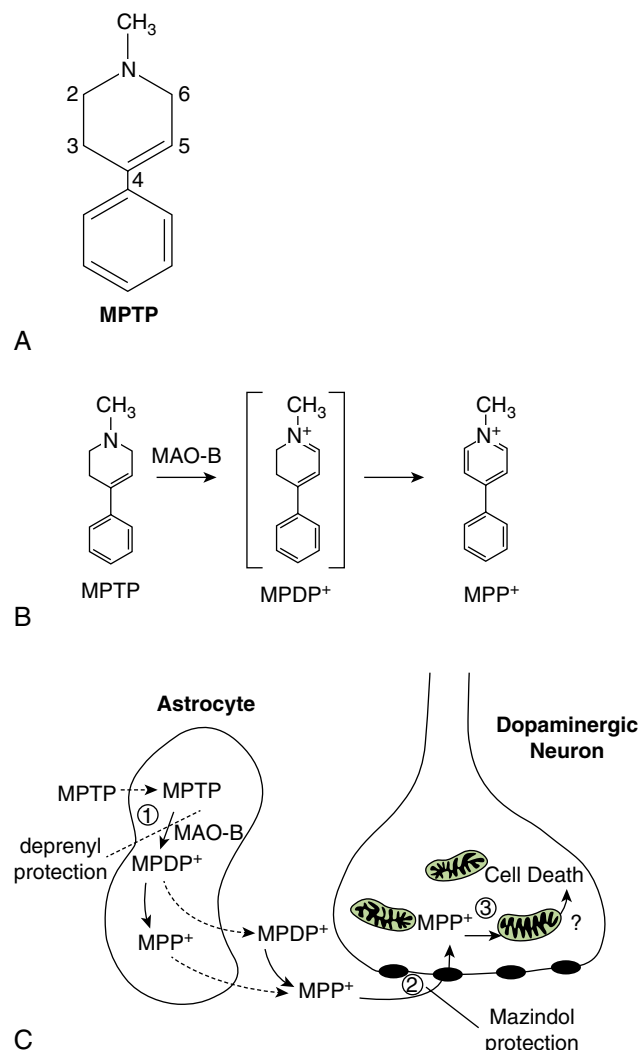


Fig. 5.14 (A) The chemical structure of MPTP. (B) The conversion of MPTP to MPP⁺, which is the charged molecule taken up by the dopamine transporter into dopamine neurons and then acts as a toxin to the cells mitochondria, shown in (C). MAO-B, Monoamine oxidase B; MPDP⁺, 1-methyl-4-phenyl-2,3-dihydropyridinium; MPP⁺, 1-methyl-4-phenylpyridinium; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

Mitochondrial dysfunction

Mitochondria appear to play an important role in the pathogenesis of PD (Banerjee et al., 2009). The finding that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) intoxication causes parkinsonism (Langston et al., 1983), and the discovery that MPTP selectively destroys dopamine neurons and impairs complex 1 activity in the mitochondria (Nicklas et al., 1987) led to studying mitochondria in PD patients (Fig. 5.14). Decreased complex 1 activity is seen in the SNc of PD brains and not elsewhere nor in other forms of parkinsonism (Mizuno et al., 1989; Schapira et al., 1990). Another complex 1 toxin, rotenone, which is a commonly used pesticide, also damages SNc neurons in animals (Betarbet et al., 2000). We will see later, when discussing the role of gene mutations in PD, that the proteins from four genes, *PRKN*, *PINK1*, *DJ-1*, and *VPS13C*, related to PD, help maintain the integrity and healthy function of the mitochondria, and loss of function of these genes results in PD. Mitochondrial

dysfunction impairs adenosine triphosphate (ATP) production, which hinders energy-dependent mechanisms in cells.

Mitochondrial dysfunction can be both a cause and a consequence of oxidative stress. Deregulation of mitochondrial respiration leads to generation of reactive oxygen species, contributing to oxidative stress, and oxidative and nitrosative stress deteriorate mitochondrial function. An early event in MPTP toxicity is oxidative stress, which is the consequence of an inability to transport electrons because of the inhibition of mitochondrial complex 1. The accumulating electrons are a source of oxidative stress (Zhou et al., 2008). Besides their role in electron transport and oxidative phosphorylation, mitochondria are a major cellular source of free radicals, affect calcium homeostasis, and instigate cell-death pathways via apoptosis (Henchcliffe and Beal, 2008; Schapira, 2008).

PARP and cell death by parthanatos

In addition to necrosis and apoptosis, parthanatos is another form of cell death. The term was coined to combine PAR and Thanatos, the personification of death in Greek mythology (David et al., 2009). PAR is the shorthand name for poly(adenosine diphosphate [ADP]-ribose), a polymer required in this form of cell death (along with another requirement, apoptosis-inducing factor).

When mitochondria are damaged, as discussed in the previous section, they release a mitochondrial protein called apoptosis-inducing factor (AIF). AIF enters the cytosol and then into the cell's nucleus to trigger a caspase-independent pathway of cell death, known as parthanatos. (The programmed cell death pathway known as apoptosis is caspase-dependent and is triggered by the release of cytochrome c from the mitochondria). AIF is activated in the nucleus by PAR to initiate DNA fragmentation and chromatin condensation, leading to cell death. This is a common cell death pathway in stroke, diabetes, and myocardial infarction (Fatokun et al., 2014). It is now considered the most common cell death pathway in PD. PAR is a polymer of various lengths and can be linear or branched. PAR is generated by the nuclear enzyme poly(ADP-ribose) polymerase-1 (PARP-1). PARP-1 catalyzes the transfer of ADP-ribose units from nicotinamide adenine dinucleotide (NAD) to protein targets. A normal function of PARP-1 is the repair of DNA breaks. Parthanatos also can be triggered by DNA damage, initiating activation of PARP-1 to generate PAR. PAR then leaves the nucleus to enter the cytosol and then into mitochondria, where it causes the release of AIF. Thus, there is a reciprocal mechanism between PAR and AIF. PAR is degraded by the enzyme poly(ADP-ribose) glycohydrolase (PARG) (Fatokun et al., 2014).

In 1999 the Dawson group discovered that MPTP-treated mice developed a high level of PARP in the brain (Mandir et al., 1999). In a subsequent experiment, they genetically engineered mice to disable the production of PARP and found that the ability of MPTP to destroy dopamine neurons was virtually eliminated. The investigators suggested that PARP inhibitors might be a useful treatment for people with PD. Japanese investigators in 2004 tested a PARP inhibitor in the MPTP mouse model and showed striking ability to reduce the degeneration of nigral neurons (Iwashita et al., 2004). Around the same time, postmortem studies showed that people with PD had increased levels of PARP in the brain

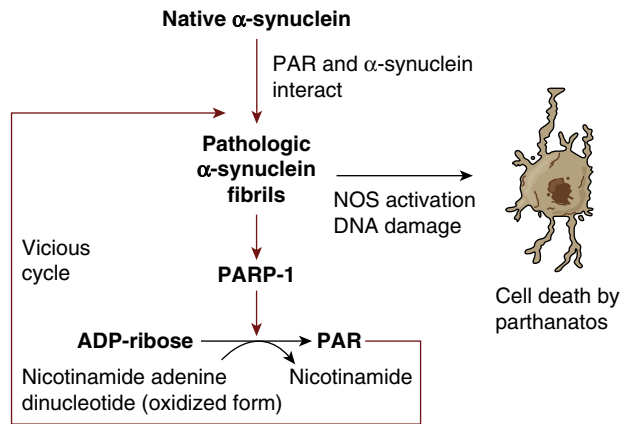


Fig. 5.15 Vicious cycle of poly(ADP-ribose) polymerase (PARP) activity in Parkinson disease. PARP-1 produces poly(adenosine diphosphate [ADP]-ribose) (PAR), which accelerates the fibrilization of alpha-synuclein and triggers parthanatos, a PARP-dependent form of cell death. This may contribute to the progressive neurodegeneration observed in PD. NOS, Nitric oxide synthase. (From Brundin P, Wyse R: *Cancer enzyme affects Parkinson's disease. Science*. 2018;362[6414]:521–522.)

(Soós et al., 2004). In 2018 the Dawson group reported that in the animal model in which preformed alpha-synuclein fibrils are injected to induce the spread of the toxic alpha-synuclein to cause neuronal death via parthanatos and loss of dopamine neurons, there is activation of PARP-1 and generation of PAR. Both PARP inhibitors and genetic deletion of PARP-1 prevented this pathologic process (Kam et al., 2018). They also showed that the presence of PAR converted pathologic alpha-synuclein to a more toxic strain, which allows for a vicious cycle whereby toxic fibrils induce PARP-1 activation, which generates PAR that in turn eventually makes the toxic fibrils even more toxic (Fig. 5.15). The investigators also measured PAR levels in autopsied brains and in the CSF of patients with PD and found elevated levels in both tissues. This suggests that PARP activation plays a role in PD pathogenesis. PARP inhibitors, already used in cancer therapy, should be tested in PD, but those currently on the market do not penetrate into the brain. Appropriate drugs will need to be developed (Thapa et al., 2021).

Calcium

Whereas most neurons in the CNS fire their action potential with the sudden influx of sodium ions, the adult SNc neurons use the influx of calcium ions as the generator of their action potential (Surmeier, 2007; Surmeier et al., 2016). Evidence indicates that the increase of intracellular calcium in these neurons plays a role in their susceptibility to cell death. This topic is discussed in more detail in the discussion of endogenous factors contributing to the selective vulnerability of dopaminergic neurons in the SNc.

Aggregation of alpha-synuclein to form toxic (rogue, prion-like) proteins

Alpha-synuclein plays a central role in the majority of people with PD. This discovery stemmed from the discovery that the mutated gene for alpha-synuclein can cause autosomal dominant PD (Polymeropoulos et al., 1997), discussed later

in the Genetics section. The protein is present in Lewy bodies (Spillantini et al., 1997) and in dementia with Lewy bodies (DLB), and in multiple system atrophy (MSA). Subsequent investigations elicited the properties of the protein, finding that the soluble monomeric form can combine into oligomers, and these in turn can form amyloid fibrils. It is the fibrillary form that is found in Lewy bodies and Lewy neurites. Braak and colleagues (2006), by studying postmortem cases of non-PD individuals, found deposition of Lewy neurites, which were usually first seen in the olfactory bulb and in the dorsal motor nucleus of the vagus. After these regions encompassed the Lewy neurites, adjoining regions also began accumulating them. When Lewy bodies were found in some implanted fetal dopamine neurons in some long-term survivors of fetal cell implants, the idea arose that forms of alpha-synuclein can be a prion-like protein (Li et al., 2008; Kordower et al., 2008). Then studies in tissue culture showed that alpha-synuclein fibrils can transfer from cell to cell, followed by studies in rodents in which preformed fibrils injected into brain resulted in the spreading of Lewy pathologic findings and cell death (Luk et al., 2012). A possible mechanism of cell death has now been elucidated by the finding that the fibrils activate PARP-1 to generate PAR, resulting in PAR-mediated cell death or parthanatos (Kam et al., 2018). The parthanatos story was discussed earlier, and the details of alpha-synuclein will be discussed in more detail in the section on alpha-synuclein as a rogue protein.

Unwanted proteins that are misfolded, oxidized, or nitrosylated need to be repaired or eliminated from the cell before they accumulate and damage the cell. Initially, the cell attempts to repair the damaged protein via chaperone-mediated mechanisms. If repair is not successful, elimination would proceed through degradation by the ubiquitin-proteasomal system (UPS) or by autophagy via the lysosome (Kopito, 2000; Pan et al., 2008). Autophagy appears to play a major role in removing alpha-synuclein and other unwanted proteins. This mechanism is described later in this chapter.

A host of etiologic factors trigger the various pathogenic mechanisms discussed earlier, with genetic, environmental, and endogenous factors being suspected as major players. An interaction between genes and the other two seem important; that is, certain gene mutations act to increase susceptibility to neuronal damage.

Other mechanisms

Excitotoxicity from excessive glutamatergic activity results in an increase in intracellular calcium and can damage mitochondria; this has been implicated in PD (Beal, 1998). Parthanatos is the death pathway. Nitrosative stress is induced by nitric oxide forming peroxynitrite, leading to protein nitration, and has also been suggested as a pathogenic factor (Tsang and Chung, 2009). Inflammation is seen in PD SN (McGeer et al., 1988a,b) but is not considered an early event (Zhou et al., 2008). Rather, inflammation appears to augment the continuing degeneration (Tansey et al., 2007; Hirsch and Hunot, 2009; Saijo et al., 2009; Przedborski, 2010). Apoptosis was thought to represent the cellular death mechanism in PD (Mochizuki et al., 1996; Hirsch et al., 1999), but now parthanatos is considered the major pathway (David et al., 2009).

Genetics as an etiologic factor of PD

Familial PD

Families with PD occurring in several members have been recognized over the years, with approximately 10% of newly diagnosed patients reporting someone else in the family having PD. [Allen \(1937\)](#) was one of the first to describe the occurrence of PD in family members. Perhaps the largest pedigree of PD described to date and with many generations affected was that reported by Mjones (1949) of a Swedish and Swedish American family. He found an autosomal dominant inheritance pattern in this family with 60% penetrance. Subsequently, the genetic alterations in this family were found to be triplications and duplications of the synuclein gene, *SNCA* ([Fuchs et al., 2007](#)). But, generally, because most PD patients have a sporadic occurrence without a positive family history, the disease was for over 100 years not thought to have a genetic cause.

Twin Studies

To study the possibility of a genetic cause of PD, though, [Duvoisin, Eldridge, and colleagues \(1981\)](#) evaluated twins with PD. They found zero concordance in 12 monozygotic twin pairs and concluded that “genetic factors appear not to play a major role in the etiology of PD.” This group ([Ward et al., 1983](#)) continued to analyze twin pairs and subsequently in 43 monozygotic (MZ) and 19 dizygotic (DZ) pairs, with the index case having definite PD, the frequency of PD in MZ twins was similar to that expected in an unrelated control group matched for age and sex. The authors again concluded that “the major factors in the etiology of PD are nongenetic.” A Finnish twin study 5 years later ([Martilla et al., 1988](#)) also found low concordance in MZ twin pairs and also concluded that PD appears to be “an acquired disease not caused by a hereditary process.” However, Bill Johnson, then at Columbia University, began to question the conclusions of the twin studies ([Johnson et al., 1990](#)), saying they were too small to be statistically conclusive and recommended that linkage studies be conducted. A subsequent twin study found that twins with a young onset of PD had a higher concordance rate in MZ twins than in dizygotic twins, but the difference was lost in twins with an older age at onset ([Tanner et al., 1999](#)). One possible explanation of discordance in MZ twins was the finding there was decreased mitochondrial functionality and a tendency for a higher number of somatic mtDNA variants among the affected MZ twins ([Dulovic-Mahlow et al., 2021](#)).

The momentum toward a genetic cause of PD

In 1990, Golbe, Duvoisin, and colleagues described a large kindred with autosomal dominant PD originating in Contoursi, Italy, with some of the family having emigrated to the United States ([Golbe et al., 1990](#)). This led Duvoisin to rethink his previous conclusions that PD is largely nongenetic (Duvoisin and Johnson, 1991). At this time there were also reports that FDOPA PET scans can detect decreased FDOPA uptake in some nonaffected relatives, including twins with an affected co-twin ([Brooks, 1991](#)). A large PET study in twins indicated that the concordance for decreased striatal FDOPA uptake in PD twins is greater than previously realized ([Burn et al., 1992](#)). With the availability of

the Contoursi kindred and with the tools of linkage analysis, the stage was set for finding a gene mutation in familial PD.

Finding the first gene mutation in PD

Linkage analysis was carried out on the Contoursi kindred, and after several years of searching, linkage to chromosome 4q21-q23 was found ([Polymeropoulos et al., 1996](#)). By the next year, [Polymeropoulos and colleagues \(1997\)](#) identified the mutated gene, *SNCA*, for the protein alpha-synuclein. The Contoursi family actually originated in Greece and immigrated to Italy. The mutation seen in this family (Ala53Thr) was also found in three small, unrelated Greek families. Subsequently, five other mutations were found in *SNCA*, all of which also caused autosomal dominant PD, namely Ala30Pro, in a German family ([Krüger et al., 1998](#)), Glu46Lys in a Spanish family ([Zarranz et al., 2004](#)), Gly51Asp in a French family ([Lesage et al., 2013](#)) and a British family ([Kiely et al., 2013](#)), His50Gln in two unrelated people of English descent ([Appel-Cresswell et al., 2013](#); [Proukakis et al., 2013](#)), and Ala53Glu in Finnish families because of a founder effect ([Pasanen et al., 2014, 2016](#)).

Families with *SNCA* mutations have a younger age at onset (usually in their 40s), a more rapidly worsening course of PD, and also some early cognitive impairment. So, the gene mutation, on average, causes a more severe form of the disease than the typical adult-onset sporadic case. The *SNCA* gene was originally labeled PARK1.

Although all these *SNCA* mutations are rare in causing all worldwide cases of both familial and sporadic PD, the protein alpha-synuclein has taken on a premier and most important role as being highly likely involved in the disease's pathogenesis, including the sporadic cases. Immediately after the gene mutation was discovered ([Polymeropoulos et al., 1997](#)), [Spillantini and colleagues \(1997\)](#) found that fibrillary alpha-synuclein is a major component of the Lewy body, a finding confirmed the following year ([Mezey et al., 1998](#)). By good fortune, the Goedert laboratory of protein chemistry had been studying alpha-synuclein and even had generated antibodies against it. When the Polymeropoulos paper was published, the Goedert laboratory immediately decided to apply their alpha-synuclein antibody to autopsied tissue from patients with PD and discovered that Lewy bodies contain alpha-synuclein ([Spillantini et al., 1997](#)).

In fact, staining microscopic brain slices with the antibody for alpha-synuclein has become the pathologist's tool to detect Lewy bodies and probably accounts for the recognition that diffuse Lewy body disease (DLBD), also known as dementia with Lewy bodies (DLB) and Lewy body dementia (LBD), is the second most common cause of dementia after Alzheimer disease (AD). Before staining for alpha-synuclein, ubiquitin antibodies had been used because ubiquitin is another protein found within the Lewy body. Ubiquitin is located in the central core and alpha-synuclein in the surrounding halo ([Fig. 5.16](#)). Autopsies on patients with mutated or excessive amounts of alpha-synuclein show an abundance of Lewy bodies ([Seidel et al., 2010](#)).

Phosphorylation of alpha-synuclein at Ser129 promotes insoluble fibril formation, and the alpha-synuclein found in Lewy bodies is phosphorylated at Ser129 ([Anderson et al., 2006](#)). It appears that when cytosolic alpha-synuclein becomes phosphorylated, it eventually becomes incorporated into Lewy neurites and Lewy bodies.

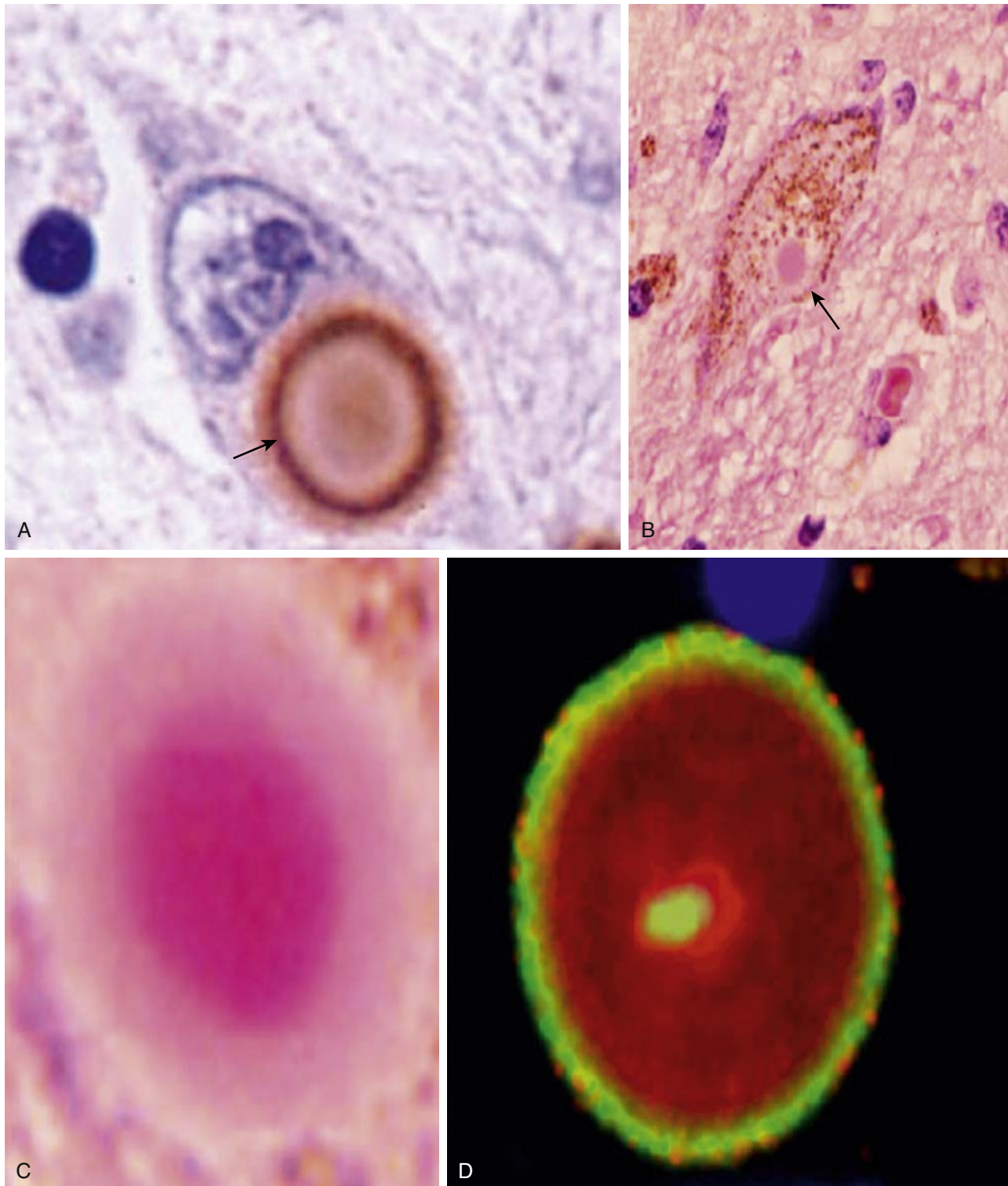


Fig. 5.16 Depictions of alpha-synuclein in substantia nigra (SN) Lewy body. (A) Lewy body in substantia nigra (SN) immunostained for alpha-synuclein. The arrow depicts the deposition of alpha-synuclein in the halo area of the Lewy body. (B) Lewy body in a melanized SN neuron stained with hematoxylin and eosin. (C) High-power view of a Lewy body showing a dense central core of various nitrated, phosphorylated, and ubiquitinated proteins surrounded by a pale halo composed of neurofilaments and alpha-synuclein. (D) Confocal image of a dual-labeled nigral Lewy body stained for ubiquitin (red) and alpha-synuclein (yellow). (A, From Hishikawa N, Hashizume Y, Yoshida M, Sobue G. Clinical and neuropathological correlates of Lewy body disease. *Acta Neuropathol.* 2003;105[4]:341–350. B–D, From Olanow CW, Brundin P: Parkinson's disease and alpha synuclein: Is Parkinson's disease a prion-like disorder? *Mov Disord.* 2013;28[1]:31–40.)

Phosphorylation of alpha-synuclein at tyrosine 39 is promoted by the tyrosine kinase c-Abl. Overexpression of c-Abl in a mouse model of PD accelerates alpha-synuclein aggregation, neuropathologic conditions, and neurobehavioral deficits, whereas deletion of its gene reduced these events (Brahmachari et al., 2016). The c-Abl kinase inhibitor, nilotinib, was shown to induce alpha-synuclein protein degradation via the autophagy and proteasome pathways (Mahul-Mellier et al., 2014). C-Abl is activated in the brain of PD patients and in MPTP-mice, where it inhibits parkin through tyrosine phosphorylation leading to the accumulation of parkin substrates and neuronal cell death (Mahul-Mellier et al., 2014). In MPTP mice, nilotinib was found to be protective against loss of dopamine neurons (Karuppagounder et al., 2014). An open-label trial in six patients with PD was reported to improve the patients (Pagan et al., 2016), but subsequently two controlled clinical trials failed to find benefit.

Wild-type alpha-synuclein has several functions in neurons, related to synaptic vesicle function (Sulzer and Edwards, 2019). It is important for vesicle trafficking, vesicle docking and priming, vesicle fusion, and neurotransmitter release involving the SNARE protein complex assembly (Deleersnijder et al., 2013). alpha-Synuclein has also been found to play a role in endocytosis (Schechter et al., 2020; Fakhree et al., 2021).

Other gene mutations in PD labeled as PARK

PARK2

After the *SNCA* gene mutation was found, other investigators began collecting families with PD and conducting linkage analyses on them and then cloning the gene when linkage was obtained. Japanese investigators discovered the second gene to cause PD, which they called *parkin* (now *PRKN*) and designated as PARK2, with the protein also called parkin (Kitada et al., 1998). The gene mutation was initially reported in a family with autosomal recessive juvenile parkinsonism without Lewy bodies that had been linked to chromosome 6q25.2-q27 (Matsumine et al., 1998). In the postmortem study by Pouloupoulos and colleagues (2012), six of nine autopsies of autosomal recessive *PRKN* mutations had no Lewy bodies, one had Lewy body-like inclusions in the PPN and anterior horn cell, and two had Lewy bodies in the SN.

Discovery was aided because many patients had deletions of large sections of chromosome 6, where the gene resides. *PRKN* is a large gene in which almost 200 pathologic allelic variants have been described, including exon rearrangements, point mutations, duplications, triplications, insertions, and deletions, many of them recurrent in different populations (Lesage and Brice, 2009; Puschmann, 2013). Structural variants are much more common than missense mutations (Kasten et al., 2018).

PRKN mutations have now been identified pan-ethnically and are thought to be the cause of approximately 50% of familial young-onset PD and 15% to 20% of sporadic young-onset PD (younger than 50 years). The identification of *PRKN* mutations is inversely correlated with age at onset, with the earliest age at onset having the greatest association. However, PARK2 does not appear to be restricted to young-onset PD, and *PRKN* mutations have been identified in individuals over 50 (Lücking et al., 2000). Juvenile

PRKN-related PD is associated with mutations in both *PRKN* alleles (homozygotes or compound heterozygotes).

The frequency and penetrance of *PRKN* mutations have yet to be determined. *PARK2*, especially in juvenile cases, has been characterized by slow clinical progression, sustained response to levodopa, high likelihood of levodopa-induced dyskinesias, dystonia, sleep-benefit, and hyperreflexia. The slow rate of loss of FDOPA striatal uptake in those with symptomatic and asymptomatic *PRKN* carriers, is compatible with the slow clinical worsening in this form of PD (Pavese et al., 2009; Doherty et al., 2013).

Some heterozygotes have been recognized as having adult-onset PD with Lewy bodies (Farrer et al., 2001; Pramstaller et al., 2005; Sharp et al., 2014). A single parkin mutation (heterozygote) may be responsible for instances of later onset PD (Foroud et al., 2003). However, it is likely that heterozygotes with PD and with Lewy bodies are simply people with sporadic PD who happen to carry a single *PRKN* mutation. There are several reasons to think this. Heterozygotes with PD have decreased sense of smell similar to sporadic cases, whereas recessive PD resulting from homozygous *PRKN* mutations do not have loss of smell (Alcalay et al., 2011). Heterozygotes with PD have a similar age at onset and rate of worsening as sporadic PD, whereas homozygotes start early in life and progress very slowly; they do not develop many of the nonmotor features seen in sporadic PD, including dementia (Doherty et al., 2013). Despite all the previously mentioned evidence, heterozygous mutations could add to the risk for developing PD. (Huttenlocher et al., 2015).

PARK3

The locus for PARK3 has been localized by linkage to chromosome 2p13 in a small group of European families with autosomal dominant PD with incomplete penetrance (Gasser et al., 1998). Affected individuals have clinical and pathologic findings similar to those of sporadic late-onset PD, including age of onset. The sepiapterin reductase gene (*SPR*) appeared the likely candidate for PARK3 (Karamohamed et al., 2003; Sharma et al., 2006). Sepiapterin reductase is an enzyme in the pathway for tetrahydrobiopterin synthesis, a cofactor for tyrosine hydroxylase. However, a large association study for the *SPR* gene revealed no association for PD worldwide, so doubt remains as to the cause of PARK3. At present PARK3 is considered a susceptibility gene. Mutations in *SPR* also produce the phenotype of dopa-responsive dystonia (see Chapter 11).

PARK4

The evolution of the gene identification for PARK4 is a fascinating story. Waters and Miller (1994) described a kindred with autosomal dominant Lewy body parkinsonism in four generations, with an early age at onset (PARK4). The kindred was extended (Muentner et al., 1998; Farrer et al., 1999; Gwinn-Hardy et al., 2000), and action tremor similar to essential tremor and dementia were prominent within the family and widespread Lewy bodies were seen in the cerebral cortex. Linkage was initially reported to chromosome 4p, but this haplotype also occurred in individuals in the pedigree who did not have clinical Lewy body parkinsonism but rather had postural tremor only (Farrer et al., 1999). A second genome-wide search in this family found linkage

on chromosome 4q and the mutation to be a triplication of a region of the chromosome that includes the *SNCA* gene (Singleton et al., 2003), the same gene that is mutated in PARK1. Instead of a mutation, though, this triplication produces a doubling of the normal, wild-type alpha-synuclein protein. A second PD family (Swedish American) with PD-dementia with triplication of *SNCA* also has been reported (Farrer et al., 2004). The large Swedish family reported originally by Mjones (1949) was genetically analyzed and found to consist of duplications and triplications of normal *SNCA* (Fuchs et al., 2007). The remarkable thing is that the Mjones family has an alpha-synuclein duplication in one branch, and a triplication in the other, with a correspondingly different clinical picture (late versus early onset, respectively). The fact that excess normal alpha-synuclein protein can cause PD is extremely important because it indicates that too much alpha-synuclein, and not just mutations, can be a causative factor. Thus alpha-synuclein protein can be considered to play a central role in the pathogenesis of PD. Both making too much alpha-synuclein protein and blocking its degradation could give rise to an excessive amount of alpha-synuclein.

A comparison of age at onset of PD among triplications and duplications and the missense mutations of the *SNCA* gene showed that duplications and triplications resulted in an earlier age at onset compared with mutated *SNCA* (Fig. 5.17).

PARK5

PARK5, an autosomal dominant mutation of the gene for ubiquitin-carboxy-terminal-hydrolase L1 (*UCHL1*), was found in a single family and was mapped to chromosome 4p14 (Leroy et al., 1998). Additional families with this mutation are necessary before concluding that *UCHL1* is a definite causative gene. However, because this enzyme is part of the UPS, it implicates this degradative pathway as being important in the pathogenesis of PD (see later). Another potential pathogenic mechanism is the association of *UCHL1* with cellular membranes, including the endoplasmic reticulum (Liu et al., 2009). The membrane-associated form of *UCHL1* has been correlated with the intracellular level of alpha-synuclein.

PARK6

Families with autosomal recessive, young-onset PD in southern Europe were mapped to chromosome 1p35-p36, labeled as PARK6 (Valente et al., 2002), and Valente and colleagues (2004) identified two homozygous mutations in the phosphatase and tensin homolog (*PTEN*)-induced putative kinase 1 (*PINK1*) gene. Novel homozygous mutations in this gene were subsequently found in six unrelated Asian families (Hatano et al., 2004). Other families around the globe have been reported, and heterozygosity appears to increase susceptibility to developing PD (Hedrich et al., 2006). The protein *PINK1* is located on the mitochondrial membrane and functions as a serine/threonine kinase. The clinical features of patients with *PINK1* mutations resemble those with parkin mutations, namely juvenile onset, slowly progressive PD. Both parkin and *PINK1* play a role in the autophagy of damaged mitochondria (process is called mitophagy). After the depolarization of mitochondria, *PINK1* is activated and

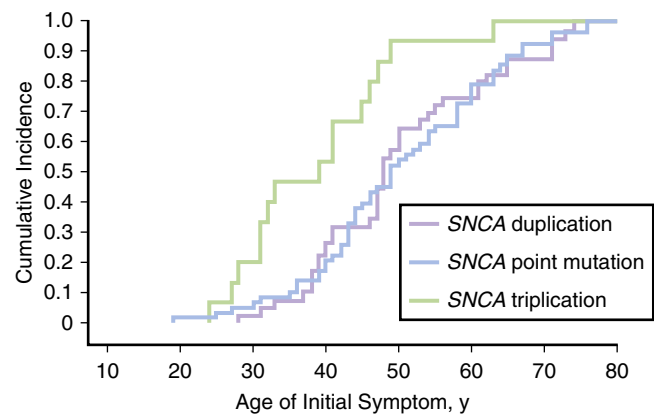


Fig. 5.17 Cumulative incidence of PD onset among *SNCA*-induced PD patients. Those with triplications of *SNCA* have onset at a young age than those with duplications or missense mutations. (From Trinh J, Guella I, Farrer MJ: Disease penetrance of late-onset parkinsonism: A meta-analysis. *JAMA Neurol.* 2014;71[12]:1535–1539.)

phosphorylates ubiquitin, which recruits cytosolic parkin to the mitochondria and then activates autophagosomes to engulf the impaired mitochondria, promoting mitophagy. Excessive parkin can rescue the *PINK1* mutant phenotype, which supports the notion that parkin works downstream from *PINK1* in a common pathway. One autopsy of a young-onset patient with PD resulting from *PINK1* mutations showed the presence of Lewy bodies (Samaranch et al., 2010).

PARK7

PARK7, the *DJ-1* gene mutation, is another cause of early-onset, autosomal recessive PD and is due to mutations on chromosome 1p36 (Bonifati et al., 2003). The mutations and gene identification were found in a consanguineous Dutch family and families in Italy and Uruguay. PARK7, like *PRKN* and *PINK1*, is characterized by slow progression and a good response to levodopa (Kasten et al., 2018). No autopsies have been reported for individuals with *DJ-1*. The crystal structure of *DJ-1* reveals a redox-reactive center. *DJ-1* may be activated in the presence of reactive oxygen species under conditions of oxidative stress. *DJ-1*, therefore, is an important redox-reactive signaling intermediate, controlling oxidative stress (Kahle et al., 2009). *DJ-1*, like *PRKN* and *PINK1*, is important for mitochondrial function (Cookson, 2010). Knockout mutants of *DJ-1* enhance mitochondrial oxidative stress produced by pacemaking of SNc neurons (Guzman et al., 2010). Research on the pathogenic mechanisms from the PARK2, PARK6, and PARK7 mutations led to their involvement with mitochondrial function, including mitochondrial degradation via mitophagy. The pathogenic mechanism is discussed later in the section on Clues to pathogenesis from monogenic PD.

PARK8

The most common PD gene found so far has been PARK8 (*LRRK2*), the gene located on chromosome 12q12 for the protein leucine-rich repeat kinase 2 (*LRRK2*) (Zimprich et al., 2004), which is also called dardarin (Paisan-Ruiz et al., 2004). Initially, linkage to chromosome 12 was

reported in a large Japanese autosomal dominant family without Lewy bodies (Funayama et al., 2002). But the Zimprich and Paisan-Ruiz families included subjects both with Lewy body pathologic findings and tangle pathologic findings and without Lewy bodies. One *LRRK2* mutation, G2019S, is the most common and is seen in more than 2% in sporadic North American and English PD patients (Gilks et al., 2005; Nichols et al., 2005). The highest frequencies are in the Portuguese (Bras et al., 2005), Ashkenazi Jewish (Clark et al., 2006; Ozelius et al., 2006), and North African Arab (Lesage et al., 2006) patients, even in the absence of a family history of PD. The clinical, pathologic, and genetic epidemiology of *LRRK2* were reviewed by Haugarvoll and Wszolek (2006) and mixed pathologic findings resembling typical PD, tauopathies (tangles), and MSA were seen. However, patients with typical MSA were not found to have the *LRRK2* G2019S mutation (Ozelius et al., 2007). In the Chinese population the G2019S mutation is rare, but about 9% of Chinese PD patients have a heterozygous G2385R mutation (Fung et al., 2006; Farrer et al., 2006). Whereas the G2019S mutation usually leads to a milder form of PD than sporadic PD, the G2385R mutation typically causes a more rapid form (Marras et al., 2016a). *LRRK2* mutations show the typical age at onset and are not prone to be young-onset (Clark et al., 2006). Penetrance is not complete, and its rate has produced variable results. In one report, it increases with age, from 17% at about age 50 years to 85% at age 70 (Hardy et al., 2006), and in another report the penetrance rate was 24% at the age of 80 (Clark et al., 2006). A 2017 study found the penetrance rate of the G2019S mutation in Ashkenazi Jewish relatives of 26% and in non-Ashkenazi Jewish relatives of 42.5% (Lee et al., 2017).

The risk for developing PD in relatives predicted to carry an *LRRK2* G2019S mutation was 0.26 (95% confidence interval [CI], 0.18–0.36) to age 80 years and was almost 3-fold higher than in relatives predicted to be noncarriers (hazard ratio [HR] 2.89, 95% CI, 1.73–4.55, $P < 0.001$) (Marder et al., 2015). The ages at onset of the several *LRRK2* mutations differ from each other (Figs. 5.18 and 5.19). Variations in the *DNM3* (dynamitin3) gene was found to modify the age at onset in the G2019S carriers (Trinh et al., 2016).

Only about two-thirds of patients with the *LRRK2* G2019S mutation have Lewy bodies; nonmotor features of cognitive impairment/dementia, anxiety, and orthostatic hypotension were correlated with the presence of Lewy bodies, whereas those without Lewy bodies had primarily a more benign and just motor phenotype of PD (Kalia et al., 2015). This correlation reinforces the concept that Lewy bodies in people with PD lead to a more progressive, cognitive impairment and people without Lewy bodies do not have cognitive impairment. This fits with PD resulting from homozygous *PRKN* mutations; these patients typically do not progress to cognitive impairment (Doherty et al., 2013). Thus, not only is penetrance variable but age at onset and phenotype are also, even among identical twins. This suggests that other genes or epigenetic factors must play a role in *LRRK2* expression.

How *LRRK2* causes PD is not clear. Increased kinase activity appears to be involved. Enhanced kinase activity (~3-fold) has been consistently reported for G2019S; but four disease mutants (R1441C, R1441G, Y1699C, and I2020T) have kinase activity less than 2-fold of the wild-type protein (Dauer and Ho, 2010). There are now four mutations

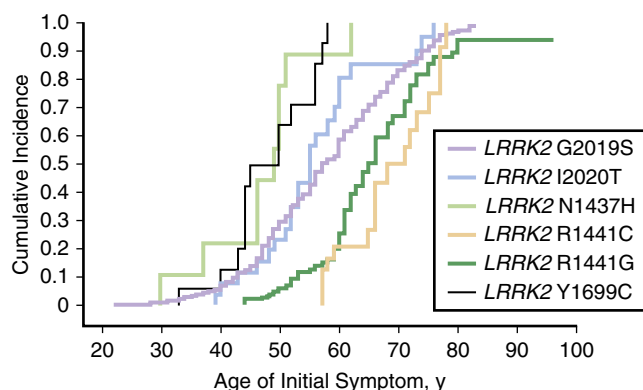


Fig. 5.18 Cumulative incidence of PD onset among *LRRK2*-induced PD patients. The most common mutation in Europeans, North Africans, and Ashkenazi Jews is the G2019S mutation, and its curve would be similar to that of sporadic PD. (From Trinh J, Guella I, Farrer MJ: Disease penetrance of late-onset parkinsonism: A meta-analysis. *JAMA Neurol.* 2014;71[12]:1535–1539.)

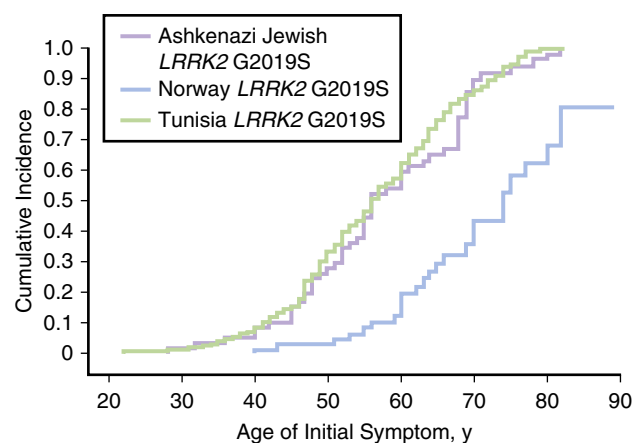


Fig. 5.19 Cumulative incidence of PD onset among *LRRK2* G2019S mutations with different ethnic backgrounds. The North Africans and Ashkenazi Jews have the same distribution of age at onset, whereas the Norwegian carriers have a much later age at onset. (From Trinh J, Guella I, Farrer MJ: Disease penetrance of late-onset parkinsonism: A meta-analysis. *JAMA Neurol.* 2014;71[12]:1535–1539.)

at the 1441 site: R1441C, R1441G, R1441H, and R1441S. All show a similar clinical phenomenology (Mata et al., 2017). Inhibitors of *LRRK2* kinase have been found to be protective in both in vitro and in vivo models of *LRRK2*-induced neurodegeneration. These results establish that *LRRK2*-induced degeneration of neurons in vivo is kinase dependent (Lee et al., 2010). *LRRK2* also regulates neurite process formation, which is impaired by mutations (MacLeod et al., 2006). Mutant *LRRK2* also activates programmed cell death signaling (Ho et al., 2009).

PARK9

PARK9 is actually a Parkinson-plus disorder rather than PD. This autosomal recessive disorder is the result of a mutation of lysosomal type 5 ATPase, *ATPase*, *ATP13A2*, on chromosome 1q36. There is juvenile onset, and the disorder was originally known as the Kufor-Rakeb syndrome, after the village in Jordan where the affected families reside (Najim al-Din et al., 1994). This syndrome had features of Parkinson-plus

with pyramidal signs, dystonia, and supranuclear gaze palsy. The disorder is levodopa-responsive, and some cases show putaminal and caudate iron accumulation, making it one of the neurodegenerations with brain iron accumulation (NBIA) (Schneider et al., 2010). See discussion of NBIA in Chapter 11.

PARK10

A genome-wide screen on 117 Icelandic patients with classic late-onset PD and 168 of their unaffected relatives from 51 families resulted in linkage to chromosome 1p32 (Hicks et al., 2002). This susceptibility gene for PD was designated as PARK10. In the ensuing years, a number of genetic studies, including genome-wide association studies (GWAS), have led to mixed results, with most studies unable to find a link to 1p32 (Farrer et al., 2006; Goris et al., 2006; Li et al., 2007; Wan et al., 2014). However, a 2015 GWAS studies considered PARK10 to be a major locus for PD (Beecham et al., 2015), but those results could not be confirmed (Simón-Sánchez et al., 2015). A subsequent analysis by two impartial geneticists concluded that there is not yet convincing evidence for PARK10 (Olszewska and Lynch, 2016).

PARK11

A genome-wide screen on 150 families with PD resulted in finding linkage for a susceptibility gene on chromosome 2q36-q37, designated as PARK11 (Pankratz et al., 2003a). Mutations in the gene coding for GRB10-interacting GYF protein 2 (*GIGYF2*) was reported (Lautier et al., 2008), but this has been questioned by other investigators (Guo et al., 2009; Nichols et al., 2009).

PARK12

A genome-wide search also found a positive lod score for a locus on chromosome Xq21-q25 (Pankratz et al., 2003), which has been designated as PARK12.

PARK13

Using a candidate gene approach based on the phenotype of motor neuron degeneration in mice, a genome search in German PD patients found a novel mutation of a mitochondrial serine protease high temperature requirement protein A2 (*HTRA2*) in four patients (Strauss et al., 2005; Plun-Favreau et al., 2008). This mutation has been listed as PARK13. However, a subsequent large-scale genetic association study designed to evaluate the contribution of PARK13 to PD found no association between them on a world-wide population (Krüger et al., 2011).

PARK14

Homozygosity for a missense mutation in the *PLA2G6* gene was discovered in a large consanguineous Pakistani family with neurodegeneration with brain iron accumulation (NBIA2), a condition also known as infantile neuroaxonal dystrophy (Morgan et al., 2006). Spasticity, cerebellar ataxia, and optic atrophy are common in these infants (Kurian et al., 2008). However, the phenotypic spectrum has been

found to be much broader. It can cause autosomal recessive dystonia-parkinsonism at all ages, including adults, and without evidence of brain iron accumulation (Paisan-Ruiz et al., 2009). It has been labeled PARK14. Mutations and young-onset cases of parkinsonism-dystonia with this mutation occur in East Asians and Europeans. The patients respond to levodopa and can develop levodopa-induced dyskinesias. Autopsy findings can resemble those of infantile axonal dystrophy with that phenotype or that of typical sporadic PD for young-onset PD phenotype (Miki et al., 2017a). The mutation results in mitochondrial malfunction (Chiu et al., 2018). The *PLA2G6* gene codes for the protein/enzyme, calcium-independent group VI phospholipase A2 β , and this protein has been found to be present in the core of SN Lewy bodies, not only in patients with PARK14, but also in patients with sporadic PD (Miki et al., 2017b).

PARK15

Parkinsonism with spasticity occurring in the first decade of life has been called pallido-pyramidal syndrome (Davison, 1954). One of Davison's cases had been reported in 1917 by Ramsay Hunt as juvenile PD with progressive atrophy of the globus pallidus (Hunt, 1917). It is an autosomal recessive disorder that responds very well to levodopa therapy (Horowitz and Greenberg, 1975; Bronstein and Vickrey, 1996). It also has been called parkinsonism-pyramidal syndrome, and the mutation was found in the *FBXO7* gene coding for the F-box only protein 7 (Di Fonzo et al., 2009). It has been labeled PARK15. The *FBXO7* protein is a member of the Skp1-Cullin-F-box-type E3 ubiquitin ligases, which play important roles in targeting proteins for ubiquitination (Deng et al., 2013b). *FBXO7* mutants aggravate protein aggregation in mitochondria and inhibit mitophagy (Zhou et al., 2018). *FBXO7* immunoreactivity has been found in a large proportion of alpha-synuclein-positive inclusions (Lewy bodies, Lewy neurites, glial cytoplasmic inclusions), where it colocalized with alpha-synuclein in PD and MSA cases (Zhao et al., 2013).

PARK16

PARK16 was discovered by a large GWAS in the Japanese population on chromosome 1q32 (Satake et al., 2009). This finding was replicated in a large GWAS in the European population (Simon-Sanchez et al., 2009), as did another replication study, which also showed an association in ethnic Chinese but no association in Whites of European ancestry (Vilariño-Güell et al., 2010).

PARK17

A Swiss kindred was identified with autosomal-dominant, late-onset PD that was found to be caused by a mutation in the gene (*VPS35*) coding for the protein vacuolar protein sorting 35 (Vilariño-Güell et al., 2011). There are at least five potential genes in this chromosomal area. Other Swiss families were also affected, and subsequently the mutation was found in other ethnic groups (Sharma et al., 2012; Deng et al., 2013a). The clinical features are that of tremor-predominant, dopa-responsive, adult-onset parkinsonism and termed PARK17. Penetrance appears to be incomplete

(Zimprich et al., 2011). Vacuolar protein sorting 35 is a critical component in the retromer system for mediating intracellular retrograde transport of endosomes to the trans-Golgi network (Pan and Yue, 2014). The retromer complex modulates protein recycling and clearance. *VPS35* is also involved in mitochondrial fission; mutations cause mitochondrial fragmentation and cell death (Wang et al., 2016).

PARK18

A mutation in the *EIF4G1* gene on chromosome 3q27 was found in European and American families, all with the same ancestral haplotype (Chartier-Harlin et al., 2011). *EIF4G1* is involved in transcription/translation mechanisms, and a link was found between *VPS35* and *EIF4G1* in alpha-synuclein-related neurodegeneration (Dhungel et al., 2015). Dhungel and colleagues (2015) predicted that *EIF4G1* toxicity under conditions of *VPS35* deficiency may be caused by loss of retromer function, and they showed how dysfunctions of this pathway results in the accumulation of protein misfolding. A *VPS35* mutation exacerbates alpha-synuclein accumulation and toxicity, whereas its overexpression is neuroprotective.

PARK19

A mutation in the *DNAJC6* gene was found in a consanguineous Turkish family (Köroğlu et al., 2012). The phenotype was that of juvenile parkinsonism that presented with intellectual disability, pyramidal signs, and epilepsy. The gene mutation was independently discovered in two non-Turkish families (Edvardson et al., 2012). Additional families with novel mutations in *DNAJC6* presented as young-onset PD, resembling typical adult-onset PD (Olgiati et al., 2016). *DNAJC6* encodes the heat shock protein 40 (HSP40) auxilin, a protein that is selectively expressed in neurons and confers specificity to the ATPase activity of its partner heat shock cognate 70 (Hsc70) in clathrin uncoating. PARK19 supports the involvement of synaptic vesicles endocytosis and trafficking in PD pathogenesis. Juvenile PD and young-onset PD caused by mutations in the *DNAJC6* gene have been labeled as PARK19A and PARK19B, respectively. The former, caused by nonsense mutations, results in a severe phenotype, whereas the latter, caused by missense mutations, results in a more typical form of PD (Lunati et al., 2018).

PARK20

Another recessive form of juvenile parkinsonism results from mutations in the *SYNJ1* gene. Mutations were found in a consanguineous Iranian family (Krebs et al., 2013). Mutations were also found in consanguineous Italian families with parkinsonism, dystonia, cognitive deterioration, supranuclear vertical gaze palsy, and seizures (Quadri et al., 2013; Olgiati et al., 2014). Other ethnic families since have been reported. The presence of seizures in juvenile PD should lead one to suspect PARK20. Response to levodopa was partial. *SYNJ1* encodes synaptojanin 1, a phosphoinositide phosphatase protein with essential roles in the postendocytic recycling of synaptic vesicles. With nonfunctioning synaptojanin 1, early endosome formation is impaired; they become enlarged and more numerous (Fasano et al., 2018). Synaptojanin 1 is a major presynaptic phosphatase that dephosphorylates

phosphoinositide that is on the surface of early endosomes. This reaction is needed for the removal of the clathrin protein that coats the early endosome (Cao et al., 2017).

PARK21

An autosomal dominant mutation was found in the *DNAJC13* gene on 3q22 in a large Saskatchewan Mennonite family (Vilariño-Güell et al., 2014). Other families with a similar Dutch-German-Russian ethnic background had the identical mutation. Clinically, they presented with typical adult-onset PD, responded to levodopa, and had a slow progression (Appel-Cresswell et al., 2014). The same original family was studied by Deng and colleagues (2016), who found the abnormal mutated gene to be *TMEM230* mapped to 20p13. *TMEM230* encodes for transmembrane protein 230, which is involved with vesicle and endosomal trafficking. The neuropathology shows Lewy bodies, and the protein is present in the Lewy bodies (Deng et al., 2016). Because the original affected family has a heterozygous missense variant in two different genes, the molecular basis of the disease in this family is unclear.

PARK22

An autosomal dominant Japanese family with adult-onset PD was found to have a mutation in the *CHCHD2* gene that encodes for coiled helix domain protein 2 (Chdp2) (Funayama et al., 2015). Another Japanese family had the identical missense mutation, and the analysis of a Japanese databank revealed a few other mutations. Clinically the patients resemble those with typical sporadic PD; no autopsies have been performed on the affected individuals. *CHCHD2* mutations are rare in Europeans (Jansen et al., 2015) and appear to be more prevalent in the East Asian population (Foo et al., 2015). PARK22 is considered a risk factor for PD in the Asian population (Li et al., 2016). Chdp2 localizes to the mitochondrial intramembrane space and is involved in the biogenesis and regulation of enzymes in the mitochondrial respiratory chain. It is particularly linked to cytochrome c oxidase.

PARK23

A search for other causes of autosomal recessive, early-onset PD led to the discovery of a mutation in *VPS13C*, which encodes vacuolar protein sorting 13C (Lesage et al., 2016). The phenotype is that of rapid and severe disease progression with early cognitive decline. Pathologic examination shows Lewy bodies. Vacuolar protein sorting 13C partly localizes to the outer membrane of mitochondria. Reduced function results in lower mitochondrial membrane potential and causes mitochondrial fragmentation. Notably, the mutation exacerbates PINK1/Parkin-dependent mitophagy.

GBA

Although not designated with a PARK label, heterozygotic mutations of the lysosomal enzyme, beta-glucocerebrosidase (*GBA*) gene on chromosome 1q21 (homozygotes are the cause of Gaucher disease) have been associated with PD (Aharon-Peretz et al., 2004, 2005; Goker-Alpan et al., 2004;

Clark et al., 2005) and in other Lewy body disorders (Goker-Alpan et al., 2006). Mutations of *GBA* are most common in the Ashkenazi Jewish population (~8.4% of this ethnic population carry a mutation, the most common being N370S), but all ethnic groups have a variety of *GBA* mutations. Between 17% and 30% of the Ashkenazi sporadic PD patients are heterozygotes for the *GBA* mutation (Aharon-Peretz et al., 2005; Clark et al., 2007). The *GBA* mutation is associated with onset younger than 50 years compared with the older age onset in sporadic PD (Clark et al., 2007). Heterozygous mutations have been found in patients with PD in all ethnic groups and has been designated a risk factor for PD. In fact, it is the highest risk-factor gene for developing PD. About 3% of non-Ashkenazi patients have a mutation. The overall odds ratio (OR) of a PD patient to carry a *GBA* mutation is 5.4 (Sidransky and Lopez, 2012). Being a lysosomal enzyme, it implies a link between autophagy malfunction and PD (see details in the later section *GBA* and the lysosome).

Evaluating eight mutations of *GBA* among 420 patients with PD and 4138 controls of Israeli Ashkenazi origin, the relative frequency of mutation carriers was 18% versus 4% and severe mutations were associated with a 13-fold increased risk for PD compared with a 2-fold risk increase in subjects with mild mutations (Gan-Or et al., 2008). In addition, 14% of the studied patients had the G2019S *LRRK2* mutation. Thus, more than a third of all PD Ashkenazi Jewish patients carried the *GBA* or the *LRRK2* mutation. In one study involving a Japanese population of 534 patients with PD and 544 controls, 55 patients with PD (9.4%) and only 2 controls (0.37%), OR 28.0, had at least one of 11 pathogenic heterozygous variants in the *GBA* gene (Mitsui et al., 2009). In another study, involving 790 British (non-Jewish) PD patients and 257 controls, *GBA* mutations were found in 33 (4.18%) patients and 3 (1.17%) controls (OR, 3.7) (Neumann et al., 2009). The *GBA*-positive patients were younger at onset, 45% had visual hallucinations, and 48% had cognitive decline or dementia. There is also more autonomic dysfunction (O'Regan et al., 2017). Diffuse neocortical Lewy-body pathologic findings occurred more frequently in the 17 *GBA*-positive patients examined at autopsy than in controls. A large worldwide 16-center collaborative project involving 5691 patients with PD and 4898 controls revealed an OR for any *GBA* mutation in patients versus controls as 5.43 (Sidransky et al., 2009).

The risk for developing PD for those carrying a *GBA* mutation is age- and mutation-related, with about a 2% to 14% risk by age 65 and about 11% to 30% by age 85 (Rana et al., 2013). The pathogenic mutations of *GBA* causing Gaucher disease are the ones most likely to cause PD and result in a more rapid progressive form of the disease, including the development of dementia (Thaler et al., 2018). However, one nonpathogenic mutation for Gaucher, E326K mutation, was found to result in a lower risk for causing PD, but when it does, it is at high risk for causing dementia (Davis et al., 2016). Other gene variants have been found to influence the age at onset and severity of PD and dementia with Lewy bodies due to a *GBA* mutation (Blauwendraat et al., 2020).

Compared with sporadic PD, parkinsonism in patients with Gaucher disease is more frequent, occurs at an earlier age, responds less well to levodopa, and is more frequently associated with cortical dysfunction (Kraoua et al., 2009). Enzyme replacement therapy and substrate reduction

therapy were ineffective. The independently increased risk for *GBA* mutations in patients with PD, together with the identification of mutations in a lysosomal type 5 *P-type ATPase* gene responsible for the PARK9 locus suggest the link between neurodegeneration producing the PD phenotype and impaired autophagic lysosomal mechanisms (Pan et al., 2008). For those with Gaucher disease, 5% to 7% develop PD by age 70, and 9% to 12% before age 80 years (Rosenbloom et al., 2011). Despite the bad prognosis of more rapid PD for those with *GBA* mutations, only a minority with such a mutation actually develops PD.

POLG1

Families with compound heterozygosity in the DNA polymerase gamma 1 (*POLG1*) were discovered to have early-onset PD in addition to a polyneuropathy (Davidzon et al., 2006; Orsucci et al., 2011). This enzyme is involved in the replication of mitochondrial DNA, indicating that impaired mitochondrial function can lead to PD. Mutations in *POLG1* cause mitochondrial DNA depletion or deletion syndromes, most commonly resulting in myopathy, progressive external ophthalmoplegia (PEO), neuropathy, ataxia, seizures, and even liver failure and encephalopathy (Horvath et al., 2006). Inheritance can be autosomal dominant or recessive and can have onset throughout life. *POLG1* mutations have also been found in several families with PEO and parkinsonism and with parkinsonism without other features. These patients have a loss of dopaminergic cells and some response to anti-Parkinson medications (Orsucci et al., 2011).

Perry syndrome

Perry syndrome is a rapidly progressive disease with autosomal dominant parkinsonism, hypoventilation, depression, and weight loss (Perry et al., 1975; Wider and Wszolek, 2008). In addition to severe neuronal loss in the SN and LC, there is loss of putative respiratory neurons in the ventrolateral medulla and raphe nucleus (Tsuboi et al., 2008). There are neuronal and glial inclusions that stain positive for TAR DNA-binding protein-43 (TDP-43) (Wider et al., 2009), as seen in amyotrophic lateral sclerosis (ALS) and frontotemporal degeneration. Mutations in the *DCTN1* gene, which codes for dynactin 1, have been found (Farrer et al., 2009). The dynactin complex is important for many cellular transport functions, including axonal transport of vesicles. After reviewing 87 cases of Perry syndrome, diagnostic criteria have been established (Mishima et al., 2018). Identifying a *DCTN1* gene mutation or TDP-43 pathologic findings is part of the criteria, along with the four cardinal clinical features or a family history of parkinsonism. The authors recommend changing the name to Perry disease.

Infantile and juvenile dystonia-parkinsonism

Infantile and juvenile dystonia-parkinsonism disorders can be seen with several genetic disorders. Homozygous loss-of-function mutations in the *SLC6A3* gene encoding the dopamine transporter (DAT) has been reported (Kurian et al., 2009). Such mutations have been associated with attention deficit hyperactivity disorder. One would expect increased synaptic dopamine and therefore a hyperkinetic disorder

rather than a parkinsonian-dystonia disorder, which is usually associated with a deficiency of striatal dopamine and thus decreased synaptic dopamine reaching the dopamine receptor. The CSF contained an elevated level of HVA, the final metabolite of dopamine, indicating a high turnover of dopamine. It would appear that the synaptic dopamine is being rapidly metabolized by monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT). Perhaps the dopamine receptor was downregulated. There was a poor response to levodopa therapy.

Other familial or childhood-onset dystonia-parkinsonisms are those resulting from homozygous mutations of the gene for tyrosine hydroxylase and the heterozygous mutations for the gene for the tyrosine hydroxylase cofactor, *GTPCH1*. Homozygous mutations of the manganese transporter gene, *SLC30A10*, also results in childhood-onset dystonia-parkinsonism. Most of the NBIAs manifest as a combination of dystonia and parkinsonism. These and the other conditions listed in this section are discussed in [Chapter 11](#). The list goes on and can be found in a tabulation by [Marras and colleagues \(2016b\)](#).

Impact on development of dopamine neurons by other genes

Emerging evidence indicates that some patients with parkinsonism are born with fewer than normal dopaminergic neurons as a result of some *in utero* or perinatal event or as a result of mutations in genes that code for various transcription factors, such as the nuclear receptor–related 1 (*NURR1*) ([Bensinger and Tontoz, 2009](#)), human achaete-scute homolog 1 (*HASH1*), paired-like homeodomain transcription factor 3 (*PITX3*), and other genes necessary for the development and maintenance of the dopaminergic system ([Le et al., 2009](#)).

A summary of the genetic alterations described earlier are presented in tabular form in [Tables 5.3](#) and [5.4](#). [Table 5.4](#) also includes genetic mutations without the PARK label that are not described previously, to provide additional information about many more genes that can cause parkinsonism.

Only a few of the genes listed in the [Tables 5.3](#) and [5.4](#) are listed as disease-causing genes. Most are genes that increase the risk for developing PD. Many of the moderate- and low-risk genes were discovered by GWAS ([Keller et al., 2012](#); [Nalls et al., 2014](#); [Chang et al., 2017](#)). It is widely thought that several common gene mutations individually provide very low risk for developing PD, but a combination of such mutations raises the risk and can lead to developing the disease. [Fig. 5.20](#) depicts the rare frequency of gene mutations that cause PD and the common frequency of gene mutations that provide risk for developing PD.

Genome-wide association studies

GWAS have been extensively used to uncover new genes that contribute to developing PD. Huge sample sizes are necessary, and the genotypes of the data set are used to compare people who have PD and equally large sample of control subjects. A very large meta-analysis using the many previously published individual GWAS searches included 13,708 cases and 95,282 controls ([Nalls et al., 2014](#)). This study replicated 24 known single nucleotide polymorphisms (SNPs) and found 6 new ones. The results are shown in [Fig. 5.21](#). An interesting method

of presenting the known genes that are involved in PD was presented by [Singleton and Hardy \(2016\)](#) and is shown in [Fig. 5.22](#). A 2017 GWAS study used the data collected by 23andMe ([Chang et al., 2017](#)). This included 6476 PD cases of European ancestry that were independent from those previously reported study by [Nalls and colleagues \(2014\)](#) and 302,042 controls who did not report having PD and were of ancestry similar to that of the cases. By combining the data sets of these two studies, the investigators found 17 novel loci. These results are shown in [Fig. 5.23](#). GWAS studies continue to be performed with larger datasets, resulting in finding new gene mutations with risk of causing PD ([Nalls et al., 2019](#); [Iwaki et al., 2019](#)). For the reader who desires more information on the genetics of PD, there are a number of review articles covering the genetics of PD and a 2018 one by [Deng and colleagues \(2018\)](#). [Singleton and Hardy \(2019\)](#) helpfully outline the pathogenic mechanisms caused by these large number of identified genetic loci.

Environmental factors that increase or decrease the risk for developing PD

Environmental toxic factors

A gene–environmental interaction is a common theme in the cause of PD. With the discovery of MPTP as a toxin causing parkinsonism as a result of dopamine neuron degeneration ([Langston et al., 1983](#)), an environmental cause seemed plausible. MPTP is the protoxin; it is oxidized by MAO-B in the tissues to 1-methyl-4-phenylpyridinium (MPP⁺), which can be taken up into dopamine nerve terminals via the DAT (see [Fig. 5.14](#)). Once there, it inhibits complex I in the mitochondrial respiratory chain, thereby reducing ATP synthesis and increasing superoxide radicals (for review, see [Dauer and Przedborski, 2003](#)). But MPTP-induced parkinsonism is not PD; moreover, inhibition of MAO-B with selegiline ([Parkinson Study Group, 1993](#)) or rasagiline ([Parkinson Study Group, 2004](#)) does not halt progression of PD. Rotenone is used to poison unwanted fish in lakes, and like MPP⁺, inhibits complex I and can cause experimental parkinsonism ([Betarbet et al., 2000](#)). Whether it is an important environmental factor is questionable, although the association of PD in humans with pesticide exposure is positive whereas exposure to other chemicals is not ([Frigerio et al., 2006](#)). Two pesticides in particular, maneb and paraquat, show a high risk for PD, and the risk is even greater if a person is exposed to both ([Costello et al., 2009](#)).

Chlorinated solvents are associated with an increased risk for PD ([Marras et al., 2017](#)). One pesticide known to cause dopaminergic damage is ziram, which inhibits the UPS in primary ventral mesencephalic cultures ([Chou et al., 2008](#)). In an analysis of serum samples of 50 PD patients and 43 controls, beta-hexachlorocyclohexane (β -HCH) was more often detectable in patients with PD (76%) than in controls (40%) ([Richardson et al., 2009](#)). One study showed the world's highest prevalence of PD may be among the Amish in the northeast United States. The prevalence of PD was 5703 in 100,000 (nearly 6%) of people 60 years old or older, more than 3 times the prevalence for the rest of the United States ([Racette et al., 2009](#)). Because normal subjects were more related to each other (0.0102, standard deviation [SD] = 0.0266) than subjects with clinically definite PD (0.0054, SD = 0.0100; $P = 0.00003$) suggests that environmental factors, such as high

Table 5.3 Gene alterations causing parkinsonism with a PARK label (and a few others)

Gene	Locus	Protein	Mode of inheritance	Mean age at onset	Progression; Clinical features	Protein function
SCNA (PARK1)	4q22.1	Alpha-synuclein; A53T, A30P, and E46K mutations	AD	45 (20–85)	Rapid; dementia, hypoventilation, myoclonus, abnormal extraocular movements, incontinence	Possibly synaptic vesicle trafficking; elevated in bird song learning
PRKN (PARK2)	6q26	Parkin	AR in juvenile onset; AD in older onset	Young (3–64); usually less than 20	Very slow; dystonia at onset; sleep benefit; no Lewy bodies in AR juvenile form	Ubiquitin E3 ligase, attaches short ubiquitin peptide chains to proteins for degradation
SPR PARK3	2p13	Sepiapterin reductase	AD	59 (37–89)	Slow; indistinguishable from idiopathic PD	Synthesis of tetrahydrobiopterin
SCNA (formerly PARK4)	4q22.1 gene duplication and triplication	Excess wild-type alpha-synuclein	AD	33	Rapid; wide range of symptoms from idiopathic PD to dementia with Lewy bodies	Same as PARK1
UCHL1 (PARK5)	4p13	Ubiquitin-C-terminal hydrolase L1	AD	~50	Indistinguishable from idiopathic PD	Removes polyubiquitin in ubiquitin-proteasomal cycle
PINK1 (PARK6)	1p36.12	PTEN-induced putative kinase 1	AR	40 (30–68)	Slow	Mitochondrial serine-threonine kinase; modulates mitochondrial dynamics
DJ-1 (PARK7)	1p36.23	DJ-1	AR	33 (27–40)	Slow; as in parkin, but with behavioral problems and focal dystonia	Possible atypical peroxiredoxin; protects against oxidative stress
LRRK2 (PARK8)	12q12	Leucine rich repeat kinase 2 (also known as dardarin)	AD	~60	Indistinguishable from idiopathic PD; ↓ penetrance	Probably a cytoplasmic kinase
ATP13A2 (PARK9) (Kufor-Rakeb syndrome)	1p36.13	Lysosomal ATPase	AR	12–16	Kufor-Rakeb syndrome, similar to PD and to pallido-pyramidal syndrome (PARK15)	Maintain acid pH in lysosome
PARK10	1p32	Unknown	AR	Typical late onset	Standard PD; families in Iceland	—
(GIGYF2 in doubt) (PARK11)	2q37.1	GRB10-interacting gyf protein 2 (in doubt)	AD	Typical late onset	Indistinguishable from idiopathic PD	Gene identification is in doubt
PARK12	Xq21-q25	Unknown	X-linked recessive	Typical late onset	Indistinguishable from idiopathic PD	—
HTRA2 (PARK13)	2p13.1	High temperature requirement protein A2 (HTRA2)	AD	Typical late onset	Indistinguishable from idiopathic PD	Serine protease primarily localized in the endoplasmic reticulum and mitochondria

Continued

Table 5.3 Continued

Gene	Locus	Protein	Mode of inheritance	Mean age at onset	Progression; Clinical features	Protein function
<i>PLA2G6</i> (PARK14)	22q13.1	Phospholipase A2 group VI	AR	Infants, children, and adults	(1) Infantile neuroaxonal dystrophy with spasticity, ataxia and iron accumulation (NBIA2, PLAN); 2) dystonia-parkinsonism in adults without iron	Phospholipase A2, releases fatty acids from phospholipids
<i>FBXO7</i> (PARK15)	22q12.3	F-box only protein 7	AR	Childhood onset	Pallido-pyramidal disease; parkinsonian-pyramidal syndrome	Component of modular E3 ubiquitin protein ligases; functions in phosphorylation-dependent ubiquitination
PARK16	1q32	Unknown	Unknown	Typical late onset	Discovered by genome-wide association studies in Japan and Europe	—
<i>VPS35</i> (PARK17)	16q11.2	Vesicle protein sorting 35	AD	Typical late onset	Original large Swiss family, then an Austrian family and a German man	Mediates retrograde transport between endosomes and the trans-Golgi network
<i>EIF4G1</i> (PARK18)	3q27.1	Eukaryotic initiation factor 4-gamma, 1	AD	Typical late onset	Families from France, Ireland, Italy, and the United States, and all affected carriers appear to have the same ancestral haplotype	Facilitates the recruitment of mRNA to the ribosome
<i>DNAJC6</i> PARK19A	1p31.3	Auxilin	AR	Juvenile	Palestinian, Turkish, and Yemeni families. Rapidly progressive, mental retardation, pyramidal signs	Clathrin-mediated endocytosis
<i>DNAJC6</i> PARK19B	1p31.3	Auxilin	AR	Young-onset	Caucasian families in the Netherlands and in Brazil. Typical PD corresponding to this age at onset	Clathrin-mediated endocytosis
<i>SYNJ1</i> PARK20	21q22.11	synaptojanin 1	AR	Young-onset; 20s	Iranian, Sicilian, and Italian siblings. May have childhood seizures. Apraxia of eyelid opening	Synaptic vesicle recycling
<i>DNAJC13</i> versus <i>TMEM230</i> PARK21	3q22 versus 20p13	DnaJ heat shock protein family (Hsp40) member C13 versus transmembrane protein 230	AD	Typical late onset with Lewy bodies	Dutch, German, Russian families (see text for two genes identified in the same family)	Chaperone for clathrin-mediated endocytosis versus vesicle and endosomal trafficking

Continued

Table 5.3 Continued

Gene	Locus	Protein	Mode of inheritance	Mean age at onset	Progression; Clinical features	Protein function
<i>CHCHD2</i> PARK22	7p11.2	Coiled-coil-helix-coiled-coil-helix domain containing 2	AD	Typical late onset	Japanese family originally	Translocates from the mitochondrial intermembrane space to the nucleus, where it binds to a highly conserved 13 nucleotide oxygen responsive element in the promoter of cytochrome oxidase 4I2
<i>VPS13C</i> PARK23	15q22.2	Vacuolar protein sorting 13C	AR	Young onset	Rapid, severe progression	Mitochondrial membrane potential

Table 5.4 Some gene alterations causing parkinsonism without a PARK label

Gene	Locus	Protein	Mode of inheritance	Mean age at onset	Progression; Clinical features	Protein function
<i>GBA</i>	1q21	Beta-glucocerebrosidase	AD	Slightly younger than average	Indistinguishable from idiopathic PD; all ethnic groups; most common in Ashkenazi Jews; homozygotes → Gaucher disease	Lysosomal enzyme; metabolizes membrane lipid glucosylceramide to ceramide and glucose
<i>NR4A2</i>	2q24.1	Nurr1	AD	Typical late onset	Indistinguishable from idiopathic PD	Dopamine cell development; transcription activator
<i>RIT2</i>	18q12.3	GTPase	GWAS study	Typical late onset	Indistinguishable from idiopathic PD	GTPase and calmodulin binding
<i>PRKAR1B</i>	7p22.3	Cyclic-AMP dependent protein kinase A	AD	Late onset	Features of parkinsonism and dementia with unusual filaments on pathology	Essential enzyme in the signaling pathway of the second messenger cAMP
<i>DCTN1</i>	2p13	Dynactin 1	AD	Early onset	Perry syndrome; familial parkinsonism with hypoventilation, depression, and weight loss; neuronal and glial inclusions that stain positive for TAR DNA-binding protein-43 (TDP-43)	Cellular transport functions, including axonal transport
<i>POLG1</i>	15q26.1	Mitochondrial Polymerase gamma A subunit	AD	Early onset	Families with PD and peripheral neuropathy	DNA polymerase gamma-1, replication of mitochondrial DNA

Continued

Table 5.4 Continued

Gene	Locus	Protein	Mode of inheritance	Mean age at onset	Progression; Clinical features	Protein function
<i>GCH1</i> Dopa-responsive dystonia (DYT5A)	14q22.1- q22.2	GTP cyclo-hydrolase 1	AD	Childhood-onset with gait disorder; adult-onset with parkinsonism	Dopa-responsive dystonia; penetrance is higher in females	Cofactor for tyrosine hydroxylase
<i>TH</i> (DYT5B)	11p15.5	Tyrosine hydroxylase	AR	Infantile parkinsonism and dystonia	Dopa-responsive dystonia	Converts tyrosine to levodopa
<i>SLC6A3</i> (<i>DAT1</i>)	5p15.3	Solute carrier family 6; dopamine transporter	AD	Infantile parkinsonism and dystonia	Elevated CSF HVA; poor response to L-dopa	Reuptake dopamine from synapse
<i>ATXN2</i> (<i>SCA2</i>)	12q24	Ataxin-2	AD	Young and late onsets	Ataxia, but can have a parkinsonian phenotype	Ataxin-2 is predominantly located in the Golgi apparatus
<i>TBP</i> <i>SCA17</i>	6q27	TATA-binding protein	AD	East Asians	Ataxia, but can have a parkinsonian phenotype	Transcription initiation factor
<i>RAB39B</i> Waisman syndrome	Xq28	Rab GTPase	XR	Mentally retarded boys	Starts with mental retardation, then PD	Vesicular trafficking
<i>SLC30A10</i>	1q41	Manganese transporter	AR	Children	Dystonia-parkinsonism	High manganese levels
<i>SLC39A14</i>	8p21.3	Divalent metal transporter	AR	Children	Dystonia-parkinsonism	High manganese levels

NOTE: A more complete listing of genetic mutations that can cause parkinsonism is presented in Chapter 1., Overview, Table 1.5.

AD, Autosomal dominant; AR, autosomal recessive; cAMP, cyclic adenosine monophosphate; CSF, cerebrospinal fluid; HVA, homovanillic acid; NBIA, neurodegenerations with brain iron accumulation; PD, Parkinson disease; PLAN, PLA2G6 associated neurodegeneration.

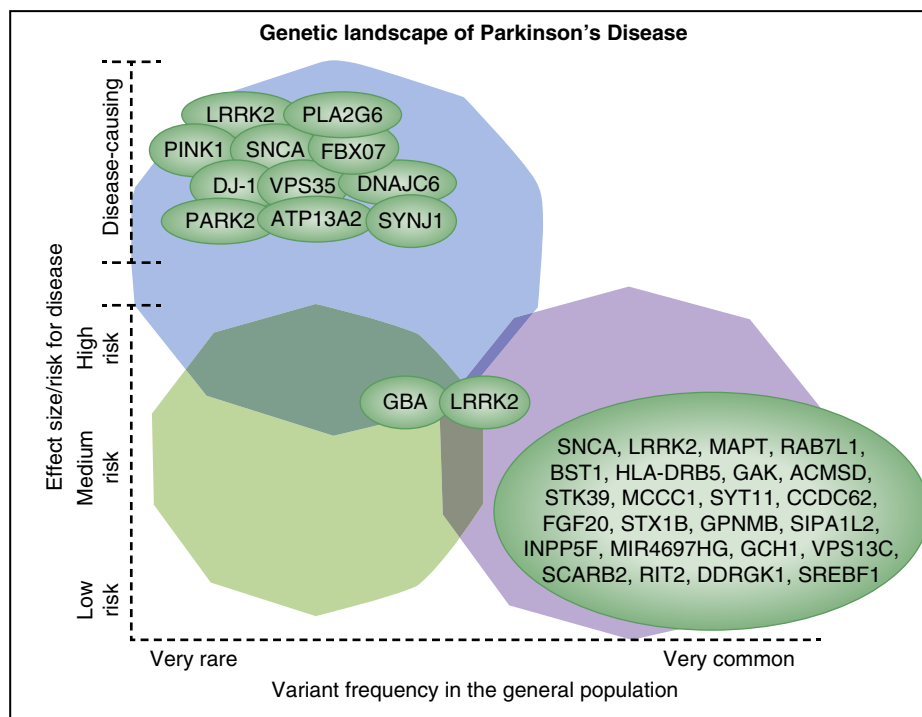


Fig. 5.20 Diagram depicting rare gene mutations causing PD (upper left corner of figure) and very common genes whose variations deliver low risk for developing PD. A combination of these low-risk variants in a given person enhances the risk and could lead to manifesting PD. Two genes, GBA and LRRK2, confer high risk. Note that specific mutations in LRRK2, such as the G2019S missense mutation, is a causal mutation, and thus this gene is also situated in upper left corner of this graph. (From Brás J, Guerreiro R, Hardy J: *SnapShot: Genetics of Parkinson's disease*. *Cell*. 2015;160[3]:570–570.e1.)

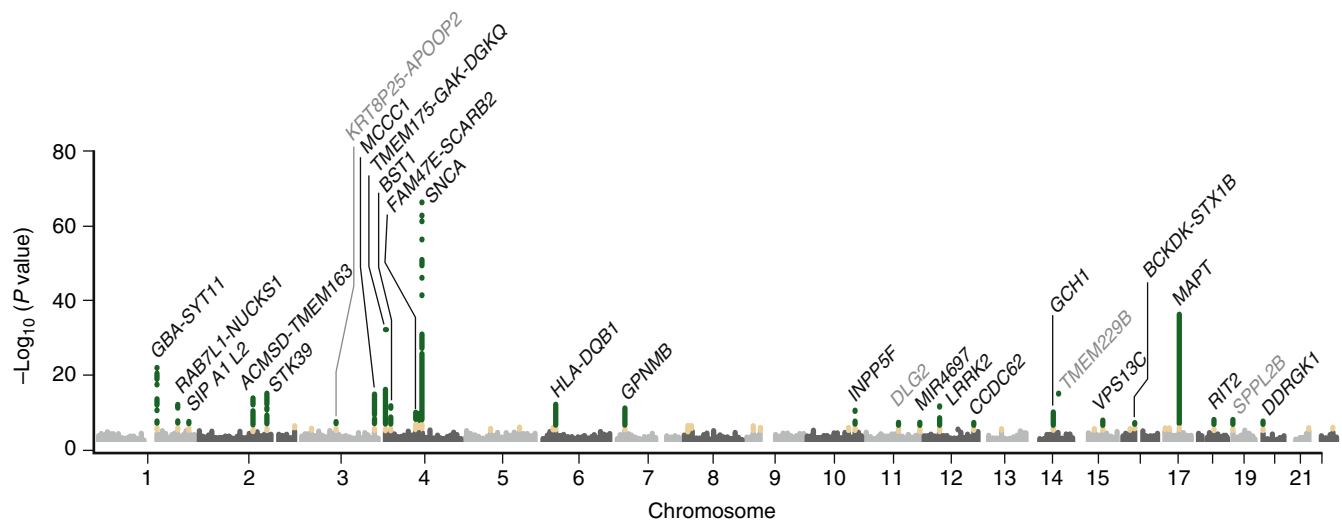
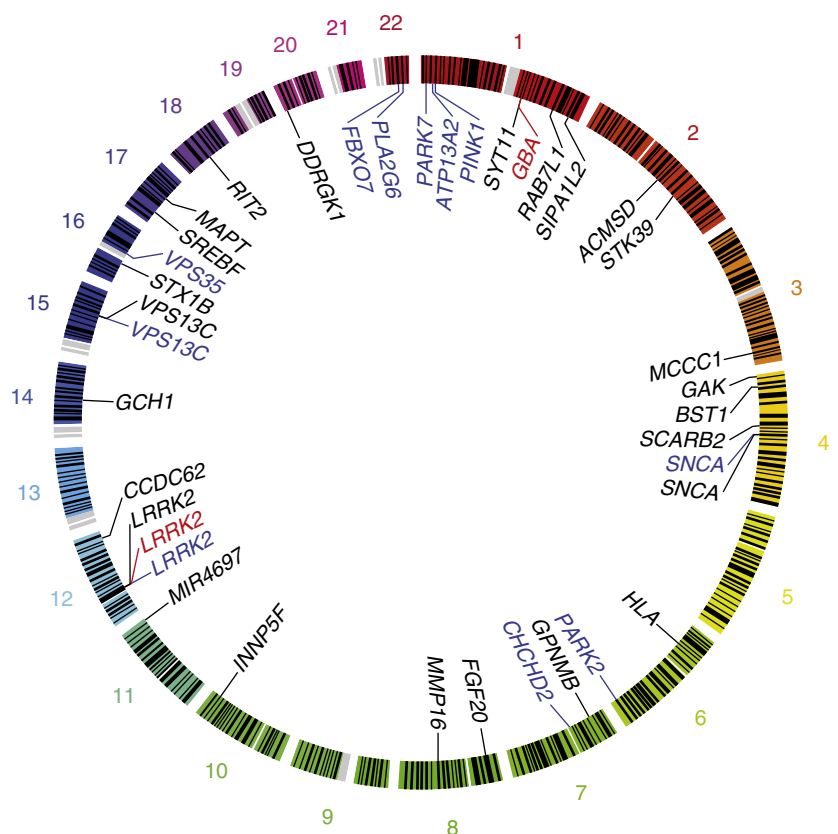


Fig. 5.21 Results from a meta-analysis of several genome-wide association studies data sets. Known as a Manhattan plot because of the skyscraper-like towers indicating statistical significance of the individual gene findings, the graph shows the chromosomal locations of the discovered genes related to PD. The height of the towers relate to the log scores, in which the higher the score, the greater the statistical likelihood of its significance. The horizontal axis shows the chromosomal location for the listed genes. (From Nalls MA, Pankratz N, Lill CM, et al: Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease. *Nat Genet.* 2014;46[9]:989–993.)

Fig. 5.22 Circular presentation of the genes and their loci associated with PD. Genes with causal mutations are shown in blue. Genes that contain moderate risk mutations for PD are shown in red. Those with lower risk are shown in black. (From Singleton A, Hardy J J: *The evolution of genetics: Alzheimer's and Parkinson's diseases*. *Neuron*. 2016;90[6]:1154–1163.)



use of pesticides (Shrestha et al., 2020), may contribute to the high prevalence of PD in this community. To investigate occupation, specific job tasks or exposures and risk for parkinsonism and clinical subtypes, a multicenter case-control study comparing lifelong occupation and job-task histories was created to determine associations with parkinsonism.

In addition to pesticides, there is also some evidence that exposure to cleaning solvents, particularly trichloroethylene, increases the risk for PD (Goldman et al., 2012; De Miranda

et al., 2021). Other putative risk factors are head trauma, certain occupations, and milk consumption (Tanner, 2010). Traumatic brain injury late in life was found to be a risk factor for developing PD (Gardner et al., 2015). Methamphetamine has been associated with more PD (Callaghan et al., 2011). Infectious agents remain a possible etiologic factor. For example, the highly pathogenic H5N1 avian influenza viruses enter the CNS and cause activation of microglia and alpha-synuclein phosphorylation and aggregation; in the SN

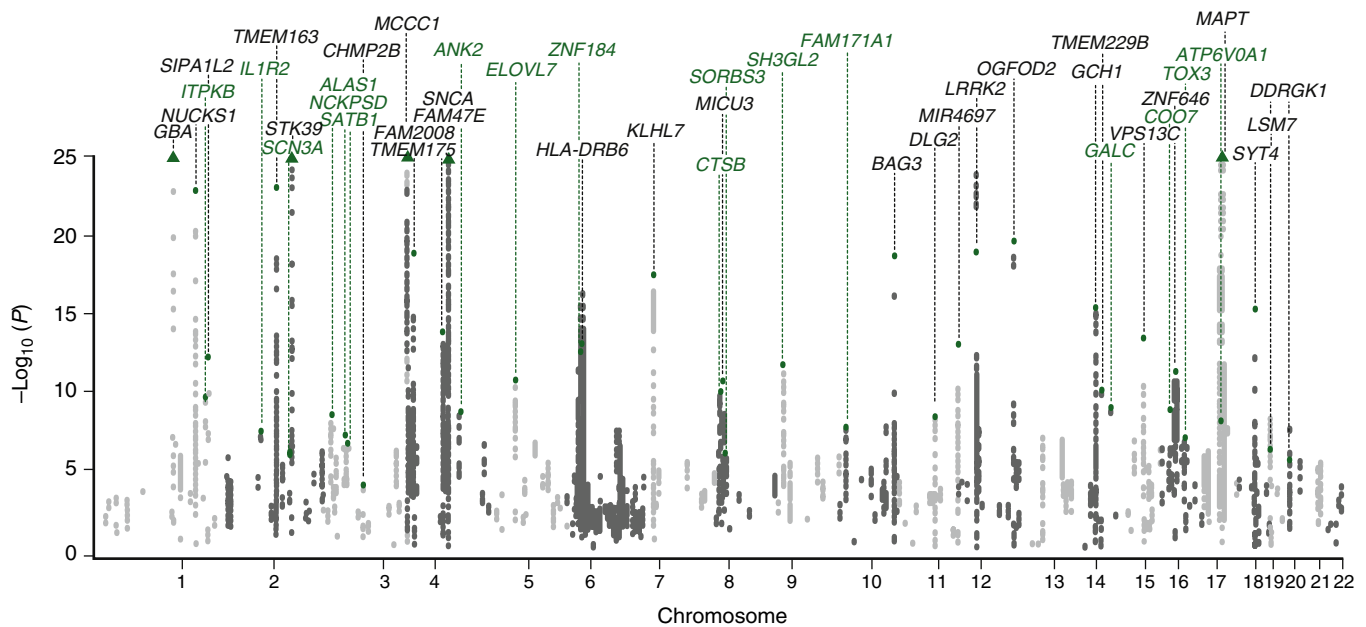


Fig. 5.23 Manhattan plot of the results from the largest genome-wide association study. The top single nucleotide polymorphisms (SNPs) in associated regions are indicated by pink symbols. Candidate genes for previously associated loci are labeled in black ($P < 5 \times 10^{-8}$ in the discovery phase) or gray text ($P > 5 \times 10^{-8}$ in the discovery phase); candidate genes for newly identified loci are labeled in red. The y-axis shows the two-sided unadjusted $-\log_{10}(P)$ values for association with PD. SNPs with $P < 1 \times 10^{-25}$ are indicated by triangles. (From Chang D, Nalls MA, Hallgrímsdóttir IB, et al. (2017). A meta-analysis of genome-wide association studies identifies 17 new Parkinson's disease risk loci. *Nat Genet.* 49(10):1511–1516.)

there is loss of dopaminergic neurons (Jang et al., 2009a). Viruses known to induce parkinsonism include Coxsackie, Japanese encephalitis B, St. Louis, West Nile, and HIV viruses (Jang et al. 2009b). With the widespread Covid-19 pandemic, there is concern that the virus in the brain could result in a trigger leading to PD, but there is no evidence of this at the present time (Sulzer et al., 2020). Coronavirus antidiodes had been detected in the CSF of patients with PD (Fazzini et al., 1992). Bacterial infections have also been proposed as a possible factor among potential multiple-hits (Patrick et al., 2019).

Marras and colleagues (2017) summarized information about environmental risk factors in the bicentenary celebratory publication of James Parkinson's "Essay," and their table is reproduced as Table 5.5.

There is little consistent evidence for other environmental factors as risk factors. Against a strong, new environmental factor is the lack of clusters of PD and an unchanging incidence rate over decades (Rocca et al., 2001). With the discovery of individual genes causing PD, a major genetic contribution to the etiology of PD has become predominant. It is likely that there are specific genes that can cause familial PD and susceptibility genes that make the individual with those genes sensitive to triggers to pathogenesis from environmental or endogenous factors, such as oxidative stress.

Among associated health factors, a meta-analysis on diabetes reported an increased risk for developing PD among persons with diabetes compared with a nondiabetic population (Schemhammer et al., 2011; Yue et al., 2016). Patients with inflammatory bowel disease (IBD) have an increased risk for developing PD (Peter et al., 2018; Brudek, 2019); for the IBD patients treatment with antitumor necrosis factor (anti-TNF) therapy was associated with a marked decrease incidence in the development of PD (Peter et al., 2018).

Endogenous factors, such as dopamine in nigral neurons and autonomous cell firing through calcium channels with

the ageing process, are discussed later in the discussion of pathogenesis.

Environmental protective factors

Two environmental factors consistently associated with a reduced risk for developing PD are smoking and caffeine consumption. In the more than 140,000 men and women in the Cancer Prevention Study II Nutrition Cohort, there was a lower risk for developing PD that correlated with (1) more years smoked, (2) smoking more cigarettes per day, (3) older age at quitting smoking, and (4) fewer years since quitting smoking (Thacker et al., 2007). It was concluded that the dependence of this association on the timing of smoking during life is consistent with a biologic effect. A long-term follow-up survey of mortality in British doctors found that dying from PD is statistically less in smokers; moreover, the longer time that smokers had stopped smoking (i.e., being free from smoking), there was a decline in this protection benefit (Mappin-Kasirer et al., 2020). The authors concluded that their study shows a causal benefit of smoking. Although the factor(s) are not certain in regard to what provides this protection, and many suspect it might be nicotine, one factor that seems plausible is that cigarette smoke inhibits brain MAO (Fowler et al., 2003a,b, 2005), an enzyme implicated in the pathogenesis of PD (see section on Oxidative Stress for details).

Coffee consumption was also found to be associated with a lower risk for developing PD. First discovered by Ross and colleagues (2000) in Japanese American men in Hawaii, this association has held up in subsequent epidemiologic studies. Ascherio and colleagues (2001) evaluated this association in two other large cohorts being followed and found a similar association with coffee consumption and a mild lowered risk for developing PD in men (the authors speculated that estrogen use in women eliminated the caffeine

Table 5.5 Pesticides, effect modification, and risk of Parkinson disease

Toxicant	Exposure type	Effect size	Genetic modifier	Modified effect size	Environmental modifier	Modified effect size
Paraquat	Occupational, residential	~2–3 fold ↑ risk	GST T1 null	~11 fold ↑ risk	1. Maneb, ziram	1. ~ 3–4 fold ↑ risk
					2. Head injury	2. ~3 fold ↑ risk
					3. Low dietary PUFAs	3. ~4 fold ↑ risk
					4. Not using PPE	4. ~4 fold ↑ risk
Rotenone	Occupational	~2–3 fold ↑ risk	Unknown	—	1. High dietary saturated fat	1. ~6 fold ↑ risk
					2. PPE	2. ~5 fold ↑ risk
Organochlorines: dieldrin, DDT, hexachlorocyclohexanes	Occupational, gardening, residential	~2 fold ↑ risk	1. CYP 2D6 PM	1. 2–4 fold ↑ risk	Unknown	—
			2. ABCB1 variants	2. 2–5 fold ↑ risk		
Organophosphates: malathion, parathion, chlorpyrifos, diazinon	Occupational, residential	~2–5 fold ↑ risk	PON1 variant	~2–3 fold ↑ risk	Unknown	—
Permethrin	Occupational, impregnated clothing, home use	Not significant	—	—	No PPE	~4 fold ↑ risk
Benomyl	Ambient occupational or residential	~0.5 fold ↑ risk	SKP 1 variant	~7 fold ↑ risk	Unknown	—

ABC B1, ATP binding cassette B1; CYP, cytochrome P 450; DA, dopamine; GST T1, glutathione S transferase T1; PUFAs, polyunsaturated fatty acids; PM, poor metabolizer; PON1, Paraoxonase 1; PPE, personal protective equipment; UPS, ubiquitin protease system; SKP 1, S phase kinase associated protein 1 variant.

From Marras C, Tanner C, Ross W, Langston W: *Etiopathogenesis: Environmental factors*. In: Obeso JA, Stamelou M, Goetz CG, et al: *Past, Present, and future of Parkinson's disease: A special essay on the 200th Anniversary of the Shaking Palsy*. *Mov Disord*. 2017;32(9):1264–1310.

benefit). Focus centered on caffeine and then speculation about the adenosine A2A receptor because this is affected by caffeine (Checkoway et al., 2002; Hernan et al., 2002; Schwarzschild et al., 2002; Ascherio et al., 2003, 2004). In addition to coffee, consuming tea was also associated with a reduced risk for developing PD (Tanaka et al., 2011).

A higher serum urate level was found to correlate with a reduction in developing PD (Weisskopf et al., 2007). Subsequent studies evaluating urate levels in plasma in the PRECEPT (Schwarzschild et al., 2008) and CSF in the DATATOP (Ascherio et al., 2009) clinical trials found that higher urate levels in men were associated with a slower rate of progression of PD. Urate has antioxidant properties. A clinical trial was undertaken with inosine, a urate precursor. Unfortunately, inosine was ineffective in slowing the worsening of PD (<https://www.michaeljfox.org/foundation/news-detail.php?parkinson-inosine-trial-ending-early>).

Use of anti-inflammatory drugs (Gagne and Power, 2010; Gao et al., 2011) and statins (Gao et al., 2013; Undela et al., 2013; Lin et al., 2016) have been reported to reduce the risk for developing PD; so has adhering to a Mediterranean diet (Maraki et al., 2019; Molsberry et al., 2020) or a quasi-vegan diet (McCarty and Lerner, 2020). Various lifestyle factors were investigated as to their effect on the development or progression of PD, and it was reported that coffee, caffeinated tea, moderate alcohol consumption, and physical activity were associated with reduced risk (Paul et al., 2019; Hughes et al., 2019). On the other hand, those who never

drank liquor and those who drank more heavily were at an increased risk. In the study by Paul and colleagues (2019), smoking was associated with an increased risk, which is at odds with most studies investigating smoking.

Beta2-adrenoreceptor (β2AR) agonists have now been suggested as agents to reduce the risk for developing PD. Scherzer's laboratory developed a high-throughput gene expression assay for the human alpha-synuclein gene, SNCA, using neuronal cells (Mittal et al., 2017). They screened more than 1100 compounds and discovered that the β2AR is a regulator of the SNCA. β2AR ligands modulate SNCA transcription through acetylation of histone 3 lysine 27 (Mittal et al., 2017). They found that the β2AR agonists, metaproterenol, clenbuterol, and salbutamol lowered alpha-synuclein production in a dose- and time-dependent manner. They then tested the effect in vivo, injecting clenbuterol intraperitoneally and found that it crossed the blood-brain barrier. In a randomized, placebo-controlled trial in wild-type mice, clenbuterol lowered endogenous alpha-synuclein protein and mRNA levels in the SN. Using neurons from mice with a deletion of the β2AR gene, they found that endogenous SNCA mRNA and alpha-synuclein protein levels were increased by 100% and 120%, respectively. Moreover, they found that the beta-blocker propranolol increased endogenous alpha-synuclein mRNA and protein levels. They used the MPTP mouse model and showed that clenbuterol protected against MPTP-induced degeneration of tyrosine hydroxylase-containing neurons in the SNc. The investigators also looked at a Norwegian database that tracks all

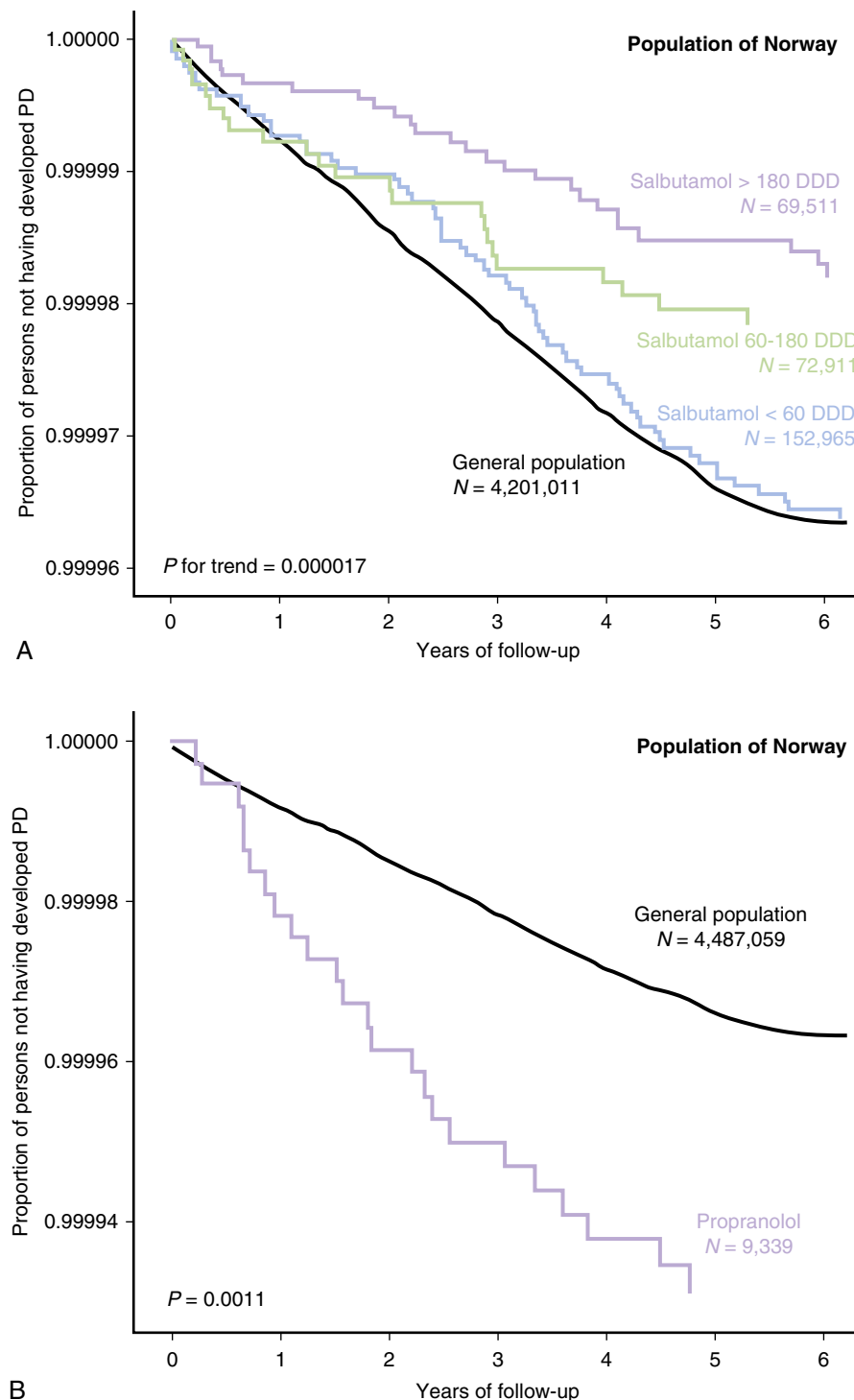


Fig. 5.24 Survival curves on not developing PD in Norwegians treated with salbutamol (A) or propranolol (B). Graph A shows dosage effect of salbutamol, with the highest dose being most protective against developing PD. The solid black lines in graphs A and B represent the Norwegian population not on these drugs.

drug prescriptions in that country. Salbutamol was associated with decreased risk for PD, with a rate ratio of 0.66; in contrast, propranolol was associated with a markedly increased risk for PD, with a rate ratio of 2.20 (Fig. 5.24). Finally, the investigators looked at stem cells from a patient with a triplication of the *SNCA* gene. When the cells were treated with clenbuterol, the endogenous *SNCA* mRNA expression and alpha-synuclein protein levels were significantly reduced.

Gronich and colleagues (2018) analyzed the risk for developing PD in a large Israeli health database, and the results

supported the work by Scherzer's study (Mittal et al., 2017). Use of beta-2 agonists statistically lowered the risk for developing PD, whereas propranolol increased it. Interestingly, the use of beta-1 antagonists had no effect (Gronich et al., 2018). On the other hand, a subsequent study, using the U.S. Medicare database analyzing 48,295 incident PD cases and 52,324 controls, and eliminating smokers and those with tremor (an indication for propranolol therapy, concluded that neither beta2-adrenoreceptor agonists nor propranolol alter the risk for developing PD (Searles Nielsen et al., 2018)).

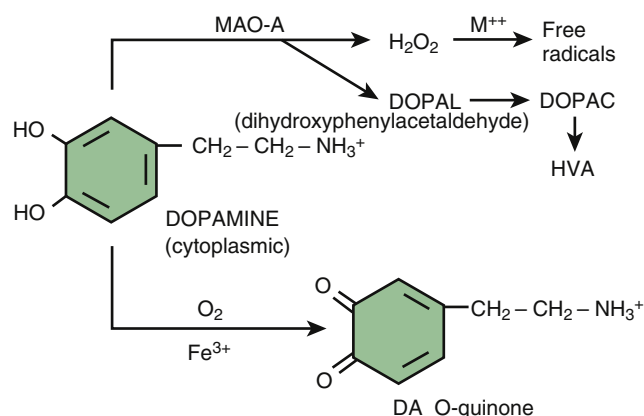


Fig. 5.25 Auto-oxidation and enzymatic oxidation of dopamine (DA) to form oxyradicals and dihydroxyphenylacetaldehyde (DOPAL). DOPAC, 3,4-Dihydroxyphenylacetic acid; HVA, homovanillic acid; MAO-A, monoamine oxidase-A.

Endogenous factors in dopamine neurons that contribute to the cause of PD: alpha-synuclein, cytosolic dopamine, and calcium

Gene mutations described previously are not restricted to the cells that succumb in PD. Therefore, there must be other factors that make these cells, in particular, more vulnerable. There are some unique features of dopamine neurons, and it is plausible that one or more contributes to the selective vulnerability of these cells. Three of them have gained prominence: (1) the presence of dopamine, the oxidation of which can lead to oxidative stress; (2) the interaction between dopamine and alpha-synuclein; and (3) the autonomous firing of the SNc dopaminergic neurons using influx of calcium ions to trigger the action potential.

Dopamine induces oxidative stress

The SNc neurons are dopaminergic, and this monoamine provides a steady source of oxidative stress (Fahn and Cohen, 1992). Levodopa and dopamine can be auto-oxidized to oxyradicals (semiquinones and quinones) and dopamine can be enzymatically oxidized by MAO-A (located in the dopamine nerve terminals) to form the intermediate dihydroxyphenyl-acetaldehyde (DOPAL) and final metabolite, HVA (Fig. 5.25). For every molecule of dopamine metabolized by MAO, a molecule each of DOPAL and hydrogen peroxide is formed, with the latter being a precursor of more oxyradicals. DOPAL has been found to enhance aggregation of alpha-synuclein (Burke, Kumar et al., 2008). This may be an important mechanism of nigral neuron cell death because injection of DOPAL into rat nigra results in dopamine neuron loss (Burke, Kumar et al., 2008).

One of the cell's defense mechanisms against oxyradicals is to condense these oxidized compounds and turn them into insoluble neuromelanin (Sulzer et al., 2000) (Fig. 5.26). This could explain why the most susceptible cells are those with the most neuromelanin (Hirsch et al., 1988, 1989), not necessarily because neuromelanin itself is toxic, but rather because its presence indicates these are the cells with the most oxidative stress. Cytosolic dopamine quinone can also form adducts with other compounds, including cysteine to make a toxic compound.

Interaction between dopamine and alpha-synuclein

In the dopamine neuron, a special situation occurs for wild-type alpha-synuclein. Wild-type alpha-synuclein is present in the cytoplasm in both a soluble monomeric form that is natively unfolded and as aggregation-resistant alpha-helix-rich tetramers (Dettmer et al., 2015). These forms are in equilibrium, with the tetramers being the larger component. The ratio reverses in PD because the equilibrium shifts when the monomeric protein combines to form oligomers, which are toxic. A diagram of normal soluble monomeric alpha-synuclein forming oligomers, fibrils, and aggregates and their deposition in Lewy bodies is seen in Fig. 5.27. Also called protofibrils, oligomers are beta-sheets that consist of spheres, chains, and rings (Lansbury and Brice, 2002)].

By virtue of alpha-synuclein containing an alpha helix domain, it can associate with vesicle membranes (Clayton and George, 1998). A potential role for binding to synaptic vesicles is suggested by an enhanced synaptic recovery for evoked dopamine release in the knockout animal (Maroteaux et al., 1988) and alterations in the distal synaptic vesicle pool in mutants (Abeliovich et al., 2000; Cabin et al., 2002). These protofibrils permeabilize the synaptic vesicles that store dopamine by forming pore-like assemblies on their surface (Mosharov et al., 2006). This allows leakage of vesicular dopamine into the cytosol, thus enriching cytosolic dopamine to enhance oxidative stress. A vicious cycle is at play because cytosolic dopamine reacts with alpha-synuclein to form a covalent adduct that slows the conversion of protofibrils to fibrils, thus sustaining the presence of the protofibrils (oligomers) (Conway et al., 2000; Rochet et al., 2004). The presence of the oligomers then leads to more permeabilization of the synaptic vesicles and more cytosolic dopamine (Sulzer, 2010).

Another critical peculiarity of alpha-synuclein-dopamine adducts is that they block chaperone-mediated autophagy (CMA) by binding and blocking the receptors on the lysosome from accepting other proteins from being broken down by the CMA mechanism (Martinez-Vicente et al., 2008). This would lead to accumulation of toxic proteins in the cell, which would lead to the cells dysfunction and death. A more complete discussion about the role of autophagy in removing damaged proteins is presented later in the section on autophagy.

Calcium influx into SNc dopaminergic neurons

A remarkable feature in the pathologic process of PD is that whereas SN dopamine neurons, particularly those located in the ventral tier of the SNc, undergo selective death, the neighboring dopamine neurons of the VTA are generally unaffected. The reason for this selective pattern of dopaminergic neuronal death remains unclear and could be an important clue to the pathogenesis of PD. There are differences between the dopaminergic neurons in the SN and the VTA. In the VTA, there is less neuromelanin (apparently indicating less long-term oxidative stress from cytosolic dopamine) and there is more of the calcium binding protein, calbindin (Iacopino et al., 1992). The expression of the vesicular monoamine transporter (VMAT2) that delivers cytosolic dopamine into the synaptic vesicles also may be somewhat higher in the VTA (Peter et al., 1995). A likely major distinguishing difference relates to calcium. Adult SNc dopaminergic neurons

fire autonomously because of calcium ion influx, but VTA dopaminergic neurons use sodium ions (Surmeier, 2007).

A physiologic explanation has been suggested by Surmeier (2007). Unlike most neurons in the brain, SNc dopamine neurons are autonomously active; that is, they generate action potentials at a clock-like 2 to 4 Hz in the absence of synaptic

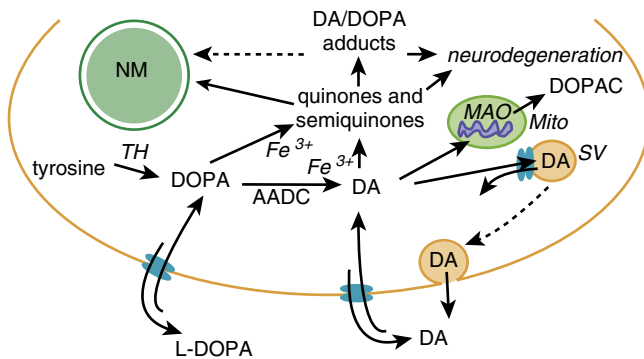


Fig. 5.26 Metabolic pathways for levodopa and dopamine forming neuromelanin in dopaminergic nerve cells. AADC, Amino acid decarboxylase; DA, dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid; MAO, monoamine oxidase; Mito, mitochondria; NM, neuromelanin; SV, synaptic vesicle; TH, tyrosine hydroxylase. (From Sulzer D, Bogulavsky J, Larsen KE, Behr G, Karatekin E, Kleinman MH, et al: Neuromelanin biosynthesis is driven by excess cytosolic catecholamines not accumulated by synaptic vesicles. *Proc Natl Acad Sci U S A*. 2000;97:11869–11874.)

input. In this respect, they are much like cardiac pacemakers. Juvenile dopamine-containing neurons in the SNc use sodium ion influx as the pacemaking mechanism. But these mechanisms remain latent in adulthood (Chan et al., 2007). Instead, the adult autonomous activity is generated by Ca^{++} ions, whereas most neurons use channels that allow Na^{+} ions across the membrane. The SNc dopamine neurons rely on L-type Ca(v)1.3 Ca^{++} channels. With increased intracellular calcium, mitochondria function can be affected with increased demand on oxidative phosphorylation, leading to increased production of reactive oxygen species and eventually cellular damage. As the cells undergo more stress over time, they “age faster.” This would be a link with the risk factor of age (Surmeier, 2007). Blocking Ca(v)1.3 Ca^{++} channels in adult neurons induces a reversion to the juvenile form of pacemaking (Chan et al., 2007). Such blocking (“rejuvenation”) protects these neurons in both in vitro and in vivo models of PD, pointing to a new strategy that could slow or stop the progression of the disease (Chan et al., 2007; Surmeier, 2007). Already underway is a phase III clinical trial evaluating the calcium-channel blocker isradipine to determine whether this will slow the worsening of early PD.

An intriguing finding is that a case-control analysis within the U.K.-based General Practice Research Database revealed that calcium-channel blockers when used to treat hypertension are associated with a lower prevalence of PD in those individuals

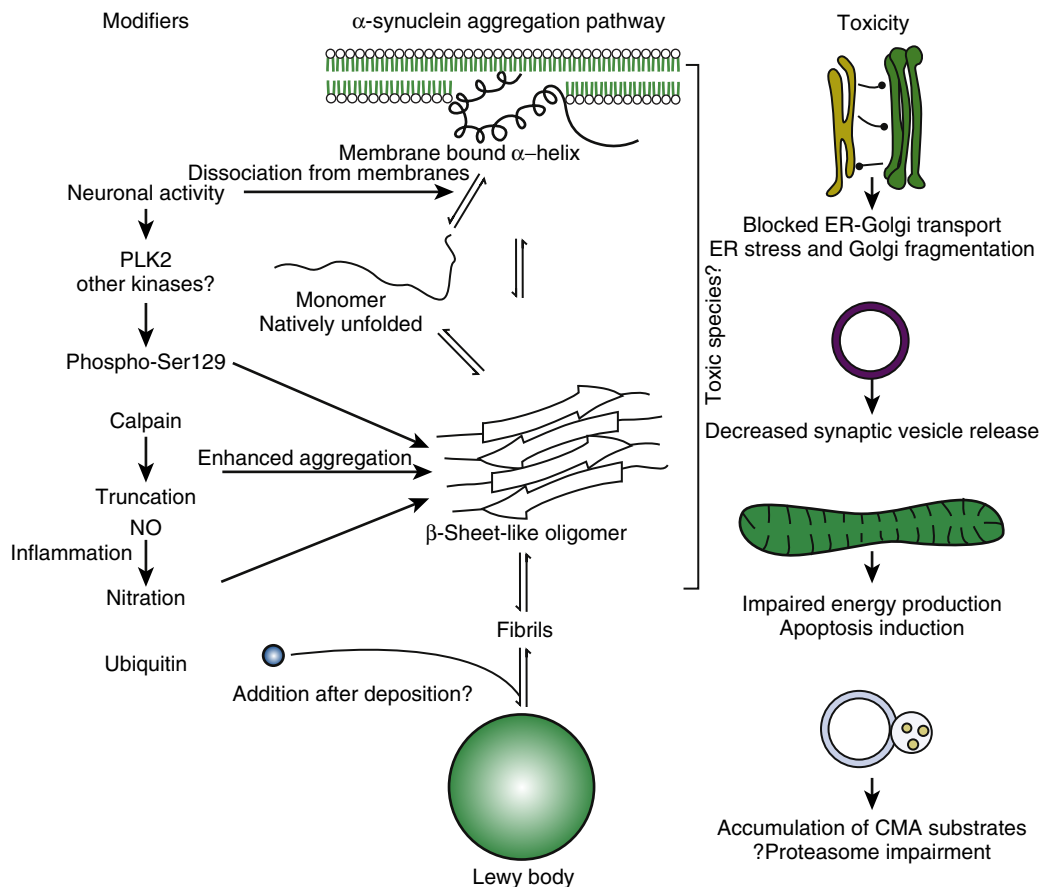


Fig. 5.27 Schematic showing the different forms of alpha-synuclein and the pathway to fibrillogenesis. Natively unfolded or disordered alpha-synuclein monomers also can be in an alpha helical form when within a membrane. It can form beta-sheet-rich oligomers that comprise a transient population of protofibrils of heterogeneous structure that may include spheres, chains, or rings. The protofibrils may give rise to more stable amyloid-like fibrils. Alpha-synuclein fibrils eventually aggregate and precipitate to form LBs in vivo. CMA, Chaperone-mediated autophagy; ER, endoplasmic reticulum; NO, nitric oxide. (From Cookson MR: Alpha-synuclein and neuronal cell death. *Mol Neurodegener*. 2009;4–9.)

compared with other antihypertensive therapies (Becker et al., 2008). This finding has been substantiated by a similar epidemiologic analysis of the Danish medical database. Subjects prescribed centrally acting dihydropyridines (calcium channel blockers) before 2 years before the index date (onset of PD in the affected) were less likely to develop PD (OR, 0.73; 95% CI, 0.54–0.97) (Ritz et al. 2010). In contrast, risk estimates were close to null for the peripherally acting dihydropyridine amlodipine, and for other antihypertensive medications.

Mosharov and colleagues (2009) found that an interaction among Ca^{++} , cytosolic dopamine, and alpha-synuclein appears to underlie the susceptibility of SN neurons in PD. Alpha-synuclein is critical, for without it, dopaminergic neurons are resistant to L-dopa toxicity. Ca^{++} influx through L-type channels elevates dopamine synthesis to potentially toxic levels (Mosharov et al., 2009). Fig. 5.28 illustrates how Ca^{++} influx influences mitochondria and oxidative stress and may lead to cell death. Fig. 5.29 illustrates how all the previously mentioned endogenous factors influence the pathogenesis of PD.

Where does the pathologic process of PD begin? And how does it progress? Braak staging system

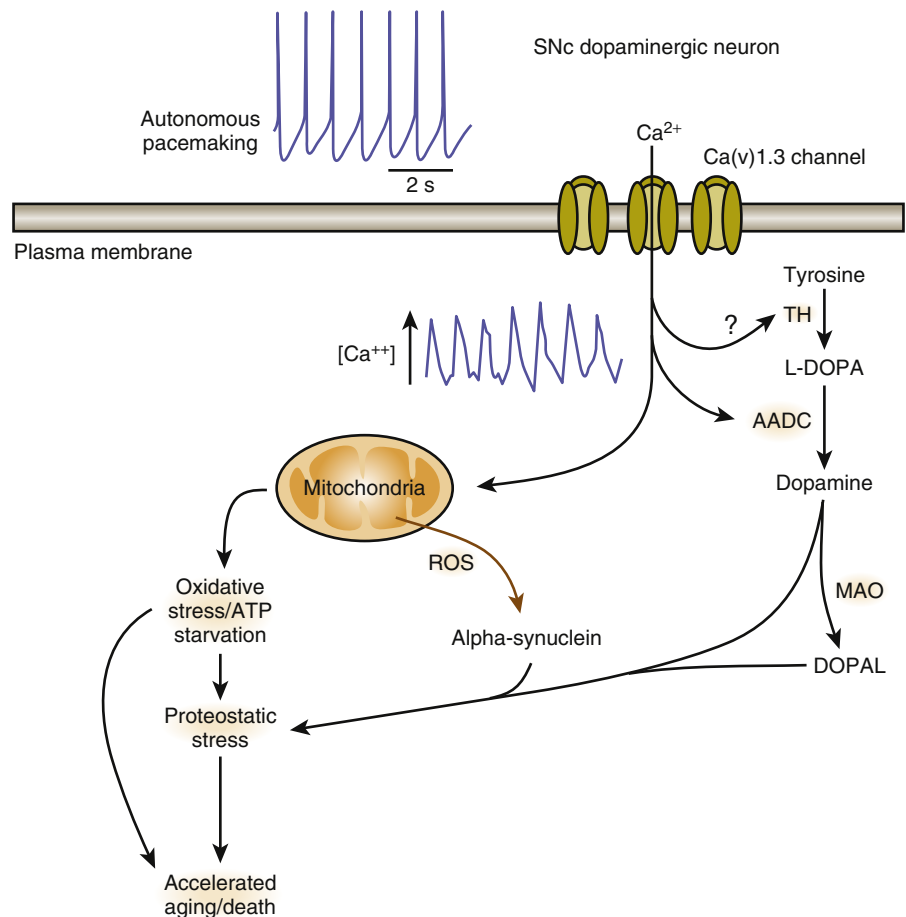
Following the development of Lewy neurites

Braak and colleagues, using staining techniques to identify alpha-synuclein in neurons (Lewy neurites), studied 30

autopsied brains that were observed to have incidental Lewy body pathologic findings (Del Tredici et al., 2002). Instead of finding alpha-synuclein-staining fibers in the SN, they found them in noncatecholaminergic neurons of the dorsal glossopharyngeus-vagus complex, in projection neurons of the intermediate reticular zone, and in specific nerve cell types of the gain-setting system (ceruleus-subceruleus complex, caudal raphe nuclei, gigantocellular reticular nucleus), olfactory bulb, olfactory tract, and/or anterior olfactory nucleus, all in the absence of nigral involvement (Fig. 5.30). None of the melanized areas were affected, and the first of these to show Lewy changes was the LC. Based on the findings of the location of Lewy neurites, these investigators proposed that PD begins in the lower brainstem and the olfactory apparatus.

Braak followed this study with one investigating Lewy neurites in 41 autopsies that were characteristic of PD clinically and pathologically and in 69 others who had no clinical features but whose autopsies showed Lewy neurites so that he could determine whether there was a pattern of progression (Braak et al., 2003, 2004). A pattern of alpha-synuclein-immunopositive Lewy neurites and Lewy bodies was discerned, in which these features began in the anterior olfactory nucleus and in the lowest part of the brainstem (stage 1) and then progressed rostrally up the brainstem. The raphe and LC were the next to be involved (in stage 2). The SN became involved in stage 3, the mesocortex and thalamus in stage 4, the neocortex association areas and prefrontal cortex in stage 5, and the entire neocortex, but only mildly so

Fig. 5.28 Calcium enhancement of dopamine synthesis leads to increased stress in substantia nigra dopaminergic neurons. AADC, Amino acid decarboxylase; ATP, adenosine triphosphate; DOPAL, dihydroxyphenyl-acetaldehyde; MAO, monoamine oxidase; ROS, reactive oxygen species; SNc, substantia nigra pars compacta; TH, tyrosine hydroxylase. (From Surmeier DJ. A lethal convergence of dopamine and calcium. *Neuron*. 2009 Apr 30;62(2):163-4.)



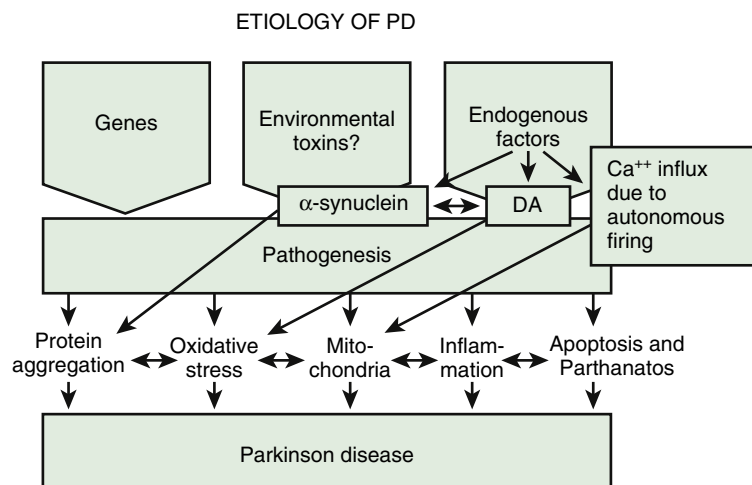


Fig. 5.29 Endogenous factors contributing to the pathogenesis of dopamine (DA) neuron loss in PD.

in primary motor and sensory areas, in stage 6 (Fig. 5.31). As the stages develop, the sites involved in the earlier stages become more severely affected.

In a subsequent titled lecture, Braak and colleagues (2006) reinforced his staging system and cited support from other neuropathologic reports. They state that their samples did not include cases of diffuse Lewy body disease, which has its Lewy bodies starting in the cerebral cortex. All 110 cases they examined fell into one of six different subgroups based on the location of the brain regions involved. Each of the subgroups displayed newly affected regions and worsened those previously involved. They pointed out that long unmyelinated axons, which the nigrostriatal pathway has, are the susceptible sites for Lewy neurites.

Although alpha-synuclein accumulation may not start in the nigra, unless the nigra becomes involved, the symptoms of PD do not develop. On the other hand, it is possible that symptoms of decreased sense of smell, depression, decreased assertiveness, impaired spatial sense, and even constipation may be preclinical symptoms of PD (Fig. 5.32) (Langston, 2006). Such a concept is leading researchers to seek clinical and laboratory biomarkers to detect PD before it becomes manifest with motor symptoms.

Are Lewy bodies and Lewy neurites toxic or protective?

Since Lewy bodies were first discovered, most neurologists and neuropathologists assumed that they somehow contribute to the cause or pathogenesis of the disease. This assumption has come under serious doubt. In fact, there is a large school of scientists who consider the formation of Lewy bodies as a means for the neuron to protect itself. Initiated by Lansbury and colleagues (2002, 2006), the concept has evolved that oligomers (protofibrils) of alpha-synuclein are toxic, in part because they permeabilize synaptic vesicle membranes. The protofibrils can be fibrillated (aggregated) into amyloid, thereby removing them into Lewy neurites and Lewy bodies and thus protecting the neuron (Figs. 5.33 and 5.34). In this proposal, these aggregates thus represent a protective mechanism by the cell against oligomer toxicity. One study addressed the question of toxicity of oligomer versus fibrils by comparing the effects of alpha-synuclein mutations on oligomerization and aggregation (Lázaro et al., 2014).

The results showed that all mutants enhance oligomerization, but not all are inducers of aggregation. This supports oligomers as being the more important toxic form of alpha-synuclein. However, a number of neuroscientists think the fibrils are the toxic element. In support of this, the inoculation of preformed alpha-synuclein fibrils into the brain results in the spread of toxic alpha-synuclein and neuronal degeneration, first reported by Luk and colleagues (2012). The question as to which are more toxic, oligomers or fibrils, remains an uncertain and controversial point (Chartier and Duyckaerts, 2018).

Is the Braak staging system for PD established as denoting the progression of pathology in PD?

The contributions by Braak and colleagues (2003, 2004, 2005) have had a profound impact on a new understanding of PD and has generated new ideas and testable hypotheses for how PD might start and the way PD worsens over time. With Braak's proposal, a feature in PD is that alpha-synuclein would enter the brain through regions connected to autonomic and olfactory centers, and this is a serious area of current research. The Braak concept/hypothesis that PD begins in the caudal medulla and spreads rostrally has been tested by other neuropathologists, and many have found that Lewy bodies and neurites first occur in the medulla in over 80% of postmortem proven cases of PD (Parkkinen et al. 2008; Dickson et al., 2010).

An early comprehensive appraisal of the Braak hypothesis was conducted by Burke, Dauer, and Vonsattel (2008). From their analysis, it is clear that the caudal to rostral spread of Lewy neurites is not entirely universal. But based on more research over time, it appears that, although a universal spread of pathologic conditions does not explain all cases of PD, a majority of cases seem to follow the pattern depicted by Braak. Dickson and colleagues (2010) studied the density and distribution of Lewy bodies in several conditions. They found that the proportion of cases that fit the Braak PD staging scheme was 67% for incidental Lewy bodies (N = 12); 86% for progressive supranuclear palsy (PSP) with incidental Lewy bodies (N = 18); 86% for pure Lewy body disease with minimal or no Alzheimer type pathology (N = 52); 84% for LBD with concomitant AD (N = 84); and only 6%

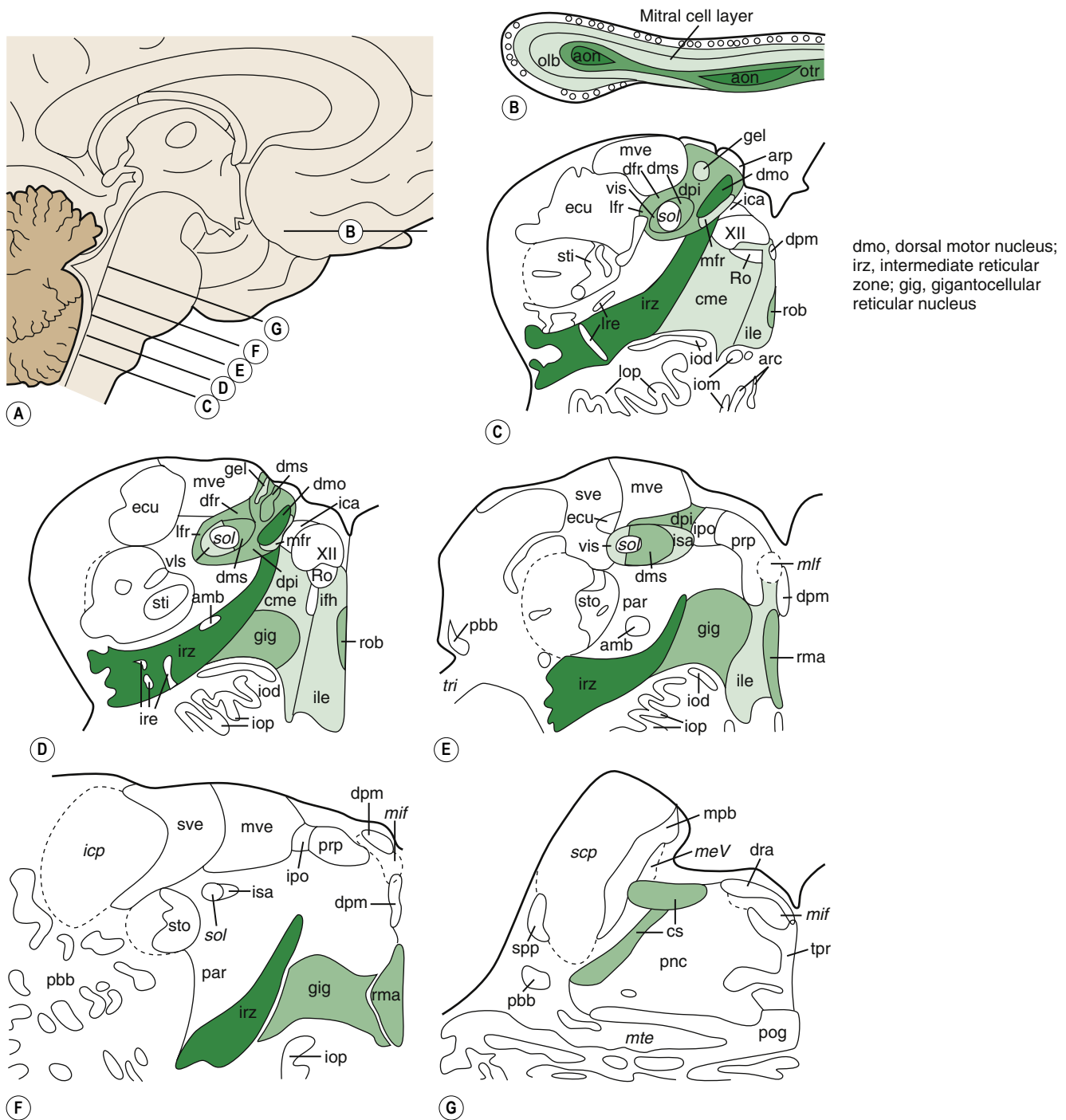


Fig. 5.30 Location of Lewy neurites in people with incidental Lewy bodies, and without clinical PD or dementia with Lewy bodies (DLB). The more intense the color, the greater amount of Lewy neurites are present. (Del Tredici K, Rub U, DeVos RA, Bohl JR, Braak H: Where does Parkinson disease pathology begin in the brain? *J Neuropathol Exp Neurol.* 2002;61[5]:413–426.)

for AD with amygdala-predominant Lewy bodies (N = 64). They conclude that the PD staging scheme is valid, except in the setting of advanced AD.

In their extensive review of the literature, Halliday and colleagues (2012) tabulated and discussed the research favoring and opposing the conclusions of the Braak hypothesis. The current view is that for most cases of PD, the Braak hypothesis fits. However, despite the neuropathologic processes fitting the Braak concept, there is no correlation between Braak

stages and the clinical severity of PD based on Hoehn and Yahr staging (Burke et al., 2008).

What does fit with the Braak hypothesis is that some non-motor features of PD appear before the motor signs as predicted by the Braak staging hypothesis. For example, loss of sense of smell, RBD and autonomic nervous system involvement often occur before the motor features of PD. The autonomic nervous system involvement could explain the constipation seen in PD. A case-control study at the Mayo

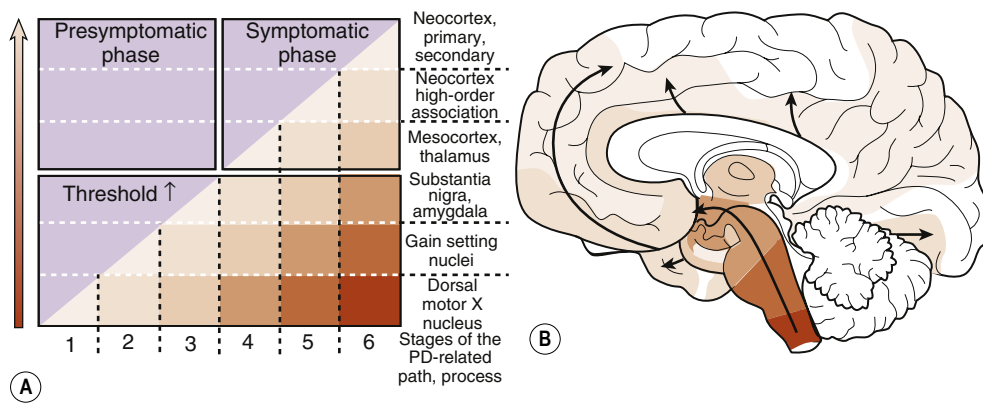


Fig. 5.31 Braak staging of PD based on development of Lewy neurites. (From Braak H, Ghebremedhin E, Rub U, Bratzke H, Del Tredici K: Stages in the development of Parkinson's disease-related pathology. *Cell Tissue Res.* 2004;318[1]:121–134.)

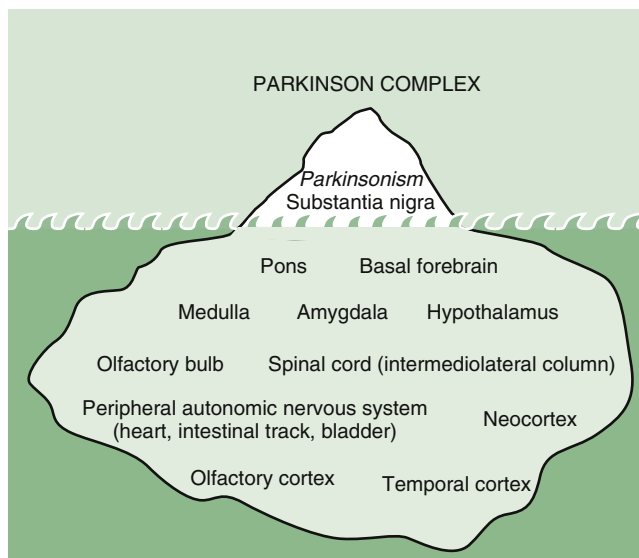


Fig. 5.32 Clinical PD diagrammed as being overt manifestation of a more complex disorder, in which several nonmotor features are considered part of PD. (From Langston JW: The Parkinson's complex: Parkinsonism is just the tip of the iceberg. *Ann Neurol.* 2006;59[4]:591–596.)

Clinic matched each incident case of PD (N = 196) by age and gender to the general control population (Savica et al., 2009). Constipation preceding PD was more common in cases than in controls ($P = 0.0005$). This association of constipation was found to have occurred for 20 or more years before the onset of motor symptoms of PD. Bowel movement frequency was monitored and compared with post-mortem SN neuronal loss in the Honolulu-Asia Aging Study (Petrovitch et al., 2009). There were evaluations in 414 men aged 71 to 93 years who later had postmortem evaluations. Men with one or more bowel movements daily were significantly higher compared with those with fewer than one daily. This was supported in another study evaluating a large database that showed those with severe constipation were strongly more likely to develop PD, with a risk greater than 3-fold (Lin et al., 2014). Constipation was associated with low SN neuron density independent of the presence of Lewy bodies. Incidental Lewy bodies were evaluated in these men. For men with fewer than one, one, and more than one bowel movement per day, corresponding percentages of incidental Lewy bodies were 24.1%, 13.5%, and 6.5%, respectively (Abbott et al., 2007), reflecting that fewer bowel movements

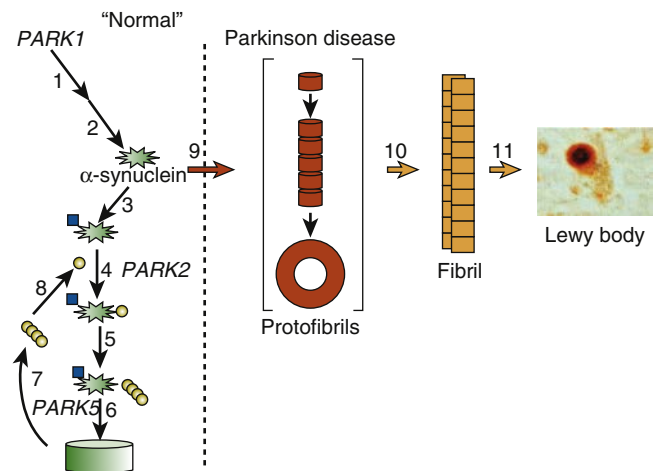


Fig. 5.33 Excess or altered alpha-synuclein that is unable to be removed by the cell can form oligomers (protofibrils) and ultimately fibrils, which are deposited in Lewy bodies. (Lansbury PT, Brice A: Genetics of Parkinson's disease and biochemical studies of implicated gene products. *Curr Opin Genet Dev.* 2002;12:299–306.)

were associated with more Lewy bodies. This was supported in another study evaluating a large database that showed those with severe constipation were strongly more likely to develop PD, with a risk greater than 3-fold (Lin et al., 2014).

Olfaction dysfunction (hyposmia) also precedes the motor signs of PD. Olfaction was assessed in 2267 men in the Honolulu-Asia Aging Study and followed for up to 8 years (Ross et al., 2008). The odds ratio for developing PD in the lowest quartile of smell sensitivity was 5.2 compared with the top two quartiles. In another prospective study, involving nonaffected relatives of PD patients, 40 hyposmic and 38 normosmic individuals were studied at baseline and 2 years later with clinical evaluation and a DAT scan (Ponsen et al., 2004). By 2 years, 10% of the individuals with hyposmia, who also had strongly reduced DAT binding at baseline, had developed clinical PD as opposed to none of the other relatives in the cohort. In the remaining nonparkinsonian hyposmic relatives, the average rate of decline in DAT binding was significantly higher than in the normosmic relatives. These results indicate that idiopathic olfactory dysfunction is associated with an increased risk for developing PD of at least 10%.

Supporting evidence that the peripheral nervous system is affected before CNS Lewy neurites was the finding that cardiac sympathetic denervation, as measured by MIBG scintigraphy, precedes nigrostriatal loss (Tijero et al., 2010).

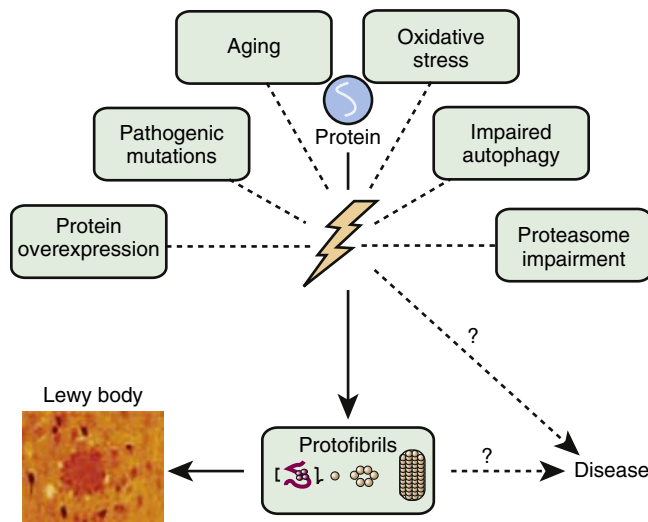


Fig. 5.34 Factors that lead to the formation of alpha-synuclein protofibrils that could result in neurodegeneration. (From Lansbury PT, Lashuel HA. A century-old debate on protein aggregation and neurodegeneration enters the clinic. *Nature*. 2006;443(7113):774–779.)

If RBD develops from involvement of the pontine-medullary area, then RBD should precede clinical PD. But not every person with PD has RBD, and not everyone with (idiopathic) RBD develops PD, although over 80% develop PD or a related synucleinopathy (DLB, MSA, primary autonomic failure) clinically (Iranzo et al., 2013; St Louis et al., 2017). Postmortem correlation studies are very impressive; they show that over 80% of those with idiopathic RBD will develop a synucleinopathy (Boeve et al., 2013; Schenck et al., 2013). Even those who had not presented a neurodegenerative disorder after 10 years of onset of idiopathic RBD have evidence on detailed examination of some feature of a neurodegenerative process (Yao et al., 2018).

Some earlier studies found a lower incidence of developing PD, probably because of not following the patients long enough. Postuma and colleagues (2009) followed patients with idiopathic RBD and found the risk for developing any neurodegenerative disease (PD, DLB, MSA, or AD) is 17.7% by 5 years, 40.6% by 10 years, and 52.4% by 12 years. In a subsequent prospective study, the risk for developing a neurodegenerative synucleinopathy (PD, MSA, or DLB) in people with idiopathic RBD was 30% at 3 years, rising to 66% at 7.5 years (Postuma et al., 2015). Even those who had not presented a neurodegenerative disorder after 10 years of onset of idiopathic RBD have evidence on detailed examination of some feature of a neurodegenerative process (Yao et al., 2018).

In the survey of their PD patients, Scaglione and colleagues (2005) found that only 33% had RBD. Of these, PD preceded RBD in 73%, an average of 8 years after onset of PD. In another study, RBD preceded PD in only 22% (De Cock et al., 2007).

In addition to the critique about the Braak hypothesis by Burke and colleagues (2008), mentioned earlier, there are additional findings that do not seem to fit with the Braak hypothesis (Rietdijk et al., 2017). For example, neuroimaging of serotonergic and noradrenergic systems by PET failed to show their dysfunction ahead of the dopaminergic system in PD (Brooks, 2010) even though that would have

been predicted in the Braak hypothesis. Brooks (2010) also showed that microglial activation in the cerebral cortex as detected by PET can precede clinical dementia in early PD, suggesting a Braak level 5 or 6 at that early stage.

Braak and colleagues are now estimating that the disease (pathologic process of Lewy neurites) begins in the olfactory and autonomic system by approximately 20 years before the onset of the motor symptoms of PD, and they have tried to correlate Braak staging with the Hoehn and Yahr staging of clinical PD (Hawkes et al., 2010) (Fig. 5.35).

The monogenic causes can be dichotomized into two pathologic conditions related to the spread/worsening of PD to involve the cerebral cortex and cause dementia as a major late stage feature. The gene mutations that lead primarily to impairment of mitochondrial mitophagy (PRKN, PINK1 DJ-1) typically do not cause dementia or a number of other nonmotor features (e.g., hyposmia, RBD). In contrast, the gene mutations leading to the accumulation of alpha-synuclein and formation of alpha-synuclein oligomers and fibrils typically result in a spread of PD to involve nonmotor features, including dementia. It is likely that alpha-synuclein becomes a rogue protein that results in this unfortunate progression of PD (discussed later in the section Rogue Protein Hypothesis). The concept that the presence of Lewy bodies, a marker of rogue protein alpha-synuclein, is associated with the typical and more alarming form of PD is supported by the studies showing those patients with the LRRK2 G2019S mutation who have Lewy bodies at autopsy have the typical progressive type whereas those who do not have Lewy bodies are relatively free of the terrible nonmotor features of PD, such as AD dementia (Kalia et al., 2015). These non-Lewy body cases still have all the motor features of PD, including the late development of freezing of gait and postural instability. Fig. 5.36 depicts the monogenic forms that have Lewy bodies with typical worsening of PD and those monogenic forms that do not have Lewy bodies with a milder form of PD.

Clues on pathogenesis from monogenic PD

PARK1 (SNCA) and PARK4 (SNCA) and alpha-synuclein accumulation as Lewy neurites and Lewy bodies: impaired autophagy

Based on the presence of alpha-synuclein in Lewy bodies and on the pattern of progressive Lewy neurite formation from the caudal to rostral areas of the brain, it is clear that alpha-synuclein has a special place in the pathogenesis of PD. The normal function of alpha-synuclein, however, may have little or nothing to do with its role in pathogenesis. Its ability to self-aggregate, its presence in Lewy bodies, the apparent ability of pathogenic mutations or nitrated- or dopamine-reacted proteins to be more prone to aggregation, the ability of protofibrils to disrupt membrane, and the identification of PARK4 as a triplication of the chromosomal region that contains the alpha-synuclein gene, all seem to point to a toxic function of aggregated alpha-synuclein itself. This notion is also supported by the finding that mice that lack alpha-synuclein expression are resistant to MPTP toxicity, although neuronal and synaptic vesicle uptake appear unaltered (Dauer et al., 2002). Expression of mutant alpha-synuclein also causes an

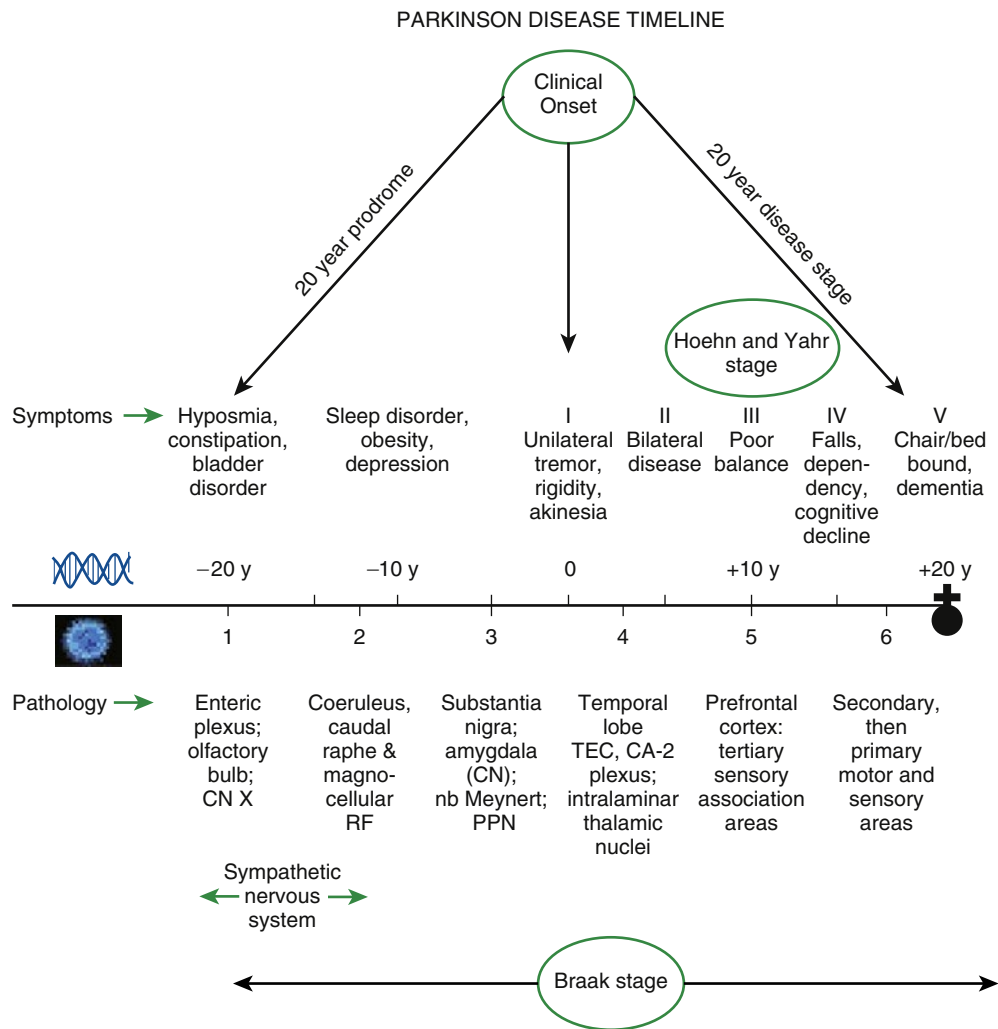


Fig. 5.35 Diagram of 40-years' duration of PD, with 20 years being premotor. CN, cranial nerve; PPN, pedunculopontine nucleus. (From Hawkes CH, Del Tredici K, Braak H. A timeline for Parkinson's disease. *Parkinsonism Relat Disord.* 2010;16[2]:79–84.)

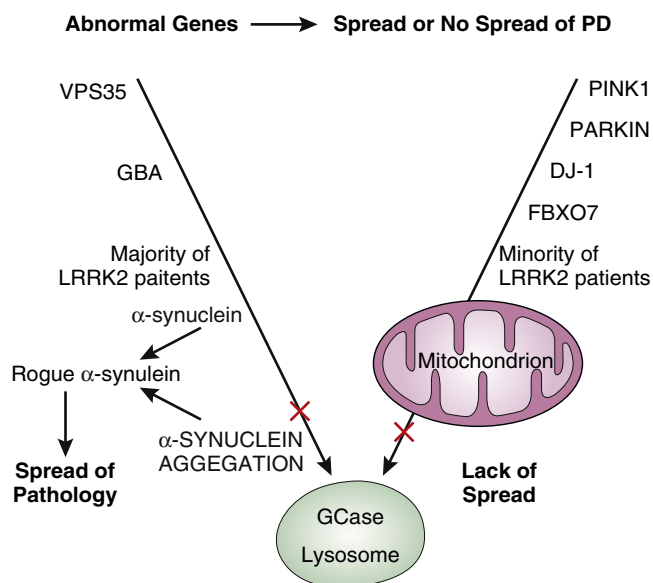


Fig. 5.36 Dichotomy of abnormal gene mutations related to spread or no spread of PD. GBA, Beta-glucocerebrosidase

apparent increase in cytosolic dopamine levels, suggesting a link between genetic and oxidative stress pathways (Lotharius et al., 2002). Thus, it may be that in some cases the initiation of the disease stems from inappropriate or dysregulated degradation of this protein. The accumulated, insoluble, aggregated alpha-synuclein appears to play a vital role in the pathogenesis, leading to the suggestion that impaired protein degradation may be a key problem. The spread of aggregated alpha-synuclein in the CNS has become a major research focus, as discussed later in the section on the Rogue Protein Hypothesis.

The key mechanisms through which misfolded or toxic proteins are degraded are the UPS and autophagy via the lysosome. The cell initially attempts to restore such proteins using specific chaperones (heat shock proteins) (Kopito, 2000), but if that is unsuccessful, the cell degrades the protein. The first attempt by the cell to remove these unwanted proteins is via the UPS. If that is unsuccessful, the process of autophagy is employed using the lysosomes (Martinez-Vicente and Cuervo, 2007; Pan et al., 2008). Attention was initially directed to UPS because of the normal function of the proteins of PARK 2 (parkin) and PARK5 (UCHL-1) as part of the UPS. The former is an E3 ligase and the latter separates

the polyubiquitin chain into its separate components, both of which are active processes in the UPS. However, subsequent studies indicated that parkin's role in the pathogenesis of PD is related to its involvement in mitochondria integrity and function (Mortiboys et al., 2008).

After the discovery that alpha-synuclein is mostly degraded via chaperone-mediated autophagy and that mutant alpha-synuclein blocks the autophagy of itself and also other substrates that are normally degraded this way (Cuervo et al., 2004), perturbed autophagy became recognized as the most important mechanism by which alpha-synuclein accumulates and then becomes aggregates forming oligomers, fibrils, and Lewy neurites.

Autophagy takes place within the lysosome by three different mechanisms: macroautophagy, microautophagy, and chaperone-mediated autophagy (Martinez-Vicente and Cuervo, 2007; Pan et al., 2008).

1. *Macroautophagy* involves the "in bulk" degradation of complete regions of the cytosol. Initially, these regions are sequestered by a limiting membrane, which seals to form a double membrane compartment known as an autophagosome. Because this vesicle lacks any enzymes, the trapped contents are not degraded until the autophagosome fuses with a lysosome, which provides all the hydrolases required for degradation of the contents. Macroautophagy occurs under stress conditions and has two major purposes: as a source to generate essential macromolecules and energy in conditions of nutritional scarcity or as a mechanism for the removal of altered intracellular components. Mitophagy is the macroautophagy of

damaged mitochondria. Both PINK1 and parkin proteins play a role in initiating mitophagy.

2. *Microautophagy* involves sequestering cytosolic material directly into the lysosome through invaginations into the lysosomal lumen, where they are rapidly degraded. Microautophagy participates in the continuous turnover of cellular components in normal cellular conditions.

3. *Chaperone-mediated autophagy (CMA)* is a mechanism to remove selected proteins, which are recognized by protein chaperones that deliver them to the surface of the lysosome. The substrate proteins interact with a receptor protein at the lysosomal membrane, and, assisted by a chaperone located inside lysosomes, the substrate proteins cross the membrane to be degraded in the lysosomal lumen. With impairment of the UPS and CMA, the misfolded protein could form fibrils or oligomers and would need to be handled by macroautophagy. In conditions in which not even macroautophagy can remove the altered proteins, these aggregates usually trap other still-functional proteins inside aggregates. This is a serious event and can lead to cell death.

Wild-type alpha-synuclein is degraded by the UPS and chaperone-mediated autophagy (Cuervo et al., 2004, 2010). Mutated alpha-synuclein is unable to enter the lysosome; it becomes trapped at the lysosomal surface and that blocks other material from entering the lysosome and from being degraded. Thus, mutated alpha-synuclein is not degraded and "gums" up the process for other substrates. In addition to mutated alpha-synuclein being unable to penetrate the lysosome, the same problem exists for altered alpha-synuclein (phosphorylated, nitrated, or oxidized alpha-synuclein); these compounds bind to lysosomal membrane

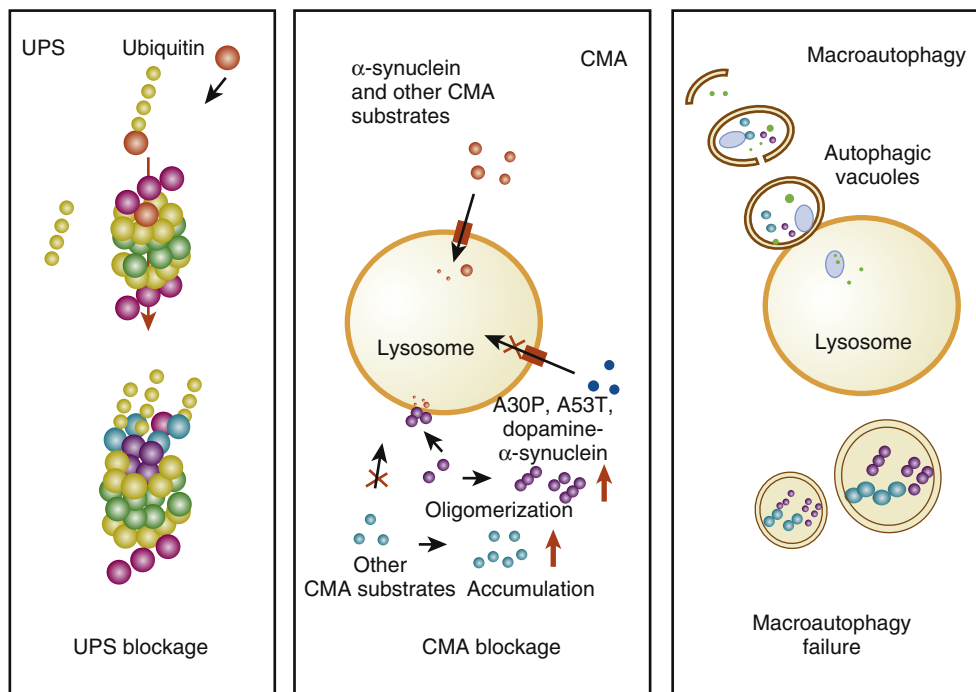


Fig. 5.37 Altered alpha-synuclein degradation in Parkinson disease. Normal alpha-synuclein can be selectively degraded by the ubiquitin-proteasome system (UPS, left) or in lysosomes by chaperone-mediated autophagy (CMA; middle). Pathogenic mutations and certain posttranslational modifications in alpha-synuclein promote its organization into complex structures no longer amenable for degradation via the proteasome or CMA (left and middle bottom). Furthermore, alpha-synuclein oligomers and preaggregates can block those two proteolytic systems. Macroautophagy undertakes the removal of organized abnormal alpha-synuclein and delivers it to lysosomes in sealed double membrane vesicles (autophagosomes; right). Changes in the lysosomal system as a result of the increasing amount of toxic alpha-synuclein complexes or indirectly through the action of aggravating factors, such as aging or oxidative stress, could result in macroautophagy failure and the consequent cellular compromise (right bottom). (From Cuervo AM, Wong ES, Martinez-Vicente M. Protein degradation, aggregation, and misfolding. *Mov Disord.* 2010;25(Suppl. 1):S49–S54.)

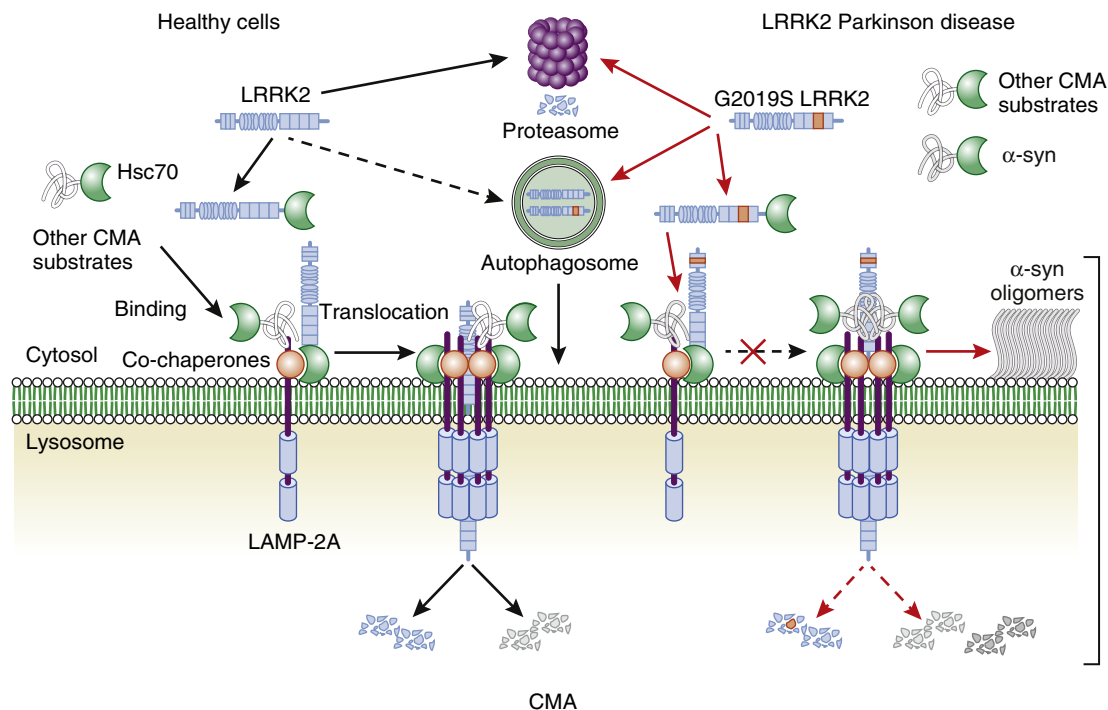


Fig. 5.38 The interaction between LRRK2 and alpha-synuclein (α -syn) in chaperone-mediated autophagy (CMA) in PD neurons. In healthy cells (left side of figure), wild-type LRRK2 is predominantly degraded by the ubiquitin-proteasome system (UPS) and CMA. This process requires binding to the cytosolic chaperone Hsc70, recognition of the substrate-Hsc70 complex by LAMP-2A (a CMA receptor) on the lysosomal membrane, subsequent oligomerization of LAMP-2A to form the translocation complex and lysosomal import of the substrate for proteolytic degradation of the damaged LRRK2 protein. In LRRK2-associated PD neuron (right side of figure), the pathways that degrade mutant LRRK2 are dysregulated, with greater contributions from UPS and macroautophagy and less from CMA. The latter is a result of inhibition by mutant LRRK2 of LAMP-2A oligomerization and subsequent formation of the CMA translocation complex. Blockage of CMA by mutant LRRK2 results in impaired degradation of cytosolic CMA substrates, including α -syn. Moreover, mutant LRRK2 cells show enhanced formation of alpha-synuclein oligomers on the lysosomal membrane. (From Yue Z, Yang XW: *Dangerous duet: LRRK2 and α -synuclein jam at CMA*. *Nature Neurosci.* 2013;16[4]:375–377.)

with high affinity and are not translocated into the lysosome (Fig. 5.37) (Martinez-Vicente and Cuervo, 2007). As mentioned earlier in the discussion about endogenous factors leading to selective vulnerability of dopamine neurons, the same problem develops with adducts of alpha-synuclein and dopamine; these adducts block the translocation of other CMA-attached proteins into the lysosome.

It has been discovered that LRRK2 protein is also degraded by CMA (Orenstein et al., 2013). However, pathogenic mutants of LRRK2, incl G2019S, are poorly degraded by this pathway, and an accumulation of lysosomal bound LRRK2 protein occurs as a result of inability of the CMA translocation process. This self-perpetuating inhibitory effect on CMA blocks protein degradation, including that of alpha-synuclein. The inability to degrade normal alpha-synuclein will lead to its accumulation, and then oligomer and fibril formation, including Lewy bodies (Yue and Yang) (Fig. 5.38).

PARK2 (PRKN), PARK6 (PINK1), PARK7 (DJ-1) and mitochondria

The proteins parkin and PINK1 are involved in the degradation of damaged mitochondria. This degradation process takes place via macroautophagy, which is referred to as mitophagy when it involves the mitochondria. PINK1 is situated on the mitochondria and becomes activated when mitochondria are damaged. PINK1 is a kinase and phosphorylates ubiquitin, which recruits cytosolic parkin to the mitochondria and then activates autophagosome formation

to engulf the impaired mitochondria, promoting mitophagy. If mitochondria are not degraded, they become swollen and damage the cell. When expressed in a *Drosophila* model of PD, wild-type parkin protects against LRRK2 G2019S mutant-induced dopaminergic neurodegeneration (Ng et al., 2009). Parkin overproduction is cytoprotective and rescues *PINK1* mutant phenotype, indicating PINK1 is upstream from parkin in a common pathway. Parkin may play a role in sporadic PD because it is inactivated by nitrosative, oxidative, and dopaminergic stress (Dawson and Dawson, 2009).

DJ-1 appears to play a role in protecting against oxidative stress, including that produced by dopamine (Lev et al., 2009). *DJ-1* deficiency sensitizes dopamine neurons to oxidative stressors in vitro and in the intact CNS (Abeliovich and Beal, 2006). Overexpression appears to protect against oxidative insults. The loss of DJ-1, which is an antioxidant, does not affect mitochondrial respiration or mitochondrial calcium levels but increases reactive oxidant species, leading to elevated mitochondrial permeability transition pore opening and reduced mitochondrial transmembrane potential (Giame et al., 2012).

PARK8 (LRRK2)

The PARK8 mutation is the one with the highest prevalence for PD of all the known gene mutations. The protein dardarin, also known as leucine-rich repeat kinase 2 (LRRK2), has GTPase and kinase enzymatic domains plus at least two protein-protein interaction domains (Hardy et al., 2006). The common

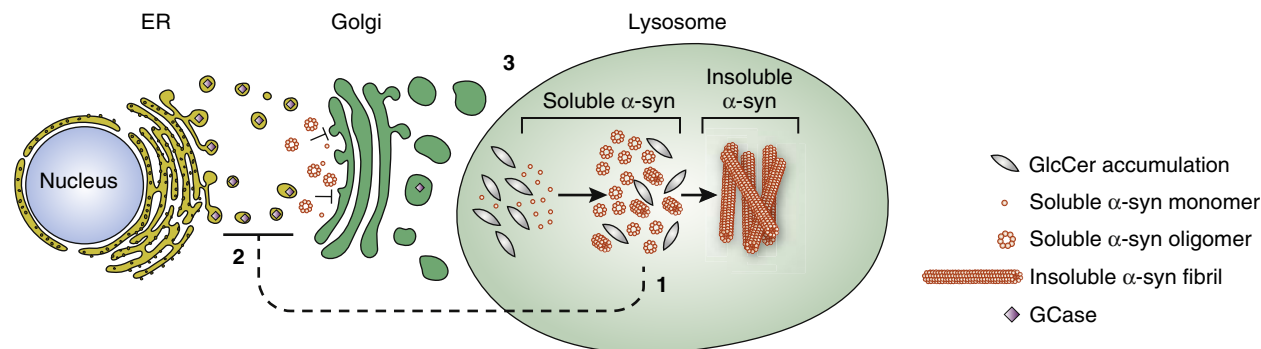


Fig. 5.39 Pathogenic positive feedback loop between decreased glucocerebrosidase (GCase) in the lysosome and alpha-synuclein (α -syn). (1) Lysosomal glucosylceramide (GlcCer) accumulation accelerates and stabilizes soluble α -syn oligomers (bold arrow), which eventually convert into insoluble fibrils (thin arrow). (2) Accumulation of α -syn blocks the endoplasmic reticulum (ER)-Golgi trafficking of GCase. (3) Decrease of GCase in the lysosome further amplifies GlcCer accumulation and stabilization of soluble α -syn oligomers and results in a stronger inhibition of GCase ER-Golgi trafficking with each pathogenic cycle. This mechanism could play a role in sporadic PD, as illustrated in Fig. 5.39. (From Mazzulli JR, Xu YH, Sun Y, Knight AL, McLean PJ, Caldwell GA, et al: *Gaucher disease glucocerebrosidase and α -synuclein form a bidirectional pathogenic loop in synucleinopathies*. *Cell*. 2011;146[1]:37–52.)

G2019S mutation and an adjacent mutation are located at the N-terminal portion in the kinase domain. This site contains the Mg^{++} ion required for kinase function. Mutated *LRRK2* is disinhibited, has increased kinase activity, and induces a progressive reduction in neurite length and branching both in primary neuronal cultures and in the intact rodent CNS (MacLeod et al., 2006). In contrast, *LRRK2* deficiency leads to increased neurite length and branching (MacLeod et al., 2006). Because most patients with *PARK8* have Lewy bodies, the biochemical defect appears to be upstream of alpha-synuclein. But because some patients do not have Lewy bodies and may have other inclusions, such as tau tangles, the exact pathogenesis of *PARK8*'s effect is still not clear. As mentioned previously in the section on autophagy and described in Fig. 5.38, the G2019S mutant is blocked from chaperone-mediated autophagy, resulting in the blockage of native alpha-synuclein from entering the lysosome also, thereby building up molecules of alpha-synuclein that can eventually oligomerize. Why a minority of the G2019S mutants do not develop Lewy bodies remains a mystery and possibly an important clue of other aspects of *LRRK2*'s role in causing PD.

GBA and the lysosome

The enzyme glucocerebrosidase (GCase) (also called glucosylceramidase) is located in the lysosomes of cells, where it splits glucocerebroside (a cell membrane glycolipid) into glucose and ceramide. Homozygous or compound heterozygous mutations causing GCase deficiencies result in Gaucher disease, a rare pan-ethnic autosomal recessive lysosomal storage disorder (types 1, 2, and 3). This occurs in 1:40,000 to 60,000 live births in the general population and in 1:850 in the Ashkenazi Jewish population. Over 300 *GBA* pathogenic mutations and polymorphisms have been reported. The most common in the Ashkenazi Jewish population are N370S, L444P, 84GG, IVS+1, V394L, and R496H. In non-Jews, L444P is the most common mutation. Europeans may also have the N370S mutation, but Asians do not. The most common mutations in the Japanese are L444P and R120W. In addition to *GBA* mutations being a genetic risk factor of PD, they are also risk factors for developing LBD in addition to PD dementia (Nalls et al., 2013). The age-specific risk for developing PD in Ashkenazi Jews who are carriers of a *GBA* mutation is 1.5% at age 60, 5.2% at age 70, and 7.7% at age

80 years (Alcalay et al., 2014). Some common SNP variants have been found to coregulate expression of *GBA* to delay PD onset (Schierding et al., 2020).

Glucocerebrosidase enzymatic activity in blood was compared in PD patients with and without a *GBA* mutation (Alcalay et al., 2015). As expected, those with a *GBA* mutation had lower GCase activity than PD patients without a mutation. But PD patients without a *GBA* mutation had a slight but statistically significant lower GCase activity than a control population without PD, indicating that GCase may also play a role in sporadic PD. GCase protein and enzyme activity is reduced in the brain, especially in the SN, in both *GBA* mutant PD and sporadic PD (Gegg et al., 2012). In a *Drosophila* model of PD, increasing glucocerebrosidase expression reduces the spread of protein aggregation (Jewett et al., 2021).

There is evidence that GCase and alpha-synuclein each affect the other (Mazzulli et al., 2011). For example, decreased lysosomal GCase results in the accumulation of glucosylceramide (GlcCer), the substrate for GCase substrate. This increase of GlcCer stabilizes alpha-synuclein oligomers and fibrils. There is also an effect on GCase triggered by excess alpha-synuclein. The accumulation of alpha-synuclein inhibits the normal GCase by inhibiting transport of immature GCase through the endoplasmic reticulum (ER)-Golgi apparatus. These findings suggest that the bidirectional effect of alpha-synuclein and GCase forms a positive feedback loop that may lead to a self-propagating disease (Figs. 5.39 and 5.40). Therefore, targeting GCase in lysosomes may represent a specific therapeutic approach for PD and other synucleinopathies. Augmenting GCase in an animal model reduced the level of alpha-synuclein (Sardi et al., 2013). Another approach has been to use a chaperone, ambroxol, to escort GCase through the ER-Golgi apparatus. Ambroxol was tested in a study with Gaucher disease and *GBA* heterozygous fibroblasts and was found to increase GCase activity (McNeil et al., 2014). Ambroxol is now being tested in a controlled clinical trial.

Several groups of investigators have concluded, based on the multiple genes that can cause or be a risk factor in causing PD, that almost all these genes play a role in endosome trafficking from the cell membrane to the lysosome (Abeiovich and Gitler, 2016; Schreij et al., 2016; Bandres-Ciga et al., 2019). This endocytic membrane trafficking pathway, thus, appears to be a common element in the pathogenesis of PD (Fig. 5.41).

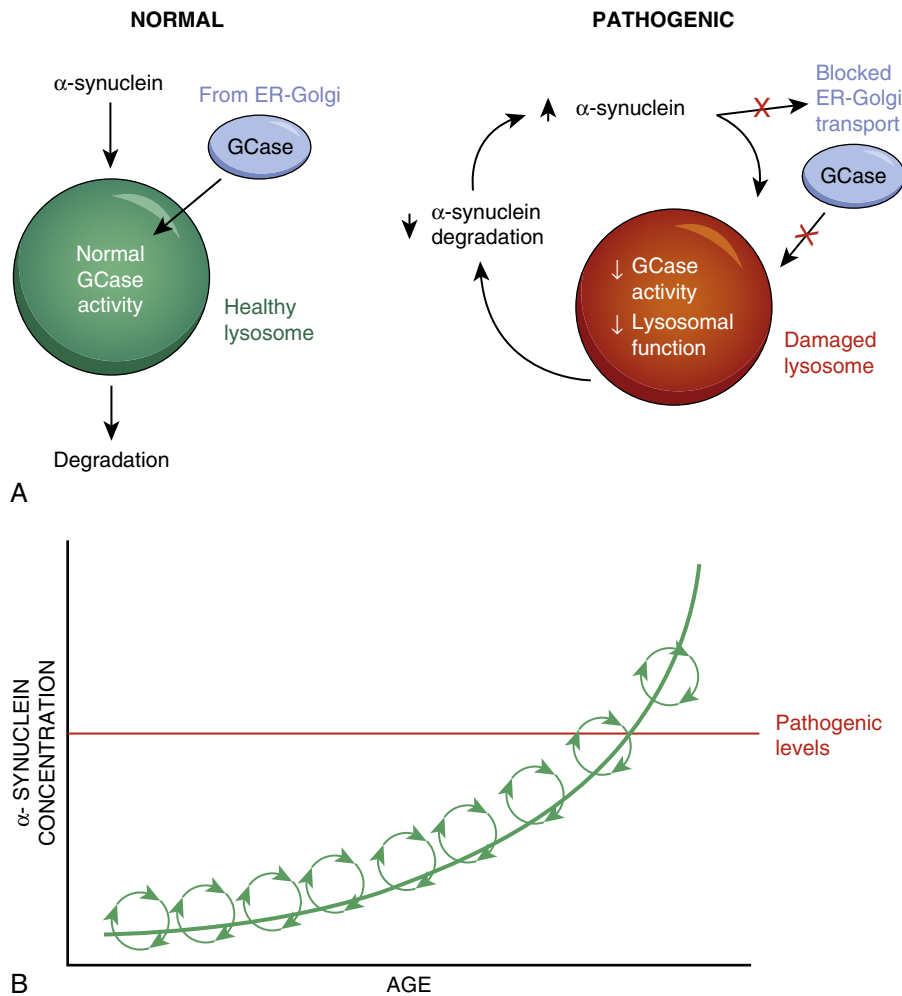


Fig. 5.40 Diagrams of the bidirectional relationship between glucocerebrosidase (GCase) and alpha-synuclein (α -syn) and the potential to reach pathogenic levels of α -syn. (A) Under normal circumstances, α -syn is imported into the lysosome for degradation. The enzyme GCase is also imported into the lysosome after the enzyme matures through the endoplasmic reticulum (ER)-Golgi pathway. In pathogenic situations, accumulation of α -syn may block ER-Golgi transport, leading to loss of GCase in the lysosome. This amplifies the effects by limiting degradation of α -syn, causing further accumulation of the protein. (B) If the series of positive feedback loops (small circles with arrows) continues over time, then α -syn levels will tend to increase with age. Presumably, at a certain point, α -syn will exceed a pathogenic threshold (indicated by the red line) and be associated with disease. (From Cookson MR: A feedforward loop links Gaucher and Parkinson's diseases? *Cell*. 2011;146(1):9–11.)

Lewy bodies in fetal dopaminergic neurons; rogue protein hypothesis; is PD a prion-like disorder?

In the May 2008 issue of *Nature Medicine* three papers were published about postmortem findings of Lewy bodies in a few of the many surviving fetal dopaminergic neurons that were implanted into subjects with PD more than 11 years earlier. In two of the papers, three of the subjects—implanted 11, 14, and 16 years earlier—had rare alpha-synuclein-containing inclusions resembling Lewy bodies (Kordower et al., 2008a; Li et al., 2008). In the third paper, these alpha-synuclein-containing inclusions were sought but not found in the brains of five subjects who were implanted 9 to 14 years earlier (Mendez et al., 2008). A fourth patient with PD who died 14 years posttransplantation also was found to have Lewy bodies in some of the otherwise numerous healthy grafted cells (Kordower et al., 2008b).

The Lewy body findings suggest a factor in the host striatum that can lead to alpha-synuclein accumulation and Lewy body formation. It also suggests that some factor(s) in the striatum may play a role in PD pathogenesis. This would imply that dopamine nerve terminals—and not the cell bodies—may be the initial site of pathologic processes for the demise of the dopaminergic nigrostriatal neuron. The

findings support the concept that the pathogenic process is chronically active in the PD brain, as McGeer and colleagues (1988a) have pointed out by their observations of continuing inflammation in the striatum. One speculation is that a prion-like mechanism might explain how PD pathologic processes can transfer from the host to the graft (Kordower and Brundin, 2009).

Desplats and colleagues (2009) explored that possibility of neuron-to-neuron transfer and showed that labeled alpha-synuclein can transfer from neuronal cells to neural stem cells in both in vitro and in vivo systems. Alpha-synuclein was transmitted via endocytosis to neighboring neurons and neuronal precursor cells, forming Lewy-like inclusions. With impaired autophagy, there was accumulation of transmitted alpha-synuclein and inclusion formation. The authors suggest that this mechanism may explain the topographic progression of Lewy pathology in PD suggested by Braak and associates (2003). Olanow and Prusiner (2009) proposed that the topographic spread of alpha-synuclein would be analogous to the spread of prion protein in prion diseases. Supporting this concept, Hansen and colleagues (2011) showed that exogenous dopaminergic cells can take up alpha-synuclein when grafted into mice with overexpressed alpha-synuclein.

Next, scientists showed that preformed alpha-synuclein fibrils, after injection into the brains of animals, can be

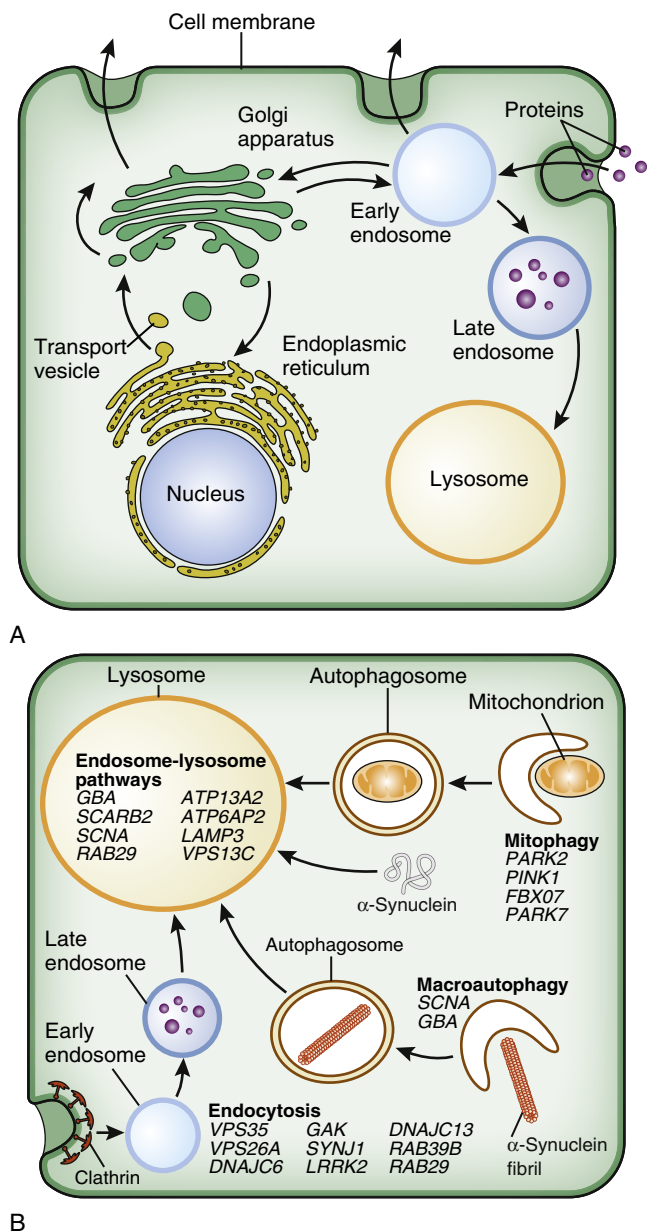


Fig. 5.41 Endocytic membrane trafficking pathway. (A) Diagram of various membrane enclosed vesicles that are formed and used in the cell to transport proteins and lipid to different destinations within the cell and also to transport them for exocytosis. (B) Association of the various genes involved on PD pathogenesis with the several components of the endocytic membrane trafficking pathway. (From Abeliovich A, Gitler AD: Defects in trafficking bridge Parkinson's disease pathology and genetics. *Nature*. 2016;539[7628]:207–216.)

incorporated and then spread along anatomically connected pathways (Volpicelli-Daley et al., 2011). Lewy neurites first developed in axons and propagated to form Lewy body inclusions in the perikarya. Accumulation of pathologic alpha-synuclein led to selective decreases in synaptic proteins, progressive impairments in neuronal excitability and connectivity, and, eventually, neuron death. When the alpha-synuclein fibrils are injected into the striata of wild-type mice, cell-to-cell transmission of pathologic alpha-synuclein and Parkinson-like Lewy pathologic findings in anatomically interconnected regions resulted (Luk et al., 2012). This Lewy pathologic accumulation resulted in progressive loss

of dopamine neurons in the SNc, but not in the adjacent VTA, and was accompanied by reduced dopamine levels culminating in motor deficits. The spread of alpha-synuclein fibrils appears to follow strict anatomical pathways in both anterograde and retrograde spread, compatible with transsynaptic spread (Masuda-Suzukake et al., 2013; Rey et al., 2013). Intranasal administration of α -synuclein preformed fibrils into primates results in iron accumulation in the substantia nigra (Guo et al., 2021).

Extracellular alpha-synuclein appears to play a role in neurodegeneration. Neurons secrete monomeric and oligomeric alpha-synuclein through unconventional exocytosis (Lee et al., 2014). Extracellular alpha-synuclein is taken up by neurons and glia through endocytosis and undergoes endocytic trafficking for degradation in lysosomes. The cell surface protein LAG3 strongly binds alpha-synuclein fibrils, not the monomer, and activates the fibrils entry into the cell (Mao et al., 2016). The LAG3 protein, thus, is a potential target for future therapy aimed at halting progression of PD.

Alpha-synuclein aggregates can be transmitted from neuron to neuron via the extracellular milieu and can propagate aggregates by a “seeding” mechanism. Targeting of extracellular alpha-synuclein—for example, promoting its clearance—might be another promising therapeutic strategy for modifying the progression of Lewy body diseases. This is the rationale of evaluating monoclonal antibodies against alpha-synuclein as a treatment for PD. In animal studies, alpha-synuclein immunotherapy blocked uptake and propagation of misfolded alpha-synuclein and neurodegeneration (Tran et al., 2014). Several clinical trials testing different antibodies against alpha-synuclein in patients with early PD are currently under way.

Because of the spread of pathologic alpha-synuclein, this protein has been considered by some investigators to have the hallmarks of a prion protein (Olanow and Prusiner, 2009; Angot et al., 2010; Masuda-Suzukake et al., 2013; Olanow and Brundin, 2013; Recasens and Dehay, 2014; Reyes et al., 2014; Chu and Kordower, 2015; Brundin et al., 2016; Brundin and Melki, 2017; Surmeier et al., 2017b). Supporting this view are the results of a study in which Lewy body extracts from PD brains injected into mice and primates triggered alpha-synuclein pathologic processes and neurodegeneration (Recasens et al., 2014). However, the prion hypothesis lacks at least one substantial requirement; that is, there are no cases of human-to-human transmission (Irwin et al., 2013)]. Therefore, we refer to the prion-like nature of alpha-synuclein as being a “rogue protein.”

The rogue protein hypothesis has led scientists to consider that alpha-synuclein may enter the body through the nose or the gut because the earliest locations of alpha-synuclein aggregates found by Braak colleagues and colleagues (2003) were in the olfactory bulb and the caudal medulla, the region in the CNS where the vagus nerve, that innervates the gut, arises. Shannon and colleagues (2012b) looked for the presence of alpha-synuclein in the submucosa of the distal colon in 10 patients with early, untreated PD and found alpha-synuclein in all 9 suitable for study but not in any controls (46, half with IBD). They then searched for colonoscopy biopsies in PD patients in whom the colonoscopy was performed years before the onset of PD. They found three such patients whose biopsies were performed 2 to 5 years before the onset of PD; all three had alpha-synuclein in the

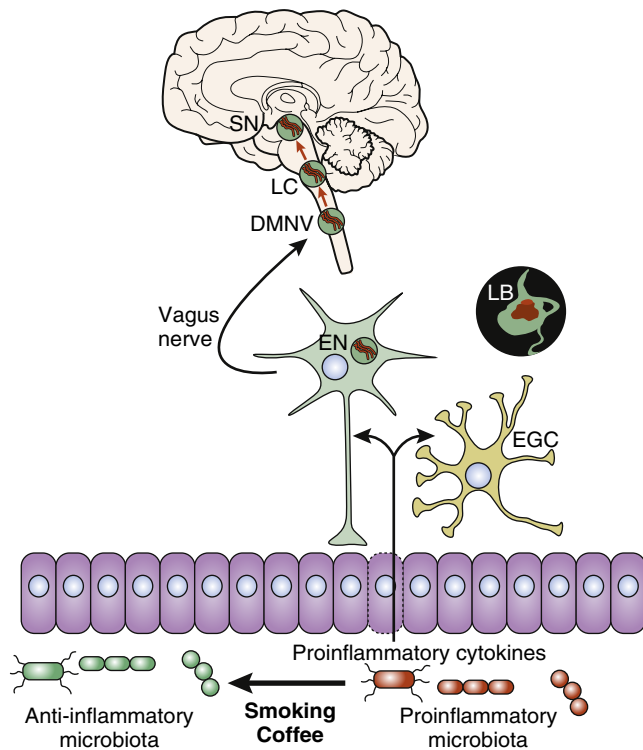


Fig. 5.42 Hypothesis to explain why smoking and coffee drinking protects against developing PD. It is proposed that these agents alter the gut microbiota to an anti-inflammatory state. This would avoid misfolding of alpha-synuclein in enteric nerves that would have created the protein into a rogue state that would enter the central nervous system via the vagus nerve. DMNV, dorsal motor nucleus of the vagus; EGC, enteric glial cells; EN, enteric neurons; LB, Lewy bodies; LC, locus coeruleus; SN, substantia nigra. (From Derkinderen P, Shannon KM, Brundin P: Gut feelings about smoking and coffee in Parkinson's disease. *Mov Disord.* 2014;29[8]:976–979.)

colonic submucosa whereas none were found in any of the 23 controls (Shannon et al., 2012a). However, these alpha-synuclein results were subsequently challenged when a more sensitive immunostaining method showed the presence of alpha-synuclein in both patients and controls (Visanji et al., 2015). A thorough search for alpha-synuclein in postmortem colon in PD and control specimens concluded that there needs to be sufficient submucosa and appropriate staining to detect Lewy-type alpha-synucleinopathy (Beach et al., 2016).

Following up on the gut to brain hypothesis for spread of aggregated alpha-synuclein are several epidemiologic studies looking into whether an earlier vagotomy offered protection against developing PD (Svensson et al., 2015; Tysnes et al., 2015; Liu et al., 2017), with mixed results. The vestigial appendix has been implicated in PD; the population who had appendectomies appear to have a lower risk for developing PD (Killinger et al., 2018; Liu et al., 2018). A newly discovered nigro-vagal pathway also opens the possibility how vagal connections from the gut could be the conduit by which ingested environmental pathogens enter the CNS and ultimately induce, or accelerate, PD progression (Travagli

et al., 2020). An alternative view to consider is whether gut involvement is “brain-first” rather than “gut-first” (Borghammer and Van Den Berge, 2019).

The rogue protein hypothesis has also given rise to a new hypothesis to explain why smoking and coffee drinking are protective against developing PD (Derkinderen et al., 2014). The proposal is that both smoking and coffee consumption change the composition of the microbiota in the gut in a way that mitigates intestinal inflammation. This, in turn, would lead to less misfolding of the alpha-synuclein in enteric nerves, reducing the risk for PD by minimizing propagation of the protein aggregates to the CNS, where they otherwise can induce neurodegeneration (Fig. 5.42).

There is a great deal of uncertainty about the role of peripheral alpha-synuclein in the pathogenesis of PD. In one study, Lewy body type alpha-synuclein aggregates from postmortem PD stellate ganglia were inoculated into mice but this does not trigger nigrostriatal neurodegeneration or alpha-synuclein pathologic processes (Recasens et al., 2018). These results argue against a putative role of peripheral alpha-synuclein in promoting PD-like pathologic changes in the brain. Further studies are needed to elucidate the potential origin of brain alpha-synuclein and mechanisms of peripheral alpha-synuclein in PD pathogenesis.

Multiple-hit hypothesis with a central role of alpha-synuclein

Although the many etiologic and pathogenic factors described earlier all result in the common denominator of loss of dopaminergic SNc cells and clinical PD, it is difficult to come to grasp with a single unifying concept. Sulzer (2007) attempts to do just that with his multiple-hit hypothesis. He suggests that “multiple hits” that combine toxic stress, for example, from dopamine oxidation or mitochondrial dysfunction, with an inhibition of a neuroprotective response, such as loss of function of parkin or stress-induced autophagic degradation underlie selective neuronal death.

Despite the multiple hits that may be necessary for sporadic PD, alpha-synuclein appears to play a central role. This concept is supported by (1) its presence in Lewy bodies, which are found in the great majority of cases except those caused by *PRKN*, some cases of *LRRK2*, and possibly *DJ-1*; (2) awareness that excess of wild-type alpha-synuclein can cause PD; and (3) indications that it may develop prion-like properties. This would imply that preventing the accumulation of alpha-synuclein or finding means to eliminate it could be an effective approach to arrest and even reverse the disease process. A summary diagram illustrating how some of the genetic and pathogenic factors result in dopaminergic neuronal death is presented in Fig. 5.43. It should be noted that Braak and colleagues used the term “dual hit” to refer to entry of a probable virus into the CNS via the nose, with the pathogen swallowed with saliva to the gut and then into the brain via the vagus nerve (Hawkes et al., 2009).

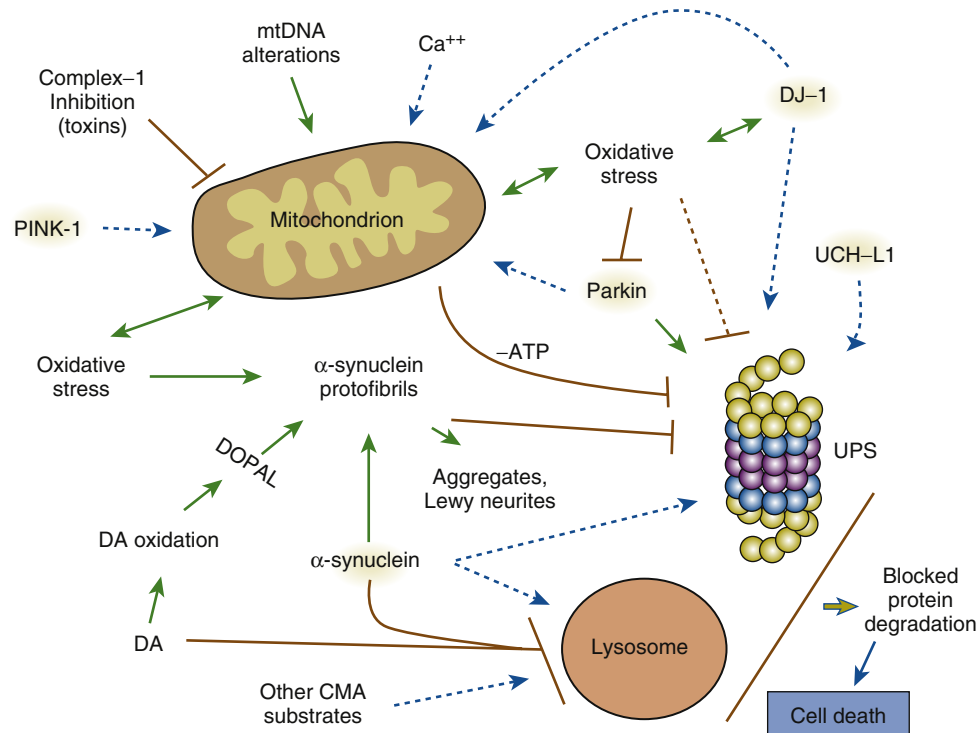


Fig. 5.43 Diagram linking some of the genetic and pathogenic factors leading to impaired protein degradation in dopaminergic substantia nigra pars compacta neurons via the lysosome and the ubiquitin-proteasomal system (UPS). Multiple hits may be involved before cell death develops. ATP, Adenosine triphosphate; CMA, chaperone-mediated autophagy; DA, dopamine; DOPAL, dihydroxyphenyl-acetaldehyde. (Design of diagram modified from Moore DJ, West AB, Dawson VL, Dawson TM: Molecular pathophysiology of Parkinson's disease. *Annu Rev Neurosci.* 2005;28:57–87.)

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Medical treatment of the motor features of Parkinson disease

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Introduction

The clinical symptoms and signs of Parkinson disease (PD) can be conveniently divided into motor and nonmotor features, necessitating individualization of therapy tailored to each patient's needs (Jankovic and Tan, 2020). Although the nonmotor aspects of PD can be equally incapacitating for people with PD, it is the motor component that defines the disease, for without the motor component, the diagnosis cannot be established. This chapter focuses on the treatment of the motor features of PD and motor complications of dopaminergic treatment. The description and treatment of the nonmotor features of the disease are discussed in Chapter 8. The surgical treatment of PD is discussed in Chapter 7 (with the exception of intrajejunal infusion of levodopa, which is covered in this chapter).

The most efficacious drug available for the medical treatment of PD is levodopa, which was introduced in its high-dose therapeutic form over 50 years ago (Cotzias et al., 1967, 1969). An entire issue of the journal *Movement Disorders* was devoted to this drug in celebration of 50 years of its use (Fahn and Poewe, 2015), and the reader is referred to that issue for details regarding the discovery and development of levodopa. Levodopa remains the gold standard for reducing many of the motor features of PD. If levodopa could be used without the development of motor complications, the symptomatic treatment of this disease would be straightforward. However, 30% to 50% of PD patients develop motor complications after 5 years of treatment with levodopa. Motor complications include motor fluctuations with "wearing off," dyskinesia, and dose failure. The occurrences of motor complications are primarily related to the progression of the underlying disease rather than the

duration of levodopa therapy. Hence, there is no rationale for "levodopa phobia," withholding symptomatic treatment with dopaminergic agents until disability or loss of employment (Espay and Lang, 2017). But there is a need for addressing these complications. These include new delivery systems for levodopa, additional medications that can prolong the effect of levodopa, using other longer acting dopaminergic agents, and treatments for dyskinesia. Although deep brain stimulation (DBS) does address motor complications, it will be discussed in a separate chapter.

The typical natural history of PD is someone who develops the first symptoms around age 60 and lives approximately 20 years. A typical pattern of progression is shown in Fig. 6.1. In early PD, treatment may be straightforward. As the disease progresses, motor and nonmotor complications make treatment more challenging. Topics in this chapter will include potential disease-modifying therapies, initiating pharmacologic treatment, and addressing motor complications.

Treating PD is complicated. There is heterogeneity of PD, with some patients having tremor predominant form, some with gait difficulty and postural instability, and some with mixed phenotype and additional motor and nonmotor features (Thenganatt and Jankovic, 2014). Variation in the clinical response to dopaminergic drugs occurs, with some patients responding dramatically and others with more modest improvement. There can be varying treatment goals, with some patients desiring to continue employment and others who want to minimize medications. Finally, numerous adverse effects can intervene and limit the usefulness of some of the treatments. The clinician treating PD must be familiar with the large variety of drugs to treat the motor and nonmotor symptoms, including the indications for the drug, side effect profile, and limitations.

PD disease-modifying treatments

Pharmacologic agents

Disease-modification is a term used to indicate slowing of clinical worsening and is not equivalent to neuroprotection (slowing of disease pathologic progression). All clinical trials discussed later were designed to test disease modification. In this chapter, we will use the term “neuroprotection” instead of “disease modification” in an effort to use just one label. *Neuroprotection* can be divided into at least three different classes of action: slowing the pathogenetic cascade that leads to cell death so that the natural history of the disease is less

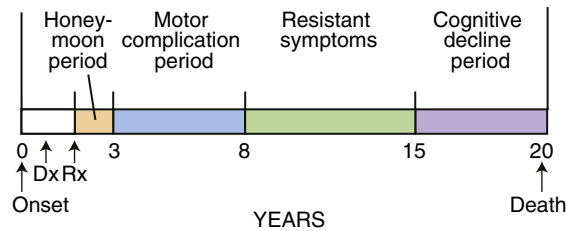


Fig. 6.1 Therapeutic response in a prototypical patient with PD with onset at age 60 and death 20 years later. Despite best available therapies, the clinical features of the disease progress through these phases. Dx, Time at diagnosis; Rx, time dopaminergic treatment is begun.

progressive (neuroprotection), restoring injured dysfunctional neurons to good health (neurorescue, neurorestoration), and replacing dead neurons (Fig. 6.2).

Currently, despite many clinical studies, no agent has demonstrated restorative properties or efficacy in slowing progression of PD (Table 6.1). In most of the studies in Table 6.1, worsening of severity of PD was measured quantitatively by the Unified Parkinson's Disease Rating Scale (UPDRS) [Fahn and Elton, 1987]. Drugs that have been specifically

SLOWING THE DISEASE PROGRESSION

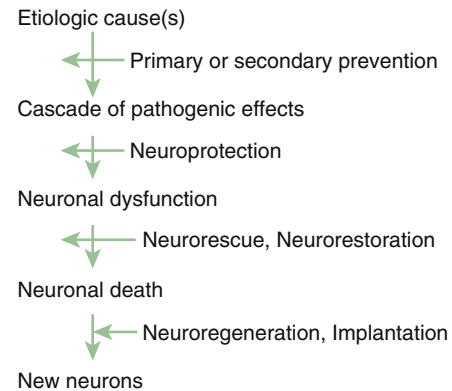


Fig. 6.2 Neuroprotection concepts: terminology.

Table 6.1 Controlled neuroprotective clinical trials in PD: all unsuccessful

Year/reference	Trial	Agent	N	Primary outcome variable
1993; Parkinson Study Group	DATATOP	Tocopherol	800	Need for levodopa
2003; Rascol et al.	Riluzole	Riluzole	1084	Need for levodopa
2003; Nutt et al.	Intraventricular infusion of GDNF	GDNF	50	Change in UPDRS
2006; Lang et al.	Intraputamenal infusion of GDNF	GDNF	34	UPDRS and F-DOPA PET
2006; Olanow et al.	Antiapoptotic propargylamine	TCH346	301	Need for levodopa
2006 2008; NINDS NET-PD Investigators	Anti-inflammatory; FS-1 study	Minocycline	200	UPDRS
2007; NINDS NET-PD Investigators	Neuroimmunophilin-ligand compound; FS-Too study	(GPI-1485)	213	UPDRS and need for levodopa
2007; Parkinson Study Group PRECEPT Investigators	Antiapoptotic drug; mixed lineage kinase inhibitor; PRECEPT study	CEP-1347	800	Need for levodopa
2007; Storch et al.	Mitochondrial agent	Coenzyme Q10	131	UPDRS
2010; Marks et al.	Trophic factor; intraputamenal infusion	AAV2 Neurturin	58	UPDRS practically defined off score
2013; Schapira et al.	Dopamine agonist; PROUD study	Pramipexole	535	Delayed-start design; UPDRS
2014; Parkinson Study Group QE3 Investigators	Mitochondrial agent; QE-3 trial	Coenzyme Q10	600	UPDRS
2015; Olanow et al.	Trophic factor; intraputamenal and intranigral infusion	AAV2 Neurturin	51	UPDRS practically defined off score
2015; Writing Group for the NINDS Exploratory Trials in Parkinson Disease (NET-PD) Investigators	LS-1 trial	Creatine	1741	Combination of multiple outcomes
2015; NINDS Exploratory Trials in Parkinson Disease (NET-PD) FS-ZONE Investigators	Peroxisome proliferator activated receptor γ (PPAR- γ) agonist; FS-ZONE study	Pioglitazone	210	Change in UPDRS
2019 Verschuur et al.	Levodopa delayed start design; LEAP study	Levodopa	445	Change in UPDRS
2019 https://www.michaeljfox.org/news/parkinsons-inosine-trial-ending-early	Urate prodrug; SURE-PD3 study	Inosine	298	Change in MDS-UPDRS
2020; Parkinson Study Group STEADY-PD III Investigators.	Calcium channel blocker; STEADY-PD III	Isradipine	336	Change in MDS-UPDRS

F-DOPA PET, ^{18}F -dopa positron emission tomography; FS, Futility Study; GDNF, glial-derived neurotrophic factor; UPDRS, Unified Parkinson's Disease Rating Scale; LS-1, Large Simple trial -1; AAV2, adeno-associated virus 2.

evaluated in controlled clinical trials for slowing disease progression include selegiline and tocopherol (Parkinson Study Group, 1989b, 1993), selegiline alone (Myllylä et al., 1992; Parkinson Study Group, 1996a; Palhagen et al., 1998, 2006); TCH346 (an antiapoptotic propargylamine that inhibits glyceraldehyde 3-phosphate dehydrogenase) (Waldmeier et al., 2000; 2006; Olanow et al., 2006), riluzole (Rascol et al., 2003), neuroimmunophilin (National Institute of Neurological Disorders and Stroke [NINDS] NET-PD Investigators, 2007), coenzyme Q₁₀ (Shults et al., 2002; NINDS NET-PD Investigators, 2007), glial cell line–derived neurotrophic factor (GDNF) (Nutt et al., 2003; Lang et al., 2006), rasagiline (Parkinson Study Group, 2004a; Olanow et al., 2009), minocycline and the energy enhancer creatine (Tilley et al., 2006; NINDS NET-PD Investigators, 2006, 2008; Writing Group for the NINDS Exploratory Trials in Parkinson Disease [NET-PD] Investigators, 2015), CEP-1347 (an inhibitor of the mixed lineage kinase-3 family) (Parkinson Study Group PRECEPT Investigators, 2007), neurturin (Marks et al., 2010; Olanow et al., 2015), GM1 ganglioside (Schneider et al., 2013), pramipexole (Schapira et al., 2013), coenzyme Q10 (Parkinson Study Group QE3 Investigators, 2014), intranasal reduced glutathione (Mischley et al., 2015), pioglitazone (NINDS Exploratory Trials in Parkinson Disease [NET-PD] FS-ZONE Investigators, 2015), exenatide (Aviles-Olmos et al., 2013, 2014; Athauda et al., 2017), isradipine (Simuni et al., 2010, 2019; Parkinson Study Group, 2013), inosine (Parkinson Study Group SURE-PD Investigators, 2014; Press Release, 2019A), isradipine (Parkinson Study Group, 2019), and levodopa (Fahn et al., 2004; Verschuur et al., 2019; and most recently nilotinib (Simuni et al., 2020 (see Table 6.1).

Some controlled studies of disease-modifying treatments have demonstrated success in achieving the primary outcome, but each of these was confounded by the symptomatic effect of the agent being tested, and none are approved for neuroprotection (Table 6.2).

Despite the fact that many of the drugs listed previously showed promise in animal models and in small early studies, each failed in larger controlled trials or were confounded by the effect of the drug in improving motor symptoms. In part, some of the reasons for these failures may be the lack of appropriate animal models for progressive PD, the heterogeneity of PD that suggests there may be different mechanisms of disease, and lack of a biomarker for progression of disease.

Several studies are currently in progress looking at newer agents to determine whether they have such a

disease-modifying effect. Alpha-synuclein antibodies and other antisynuclein strategies are currently being investigated in clinical trials (Jankovic, 2019; Savitt and Jankovic, 2019).

Exercise

Although exercise is important to everyone to maintain health, it may be particularly helpful in PD. However, despite the increasing literature citing the benefits of exercise, many do not participate in a regular exercise regimen. A cross-sectional study noted that the obstacles to exercise in PD include lack of certainty of the benefit, lack of time, and fear of falling during exercise (Ellis et al., 2013). Many types of exercise have been reported to improve the symptoms of PD and reduce falls (Amano et al., 2013; Bhatt et al., 2013; Briennes and Emerson, 2013; Corcos et al., 2013; Ellis et al., 2013; Mhatre et al., 2013; Shulman et al., 2013; Ayan et al., 2014; Li et al., 2012, 2014; Park et al., 2014; Schenkman et al., 2018). In fact, tai chi, progressive resistance, treadmill, forced bicycle riding, tango, and many other forms of exercise have improved symptoms. However, most of these require regular exercise of approximately 3 to 4 times per week for at least 30 minutes. The benefits from exercise tend to wane if the patient fails to adhere to the program. Freezing of gait, which is a difficult parkinsonian motor feature to treat, was found to be reduced in a controlled clinical trial evaluating exercises with motor complexity – so-called adapted resistance training with instability (Silva-Batista et al., 2020).

Physical therapy is one technique that can motivate patients to exercise. However, many become noncompliant after completion of the therapy. Physical therapy strategies can lead to improved activities of daily living (ADLs), improved gait, and treatment of musculoskeletal issues that are secondary to PD, including frozen shoulder and back pain.

PD leads to decreased motivation and increased passivity. An active exercise program, even early in the disease, can help overcome this. Furthermore, such a program involves patients in their own care, allows muscle stretching and full range of joint mobility, and enhances a better mental attitude toward fighting the disease. By being encouraged to take responsibility in fighting the devastations of the disease, the patient becomes an active participant. Physical therapy, which can be implemented in the form of a well-constructed exercise program, is useful in all stages of disease. In early stages, a physical therapy program can instruct the patient in the proper exercises and the regimen forces the patient to

Table 6.2 Controlled neuroprotective clinical trials in PD: significant in reaching endpoint

Year/reference	Trial	Agent	N	Primary outcome variable
1993; Parkinson Study Group	MAO-B inhibitor; DATATOP	Selegiline	800	Need for levodopa
1994; Parkinson Study Group	MAO-B inhibitor; ROADS	Lazabemide	321	Need for levodopa
1995; Olanow et al.	MAO-B inhibitor; SINDEPAR	Selegiline	101	Change in UPDRS
2002; Shoulson et al.	MAO-B inhibitor; BLIND-DATE	Selegiline	368	UPDRS and freezing of gait
2004a; Parkinson Study Group	MAO-B inhibitor; TEMPO	Rasagiline	404	Delayed-start UPDRS
2004b; Parkinson Study Group	ELLDOPA	Levodopa	361	UPDRS after washout
2006; Palhagen	MAO-B inhibitor; Swedish study	Selegiline	157	Need for levodopa and UPDRS
2009; Olanow et al.	MAO-B inhibitor; ADAGIO	Rasagiline	1176	Delayed-start UPDRS
2017; Athauda et al.	Glucagon-like peptide-1 agonist	Exenatide	62	MDS-UPDRS motor scores in practically defined “off” state

MAO-B, Monoamine oxidase B; UPDRS, Unified Parkinson's Disease Rating Scale.

exercise if he or she lacks the motivation to exercise on his or her own. In advanced stages of PD, physical therapy may be even more valuable by keeping joints from becoming frozen and providing guidance how best to remain independent in mobility. Therefore, exercise is beneficial in both the early and later stages. It has been shown that PD patients who exercise intensively and regularly have better motor performance [Reuter et al., 1999; Behrman et al., 2000; Craig et al., 2006; Ahlskog, 2018; Schenkman et al., 2018] and quality of life [Rodrigues de Paula et al., 2006; Rafferty et al., 2017].

Three relatively new exercise programs have become popular with patients: Lee Silverman Voice Treatment (LSVT) BIG (Dashtipour et al., 2015), Rock Steady Boxing, and dancing. When patients are in an exercise community, it appears that they are more likely to continue to exercise and view it as beneficial. The motivation provided by a group session that is ongoing is likely one of the reasons that these are successful. At this time, there are few studies of these interventions

A number of reports suggest that exercise may be more than a symptomatic treatment. Investigators have determined that exercise may have positive effects on the underlying pathophysiologic processes of PD. In animal models, there is an increase in neurotrophic factors, reduced neuroinflammation, and a reversal of dendritic spine loss in the striatum (Palasz et al., 2019; Sacheli et al., 2019; Tang et al., 2019; Xu et al., 2019; Liu et al., 2020). Basic scientific studies have discovered that exercise, particularly enriched exercise, can reduce the loss of dopaminergic neurons after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) exposure. When such exercise is initiated shortly after rodents were given experimental lesions of the nigrostriatal dopamine pathway, the result was a significantly lesser amount of damage to the dopamine pathway (Tillerson et al., 2001, 2002, 2003; Bezard et al., 2003; Cohen et al., 2003; Fisher et al., 2004; Mabandla et al., 2004). The mechanism appears to be to the induction of increased trophic factors, such as GDNF (Smith and Zigmond et al., 2003; Zigmond and Smeysne, 2014) and brain-derived neurotrophic factor (BDNF) (Bezard et al., 2003). Exercise also appears to reverse dendritic spine loss in direct and indirect striatal medium spiny neurons (Toy et al., 2014) and to enhance neuroplasticity in motor and cognitive pathways (Petzinger et al., 2013). An imaging study found that habitual exercisers had greater dopamine release in the caudate nuclei than do sedentary subjects when measured before and after stationary cycling (Sacheli et al., 2018).

Therapeutic choices available for PD

Treatment of patients with PD can be divided into three major categories: physical (and mental health) therapy, medications, and surgery. Physical exercise and physiotherapy were discussed previously. Speech therapy plays a similar role in those with problems of communication. Dysarthria, palilalia, and tachyphemia are difficult to treat, but hypophonia can be overcome by training the patient to shout, known as the LSVT (Ramig et al., 2001). In a controlled clinical trial, LSVT LOUD was found to be statistically superior to increasing speech amplitude and clarity than another form of speech therapy or no therapy (Ramig et al., 2018). Psychiatric assistance may be required to handle depression and the social and familial

problems that can develop with this chronic, disabling illness. Electroconvulsive therapy (ECT) may have a role in patients with severe, intractable depression; some psychiatrists have been promoting it to help overcome the motor symptoms of PD, but at best ECT provides only short-term motor benefit, and it may not be replicated on repeat treatments.

Individualize therapy

The treatment of PD needs to be individualized; that is, each patient presents with a unique set of symptoms, signs, response to medications, and a host of social, occupational, and emotional problems that need to be addressed. Although early in the disease the treatment may be straightforward, with progression of PD the occurrence of motor complications, drug side effects, and nonmotor issues such as dementia, depression, and apathy, increases the complexity of decision making when selecting pharmacologic interventions. The major goal is to keep the patient functioning independently as long as possible. Determine what the issues are for the individual patient by asking the patient to list the specific symptoms that trouble him or her the most (Lim et al., 2017). Attempt to treat the most troublesome symptoms; this is the way to maximize quality of life.

Medications available for PD

As will be emphasized below, the most effective pharmacotherapeutic agent for the motor features of PD is dopamine replacement with its precursor, levodopa. A major problem is that 75% of patients have serious complications after 6 years of levodopa therapy (Table 6.3) (Fahn, 1992), and younger patients (less than 60 years of age) are particularly prone to develop the motor complications of fluctuations and dyskinesias (Quinn et al., 1987; Kostic et al., 1991; Gershanik, 1993; Wagner et al., 1996). As the result of these motor complications, a number of other pharmaceuticals (and surgeries) have been developed to either substitute for levodopa or treat the motor complications of levodopa.

The International Parkinson and Movement Disorder Society (MDS) published a review of evidence-based efficacy on the various treatments for the motor features of PD (Fox et al., 2018). Selection of the most suitable drugs for the individual patient and deciding when to use them in the course of the disease are challenges to the treating clinician. Because PD is a chronic progressive disease, patients require lifelong

Table 6.3 Five major responses to more than 5 years of levodopa therapy (N = 330 patients)

	N*	%
1. Smooth, good response	83	25
2. Troublesome fluctuations	142	43
3. Troublesome dyskinesias	67	20
4. Toxicity at therapeutic or subtherapeutic dosages	14	4
5. Total or substantial loss of efficacy	27	8

*36 had both no. 2 and no. 3.

Data from Fahn S: Adverse effects of levodopa. In: Olanow CW, Lieberman AN (eds): The Scientific Basis for the Treatment of Parkinson's Disease, Carnforth, England, Parthenon Publishing Group, 1992, pp. 89–112.

treatment. Medications and their doses will change over time as adverse effects and new symptoms are encountered.

Dopaminergic Agents (Table 6.4)

Levodopa

It has been more than 50 years since the introduction of levodopa for the treatment of PD. This followed the discovery that the motoric symptoms of PD (bradykinesia, rigidity, tremor) are related to striatal dopamine deficiency (Hornykiewicz, 1966). Fahn (2008, 2015) reviewed the discovery of levodopa as a treatment for PD. Dopamine replacement therapy remains the major medical approach to treating the motor features of the disease. Table 6.4 lists these dopaminergic drugs. The most powerful drug is levodopa, the immediate precursor of dopamine. Dopamine, being a charged molecule, is unable to enter the brain via the blood-brain barrier. Levodopa crosses the gut and the blood-brain barrier via specific transporters. These large amino acid transporters are also used by the aromatic amino acids that are present in many proteins, which can interfere with L-dopa transfer. Levodopa is absorbed only in the proximal small intestine (Lovenberg et al., 1962). Hence, slowing of gastric emptying and reduction in transit time will affect the absorption. The absorption of levodopa may be increased by eradicating gastric *Helicobacter pylori* with omeprazole, amoxicillin, and clarithromycin in PD patients documented to be infected with this bacterium (Pierantozzi et al, 2006; Lee et al., 2008). About 50% of the general population is infected with the bacterium.

Once in the central nervous system (CNS), levodopa is metabolized to dopamine by aromatic amino acid decarboxylase (dopa decarboxylase) and is pharmacologically active at striatal dopamine receptors, in essence providing the dopamine that is depleted through the degeneration of dopamine-producing cells in the substantia nigra (SN). Levodopa in the periphery is frequently associated with nausea and vomiting as a result of its peripheral conversion by

dopa decarboxylase to dopamine, which stimulates the area postrema (vomiting center), an area of the brainstem where the blood-brain barrier does not exist. Therefore, L-dopa is usually combined with a peripheral decarboxylase inhibitor (Gershanik, 2015), which prevents the peripheral conversion of levodopa to dopamine and alleviates the peripheral side effects, including nausea and vomiting. Further, by reducing the metabolism of levodopa in the periphery, more levodopa is available to enter the CNS. The peripheral decarboxylase inhibitors benserazide and carbidopa potentiate levodopa, allowing about a four-fold reduction of levodopa dosage to obtain the same benefit. Typically, if starting carbidopa/levodopa, the 25/100 mg tablet is used, providing the highest ratio of carbidopa to levodopa. If additional carbidopa is needed for patients in whom nausea persists, it can be prescribed (Lodosyn) and patients can obtain it from their pharmacy. Carbidopa and benserazide are peripheral dopa decarboxylase inhibitors. In the United States the only dopa decarboxylase inhibitor available is carbidopa. The combination of the two (carbidopa/levodopa) was initially branded as Sinemet (Latin for “without emesis”) but is now available primarily as a generic preparation. In many other countries, benserazide is also available and in combination with levodopa. Because both drugs are azides, they are unable to penetrate the blood-brain barrier and do not interfere with the central effects of L-dopa. Tablets of carbidopa/levodopa are available as 10/100, 25/100 and 25/250 mg. The generic preparations differ in their formulations, and some patients find that one generic product may be superior to another. In non-U.S. countries, benserazide is combined with levodopa, with the brand name Madopar. Because L-dopa is a short-acting drug with a half-life of approximately 90 minutes, it has been reformulated to increase its half-life. Extended-release carbidopa/levodopa, with the brand name Sinemet CR, is a polymer release tablet formulation available as a 25/100-mg or 50/200-mg product with a more prolonged half-life. However, the CR preparation has time to peak level approximating 2 hours, compared with 30 minutes for L-dopa, making its onset of action delayed. In a clinical setting, the onset of action and clinical benefit profile may be problematic and unpredictable in a patient (Stocchi et al., 1994). However, the extended-release formulation may be more helpful, particularly at night when wearing off of levodopa may result in awakening from sleep. If the tablets are cut in half, the duration is not as prolonged.

The second extended-release formulation of carbidopa/levodopa is Rytary, formally IPX066, which was approved by the U.S. Food and Drug Administration (FDA) in 2015. Rytary is provided in capsules filled with microbeads of carbidopa and levodopa, dissolving at different rates. Rytary capsules contain a combination of both extended- and immediate-release forms, with 32% being immediate release (Mittur et al., 2017). An important element in the capsule is the presence of a weak acid, tartaric acid, within its own extended-release microbead. An acidic environment keeps levodopa stable (Lovenberg et al., 1962). The goal was to make the onset of action more predictable and yet have the effect be longer lasting. This formulation is intended for PD patients with end-of-dose wearing off of benefit. In the pivotal clinical trials there was an increase of hours of “on time,” and reduction in “off time” (Pahwa et al., 2014). However, the dose of levodopa was approximately 30% higher in the Rytary

Table 6.4 Dopaminergic agents used for treatment of Parkinson disease

Dopamine precursor (usually in combination with decarboxylase inhibitor carbidopa or benserazide)

Levodopa (Sinemet, Madopar)

Extended-release levodopa (Sinemet CR, Rytary), inhalational levodopa (Inbrija), orally dissolving carbidopa/levodopa (Parcopa), intestinal gel (Duopa)

Dopamine agonists*

Pramipexole (immediate and extended release) (Mirapex), ropinirole (immediate and extended release) (Requip), rotigotine dermal patch (Neupro), piribedil†, apomorphine (injectable as rescue [Apokyn], sublingual (Kynmobi) or continuous infusion†)

NMDA receptor antagonist/indirect dopaminergic effects

Amantadine, amantadine extended release

Levodopa-enhancing agents

Catechol-O-methyltransferase inhibitors: entacapone, tolcapone, opicapone

Type B MAO inhibitor: selegiline (Eldepryl), Zydys selegiline (Zelapar), rasagiline (Azilect), safinamide (Xadago)

*Ergoline-derived dopamine agonists bromocriptine, pergolide, cabergoline, and lisuride are not used in the treatment of Parkinson disease resulting from cardiac valvular fibrosis.

†Not available in the United States.

group. Ryтары comes in multiple dosing formulations (carbidopa/levodopa 23.75 mg/95 mg, 36.25 mg/145 mg, 48.75 mg/195 mg, 61.25 mg/245 mg). As clinical studies have demonstrated, patients are able to reduce the number of times per day that the medication is taken, although often they must take several capsules at a single dose. Altering the dose (increasing or decreasing) may require multiple prescriptions. The side effect profile is similar to that of levodopa. Switching a patient from regular carbidopa/levodopa to Ryтары can be challenging in the more fragile patient. In Europe, the brand name is Numient (Mittur et al., 2017). In the United States, Ryтары is available only through specialty pharmacies.

A formulation of levodopa that was approved by the FDA in 2018 is the inhalational powder, CVT-301 (Inbrija) (Freed et al., 2013; LeWitt et al., 2016). Inhalational levodopa was approved as a rescue therapy for patients who have wearing off of their oral levodopa. Inhalational levodopa has the advantage of not being dependent on the gastrointestinal system and is absorbed directly through the pulmonary system. It uses a breath-actuated delivery system and is administered through a specially designed inhaler. Patients using this treatment need training in its administration, including the method of inhalation and timing of dosing. Using CVT-301, plasma levodopa concentrations increased more rapidly and predictably compared with oral levodopa. (Stocchi et al., 2018) A randomized study in 86 PD patients taking oral levodopa with more than 4 “off” periods per day and more than 2 hours of “off” time demonstrated that CVT-301 in addition to their usual levodopa improved motor scores, reduced “off” time, and demonstrated a time to “on” that was superior to placebo (LeWitt, Hauser et al. 2016). The main side effects were cough, nausea, and dizziness, affecting approximately 7% of those enrolled. A subsequent study demonstrated that there were no changes in pulmonary function with continued use of CVT-301 (LeWitt et al., 2018). Currently, CVT 301 is approved by the FDA as Inbrija for intermittent treatment of “off” episodes in PD patients currently taking oral levodopa. It is available in 42-mg capsules, with 2 capsules per dose. It is recommended for use up to five times per day and is available only through a specialty pharmacy.

There is also a dispersible formulation of carbidopa/levodopa that dissolves in the mouth and is swallowed with saliva (Parcopa) and is available as generic equivalents. Dispersible carbidopa/levodopa can be taken without water, which may be an advantage for some patients, such as those who have trouble swallowing or who need to be without food or water before and after surgery.

Some undergoing clinical trials with formulations of levodopa are deuterium-labeled levodopa (Malmlöf et al., 2015), gastric-retention levodopa (Chen et al., 2012; Verhagen Metman et al., 2015; LeWitt et al., 2014a), subcutaneous infusion levodopa (Caraco et al., 2013; Olanow et al., 2021), and a levodopa prodrug (LeWitt et al., 2014b).

Although levodopa is an effective symptomatic treatment for PD, it does not treat some of the motor features that develop in advanced PD, such as flexed and twisted dystonic postures, loss of postural reflexes (a major cause of falling), and freezing of gait. Levodopa does not prevent continued worsening of the disease itself, it has limited effectiveness against most of the nonmotor features of PD (e.g., cognitive decline, mood alterations, loss of motivation, autonomic dysfunction) (covered in Chapter 8), and it is associated with motor fluctuations (wearing off, unpredictable “off”) and dyskinesias (discussed later in a separate section). Because of the latter problems, other dopaminergic drugs have been developed (see Table 6.4).

The association of levodopa with malignant melanoma has been controversial. Levodopa is an intermediary metabolite in the synthesis of skin melanin (via the enzyme tyrosinase). Whether this action of levodopa gives rise to melanoma remains a question. A review of the literature does not provide evidence of a definite relationship between treatment with levodopa and the development or reemergence of malignant melanoma (Pfutzner and Przybilla, 1997; Zanetti et al., 2006; Olsen et al., 2007). Epidemiologic studies have shown that people with PD have an increased prevalence of malignant melanoma (Olsen et al., 2006). A clinical trial in which the development of melanoma was a secondary outcome measure showed that patients with PD on the placebo arm of the trial had a much higher rate of developing malignant melanoma than would have been predicted; no association between levodopa therapy and the incidence of melanoma was found (Constantinescu et al., 2007). Yet it would seem prudent not to treat with levodopa in patients with a history of a malignant melanoma if other antiparkinson agents remain effective. Once it becomes necessary to use levodopa to improve quality of life, these patients need to be informed of this potential risk and should be examined regularly by their dermatologist or oncologist.

Enzyme inhibitors

Besides being metabolized by aromatic amino acid decarboxylase (often called dopa decarboxylase), levodopa is also metabolized by catechol-O-methyltransferase (COMT) to form 3-O-methyldopa. Three COMT inhibitors are currently available: tolcapone, entacapone, and opicapone. These agents extend the plasma half-life of levodopa with only a small increase in its peak plasma concentration, and can thereby prolong the duration of action of each dose of levodopa. These drugs are used in conjunction with levodopa to reduce the wearing-off effect (Rinne et al., 1998b), a

Table 6.5 Formulations of carbidopa/levodopa

Currently marketed	Common trade name
Standard formulation, also known as immediate-release	Sinemet
Orally disintegrating tablets	Parcopa
Extended-release formulation	Sinemet CR
Extended-release microspheres	Ryтары
Intestinal gel	Duopa in United States; DuoDopa elsewhere
Levodopa dry powder aerosol	Inbrija
Under Development	Research Label
Deuterated levodopa	D3-L-DOPA
Gastroretentive carbidopa/levodopa swelling tablets	DM-1992
Gastroretentive Accordion Pill carbidopa/levodopa	AP CD/LD
Soluble carbidopa/levodopa solution	ND-0612
Levodopa prodrug	XP21279

common motor fluctuation adverse effect of levodopa therapy. The net effect with multiple dosings per day, though, is to elevate the average plasma concentration while smoothing out the variations in the concentration. Tolcapone has two potential adverse effects that need to be explained to the patient. The most serious is that a small percentage of patients will develop elevated liver transaminases, and patients need to have baseline and follow-up liver function tests. Death from hepatic necrosis has occurred in three patients who had no liver function surveillance (Watkins, 2000). Entacapone has not been shown to induce these hepatic changes. In addition with tolcapone, a small percentage of patients will develop diarrhea that does not appear for about 6 weeks after starting the drug. The diarrhea can be explosive, so the patient might not have any warning. Entacapone appears not to have these adverse effects. Many clinicians think that tolcapone is more effective than entacapone in reducing motor fluctuations, but one should not prescribe the former unless the latter has not been effective in relieving wearing off. Patients on entacapone can be easily switched to tolcapone if the former had less than the desired effect, and a double-blind comparison showed tolcapone to be slightly more effective in reducing the amount of “off” time (The Entacapone to Tolcapone Switch Study Investigators, 2007). If tolcapone is to be used, we advise starting at a low dose of 100 mg/day and increase gradually to 100 mg three times daily. Entacapone has a short half-life, so a dose of 200 mg is taken with each dose of levodopa (Kiebert et al., 1997a). One formulation (Stalevo) combines carbidopa, levodopa, and 200 mg entacapone into a single tablet; the dose of a tablet of Stalevo represents the amount of levodopa in the tablet.

Adding entacapone to patients on levodopa who are not experiencing motor fluctuations did not add any improvement to motor performance in one study (Olanow et al., 2004) but improved the ADLs score in another (Brooks and Sagar, 2003). In the FIRST-STEP study, levodopa/carbidopa/entacapone (LCE) 100/25/200 mg 3 times daily, was compared with levodopa/carbidopa (LC) 100/25 mg 3 times daily in patients with early PD for 39 weeks (Hauser et al., 2009). LCE treatment resulted in slightly better Unified Parkinson's Disease Rating Scale (UPDRS) Part II ADLs scores ($P = 0.025$) but not Part III motor scores.

The concept that intermittent brain levels of levodopa and dopamine contribute to the development of motor complications (see later in discussion of advanced PD) has led to the concept that continuous dopaminergic stimulation may avoid these complications from levodopa. So far, one study (STRIDE-PD) testing this hypothesis has yielded the opposite effect, that is, an earlier onset of dyskinesias (Stocchi et al., 2010). A total of 747 patients with early PD were randomized to LCE 100/25/200 mg or LC 100/25 mg with flexible dosing to reach 400 mg/day, with a dose 3.5 hours apart. The results showed that time to dyskinesia was statistically significantly shorter in LCE-treated patients compared with LC-treated patients. The incidence of dyskinesia during the study period was higher in LCE-treated patients in comparison to the LC group.

Direct Dopamine Agonists

The next most powerful drugs, after levodopa for the treatment of PD motor symptoms are the dopamine agonists.

Available dopamine agonists for the treatment of PD are listed in Table 6.4. The ergoline direct dopamine agonists are no longer considered a treatment for PD because of their association with cardiac valve fibrosis. Cabergoline is the longest acting and could be taken just once per day (Ahlskog et al., 1996; Hutton et al., 1996); it theoretically could be most important in terms of preventing or reducing the wearing-off effect because of its long duration of action, but it has not been tested for this use. Piribedil is relatively weak but has been touted as having an antitremor effect.

Apomorphine and rotigotine cannot be absorbed with oral administration. Rotigotine can be absorbed transdermally and is marketed as an applied skin patch (Parkinson Study Group, 2003; Poewe and Luessi, 2005; LeWitt et al., 2007; Poewe et al., 2007; Watts et al., 2007), which is useful for patients unable to swallow medications, such as after gastrointestinal surgery. Despite its continuous absorption by transdermal patch, rotigotine did not prove effective in clinical trials in combating the wearing-off problem that is commonly seen with levodopa therapy. It takes higher doses of rotigotine to reduce “off” time (Nicholas et al., 2014). Rotigotine is a relatively weak dopamine agonist. Apomorphine needs to be injected subcutaneously or absorbed sublingually. It is the strongest agonist and can mimic the effectiveness of levodopa. In Europe it is often used as a subcutaneous infusion to overcome the wearing-off problem seen with levodopa therapy. In the United States it is marketed as single intramuscular injections and as a sublingual film to rescue patients who are in a deep “off” state; clinical trials on the efficacy and safety of subcutaneous infusions are under way in the United States. The FDA failed to approve sublingual administration of apomorphine in 2019 and requested further information, particularly related to oral irritation. In the pivotal trial involving 109 patients who were randomly assigned to receive apomorphine sublingual film ($n = 54$) or placebo ($n = 55$), there was a significant and clinically meaningful reduction in the MDS-UPDRS Part III score between predose and 30-minute postdose at week 12 with sublingual apomorphine compared with placebo (Olanow et al., 2019). Besides oropharyngeal irritation, other treatment-emergent adverse events included somnolence and dizziness. The FDA ultimately approved sublingual apomorphine on May 21, 2020 (Press Release, 2020).

The other dopamine agonists in Table 6.4 are effective orally. Bromocriptine is the weakest clinically compared to the others. Pergolide, pramipexole, and ropinirole appear to be comparable in clinical practice, but some patients will respond better to one than the others. There are some differences of these agonists in their affinity for the dopamine receptor subtypes, as depicted in Tables 6.6 and 6.7. Only apomorphine (strong) and pergolide (modest) have agonist

Table 6.6 Dopamine agonists actions on the dopamine receptors

Agonist	D1	D2	D3	D4	D5
Bromocriptine	—	++	++	+	+
Lisuride	+	++	?	?	?
Pergolide	+	++	+++	?	+
Cabergoline	—	+++	?	?	?
Ropinirole	—	++	++++	+	—
Pramipexole	—	++	++++	++	?

Table 6.7 Dopamine agonists and affinities for the dopamine D1, D2, and D3 receptors

Agonist	D1	D2	D3	D2/D3 ratio
Bromocriptine	0	+++	++	10:1
Pergolide	+	+++	+++	1:1
Ropinirole	0	++	+++	1:10
Pramipexole	0	++	+++	1:10

Data extracted from Perachon S, Schwartz JC, Sokoloff P: Functional potencies of new antiparkinsonian drugs at recombinant human dopamine D-1, D-2 and D-3 receptors. *Eur J Pharmacol.* 1999;366:293–300.

activity at the dopamine D1 receptor. The activation of the D2 receptor is known to be important in obtaining an anti-PD response, whereas it is unknown how important D3 receptor activation is for improving the anti-PD response. Bromocriptine, pergolide, pramipexole, and ropinirole activate the dopamine D3 and D2 receptors, but their ratios of affinities for these two receptors are different (see Table 6.7) (Perachon et al., 1999). All dopamine agonists are less likely to induce dyskinesias compared with levodopa (Schrage et al., 1998). The agonists can be used as adjuncts to levodopa therapy (e.g., Lieberman et al., 1998; Pinter et al., 1999) or as monotherapy (e.g., Kieburtz et al., 1997b; Brooks et al., 1998; Kulisevsky et al., 1998; Rinne et al., 1998a; Sethi et al., 1998). Adverse effects that are more common with dopamine agonists than with levodopa are impulse control disorders (Weintraub et al., 2010), drowsiness, sleep attacks, confusion, orthostatic hypotension, nausea, and ankle/leg edema associated commonly with erythema (Parkinson Study Group, 2000; Rascol et al., 2000). Edema can spread to involve other areas of the body, including the arms and face.

Apomorphine, being water soluble and injectable, can be employed as a rapidly acting dopaminergic agent to overcome “off” states, that is, provide a rescue. It is either injected, infused subcutaneously or absorbed sublingually. Because of its emesis-producing propensity, the patient must be pretreated with an antiemetic, such as domperidone or trimethoprim. In the United States, apomorphine is FDA-approved, so far, for subcutaneous injections to overcome an “off” episode. In Europe it is also being used by continuous subcutaneous infusion to provide a smooth response for patients who fluctuate between dyskinetic and “off” states. Apomorphine is the most powerful of the dopamine agonists and activates both the dopamine D1 and D2 receptors.

Having several dopamine agonists to choose from allows the opportunity to find one that is better tolerated and that might have a better effect. Adverse effects may be the deciding factor as to which drug will work best for a patient. Unfortunately, all of these drugs can induce confusion and hallucinations in elderly patients. Leg edema occurs in some patients, usually after a few years. Pramipexole, ropinirole, and other dopaminergics, though with probably less frequency, can cause daytime sleepiness and sleep attacks (sudden falling asleep without warning of drowsiness). This could be dangerous for the patient who drives an automobile, and motor vehicle accidents have occurred when patients fell asleep at the wheel (Frucht et al., 1999; Ferreira et al., 2000; Hoehn, 2000; Schapira, 2000). So when deciding to place a patient on pramipexole or ropinirole, the physician should determine the extent of driving to be done by the patient, and warn the patient

about this potential hazard. Short trips (e.g., 10 minutes or so) should be without risk. Should sudden falling asleep occur in any nondriving activity, this event can serve as a warning against driving or else it would be best to taper and even discontinue these medications if driving is necessary. Dopamine agonists also are more likely to induce impulse control problems, such as gambling, hypersexuality, shopping, and binge eating (Weintraub et al., 2010) (see Chapter 8). The dopamine agonist withdrawal syndrome, in which symptoms of withdrawal are sustained, is another risk with these drugs (Rabinak and Nirenberg, 2010). The risk for impulse control problems with dopamine agonists has led many neurologists to shy away from using these drugs in favor of levodopa.

Other Agents

Amantadine has several actions, including antimuscarinic, that block dopamine reuptake from dopaminergic synapses. It is also a noncompetitive antagonist of the N-methyl-D-aspartic acid (NMDA) glutamate. Its dopaminergic action make it a useful drug to modestly reduce symptoms of PD, although this symptomatic effect tends to be transient, lasting a few months. The amantadine side effect profile includes livedo reticularis, ankle edema, visual hallucinations, and confusion, the latter two mainly in older individuals or those with a cognitive deficit. Amantadine is more commonly used to help overcome levodopa-induced dyskinesias. So far, it is the only drug that has shown this ability without worsening parkinsonism. Amantadine is also available in an extended-release formulation with the brand name Gocovri. This preparation of long-acting amantadine has been FDA-approved for reducing levodopa-induced dyskinesia. It is taken one time a day in the evening. During the night, the levels of amantadine increase and reach a stable plasma level during the day. The pivotal clinical trial demonstrated that there was an increase in “on” time of up to 2 hours compared with placebo and a reduction in dyskinesia. The side effect profile is similar to that of amantadine, as noted earlier (Oertel et al., 2017; Pahwa et al., 2017).

Domperidone is a peripherally active dopamine receptor blocker and is useful in preventing gastrointestinal upset from levodopa and the dopamine agonists. Although it does not enter the CNS, it can still block the dopamine receptors in the area postrema, thereby preventing nausea and vomiting. By not penetrating the CNS, it does not block the dopamine receptors in the striatum, thus not interfering with the action of dopamine or dopamine agonists. Domperidone is available in most countries world-wide, but is not marketed in the United States.

Monoamine oxidase (MAO) inhibitors (MAOIs) offer mildly effective symptomatic benefit. MAO is composed of two isoenzymes, MAO-A and MAO-B, which are located in the mitochondria; each has selective substrates that it deaminates and oxidizes. In brain, MAO-A acts on serotonin and norepinephrine; both MAO-A and MAO-B act on dopamine. MAO-A is located in neurons and MAO-B in glia. In peripheral organs, tyramine is a substrate for MAO-A, but not MAO-B (Finberg and Tenne, 1982). The original MAOIs developed for their antidepressant effects (e.g., phenelzine and tranylcypromine) were associated with the “cheese effect” (hypertensive crisis). These agents are nonselective and inhibit both MAO-A and MAO-B activity (Krishnan, 2007). The cheese effect is due to the inhibition of MAO-A in the intestinal tract; thus,

the gut is unable to deaminate ingested tyramine, allowing tyramine to be absorbed into the body. Tyramine is present in certain food substances, particularly fermented meats and cheeses, soy sauce, and red wine. A high-tyramine meal results in absorption of tyramine from the gut. Tyramine is taken up into noradrenergic nerve terminals and acts as a false neurotransmitter, displacing norepinephrine from nerve terminals (Fischer et al., 1965). This excess release of norepinephrine from the nerve terminals produces the hypertensive crisis. The relatively selective MAO-B inhibitors selegiline, rasagiline, and safinamide, in the recommended therapeutic dosages, do not cause a hypertensive crisis, but they offer little antidepressant effect either. However, excessively high doses of these drugs will also inhibit MAO-A, so higher than the recommended doses could result in serious side effects.

Selegiline and rasagiline are both irreversible, selective MAO-B inhibitors with a similar chemical structure; both are propargylamine compounds. Safinamide is a reversible MAO-B inhibitor. None of these compounds have been compared head-to-head with each other to determine their relative effectiveness. The standard dose is 1 mg/day for rasagiline, 10 mg/day for selegiline, and 50 to 100 mg/day for safinamide. At these doses, the drugs are highly selective for MAO-B and do not require the patient to be on a low-tyramine diet. A controlled tyramine challenge showed that rasagiline up to 2 mg/day did not induce a significant blood pressure or pulse change when tyramine was added (deMarcaida et al., 2006). All three drugs are approved as adjunct therapy with levodopa. Their action is to enhance the action and prolong the duration of levodopa effect and thus reduce the wearing off.

Selegiline and rasagiline have mild symptomatic effects when used alone (Parkinson Study Group, 1993, 1996a,b, 2002a, 2004a; Rabey et al., 2000; Olanow et al., 2009). These two drugs are commonly used as initial pharmacotherapy for PD. Safinamide was reported not to be efficacious in reducing PD symptoms in the absence of levodopa (Fox et al., 2018). When used in the presence of levodopa therapy, the MAO-B inhibitors potentiate levodopa's effect (Lees, 1995). The selective MAO-B inhibitors can be used safely with selective serotonin uptake inhibitors without producing the serotonin syndrome, provided the dosages are in the approved range of MAO-B selectivity and to avoid inhibiting MAO-A (Panisset et al., 2014; Smith et al., 2015).

Zydis selegiline is a form of selegiline that dissolves in the mouth and is absorbed through the oral mucosa, avoiding first pass metabolism in the liver (Waters et al., 2004). Zydis selegiline is formulated as freeze-dried tablets and is marketed as Zelapar. High doses of zydis selegiline can inhibit MAO-A in the brain (Fowler et al., 2015) and by bypassing the intestinal tract avoid the cheese effect.

Selegiline is also available in a dermal patch (marketed as Emsam), in a dosage high enough to also inhibit MAO-A in the brain. Emsam is marketed as an antidepressant agent. Emsam does not cause the cheese effect because selegiline was absorbed transdermally, bypassing the gut and thereby avoiding the inhibition of intestinal MAO-A (VanDenBerg, 2012). However, this is not approved for use in PD.

Rasagiline is metabolized to aminoindan, selegiline to L-amphetamine and L-methamphetamine, and safinamide to its acid form. Their effects in treating clinical fluctuations and as possible disease-modifying agents are discussed later

Table 6.8 Nondopaminergic agents for motor symptoms

Antimuscarinics: trihexyphenidyl, benzotropine, ethopropazine, etc.
Antihistaminics: diphenhydramine, orphenadrine
Antiglutamatergics: amantadine, dextromethorphan, riluzole
Benzodiazepines: alprazolam, lorazepam, diazepam
Muscle relaxants: cyclobenzaprine, diazepam, baclofen
Adenosine A _{2A} receptor antagonist: istradefylline
Neurotrophins: neuroimmunophilins, GDNF, and neurturin all failed in clinical trials
Antioxidants: tocopherol and coenzyme Q10 failed in phase III clinical trials
GDNF, Glial cell line–derived neurotrophic factor.

in the appropriate sections (Treatment of motor fluctuations associated with levodopa therapy and Selegiline, rasagiline, and antioxidants).

Inhibitors of both MAO-A and MAO-B would offer greater inhibition of dopamine oxidation in the brain, and thus the combination would theoretically be more capable of reducing oxidative stress and providing more symptomatic effect (Fahn and Chouinard, 1998). But tranylcypromine and phenelzine (both nonselective inhibitors of MAO-A and MAO-B) cannot be taken in the presence of levodopa therapy because of the cheese effect, and even in the absence of levodopa, patients on these drugs need to adhere to a reduced-tyramine diet (Gardner et al., 1996).

We will return to discuss MAOIs and antioxidants later in their possible role in treating early-stage PD. Next, we will review the nondopaminergic drugs that are useful in treating the motoric problems of PD (Table 6.8).

COMT inhibitors (COMTIs) are useful only in the presence of levodopa therapy. COMT catalyzes the methylation of catechols (e.g., levodopa and dopamine). By inhibiting this enzyme peripherally, the half-life of levodopa is lengthened somewhat. Drugs in this class are entacapone, tolcapone, and opicapone. Opicapone is a long-acting drug, taken at bedtime; it was approved by the FDA in 2019. Opicapone was approved by the FDA in 2019. All three are discussed in more detail in the section related to the treatment of the wearing-off effect, for which these drugs can be useful.

Nondopaminergic Agents for Motor Symptoms

Some nondopaminergic agents (see Table 6.8) are also useful to treat motoric PD symptoms, particularly antimuscarinic drugs (commonly referred to as anticholinergics), which have been widely used since the 1950s, but these are much less effective than the dopaminergic agents, including amantadine. The original use of antimuscarinic alkaloids date back to the time of Charcot, and synthetic agents became available and popular in the 1950s (see review by Fahn, 2015). Antimuscarinic drugs are somewhat helpful in reducing all symptoms of PD, but they have found special favor in reducing the severity of tremor. However, because of sensitivity to memory impairment in all groups and hallucinations in the elderly population, antimuscarinic drugs usually should be avoided in patients over the age of 70 years. The antihistaminics (diphenhydramine, orphenadrine, and others), tricyclics (amitriptyline and others), and cyclobenzaprine (Flexeril) have milder anticholinergic properties that can make them useful in PD, particularly in older patients who

should not take the stronger anticholinergics because of their propensity to impair short-term memory at that age level.

Amantadine, listed in Table 6.4 as a dopaminergic agent, is listed also in Table 6.8 because it has antiglutamatergic effects; this property appears to account for its usefulness in reducing choreic dyskinesias induced by levodopa (Rajput et al., 1997; Metman et al., 1998a; Sawada et al., 2010; Ory-Magne et al., 2014). An extended-release form of amantadine was found to be effective to reduce levodopa-induced dyskinesias in a controlled clinical trial (Pahwa et al., 2015, 2017) and has been approved by the FDA for this indication. Dextromethorphan is another antiglutamatergic agent, and it has been found effective in reducing the severity of dyskinesias by 50% (Metman et al., 1998b).

Another useful class of drugs is the benzodiazepines to decrease parkinsonian tremor that is exacerbated by stress. These drugs reduce anxiety and by calming a patient provide a lessening of tremor. Diazepam is usually well tolerated and does not exacerbate parkinsonian symptoms, whereas chlor-diazepoxide can (Schwarz and Fahn, 1970). Lorazepam and alprazolam are other useful benzodiazepine agents; the latter has the added benefit of being short-acting, so it can be used when needed. It also has some antidepressant effects. The benzodiazepines can cause drowsiness, so it is best to start with a small dose and increase it if tolerated. The muscle relaxants listed in Table 6.8 might help in treating “off” and peak-dose dystonias. Because oxidative stress appears to play a role in the pathogenesis of PD, high dosages of antioxidant vitamins, tocopherol, and coenzyme Q10 have been tried for patients with PD and failed in clinical trials (Parkinson Study Group, 1993; Parkinson Study Group QE3 Investigators, 2014).

Stress, excitement, and anxiety make parkinsonian symptoms worse, especially tremor. In fact, tremor that is otherwise well controlled with medication can reemerge under stress, excitement, and anxiety. The benzodiazepines, by reducing anxiety, can partially offset this worsening of tremor. Apathy and fatigue are common in PD, and no medication as yet has been found satisfactory.

Adenosine A_{2A} receptors are located on gamma-aminobutyric acid (GABA) neurons in the striatum and antagonize the effect of dopamine on these neurons (Benarroch, 2008). Antagonizing adenosine A_{2A} receptors has a behavioral effect similar to enhancing dopaminergic transmission. Several of these receptor antagonists (Table 6.8) have undergone clinical trials for patients with motor fluctuations (Bara-Jimenez et al., 2003; Hauser et al., 2003; LeWitt et al., 2008; Stacy et al., 2008; Hauser et al., 2014), but the results were mixed, with insufficient relief of fluctuations and enhanced dyskinesias (Antonini and Poewe, 2014). However, after further clinical trials, istradefylline was found effective in reducing clinical fluctuations (Sako et al., 2017) and was approved for this indication by the FDA in 2019 under the label of Nourianz. Because of its favorable side effect profile, istradefylline may be particularly useful in elderly patients with troublesome motor fluctuations who may have comorbid depression or cognitive impairment (Torti et al., 2018).

Various sleep problems are encountered in PD. Excessive drowsiness can occur after a dose of levodopa or dopamine agonist. Modafinil and methylphenidate can sometimes help overcome this problem. Insomnia needs to be treated, otherwise quality of life suffers and daytime sleepiness is

enhanced. For insomnia, mild hypnotic drugs such as melatonin, antihistamines, trazodone, and mirtazapine can be used with satisfying results. Stronger hypnotics, such as zolpidem and benzodiazepines, can be safely used if the milder drugs are not effective.

Treatment of early-stage PD (mild symptoms, no threat to activities; these patients would be good candidates to participate in neuroprotective trials)

The earliest stage of PD begins when the first motor symptoms are noticed and the diagnosis is made. At this stage, symptoms are mild and there is no threat to the patient's activities. The designation of “early stage” lasts until the symptoms begin to become troublesome to the patient or quality of life is affected, and intervention with symptomatic medications is needed. All symptomatic drugs can induce side effects, and if a patient is not troubled by mild symptoms socially or occupationally, the introduction of these drugs can be delayed until symptoms become more pronounced. The clinician needs to discuss this choice with the patient and the patient's family. Levodopa, the most effective symptomatic drug, failed to show evidence of a neuroprotective effect in a delayed-start design clinical trial (Verschuur et al., 2019) (Fig. 6.3). Most neurologists do not use levodopa or other potent antiparkinson agents when the diagnosis is first established, and the disease manifests with no threat to physical, social, or occupational activities (Fahn, 1991, 1999; Fahn et al., 1996).

Because symptomatically beneficial medications are not needed, and because there is no proven neuroprotective treatment, patients in the early, recently diagnosed stage of PD are excellent candidates for participating in a controlled

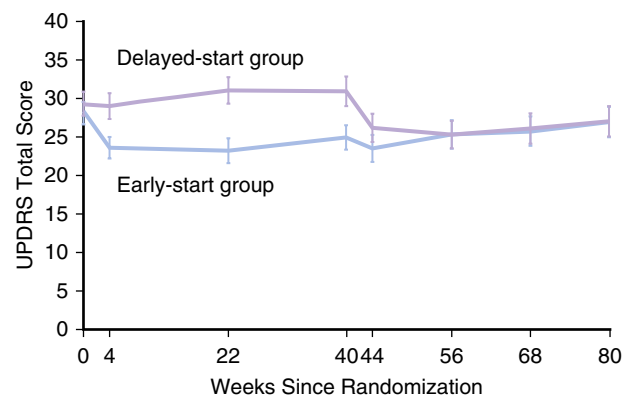


Fig. 6.3 Levodopa 100 mg three times daily in a delayed-start design clinical trial. The early-start group began therapy at the start of the study. The delayed-start group received placebo for the first 40 weeks of the study. At week 40, all subjects were told that they would be given levodopa 100 mg three times daily and received it. During the first 40 weeks, the levodopa group manifested improvement on the Unified Parkinson Disease Rating Scale (UPDRS), whereas the placebo group worsened. When the placebo group received levodopa therapy at week 40, they rapidly improved and caught up with the early-start group. (From Verschuur CVM, Suwijn SR, Boel JA, Post B, Bloem BR, van Hilten JJ, et al: Randomized delayed-start trial of levodopa in Parkinson's disease. *N Engl J Med*. 2019;380[4]:315–324. <https://doi.org/10.1056/NEJMoa1809983>. PubMed PMID: 30673543.)

clinical trial in which a placebo is one of the treatment arms. In the past decades, several literature reviews of clinical trials related to neuroprotection in PD have been published (Fahn and Sulzer, 2004; LeWitt, 2006; Seidl and Potashkin, 2011 and Suchowersky et al., 2006). The MAO-B inhibitors have figured largely in clinical trials for neuroprotection (disease-modification).

MAO-B inhibitors: selegiline and rasagiline

As can be seen from Table 6.2, the MAO-B inhibitors that have been tested in neuroprotection trials were all able to slow the rate of worsening of the motor features of PD. The irreversible inhibitors, selegiline and rasagiline are available commercially, but even lazabemide, a reversible MAO-B inhibitor, never marketed, also was effective. Not a single study with an MAO-B inhibitor failed a clinical trial in being superior to a placebo. The major question is whether this effect is all from its symptomatic effect or some of its benefit is from a neuroprotection (disease-modification) effect.

The first controlled clinical trial for the purpose of evaluating medications as neuroprotective agents for PD was the test for selegiline in the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) study (Parkinson Study Group, 1989a,b, 1993). Selegiline was called deprenyl at the time the trial was begun. Selegiline is a propargyline drug and has a long duration of action (MAO-B inhibition half-life of 40 days) (Fowler et al., 1994). The DATATOP study evaluated the antioxidant, alpha-tocopherol (vitamin E), along with selegiline in a 2 × 2 design. Patients were enrolled in the study early in the course of their illness and did not require symptomatic therapy. They were placed on selegiline (5 mg twice daily), alpha-tocopherol (1000 IU twice daily), the combination, or double placebo, with approximately 200 subjects in each of the four treatment arms. The primary endpoint was the need for dopaminergic therapy, that is, levodopa. The study showed that tocopherol had no effect in delaying parkinsonian disability, but selegiline delayed symptomatic treatment by 9 months (Fig. 6.4) (Parkinson Study Group, 1993). It also reduced the rate of worsening of the UPDRS by half (Table 6.9). Other investigators subsequently conducted other studies testing selegiline, showing similar beneficial results (Myllyla et al., 1992; Olanow et al., 1995; Palhagen et al., 1998, 2006).

Because selegiline has a mild symptomatic effect that is long lasting (Parkinson Study Group, 1993), one might explain its ability to delay progression of disability entirely on this symptomatic effect. In favor of some neuroprotective effect is that after 2 months of washout of the drug, patients had slightly milder PD than did those on placebo (Parkinson Study Group, 1993). But because of selegiline's very long duration of action as an inhibitor of MAO-B (Parkinson Study Group, 1995), this observation could represent an insufficient washout period. Furthermore, selegiline's benefit in delaying the introduction of levodopa gradually diminishes over time (Parkinson Study Group, 1993), with the best results occurring in the first year of treatment. The odds ratio increased from 0.35 for the first 6 months, to 0.38 in the second 6 months, to 0.77 in the third 6 months, and to 0.86 after 18 months. Follow-up of DATATOP subjects showed that placebo-treated subjects fared better than selegiline-treated subjects when the drug was reintroduced

after a 2-month washout period and that the two groups were identical in developing levodopa complications (Parkinson Study Group, 1996a,b). The net understanding by the year 2000 was that there is no convincing evidence that selegiline delayed the need for levodopa because of any protective effect; all results could be those of a drug with a continuing mild symptomatic benefit.

On the other hand, basic scientific research was finding that in animal models tiny doses of selegiline have a neuronal rescue effect (Tatton, 1993). This effect is separate from its MAO inhibitor mechanism of action. Ultimately this finding led to investigations of other agents for their rescue effect, resulting in the discovery of a propargyline drug without MAO inhibition (TCH346) that was tested in a clinical trial (Waldmeier et al., 2000, 2006). This drug failed to be better than placebo (Olanow et al., 2006).

When the results of the DATATOP study were analyzed to better understand the development of freezing of gait, it was discovered that the group who were treated with selegiline had a statistically significantly decreased risk for developing freezing of gait (Fig. 6.5) (Giladi et al., 2001). It could not be discerned whether this benefit was because of selegiline's mild symptomatic benefit or of some unknown

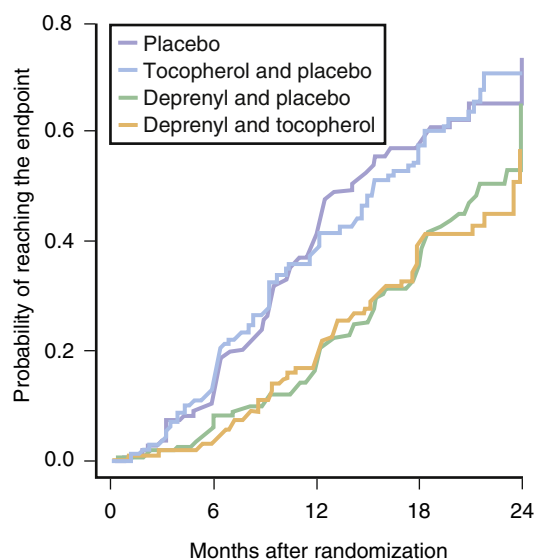


Fig. 6.4 DATATOP endpoints. Kaplan-Meier curves of the cumulative probability of reaching the endpoint (need for dopaminergic therapy) in DATATOP. (From Parkinson Study Group. Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med.* 1993;328:176–183.)

Table 6.9 Average annual rate of worsening in UPDRS scores (results are mean ± standard deviation)

Treatment	Total UPDRS
Placebo	14.02 ± 12.32
Tocopherol	15.16 ± 16.12
Selegiline	7.00 ± 10.76
Tocopherol and selegiline	7.28 ± 11.11
P Value	<0.001

UPDRS, Unified Parkinson's Disease Rating Scale. Higher numbers represent more severe worsening of PD.

From Parkinson Study Group: Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med.* 1993;328:176–183.

neuroprotection effect. Whichever it was, the authors concluded that one should consider using selegiline in patients who are likely to develop freezing of gait those with (absence of tremor, gait involvement as the initial symptom).

Subsequently, based on the BLIND-DATE study, there is evidence that the decreased risk for freezing of gait with selegiline is not simply from its symptomatic effect as an enhancer of dopamine. The investigators of the DATATOP study, while continuing to follow their subjects, carried out a rerandomization of the subjects into a new controlled trial (called the BLIND-DATE study). A total of 368 subjects who were now taking both selegiline and levodopa therapy agreed to be randomized to either selegiline or placebo while remaining on open-label levodopa. The results were dramatic. Over an almost 2-year period, the subjects on selegiline required a lower dosage of levodopa, had a slower rate of worsening of symptoms and signs of PD (Table 6.10), and had less freezing of gait (Fig. 6.6) (Shoulson et al., 2002). These results

support the view that selegiline does provide some neuroprotective effect or else it has a symptomatic effect separate from a dopaminergic effect. The possibility that this benefit is derived from an antiapoptotic effect rather than its antioxidative effect is discussed later.

A similar study was carried out in Sweden by Palhagen and colleagues (2006), who followed patients for at least 7 years after they entered a controlled clinical trial evaluating selegiline versus placebo in those with early, untreated PD. Then, when any subject required symptomatic therapy, open-label levodopa was added while the blind was maintained on selegiline versus placebo. During the 7 years of follow-up from the start of the study, the selegiline-treated group had a statistically significantly slower rate of worsening of clinical signs and symptoms as measured by UPDRS scores. Like the study by Shoulson and colleagues (2002) mentioned earlier, this also shows the added benefit that selegiline provides in slowing clinical symptoms. Whether this can be attributed to a neuroprotective effect or to a symptomatic effect that does not appear to be through dopamine is undetermined by the two studies.

The safety of selegiline was raised, though, in an open-label clinical trial in the United Kingdom (Lees, 1995). The use of selegiline when combined with levodopa was reported to be associated with a higher mortality rate than was seen in the patients assigned to levodopa treatment alone. Analysis of this result by others found a number of flaws in the study to refute this conclusion (Olanow et al., 1996). The U.K. investigators followed up their report with a more detailed analysis of the cause of death (Ben-Shlomo et al., 1998). The excess mortality in the selegiline plus levodopa group was greatest in the third and fourth years of treatment. The cause of the increase in deaths showed the excess to be from PD only and to occur particularly in patients with dementia and a history of falls. No significant differences in mortality were found for revised diagnosis, disability rating scores, autonomic or cardiovascular events, other clinical features, or drug interactions. Other studies with selegiline have failed to find any excess mortality from the combination treatment with levodopa (Myllyla et al., 1997; Aaltonen et al., 1998; Olanow et al., 1998). After being followed by the Parkinson Study Group an average of 8.2 years, the subjects in the

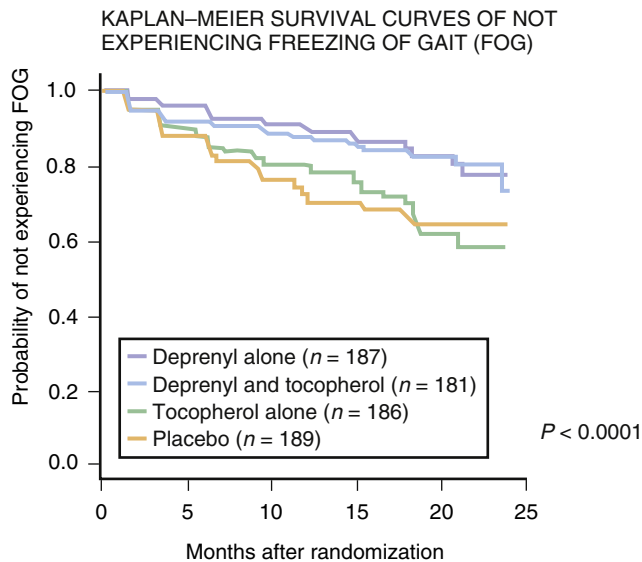


Fig. 6.5 Freezing in DATATOP. Kaplan–Meier curves showing probability of not experiencing freezing of gait in the absence of levodopa in the DATATOP study. (From Giladi N, McMahon D, Przedborski S, Flaster E, Guillory S, Kostic V, et al: *Motor blocks in Parkinson's disease*. *Neurology*. 1992;42:333–339.)

Table 6.10 Change in total UPDRS in the BLIND-DATE study after randomization to either selegiline or placebo while taking levodopa

Duration after randomization	Placebo	Selegiline	Difference
1 month	0.50 ± 7.73	−1.52 ± 7.54	2.02
3 months	1.57 ± 9.41	−0.85 ± 9.42	2.42
9 months	4.18 ± 10.12	1.63 ± 10.61	2.55
15 months	5.63 ± 10.73	0.46 ± 10.88	5.17
21 months	7.06 ± 12.70	1.51 ± 10.36	5.55
† L-dopa mg/day	181 ± 246	106 ± 205	$P = 0.003$

Higher UPDRS scores represents more severe PD. UPDRS results, $P = 0.0002$.

UPDRS, Unified Parkinson's Disease Rating Scale.

From Shoulson I, Oakes D, Fahn S, et al. Impact of sustained deprenyl (selegiline) in levodopa-treated Parkinson's disease: A randomized placebo-controlled extension of the deprenyl and tocopherol antioxidative therapy of parkinsonism trial. *Ann Neurol*. 2002;51:604–612.

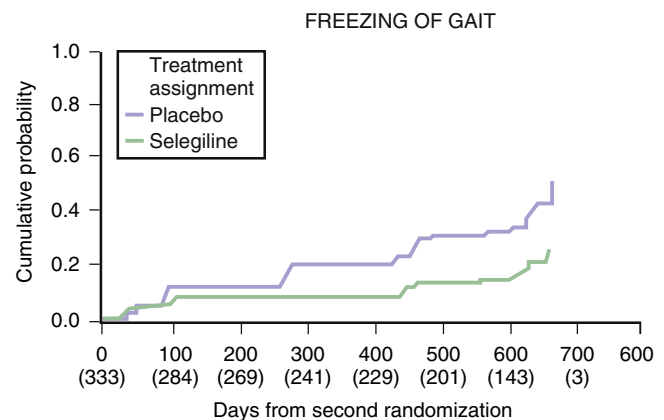


Fig. 6.6 Freezing in BLIND-DATE. Kaplan–Meier curves showing probability of experiencing freezing of gait in the presence of levodopa in the BLIND-DATE study. (From Shoulson I, Oakes D, Fahn S, et al: *Impact of sustained deprenyl (selegiline) in levodopa-treated Parkinson's disease: A randomized placebo-controlled extension of the deprenyl and tocopherol antioxidative therapy of parkinsonism trial*. *Ann Neurol*. 2002;51:604–612.)

DATATOP study showed no difference in mortality between the groups assigned to treatment with selegiline, tocopherol, or placebo; the death rate averaged 2.1% per year (Parkinson Study Group, 1998), much lower than in the U.K. study.

A meta-analysis of 17 controlled clinical trials involving MAO-B inhibitors found that no significant difference in mortality existed between patients on the inhibitors compared with control subjects (Ives et al., 2004). The analysis also found that subjects randomized to MAO-B inhibitors had significantly better total scores, motor scores, and ADL scores on the UPDRS at 3 months compared with patients taking placebo; they were also less likely to need additional levodopa or to develop motor fluctuations. No difference existed between the two groups in the incidence of side effects or withdrawal of patients.

High-dosage tocopherol also has been suggested to increase mortality, but analysis of the DATATOP cohort followed for up to 13 years failed to find any difference in mortality between the groups on vitamin E and the group on placebo (Marras et al., 2005).

In an analysis of retrospective observational data from Scotland (Donnan et al., 2000) comparing PD patients with a comparable control population, the patients with PD had a higher rate of mortality than those without PD (rate ratio [RR], 1.76; 95% confidence interval [CI], 1.11–2.81). There was significantly greater mortality in monotherapy (RR, 2.45, 95% CI, 1.42–4.23) relative to the comparators, adjusting for previous cardiovascular drug use and diabetes. However, there was no significant difference in mortality in patients with PD who received combination therapy of selegiline with levodopa and other drugs in relation to the comparators (RR, 0.92, 95% CI, 0.37–2.31). Thus, from this study, selegiline did not increase the mortality rate, whether used as monotherapy or in combination with levodopa. In fact, levodopa monotherapy had the highest mortality rate.

Rasagiline, based on the delayed-start studies, TEMPO (Parkinson Study Group, 2004a) and ADAGIO (Olanow et al., 2009), also can reduce the rate of clinical worsening in patients with early PD. But there were inconsistent outcomes between these two studies. In TEMPO, the 2-mg dose of rasagiline had a superior result compared with the 1-mg dose. In ADAGIO, only the 1-mg dose was superior to placebo; the 2-mg dose was no better than placebo (Fig. 6.7). Starting a symptomatically effective drug early does not automatically lead to a reduced rate of clinical worsening as tested by the delayed-start design. For example, pramipexole, an effective dopaminergic agent, does not give a superior clinical result if started early compared with starting it later (Schapira et al., 2013). Thus, there would appear to be a special property of the MAOIs to be able to delay clinical worsening in a delayed-start study.

As mentioned earlier, the dose of selegiline and rasagiline should not exceed their specificity as selective type B inhibitors of MAO. Selegiline greater than 10 mg/day and rasagiline greater than 2 mg/day will also inhibit MAO-A. In one example, a woman given rasagiline at 4 mg/day in the presence of levodopa therapy developed the serotonin syndrome of hyperpyrexia, confusion, agitation, and episodic periods of unconsciousness (Fernandes et al., 2011). Because selegiline is metabolized to L-amphetamine and L-methamphetamine, insomnia could develop and one should avoid taking it late in the day. It may be necessary to limit selegiline to 5 or 10 mg in the morning only if insomnia is a problem. Male

impotence is not common with MAO inhibitors. In the presence of levodopa, MAOIs potentiate levodopa's effect, and lower doses of levodopa can usually be achieved (Lees, 1995; Shoulson et al., 2002). Selegiline does not prevent the development of levodopa-induced complications of fluctuations and dyskinesias (Parkinson Study Group, 1996b). Selegiline decreases the risk for patients developing freezing of gait (Giladi et al., 2001; Shoulson et al., 2002). It is not clear if rasagiline has this ability. Interestingly, MAO-A inhibitors, but not MAO-B inhibitors, have been shown to reduce stress-induced freezing behavior in rats (Maki et al., 2000).

The DATATOP study showed that selegiline inhibits MAO activity by about 20% in the CNS (Parkinson Study Group, 1995). Because the original premise for the DATATOP study was that selegiline might be neuroprotective by inhibiting MAO (reducing formation of hydrogen peroxide and thereby decreasing oxidant stress), the CSF analysis of homovanillic acid indicates that selegiline is a poor inhibitor of CNS MAO. This finding could explain the lack of success of selegiline as a powerful neuroprotective agent. Whether a more potent MAOI could be more successful remains to be determined. In the meantime, it is reasonable for patients to consider an inhibitor of both types A and B, as possibly augmenting inhibition of MAO in brain. However, such MAOIs can induce the cheese effect, so a low-tyramine diet needs to be followed. Such MAOIs can be used only in the absence of levodopa because the presence of levodopa will create marked blood pressure fluctuations.

Another MAO-B inhibitor, safinamide, offers modest symptomatic benefit of PD (Schapira et al., 2016; Borgohain et al., 2014; Cattaneo et al., 2019), but it has not been tested for a potential neuroprotective effect. Safinamide is a reversible MAO-B inhibitor, in contrast to selegiline and rasagiline, which are irreversible inhibitors. Safinamide also blocks sodium voltage-sensitive channels and modulates stimulated release of glutamate (Perez-Lloret and Rascol, 2016). Thus, there may other clinical benefits or adverse effects from this drug. It was approved by the FDA in 2017 as an add-on drug for treating the wearing-off effect.

Dopamine agonists

Dopamine agonists are the next most powerful drugs after levodopa in reducing the motor symptoms of PD. Controlled clinical trials compared four different dopamine agonists against levodopa in patients with PD who were in need of symptomatic therapy: cabergoline and levodopa (Rinne et al., 1998a), ropinirole and levodopa (Rascol et al., 2000), pramipexole and levodopa (the CALM-PD trial) (Parkinson Study Group, 2000), and pergolide and levodopa (Oertel et al., 2006). The clinical outcomes of these studies are discussed later.

In this section, the results of the neuroimaging component of these trials are discussed. In the CALM-PD (pramipexole versus levodopa) trial, the 4-year imaging results show a statistically significant lesser rate of decay of dopamine transporter (DAT) binding (β -CIT SPECT) (a marker of integrity of nerve terminals of the dopaminergic nigrostriatal fibers) in the striatum in the group originally assigned to pramipexole treatment (Fig. 6.8) (Parkinson Study Group, 2002b). A separate study evaluating FDOPA positron emission tomography (PET) scans, a marker of dopa uptake and dopa decarboxylase activity, showed a similar statistically significant lesser rate of decay of labeling in the striatum in a controlled

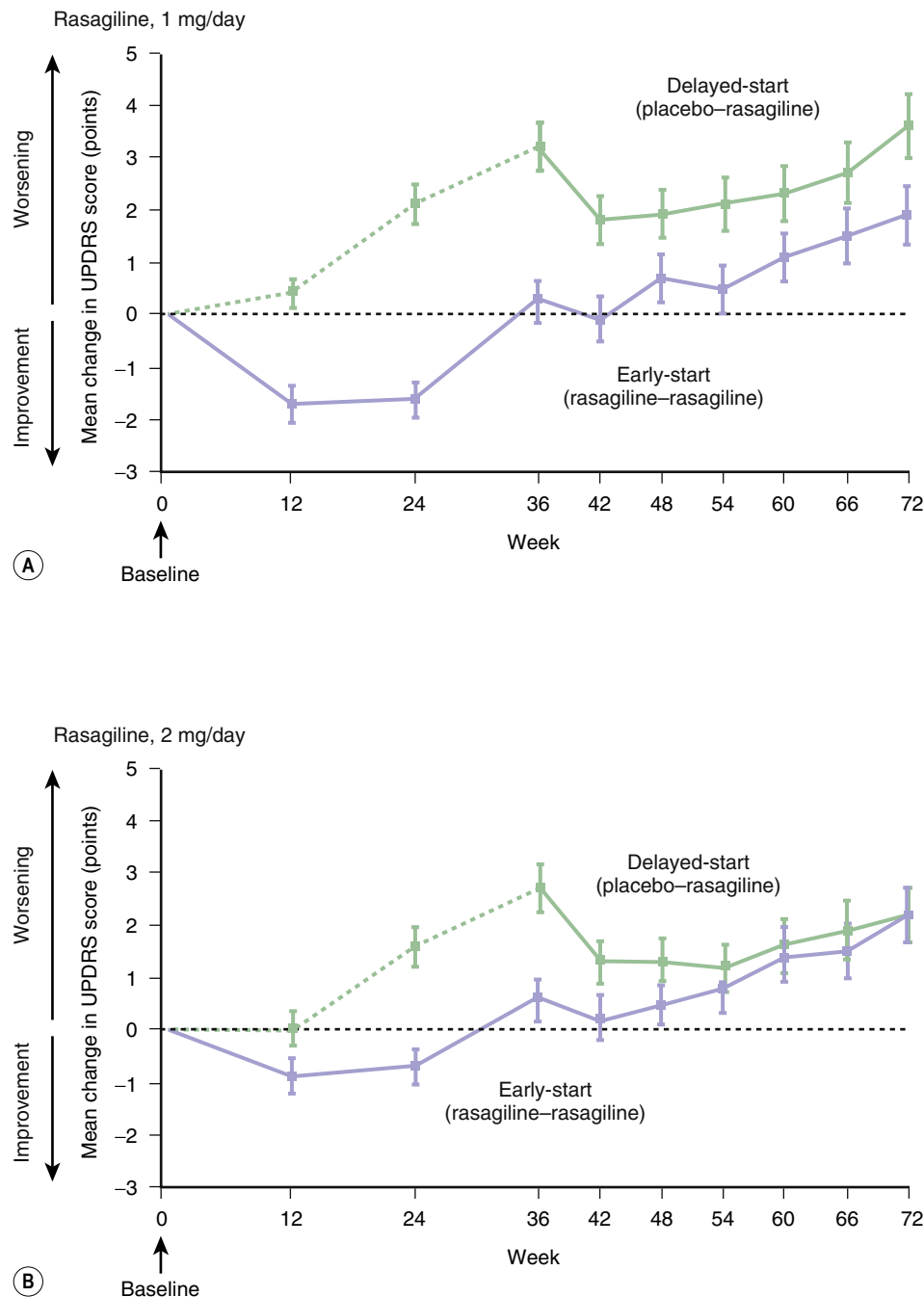


Fig. 6.7 ADAGIO trial showed (top graph) that 1 mg/day (top graph) of rasagiline resulted in a lower Unified Parkinson's Disease Rating Scale (UPDRS) score at 18 months if started earlier rather than 9 months later, but the 2 mg/day dose (bottom graph) showed no difference whether started earlier or later. (From Olanow, C. W., Kieburtz, K., Odin, P., Espay, A. J., Standaert, D. G., Fernandez, H. H., et al. (2014). Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: A randomised, controlled, double-blind, double-dummy study. *The Lancet Neurology*, 13(2), 141–149. doi:10.1016/S1474-4422(13)70293-X.Epub 2013 Dec 20.)

trial in the group assigned to ropinirole compared with the group assigned to levodopa therapy (Whone et al., 2003).

Because there was no placebo comparator in either study, interpretation is difficult. Whether dopamine agonists slow the rate of progression of PD, whether levodopa hastens it, and whether both explanations are playing a role are possibilities. Another possibility would be a pharmacodynamic effect on the DAT and dopa decarboxylase by either the agonists or levodopa. For example, if levodopa downregulated the DAT, β -CIT SPECT binding would be reduced. If levodopa downregulated dopa decarboxylase, FDOPA PET

binding would be reduced. Short trials of levodopa showed no change in these imaging markers, so there is no evidence that levodopa affects either type of imaging study in such a pharmacologic manner. But a consensus conference concluded that there is insufficient information about the effect of medications on dopaminergic imaging to recommend neuroimaging as a biomarker for disease progression in the presence of medication (Ravina et al., 2005). Without knowing whether the agonists actually slow the rate of progression, it is not possible to recommend the starting treatment on the basis of these results alone. Pramipexole was later

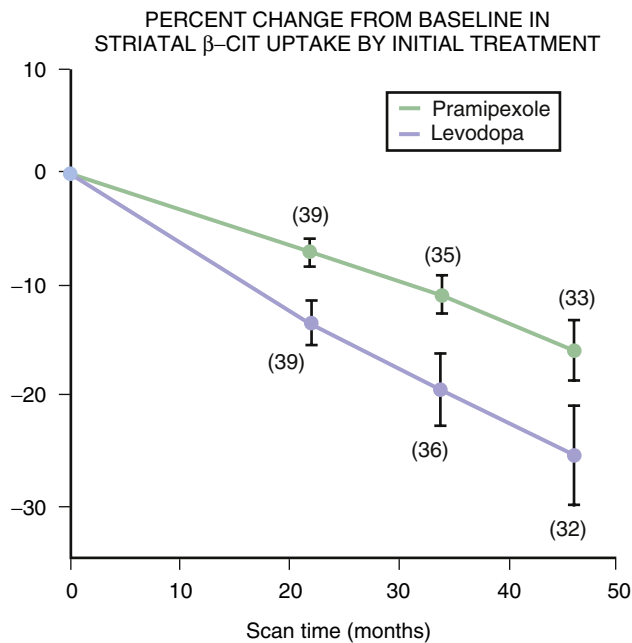


Fig. 6.8 Striatal β -CIT SPECT binding in the CALM-PD study. The lower the score indicates less severe PD. (From Parkinson Study Group: Dopamine transporter brain imaging to assess the effects of pramipexole vs levodopa on Parkinson disease progression. *JAMA*. 2002;287:1653–1661.)

tested in a delayed-start clinical trial and failed to show any slowing of PD (Schapira et al., 2013).

Inhibiting calcium entry

Substantia nigra pars compacta (SNc) dopamine neurons are autonomously active; that is, they generate action potentials at a clock-like 2 to 4 Hz in the absence of synaptic input (Surmeier et al., 2005). In this respect, they are much like cardiac pacemakers. Juvenile dopamine-containing neurons in the SNc use sodium influx as the pacemaking mechanisms common to neurons not affected in PD, but the sodium mechanism remains latent in adulthood (Chan et al., 2007a). Instead, the autonomous activity is generated by Ca^{++} influx (Mercuri et al., 1994; Chan et al., 2007a; Surmeier, 2007). The SNc dopamine neurons rely on L-type $\text{Ca}(\text{v})1.3$ Ca^{++} channels. With increased intracellular calcium, mitochondria function can be affected with increased demand on oxidative phosphorylation, leading to increased production of reactive oxygen species and eventually cellular damage. As the cells undergo more stress over time, they thus “age faster.” This would be a link with the risk factor of age (Surmeier, 2007). Blocking $\text{Ca}(\text{v})1.3$ Ca^{++} channels in adult neurons induces a reversion to the juvenile form of pacemaking. Such blocking (“rejuvenation”) protects these neurons in both in vitro and in vivo models of PD, pointing to a new strategy that could slow or stop the progression of the disease (Chan et al., 2007a; Surmeier, 2007).

As it turns out, use of calcium channel blockers for treating hypertension has been shown to be associated with less risk for developing PD in two database-mining studies (Becker et al., 2008; Ritz et al., 2010), but not in a third (Simon et al., 2010). A clinical trial to evaluate the dihydropyridine isradipine, a calcium channel blocker, was shown to be well tolerated (Simuni et al., 2010; Parkinson Study Group, 2013), but the results of a phase III clinical trial failed to show any

difference between isradipine and placebo in the progressive worsening of PD (Simuni, 2019; Parkinson Study Group STEADY-PD III Investigators, 2020) (see Table 6.1).

Uric acid

Because elevation in blood uric acid has been thought to be potentially neuroprotective, the prourate drug inosine has been tested in patients with early-stage PD, but the phase III trial (SURE-PD) ended early because the investigators thought they would not be able to show that inosine slows Parkinson’s progression (<https://www.michaeljfox.org/news/parkinsons-inosine-trial-ending-early>) (see Table 6.1).

Conclusions on treating Early-Stage PD

In this earliest stage of PD, we follow a recommendation that Fahn has advised, namely patients need to be informed about the disease and the advantages of a daily exercise program. Furthermore, although there is no medication proven to slow the worsening of the disease, it is reasonable to initiate therapy with a MAO-B inhibitor listed in Table 6.1 (selegiline or rasagiline) that has consistently been shown to reduce motor severity compared to a placebo, and may have some disease-modifying effect. Because selegiline has been the only drug shown in controlled clinical trials (even in the presence of levodopa therapy) to delay development of freezing of gait (Shoulson et al., 2002; Fig. 6.6), Fahn prefers this medication.

Treatment of mild-stage PD (when symptoms and signs begin to interfere with activities of daily living)

Strategy

The mild stage of PD occurs when the signs and symptoms of the illness are beginning to interfere with daily activities or with quality of life. The judgment to initiate symptomatic drug therapy is made in discussions between the patient and the treating physician. According to a survey (Parkinson Study Group, 1989a) the most common problems that clinicians consider important for the decision to initiate symptomatic agents are (1) threat to employability; (2) threat to ability to handle domestic, financial, or social affairs; (3) threat to ability to handle ADLs; and (4) appreciable worsening of gait or balance. According to a Norwegian quality of life study (Karlsen et al., 1999), the factors that produce the highest distress for PD patients compared with healthy elderly people are depressive symptoms, self-reported insomnia, and a low degree of independence, as measured by the Schwab and England scale. Severity of parkinsonian motor symptoms contributed, but to a lesser extent. A sense of lack of energy was seen in half of the PD patients compared with a fifth of controls, and this could be only partially accounted for by depressive symptoms and the UPDRS motor scores.

The choice of drugs to improve motor symptoms is wide (see Tables 6.4 and 6.8), but the degree of disability and the age (or mental acuity) of the patient are two critical factors in making the selection. If the delay in initiating symptomatic treatment was so prolonged that the symptoms threaten employment or endanger falling, one needs to begin levodopa to get a quick, effective response. The advantages of using

levodopa when the symptoms are this pronounced, in preference to a dopamine agonist or other medications, are that a therapeutic response is both rapid and virtually guaranteed, because nearly all patients with PD will respond to levodopa and relatively quickly. In contrast, only a minority of patients with severe symptoms will benefit sufficiently from a dopamine agonist given alone, and it takes more time (often months) to build up the dose to adequate levels to discover this. If levodopa is to be used, inhibitors of type A MAO must be discontinued. If selegiline (or another selective type B MAOI) was the MAOI that was used, this drug can be continued.

If the symptoms are not severe enough to require levodopa and the patient is younger than 60 (younger than 70 if the patient is mentally young), we prefer to employ a dopa-sparing strategy to avoid, as long as possible, the development of levodopa-induced dyskinesias and motor fluctuations (mainly the wearing-off effect). These motor complications are more likely to occur in younger patients (Quinn et al., 1987; Kostic et al., 1991; Gershanik, 1993; Wagner et al., 1996). Besides MAO-B inhibitors, which the patient may already be taking, the choices are dopamine agonists, amantadine, and anticholinergics. Dopamine agonists are the most potent antiparkinsonian agents among this group of drugs. Four-year results of the pramipexole versus levodopa trial reveal that levodopa is clinically more potent but is also much more likely to induce dyskinesias and clinical fluctuations (Holloway and Parkinson Study Group, 2004). In general, for patients older than 70 years or those with any cognitive impairment, employ levodopa as the initial therapy. Not only is there less need for a dopa-sparing strategy in these elderly patients but they are also more susceptible to confusion, psychosis, or drowsiness from other antiparkinson drugs, including dopamine agonists. Levodopa provides the greatest benefit for the lowest risk of these adverse effects compared with the other drugs. Another consideration is for those patients who need to drive an automobile extensively for their work. The risk for falling asleep at the wheel is greatest for those taking dopamine agonists (Frucht et al., 1999; Korner et al., 2004).

Rationale for using a dopa-sparing strategy in young patients

As was mentioned earlier, patients younger than 60 years of age are particularly prone to develop the motor complications of fluctuations and dyskinesias (Quinn et al., 1987; Kostic et al., 1991; Gershanik, 1993; Wagner et al., 1996). Some physicians therefore recommend using a dopa-sparing strategy, rather than levodopa, in younger patients when beginning therapy, in an attempt to delay the onset of these problems (Quinn, 1994b; Montastruc et al., 1999; Fahn and Kang, 2016). But others prefer starting with levodopa (Weiner, 1999). A conference on this topic failed to produce a consensus (Agid et al., 1999). There is evidence that duration and severity of disease is a more critical risk factor than duration of levodopa therapy in causing dyskinesias (Cilia et al., 2014).

Choice of drug when employing a dopa-sparing strategy

Dopamine agonists

The dopamine agonists are the group of agents that is next most powerful in reducing the symptoms of PD after

levodopa therapy. Thus, they are a good choice. Based on a controlled clinical trial, there is no evidence that they provide neuroprotection (Schapira et al., 2013), just symptomatic effect. Perhaps the main reason many patients are started with this class of drugs is that they are less likely to induce dyskinesias and motor fluctuations (Rinne et al., 1998a; Parkinson Study Group, 2000; Rascol et al., 2000; Holloway and Parkinson Study Group, 2004).

Rinne (1989a,b) first proposed that early use of the dopamine agonists will reduce the likelihood of developing complications from chronic levodopa therapy. However, the Rinne reports were on retrospective analyses, using historical rather than contemporary controls. In one double-blind study, Weiner and colleagues (1993) could not confirm Rinne's findings. However, in another controlled trial, Montastruc and colleagues (1994) reported that there were fewer motor complications in patients who started on bromocriptine, to which levodopa was later added. Studies of dopamine agonists as primary monotherapy in early PD have shown that, even with sustained treatment, drug-induced dyskinesias rarely develop, but that monotherapy is successful for more than 3 years in only about 30% of all PD patients (Poewe, 1998). In addition to this benefit, the dopamine agonists are the most powerful antiparkinson medications after levodopa. Therefore, if one wants to use dopa-sparing strategies, one could choose among the dopamine agonists.

The first double-blind study comparing an agonist with levodopa was with cabergoline. A smaller percentage of patients in the cabergoline group developed motor fluctuations (22%) versus 34% on levodopa ($P < 0.02$) (Rinne et al., 1998a). Controlled clinical trials comparing ropinirole (Rascol et al., 2000), pramipexole (Parkinson Study Group, 2000), and pergolide (Oertel et al., 2006) versus levodopa have shown that starting treatment with a dopamine agonist is less likely than treatment with levodopa to induce dyskinesias. On the other hand, these studies all showed that levodopa is more potent and improves UPDRS scores more than the agonists did (see Fig. 6.9). Moreover, the agonists are more likely to produce hallucinations and sedation than is levodopa.

Post hoc analysis revealed that starting treatment with ropinirole (Rascol et al., 2006) or pramipexole (Kieburtz et al., 2006)

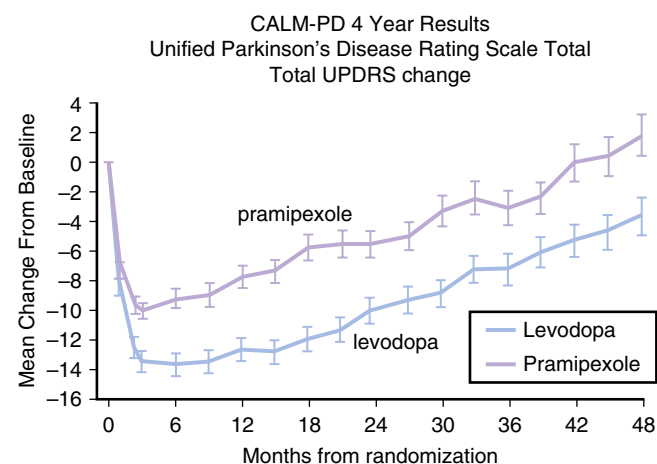
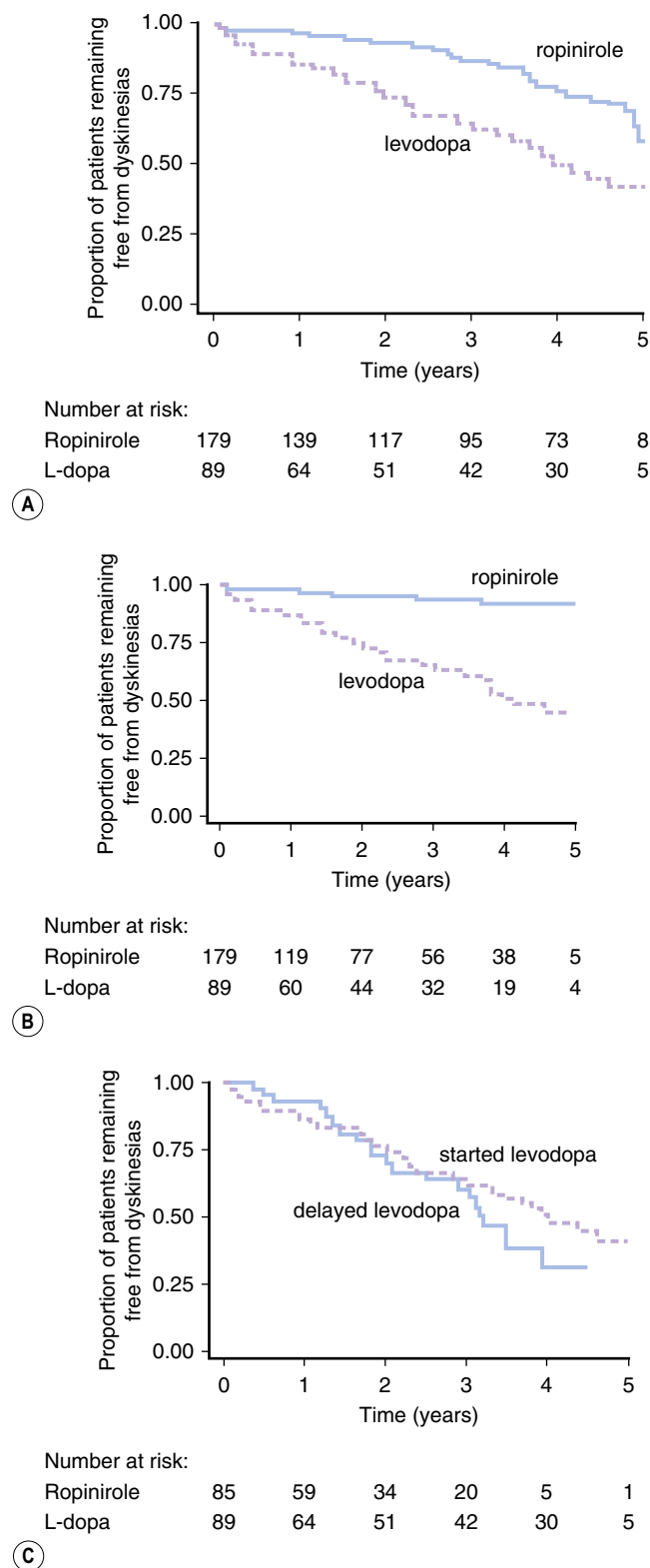


Fig. 6.9 Comparison of levodopa and a dopamine agonist in improving Unified Parkinson's Disease Rating Scale (UPDRS) scores in CALM-PD. (From Holloway RG, Parkinson Study Group: Pramipexole vs levodopa as initial treatment for Parkinson disease: A 4-year randomized controlled trial. *Arch Neurol.* 2004;61[7]:1044–1053.)



delays levodopa-induced dyskinesias by delaying the start of levodopa therapy. When levodopa is started, this “starts the clock” on developing dyskinesias see Fig. 6.10). A 10-year follow-up of the ropinirole trial showed that motor complications remained fewer in those subjects who started on ropinirole, but there was no difference in UPDRS score (Hauser et al., 2007). Of course, all subjects were taking levodopa at

Fig. 6.10 Survival analysis of remaining free of dyskinesias. Delaying levodopa delays onset of dyskinesias. Once levodopa is started, the same rate of developing dyskinesia occurs. (A) The results of the 056 study (Rascol et al., 2000). The patients who started on levodopa developed at a faster rate than those who started on ropinirole. (B) The levodopa curve is the same as in A. The ropinirole curve represents those subjects receiving ropinirole without levodopa, that is, before open-label levodopa was added. (C) The “started levodopa” curve is the same as the levodopa curve in A and B. The “delayed levodopa” curve is the development of dyskinesias in those subjects who started on ropinirole but then added levodopa at a later time point. The start time of zero in the “delayed levodopa” curve represents the time that levodopa was actually started on each individual patient in those assigned to ropinirole. The survival curves of the two groups of subjects overlap, depending entirely on the time levodopa was initiated. (From Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, Lang AE, et al; 056 Study Group: Development of dyskinesias in a 5-year trial of ropinirole and L-dopa. *Mov Disord.* 2006;21[11]:1844–1850.)

that time. A similar finding was identified in the 6-year follow-up of the CALM-PD subjects (initiating levodopa or pramipexole) (Parkinson Study Group CALM Cohort Investigators, 2009).

Several dopamine agonists are currently available for PD. The non-ergots, pramipexole (Mirapex), ropinirole (Requip), and rotigotine (Neupro), have largely displaced the ergot compounds (pergolide and bromocriptine) because of more adverse effects from the ergots. Pergolide was removed from the market in the United States because of fibroproliferative cardiac valvulopathy (Pritchett et al., 2002; Baseman et al., 2004; Horvath et al., 2004; Van Camp et al., 2004; Peralta et al., 2006; Dewey et al., 2007; Zanettini et al., 2007). The longer duration ergot cabergoline is available in some countries. Rotigotine is absorbed transdermally but not orally. Apomorphine is a powerful dopamine agonist that is administered subcutaneously, intramuscularly or sublingually to overcome “off” states.

Ergots rarely can induce red, inflamed skin (St. Anthony’s fire), which is reversible on discontinuing the drug. They also have the potential (although rare) with long-term use to induce retroperitoneal, pleuropulmonary, and pericardial fibrosis (Pfitzenmeyer et al., 1996; Ling et al., 1999; Shaunak et al., 1999). Heart valves contain 5-HT_{2B} receptors. Drugs such as fenfluramine that activate these receptors can induce thickening of the heart valves. Roth (2007) reviewed the effect on 5-HT receptors by dopamine agonists. The only two dopamine agonists that are also potent 5-HT_{2B} agonists are pergolide and cabergoline, and these are the only ones that were significantly associated with cardiac valve disease (Schade et al., 2007). Lisuride, which is an agonist at 5-HT_{2A} and 5-HT_{2C} receptors, but not at 5-HT_{2B} receptors, was not associated with valve disease. Although regurgitation was reported with bromocriptine, restrictive valvulopathy was not (Tan et al., 2009).

Pramipexole and ropinirole, as was mentioned earlier, appear to more readily produce drowsiness and sleep attacks in which patients fall asleep without warning, including while driving, although there have been rare incidences of sleep attacks with all dopamine agonists and levodopa (Frucht et al., 1999; Ferreira et al., 2000; Hoehn, 2000; Schapira, 2000). The Epworth Sleepiness Scale is not predictive as to which patient may develop a sleep attack (Hobson et al., 2002). Korner and colleagues (2004) sent a questionnaire to 12,000 patients and received responses from 63%, 42% of whom reported that they had experienced sudden onset of sleep; 10% of these had not experienced sleepiness before their first sleep attack. Predicting factors were nonergoline

dopamine agonists, age younger than 70 years, and disease duration less than 7 years. Modafinil may reduce the development of sleep attacks (Hauser et al., 2000).

Adverse effects that are more common with agonists than with levodopa are orthostatic hypotension, nausea (because nausea from levodopa is blocked by carbidopa), drowsiness, hallucinations, and leg edema. All agonists have a propensity to produce ankle and leg edema (Tan and Ondo, 2000), which is not an early problem but tends to occur after a few years of treatment. In a retrospective review of developing pedal edema with pramipexole treatment, there was no relationship between dose of pramipexole and incidence and severity of pedal edema. The risk for development of pedal edema was 7.7% in the first year after initiation of pramipexole therapy, with more rapid development of edema among those with a history of coronary artery disease (Kleiner-Fisman and Fisman, 2007). The edematous skin is often red, and some clinicians, unaware of this adverse effect, assume that there is a deep vein thrombosis. The edema and redness persists unless the drug is stopped. Diuretics are only partially effective in relieving the edema. Whether it is dangerous to continue to allow the edema to persist is not known. But continued use of the agonist can eventually result in discolored, indurated skin in the lower part of the legs where the edema was located. The tight skin prevents edema from accumulating there, so the edema is seen above the induration. Substituting one agonist for another may occasionally allow the edema to dissipate, but more often than not, once the edema has occurred, it persists in the presence of other dopamine agonists as well. The only satisfactory treatment of the edema is to discontinue the agonist, and substitute levodopa, which does not cause this problem. The edema of the legs that is induced by dopamine agonists resembles that induced by amantadine.

A new adverse effect was reported in 2010. Rabinak and Nirenberg described the dopamine agonist withdrawal syndrome (DAWS). This was defined as a cluster of physical and psychological symptoms that correlate with dopamine agonist withdrawal, causing clinically significant distress or social/occupational dysfunction, are refractory to levodopa and other PD medications, and cannot be accounted for by other clinical factors. Symptoms of DAWS resembled those of other drug withdrawal syndromes and included anxiety, panic attacks, agoraphobia, depression, dysphoria, diaphoresis, fatigue, pain, orthostatic hypotension, and drug cravings. Some of those with DAWS needed to be restarted on the dopamine agonist. When dopamine agonists need to

be withdrawn, they should be tapered very slowly to avoid inducing DAWS.

Each of the dopamine agonists easily induces orthostatic hypotension, particularly when the drug is first introduced (Kujawa et al., 2000). After that period, this complication is much less common. Therefore, it is best to start with a tiny dose, such as pramipexole 0.125 mg at bedtime) for the first 3 days and then switch from bedtime to daytime dosing for the remainder of the first week. Ropinirole can be started at 0.25 mg 3 times daily for the first week. The daily dose can be increased gradually (pramipexole 0.125 mg every 2 days for 10 days, then 0.125 mg per day weekly; ropinirole 0.5 mg per day twice weekly), building the dosage up on a 4 times daily dosing schedule until benefit or a dose of around, 4 to 6 mg/day pramipexole, or 24 mg/day (ropinirole) is reached (Table 6.11). Use the lowest dose that provides adequate benefit. An alternative is to use the extended-release formulations of pramipexole and ropinirole. These formulations allow the drug to be absorbed more slowly and over a longer period.

The choice between pramipexole and ropinirole is one of personal preference and experience and perhaps should be based on adverse effects because the benefits are similar. Some patients may benefit from both equally; some may get adverse effects from one but not the other. By having both these drugs available, the clinician has the ability to switch from one to another should one of them not be tolerated. Switching can be done rapidly using a ratio of 1:5 for pramipexole-to-ropinirole, without having to build up the dose of the new drug from a much lower level (Canesi et al., 1999). If the response is less than satisfactory, and it is desired to maintain the dopa-sparing strategy for as long as possible, one can then add amantadine or an anticholinergic can be added (see later). If none of these agents is helpful or tolerated, the patient moves into the next stage of illness, the stage in which levodopa is required. Nausea and vomiting are other potential side effects that would limit the usefulness of the dopamine agonists. These symptoms are usually avoided by increasing the dose slowly. The peripherally acting dopamine antagonist domperidone will block these gastrointestinal side effects. The usual dose is 10 to 20 mg thrice daily. Even if a dopamine agonist is effective, many patients require the addition of levodopa within a year or two.

Amantadine

Amantadine has several pharmacologic actions. It is most frequently used to reduce severity of levodopa-induced

Table 6.11 Suggested schedule for dopamine agonist therapy

Agonist	Initial dose	Titration phase	Lowest dose likely to be effective	Typical maintenance dose	Typical maximum dose
Pramipexole	0.05 mg at bedtime for 3 nights, then switch to daytime	Increase by 0.25 mg every 2 days for 10 days, using a tid schedule; then 0.125 mg/day weekly	0.75 mg tid	1.5 mg tid	2–3 mg tid
Ropinirole	0.125 mg tid	0.5 mg per day twice weekly	2 mg tid	4–5 mg tid	7–9 mg tid
Ropinirole extended release	2 mg once daily	2 mg every 1–2 weeks	6 mg	12–18 mg	24 mg/day
Rotigotine (patch)	2-mg patch once daily	2-mg patch weekly	2 mg	6–8 mg patch daily	8 mg/day

This is just one schedule; many other related schedules can be used.

dyskinesias. It was first used in the treatment of PD for amelioration of motor symptoms (Schwab et al., 1969; Fahn and Isgreen, 1975). It is a mild indirect dopaminergic agent by augmenting dopamine release from storage sites and possibly blocking reuptake of dopamine into the presynaptic terminals (Von Voigtlander and Moore, 1971). It also has some anticholinergic properties and glutamate receptor–blocking activity. In the mild stage of PD it is effective in about two-thirds of patients (Fahn and Isgreen, 1975). A major advantage is that substantial benefit, if it occurs, is seen in a couple of days. Unfortunately, its benefit in more advanced PD is often short-lived, with patients reporting a fall-off effect after several months of treatment in the absence of concomitant levodopa. The mechanism appears to be a depletion of already reduced dopamine stores in the dopaminergic nerve terminals so that the effect of amantadine is exhausted. A common adverse effect is livedo reticularis (a reddish mottling of skin) around the knees; this is not dangerous, although it can be cosmetically a problem for some patients. Occasional adverse effects are ankle edema and visual hallucinosis. Sometimes when the drug is discontinued, there can be a gradual worsening of parkinsonian signs, indicating that the drug has been helpful. The usual dosage is 100 mg twice daily, but sometimes a higher dose (up to 400 mg) may be required.

Amantadine can be useful, not only in the early phases of symptomatic therapy, thereby forestalling the introduction of levodopa or reducing the required dosage of levodopa, but also in the advanced stage of the disease as an adjunctive drug to levodopa and the dopamine agonists. It is also effective in reducing levodopa-induced dyskinesias (Rajput et al., 1997; Metman et al., 1998a; Thomas et al., 2004; Sawada et al., 2010; Ory-Magne et al., 2014; Pahwa et al., 2015; Pahwa et al., 2017), probably from its antiglutamatergic activity. This feature is described later in the discussion of treatment of advanced-stage PD.

Amantadine is excreted mostly unchanged in the urine, so the dose needs to be reduced in patients with renal impairment. The half-life is long, about 28 hours, so twice-daily dosing is adequate. CNS adverse effects of myoclonus, hallucinations, and delirium are associated with very high plasma levels of amantadine, which can be the result of over-dosage (Fahn et al., 1971) or from impaired renal function (Nishikawa et al., 2009).

Antimuscarinic drugs (anticholinergics)

The anticholinergics appear to be less effective antiparkinson agents than the dopamine agonists. The anticholinergics are estimated to improve parkinsonism by about 20%. Many clinicians find that if tremor is not relieved by an agonist or levodopa, the addition of an anticholinergic drug is often effective. Sometimes, the anticholinergic can lessen tremor severity even in the absence of levodopa, so clinicians can use such an agent as monotherapy for tremor. If this is not helpful, continuing to use the drug while a dopamine agonist or levodopa is added can be helpful. Later, if tremor is relieved by the dopaminergic agent, discontinuing the anticholinergic can be tried. Commonly used anticholinergics are trihexyphenidyl (Artane) and bntropine mesylate (Cogentin), but there are many others. To minimize adverse effects, start with low doses (trihexyphenidyl 1 mg twice

daily; bntropine 0.5 mg twice daily) and increase gradually to 2 mg three times daily for trihexyphenidyl and 1 mg three times daily for bntropine. As would be expected, if anticholinergics lessen parkinsonism and cholinergic agents aggravate parkinsonian symptoms (Duvoisin, 1967), including nicotine (Ebersbach et al., 1999).

A retrospective analysis of a database containing information of over 100,000 patients in Germany who were prescribed anti-PD medications found that about 75% were begun with levodopa. Of the others, a comparison as to how long the delay is before levodopa was prescribed showed that the anticholinergics were able to delay the introduction of levodopa far longer than MAO-B inhibitors, dopamine agonists, and amantadine (Fig. 6.11) (Reese et al., 2015). This was a surprise outcome and may reflect sustained efficacy of the anticholinergics, which work by a different mechanism than the other drugs, which was by a dopaminergic mechanism.

Peripheral anticholinergic adverse effects include blurred vision (treated with pilocarpine eye drops, which also must be used if glaucoma is present), dry mouth, and urinary retention. Pyridostigmine, up to 60 mg three times daily, if necessary, can sometimes be helpful in overcoming dry mouth and urinary difficulties. The predominant central side effects are forgetfulness and decreased short-term memory. Occasionally hallucinations and psychosis can occur, particularly in the elderly. Powerful anticholinergics should usually be avoided in patients older than 70 years because of this problem. If tremor persists in this age range despite the presence of levodopa or dopamine agonists, use drugs with a weaker anticholinergic effect, such as diphenhydramine (Benadryl), orphenadrine (Norflex), cyclobenzaprine (Flexeril), and amitriptyline (Elavil). Diphenhydramine and amitriptyline can cause drowsiness; therefore, they also can be used as a hypnotic. For tremor control, one can increase the dose gradually until a

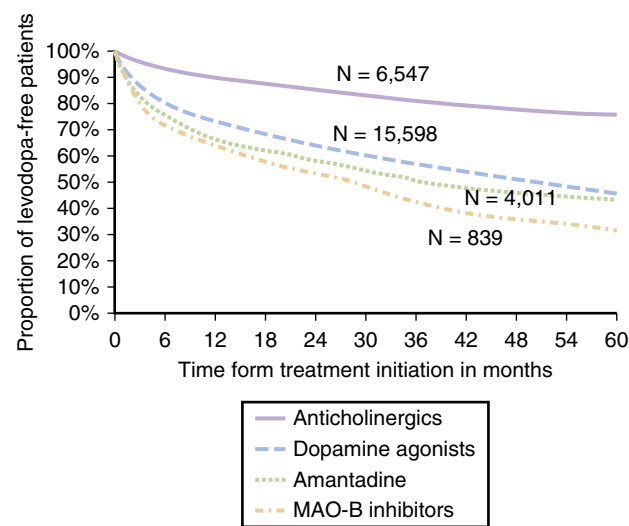


Fig. 6.11 Time to delay initiation of levodopa by anti-PD drugs. Survival curves of being free from initiating levodopa therapy after starting another anticholinergic, dopamine agonist, amantadine, or MAO-B inhibitor. Results show that the anticholinergics are more effective than the other agents. (From Reese JP, Hamer H, Oertel WH, Strzelczyk A, Mueller UO, Heilmaier C, Kostev K. Association of time-to-levodopa with initial Parkinsonian medication: a retrospective cohort study. *Int J Clin Pharmacol Ther.* 2015;53[2]:107–114, with permission from senior author.)

maximum of 50 mg three times daily is reached for diphenhydramine 100mg q12h for orphenadrine extended release, 20 mg three times daily for cyclobenzaprine; and 25 mg three times daily for amitriptyline.

There is concern that use of anticholinergic drugs in PD may hasten cognitive decline. In one study in which patients were followed for 8 years, cognitive decline was higher in those who were begun with anticholinergic drugs (Ehrt et al., 2010). Their median decline on Mini-Mental State Examination (MMSE) was 6.5 points compared with a 1 point decline in those who had not taken such drugs ($P = 0.025$). The duration of using these drugs also correlated with a greater decline in MMSE scores ($P = 0.032$).

A leading point of view: use levodopa as the first drug

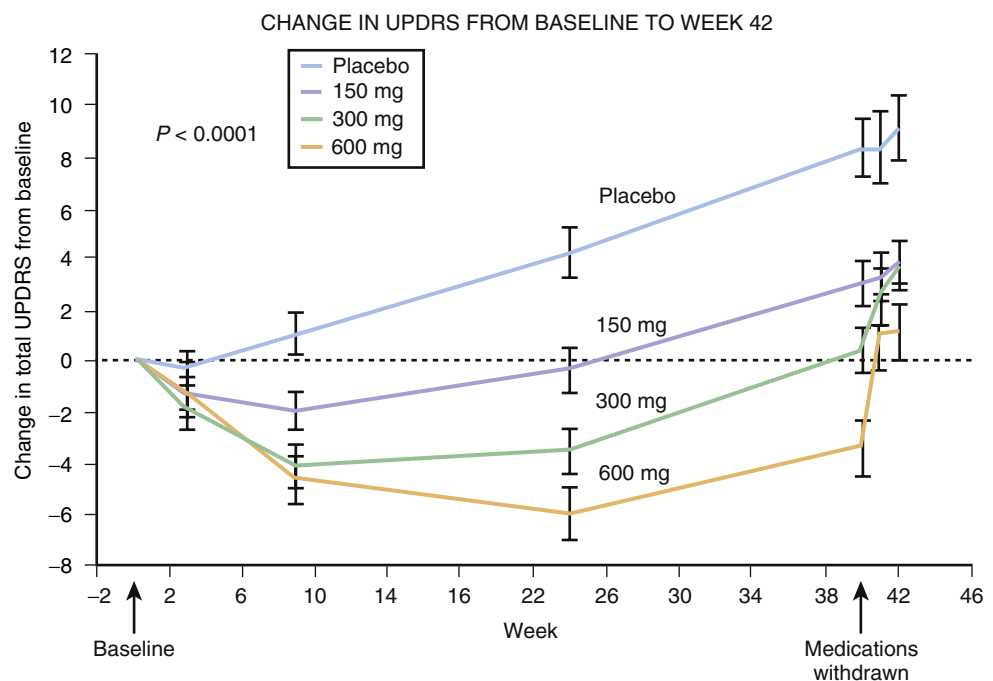
Despite the awareness that levodopa therapy will likely result in motor fluctuations and dyskinesias, there were a number of neurologists early on who advocate starting with levodopa when symptomatic therapy is needed (Agid, 1998; Agid et al., 1999; Weiner, 1999; Factor, 2000) rather than using a dopa-sparing strategy. Their argument is that there is no proof that levodopa itself causes either neurotoxicity or the motor complications of dyskinesias and “off” states. Rather, they suggest it is the severity of the disease that correlates with onset of dyskinesias. This point was subsequently demonstrated by Cilia and colleagues (2014), who compared Italians who started levodopa early with Ghanians, who started it late. Levodopa-induced dyskinesias correlated best with severity of disease and not duration of levodopa therapy. Another rationale by the early-dopa advocates was their prefer to use the most effective drug first when the symptoms are mild to provide the highest quality of life. However, the late-dopa advocates do not recommend delaying levodopa beyond when the patient needs it, but to start it as soon as the patient feels the need for more effective therapy.

What has tipped the scales in recent years in favor of using levodopa first when symptoms warrant a symptomatic drug (rather than a dopamine agonist) are two developments. First is the growing recognition of devastating impulse control disorders (discussed in Chapter 8) with dopamine agonist therapy. Second is the lack of clinical worsening of PD from early levodopa therapy as demonstrated in the ELLDOPA trial (Fahn et al., 2004), although this trial did not settle whether levodopa is ultimately neurotoxic (Fahn and Parkinson Study Group, 2005).

The ELLDOPA study was a controlled clinical trial evaluating the effect of levodopa on the natural history of PD (Parkinson Study Group, 2004b). Unexpectedly, the clinical results showed that subjects treated with levodopa had less clinical progression 2 weeks after stopping the drug than did subjects treated with placebo, and this effect was dose-dependent (Fig. 6.12). But concern has been raised that perhaps the 2-week washout of levodopa was insufficient to eliminate all of its symptomatic benefit. Moreover, the ELLDOPA study showed a discordance between the neuroimaging component and the clinical results. The DAT binding ligand imaging study was compatible with a more rapid decline of dopamine neurons. But that result has now raised the question as to whether levodopa itself interferes with this binding. Therefore, the interpretation of the ELLDOPA study remains uncertain. On the other hand, a computer simulation of the ELLDOPA results, combined with the DATATOP results, supports the conclusion that levodopa slows disease progression (Chan et al., 2007b). It is of interest that in subsequent clinical trials, such as the PRECEPT study, subjects reached endpoint at a lower level of severity of parkinsonism compared with the DATATOP study, which was conducted before the ELLDOPA study (Marras et al., 2009). Subjects may think that starting levodopa sooner is not as serious a threat to their well-being, having seen the ELLDOPA results.

The LEAP study, which was a delayed-start clinical trial of levodopa 100 mg three times daily, starting at either zero

Fig. 6.12 Levodopa dose–response curve in patients with untreated, recent-onset PD. (From Parkinson Study Group: *Levodopa and the progression of Parkinson’s disease*. *N Engl J Med*. 2004;351[24]:2498–2508.)



time point (early start) or at 40 weeks (delayed start), showed that after another 40 weeks of treatment, there was no difference in the two treatment groups (see Fig. 6.2) (Verschuur et al., 2019). The authors concluded that the study shows that levodopa is not neuroprotective. Actually, the study shows that the clinical response catches up, even if levodopa therapy is delayed. Because of the marked beneficial effect of levodopa, one cannot conclude from this study that levodopa does not have disease-modifying effect. The strong symptomatic effect could have allowed the delayed start of levodopa to “catch up” symptomatically and hide any difference in the underlying severity of the disease. Withdrawal of the levodopa allowing for the withdrawal of its symptomatic effect would be necessary to pick up a clinical difference of the underlying severity of the disease between the two groups.

Another argument possibly favoring early levodopa is that levodopa has delayed mortality, and therefore it should be used early. However, the initial improvement of mortality rates occurred when levodopa was first introduced and most likely was from the improvement of mobility, not from the drug itself. Improved or maintained mobility with another antiparkinson agent may be just as effective. Actually, mortality rates have gone back to their earlier increased level, now that levodopa has taken care of the backlog of disabled patients (Clarke, 1995). In a 2000 analysis of retrospective data from Scotland (Donnan et al., 2000) comparing PD patients with their treatment assignment, levodopa monotherapy had a higher mortality rate than did selegiline monotherapy or selegiline plus levodopa.

From the DATATOP study, the 387 subjects who reached endpoint, that is, the need for symptomatic therapy, were placed on levodopa, and their UPDRS scores were reduced by approximately 33% (from ~43 units to 29 units) (See Fig. 6.1 in Growdon et al., 1998).

Whether levodopa actually provides a better quality of life (Glozman et al., 1998; Martinez-Martin, 1998) for patients with mild-stage PD remains to be determined, particularly compared with dopamine agonists in patients with early PD. In one study, the levodopa versus pramipexole controlled clinical trial (Holloway and Parkinson Study Group, 2004), health-related quality of life (HRQL) was assessed by three different measures. All three measures resulted in similar profiles over time characterized by initial improvement over the first 3 to 6 months and followed by a gradual decline in years 2, 3, and 4 (Noyes et al., 2006). The difference in HRQL between the treatment arms widened in favor of pramipexole in years 3 and 4 for all HRQL measures used. Because levodopa had a superior result in UPDRS scores, the results suggest that pramipexole and levodopa affect HRQL via improvement on different domains of well-being: non-motor effect for pramipexole and mobility improvement for levodopa.

Whether the motor complications that are seen with chronic levodopa therapy in patients with PD are actually caused by long-term levodopa therapy or simply reflect the progression of the disease is unknown and widely debated (de Jong et al., 1987; Quinn et al., 1987; Blin et al., 1988; Roos et al., 1990; Caraceni et al., 1991; Cedarbaum et al., 1991). Advanced disease with altered sensitivity of dopamine receptors is a critical factor, but one does not see these motor complications if the patient was never exposed to levodopa

and was treated only with the other antiparkinson agents. In untreated but advanced PD, levodopa-induced dyskinesias occur shortly after levodopa is started (Onofri et al., 1998). In the parkinsonian states of postencephalitic parkinsonism and MPTP-induced parkinsonism there is rapidly severe depletion of nigral neurons (Bernheimer et al., 1973; Davis et al., 1979; Burns et al., 1983; Langston et al., 1984). These patients may develop dyskinesias and fluctuations within weeks to months after starting levodopa (Calne et al., 1969; Sacks et al., 1970; Duvoisin et al., 1972; Sacks, 1974; Langston et al., 1983; Langston and Ballard, 1984; Ballard et al., 1985). However, if patients with those diseases had been treated with dopamine agonists instead of levodopa, it is likely that those motor complications would not have occurred.

If one chooses to use levodopa in mild-stage disease, there is evidence to support keeping the dose as low as possible (Lesser et al., 1979; Poewe et al., 1986; Parkinson Study Group, 2004b; Olanow et al., 2013). One strategy is to build the dosage from carbidopa/levodopa 25/100 mg three or four times daily stepwise to 50/200 mg three or four times daily and then add supplementary medication such as amantadine, MAO-B inhibitor or a dopamine agonist if the patient needs more symptomatic relief. (For older patients, stay with levodopa and increase that if more medication is needed; see the next section.)

Treatment of moderate-stage PD (when there is an inadequate response to non-levodopa medications)

Moderate-stage PD is when the disability is beyond the scope of efficacy of dopamine agonists, amantadine, anticholinergics, and an MAO-B inhibitors; treatment with levodopa is necessary to control symptoms. The rule of thumb is to use the lowest dosage that brings about adequate symptom reversal, not the highest dosage that the patient can tolerate, in an attempt to avoid response fluctuations and dyskinesias. As shown by the ELLDOPA study (Parkinson Study Group, 2004b), higher doses of levodopa provide more improvement of parkinsonian symptoms, but higher doses also lead to more motor complications. In other words, the higher the dose, the more is the likelihood for dyskinesias. A good part of the “art of treatment” is finding the optimum dose, which means improved quality of life without troublesome adverse effects. This equates to the lowest dose that provides sufficient clinical benefit while minimizing adverse effects from the medication.

Levodopa is usually given combined with a peripheral decarboxylase inhibitor (carbidopa [Sinemet and generics] or benserazide Madopar]) to prevent the formation of dopamine peripherally, thereby usually avoiding the otherwise common peripheral adverse effects of anorexia, nausea, and vomiting. Many patients require at least 50 to 75 mg of carbidopa a day to have adequate inhibition of peripheral dopa decarboxylase. Although 10/100-mg tablets of carbidopa/levodopa are available, there is no need to use these tablets instead of the 25/100-mg tablets. In some patients, even 75 mg/day of carbidopa is inadequate, and nausea, anorexia, or vomiting still occurs. In such patients, one needs to use

higher doses of carbidopa; carbidopa tablets (Lodosyn) are available by prescription. Higher doses of carbidopa, up to 450 mg/day, have no deleterious effect on levodopa's effectiveness (Brod et al., 2012).

In tablet form, carbidopa/levodopa is marketed in both immediate-release (Sinemet and generics) and extended-release (Sinemet CR and generic carbidopa/levodopa ER) tablets; the latter provides a longer plasma half-life and lower peak plasma levels of levodopa compared with standard Sinemet. Unfortunately, Sinemet CR has not been shown to avoid the development of response fluctuations. A 5-year study in 618 dopa-naïve patients compared Sinemet CR and standard Sinemet therapy. There was no difference between the two groups in the development of either fluctuations or dyskinesias (Block et al., 1997; Koller et al., 1999). An Italian study found that using small, divided doses during the day is more likely to lead to loss of the long duration response (Zappia et al., 2000). A more extended-release form of carbidopa/levodopa is formulated in microspheres and sold as Rytary capsules (Kestenbaum and Fahn, 2015).

A pre-bedtime dose of Sinemet CR or Rytary may allow the patient some mobility during the night. Disadvantages of Sinemet CR are the lack of a rapid response with each dose and a delayed response that can be excessive, resulting in sustained severe dyskinesias that cannot be controlled except by sedating the patient. Moreover, the response to individual doses of Sinemet CR is less predictable than the response to standard Sinemet. It is complicated to use both standard Sinemet and Sinemet CR to smooth out fluctuations, but this is often necessary. Rytary is packaged so that one-third of the dose is immediate release and the other two-thirds sustained release. Finally, one should keep in mind that not all of the carbidopa/levodopa in Sinemet CR or Rytary is absorbed because some of the medication may have reached the distal small intestine before all of it was absorbed in the proximal small intestine. A dose of Sinemet CR or Rytary is equal to about two-thirds to three-fourths of an identical dose of standard Sinemet (also called immediate-release Sinemet).

For patients who develop peak dose drowsiness or confusion after immediate-release levodopa, the extended-release formulation may avoid this problem because of its slower rate of absorption and a lower peak plasma level of levodopa. However, the clinical response to Sinemet ER is less reliable than immediate-release Sinemet because of the more variable absorption of the former. For some patients, there may be merit in using a combination of immediate-release and extended-release tablets simultaneously in an effort to provide smoother, stabler plasma and brain concentrations of levodopa, in an attempt to try to lessen the development of dyskinesias and wearing off.

Sinemet CR is available in two strengths, carbidopa/levodopa 50/200-mg tablet, which is scored and can be broken in half, and a 25/100-mg unscored tablet. Crushing either tablet loses the slow-release property because the matrix is no longer intact. When Sinemet CR is added to a patient taking a dopamine agonist, a dose of 25/100 mg three times daily (built up gradually by 25/100 mg weekly) often suffices. When it is used alone, it often is necessary to use these dosages after meals to reduce initial nausea and vomiting; the dose can later be increased to 50/200 mg three or four times daily.

Immediate-release carbidopa/levodopa is available in tablets of 10/100, 25/100, and 25/250 mg. As mentioned previously, there is very little reason to ever use the 10/100-mg tablets. An exception is if droxidopa is taken as a treatment for orthostatic hypotension. Too much carbidopa would interfere with the conversion of droxidopa to norepinephrine. Because of the desire to have at least 75 mg/day of carbidopa, one should start with the 25/100-mg tablets when the drug is introduced. An increase by 25/100 mg/day per week until three-times-daily dosing is achieved is often adequate. A more conservative approach is to start with a half-tablet of a 25/100-mg tablet, and increase weekly by a half-tablet until one tablet three times daily is reached; this slower titration would reduce the likelihood of developing gastrointestinal adverse effects from levodopa. A 25/100-mg dosing three times daily is the most common plateau schedule neurologists aim for (Fahn and Mazzoni, 2006). Not every symptom of PD responds equally well. Bradykinesia and rigidity respond best, whereas tremor can be more resistant. If a response is seen, but with symptoms later returning or worsening, increasing the dose stepwise to reach 50/250 mg three times daily is a reasonable goal. A dose of 25/250 mg four times daily or higher may be required. A reasonably high dose before concluding that levodopa is ineffective is 2000 mg of levodopa per day.

Rytary is available in four strengths of carbidopa/levodopa: 23.75/95 mg, 36.26/145 mg, 48.75/195 mg, and 61.25/245 mg. Rytary is packaged in capsules. If the capsules are difficult for a patient to swallow, the capsule can be opened, and the contents can be sprinkled over food and ingested that way. The drug is more complicated than Sinemet or Sinemet CR to achieve the optimum dosage because it is a combination of immediate- and slow-release formulations of microbeads, in a ratio of one-third and two-thirds, respectively. Its main advantage is the longer half-life of levodopa. It can be useful in treating patients with wearing-off problems. It is also useful when taken at bedtime for patients who have nocturnal akinesia because of wearing off. Rytary is most commonly used in the advanced stage of PD to treat the wearing-off phenomenon.

Levodopa is also available in a combination with both carbidopa and entacapone, marketed as Stalevo. A clinical trial was conducted to determine whether entacapone should be given with levodopa when the latter is first introduced. There had been widespread belief that continuous dopaminergic therapy, which is the method used to treat fluctuations and dyskinesias, would also prevent the development of these motor complications to levodopa. (For more detailed discussion on motor complications and continuous dopaminergic stimulation, see the section entitled Treatment of advanced PD). In the clinical trial, subjects requiring dopaminergic treatment were randomized to be on either levodopa with carbidopa (LC group) or with entacapone also added to the tablet (LCE group). The opposite outcome than what was expected happened. The LCE group developed dyskinesias earlier, and more subjects in that group developed dyskinesias compared with the LC group (Stocchi et al., 2010). One possible explanation is that when levodopa dosage equivalents were calculated, the LCE group received higher dosages than the LC group. Based on the results of this study, we cannot recommend entacapone be administered at the beginning of levodopa therapy; it should be reserved for the

treatment of fluctuations, as described in the section Treatment of advanced PD.

A patient's response or lack of response to levodopa is a very important piece of information to help differentiate PD from Parkinson-plus syndromes. If the response is nil or minor, it is most likely that the disorder is not PD (Marsden and Fahn, 1982). However, a beneficial response does not ensure that a diagnosis of PD is correct. All cases of presynaptic disorders (e.g., reserpine-induced, MPTP-induced, postencephalitic parkinsonism) will respond to levodopa. In addition, patients in the early stages of multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) may improve with levodopa; later in these diseases, when dopamine receptors are lost, the response to levodopa is lost. Some patients with MSA may continue to have intact dopamine receptors in the striatum and continue to respond to levodopa. The only effective drugs in situations in which levodopa is not effective are the anticholinergics and amantadine, even though only mildly so.

It takes a mean of 9.3 ± 1.8 days to achieve maximum response when beginning treatment with Sinemet CR and 6.8 ± 3.0 days for the parkinsonism severity to return to baseline levels after stopping chronic Sinemet CR treatment (Barbato et al., 1997). This compares to a decay time of 6.2 ± 1.7 days after withdrawal of the dopamine agonist ropinirole (9–21 mg/day). These studies support the concept that the long-duration effect of levodopa and ropinirole might be due to some slowly evolving postsynaptic pharmacodynamic change in the CNS (Barbato et al., 1997).

It is important to avoid sudden withdrawal of levodopa, which is sometimes done for a surgical procedure (Stotz et al., 2004). A “neuroleptic malignant-like” syndrome can ensue, with fever, rigidity, and incoherence (Friedman et al., 1985; Hirschorn and Greenberg, 1988; Gordon and Frucht, 2001; Ueda et al., 2001). Tapering levodopa over 3 days appears to be a safe method of withdrawing the drug (Parkinson Study Group, 2004b).

As PD worsens, the duration of effectiveness of a dose of levodopa becomes shorter (Contin et al., 1998a). The effective clinical half-life of a dose of levodopa declines in relation to both worsening of symptoms and duration of disease. Although the pharmacokinetic half-life remains constant, around 90 minutes, the clinical half-life declines from a mean of 262 minutes in stage I patients, to 142 minutes in stage II, to 54 minutes in stage III. The rate of decline becomes smaller as the disease progresses. The mean annual reduction of the effective half-life slows down as the disease worsens, dropping by 37 minutes per year in stage I patients and by 6.5 minutes per year in stage III, and is about 17% per year of the disease. Contin and colleagues (1998a) determined this “effective” half-life by administering a standard oral fasting dose (100 mg) of levodopa (with a peripheral decarboxylase inhibitor). Motor response was measured by finger tapping speed and walking speed. The decline in effective half-life is equivalent to the loss of the long-duration response from levodopa to only a short-duration response as the disease worsens, and as first reported by Muentert and Tyce (1971). The loss of the long-duration response is a major factor in developing the wearing-off phenomenon. Some patients are fortunate in maintaining the long-duration response for many years or even the entire duration of their parkinsonism.

Treatment of advanced-stage PD (when there are motor complications from medications or when there is falling, freezing, or marked postural change)

Advanced PD is that stage of the disease in which there is at least one of the following conditions: (1) sufficient disability to interfere with independence despite levodopa therapy, (2) sufficient loss of postural reflexes so that one must be cautious when walking, (3) the presence of the freezing phenomenon to make walking difficult and falling likely, (4) pronounced postural deformity (i.e., dystonia), or (5) the presence of complications (fluctuations, dyskinesias, psychosis) from levodopa that now also becomes a focus of treatment. Because it is only the last group that is somewhat amenable to therapy, much of the discussion in this section will concentrate on methods to overcome these complications. In advanced PD, because of the severity of the clinical situation, all patients should be receiving levodopa therapy or at least have had a trial of this drug, but have not been able to remain on it because of disabling adverse effects. The Quality Standards Subcommittee of the American Academy of Neurology conducted an evidence-based literature review of clinical trials related to treating dyskinesias and fluctuations (Pahwa et al., 2006).

Description of motor (and sensory) complications

The motor complications can be divided into two categories: fluctuations (“off” states) and dyskinesias; in turn, these categories are subdivided into their temporal relationship with a dose of levodopa and the clinical motor and sensory phenomena seen as features of these levodopa-related complications (Table 6.12). The “off” states usually consist of a return of parkinsonian symptoms and signs, such as bradykinesia, tremor, rigidity, immobility, and freezing (“off” freezing). There are also other features of “off” states in many patients, including dystonia and a variety of nonmotor “offs.” “Off dystonia” is the presence of sustained contractions and spasms, often painful, and most common early in the morning on arising and in the feet. Because technically “off dystonia” is an abnormal involuntary movement (dyskinesia), this is listed in Table 6.12 in the dyskinesia column, but it should be recognized and treated clinically as an “off” phenomenon. “Off” dystonia shows an abnormal irregular firing of globus pallidus interna neurons similar to that seen in primary dystonia (Hashimoto et al., 2001). Nonmotor “offs” are often not recognized as an “off” state by clinicians and, instead, are misinterpreted as a psychiatric toxic state or some other type of “too much levodopa.” If not properly diagnosed, these symptoms may not be properly treated.

“Behavioral offs,” “sensory offs,” and “autonomic offs” are the categories of nonmotor symptoms that may accompany a motor (parkinsonian) “off” or may occur in the absence of any motoric parkinsonian signs. Behavioral/sensory/autonomic “offs” can consist of any combination of pain, akathisia, depression, anxiety, dysphoria, panic, drenching sweating, abdominal bloating, and dyspnea. These nonmotor symptoms are often unrecognized as “off”

Table 6.12 Major fluctuations and dyskinesias as complications of levodopa

Fluctuations ("offs")
Slow "wearing off"
"Sudden off"
"Random off"
"Super off"
Yo-yo-ing
"Delayed on"
Dose failure
Response varies in relationship to meals or protein
Weak response at end of day
Sudden transient freezing
Dyskinesias
Peak-dose chorea, ballism, and dystonia
Diphasic chorea and dystonia
End-of-day dyskinesia
"Off" dystonia
Myoclonus
Simultaneous dyskinesia and parkinsonism
Behavioral/sensory/autonomic "offs" (also called nonmotor "offs")
Pain
Akathisia
Depression
Anxiety
Dysphoria
Panic
Drenching sweats
Abdominal bloating
Dyspnea
Sensation of urinary urgency

states and, like dystonic "offs," are extremely upsetting for the patient. It is often the presence of one of these sensory and behavioral phenomena, more so than motoric parkinsonian or dystonic "offs," that drives the patient to take increasingly more levodopa, turning the patient into a "levodopa junkie." When drenching sweats were first encountered in patients with PD, it was unclear if this problem was representative of a toxicity from levodopa or from an "off" state. Finally, by monitoring plasma levels, it became clear that this was an "off" phenomenon (Sage and Mark, 1995). The behavioral/sensory/autonomic "offs" are covered in Chapter 8.

Over time, there is usually a pattern of progressively worsening motor fluctuations in patients who are on chronic levodopa therapy. Motor fluctuations usually begin as mild wearing off (end-of-dose failure). Wearing off can be defined to be present when an adequate dosage of levodopa does not last at least 4 hours. Typically, in the first couple of years of treatment with levodopa, there is both a short-duration and a long-duration response (Muentner and Tyce, 1971; Anderson and Nutt, 2011). As the disease progresses or as levodopa treatment continues, the long-duration response fades and the short-duration response becomes predominant, leading to the wearing-off effect.

As the "offs" tend to become deeper with more severe parkinsonism; simultaneously, the duration of the "on" response becomes shorter. Eventually, some patients may develop sudden "offs" in which the deep state of parkinsonism develops over minutes rather than tens of minutes, and they are less predictable in terms of timing with the

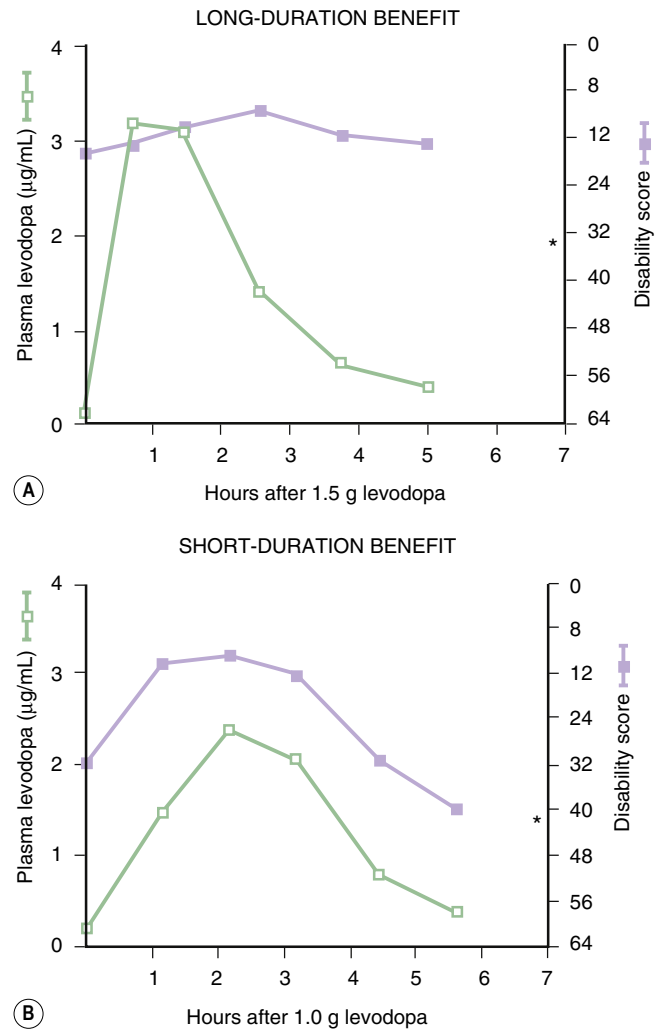


Fig. 6.13 Clinical response to a dose of levodopa. A, Long-duration response. B, Short-duration response. The asterisk represents the level of clinical disability before the dose of levodopa. (From Muentner MD, Tyce GM: L-dopa therapy of Parkinson's disease: Plasma L-dopa concentration, therapeutic response, and side effects. *Mayo Clin Proc.* 1971;46:231–239.)

dosings of levodopa and can be called random "offs" in this situation. A "super off" occurs when the "off" state is more severe than the untreated parkinsonian state. The "super off" appears either at the end of an "on" period or immediately after a dose of levodopa (Merello and Lees, 1992). The latter situation is difficult to explain (Nutt et al., 1988). Many patients who develop motor fluctuations also develop abnormal involuntary movements (i.e., dyskinesias). Yo-yo-ing is the state in which the patient moves from an "off" to "on with dyskinesia," and then back to being "off" again, with almost no time spent in between; that is a state of "on" without dyskinesias. A delayed "on" is when the levodopa takes longer than 30 minutes after being swallowed for the patient begins to see the levodopa starting to alleviate the parkinsonism, that is, for the dose to "kick in." The delay in "turning on" is the result of delayed gastric emptying. Levodopa, like other amino acids, is absorbed by an active transport system in the small intestine. But because levodopa decomposes in an alkaline medium, it is viable only in the upper small intestine, predominantly the duodenum and

proximal jejunum, where the acid juices of the stomach have allowed this region of the intestine to be acidic (Lovenberg et al., 1962). Levodopa is absorbed using the large neutral amino acid transport system.

Dose failures occur when the levodopa failed to “kick in” at all, with the levodopa remaining in the stomach. This often happens after a full meal or if the levodopa tablet is trapped on the stomach wall and never dissolved in the stomach juices. Because meals influence the speed of gastric emptying, they influence turning “on” after a dose of levodopa. Delayed “on” can occur in those patients who have lost the long-duration benefit and are now dependent on the short-duration benefit (Muentert and Tyce, 1971). Many patients respond best to levodopa given as the first dose of the day and get a weaker response with the later doses, resulting in a weak response at end of day. This may reflect lower plasma levels of levodopa with each succeeding dose. Sudden transient freezing is not technically an “off” state; it is part of the freezing phenomenon, and can occur with “off” or “on” freezing.

Levodopa-induced dyskinesias appear to be related to the degree of dopamine receptor supersensitivity. It is difficult to induce dyskinesias in normal animals or people, but with a high-enough dose, this has been achieved in monkeys (Sassin et al., 1972; Pearce et al., 2001; Togasaki et al., 2001). With increasing denervation, resulting in increased receptor sensitivity, there is more likelihood of developing choreic dyskinesias at a lower dose of levodopa (Cedarbaum et al., 1991). Dystonic reactions (forceful sustained contractions) may evolve over time in patients who earlier had choreic dyskinesias. However, some patients develop peak-dose dystonia at relatively low dosages; these may be patients with MSA (Quinn, 1994a). Dyskinesias tend to first appear and remain more severe on the side of the body that PD manifests clinically, in keeping with being contralateral to the more supersensitive dopamine receptors. In general, developing dyskinesias in PD can be viewed in a favorable light because the phenomenon indicates that dopamine receptors have remained responsive so that motor symptoms of parkinsonism can be reduced by levodopa therapy. In addition, the presence of dyskinesias does not necessarily have a significant negative effect on quality of life (Marras et al., 2004).

Dyskinesias usually occur at the peak concentration of levodopa dose in the brain. The most common dyskinetic phenomenon is chorea, and these are called peak-dose dyskinesias. Rarely, the chorea can be so severe, it takes the form of ballism. More commonly, chorea can evolve into dystonia, and many patients will have a combination of chorea and dystonia. Peak-dose dyskinesias fade as the concentration of levodopa in the brain diminishes. Diphasic chorea and dystonia is when the dyskinesias begin at the beginning or the end of the dose, labeled as D-I-D by Muentert and colleagues (1977) (Fig. 6.14). The beginning- and end-of-dose dyskinesias are typically present in the legs, whereas peak-dose dyskinesias are most common in the neck and upper body. End-of-day dyskinesias is the last end-of-dose dyskinesia of the day. “Off” dystonia is technically an “off” phenomenon, but instead of being a parkinsonian state, it is a painful dystonic state. Myoclonus can occur as a form of being overdosed from a dopaminergic agent (including amantadine) usually when there also is background mental confusion

also. Some parts of the patient’s body may be more sensitive to levodopa and then will develop dyskinesias in that body part while the rest of the body may still be in a parkinsonian “off” state, so-called simultaneous dyskinesia and parkinsonism. A more detailed description of dyskinesias is available in a review by Fahn (2000).

The behavioral/sensory/autonomic “offs” resemble the same phenomena if they were to occur unrelated to the levodopa medication. It is likely that the dopamine receptors responsible for these symptoms are not neostriatal, but rather limbic and cortical for the behavioral and sensory symptoms, hypothalamic and possibly peripheral for the autonomic symptoms. All dopamine receptors would be activated by levodopa therapy and become partially desensitized by such sustained activation. When the dopamine levels drop when the levodopa levels are low, these receptors are inadequately activated, and as a result produce symptoms as noted.

Clinical end-stage does not correlate with motor complications

Kempster and colleagues (2007) carried out a clinicopathologic correlation of PD patients with and without motor

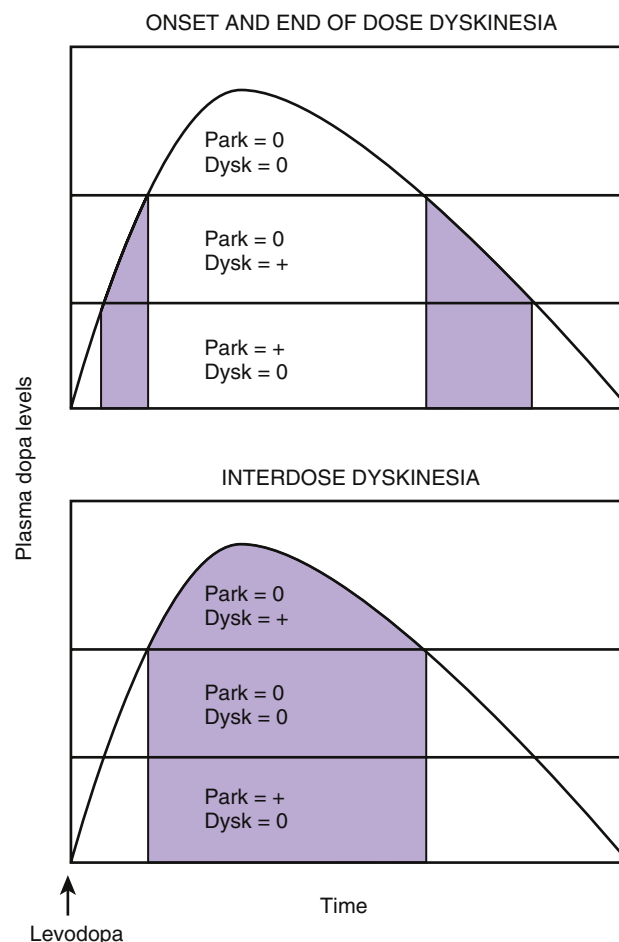


Fig. 6.14 Diagram depicting diphasic and peak-dose dyskinesias. (From Agid Y, Bonnet AM, Signoret JL, Lhermitte F: Clinical, pharmacological, and biochemical approach of “onset- and end-of-dose” dyskinesias. *Dysk, Dyskinesias; Park, Parkinson. Adv Neurol.* 1979;24:401–410.)

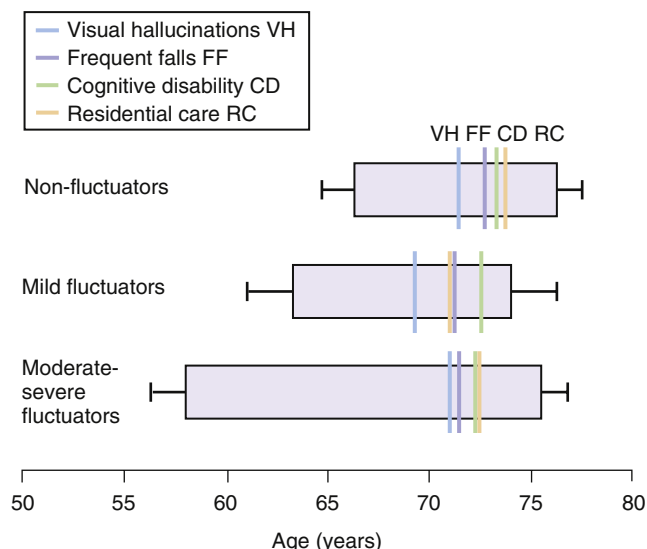


Fig. 6.15 Milestones of disease advancement and total disease course in non-fluctuators and fluctuators. Error bars for standard error of the mean. The blue rectangles represent disease duration. (From Kempster PA, Williams DR, Selikhova M, Holton J, Revesz T, Lees AJ: Patterns of levodopa response in Parkinson's disease: A clinico-pathological study. *Brain*. 2007;130[Pt 8]:2123–2128.)

complications (fluctuations and dyskinesias) (Fig. 6.15). Ninety-seven cases of proven PD brains with good clinical descriptions were available. Clinically, the cases were divided into non-fluctuators ($N = 35$), mild fluctuators ($N = 17$), and moderate-severe fluctuators ($N = 45$). Patients with motor fluctuations had a younger age of onset and longer disease course ($P < 0.001$), although mean age at death was almost the same among the groups. Four milestones of advanced disease (frequent falls, visual hallucinations, cognitive disability, and need for residential care) occurred at a similar age and at a similar time from death in each group, regardless of age at onset. Thus, the development of the milestones was not proportionate to disease duration; aging seems to be playing a major role. There were no significant differences in the severity or distribution of Lewy body or other pathologic findings. Irrespective of the pattern of levodopa response, patients reach a common pathologic endpoint at a similar age, and the duration and manifestations of end-stage disease are alike.

Pathogenesis of motor complications

There have been numerous retrospective analyses to try to discover the known major risk factors for peak-dose dyskinesias and motor fluctuations. The ones proposed have been the severity of the disease (Horstink et al., 1990a; Ahlskog and Muentner, 2001), levodopa dosage (Poewe et al., 1986; Parkinson Study Group, 2004b), age of the patient (Quinn et al., 1987; Kostic et al., 1991; Kempster et al., 2007), and duration of levodopa therapy (Horstink et al., 1990b; Roos et al., 1990; Rajput et al., 2002; Van Gerpen et al., 2006). A post hoc analysis of the clinical trial, STRIDE-PD (Stocchi et al., 2010), comparing carbidopa/levodopa with (LCE, found that the following factors are the greatest risk factors, in this order: young age at onset, higher L-dopa dose, low

body weight, LCE treatment group, female gender, and more severe UPDRS Part II (Olanow et al., 2013).

Pulsatile administration of levodopa has been proposed as a risk factor (Chase et al., 1993; Chase, 1998; Stocchi and Olanow, 2004), but an attempt to smooth out plasma levels in advance of developing dyskinesias (STRIDE-PD study) has had the opposite effect; it resulted in more and earlier dyskinesias (Stocchi et al., 2010). On the other hand, once wearing off develops, this problem can be ameliorated by smoothing out plasma levels by continuous administration (Fig. 6.16) (Shoulson et al., 1975). Perhaps one reason why adding entacapone resulted in more dyskinesias is because it raises the brain level of levodopa and thus dopamine. Many other attempts to provide a smoother dopamine level (i.e., less pulsatility) by adding agents to patients already taking levodopa ended up increasing dyskinesias. These additions were dopamine agonists (Olanow et al., 1994; Lieberman et al., 1997, 1998), COMT inhibitors (Parkinson Study Group, 1997a; Baas et al., 1997), MAO-B inhibitors (Shoulson et al., 2002; Parkinson Study Group, 2005; Rascol et al., 2005), extended-release levodopa (Block et al., 1997; Linazasoro et al., 1999), and fetal dopaminergic cell implants (Freed et al., 2001; Olanow et al., 2009b). The net effect is that despite possibly smoothing out dopamine levels in the brain, these substances also increased brain dopamine levels. Thus, pulsatility may not be an important risk factor for causing motor complications.

Fluctuations ("off" states)

The wearing-off phenomenon (also known as end-of-dose failure) is the gradual return of parkinsonism; it correlates with the falling concentration of levodopa in the plasma (and therefore the brain) (Muentner and Tyce, 1971; Shoulson et al., 1975; Fahn, 1982). The "on-off" phenomenon, as originally defined (Duvoisin, 1974b; Fahn, 1974), is a label for a sudden and random event in which the patient suddenly becomes parkinsonian. That is, the benefit from levodopa suddenly disappears, like turning off a light switch, hence the name. To avoid ambiguity, because the term "on-off" is sometimes used to refer to any type of fluctuation in parkinsonian patients, the phenomenon for "sudden offs" is labeled here as either "sudden off" or "on-off" in contrast to wearing off. In addition to worsening of motor performance during "off" states, sometimes nonmotor "offs," occur, such as decreased mood accompanied by anxiety and sometimes pain (Maricle et al., 1995; Ford et al., 1996; Hillen and Sage, 1996). These fluctuating mood and pain states can respond to the pharmacologic effects of levodopa.

On-off phenomenon

In "on-off," the patient can improve just as suddenly, even without taking another dose of levodopa. Pharmacologic studies have revealed plasma levels of levodopa to be in the declining phase when the "offs" appear (Fig. 6.17) (Fahn, 1974). It has been speculated that the "sudden off" problem is due to a sudden and transient desensitization of the dopamine receptors that would be compatible with the receptor switching from a high-affinity to a low-affinity state (Fahn, 1974). Response of a "sudden off" state to a new dose of levodopa or to a subcutaneous injection of apomorphine

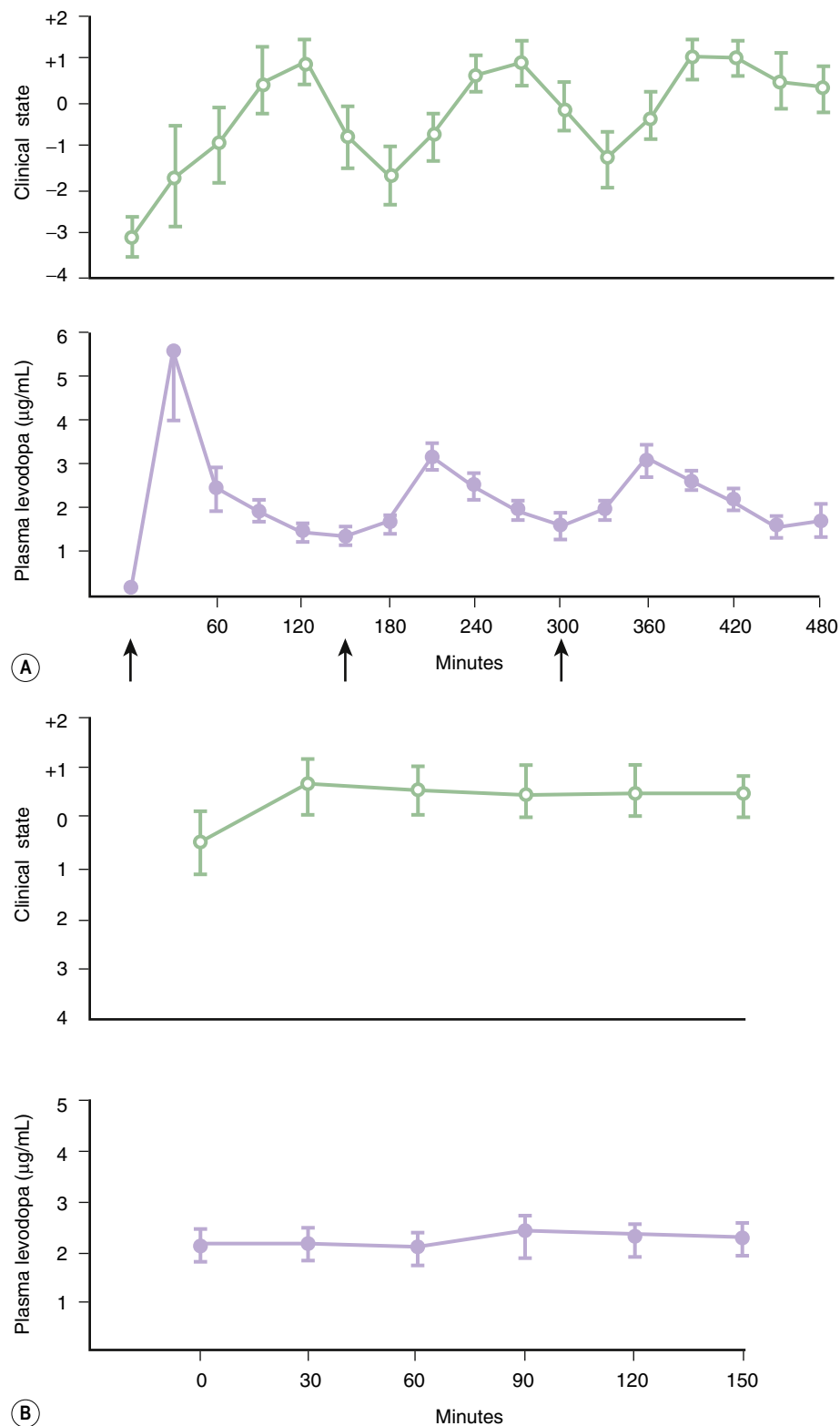


Fig. 6.16 Relationship between clinical state (upper graphs) and plasma levodopa concentration as mean scores in patients with clinical fluctuations. (A) Graphs are with the subjects taking oral levodopa at the times indicated by the arrows. (B) Graphs are with the subjects receiving intravenous levodopa infusions. (From Shoulson J, Glaubiger GA, Chase TN: "On-off" response: Clinical and biochemical correlations during oral and intravenous levodopa administration. *Neurology*. 1975;25:1144-1148.)

(Clough et al., 1984; Frankel et al., 1990) is compatible with the stimulation of a desensitized receptor; the receptor being presented with a higher concentration of dopamine (or dopamine agonist) will now respond. This result is not

incompatible with the hypothesis that a desensitized receptor might be responsible for the "sudden off." The "sudden-off" or "on-off" phenomenon occurs very infrequently; the most common "off" state is wearing off.

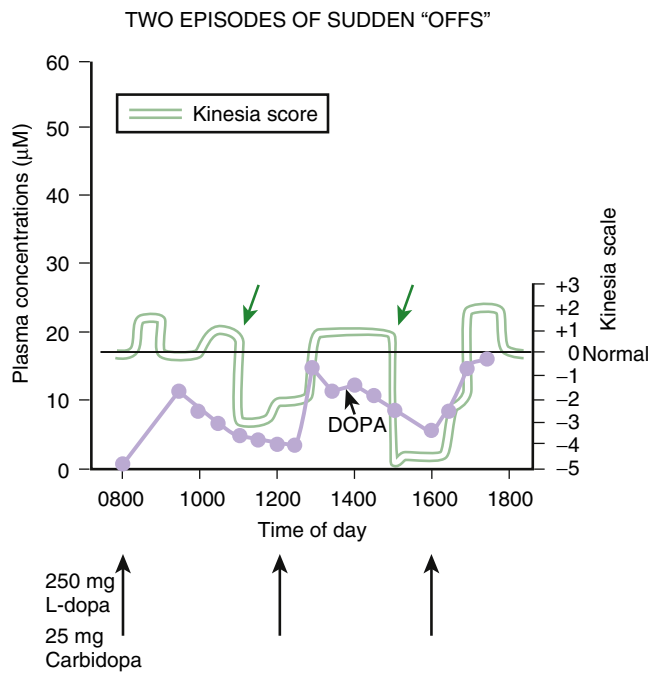


Fig. 6.17 Two episodes of “sudden offs” (thick arrows) during the declining slope of plasma levodopa concentrations. (From Fahn S. “On-off” phenomenon with levodopa therapy in parkinsonism: Clinical and pharmacologic correlations and the effect of intramuscular pyridoxine. *Neurology*. 1974;24:431–441.)

Wearing-off phenomenon

When patients have wearing off, the clinical improvement from a dose of levodopa lasts only as long as the plasma concentration of levodopa is high (Muentert and Tyce, 1971). As the plasma level gradually falls, there is a loss of clinical response. Stable patients without clinical fluctuations maintain the long-duration response despite a fall in plasma levels of levodopa. Patients with wearing off and “on-off” have lost the long-duration response and have only a short-duration response. In the study by Fabbrini and associates (1987) discontinuation of steady intravenous infusion of levodopa was followed by a decay in the plasma concentration of levodopa, identical in all groups of patients, representing an unchanged pharmacokinetic profile. With the falling plasma concentration of levodopa, stable patients maintain their clinical response with only a gradual decay in the response over time (Fig. 6.18, upper). However, the patients with wearing off and “on-off” have a rapid loss of the anti-PD effect, more closely paralleling the falling plasma concentration (see Fig. 6.18, lower) (Fabbrini et al., 1987).

In patients with a loss of the long-term benefit, if the plasma level can be maintained, the clinical response also can be maintained (Figs. 6.16, 6.19) (Shoulson et al., 1975; Hardie et al., 1984; Mouradian et al., 1990). This will be the pharmacokinetic basis of treating patients with wearing off. Providing a continuous supply of dopamine or dopamine agonist to the striatum, such as by intravenous (Nutt, 1987) or intestinal (Sage et al., 1989a,b; Bredberg et al., 1993; Kurth et al., 1993b; Nyholm et al., 2005) infusion of levodopa, or by subcutaneous infusion of dopamine agonist (Obeso et al., 1989a) can overcome this type of fluctuation. Thus, continuous benefit in the unstable patient (advanced PD) depends on a steady supply of levodopa in the plasma

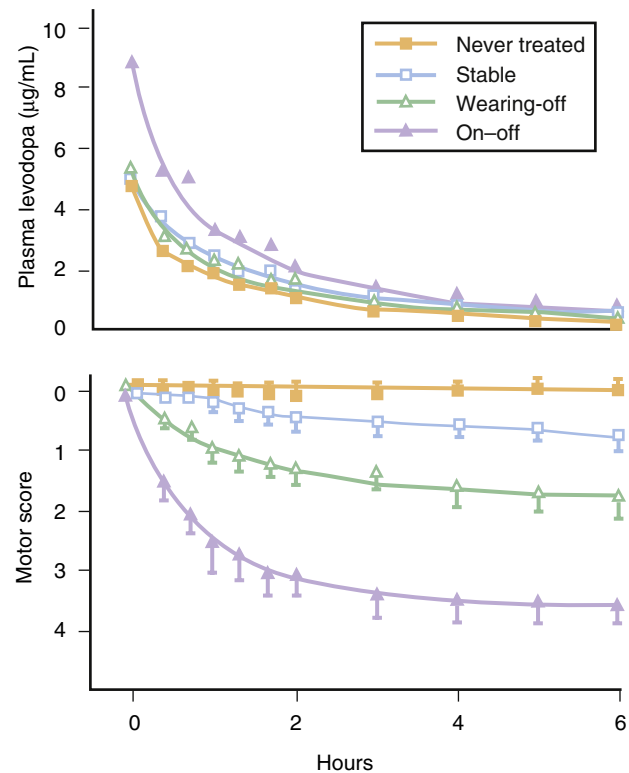


Fig. 6.18 Plasma decay curves of levodopa and decay of symptoms. The upper graph shows the falling levodopa plasma levels after stopping the drug. The curves are very similar. The lower graph shows the fading of clinical response after stopping levodopa. The most severe fluctuators have the fastest decay of the clinical benefit. Those patients with no fluctuations have a long duration benefit with no decay after stopping the drug. (From Fabbrini G, Juncos J, Mouradian MM, Serrati C, Chase TN: Levodopa pharmacokinetic mechanisms and motor fluctuations in Parkinson's disease. *Ann Neurol*. 1987;21:370–376.)

reaching the brain in a constant influx. This type of necessary bioavailability of plasma levodopa is not a factor with patients who have a smooth response to levodopa because such individuals have the long-duration benefit despite having the same type of plasma half-life of levodopa as do those with fluctuations (Fabbrini et al., 1987).

Plasma concentrations of large neutral amino acids, which compete with levodopa for transport into the brain, contributes to motor fluctuations, even when levodopa is being steadily infused (Nutt et al., 1997). These large neutral amino acids play an even bigger role when the daily dosage of levodopa is higher. On the other hand, severity of PD did not predict fluctuations during the infusions. In addition to this obvious peripheral pharmacokinetic mechanism, because fluctuations are more prominent in patients who have taken larger daily doses of levodopa, pharmacodynamic factors are also implicated.

Some other factor(s) must be playing a role. It seems that central (such as small dopamine storage capacity and dopamine receptor alterations) and peripheral pharmacokinetic and pharmacodynamic mechanisms are involved in the pathophysiology of these problems (Mouradian et al., 1988, 1989; Obeso et al., 1989b).

Small dopamine-storage capacity

After 16 hours of infusion of levodopa intravenously in patients, and then suddenly discontinuing the infusion,

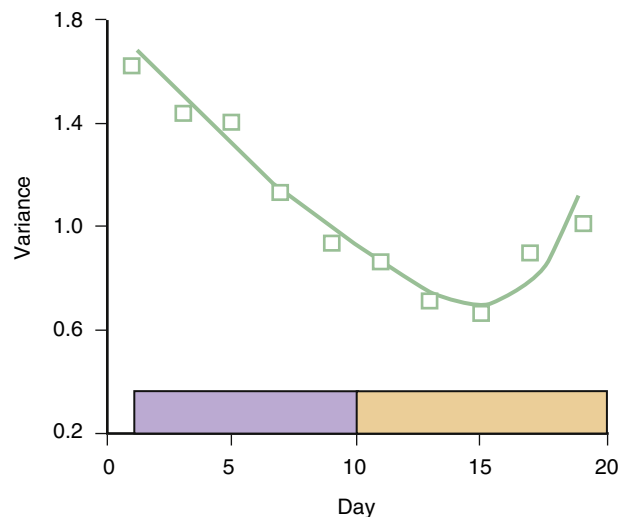


Fig. 6.19 Reduction of motor variance by continuous infusion of levodopa. Ten days of continuous intravenous infusion resulted in less clinical variation. Stopping the infusion and resuming oral doses of levodopa resulted in a return of the clinical variation, but after a lag period of sustained benefit that lasted about 5 days. (From Mouradian MM, Heuser IJE, Baronti F, Chase TN: Modification of central dopaminergic mechanisms by continuous levodopa therapy for advanced Parkinson's disease. *Ann Neurol.* 1990;27:18–23.)

patients with “on-off” and wearing off, respectively, show the fastest return of parkinsonian symptoms, compared with those with a stable response to levodopa or those who have never been treated with levodopa (see Fig. 6.18, lower) (Fabbrini et al., 1987). The patients with dyskinesias have a faster decay of their dyskinesias than of their anti-PD benefit, suggesting different receptors for the two functions are involved (Fig. 6.20) (Mouradian et al., 1989). The loss of the anti-PD effect as the plasma levodopa concentration falls in the previously described studies strongly indicates either a small buffering capacity for levodopa storage or a short-duration receptor response in patients with fluctuations.

The synaptic concentration of dopamine as a function of the timing of levodopa dosing was studied indirectly by evaluating D2 receptor ligand PET scans in patients who eventually developed wearing off and those who remained stable, as non-fluctuators (de la Fuente-Fernandez et al., 2001). The former group of patients showed higher synaptic dopamine 1 hour after a dose, but lower concentrations 3 hours later than the latter group. This result suggests increased dopamine turnover, that is, decreased storage of dopamine.

Supporting the concept of a small buffering capacity are studies performed in rats with different degrees of 6-hydroxydopamine lesions of the nigrostriatal pathway (Papa et al., 1994). The rats are then treated with twice-daily injections of levodopa. Rats with over 95% loss of dopaminergic neurons evidenced a progressive shortening in the duration of levodopa's motor effects (equivalent to wearing off) and a failure of nearly 8% of levodopa injections to elicit any response (equivalent to dose failures) after the first week of treatment. In contrast, response changes resembling those associated with wearing-off fluctuations in parkinsonian patients did not occur in the less severely lesioned rats. These results suggest that the extent of a dopamine neuron loss must exceed a relatively high threshold before intermittent levodopa treatment produces changes favoring the appearance of motor fluctuations.

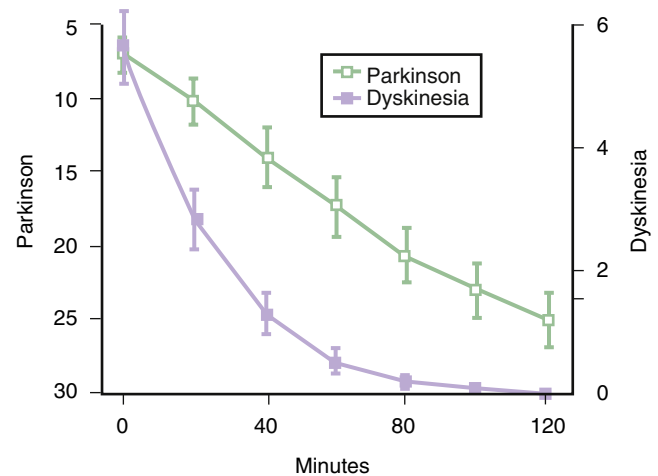


Fig. 6.20 Dyskinesias decay faster than the anti-parkinson effect when levodopa is withdrawn. (From Mouradian MM, Heuser IJE, Baronti F, Fabbrini G, Juncos JL, Chase TN: Pathogenesis of dyskinesias in Parkinson's disease. *Ann Neurol.* 1989;25:523–526.)

If the wearing-off phenomenon is due, at least in part, to loss of storage sites of dopamine in the striatum, severity of parkinsonism, regardless of duration of parkinsonism, should be associated with the wearing-off effect. This would explain why fluctuations occurred early in the course of treatment in patients with MPTP-induced parkinsonism (Ballard et al., 1985); these patients had a severe destruction of dopaminergic nigrostriatal pathway. In contrast, those with PD develop the wearing-off problem as a function of duration of treatment (McDowell and Sweet, 1976), which also could be a reflection of duration of illness.

Levodopa may contribute to the development of fluctuations

Dopamine storage capacity alone does not explain why younger patients are more prone to develop fluctuations than are older patients (Pederzoli et al., 1983). Nor would it explain why using low doses of levodopa instead of high doses would delay the development of this problem (Lesser et al., 1979; Poewe et al., 1986). Furthermore, treatment with direct-acting agonists does not eliminate the problem, although it does ameliorate it somewhat by making the depths of the “off” state less severe. These three observations would imply that levodopa itself or the peaks and valleys of supplying the brain with levodopa also may be responsible for contributing to this problem. Some investigators have found that the major risk factors for fluctuations appear to be duration (Horstink et al., 1990b; Roos et al., 1990) and dosage (Poewe et al., 1986; Fabbrini et al., 1988; Olanow et al., 2013) of levodopa therapy.

The CALM-PD clinical trial, comparing levodopa and pramipexole, clearly showed that levodopa was statistically more likely than the dopamine agonist to induce fluctuations (and dyskinesias) when assessed after 2 years (Parkinson Study Group, 2000) or 4 years of observation (Holloway and Parkinson Study Group, 2004). Whether the effect is inherent to levodopa, the potency of levodopa compared with the agonist, or the short duration of levodopa's half-life is uncertain. A further analysis of the CALM-PD data revealed that motor complications that occur within the first 4 years

of treatment of PD do not have a significant negative effect on quality of life (Marras et al., 2004).

Pharmacokinetic mechanisms

Murata and Kanazawa (1993) repeatedly administered levodopa to intact rats and found that this treatment induced (1) acceleration of DOPA absorption at the gut and the blood-brain barrier, (2) reduction of dopamine retention in the striatum, and (3) loss of “supersensitive response” of dopamine receptors. These authors concluded that long-term levodopa treatment is the cause of the wearing-off effect. Murata and colleagues (1996) subsequently studied plasma pharmacokinetics in 55 parkinsonian patients. They showed that long-term levodopa therapy markedly increased the peak levodopa concentration ($C_{\max}$) and the area under the time-concentration curve (AUC); whereas it decreased time to the peak concentration ($T_{\max}$) and the elimination half-life ($T_{1/2}$). These results suggest that long-term levodopa therapy accelerates the absorption of levodopa. These changes were seen in patients who were stable and in those with the wearing-off effect, although the fluctuators had a higher $C_{\max}$ and AUC and a shorter $T_{\max}$ and $T_{1/2}$ than the non-fluctuators. In a FDOPA PET study, Torstenson and colleagues (1997) showed that levodopa infusion during the scanning decreased FDOPA influx in mild PD, but upregulated the influx in patients with advanced PD. These findings could help explain the less graded clinical response to levodopa in advanced PD.

Pharmacodynamic mechanisms

Direct alterations of dopamine receptors and storage sites by levodopa, dopamine, or their metabolites is another possibility. D2 receptors were studied by raclopride PET scanning in patients early in the course of treatment with levodopa and then 3 to 5 years later, when motor fluctuations had appeared (Antonini et al., 1997). Raclopride binding was elevated (supersensitive receptors) after 3 to 4 months of levodopa therapy and returned to normal (downregulated) after 3 to 5 years of treatment.

One indication that dopamine receptors play a role in the loss of the anti-PD benefit as the plasma concentration of levodopa falls is the dichotomy of the decay of dyskinesia and the return of the parkinsonism (see Fig. 6.20) (Mouradian et al., 1989). The dyskinesia decays faster than does the loss of the anti-PD benefit. Dyskinesia half-time (time required to reduce severity score by 50%) was 25.3 minutes; the anti-PD half-time (time required to increase PD severity scores to 50% of their maximum) was 50.4 minutes. The shape of the two curves differs: the decay of dyskinesia is quadratic, the return of PD severity is linear. This suggests that dyskinesia effect and anti-PD effect represent different dopamine receptors (e.g., D1 and D2 receptors, respectively).

Chase and colleagues (1993, 1998) suggested that intermittent (compared with continuous) administration of levodopa contributes to this problem. Chase proposed that there is an alteration of the striatal dopaminergic medium spiny neurons, with a potentiation of glutamate receptor NMDA subtype on these GABAergic striatal efferents, and that these cells are producing the motor complications. In 6-hydroxydopamine-lesioned rats, an animal model of PD, Chase and colleagues found increased phosphorylation of striatal NMDA receptor subunits on serine

and tyrosine residues. Along with this concept is the finding from his laboratory that an NMDA antagonist can reverse the shortened levodopa response time in these rats (Blanchet et al., 1997). Furthermore, the intrastratial administration of selective inhibitors of certain serine and tyrosine kinases alleviates the motor complications (Chase et al., 2000). He thinks the same mechanism is responsible for both motor fluctuations and dyskinesias.

Although Chase incriminates intermittent administration of levodopa as the primary cause of motor complications, another potential mechanism is that dopamine can lead to the formation of free radicals by autooxidation or by enzymatic oxidation, and these oxyradicals could be the culprits attacking dopamine receptors (Fahn and Cohen, 1992; Fahn, 1996).

Once established, motor complications are seemingly irreversible. Substituting dopamine agonists for levodopa therapy diminishes the severity of the complications but does not eliminate them. Dopamine receptors may have irreversible changes, much like the irreversible alteration that is seen with tardive syndromes after exposure to dopamine receptor-blocking agents (see Chapter 17). The healing process takes a long time without exposure to the offending agent before the process disappears, which often never happens.

Altered dopamine receptors

The dose-response curve to a bolus of levodopa injected intravenously was studied in patients with “on-off” and wearing off, and those with a stable response to levodopa and those who had never been treated with levodopa (Fig. 6.21) (Mouradian et al., 1988). The antiparkinsonian response showed a linear dose-response curve in the latter two groups but an S-shape curve for the first two groups. Thus, patients with fluctuations have a brittle response to levodopa. Because the peripheral pharmacokinetics are the same in all groups, this increased sensitivity to levodopa, despite identical antiparkinsonian threshold, strongly implies an alteration of the dopamine receptor, probably the D2 receptor, in patients with fluctuations. There is also a narrow window between antiparkinsonian and dyskinetic effects in patients who have fluctuations and dyskinesias (Fig. 6.22) (Mouradian et al. 1989).

Already mentioned was that the dichotomy of the decay rates for dyskinesia and anti-PD benefit when levodopa was withdrawn after a steady intravenous infusion suggested different dopamine receptors may be responsible for dyskinesias and for the anti-PD effect of levodopa (see Fig. 6.20) (Mouradian et al., 1989). A more direct evaluation of dopamine receptors is by using a dopaminergic agent that acts only at the postsynaptic dopamine receptors for its effect. After a steady-state optimal-dose infusion of apomorphine, a direct-acting dopamine agonist that is not dependent on storage of dopamine, the apomorphine was withdrawn, and the loss of the anti-PD effect was faster in patients who had fluctuations than in stable patients with a stable response (Fig. 6.23) (Bravi et al., 1994). Because apomorphine's effect is not dependent on presynaptic terminals, postsynaptic mechanisms must play a role in the loss of the long-duration response and hence the wearing-off effect.

Other studies supporting the notion that postsynaptic dopamine receptors play a role in wearing off are those by Colosimo and colleagues (1996) and Metman and colleagues (1997a). These showed that duration of response to

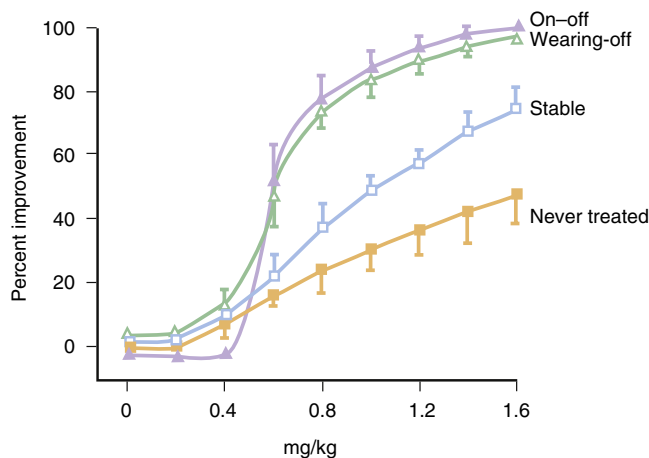


Fig. 6.21 Levodopa dose-response curves vary depending on presence or absence of motor fluctuations. Fluctuators have more sensitive DA receptors. (From Mouradian MM, Juncos JL, Fabbrini G, Schlegel J, Bartko JJ, Chase TN: Motor fluctuations in Parkinson's disease: Central pathophysiological mechanisms, Part II. *Ann Neurol*. 1988;24:372–378.)

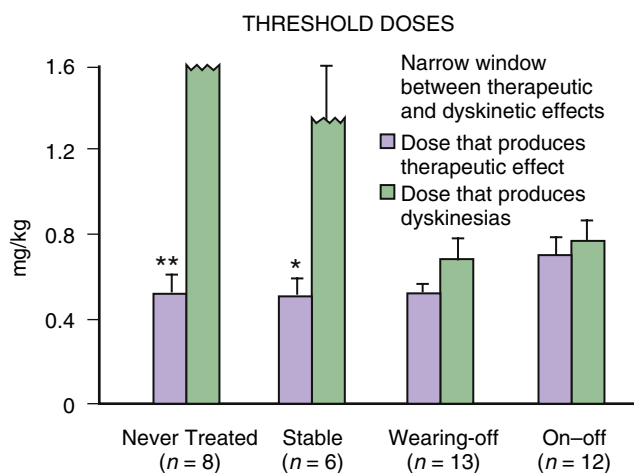


Fig. 6.22 Narrow window between antiparkinson and dyskinetic effects in fluctuators compared with non-fluctuators. (From Mouradian MM, Heuser IJE, Baronti F, Fabbrini G, Juncos JL, Chase TN: Pathogenesis of dyskinesias in Parkinson's disease. *Ann Neurol*. 1989;25:523–526.)

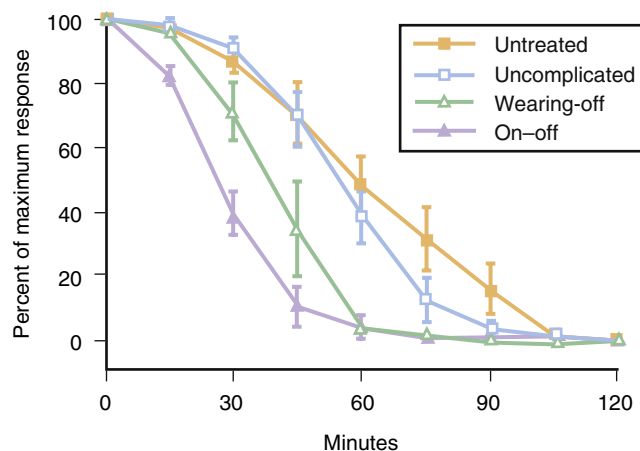


Fig. 6.23 Differential decay rates of the antiparkinsonian effect among fluctuators and non-fluctuators after withdrawal of apomorphine. (From Bravi D, Mouradian MM, Roberts JW, Davis TL, Sohn YH, Chase TN: Wearing-off fluctuations in Parkinson's disease: Contribution of postsynaptic mechanisms. *Ann Neurol*. 1994;36:27–31.)

apomorphine is shorter in advanced, complicated parkinsonians compared with early, levodopa-naïve patients or stable patients. In addition, the dose-response slope steepened, and the therapeutic window narrowed. The plasma levels of apomorphine were identical in the stable and fluctuating patients.

This conclusion was supported by another study comparing duration of response between the more and less affected sides in patients with PD to an infusion of levodopa and to subcutaneous apomorphine. Rodriguez and colleagues (1994) showed that the more affected side had a shorter response duration, increased latency, and greater response magnitude than did the less affected side. These differences were more pronounced in patients receiving chronic levodopa treatment than in untreated patients. Because apomorphine is not dependent on dopamine storage capacity, these findings suggest that postsynaptic mechanisms play an important part in the origin of motor fluctuations in PD. Could these postsynaptic mechanisms develop because of inconstant and pulsating activation of receptors by dopamine related to levodopa therapy or possibly from dopamine-mediated oxy-radicals or other toxins related to levodopa therapy?

Implicating the intermittent administration of chronic levodopa therapy

Ten days of continuous, round-the-clock administration of levodopa intravenously producing a stable plasma concentration of levodopa gradually reduced fluctuations of response to levodopa in patients with the "on-off" or wearing-off effects (see Fig. 6.19) (Mouradian et al., 1990). Because smoothing out the plasma (and brain) concentrations provided this benefit, the authors suggested that the chronic, routine method of intermittent oral treatment with levodopa may be underlying the development of motor fluctuations. Continuous intravenous treatment increased the threshold to levodopa for both the anti-PD and dyskinesia response (Table 6.13), with an increase in the therapeutic window by about 50% (computed as the difference between the dyskinesia threshold dose and the anti-PD threshold dose).

The S-shape of the dose-response curve for the fluctuators remained, but with a shift of the curve to the right indicating the decreased sensitivity to levodopa. At the increased threshold dosage for dyskinesia, the anti-PD response increased 76% (despite the shift of the curve to the right) with no change in the severity of the dyskinesias. Once the continuous infusions were discontinued, the fluctuations returned. Nutt and colleagues (1993) think that tolerance actually develops after continuous infusions; when the infusion is stopped, the duration of response is shorter after a long infusion than after a shorter one. It is well recognized that once developed, "on-off" problems are difficult to eliminate.

Two controlled clinical trials attempted to test the hypothesis that starting treatment with a longer duration form of levodopa (Block et al., 1997; Koller et al., 1999) or with levodopa combined with entacapone (also providing longer duration pharmacokinetics) (Stocchi et al., 2010) would provide less fluctuations and less dyskinesia. Both failed. The first was a 5-year study of 618 dopa-naïve patients comparing Sinemet CR and standard Sinemet therapy. There was no difference between the two groups in the development of either fluctuations or dyskinesias (Block et al., 1997; Koller et al., 1999). The second study (STRIDE-PD) (Stocchi et al.,

Table 6.13 Effect of continuous therapy with levodopa on its dose-response measures

Measure	Pretreatment mg/kg	Posttreatment mg/kg	P Value
Antiparkinsonian threshold dose	0.59 ± 0.07	0.9 ± 10.07	<0.0001
Dyskinesia threshold dose	0.66 ± 0.08	1.0 ± 0.09	<0.0001
Therapeutic window	0.061 ± 0.04	0.092 ± 0.04	

The threshold for both the antiparkinsonian and dyskinesia response increased.

Data from Mouradian MM, Heuser IJE, Baronti F, Chase TN: Modification of central dopaminergic mechanisms by continuous levodopa therapy for advanced Parkinson's disease. *Ann Neurol*. 1990;27:18–23.

2010) was discussed previously. It compared levodopa with levodopa plus entacapone. The latter resulted in more subjects with dyskinesias, and the dyskinesias occurred sooner. However, it should be mentioned that neither study adequately tested the intermittent versus continuous levodopa hypothesis for the cause of fluctuations. In terms of therapeutics, these studies showed no advantage for beginning with any other preparation of levodopa over another or with agents that prolong the serum half-life of levodopa. It should be mentioned that Rytary has the longest half-life of levodopa, but it has not been studied in terms of delaying or preventing motor complications. The same can be said for jejunal infusion of levodopa.

Summary of pathogenesis of fluctuations

Chase (1998) and Metman and colleagues (2000) summarized their views on the mechanisms leading to the development of fluctuations from levodopa therapy. They think that the fluctuations are related to altered dopaminergic mechanisms at both the presynaptic and postsynaptic levels. Wearing-off phenomena initially reflect the loss of dopamine storage capacity of the degenerating nigrostriatal system. Then, with increasing degeneration of the nigrostriatal system, swings in plasma levodopa concentrations associated with standard dosage regimens produce nonphysiologic fluctuations in intrasynaptic dopamine. As a result of long-term discontinuous stimulation, secondary changes occur at sites downstream from the dopamine system and now appear to underlie the progressive worsening of wearing-off phenomena and the eventual appearance of other response complications. Chronic intermittent stimulation of normally tonically active dopaminergic receptors activates specific signaling cascades in striatal dopaminergic medium spiny neurons, and this evidently results in long-term potentiation of the synaptic efficacy of glutamate receptors of the NMDA subtype on these GABAergic efferents as a result of increased phosphorylation of the serine and tyrosine moieties in these receptors. As a consequence of their increasing sensitivity to excitation by cortical glutamatergic projections, it would appear that medium spiny neuron function changes to favor the appearance of response fluctuations of the “on-off” type and peak-dose dyskinesias. The inability of standard levodopa treatment to restore striatal dopaminergic function in a more physiologic manner clearly contributes to the appearance of motor complications. Continuous dopaminergic replacement not only reverses these complications in parkinsonian patients but also prevents their development in animal models of PD. Nutt (2007) presented a scholarly critique of the continuous dopaminergic stimulation hypothesis and argued that an adequate clinical trial needs to rigorously test it.

Another explanation from both primate studies and post-mortem human studies is that long-term levodopa therapy

leads to glutamate receptor supersensitivity in the putamen, and this plays a role in the development of motor complications (both wearing off and dyskinesias) after long-term levodopa therapy in PD (Calon et al., 2003).

Dyskinesias

When dyskinesias first appear, their onset coincides with the onset of the antiparkinsonian effect (i.e., benefit) from levodopa (Nutt et al., 2010). The offset of the peak-dose dyskinesias also coincides with the offset of the antiparkinsonian response. The latency to the onsets of dyskinesia and the antiparkinsonian response tend to shorten during long-term levodopa therapy, suggesting that both responses were sensitized by long-term levodopa.

A PET study suggests that dopamine reuptake after its release is reduced in patients who have dopa-induced dyskinesias (Troiano et al., 2009). The study used two ligands: [(11)C]-d-threo-methylphenidate (MP) and [(11)C]-(+/-) dihydrotetabenazine (DTBZ). The former measures the function of the DAT, the latter dopamine nerve terminal density. The putaminal MP/DTBZ ratio was significantly reduced in patients with dyskinesias compared with those without.

A PET study analyzing NMDA receptors (a form of glutamate receptors) showed that dyskinetic patients had higher receptor binding than nondyskinetic patients, indicating increased glutamatergic activity in the development and maintenance of levodopa-induced dyskinesias (Ahmed et al., 2011). These findings are consistent with the results of earlier animal model studies implicating glutamergic overactivity in levodopa-induced dyskinesias (Chase and Oh, 2000). This could explain why amantadine acting as an NMDA antagonist reduces dyskinesias (Pahwa et al., 2015).

Another suggestion for a mechanism for the production of dopa-induced dyskinesias is based on postmortem chemical studies performed on primates, ranging from normal, parkinsonian, nondyskinetic dopa-treated, and dyskinetic dopa-treated (Aubert et al., 2005). These investigators found that the sensitivity of the D1 receptor is linearly related to dyskinesias. This implies that dopa-induced dyskinesia results from increased dopamine D1 receptor-mediated transmission at the level of the direct pathway. Another study in animal model suggested another mechanism. Dyskinetic animals had wide-spread extrastriatal localization of levodopa and 3-O-methyldopa compared to animals without dopa-induced dyskinesias (Fridjonsdottir et al., 2021). It was suggested that these extrastriatal brain areas become less able to modulate neuronal signaling, allowing dyskinesia to develop. A search for disruption of the blood-brain barrier in PD patients with dyskinesias was not found (Fujita et al., 2021). Disruption of autophagy from D1 receptor activation in animal models

with levodopa-induced dyskinesia has been found as another contributing factor (Feyder et al., 2021).

Risk factors for peak-dose dyskinesias were retrospectively analyzed by using the Kaplan–Meier survival method in 100 consecutive patients treated with levodopa for 1 to 18 years. Blanchet and colleagues (1996) found that 56% of patients developed dyskinesia after a mean of 2.9 years. Dyskinetic patients were significantly younger at disease onset, but their mean latency to dyskinesia induction after levodopa initiation was not different from that of older dyskinetic individuals. In the study by Kumar and colleagues (2005), the 5-year risk for dyskinesias is 50% for PD onset 40 to 59 years, and 26% with onset ages 60 to 69 and 16% age 70 or over. Dosage of levodopa is another factor in causing dyskinesias (Parkinson Study Group, 2004b; Olanow et al., 2013).

The levodopa dosage threshold for dyskinesia is much lower for patients with fluctuations than for patients with a stable response or for those who have never been treated before. This was determined by bolus injections of levodopa intravenously (see Fig. 6.22) (Mouradian et al., 1989). Those who had never been treated and those with a stable response to levodopa had such a high threshold for dyskinesias that dyskinesias never appeared in some of these patients at the highest doses tested. After 16 hours of steady intravenous infusion of levodopa, followed by sudden discontinuation, the loss of dyskinesias is faster than the return of parkinsonism (Mouradian et al., 1989). These studies indicate that dyskinetic effects and anti-parkinsonian effects may represent responses to different dopamine receptors. The investigators proposed that these are very likely the D1 and D2 receptors, respectively.

In a study looking at severity of PD after overnight drug withdrawal, Schuh and Bennett (1993) found that continuous intravenous levodopa shifted the dyskinesia dose-response curve to the right and reduced maximum dyskinesia activity, but did not significantly alter dose response for relief of parkinsonism. These results support the hypothesis that relief of parkinsonism and production of dyskinesia by levodopa occur by separate mechanisms.

Possession of a single common allele of the *BDNF* gene doubles the risk for developing levodopa-induced dyskinesia, and possessing two alleles quadruples the risk (Foltynie et al., 2009). Two alleles of the *BDNF* gene differ at position 66, encoding either a valine or methionine amino acid. In the general White population the genotype frequencies are 60% val/val, 36% val/met, and 4% met/met. Patients with PD have increased risk for developing levodopa-induced dyskinesia for each additional met allele in their *BDNF* gene.

Treatment of motor fluctuations associated with levodopa therapy

When levodopa or other antiparkinson medication no longer provides a smooth, adequate, long-duration response, treatment requires skill; it becomes an art form using approaches to control the various complications that have developed in a given patient. At this stage of treatment, the clinician is usually placed in a position analogous to that of a firefighter, being called on to “put out fires.” Every time a new problem arises in a response-complicated patient, the clinician uses his or her skill to control the new developments arising from levodopa therapy. The following subsections describe various complications and the approaches that can be taken to control them.

Wearing-off phenomenon in the absence of dyskinesias

Many choices are available to control wearing-off. When mild, it may be ameliorated with the addition of a COMT inhibitor (entacapone or opicapone) (Parkinson Study Group, 1997a; Lees et al., 2017) or an MAO-B inhibitor (e.g., selegiline and rasagiline) (Golbe et al., 1988; Parkinson Study Group, 2005). These drugs potentiate the action of levodopa by prolonging the half-life of exogenous dopamine in the brain derived from levodopa therapy. The potentiation of levodopa can also allow overdosed-type of symptoms, such as confusion and psychosis in the elderly and dyskinesias at any age. A lower dose of levodopa might be necessary if such adverse effects occur. Rasagiline, in the LARGO study, was found to have the same degree of benefit as entacapone in reducing “off” time and increasing “on” time (Rascol et al., 2005). The dose of entacapone is 200mg taken with levodopa; the dose of opicapone is 50mg at bedtime; selegiline is 5 to 10mg daily; and rasagiline is 1 to 2mg per day.

Another approach is to use standard carbidopa/levodopa alone, giving the doses closer together. But ultimately most patients will develop progressively shorter durations of effectiveness from these doses, so patients could require as many as six or more doses per day. Then, eventually, dose failures often develop. Investigation of this problem of shorter response time with smaller, more frequent doses of levodopa has shown that response time continues to increase when suprathreshold doses of levodopa are given, although increased dyskinesias also are seen (Metman et al., 1997b).

Longer acting, extended-release forms of carbidopa/levodopa can substitute for immediate release or be taken in combination with immediate-release carbidopa/levodopa. More often, Rytary, the formulation of carbidopa/levodopa with the longest half-life, is being used instead of the older form of extended-release carbidopa/levodopa (Kestenbaum and Fahn, 2015). Finding the right dose of Rytary is somewhat complicated. One method to determine the optimum dose for just the first dose of the day, allowing subsequent doses of Sinemet to remain so the patient’s PD is under control the rest of the day. Once the optimum dose of Rytary is found for the first dose of the day, that dose can be used to substitute for Sinemet in the other doses of the day. In a controlled study testing the efficacy of Rytary, the mean duration of ON time was determined following a dose of immediate release carbidopa/levodopa (CD/LD IR and a dose of Rytary. In this study Rytary significantly increased ON time per dose compared to CD/LD IR by 1.21 hours, providing more ON per dose (3.55 h vs 2.38 h) (Hauser et al., 2021).

One should keep in mind that extended-release carbidopa/levodopa (whether Sinemet CR or Rytary) is not completely absorbed before the tablet passes through the small intestine. Only about two-thirds to three-quarters of extended-release carbidopa/levodopa is absorbed. Therefore, to achieve the equivalent of 100 mg of levodopa in standard Sinemet, a patient would require between 130 and 150 mg of levodopa in Sinemet CR or Rytary.

Direct-acting dopamine agonists, which have a longer biologic half-life than that of levodopa, can be used in combination with standard Sinemet or Sinemet CR (Parkinson Study Group, 1997b). As a general rule, dopamine agonists

are useful to improve the severity of the “off” state, but can also reduce the amount of “off” time per day. Pramipexole and ropinirole are more effective than bromocriptine and are preferred. These drugs in combination with levodopa can increase dyskinesias while reducing the depths of the “offs.” In this situation, the levodopa dosage would need to be reduced. Because of its long half-life, cabergoline can be effective even with once-a-day dosage (Geminiani et al., 1996; Inzelberg et al., 1996). Using dopamine agonists and delaying the introduction of levodopa can delay the start of the wearing-off effect and reduce the risk for developing it (Montastruc et al., 1994; Przuntek et al., 1996; Rinne et al., 1998a; Parkinson Study Group, 2000; Rascol et al., 2000; Oertel et al., 2006).

The antiepileptic drug zonisamide has been shown to be effective to reduce “off” time without worsening dyskinesias (Murata et al., 2007). Adenosine A2 antagonists also may reduce “off” time. A critical factor in reducing “off” time is not to simultaneously increase dyskinesias. If a drug can accomplish this, it would be a major advance in therapeutics. So far, no drug has accomplished this except amantadine, which has both an inherent anti-PD and an antidyskinesia mechanism of action.

Patients with a deep “off” would benefit from a rescue dose of anti-PD medication. Crushing Sinemet between one’s teeth before swallowing it with water will allow for a faster time to “on” because then the powdery form of levodopa will dissolve faster in gastric juices, enabling it to enter the small intestine faster. In addition, dissolving levodopa in carbonated water (levodopa is soluble and stable in acid) and drinking it usually provides a response in about 10 to 15 minutes. Bypassing the gastrointestinal tract route is important to overcome “off” states in the presence of a full stomach after a meal. Inhalable levodopa is one method (LeWitt et al., 2016). Subcutaneous injections or intranasal sprays of apomorphine provide a similar response (Dewey et al., 1998). Etilevodopa, a dispersible form of levodopa ethylester, was expected to improve these types of delayed “off” responses (Djaldetti and Melamed, 1996), but a study by the Parkinson Study Group (Blindauer et al., 2006) of 327 patients with PD who were taking levodopa and had a latency of 90 minutes or longer each day before the onset of drug benefit (measured as time to “on”) showed that the mean improvements were similar in the etilevodopa/carbidopa and LC groups (reductions of 0.58 and 0.79 hours, respectively).

“Sudden offs”

The “sudden off” phenomenon is a more difficult problem to overcome. It is now clear that direct-acting dopamine agonists, slow-release levodopa, amantadine, and selegiline are ineffective. Subcutaneous injection of the dopamine agonist apomorphine is effective in turning the patient back “on” quickly (Hughes et al., 1993), as is an oral administration of dissolved Sinemet. To block nausea and vomiting by apomorphine, the peripheral dopamine receptor antagonist domperidone or trimethobenzamide needs to be taken in addition. Increasingly severe on-phase dyskinesias and postural instability mar the long-term therapeutic response of apomorphine in many patients.

Our approach is to use Rytary as the principal form of levodopa. Because “sudden offs” develop during the declining phase of plasma levodopa, Rytary has a better chance of maintaining the plasma level. If the clinician is not able to eliminate “sudden offs,” patients would be candidates for DBS or continuous infusion of subcutaneous apomorphine or intrajejunal levodopa.

“Random offs”

Often a “sudden off” appears unrelated to the timing of the last dose of levodopa, leading to the name “random off.” With careful plotting of these off periods, a pattern often can be seen, so these “random offs” might not be so random. These “random offs” are usually sudden in onset. The treatment strategy is the same as for “sudden offs.”

Dose failures (episodic failure to respond to each dose) (no “on”)

Failure of the patient to respond to each dose of levodopa is related to poor gastric emptying (Rivera-Calimlin et al., 1970; Fahn, 1977). A radionuclide gastric emptying study showed that PD patients had prolonged gastric emptying compared with the normal control subjects and that this was increased in fluctuating patients with dose failures compared with non-fluctuators (Djaldetti et al., 1996). The problem of dose failures can usually be overcome either by crushing a tablet of Sinemet by the patient’s teeth or by dissolving levodopa in liquid before ingesting it. For this situation, individual doses of Sinemet can be liquefied at the time it is needed. Levodopa dissolves readily in carbonated water because of the acidity of the water; the formation of bubbles that toss the Sinemet tablet around in the liquid also aids to quickly dissolving the tablet. When a dose failure occurs, the patient can take dissolved Sinemet and will usually respond in 10 to 15 minutes. Another approach is to use apomorphine injections (Ostergaard et al., 1995).

Response failures are probably more common than is usually recognized. In a survey of their patients, Melamed and colleagues (1986) found a number of patients with this difficulty. It is not clear whether the delayed gastric emptying is due to the levodopa therapy or whether the disorder develops because frequent dosing will statistically result in some tablets not passing through the stomach quickly enough to reach the small intestine where absorption takes place.

“Delayed on”

Melamed and colleagues (1986) reported that patients with fluctuations often also have a problem in getting an “on” with the first dose in the morning. These patients tend to have a longer delay with this dose than the non-fluctuator. The mechanism is not clear, but it might have to do with obtaining adequate plasma levels. We have noticed that many patients need a larger dose of levodopa as their first dose of the day to “kick-in” a response to the medication. Because the first dose is often accompanied by a higher plasma level of levodopa than later doses (Shoulson et al., 1975; Fahn, 1982), the problem might not be entirely pharmacokinetic. Rather, it is possible that the dopamine receptors are in a

low-affinity state and require more dopamine agonism to activate them. To treat the delayed “on” by obtaining a higher plasma level of levodopa sooner, the patient should dissolve Sinemet before swallowing or crush the tablet between their teeth before swallowing it with water.

“Super offs”

“Super offs” are a more severe “off” state than the standard “wearing off” or the “practically defined off,” which occurs at the beginning of the day before the first dose and about 12 hours after the patient’s last dose at bedtime the night before. Patients with pronounced tremor, for example, could have an even more severe tremor during a “super off.” The severity of the “super off” is more severe than if the patient were withdrawn from levodopa and let the natural parkinsonian state reappear. The “super off” state might represent a desensitized state of the dopamine receptor during that “super off” period. A demonstration of a “Super Off” is seen in [Video 1.32B](#) in [Chapter 1](#).

Weak response at end of day

Most patients eventually show some diurnal variation in their responsiveness to levodopa. Often, the patient reports doing best after the first morning dose and the response is less as the day wears on. An occasional patient will report the opposite, doing better at the end of the day. The mechanism for the poorer response at the end of the day might relate to decreased plasma levels of levodopa with each subsequent dose. But increasing the dose in the afternoons usually does not help. The patient might not get any improved response and could develop drowsiness or adverse mental effects instead. Nevertheless, one should try increasing the dosage of afternoon and evening levodopa. If this fails, it is worth adding slow-release levodopa, supplemental dopamine agonist, anticholinergics, or amantadine.

Response varies in relation to meals

Levodopa is absorbed only from the proximal small intestine; thus, absorption depends on passage of levodopa through the stomach to enter the small intestine. There are at least three variations of levodopa responsiveness in regard to meals. First, a full meal with delayed gastric emptying will result in a delayed and weaker response to levodopa that is ingested after or during the meal compared with taking levodopa about 20 minutes before the meal. Pharmacokinetic studies confirm that levodopa concentrations in plasma are delayed when the medication is taken in the fed state ([Contin et al., 1998b](#)). Second, patients who had normally taken levodopa with or after a meal will find that if they take it before a meal, the response is much greater and they might develop peak-dose dyskinesia. If either of these two variations is present, it can be corrected by accommodating the timing of dosages of levodopa according to the pathophysiology of the particular problem.

A third variation relates to high-protein meals. Competition with other amino acids in the diet can interfere with transport of levodopa across the intestinal mucosa and across the blood-brain barrier ([Muentert et al., 1972](#); [Nutt et al., 1984](#)). Only rarely does this competition with other

amino acids pose a serious problem for patients. Most accommodate to protein in their diet. In those rare individuals in whom any protein in any meal interferes with their response to levodopa, it is necessary to plan a meal strategy. Having nonprotein meals at breakfast and lunch, and making up for this lack by having higher protein meals at dinner, usually will be effective. If the patient goes “off” at night when he or she can best afford to be “off,” the patient can adjust to this situation.

Freezing

The freezing phenomenon ([Fahn, 1995](#)) is often listed as a type of fluctuation because the patient transiently has difficulty initiating movement. But this phenomenon probably should be considered distinct from the other types of fluctuations. Freezing takes many forms, and these have different names, such as start hesitation, target hesitation, turning hesitation, startle (fearfulness) hesitation, and sudden transient freezing. However, it is not clear whether any of these types has a different pathophysiologic mechanism. Of major importance is the need to distinguish between “off freezing” and “on freezing.” “Off freezing” is best explained as a feature of PD, and its treatment is to keep the patient from going “off.” “On freezing” remains an enigma, and this problem tends to be aggravated by increasing the dosage of levodopa. “On freezing” is not benefited by adding direct-acting dopamine agonists. Rather, it is lessened by reducing the dosage of levodopa. Both the “on” and “off” types of freezing appear to correlate with duration of illness and duration of levodopa therapy ([Giladi et al., 1992](#)). Although Narabayashi and colleagues (1986) reported benefit with l-threo-3,4-dihydroxyphenylserine (L-DOPS), supposedly a precursor of brain norepinephrine, Fahn (unpublished data) has not seen any benefit with this drug in the treatment of “on freezing.” Moreover, there is no evidence that this drug increases norepinephrine in rat brain or human cerebrospinal fluid ([Reches et al., 1984](#)).

Continuous intrajejunal infusion of levodopa/carbidopa intestinal gel

In January 2015 the FDA approved intrajejunal infusion of LC intestinal gel for the treatment of motor fluctuations in patients with advanced PD. This form of therapy had been approved in Europe a few years earlier. The FDA required a more rigorous double-blind study to show efficacy before approval could be given. The successful study required a double-dummy, double-blind design ([Olanow et al., 2014](#)). As discussed earlier, intravenous infusion of levodopa can be highly successful in treating motor fluctuations ([Shoulson et al., 1975](#); [Mouradian et al., 1990](#)) (see [Figs. 6.16, 6.19](#)).

Sage and colleagues (1989a,b) dissolved levodopa and provided it via a nasogastric tube directly into the stomach to treat patients with complex motor fluctuations. Others followed suit ([Bredberg et al., 1993](#); [Kurth et al., 1993b](#); [Nils-son et al., 1998](#)), and then Nyholm and colleagues (2005) delivered a gel form of concentrated levodopa into the duodenum via a percutaneous catheter through the abdominal wall into the stomach and threaded from there into the duodenum. This formulation of levodopa gel was marketed in Europe with the trade name of DuoDopa (Duopa in the

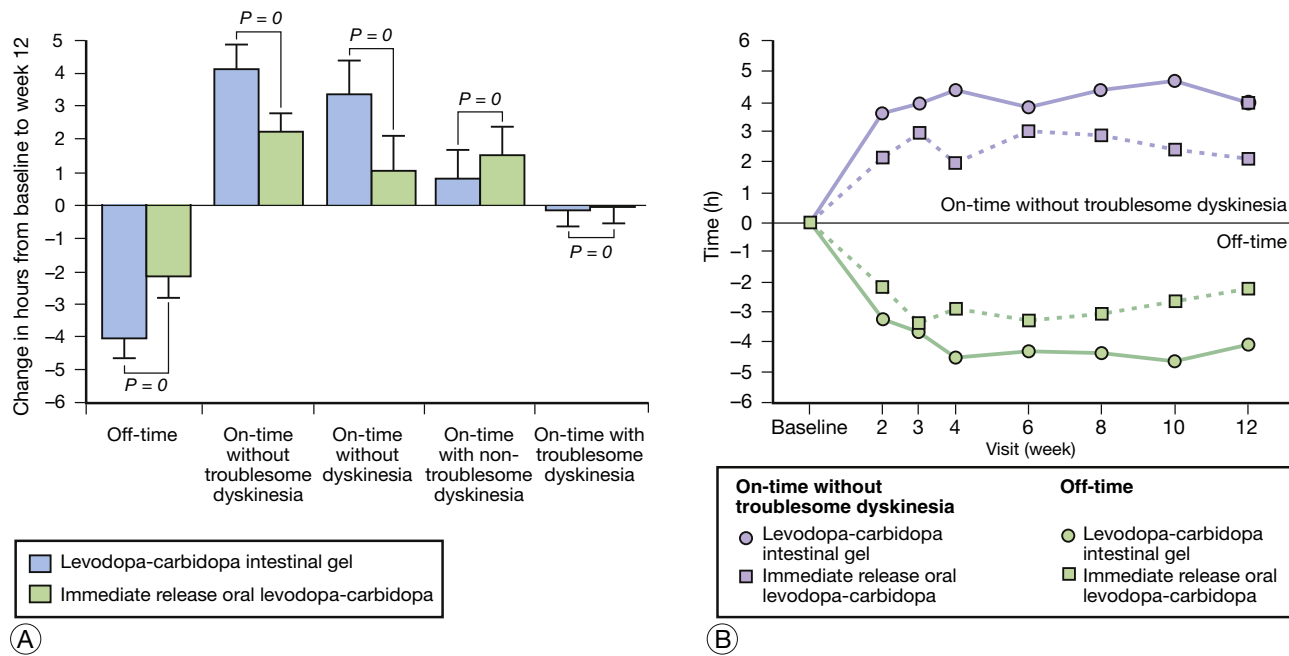


Fig. 6.24 Treatment results from the randomised, controlled, double-blind, double-dummy study of intrajeunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease. Efficacy results are based on home diaries of fluctuations. (Olanow, C.W., Kieburtz, K., Odin, P., et al., 2014. LCIG Horizon Study Group. Continuous intrajeunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study. *Lancet Neurology* 13(2):141-9.)

United States). Long-term treatment of intrajeunal infusion reported marked reduction of motor fluctuations (e.g., Nyholm et al, 2012; Zibetti et al., 2013). A variety of complications can occur at the site of the percutaneous placement of the intestinal tube. Serious gastrointestinal side effects can also develop but are rare. In one observational study of 52 patients with intestinal infusion of levodopa gel, there were 7 with ileus, colon perforation, pneumoperitoneum, gastropleural fistula, perforating ulcer, or intestinal bleeding out of a cumulative treatment period of 110 years (Klostermann et al., 2012). Safety data from four prospective studies were combined and analyzed. With 963 total patient-years of exposure, procedure/device adverse events occurred in 300 patients (76%) and serious adverse events occurred in 68 (17%) (Lang et al., 2016).

The double-dummy, double-blind trial compared continuous intrajeunal infusion of LC gel with oral Sinemet therapy. The infusion of levodopa was effective in reducing "off" time and extending "on" time without troublesome dyskinesias (Olanow et al., 2014) (Fig. 6.24). This type of treatment should be considered along with DBS and subcutaneous infusion of apomorphine for patients with troublesome motor fluctuations that do not respond to adequate medical treatment. An evaluation of 159 patients who underwent intrajeunal infusion of levodopa in 17 Italian centers, there was significant reduction of motor complications as well as improvement in the motor symptoms of PD (Antonini et al., 2020).

Treatment of dyskinesias associated with levodopa therapy

Peak dose dyskinesias

Choreic movements can occur early in the treatment with levodopa, but the incidence of these involuntary movements

increases with continuing treatment (Duvoisin, 1974a). Chorea is more common than dystonia as the type of peak-dose dyskinesia, particularly in the early stages of levodopa therapy, but with continuing treatment, individual patients can develop more dystonia and less chorea (Fahn, 2000). Many patients probably end up having a combination of chorea and dystonia. Dystonia is a more serious problem than chorea because dystonia is usually more disabling. In fact, mild chorea is not noticed as much by the patient as by the family.

Overall, except for young-onset PD, dyskinesias are troublesome in only about 40% of patients, and only about 10% cannot be managed by medication adjustments (Van Gerpen et al., 2006). Peak-dose dyskinesia is due to a dose of levodopa that is too high and is representative of an over-dosed state. The plasma levels of levodopa are high (Muentert et al., 1977), and there is presumably excess striatal dopamine. Reducing the individual dose can resolve this problem. The patient might need to take more frequent doses at this lower amount because reducing the amount of an individual dose also reduces the duration of benefit (Nutt et al., 1985). It was once thought that chorea appears only in the presence of supersensitive dopamine receptors, but if the dosage of levodopa were high enough, chorea could occur in normal individuals, as has been demonstrated in normal monkeys (Sassin et al., 1972).

Another method to reduce peak-dose dyskinesia is to substitute higher doses of a dopamine agonist while lowering the dose of Sinemet. Dopamine agonists are less likely to cause dyskinesias, and therefore can usually be used in this situation quite safely. If lowering the dose of Sinemet results in more severe "off" states, the agonists become more important and need to be increased. Sinemet CR can help some patients by keeping the peak plasma levels of levodopa at a lower level. However, there is also the danger of increased

dyskinesias at the end of the day as the blood levels become sustained from frequent dosing. Once dyskinesias appear with Sinemet CR or Rytary, they last for a considerable duration of time because of the slow decay in the plasma levels. In some patients, peak-dose chorea and dystonia occur at subtherapeutic doses of Sinemet, and lowering the dosage will render a patient even more parkinsonian. Use smaller and more frequent doses, coupled with dopamine agonists or other antiparkinsonian drugs, such as amantadine.

Amantadine is the drug with the ability to most likely reduce levodopa-induced dyskinesias (Rajput et al., 1997; Metman et al., 1998a, 1999; Luginer et al., 2000; Snow et al., 2000; Thomas et al., 2004; Sawada et al., 2010; Ory-Magne et al., 2014; Pahwa et al., 2015). It is thought that amantadine's antidyskinetic effect is through its antiglutamatergic action. Its antidyskinetic effect is dose dependent, and patients often require at least 400 mg/day. Start with 100 mg twice daily and increase stepwise to 200 mg twice daily as needed. Unfortunately, the antidyskinetic benefit from amantadine may last only a few months (Thomas et al., 2004). An extended-release formulation of amantadine has been approved by the FDA to treat levodopa-induced dyskinesias based on clinical trials showing its efficacy (Pahwa et al., 2017). This compound is given at bedtime in an attempt to reduce adverse effects that would occur during the phase of highest blood levels. Other antiglutamatergic agents reported to reduce levodopa-induced dyskinesias are dextromethorphan (Metman et al., 1998b), dextrorphan (Metman et al., 1998c), and riluzole (Merims et al., 1999).

Another possible approach is to use clozapine, the atypical neuroleptic that does not aggravate PD. Clozapine can suppress dopa-induced dyskinesias while simultaneously increasing "on" time without dyskinesias (Bennett et al., 1993, 1994; Durif et al., 1997, 2004; Pierelli et al., 1998). Adverse effects consist of sedation, sialorrhea, and orthostatic hypotension. Clozapine also can reduce dyskinesias from apomorphine (Durif et al., 1997). Olanzapine has greater dopamine D2 receptor antagonism and usually worsens parkinsonism.

Increasing serotonin activity in the SN could induce or worsen parkinsonism, as is sometimes seen with fluoxetine treatment. A trial of fluoxetine, a selective serotonin uptake inhibitor, was shown to reduce dyskinesias induced by apomorphine treatment (Durif et al., 1995), suggesting that it be considered for levodopa-induced dyskinesias. The serotonin agonist sarizotan was developed for its possible use (Barajimenez et al., 2005) as an antidyskinesia agent; but a phase III trial was unsuccessful (Goetz et al., 2007). Propranolol is another drug that has been reported to reduce dyskinesias (Carpentier et al., 1996). Buspirone appears to be somewhat effective in reducing the severity of dyskinesias (Bonifati et al., 1994), but because buspirone has resulted in aggravating tardive dyskinesia (LeWitt et al., 1993), it might have some dopamine receptor-blocking activity. Mirtazapine is an antidepressant with a novel pharmacologic profile (alpha-2 antagonist, 5HT-1A agonist, and 5HT-2, antagonist). It was tested in a small open-label trial and found to have a modest effect in reducing dopa-induced dyskinesias (Meco et al., 2004). Although opioid antagonists have been found to reduce dopa-induced dyskinesias in parkinsonian monkeys (Henry et al., 2001), high-dose naltrexone was not effective in humans (Manson et al., 2001). Other medications such as

cannabis (Carroll et al., 2004), low-dose quetiapine (Katzenschlager et al., 2004), and gabapentin (van Blercom et al., 2004) were not found to be effective.

Diphasic dyskinesias

Diphasic dyskinesias were first described by Muentner and colleagues (1977), who labeled them the D-I-D phenomenon, for dystonia-improvement-dystonia. Although most of the affected individuals have dystonia as their pattern of dyskinesia, some have choreic movements, and others have a mixture of the two types. Diphasic dyskinesia is a situation in which the dyskinesia develops as the plasma levels of levodopa are rising or falling, but not during the peak plasma level (see Fig. 6.14) (Muentner et al., 1977; Lhermitte et al., 1978; Agid et al., 1979). Clinically, the involuntary movements predominantly involve the legs (Marsden et al., 1982; Luquin et al., 1992).

This phenomenon is difficult to explain. It is possible that there is a differential sensitivity of at least two dopamine receptors. The more sensitive one would respond to lower levels of levodopa to induce the dyskinetic state. The other receptor would be activated at higher levels and inhibit the dyskinesia. Treatment of the problem is difficult. Although Lhermitte and colleagues (1978) proposed treating this condition with higher doses of levodopa, Fahn's experience (unpublished data) is that higher dosages merely induce peak-dose dyskinesia and possibly other forms of central adverse effects. On the other hand, lowering the dosage is equally unsatisfactory because increasing parkinsonism ensues. The most effective approach is to use a dopamine agonist, with its longer duration of action, as the major therapeutic agent, and levodopa as the supplementary drug. The end-of-dose dyskinesia when it appears at the end of the day at a time when no further levodopa is to be taken, is particularly troublesome for the patients who have diphasic dyskinesias. Attempts to allow the dopamine receptor to remain activated by adding dopamine agonists with the last dose of levodopa has not been helpful. Most patients are at home at the time of the last dose of the day, and they bear with the dyskinesias as the anti-PD effect of the last dose fades. Finally, when the dyskinesia is over, the patient becomes comfortable again.

"Off" dystonia and "off" painful cramps

Dystonic spasms are not always a sign of levodopa over-dosage and can also occur during an "off" state. This is particularly true in many instances of painful sustained contractions. Painful dystonic cramps most often occur when the plasma level of levodopa is low, particularly in the early morning (Melamed, 1979). A survey of 383 patients with PD revealed that 16% had experienced early morning dystonia (Currie et al., 1998). But this type of dystonia can occur at any time the patient goes "off" (Ilson et al., 1984), and early morning dystonia is a form of "off" dystonia, albeit the most common form. In this sense, "off" dystonia is a pharmacokinetic problem, and it has been correlated with low plasma levels of levodopa after an intravenous infusion was discontinued (Bravi et al., 1993). But why painful dystonic spasms should occur in addition to or instead of classic parkinsonian signs during low plasma levels of levodopa

is not clear. This phenomenon may relate to some peculiarity of the dopamine receptors and the low plasma levels of levodopa in these patients. [de Yebenes \(1988\)](#) has proposed that dystonia may occur when the ratio of norepinephrine/dopamine is high. However, there are only speculations about the pathophysiology of dystonia in general, and it is difficult to be certain of the explanation of either peak-dose dystonia or “off” dystonia, such as early-morning dystonia. Preventing “offs” is the best way to control “off” dystonia. Rytary or Sinemet CR appears to be helpful for a number of patients with early-morning dystonia ([Pahwa et al., 1993](#)). One solution is to take a dose of Rytary at bedtime. Another useful solution is for the patient to take a dose of Sinemet in the middle of the night when awakened with the need to urinate.

One should not forget that dystonia can also occur as a feature of PD. However, “off” dystonia does not appear to be merely a reflection of the dystonia of parkinsonism. If patients with “off” dystonia are given a drug holiday from levodopa, the painful dystonia will disappear after a few days, and the patient will be left with a baseline parkinsonian state and without painful dystonia (unpublished observations). The dystonic features of PD are difficult to treat.

Combination of fluctuations and dyskinesias; yo-yo-ing

Many patients with advanced PD have both clinical fluctuations (wearing-off or “on–off”) and dyskinesias (usually peak dose and sometimes end of dose). Most patients are more troubled by the “off” states in which they are fully or partially immobile than they are by dyskinesias ([Hattori et al., 2012](#)). In other words, they prefer having the dyskinesias rather than to be unable to move freely. As a result of their discomfort with the “off” states, patients tend to overdose themselves, resulting in the alternating “offs” and dyskinesias. An extreme form of this combination is “yo-yo-ing.” The term comes from the repetitive ups and downs of a yo-yo and refers to a condition in which there is little time during the day of an optimally good “on” in which the patient has neither dyskinesia nor “offs.” Moreover, in yo-yo-ing the patient usually responds to a dose of levodopa almost immediately with a peak-dose dyskinesia, followed by a predictable wearing off, with little optimum time in between these two states ([Fahn, 1982](#)).

Sudden “offs” and dose failures can further complicate the clinical situation of patients with advanced PD who have combinations of “offs” and dyskinesias (whether with good periods in between or as a yo-yo). Overcoming these highly variable clinical periods is challenging. It is a matter of attempting to smoothly activate the striatal dopamine receptors throughout the entire day. The dopamine receptors are obviously intact, but they are supersensitive to allow the dyskinesias. Hence, there appears to be a pharmacodynamic factor to account for the dyskinesias. At the same time the short plasma half-life and the need for constant bioavailability of levodopa in the plasma account for the “off” states. Thus, the “offs” are the result of a pharmacokinetic factor. Therefore, this condition should be considered a combined pharmacokinetic and pharmacodynamic problem. Treatment is virtually impossible with tablets of standard Sinemet and is even worse with Sinemet CR. The CR form has an unreliable pharmacokinetic profile.

For patients who have both “offs” and dyskinesias, Sinemet CR tends to increase and prolong the dyskinesias; in some patients the dyskinesias may be so severe that the patients have to be put to sleep to “ride them out.”

Using medications with a longer biologic half-life than levodopa is a preferred method to smooth out the clinical fluctuating state. There has been partial success using direct-acting dopamine agonists as the sole or dominant form of pharmacotherapy, with carbidopa/levodopa used sparingly. Unfortunately, the side-effect profile of dopamine agonists make these agents problematic. In some patients, particularly those with yo-yo-ing, plain levodopa (without carbidopa) may be the preferred supplement instead of carbidopa/levodopa. The presence of carbidopa augments the potency of levodopa, so it is difficult to titrate patients for smaller dose responses in the presence of carbidopa.

Another, though more cumbersome, approach to smoothly activate the dopamine receptors without severe extremes of peaks and valleys is to place the patient on sips of small doses of liquefied Sinemet throughout the day ([Metman et al., 1994](#)). Liquefied Sinemet is not stable at room temperature unless in an acidified solution. In the absence of ascorbic acid, the concentration of levodopa in water declines significantly by 48 hours ([Pappert et al., 1996a](#)). Ascorbate prolongs stability to 72 hours. Refrigeration and freezing prevents a significant decline in concentration for the full 7 days. In place of ascorbic acid, carbonated water can be used, which is easier for many patients.

To prepare liquefied Sinemet, a simple method is to dissolve 4 tablets of 25/250-mg tablets in a liter of acidified solution (dietetic soda, seltzer or other carbonated water, or ascorbic acid solution), providing a concentration of levodopa of 1 mg/mL. Prepare it fresh daily and store the liquid in a dark environment to prevent oxidation of levodopa. It can be placed in the refrigerator. Then measure out the number of milliliters needed for a dose, which is equivalent to the mg of the dose. Liquefied Sinemet has been found to improve the amount of “on” time ([Kurth et al., 1993a](#); [Pappert et al., 1996b](#)). In one double-blind trial comparing the liquid formulation versus standard tablets, no significant advantage of the liquid formulation over tablet therapy was found ([Metman et al., 1994](#)), but in another double-blind trial there was an advantage of the liquid preparation and without increasing dyskinesias ([Pappert et al., 1996b](#)). The liquid formulation can more quickly resolve “off” states and also facilitate small dose adjustments that are not possible with tablets. It seems particularly valuable for patients who have both fluctuations and dyskinesias.

A surgical approach is the infusion of levodopa/carbidopa gel (Duopa) via an the insertion of the delivery tube percutaneously through the stomach and inserted to rest within the jejunum ([Nyholm et al., 2005](#); [Antonini et al., 2007, 2008](#); [Nyholm et al., 2012](#); [Zibetti et al., 2013](#); [Olanow et al., 2014](#)). Intrajejunal infusion is more effective for treating motor fluctuations than for dyskinesias. There is concern that patients with both fluctuations and dyskinesias may have improvement of the former but at the cost of more dyskinesias. In a post hoc analysis of both double-blind and open label data sets evaluating intestinal gel infusion of levodopa, there was no major change in the amount or severity of dyskinesias in those patients who had them when entering the studies ([Antonini et al., 2016](#)).

Subcutaneous infusions of apomorphine (Colzi et al., 1998) is being used in Europe, and apomorphine infusion is being evaluated in the United States. In Europe long term follow-up shows subcutaneous apomorphine infusion to be both efficacious and safe (Katzenschlager et al., 2021).

Myoclonus

The lightning-like jerks of myoclonus can occur in untreated PD, but these are rarely disabling and are hardly commented on by patients. Klawans and colleagues (1975) described myoclonus as occurring as a complication of long-term levodopa therapy. They reported the movements as occurring as single unilateral or bilateral jerks in the extremities, most frequently during sleep. They found the serotonin antagonist methysergide helpful in controlling these. Such nocturnal myoclonus is infrequently encountered in our experience and is rarely disabling. Myoclonus occurs during the day as well. Its presence is usually ominous, indicating the presence of cognitive complications from levodopa and often representing either toxicity to levodopa in PD or some other form of parkinsonism, such as diffuse Lewy body disease (Crystal et al., 1990). Myoclonus is perhaps more common as a toxic side effect from amantadine, particularly in patients with some cognitive impairment. By withdrawing amantadine, myoclonus is eliminated in these patients.

Other motor complications

Simultaneous somatotopically specific dyskinesias and parkinsonism

Some patients have different responses to levodopa therapy in different parts of the body. For example, the head and neck regions might be more sensitive to levodopa than the legs. When the upper part of the body responds in this situation, the legs might remain parkinsonian and the patient may not be able to walk well. In this example, on higher dosages of levodopa, the legs improve, but the head and neck regions become dyskinetic. This problem might be due to different sensitivities of the striatal dopamine receptors on a somatotopic basis. That is, in the case described, the head and neck areas of the striatum would have more sensitive receptors than does the leg area. This problem is difficult to treat, and one can only titrate the dosage to the optimum response between the two extremes for each individual patient.

Loss of efficacy over time

A debated point in the treatment of parkinsonism is the cause of declining efficacy from continuing treatment with levodopa in many patients (Yahr, 1976). If the postsynaptic dopamine receptors in the striatum are not lost in this disease, why should a patient get less response from medication over time? Progression of the illness with further loss of dopamine storage sites in the presynaptic terminals is the most invoked explanation. However, loss of these structures does not automatically produce a loss of response to levodopa. For example, postencephalitic parkinsonism, with its much greater loss of dopamine in the striatum (Ehringer and Hornykiewicz, 1960; Bernheimer et al., 1973), has more, not less, sensitivity to levodopa (Calne et al., 1969; Duvoisin et al., 1972). This observation is sufficient to argue against

the concept that reduction in storage sites for dopamine is responsible for the declining efficacy of levodopa. Perhaps increasing PD is associated with loss of striatal dopamine receptors as well as the presynaptic dopaminergic neuron. Such pathology would be compatible with the rogue alpha-synuclein theory discussed in Chapter 5.

There may be additional factors contributing in part to the loss of efficacy that is seen with continuous treatment with levodopa. Some decline may arise in part from gradual downregulation of striatal dopamine receptors (Rinne et al., 1980). Not all patients develop this problem, even if it is due to the receptors being constantly exposed to high levels of dopamine. Evidence to support this concept comes from the studies of drug holidays from levodopa. After levodopa is eliminated for a short period, restoration of levodopa therapy usually provides enhanced temporary benefit (Direnfeld et al., 1980; Barrett, et al., 1980). Unfortunately, this enhanced sensitivity is short-lived, and the potential risks for aspiration during the drug holiday render this approach undesirable for the short-term benefit that can be obtained.

It is important to differentiate between loss of response despite a seemingly adequate dosage of medications and insufficient response resulting from too low a dose because of inability to tolerate adequate dosages. Secondary loss of response implies (1) a parkinsonism-plus syndrome instead of PD, (2) the development of nondopaminergic motor symptoms (flexed posture, freezing, loss of postural reflexes), (3) development of intractable bradykinesia with disease progression that had previously responded to treatment, or (4) end-stage PD. Treatment of end-stage PD requires adjusting the dosages of all medications, both up and down to find the optimum level for each.

Increased parkinsonism

A few patients on high-dosage levodopa may become more parkinsonian. This was initially reported unaccompanied by any other features of levodopa toxicity (Fahn and Barrett, 1979). This phenomenon also has been seen accompanied by confusion (Sage and Duvoisin, 1986). In both situations, improvement occurs when the dosage of levodopa is reduced. In fact, the phenomenon of increased parkinsonism without other signs of toxicity probably occurs more often than is recognized. Many physicians, unaware of this complication, are inclined to increase the dosage of antiparkinsonian medication, which does not help. Rather, a reduction of dosage should be tried first to see whether symptoms improve. This problem would appear to be related to reduced receptor sensitivity by high dosages of dopamine present in the striatum.

Increased tachyphemia and increased running gait

Some patients who are overdosed with levodopa will speak faster, running syllables together, so that it is difficult for the listener to understand what the patient is saying. At the same time as the speech is rapid (tachyphemia), the amplitude is lower so the voice is softer, aggravating the situation. If the patient purposely tries to enunciate each syllable distinctly, he or she is able to do so for a few words, but then the tachyphemia takes over again. Singing can be carried out without the tachyphemia. With speech therapy, sometimes using a

metronome for pacing, a patient can improve the pattern of speaking, but only during the treatment session. There seems to be little carry-over. Associated with tachyphemia are rapid voluntary movements (tachykinisia) in other parts of the body, displayed as such when the patient is asked to perform rapid successive movements. These are usually very fast and of small amplitude, that is, a combination of tachykinisia and hypokinesia.

This type of tachykinetic problem can also involve walking. Usually the patient moves more rapidly but with smaller steps. Gait in this instance can be mistaken for festination, which it resembles. If postural instability is impaired, such a running gait can lead to falling. Often, lowering the dosage of levodopa will allow the patient to slow down, with a resulting clarity of speech and gait. However, parkinsonian bradykinisia can become more of a problem.

Falling because of loss of postural reflexes

Falling is a common feature of PD as the illness progresses and there is increasing loss of postural reflexes. Because this particular cardinal sign of PD benefits little by levodopa therapy (Klawans, 1986), this problem persists and worsens despite pharmacotherapy (Agid et al., 1990). Because levodopa may allow the patient to be more mobile, such as allowing the patient to arise more easily from a chair and walk independently, the persistence of postural instability becomes a particular problem because it raises the hazard of increased likelihood of falling. Thus, this complication of levodopa therapy in this particular subpopulation of patients with PD is technically not a true adverse effect of the medication but rather a complication of the improvement in mobility in a patient who is at risk for falling, thereby increasing that risk. In this situation, the patient should use physical assistance, such as a walker. An alternative approach is to keep the patient sufficiently parkinsonian that he or she cannot arise without assistance.

Intractable tremor

Perhaps as many as 30% of patients with parkinsonian rest tremors fail to respond to levodopa therapy and other

antiparkinson medications. Sometimes, such persistent tremor will respond to clozapine (Friedman and Lannon, 1990; Jansen, 1994). If it is unresponsive to any medications, it can still respond to DBS of the subthalamic nucleus or the Vim nucleus of the thalamus.

Treatment of PD during surgery or prolonged conditions of oral unavailability

Levodopa is absorbed via the proximal small intestine. During periods when the patient is unable to swallow or allowed oral intake, such as during surgery, a method is needed to keep the patient's parkinsonism from being too severe. Most surgical procedures require only a short period of time for the patient to be without oral liquids or foods, and most patients can suspend taking their medications when liquids are not allowed for these periods without major difficulty. During anesthesia, parkinsonism is not a problem, so even a prolonged operation will not present a problem. It is post-operatively, if the patient is not allowed oral liquids, such as from gastric surgery, that a problem could arise. The resulting rigidity, akinesia, decreased gastrointestinal motility, and respiratory function are dangerous and could complicate the recovery process. In this situation, there are several approaches: providing Parcopa or its generic oral disintegrating tablet equivalents to dissolve in the mouth and be swallowed automatically with the saliva, rotigotine dermal patches, sublingual and subcutaneous injections of apomorphine with rectal domperidone (Galvez; Jimenez and Lang, 1996) and inhalable (LeWitt et al., 2016).

Nonmotor features of PD

A discussion of nonmotor features of PD, including the development of nonmotor side effects from treatment of PD, is covered in Chapter 8.

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Surgical treatment of Parkinson disease and other movement disorders

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Introduction

A variety of surgical treatments for Parkinson's disease (PD), including ablation or deafferentation of motor and premotor cortex, cervical cordotomy, and mesencephalic pedunculotomy, were performed in the first five decades of the twentieth century (Meyers, 1968). These procedures generally yielded relief of the movement disorder at the expense of concomitant weakness and other complications. Surgery at the level of the basal ganglia for PD was pioneered by Meyers in 1939 (Meyers, 1968). These open procedures included removal of the head of the caudate and section of the anterior limb of the internal capsule and pallidofugal pathways. After Spiegel and Wycis introduced the principles of stereotactic surgery in clinical practice in 1947, this method was applied for lesioning the pallidum and ansa lenticularis in an attempt to treat the symptoms of PD and other movement disorders (Mundinger and Reichert, 1963; Hassler et al., 1979; Grossman and Hamilton, 1991). Stereotactic thalamotomy for parkinsonian symptoms was introduced by Hassler and Reichert in 1951 (Hassler et al., 1979). Thalamotomies gradually replaced pallidotomies in the late 1950s and early 1960s (Table 7.1) because thalamotomies were thought to produce more sustained control of tremor. The introduction of levodopa in the late 1960s resulted in marked reduction in the number of functional stereotactic procedures, and only a few specialized centers continued to perform such operations.

The renewed interest in surgical treatment of movement disorders has been stimulated in part by improved understanding of the functional anatomy underlying motor control and refinement of methods and techniques in neurosurgery, neurophysiology, and neuroimaging (Krauss et al., 1998; Gross et al., 1999a; Lang, 2000b; Mazziotta, 2000;

Jankovic, 2001; Krauss, et al., 2001; Walter and Vitek, 2004; Miocinovic et al., 2013). Furthermore, important strides have been made in assessments of the outcomes of surgery and in providing useful guidelines for inclusion-exclusion criteria (Defer et al., 1999; Tan and Jankovic, 2000, 2013). As a result of increased awareness about surgical options for patients with PD, the attitudes of clinicians toward referring patients for surgery have been changing, and in one survey, 99.4% of neurologists were aware of surgery for PD (Mathew et al., 1999). In one study involving a total of 165 referrals, 84% had disorders for which deep brain stimulation (DBS) was indicated and 51% were considered good candidates (Katz et al., 2011). Furthermore, there is growing appreciation for the importance of holding surgical trials to as stringent evidentiary standards as other clinical studies and the notion of double-blind design, including "sham" operations is increasingly accepted (Prehn et al., 2006; Galpern et al., 2012). Although this review focuses primarily on surgical treatment of PD, there is growing interest in the application of surgical intervention in the treatment of a variety of movement disorders (Pollak, 1999; Krauss et al., 2001). Although the interest in surgical treatment of movement disorders is growing, there is a remarkable paucity of well-designed, randomized trials (Stowe et al., 2003).

Functional anatomy of the basal ganglia

Before discussing the indications for and the results of surgery for PD, it is helpful to review the current concepts about the functional anatomy of the basal ganglia (Figs. 7.1 and 7.2). The basal ganglia (extrapyramidal system) include the striatum, globus pallidus, substantia nigra (SN), and subthalamic nucleus (STN) (Hameleers et al., 2006; Benarroch, 2008),

Table 7.1 History of lesion therapy for Parkinson's disease and movement disorders

Investigator	Year	Therapy
Horsley	1909	Excised motor cortex for treatment of athetosis
Bucy	1939	Excised cortex for PD tremor
Bucy	1950	Lesioned caudate and globus pallidus
Klemme	1940	Resected portions of the pyramidal system
Meyers	1942	Removed globus pallidus and sectioned efferent fibers
Spiegel and Wycis	1946–1947	Introduced stereotaxic surgery on the ansa lenticularis
Putnam	1948	Incised pyramidal tract in upper cervical cord
Browder	1948	Section anterior internal capsule, pallidum, putamen
		Rigidity and tremor improved; paralysis was partial
Browder	1950	Sectioned cervical cord, no change in rigidity or tremor
Walker	1952	Section cerebral peduncles, tremor affected by paralysis
Fenelon and Thiebaut	1950	Coagulation of the ansa lenticularis
Guiot and Brion	1952	Coagulation of the efferent fibers of pallidum (leucotomy)
Cooper	1953	Ligation of the anterior choroidal artery
Hassler, Reichert	1955	Performed some of the first thalamotomies
Cooper	1954	Chemopallidectomy and chemothalamectomy (alcohol)
Cotzias	1967	Introduction of levodopa slowing development of surgical procedures
Narabayashi	1973	Microelectrode recordings for thalamotomy
Laitinen	1992	Reintroduction of pallidotomy
Gill, Alvarez	1997–2001	Introduction of subthalamotomy for PD

and thalamus (Parent and Cichetti, 1998; Hamani et al., 2004). The caudate and putamen are contiguous and comprise the striatum, and the putamen and globus pallidus are referred to as the lenticular nucleus. The cortical input from the prefrontal supplementary motor area, amygdala, and hippocampus is excitatory, mediated by glutamate. Neurons in the SN pars compacta (SNc) provide major dopaminergic input to the striatum. The interaction between the afferent

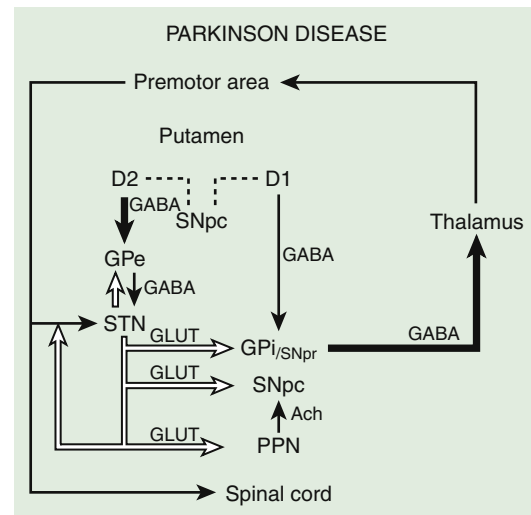


Fig. 7.1 Basal ganglia circuitry relevant to PD. ACh, acetyl choline; DA, dopamine; D1, D2, dopamine receptors; GABA, gamma-aminobutyric acid; GLUT, glutamate; GPe, globus pallidus externa; GPi, globus pallidus interna; PPN, pedunculopontine nucleus; STN, subthalamic nucleus; SN, substantia nigra pars compacta (pc) and pars reticularis (pr).

and efferent pathways is mediated by striatal interneurons that use acetylcholine as the main neurotransmitter. The SN is a melanin-containing (pigmented) nucleus in the ventral midbrain, and it consists of dopaminergic neurons. The striatal output system is mediated by the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). However, the basal ganglia appear to be more complex than is indicated by the current models (Parent and Cichetti, 1998; DeLong and Wichmann, 2007). For example, it is now well recognized that the STN provides powerful excitatory projection not only to the globus pallidus interna (GPi), but also to the striatum and globus pallidus externa (GPe) and, in turn, receives input from the cerebral cortex, SNc, and various brainstem and thalamic nuclei. Although most reports emphasize the pallidal-thalamic projection, major output from the GPi is to the brainstem nuclei, such as the pedunculopontine nucleus (PPN) (Mena-Segovia et al., 2004; Jenkinson et al., 2006; Kenney et al., 2007a; Kuo et al., 2008; Zrinzo et al., 2008; Jenkinson et al., 2009; Ferraye et al., 2010; Moro et al., 2010; Alam et al., 2011; Fournier-Gosselin et al., 2013). Some studies have also drawn attention to the role of the PPN in gait and locomotion because PD patients have a markedly reduced number of cholinergic PPN neurons (Rinne et al., 2008).

The reemergence of surgical treatment of PD, particularly pallidotomy and STN/GPi DBS (see later), has been fueled in part by improved understanding of basal ganglia circuitry, including the recognition that the STN and the GPi are overactive in experimental and human parkinsonism (Bergman et al., 1990; Limousin et al., 1995). Microelectrode-guided single-cell recordings in patients with PD showed that the average firing rate in the GPi was 91 ± 52 Hz and that in the GPe was 60 ± 21 Hz (Magnin et al., 2000). In addition, rhythmic, low-threshold calcium spike bursts are often recorded in the pallidum and medial thalamus; some but not all are synchronous (in phase) with the typical rest tremor. It has been postulated that the low-threshold calcium spike bursts contribute to rigidity and dystonia by activating the supplementary motor

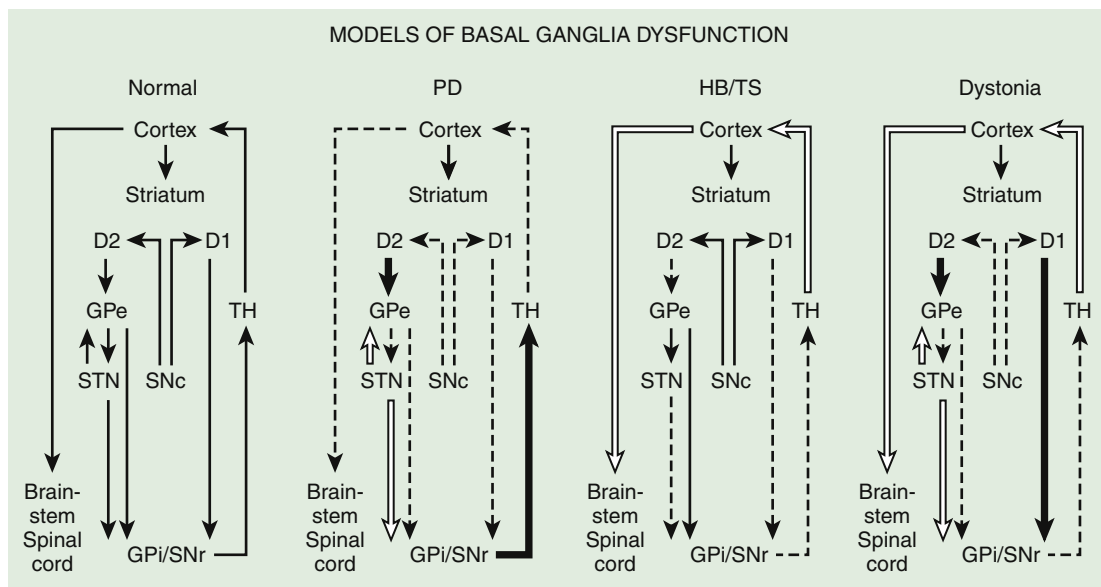


Fig. 7.2 Hypothetical models of basal ganglia dysfunction in PD, hemiballism (HB)/Tourette syndrome (TS), and dystonia. GPe, Globus pallidus externa; GPi, globus pallidus interna; SNr, substantia nigra pars reticularis; SNc, substantia nigra pars compacta; STN, subthalamic nucleus; TH, thalamus.

area. Apomorphine, a dopamine agonist, has been found to suppress the abnormal hyperactivity of the GPi and STN and to enhance the activity of the GPe on the basis of cellular recordings during surgery (Lozano et al., 2000). However, marked or complete suppression of GPi activity is associated with an emergence of dyskinesias. Indeed, levodopa- or dopamine-induced dyskinesias are associated with decreased firing frequency of the GPi neurons and a modification in the firing pattern (Boraud et al., 2001). This suggests that dopaminergic drugs and pallidotomy improve parkinsonian symptoms through a similar mechanism. Single-cell recording of the STN in patients with PD showed characteristic somatotopic organization, with neurons responding to sensorimotor stimuli localized chiefly in the dorsolateral region, and were of the irregular or tonic type (Rodriguez-Oroz et al., 2001). These two groups of neurons represent 60.5% and 24% of all STN neurons, respectively; only 15.5% of the STN neurons are oscillatory. Oscillatory activity in the basal ganglia is attracting increasingly more attention on the basis of various surgery-related neurophysiologic studies (Dostrovsky and Bergman, 2004). Microinjection of 10 to 23 μ L of lidocaine into the STN of three patients with PD produced “striking improvements in bradykinesia, limb tremor and rigidity” in all (Levy et al., 2001). Furthermore, microinjections of 5 to 10 μ L of muscimol, a GABA_A receptor agonist, in the region of the STN that showed oscillatory activity resulted in suppression of contralateral tremor in two patients. Simultaneous micro-electrode recordings showed suppression of neuronal activity in the near vicinity (up to 1.3 mm) of the injection. In a study designed to explore the effects of GPi on the STN, Sterio and colleagues (2002) showed that GPi stimulation markedly reduced the firing rate of dorsal STN cells in the ventral STN (and SN pars reticulata). In addition to providing support for STN segregation, this suggests that there is a feedforward GPi–STN interaction that needs to be incorporated in revised models of functional anatomy of the basal ganglia.

Neurophysiologic studies at the time of the implantation of stimulating electrodes or during chronic stimulation have

provided insights into the pathophysiology of movement disorders and how DBS alleviates the involuntary muscle contractions. The oscillatory nature of human basal ganglia activity in relation to movement has been reviewed (Brown et al., 2004; Afshar et al., 2013; Tan et al., 2013). Using combined magnetoencephalographic and subthalamic local field potential (LFP) recordings in 13 patients with PD at rest, Litvak et al (2011) found a temporoparietal-brainstem network coherent with the STN in the alpha (7–13 Hz) band and a predominantly frontal network coherent in the beta (15–35 Hz) band. They found that “dopaminergic medication modulated the resting beta network, by increasing beta coherence between the subthalamic region and prefrontal cortex.” Furthermore, power in the beta band (15–30 Hz) has been found to correlate with degree of bradykinesia and rigidity and theta activity has correlated with essential tremor (Priori et al., 2012). In another study, Kahan and associates (2014) showed that STN DBS modulates all the major components of the motor cortico-striato-thalamo-cortical loop and effects connectivity in resting state functional magnetic resonance imaging (fMRI). Other studies have found that increased levels of 13- to 25-Hz activity in the STN are associated with decreased grip force, similar to bradykinesia. Based on a study of 15 patients with primary dystonia treated with bilateral pallidal stimulation, modulation of oscillatory LFPs were recorded from pallidal electrodes and were correlated with surface electromyography (EMG) of the affected muscles (Liu et al., 2008). Dystonic movements were associated with increased theta, alpha, and low beta activity and the strength of the contraction correlated with an increase in frequency range of 3 to 20 Hz; the increase preceded the spasms by about 320 msec. There was a significant decrease in LFP synchronization at 8 to 20 Hz during sensory modulation, but voluntary movement increased gamma band activity (30–90 Hz). It has been suggested that DBS alleviates the hypertonic activity by desynchronizing these excessive synchronized discharges. In six patients treated for their dystonia with bilateral GPi DBS, the contralateral prefrontal overactivity was reduced (Detante et al., 2004). In one study,

at rest, broadband gamma (50–200 Hz) power in the primary motor cortex was greater in patients with segmental arm dystonia and PD groups compared with patient with dystonia without arm involvement, whereas alpha (8–13 Hz) and beta (13–30 Hz) power was comparable in all three groups (Miocinovic et al., 2015). This study provides support for physiologic overlap in patients with isolated dystonia and PD with respect to high levels of motor cortex synchronization and reduction of cortical synchronization by subthalamic DBS.

These findings have collectively contributed to the development of “closed-loop” or “adaptive” DBS (aDBS) systems, which, along with current steering electrodes and devices, will likely improve the outcomes of DBS (Priori et al., 2012; Afshar et al., 2013; Li et al., 2013; Metman and Slavin, 2015).

The basal ganglia models in dystonia are even less clear; some studies have found that the GPi neuronal activity is increased in dystonia (Sanghera et al., 2003), whereas other studies have failed to find any decrease in basal ganglia output (Hutchinson et al., 2003). Neurophysiologic studies performed during STN DBS have found that the STN receives direct input from the supplementary motor area and is thus involved in movement preparation, as demonstrated by recorded activity in the nucleus before voluntary movement (Paradiso et al., 2003).

Posteroventral pallidotomy (PVP), GPi, and STN DBS (see later) improve motor performance in patients with PD, presumably by interrupting inhibitory pallidal projections to the ventrolateral thalamus. This is supported by measurements by positron emission tomography (PET) of regional cerebral blood flow (rCBF) showing increased activity of supplementary motor area and premotor cortex (but not in primary motor cortex) after pallidotomy (Grafton et al., 1995; Eidelberg et al., 1996). One possible explanation for the apparent improvement of parkinsonian features after STN or GPi ablation or simulation is that the reduced excitability of the GPe in PD prevents the normal “brake” on STN firing and leads to overactivation of the STN and GPi. Despite some uncertainty in understanding of the mechanisms, surgical approaches are increasingly used in the treatment of patients with PD who fail to obtain satisfactory relief from pharmacologic therapy (Krauss and Jankovic, 1996; Hallett et al., 1999) (Table 7.2).

Table 7.2 Advantages and disadvantages of deep brain stimulation

Advantages

- Immediate symptomatic improvement in most cases
- Stimulation is adjustable and can be customized
- Lower risk for lesion-related complications particularly when applied bilaterally
- Lower risk with bilateral procedure (e.g., speech, swallowing, gait cognitive side effects)

Disadvantages

- Frequent adjustment visits
- Neurostimulator battery changes
- Infection risk from a foreign body
- Discomfort at the implantation sites
- Cost
- Limited financial coverage particularly for some diagnoses
- Does not address disease progression

Techniques of stereotactic surgery

Stereotactic surgery is based on a Cartesian coordinate system, which implies that any point in space may be determined by three right-angled planes defined as the *x*, *y*, and *z* axes (Krauss and Jankovic, 1996). Functional stereotactic surgery relies on the acquisition of data from various imaging modalities and its transfer to the Cartesian coordinates referenced to an apparatus, the stereotactic frame, which is rigidly fixed to the patient’s head (Hassler et al., 1979; Grossman and Hamilton, 1991). By using computed tomography, MRI, or positive-contrast ventriculography, the target coordinates for functional stereotactic surgery are determined by extrapolation referring to the coordinates of the anterior and posterior commissure. The data for the spatial relation of the target to the anterior and posterior commissure are derived from stereotactic atlases. For example, the STN target, used chiefly for STN DBS, is 10 to 12 mm lateral and 2 to 3 mm posterior to the midcommissural point and 2 to 4 mm below the anterior commissure–posterior commissure (AC-PC) line. Some surgeons have also advocated the use of the red nucleus as an internal marker for targeting the optimal region of STN stimulation (Andrade-Souza et al., 2005). Various issues related to techniques of stereotactic surgery, particularly related to DBS, have been summarized in several reviews (Gross et al., 2006; Machado et al., 2006; Rezaei et al., 2006). It is important to understand the difference between indirect and direct targeting. Indirect targeting is accomplished through the use of coordinates based on atlases. Direct targeting is accomplished by using direct visualization of a target by imaging. Most experts use indirect targeting to define a region but always use direct targeting to refine the trajectory.

To improve the accuracy despite normal anatomic variability, physiologic verification of the target by microelectrode recordings of spontaneous neuronal activity or by electric stimulation has been considered critical by some (Tasker, 1993; Obeso et al., 1998; Starr et al., 1998; Vitek et al., 2004), but other investigators think that stereotactic surgery can be performed safely and effectively without microelectrode recording, using MRI-directed targeting (Dewey et al., 2000; Patel et al., 2003b; Hamid et al., 2005) or computed tomography (CT)-guided placement (Burchiel et al., 2013). Based on experience with 60 patients (33 with PD, 26 with essential tremor, and 1 with dystonia), the authors concluded that “Placement of DBS electrodes using an intraoperative CT scanner and the NexFrame achieves an accuracy that is at least comparable to those of other methods (Burchiel et al., 2013).

Different types of stereotactic devices are available. Functional stereotactic operations are generally performed under local anesthesia to allow examination of the patient during the physiologic investigations and during application of the lesions. In some cases, generalized anesthesia may be used safely (Maltete et al., 2004). The choice of the target and the techniques for calculation of the target and for physiologic localization differ (Mundinger and Reichert, 1963; Hassler et al., 1979; Grossman and Hamilton, 1991; Tasker, 1993; Tasker and Kiss, 1995). Usually, the target is chosen contralateral to the side that is more severely affected. The stereotactic frame is fixed to the skull with screws. The patient then undergoes stereotactic CT scanning. While the coordinates

of the target are calculated, the patient is brought back to the operating room. A small area of the head in the frontal region is shaved, but in many operating rooms a hair-sparing operation may be employed. A precoronal parasagittal burr hole is made via a linear incision under local anesthesia. The arch of the stereotactic device is fixed to the frame and the electrode for recording, or stimulation is directed to the precalculated target via a cannula. The tip of the microelectrode that is used for recording has a diameter of 0.01 mm, whereas the tip of the electrode that is used to produce the lesion has an approximate diameter of 1.1 mm. After physiologic localization of the target, one to three lesions are made along the trajectory, heating the tip of the electrode to 75°C for 60 seconds. The symptomatic improvement, particularly the cessation of tremor or levodopa-induced dyskinesia, reduced rigidity, and improved performance of rapid succession movements, is usually noted immediately after placing the lesion. It is advisable to operate when the patient is “off” (before taking the morning dose of medication), because the effect of the surgery can be assessed more readily. The duration of the procedure varies. The hospital stay also varies.

Ablative lesions of the thalamus, pallidum, and subthalamic nucleus

Thalamotomy

Before the advent of levodopa therapy for PD, thalamotomy offered the most effective means of controlling disabling and embarrassing tremor. Stereotactic thalamotomy has been refined substantially since its introduction in 1947 as a result of improvements in neuroimaging and electrophysiologic and surgical techniques. The application of the procedure has broadened to disorders other than tremor, particularly dystonia, hemiballism, and severe levodopa-induced dyskinesias (Cardoso et al., 1995; Jankovic, 1998; Krauss and Grossman, 1998; Starr et al., 1998; Jankovic, Lai, Krauss, et al., 1999). We analyzed the outcome of 60 patients with medically intractable tremor who underwent a total of 62 stereotactic thalamotomies at Baylor College of Medicine (Jankovic et al., 1995). The ventral intermediate (VIM) nucleus of the thalamus was the target in all patients. The patients were followed for as long as 13 years (mean, 53.4 months) after their surgery. At the most recent follow-up visit, 36 of 42 (86%) patients with PD, 5 of 6 (83%) with essential tremor, 4 of 6 (67%) with cerebellar outflow tremor, and 3 of 6 (50%) with posttraumatic tremor had complete cessation of or moderate to marked improvement in their contralateral tremor. Patients who were taking levodopa ($n = 35$ patients) were able to reduce their daily dose by approximately 156 mg. Immediate postoperative complications, such as contralateral weakness (34%), dysarthria (29%), and confusion (23%), occurred in 58% of the 60 patients; these complications usually resolved rapidly during the postoperative period. These results are consistent with other reports, confirming the beneficial effects of thalamotomy on tremor and rigidity but no effect on bradykinesia in patients with PD (Zirh et al., 1999). Thalamotomy was also considered to be modestly effective in reducing the amplitude of kinetic tremor associated with multiple sclerosis (Alusi et al., 2001; Matsumoto et al., 2001; Thevathasan et al., 2011). In one

series, 11 consecutive patients with multiple sclerosis tremor, permanent tremor reduction was observed in 11 of the 18 upper limbs with tremor (Thevathasan et al., 2011). Some authors have suggested that thalamic stimulation in multiple sclerosis promotes local “demyelinative lesioning.”

Furthermore, thalamotomy may improve levodopa-induced dyskinesia. Improved localization of the cluster of thalamic neurons with the largest amount of tremor discharges, correlated with electromyographic activity, should produce even better results. The likelihood of marked or complete tremor relief is high when the thalamic lesion is made within 2 mm of this site (Lenz et al., 1995). High-frequency stimulation (to be discussed later) rather than lesioning of the thalamic nuclei may be more effective and safer in the treatment of tremor (Schuurman et al., 2000). Because bilateral thalamotomy can cause hypophonia, dysarthria, and dysphagia, DBS is emerging as a useful alternative in those patients who require bilateral procedures. Thalamotomy has the advantage over DBS in that there is no need for hardware; and for patients with disabling bilateral tremor, unilateral thalamotomy in combination with contralateral DBS may offer the optimal tremor control with the fewest adverse side effects. Finally, microinjections of muscimol into the region of VIM thalamus that contains the tremor-synchronous cells consistently reduced tremor, suggesting that GABA agonists might be useful in the treatment of tremor (Pahapill et al., 1999). Thalamotomy for tremor in the setting of PD has been reintroduced through the use of MRI-guided focused ultrasound therapy. There were 27 subjects and 6 were randomized to sham procedures. On-medication median tremor scores improved 62% in the ultrasound group and 22% in the sham group. There were several adverse events, including 8% mild hemiparesis, 20% orofacial paresthesia, 5% finger paresthesia, and 5% ataxia (Bond, 2017).

Pallidotomy and subthalamotomy

Although a common procedure in the 1950s and 1960s, anterior pallidotomy was later abandoned because of inconsistent results, particularly concerning tremor, and because of improved results with posterior pallidotomy and later with DBS (Okun and Vitek, 2004). Although some investigators had noted improvement of bradykinesia, this observation was not described by others (Hassler et al., 1979). Most surgeons at that time targeted the anterior dorsal portion of the GPi. More favorable results, with improvement of rigidity, bradykinesia, and tremor, were reported by the group of Leksell, who had chosen a different target, namely, the posterior and ventral aspect of the GPi. After Laitinen had reevaluated Leksell’s approach in the early 1990s (Laitinen et al., 1992), pallidotomy was quickly reintroduced in North America and Europe (Sterio et al., 1994; Dogali et al., 1995; Lozano et al., 1995). Lesioning of the most ventral segment of the GPi provides the most antidyskinetic effect (Kishore et al., 2000).

The tentative target in the posteroventral GPi is located most commonly 20 to 21 mm lateral to the midline, 4 to 5 mm below the intercommissural line, and 2 to 3 mm anterior to the midcommissural point. The accurate localization of the target within the pallidum is essential not only for optimal therapeutic results, but also to avoid lesioning of adjacent structures. Single-cell microelectrode recording

helps in delineating the borders of the GPi (Alterman et al., 1999). Different neuronal signals are identified along the pathway through the putamen, GPe, and GPi (Grafton et al., 1995). Cells with bursting discharges and low-frequency activity interrupted by pauses are characteristic for the GPe, and irregular, high-frequency discharges at a frequency of 60 to 130 Hz mark the GPi. GPi neurons may change their firing rates on movements of various joints of the limbs. It is particularly important to identify the ventral border of the GPi and the adjacent optic tract, which might be located at a distance of only 2 to 3 mm from the derived target. Stimulation via the microelectrode, which may elicit visual phenomena, is also helpful in recognizing the optic tract. The mapping might require several trajectories before the final localization for the lesion is determined. Then the radiofrequency lesioning electrode is advanced, and "macrostimulation" is applied to identify whether and at what threshold the electric current spreads to the adjacent internal capsule. If no unwanted responses are encountered, the final lesion is then made.

Lesioning of the posteroventral portion of the GPi (Laitinen et al., 1992; Dogali et al., 1995; Iacono et al., 1995; Lozano et al., 1995; Baron et al., 1996; Lai et al., 1996; Olanow, 1996; Kishore et al., 1997; Lang et al., 1997, 1999; Uitti et al., 1997; Kumar et al., 1998b; Materman et al., 1998; Starr et al., 1998; Bronstein et al., 1999; Dalvi et al., 1999; Gross et al., 1999b; Hallett et al., 1999; Samii et al., 1999; Schrag et al., 1999; Lai et al., 2000; Counihan et al., 2001) and the STN (Bergman et al., 1990; Guridi et al., 1993; Limousin et al., 1995; Obeso et al., 1998; Alvarez et al., 2001; Barlas et al., 2001; Guridi and Obeso, 2001; Strutt et al., 2008) has an advantage over thalamotomy because this procedure improves not only tremor, but also bradykinesia and rigidity. Although some investigators (Subramanian et al., 1995) have suggested that PVP is as effective as thalamotomy in controlling parkinsonian tremor, others (Dogali et al., 1995) think that pallidotomy provides only partial relief of tremor. The latter authors suggest, however, that thalamotomy has a higher complication rate, particularly with respect to dysarthria and impairment of balance. In our series, only 6 of 60 (10%) patients had persistent dysarthria and none had persistent loss of balance (Jankovic et al., 1995). However, because the two procedures have never been compared in a controlled fashion, it is difficult to comment on possible differences in efficacy and complication rates.

When a lesion is precisely localized to the GPi by neuroimaging (Krauss et al., 1997; Desaloms et al., 1998; Kondziolka et al., 1999) or by microelectrode recording techniques (Lang et al., 1997), the benefits can be quite dramatic. Subsequent follow-up of 39 patients who were followed for 6 months, 27 who were followed for 1 year, and 11 who were followed for 2 years provided additional evidence of long-term efficacy of this procedure (Lang et al., 1997). There was a 28% reduction in the "off" motor score in 6 months and an 82% improvement in contralateral "on" dyskinesias. The motor improvement was generally sustained during the 2-year follow-up, although the improvement in ipsilateral and axial symptoms gradually waned. In another study of 15 PD patients who were followed postoperatively for 1 year, the total Unified Parkinson's Disease Rating Scale (UPDRS) score improved by 30% at 3 months, and the score remained improved at 1 year ($P < .001$) (Baron et al., 1996). In addition, there was a

marked improvement in contralateral rigidity, tremor, and bradykinesia and improvement in gait, balance, and freezing. Although contralateral dyskinesia and tremor remain improved, all other symptoms of PD usually worsen 3 years after the surgery (Pal et al., 2000).

The most robust beneficial effect of pallidotomy is improvement in levodopa-induced dyskinesia (Jankovic, Lai, Ben-Arie, et al., 1999; Jankovic, Lai, Krauss, et al., 1999; Fine et al., 2000; Lai et al., 2000; Lang, 2000a; Counihan et al., 2001). At Baylor College of Medicine, we followed 101 consecutive patients who underwent (PVP) procedures performed at our center and returned for at least one postoperative evaluation after 3 months (Lai et al., 2000). All had standardized clinical evaluations within 1 week before surgery and every 3 to 6 months after surgery. Data were collected during "on" and practically defined "off" periods for the UPDRS, Hoehn and Yahr stage, Schwab and England Activities of Daily Living (ADL) scale, and movement and reaction time. In addition, the severity and anatomic distribution of dyskinesia, neuropsychologic status, average percent of "on" time with and without dyskinesia, and clinical global impression were assessed during a longitudinal follow-up. Eighty-nine patients (46 men and 43 women) underwent unilateral PVP, and 12 patients (6 men and 6 women) had staged bilateral PVP. At 3 months after unilateral or staged bilateral PVP, 84 of the 101 patients reported marked or moderate improvement in their parkinsonian symptoms. Postoperative UPDRS mean total motor score improved in the "off" state by 35.5%, and the mean ADL score improved by 33.7% ($P < .001$). Rigidity, bradykinesia, and tremor scores also markedly improved after PVP, particularly on the contralateral side. Levodopa-induced dyskinesia was markedly reduced, and daily "on" time increased by 34.5% ($P < .001$). Seven patients had transient perioperative complications, including confusion, expressive aphasia, pneumonia, and visual changes. Improvements in parkinsonian symptoms were maintained in both "off" and "on" states in 67 patients at 12 months after PVP and in 46 patients who were followed for a mean period of 26.3 months. Patients who underwent staged bilateral PVP benefited further from the second procedure. Of 12 patients, 5 experienced some adverse event. On the basis of this large series of patients with extended follow-up, we conclude that PVP is an effective and relatively safe treatment for medically resistant PD, especially for dopa-induced dyskinesia, tremor, rigidity, and bradykinesia. Motor fluctuations also improved. Benefits are most noticeable on the side contralateral to the PVP. Sustained (>1 year) improvement in motor function after bilateral pallidotomy also has been demonstrated by others (Counihan et al., 2001). Clinical improvement has been sustained for longer than 2 years. In a "blinded" review of videotapes, Ondo and colleagues (1998b) showed a significant improvement in "off" UPDRS scores in patients undergoing pallidotomy. Unilateral pallidotomy was found to be an effective treatment in a multicenter single-blind, randomized trial (de Bie et al., 1999). In comparison to a control group who did not receive surgery, the pallidotomy patients improved their UPDRS 3 "off" motor score from 47 to 32.5, whereas the score in the control group increased from 52.5 to 56.5 ($P < .0001$). Furthermore, "on" UPDRS scores improved by 50%, chiefly as a result of marked improvement in dyskinesias. Most important, there was a significant improvement in the quality of

life in patients who were treated surgically in comparison to those who were treated medically. In a follow-up study, the investigators showed that the benefits persist for at least 1 year and that patients with 1000 levodopa equivalent units or lower were most likely to improve (de Bie et al., 2001). An improvement in the quality of life, using various measures, has been demonstrated by other pallidotomy series (Martinez-Martin et al., 2000). This improvement may persist for up to 5.5 years (Baron et al., 2000; Fine et al., 2000). Evidence-based analysis of the effects of medical and surgical interventions on health-related quality of life (HRQL) of measures concluded that only unilateral pallidotomy, STN DBS, and rasagiline have been shown to be efficacious in improving HRQL, but there is “insufficient evidence” that many well-established treatments, including levodopa and dopamine agonists, improve HRQL (Martinez-Martin and Deuschl, 2007). The longest follow-up, over 10 years, after pallidotomy showed that although the patients clearly benefited from the procedure, the levodopa dosage had to be increased as a result of the disease progression, and most patients gradually became troubled by various mental and medical complications associated with the disease and aging (Hariz and Bergenheim, 2001). In a randomized trial of pallidotomy versus medical therapy, Vitek and colleagues (2003) found pallidotomy more effective, as suggested by a 32% reduction in total UPDRS compared with 5% at 6 months.

Pallidotomy improves not only levodopa-induced dyskinesias, but also PD-related bradykinesia. This is best demonstrated by the finding of improved movement time and reaction time during the practically defined “off” state after pallidotomy (Jankovic, Ben-Arie, et al., 1999). Unilateral pallidotomy was also associated with improved simple and choice reaction times during the optimal “on” period (Hayashi et al., 2003). Kimber and colleagues (1999) suggested that the improvement in bradykinesia after pallidotomy may be explained by “greater efficacy of external cues in facilitating movement after withdrawal of the abnormal pallidal discharge.” Pfann and colleagues (1998) also showed that “off” bradykinesia improves after pallidotomy but could not demonstrate any improvement in “on” bradykinesia. We also found a remarkable improvement in freezing contralateral to the lesion in several of our patients and objective evidence of benefits in gait and balance (Robert-Warrior et al., 2000; Jankovic et al., 2001). Improvements in gait (Baron et al., 1996; Siegel and Verhagen Metman, 2000) and postural stability (Melnick et al., 1999) were also reported in other pallidotomy series (Bakker et al., 2004).

Pallidotomy requires a multidisciplinary approach involving skilled neurologists, neurosurgeons, neuroradiologists, physiologists, physiatrists, and nurses to obtain optimal results (Bronstein et al., 1999). Even when performed by a team of experienced clinicians, pallidotomy can be associated with potentially serious complications. The reported complications include transient confusion, expressive aphasia, hemiparesis, facial paresis, pneumonia, and visual changes, such as homonymous hemianopia (Laitinen et al., 1992; Shannon et al., 1998).

Cognitive function and various neuropsychologic measures have been studied extensively in patients after surgery for PD, and these domains have been found to be generally preserved, particularly after unilateral pallidotomy

(Masterman et al., 1998; Perrine et al., 1998; Rettig et al., 1998; York et al., 1999; Lombardi et al., 2000; Rettig et al., 2000; Saint-Cyr and Trépanier, 2000; Green et al., 2002; Contarino et al., 2007), although subtle changes in verbal fluency and possibly executive functions have been noted after left pallidotomy (Schmand et al., 2000) and after bilateral pallidotomy (Scott et al., 1998). Staged bilateral pallidotomy, although beneficial in most patients, results in increased risk for complications, particularly worsening of speech and other bulbar functions (Intemann et al., 2001). Bilateral simultaneous pallidotomy may be associated with even more frequent and severe complications, such as depression, obsessive-compulsive disorder, abulia, pseudo-bulbar palsy, apraxia of eyelid opening, and visual field deficits (Ghika et al., 1999). In a systematic review of morbidity and mortality associated with unilateral pallidotomy, de Bie and colleagues (2002) found that the risk for permanent adverse effects was 13.8%, and symptomatic infarction or hemorrhage occurred in 3.9%; mortality was 1.2%. Several investigators have used implanted DBS electrodes to produce lesions in the thalamus for treating tremor and in the pallidum for treating levodopa-induced dyskinesias (Raoul et al., 2003). Although pallidotomy is used primarily to improve parkinsonian symptoms and levodopa-induced dyskinesias, bilateral pallidal lesions in otherwise normal individuals result in inadequate anticipatory and compensatory postural reflexes, bradykinesia, and other signs of motor impairment (Haaxma et al., 1995). This apparent paradox is difficult to explain with the current models of basal ganglia circuitry, but it suggests that nigrostriatal dopaminergic deficiency causing activation of the GPi is a necessary prerequisite for the beneficial effects of pallidotomy. Pallidotomy has now been essentially abandoned in favor of DBS, and prior pallidotomy has been shown to be a poor predictor of outcome from STN DBS (Ondo et al., 2006).

The mechanism by which pallidotomy improves levodopa-induced dyskinesia is not known, but single-cell recordings in the GPi of parkinsonian monkeys show a marked reduction in firing rates only when dyskinesias were present (Papa et al., 1999). The average firing rate decreased from 46 Hz during the “off” state to 26 Hz during the “on” state and to 7.6 Hz during dyskinesia. It has been hypothesized that either overactive GPi (in a parkinsonian state) or low GPi activity (during dyskinesias) results in an abnormal (“noisy”) input to the thalamocortical circuit. Pallidotomy tends to eliminate the “noise” and “normalize” the output.

Because pallidotomy has such a robust effect on levodopa-induced dyskinesia, including dystonia, the procedure has been applied in the treatment of primary and secondary dystonia (Jankovic, 1998; Ondo, Desaloms, et al., 2001; Yoshor et al., 2001). In a series of patients with generalized dystonia, about 50% improvement on various dystonia rating scales was observed after pallidotomy (Ondo et al., 1998a). Some patients, particularly those with primary generalized dystonia, however, had a marked improvement, and as a result of the surgery, their dystonia-related disability changed from a dependent state to completely independent functioning.

The greatest effect of GPi ablation or DBS is on levodopa-induced dyskinesias; therefore, these procedures also have been tried in the treatment of other hyperkinesias, such as generalized dystonia (Jankovic, 1998; Coubes et al., 2000; Ondo, Desaloms, et al., 2001; Albright, 2003; Coubes et al.,

2004; Diamond and Jankovic, 2005; Vidailhet et al., 2005; Kupsch et al., 2006; Vidailhet et al., 2007; Tisch et al., 2007; Isaias et al., 2008, 2009; Sensi et al., 2009), cervical dystonia (Krauss et al., 1999, 2002; Parkin et al., 2001; Hung et al., 2007; Kiss et al., 2007; Moro et al., 2009), cranial-cervical dystonia (Hebb et al., 2007; Ostrem et al., 2007; Markaki et al., 2010; Reese et al., 2011; Ostrem et al., 2011), cervical dystonia (Ostrem et al., 2011), chorea and ballism (Thompson et al., 2000; Hashimoro et al., 2001; Krauss and Mundinger, 2001; Edwards et al., 2012), and tics associated with Tourette's syndrome (TS) (Cosgrove and Rauch, 2001). In a study of 9 patients with primary cervical dystonia STN DBS resulted in an improvement of the TWSTRS total score from a mean of 53.1 (± 2.57) to 19.6 (± 5.48) ($P < 0.001$) at 12 months (Ostrem et al., 2011). In addition, various quality of life measures also improved, but adverse effects included depression and weight gain; transient dyskinetic movements during stimulation was observed in all patients. Dystonic head tremor can also improve markedly with DBS of the ventrolateral thalamus, as demonstrated by blinded video rating of 7 patients (Pauls et al., 2014).

High-frequency stimulation of the STN has become an accepted treatment option for patients with moderately advanced PD (see later), but subthalamotomy has not been studied extensively (Tarsy, 2009). Because of its key role in the pathogenesis of PD, the STN has become a primary target for surgical treatment of PD. Although hemichorea/hemiballism is a well-recognized complication of a lesion in the STN, such hyperkinesias are very rare when the STN is lesioned (or stimulated) in the setting of PD (Barlas et al., 2001; Guridi and Obeso, 2001). This suggests that as a result of reduced activity of the "direct" GABAergic pathway from the striatum to the GPi, the parkinsonian state increases the threshold for such hyperkinesias. In PD, an STN lesion reduces excitation of the GPi and simultaneously further reduces the hypoactivity of the GPe, compensating for the GPi hypoactivity, self-stabilizing the basal ganglia output, and reducing the risk for hemichorea/hemiballism. Alvarez and colleagues (2005) reported their experience in 11 patients after unilateral dorsal subthalamotomy. They found a significant reduction in UPDRS score, which was maintained in four patients for 24 months. Despite the location of the lesion, the procedure was not complicated by hemiballism. They followed the initial experience in 89 patients treated with unilateral subthalamotomy, 68 of whom were available for evaluations after up to 36 months (Alvarez et al., 2009). In addition to significant reduction in the UPDRS scores, levodopa daily dose was reduced by 45%, 36% and 28% at 12, 24, and 36 months after surgery. Postoperative hemichorea/ballism was noted in 14 patients (15%), and it required pallidotomy in 8. Thus subthalamotomy seems to be a useful alternative to STN DBS when the latter is not accessible for economic or other reasons. In another study, unilateral dorsal subthalamotomy, particularly when combined with lesions in the H2 field of Forel and the zona incerta, resulted in a marked improvement in contralateral tremor, rigidity, and bradykinesia (Patel et al., 2003a). In 1 patient, a lesion confined to the STN produced "dyskinesia" that required H2/zona incerta DBS. In a series of 12 patients who underwent unilateral subthalamotomy, Su and colleagues (2003) showed a 30% to 38% improvement in UPDRS II and III and an 85% improvement in dyskinesia, with 42% reduction in levodopa

dosage. The benefits persisted for about 18 months. Complications included 3 (25%) cases of hemiballism; 2 of these patients recovered spontaneously, and 1 died of aspiration pneumonia. In a long-term (>3 years) follow-up of 18 patients with PD, bilateral subthalamotomy was associated with a significant improvement of activities of daily living (ADLs), reduction of levodopa-related dyskinesia by 50%, and lowering of levodopa dose by 47%, but the response was quite variable (Alvarez et al., 2005). Bilateral subthalamotomy was performed through DBS electrodes in a 60-year-old man with PD as a rescue option for DBS device-related infection (Deligny et al., 2009). One potential advantage of subthalamotomy compared with pallidotomy is that the latter may adversely affect subsequent response to levodopa, DBS, or other restorative therapies, because these depend on the normal function of the outflow nuclei. Subthalamotomy, however, also seems to reduce the metabolic activity of the ipsilateral GPi, midbrain, pons, and thalamus (Su et al., 2001). Other studies in patients undergoing subthalamotomy provide evidence that STN is part of a central inhibitory network (Obeso et al., 2014).

MRI-guided focused ultrasound has been introduced as a technique for subthalamotomy. In a 2018 pilot study, 10 patients with markedly asymmetrical PD were enrolled for a focused ultrasound unilateral subthalamotomy procedure. At 6 months there were 38 adverse events, and 7 were persistent at 6 months. The most severe were "off-medication dyskinesia in the treated arm (one patient, almost resolved by 6 months); on-medication dyskinesia in the treated arm (one patient, resolved after levodopa dose reduction); and subjective speech disturbance (one patient)." Six patients had transient gait ataxia. The International Parkinson and Movement Disorder Society (MDS)-UPDRS III score improved by 53% compared with the off-medication state (Martinez-Fernandez, 2018).

Gamma knife

Because of the importance of proper localization, several reports have raised concerns about the role of gamma knife (GK) in the treatment of various movement disorders (Friedman et al., 1996; Okun et al., 2001). Okun and colleagues (2001) described eight patients who, over a period of 6 months, were treated with GK surgery for PD and developed serious complications; one died as a result of aspiration pneumonia secondary to dysphagia. Other complications included hemiplegia, hemianopsia, limb weakness, speech and voice impairment, sensory deficit, and uncontrollable laughter. The authors concluded that these complications were related in all cases to missing the intended target and a resultant involvement of adjacent structures. Some problems may also relate to delayed effects of radiation necrosis, which might not have been fully appreciated in earlier reports on GK. Because their report represents only a small subset of patients treated with GK in their institution, the overall frequency of GK-related complications is not known. Nevertheless, this study sounded a loud alarm by drawing attention to the possibility that this procedure, often promoted as safer than the surgical treatment requiring penetration of the skull and brain parenchyma with a lesioning or stimulating electrode, can be associated with serious complications.

This study must be interpreted cautiously, however, because this was not a controlled study in which patients were randomized to receive GK, ablative procedure, or DBS. Nevertheless, the report by [Okun and colleagues \(2001\)](#) is important because it highlights two major limitations of GK in the treatment of movement disorders. It does not allow microelectrode recordings to verify the location of the target, and it is associated with an unacceptably high rate of immediate and delayed complications. Although GK thalamotomy has been reported to improve ET ([Niranjan et al., 2000](#)), a study of 18 patients concluded that this procedure provides “only modest antitremor efficacy” ([Lim et al., 2010](#)). Nevertheless some reports have suggested that GK thalamotomy is effective in ameliorating action tremor associated with multiple sclerosis ([Niranjan et al., 2000](#)) and with other movement disorders ([Friedman et al., 1999](#)). A 2015 single-blinded study of GK had 50 patients and 14 had parkinsonism, and overall the cohort improved. There was a 54% improvement in upper limb tremor score. There was a single case of a transient hemiparesis associated with excessive edema ([Witjas, 2015](#)).

Deep brain stimulation

Ablative procedures have been largely replaced by DBS after the 1987 discovery that high-frequency stimulation of the thalamus mimics the therapeutic effects of lesioning in controlling tremor ([Benabid et al., 1987, 1991, 2009](#)). It has long been known that high-frequency (>100 Hz) stimulation employed during thalamotomies at the site of the planned lesion temporarily suppresses tremor ([Munding and Reichert, 1963; Meyers, 1968; Hassler et al., 1979](#)). Because of the ability to customize the stimulation parameters and the relatively low risk for complications, DBS is now considered the preferred surgical treatment for disabling PD-related tremor, ET, levodopa-related complications, generalized dystonia, and other movement disorders ([Tasker, 1998](#)). This application of chronic thalamic stimulation in the treatment of movement disorders in the 1960s was later adopted for the treatment of chronic pain. Hypothalamic DBS is currently used for the treatment of various pain disorders, including migraines and cluster headaches ([Leone et al., 2003](#)). The U.S. Food and Drug Administration (FDA) approved DBS for the treatment of ET in 1997, PD in 2002, and granted a special Humanitarian Device Exemption for dystonia in 2003. The major historical milestones in the evolution of DBS have been previously reviewed ([Miocinovic et al., 2013](#)).

Depending on the desired effects, various subcortical nuclei, such as the VIM nucleus of the thalamus, GPi, STN, zona incerta, PPN, and other subcortical nuclei and even cortical areas, have been targeted for stimulation ([Benabid et al., 1991, 1996; Caparros-Lefebvre et al., 1993; Limousin et al., 1995; Koller et al., 1997; Krack et al., 1998a, 1998b; Limousin et al., 1998; Ondo et al., 1998c; Pollak et al., 1998; Starr et al., 1998; Tasker, 1998; Volkmann et al., 1998; Koller et al., 1999; Limousin et al., 1999; Deep-Brain Stimulation for Parkinson's Disease Study Group, 2001; Krauss et al., 2001; Lopiano et al., 2001; Volkmann et al., 2001; Kumar, 2002; Okun and Foote, 2005; Perlmutter and Mink, 2006; Halpern et al., 2007; Stefani et al., 2007; Limousin and Martinez-Torres, 2008; Yu and Neimat, 2008; Lyons, 2011; Wichmann and DeLong, 2011](#)) (Table 7.3 and Fig. 7.3).

Table 7.3 Targets for deep brain stimulation in the treatment of various movement and other disorders

Thalamus

Tremor (essential tremor, Parkinson disease, multiple sclerosis, trauma)—VIM
Dystonia—VIM
Ballism—VIM
Myoclonus—VIM
Tics (Tourette syndrome)—centromedian-parafascicular complex

Globus pallidus interna

Dyskinesia (levodopa-induced, tardive)
Dystonia
Tics (Tourette syndrome)
Chorea (Huntington disease)

Subthalamic nuclei

Tremor, rigidity, bradykinesia
Lower levodopa → dyskinesia

Other targets

Globus pallidus externa, anterior capsule, caudal zona incerta, pedunculopontine nucleus

VIM, Ventral intermediate nucleus of the thalamus.

DBS involves the implantation of the following hardware: (1) a DBSTM lead with four electrodes that are surgically inserted into the desired target and fixed at the skull with a ring and cap, (2) an extension wire that passes from the scalp area under the skin to the chest, and (3) an implantable pulse generator, a pacemaker-like device (unilateral Soletra or bilateral Kinetra, Medtronic Activa, ITREL model, St. Jude Libra DBS device, or other devices), which can deliver pulses with adjustable parameters (frequency, amplitude, width, modes, and polarities) ([Kumar, 2002; Vesper et al., 2002](#)). The implantable pulse generator is placed under the skin, usually in the upper chest area near the collarbone. The patient can activate or deactivate the DBS system by placing a magnet or access review device, a small mouselike computer, over the chest area overlying the implantable pulse generator. Guidance on how to troubleshoot hardware complications and the utility of measuring impedance need to be better defined ([Farris et al., 2008](#)). In the Medtronic Soletra and Kinetra devices the impedance measurement should be less than 50 ohms (Ω) and current greater than 250 μ A, but for an open circuit the impedance is usually greater than 2000 Ω and current less than 7 μ A for Soletra and greater than 4000 Ω and current less than 15 μ A for Kinetra. In 7 patients with poor response to STN DBS, reimplantation of the electrodes presumably corrected misplacement, resulting in improvement in PD symptoms ([Anheim et al., 2008](#)). There is considerable controversy whether constant current stimulation provides more accurate control of the electrical field spread produced by these devices than constant voltage ([Lempka et al., 2010; Okun et al., 2011](#)). Constant current devices have been proposed to have a theoretical advantage over voltage-driven devices in that the generated field of stimulation within brain tissue should be stable in size, whereas stimulation fields produced by voltage-driven devices are susceptible to changes in tissue impedance.

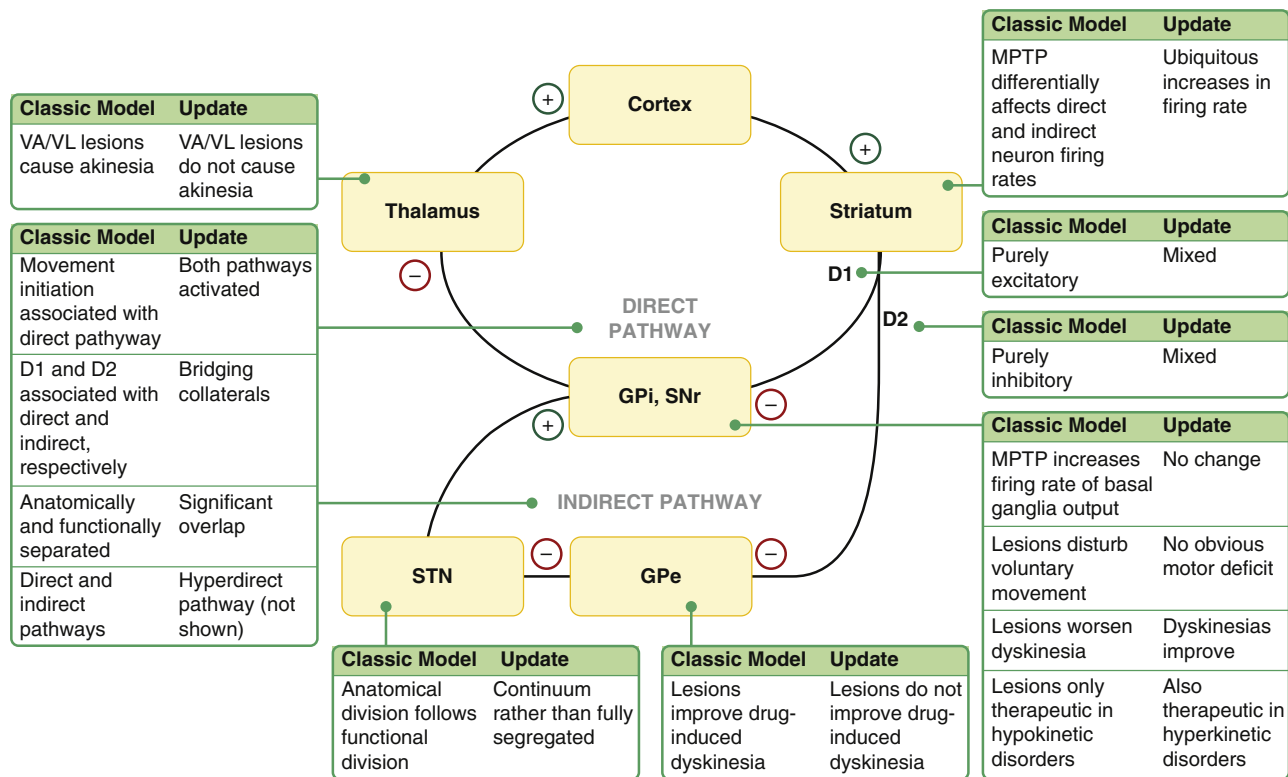


Fig. 7.3 Basal ganglia deep brain stimulation targets based on the classic box model and updates based on current understanding. GPe, Globus pallidus externa; GPi, globus pallidus interna; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; SNr, substantia nigra pars reticularis; STN, subthalamic nucleus.

Guidelines for reporting results of various DBS studies have been proposed and include the preoperative information (patient selection and evaluation), intraoperative information (targeting and lead location), and postoperative information (programming, outcome data, and adverse events) (Vitek, et al., 2010).

In addition to appropriate selection of patients it is critical that the most relevant and sensitive measures are used to assess the response to the therapeutic intervention, especially surgery because this intervention is particularly susceptible to a placebo effect (Keitel et al., 2013). Indeed when evaluating the outcomes of DBS it is critical to take into account the role of expectation of benefit and the placebo, nocebo, lessebo, and lesion effects (Mestre et al., 2016). In this regard, instruments have been developed using questionnaires, such as questions on life satisfaction: “general life satisfaction” (Questions on Life Satisfaction [QLSM-A]) and “satisfaction with health” (QLSM-G), in which each item is weighted according to its relative importance to the individual. In one study these instruments were validated against the 36-item short form health survey (SF-36) and the EuroQol (EQ-5D) (Kuehler et al., 2003). When the initial questionnaires were reduced to 12 items for a “movement disorder module” (QLSM-MD), and 5 items for a “deep brain stimulation module” (QLSM-DBS), psychometric analysis revealed Cronbach (alpha) values of 0.87 and 0.73, and satisfactory correlation coefficients for convergent validity with SF-36 and EQ-5D. Several quality-of-life instruments have been used in assessing the response to DBS (Kuehler et al., 2003; Diamond and Jankovic, 2005, 2009; Martinez-Martin and Deuschl, 2007). Using the Sickness Impact Profile (SIP), improvements in various dimensions were maintained at 3 to 4 years after

STN (N = 45) or GPi DBS (N = 20); 40% of STN DBS and 24% of GPi DBS patients were able to sustain their 6-month improvements at 3 to 4 years after surgery (Volkman et al., 2009). In a prospective analysis of 21 patients before and after STN DBS for medically refractory PD, patients experienced an improvement in HRQL as measured by various items of the movement disorder and health modules of the QLSM, specifically, QLSM items pertaining to energy level/enjoyment of life, independence from help, controllability/fluidity of movement, and steadiness when standing and walking showed significant improvements, although items concerning general life issues (e.g., occupational function, interpersonal relationships, leisure activities) did not improve (Ferrara et al., 2010). Thus, following STN DBS, symptomatic and functional improvements translate into higher HRQL, with high satisfaction in domains related to movement disorders and general health. The cost associated with STN DBS has been estimated to be about \$60,000 per patient over 5 years (McIntosh et al., 2003).

The mechanism of benefits of DBS produced by the electrical stimulation is not known, but in some cases improvement can be observed even before the stimulator is activated (Table 7.4). This microlesioning effect may last several days or even weeks (Maltete et al., 2009; Okun et al., 2011). Besides microlesion effect, the following mechanisms have been suggested to explain the beneficial effects of DBS: (1) disruption of the network (“jamming” of feedback loop from the periphery), (2) depolarization block, (3) functional ablation by desynchronizing a tremorogenic pacemaker, (4) preferential activation of large axons that inhibit GPi neurons, (5) stimulation-evoked release of GABA (Dostrovsky et al., 2002; Garcia et al., 2005), (6) release of adenosine

Table 7.4 Possible mechanisms of deep brain stimulation

Microlesioning
Disrupts the network ("jamming")
Depolarization block
Functional ablation by desynchronizing a tremorigenic pacemaker
Preferential activation of large axons
Stimulation-evoked release of gamma-aminobutyric acid, adenosine
Stimulation-induced (time-locked) modulation of pathologic network activity
Overriding of pathologic bursts and oscillations and replacing them with more regular firing
Activation and excitation of the target nucleus (rather than inhibition as seen with lesioning)
Marked increase in the release of adenosine triphosphate, resulting in accumulation of its catabolic product, adenosine
• Adenosine A1 receptor activation depresses excitatory transmission in the thalamus and reduces tremor (and deep brain stimulation-induced side effects)

Modified from Hilker R, Voges J, Ghaemi M, et al. Deep brain stimulation of the subthalamic nucleus does not increase the striatal dopamine concentration in parkinsonian humans. *Mov Disord.* 2003;18:41–48; Bekar L, Libionka W, Tian GF, et al. Adenosine is crucial for deep brain stimulation-mediated attenuation of tremor. *Nat Med.* 2008;14:75–80.

(Bekar et al., 2008), (7) overriding of pathologic bursts and oscillations and replacing them with more regular firing (Birdno and Grill, 2008; Johnson et al., 2008; Hammond et al., 2008), and (8) activation and excitation of the target nucleus (rather than inhibition as seen with lesioning) (Hilker et al., 2008). Additionally, much is known about the biologic changes associated with DBS; however, it is unclear which changes are responsible for the mechanisms of action. Changes include neurophysiologic, neurochemical, neurovascular, neurogenic, and neuro-oscillatory (Okun, 2012). Studies have shown that electrical stimulation consisting of short (<1 ms) duration pulses preferentially activates axons rather than somas (Nowak et al., 1998). In support of the hypothesis of DBS preferentially activating large axons is the observation in one patient in whom stimulation inhibited GPi firing recorded with another microelectrode 600 to 1000 microns away (Wu et al., 2001). The effects of stimulation appear to be restricted to an area of 2 to 3 mm from the macroelectrode (at 2 mA, 2 V, and impedance of 1000 Ω). This would be similar to a bipolar stimulation with two adjacent contacts 1.5 mm apart. Unipolar stimulation seems to have a significantly higher efficacy than bipolar stimulation, but this is accompanied by a higher rate of side effects (19% versus 0%); approximately 0.4 to 0.5 V higher amplitude was required for bipolar than unipolar stimulation to achieve the same effect (Deli et al., 2011). It is of interest that in addition to the contralateral improvement, there also may be an ipsilateral improvement. In one study, there was a 4.96 ± 11.79 point improvement in the motor UPDRS on the side ipsilateral to STN or GPi DBS (Shemisa et al., 2011).

More recent studies suggest that the observed 15- to 30-Hz oscillations of the STN might reflect synchronization with cortical beta oscillation via the corticosubthalamic pathway and might relate to mechanisms of bradykinesia, because stimulation at the 15-Hz rate worsens bradykinesia and dopaminergic drugs promote faster oscillations (about 70 Hz) and improve bradykinesia, similar to the high-frequency stimulation associated with DBS (Levy et al., 2002). Studying

the effects of STN DBS in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) monkeys, Hashimoto and colleagues (2003) showed that the activation of the STN efferent fibers results in a change in firing pattern of pallidal neurons, and they postulated that this could underlie the beneficial effects of chronic STN DBS. In contrast to the popular notion that DBS inhibits the target nucleus, DBS has been shown actually to activate the cerebellothalamocortical pathway (Molnar et al., 2004). Indeed, studies have suggested that stimulation-induced, time-locked modulation of pathologic network activity represents the most likely mechanism of the effects of DBS (McIntyre et al., 2004). DBS could have a dual effect, switching off a pathologically disrupted activity but also imposing a new discharge (in the upper gamma-band frequency) that results in beneficial effects (Garcia et al., 2005; Hammond et al., 2008). The most suitable target for DBS electrode is probably a region of the brain where DBS can most effectively interfere with spontaneous pathologic patterns by introducing regular rhythmical activity without causing additional adverse effects (Hammond et al., 2008). The frequency of stimulation might markedly influence the effects. For example, low-frequency (0.1–30 Hz) stimulation of STN has been shown to depolarize glutamatergic and GABAergic synaptic terminals, evoking excitatory and inhibitory postsynaptic potentials. Animal studies have shown that STN DBS (130 Hz for 1 hour) increases extracellular dopamine in the ipsilateral denervated striatum (Meissner et al., 2003). Although this has not yet been confirmed in patients, indirect evidence from [^{11}C]raclopride PET studies have not provided any evidence that STN DBS induces dopamine release (Hilker et al., 2003). In untreated parkinsonian animals and patients, the neuronal activity in STN and GPi is dominated by low-frequency (11–30 Hz) oscillation that is increased with levodopa to greater than 70 Hz. The therapeutic effects of high-frequency DBS might be mediated through the same mechanism (Brown et al., 2004). The role of adenosine in the effects of DBS on tremor has been suggested by the observation of a marked increase in the DBS-induced release of adenosine triphosphate (ATP) from local astrocytes, which metabolizes to adenosine (Bekar et al., 2008). Previous studies have demonstrated that adenosine A1 receptor activation depresses excitatory transmission in the thalamus and reduces tremor, whereas caffeine, a nonselective adenosine receptor antagonist, can trigger or exacerbate tremor. In summary, DBS tends to inhibit neuronal bodies, excite neighboring axons, and cause astrocytes to release calcium, which leads to release of glutamate and adenosine and increased cerebral blood flow with possible proliferation of distal precursor cells (Okun, 2012). The various mechanisms by which DBS improves neurologic and psychiatric function have been a subject of several reviews (Perlmutter and Mink, 2006; Kringelbach et al., 2007; Tye et al., 2009).

The abnormal motor cortical overactivity associated with PD is reduced with STN DBS (Payoux et al., 2004). Frontal cortex function, as measured by contingent negative variation, has been improved by bilateral STN DBS (Gerschlager et al., 1999). Metabolic changes in ipsilateral premotor cortex and cerebellum bilaterally, measured by [^{18}F]fluorodeoxyglucose and PET, correlated with clinical improvement related to GPi DBS (Fukuda et al., 2001b). Other rCBF studies showed that when the STN DBS is on, the ipsilateral rostral supplementary motor area and premotor cortex are activated

during contralateral movement, but there was a reduction in rCBF in primary motor cortex during rest (Ceballos-Baumann et al., 1999). Modulation of cortical activity also may be responsible for improved bladder function with STN DBS (Herzog et al., 2006).

The placement of the electrode can be verified radiographically. Although computed tomography scan, rather than MRI, has been recommended by some, several studies have concluded that standard MRI (Tronnier et al., 1999; Jech et al., 2001) and fMRI (Arantes et al., 2006) can be safely performed in patients with implanted neurostimulation systems, although transient and permanent neurologic deficits have been rarely reported after MRI (Spiegel et al., 2003; Henderson et al., 2005; Rezai et al., 2005).

Using PET, Ceballos-Baumann and colleagues (2001) found that VIM DBS in patients with ET was associated with increased rCBF in the ipsilateral motor cortex and a decrease in rCBF in the retroinsular (parietoinsular vestibular) cortex. They suggested that the latter affects function of the vestibular-thalamic-cortical projections and might therefore explain the frequent occurrence of disequilibrium in patients treated for tremor with VIM DBS, a reversible complication of this therapy. The authors also postulated that the increased synaptic activity in the motor cortex overrides the abnormal tremor-related rhythmic neuronal bursting. In another study (Ceballos-Baumann et al., 2001), the authors suggested that the beneficial effects of VIM DBS are due to nonphysiologic activation of thalamofrontal projections or frequency-dependent neuroinhibition. This has been also confirmed by Perlmutter and colleagues (2002). In another study involving fMRI during DBS of STN (three patients) and thalamus (one patient), Jech and colleagues (2001) showed an increase in blood oxygenation level-dependent signal in the subcortical regions ipsilateral to the stimulated nucleus. The authors concluded that this effect cannot be explained simply by a mechanism of depolarization blockade; rather, it is caused by "overstimulation" of the target nucleus resulting in the suppression of its spontaneous activity.

DBS in tremor

Thalamic stimulation appears to be particularly effective in the treatment of parkinsonian tremor and ET (Koller et al., 1997, 1999, 2001; Ondo et al., 1998c; Pahwa et al., 1999; Pollak et al., 1998; Krauss et al., 2001b; Rehnrcrona et al., 2003; Flora et al., 2010) (Videos 7.1, 7.2). In the North American Multi-Center Trial, 25 ET and 24 PD patients were followed for 1 year after implantation (Koller et al., 1997). Combined blinded tremor ratings (0–4) in ET patients randomized to "on" were 0.9 compared with 2.7 for those randomized to "off" stimulation. All subjective functional measures improved, and 9 of 29 patients (31%) had complete tremor cessation. In PD patients, "on" randomized scores were 0.6 compared with 3.2 for those who were randomized to "off." Of the patients, 58% (14 of 24) had complete tremor cessation. Subjective functional measures (UPDRS II), however, were not significantly improved. Complications were manageable and included paresthesia, headache, disequilibrium, dystonia, and device failure. Results were similar at 1 month and 1 year after implantation. Although some loss of efficacy and device-related complications have been encountered after 2 years of follow-up, the

authors concluded that unilateral DBS of the thalamus has long-term efficacy in patients with ET (Koller et al., 2001). In a multicenter European study in which 37 patients with ET were followed for a mean of 6.5 years, unilateral or bilateral VIM DBS offered long-term benefits and safety (Sydow et al., 2003). Our experience at Baylor is similar to that reported in other centers. In a blinded and open-label trial of unilateral thalamic DBS in 33 patients (14 ET and 19 PD) with severe tremor refractory to conventional therapy, ET and PD patients demonstrated an 83% and 82% reduction ($P < 0.0001$), respectively, in observed contralateral arm tremor (Ondo et al., 1998c). All measures of tremor, including writing samples, pouring tests, subjective functional surveys, and disability scores, significantly improved. We found that bilateral thalamic DBS is more effective than unilateral DBS in controlling bilateral appendicular and midline tremors of ET and PD, and thalamic DBS does not seem to improve meaningfully any parkinsonian symptoms other than tremor (Ondo, Almaguer et al., 2001). Although unilateral VIM DBS can markedly improve midline tremor, this improvement is significantly enhanced by bilateral procedure (Putzke et al., 2005). Several studies have found that gait and balance may be impaired in some, but not all, patients treated for ET with VIM DBS (Earhart et al., 2009). One long-term study found that bilateral VIM DBS was often associated with dysarthria, loss of balance, and incoordination (Pahwa et al., 2006). Similar findings were reported in a 6-year follow-up of 38 PD patients treated with VIM DBS in a multicenter European study (Hariz et al., 2008). The authors suggest that unilateral VIM DBS should be reserved for elderly PD patients with predominant unilateral tremor, but STN DBS may be a better choice for other patients with tremor-dominant PD. This recommendation is supported by other studies showing benefit of STN DBS in PD patients with prominent tremor (Fraix et al., 2006; Diamond, Shahed, Jankovic, 2007; Hamel et al., 2007). VIM DBS has been found to be associated with modest improvement, rather than tremor augmentation as was previously suggested, in ipsilateral tremor in patients with ET (Ondo, Vuong, et al., 2001). Other studies have demonstrated bilateral effects of unilateral thalamic DBS (Kovacs et al., 2008). A review of long-term efficacy of VIM DBS in 39 patients (20 PD, 19 ET) showed that the benefits might be maintained for at least 6 months (Rehnrcrona et al., 2003). In one study, three of eight patients with PD no longer required DBS after 3 to 5 years because the tremor markedly improved (Kumar et al., 2003). In addition to reducing the amplitude, VIM DBS increased the frequency of ET by 0.5 to 2 Hz at low inertial loads, made the tremor more irregular, and reduced the tremor-electromyography coherence (Vaillancourt et al., 2003). About a quarter of ET patients experience worsening of ET after DBS, but this is thought to be more likely because of progression of the disease rather than tolerance (Favilla et al., 2012). However, waning of benefit is an increasingly recognized problem. In one study among 45 patients treated with VIM DBS for their ET, 73% reported waning benefit at some point during a mean follow-up period of 56 months (range, 12–152 months) (Shih et al., 2013). ►

The largest prospective study of ET was published using the Abbott constant current device. This was a prospective controlled multicenter study. There were 127 patients with VIM DBS. "The blinded, primary outcome variable ($n = 76$) revealed a mean improvement of 1.25 ± 1.26 points in the

target limb tremor rating scale (TRS) score in the arm contralateral to DBS ($P < 0.001$). There were also improvements in quality of life, depression, and ADLs. There were 47 patients who had the contralateral Vim implanted, and there was also a significant effect at tremor suppression on the contralateral side. There were three infections, three bleeds, and three device explants (Wharen, 2017).

To compare thalamic DBS with thalamotomy, Schuurman and colleagues (2000) conducted a prospective, randomized study of 68 patients with PD, 13 with ET, and 10 with multiple sclerosis. They found that the functional status improved more in the DBS group than in the thalamotomy group, and tremor was suppressed completely or almost completely in 30 of 33 (90.9%) in the DBS group and in 27 of 34 (79.4%) in the thalamotomy group. Although one patient in the DBS group died after an intracerebral hemorrhage, DBS was associated with significantly fewer complications than was thalamotomy. Similar results were obtained on this group after a 5-year follow-up, with the outcomes still favoring the DBS group (Schuurman et al., 2008). In one study of VIM DBS, dysarthria worsened when both stimulators were turned on in 3 of 6 patients (Pahwa et al., 1999). DBS also has been found to be effective in rare patients with disabling task-specific tremors (Racette et al., 2001). In addition to improving distal tremor associated with PD and ET, VIM DBS can effectively control ET-related head tremor, which usually does not respond to conventional therapy (Koller et al., 1999). Other midline tremors, such as voice, tongue, and face tremor, also may improve with unilateral VIM DBS, although additional benefit can be achieved with contralateral surgery (Obwegeser et al., 2000; Putzke et al., 2005). In addition, VIM DBS appears to improve postural stability (Pinter et al., 1999). Furthermore, unilateral thalamic DBS for ET has been found to be cognitively safe and to improve anxiety and quality of life in terms of ADLs and psychological well-being (Tröster et al., 1999). Several studies have demonstrated that VIM DBS improves ADLs and quality of life, and one study showed that these improvements may be sustained for up to 7 years after implantation (Hariz et al., 2008).

Several studies have sought to determine the optimal stimulation parameters. Algorithms for programming of the stimulation parameters have been suggested (Volkman et al., 2006) but programming is generally based on the judgment of the programmer. Charge is the product of pulse width and current (current = voltage/impedance). Charge density is defined as the charge divided by the geometric surface area of the electrode. Short pulse widths require high current but low charge and are thus more efficient at exciting neural elements and reducing the risk for neural damage. Linear voltage increases above 3 V do not correlate to a linear increase in the volume of neural elements excited, but significantly increase power consumption (Kuncel, 2002). Although the amount of tremor suppression does not substantially increase in frequencies above 100 Hz, power consumption increased markedly at the higher frequencies (Kuncel et al., 2006). Power consumption (and battery drain) is determined by calculating the voltage squared (V^2) times the pulse width (PW) and frequency (F) divided by the impedance (Z).

$$P = \frac{V^2 \times PW \times F}{Z}$$

Bin-Mahfoodh and colleagues (2003) evaluated 14 implantable pulse generators (IPGs) that needed battery replacement out of 163 single-channel batteries implanted over 7 years and found that the higher the total electrical energy delivered as calculated by the power consumption formula, the shorter is the battery life span. A review of all battery replacements in patients at Baylor College of Medicine found 122 batteries needed replacement in 73 patients. The main predictors of a shorter battery life were greater amplitude, pulse width, and not using exclusive bipolar settings (Ondo et al., 2007). O'Suilleabhain and associates (2003), studied 13 VIM thalamic stimulators (8 for ET and 5 for PD) and measured tremor with an electromagnetic tracker. They randomly programmed 78 combinations of voltages (0, 1, 2, 3, or 4 V), pulse widths (60, 90, or 120 μ s), and frequencies (130, 160, or 185 Hz) for both monopolar and bipolar polarity configurations. The voltage response curve for ET was flatter than for PD patients. Monopolar configurations were up to 25% more effective than bipolar but this configuration tended to shorten calculated battery life by 35%. The longest pulse width tested was up to 30% more effective than the shortest, but frequency changes had little effect on tremor amplitude. The authors recommended that there was no need to increase the frequency above 130 Hz, and another study concluded that stimulation frequency of 100 Hz is generally the optimal frequency and that there is little if any additional benefit from a higher frequency (Ushe et al., 2006). Low-frequency (10 Hz) STN DBS has been shown to improve verbal fluency but worsen motor function in a double-blind randomized crossover study of 12 patients with PD (Wojtecki et al., 2006). Moro and associates (2006) studied 44 patients with PD who had a long-term (mean, 3.5 years), stable response to STN DBS. Each underwent reprogramming of their stimulation by a neurologist expert in both PD and DBS, along with medication adjustments. Scores on the UPDRS were compared before reprogramming and up to 14 months thereafter. In half the patients (24 [54.6%]), UPDRS II and III scores improved significantly after reprogramming, by 15.0% and 29.5%, respectively. Anti-PD drug use decreased significantly as well, by 29.5%, in these responders. No improvement was seen in 16 patients (36.4%), and the condition of 4 patients (9.1%) worsened. These results suggest that patient outcomes with STN DBS can be improved when a neurologist expert in movement disorders and DBS programming is directly responsible for patient care. Another way to improve response to DBS is to employ phase-dependent modulation of tremor amplitude. In a study of 10 patients with ET and electrodes placed in the thalamus, stimulation near the postural tremor frequency entrained tremor and depending on which phase of the tremor cycle the stimulus was delivered the tremor could be suppressed by as much as 27% (Cagnan et al., 2013). Thus, when customized to each individual patient, phase-dependent stimulation may improve the outcome with lower demand on battery power and lower risk for tolerance. DBS has been found to be safe and effective in patients followed for up to 10 years with a hardware complications rate of 23% of patients over that period of observation (Baizabal-Carvallo et al., 2014).

VIM DBS has been found to be useful not only in the treatment of troublesome tremors associated with ET and PD but also in orthostatic tremor (Espay et al., 2008), and cerebellar

outflow tremor associated with multiple sclerosis and post-traumatic tremors (Montgomery et al., 1999; Matsumoto et al., 2001; Wishart et al., 2003; Lyons and Pahwa, 2008) (Video 7.3). Thalamic DBS also may be effective in the treatment of levodopa-induced dyskinesia, possibly owing to involvement of the center median and parafascicularis complex (Caparros-Lefebvre et al., 1999). Thalamic DBS, however, does not seem to provide any benefit in PD-related gait difficulty (Defebvre et al., 1996). Bilateral ventralis oralis anterior thalamic DBS also has been reported to be effective in a patient with severe postanoxic generalized dystonia and bilateral necrosis of the basal ganglia (Ghika et al., 2002). Medically intractable myoclonus was reported to improve 80% with VIM DBS in one case of myoclonus-dystonia syndrome (Trottenberg et al., 2001a), and GPi DBS has been found to be effective in relieving myoclonus-dystonia syndrome (Magarinos-Ascone et al., 2005). ▶

In addition to VIM as a target for patients with disabling tremor, STN DBS also has been found useful in the treatment of severe proximal tremor (Kitagawa et al., 2000) and rest and postural tremor in PD (Sturman et al., 2004). A short pulse width ($\leq 60 \mu\text{s}$) of the posterior subthalamic area below the inferior border of the thalamic nucleus ventralis intermedius seems to provide the most optimal therapeutic effect and most robust tremor suppression (Groppa et al., 2014).

DBS in PD and levodopa-related complications

Several studies have demonstrated that DBS of the GPi and STN improves not only parkinsonian tremor, but also other PD-related symptoms and prolongs the “on” time (Pahwa et al., 1997; Limousin et al., 1998; Pollak et al., 1998; Moro et al., 1999; Deep-Brain Stimulation for Parkinson’s Disease Study Group, 2001; Lanotte et al., 2002; Alvarez et al., 2005; Fasano et al., 2012; Okun, 2012) (Videos 7.4, 7.5). Although levodopa improves predominantly finger bradykinesia, STN DBS improves predominantly proximal and axial bradykinesia (Timmermann et al., 2008). Elderly patients (older than 70 years) seem to benefit as much as younger patients with respect to a reduction in dyskinesias and motor fluctuations, but during the “off” times, older patients have more difficulties with ADLs and axial symptoms, particularly if they had some gait problems before surgery (Russmann et al., 2004b). Depending on the location of the stimulating electrode, pallidal stimulation has a variable effect on parkinsonian features versus levodopa-induced dyskinesias. In one study, stimulation of the dorsal GPi improved parkinsonian features, but stimulation of the posteroventral GPi improved levodopa-induced dyskinesia and worsened gait and akinesia (Bejjani et al., 1997). In another study, stimulation of the most ventral part of the GPi improved rigidity and eliminated levodopa-induced dyskinesia but produced marked bradykinesia, whereas stimulation of the most dorsal contacts improved bradykinesia and induced dyskinesia (Krack et al., 1998a). Best results could be obtained by stimulating the intermediate contacts. Similar results were reported by Durif and colleagues (1999), who found that ventral GPi stimulation was more effective than dorsal stimulation for alleviating rigidity and levodopa-induced dyskinesia. But in contrast to Krack and colleagues (1998a), whose target was posterolateral to the location of the target used by Durif and colleagues (1999), the latter group found that ventral

stimulation also improved bradykinesia. They concluded that “chronic stimulation in the anteromedial GPi shows that this is a safe and effective treatment for advanced PD.” GPi DBS has been found not only to improve “off” state UPDRS and movement onset time and spatial errors, but also to enhance motor activation responses as measured by concurrent PET recordings of rCBF in the sensorimotor cortex, supplementary motor area, and anterior cingulate gyrus (Fukuda et al., 2001a). Normalization of abnormal pattern of cerebral blood flow and an increase in cerebral blood flow in supplementary motor area and anterior cingulate cortex also has been found with STN DBS, and this correlated with improvement in bradykinesia (Strafella et al., 2003). This effect was more robust with bilateral than unilateral stimulation. Hershey and colleagues (2003), however, found that STN DBS increased blood flow in the midbrain, globus pallidus, and thalamus but decreased blood flow in cortical areas. They concluded that “STN stimulation appears to drive, rather than inhibit, STN output neurons.” This is consistent with the model that increased STN output driven by STN DBS leads to excitation of pallidal neurons, which increases inhibitory output to the thalamus resulting in thalamocortical inhibition. This is supported by the observed decrease in overactivity of supplementary motor area (SMA) and other areas of overactivity presumably recruited to compensate for abnormal motor initiation as measured by resting rCBF (Grafton et al., 2006). In one study, bilateral STN DBS was associated with increased rCBF in both thalami and right midbrain and decreased rCBF in the right premotor cortex (Karimi et al., 2008). The increased rCBF in the thalami correlated with improved bradykinesia and decreased rCBF in the SMA correlated with improvement in rigidity. It is, however, still not fully understood how rCBF reflects “normalization” of the abnormal pattern of neuronal firing in the target nuclei. ▶

The localization of STN has been facilitated by the neurophysiologic characterization of the STN (Hutchinson et al., 1998). The mean firing rate was found to be 37 Hz. The firing pattern was irregular and movement sensitive. In addition, tremor cells were identified in the STN and ventral pallidum. Macroelectrode STN stimulation completely suppressed contralateral tremor (Ashby et al., 1999). In a 1-year follow-up of 24 PD patients treated with bilateral STN stimulation, the UPDRS II and III improved by 60% and the mean dose of dopaminergic drugs was reduced in half (Limousin et al., 1998). Krack and colleagues (1998b) found a 71% reduction in the UPDRS score in patients treated with STN DBS. Using subjective evaluation of contralateral wrist rigidity, Rizzone and colleagues (2001) studied the effects of various STN stimulation parameters in patients with PD during a drug-free state. They found that stimulus rates higher than 90 Hz and a pulse width larger than 60 μs rarely produce additional benefits and are associated with narrowing of the therapeutic window. On the basis of longitudinal experience in a large number of patients, a monopolar stimulation with 2 V, pulse width 60 μs , and frequency of 100 to 130 Hz is usually found to provide maximal benefit (Ushe et al., 2004). There is a characteristic pattern of emergence of tremor within minutes of discontinuation of the DBS, followed by slow and steady worsening of axial signs over 3 to 4 hours, with 90% of the UPDRS score worsening occurring within 2 hours after DBS is turned off (Temperli et al., 2003).

Video 7.3 Deep brain stimulation for multiple sclerosis–related tremor.

Video 7.4 Deep brain stimulation for Parkinson disease.

Video 7.5 Deep brain stimulation for Parkinson disease.

When the STN DBS is turned on, a similar but faster rate of improvement is observed. In an analysis of the effects of 25 electrodes used in STN DBS, placement in the dorsolateral STN border was associated with best clinical results and least energy consumption (Herzog et al., 2004) and stimulation of the dorsal border of STN has been associated with the most robust clinical improvement (Maks et al., 2009). Stimulation of the MRI-defined lateral segment of the STN was associated with significantly better clinical improvement, lower stimulation parameters, and less need for postoperative dopaminergic medication compared with stimulation with contacts placed within the medial region of the STN (Wodarg et al., 2012). On the other hand, ventral stimulation was associated with more adverse cognitive and mood changes (Okun et al., 2009).

Stereotactic surgery is the most effective and predictable treatment for levodopa-induced dyskinesia resistant to pharmacologic therapy (Guridi et al., 2008). In a multicenter, prospective, double-blind, crossover study in 134 patients with advanced PD treated with DBS of STN or GPi, the UPDRS motor scores improved by 49% ($P < 0.001$) and 37% ($P < 0.001$), respectively, in comparison to the nonstimulated state (Deep-Brain Stimulation for Parkinson's Disease Study Group, 2001). Furthermore, 6 months after implantation compared with baseline, the percent time "on" without dyskinesias increased from 27% to 74% ($P < 0.001$) and from 28% to 64% ($P < 0.001$) with STN and GPi DBS, respectively. Although the levodopa dosage remained unchanged in the GPi group, the daily levodopa dose equivalents were reduced by 37% in the STN DBS group ($P < 0.001$) (Fig. 7.4). Adverse events included intracranial hemorrhage in 7 patients and infection necessitating removal of the leads in 2 patients. Although the largest and best-designed study, it

was criticized because of methodologic flaws (e.g., absence of true blindness), short follow-up, and underreporting of adverse effects (Obeso et al., 2002). In a blinded assessment at 1 year after implantation of STN DBS in 30 patients, the motor UPDRS score decreased by only 30%, but duration of daily wearing off decreased by 69%, and levodopa requirements decreased by 30% (Ford et al., 2004). In a double-blind study of 7 patients treated with STN DBS, Kumar and colleagues (1998a) found 58% improvement in the UPDRS motor score in a medication-off state when the stimulator was turned on. Furthermore, there was an 83% improvement in levodopa-induced dyskinesias, and the total drug dosage decreased by 40%. In another study involving 23 patients with PD treated with bilateral STN DBS, Houeto and colleagues (2000) showed that the procedure decreased levodopa-induced motor fluctuations, dyskinesias, and daily dose of levodopa by 61% to 78%. Similarly, Fraix and colleagues (2000) showed in 24 patients with PD treated with bilateral STN DBS that the observed improvement in levodopa-induced dyskinesia was associated with a reduction in levodopa dosage. In another study, the combination of reduced levodopa and STN stimulation reduced the duration of diphasic and peak-dose dyskinesias by 52% and reduced "off" period dystonia by 90% and "off" period pain by 66% (Krack et al., 1999). In another, much smaller, study involving only 15 patients with PD treated with bilateral STN DBS, the overall levodopa daily dose was reduced by 80.4%, and levodopa was withdrawn in 8 (53%) patients (Molinuevo et al., 2000). In a long-term follow-up, they showed that 10 of 26 (38%) patients were maintained on STN DBS monotherapy after 1.5 years of treatment (Valdeoriola et al., 2002). Similarly, Vingerhoets and colleagues (2002) found that 21 ± 8 months after implantation of bilateral STN DBS under stereotactic guidance, microelectrode recording, and clinical control in 20 patients, the UPDRS III "off medication" score decreased by 45% and was similar to the UPDRS III "on medication" score. Furthermore, medication was reduced by 79% and 10 (50%) were able to withdraw their medications completely. In a subsequent study of two groups of 6 STN DBS-treated patients, the investigators showed that patients who were able to discontinue their medication and were subsequently challenged with levodopa had much less severe levodopa-induced dyskinesia than did those who had continued on levodopa, thus supporting "dopaminergic stimulation and striatal desensitization as major determinants of levodopa-induced dyskinesia in PD" (Russmann et al., 2004a). In a 2-year follow-up of 20 patients with STN DBS, the 50.9% UPDRS motor score reduction observed at 6 months was maintained during the follow-up period (Herzog et al., 2003). In a 5-year prospective study of the first 49 patients, mean age 55 years, treated with bilateral STN DBS, assessed during "on" and "off" states at 1, 3, and 5 years, the Grenoble group found a 54% improvement in "off" motor function compared with baseline and 49% improvement in ADLs (Krack et al., 2003). Speech was apparently the only motor function that did not improve. Except for improved dyskinesia and lower daily levodopa dose, there was no additional improvement in "on" motor function beyond 1 year, and the axial symptoms continued to deteriorate after the first year. Of the initial 49 patients, 7 did not complete the study, 3 died, 4 were lost to follow-up, 3 developed dementia after 3 years, 1 committed suicide, and 1 had

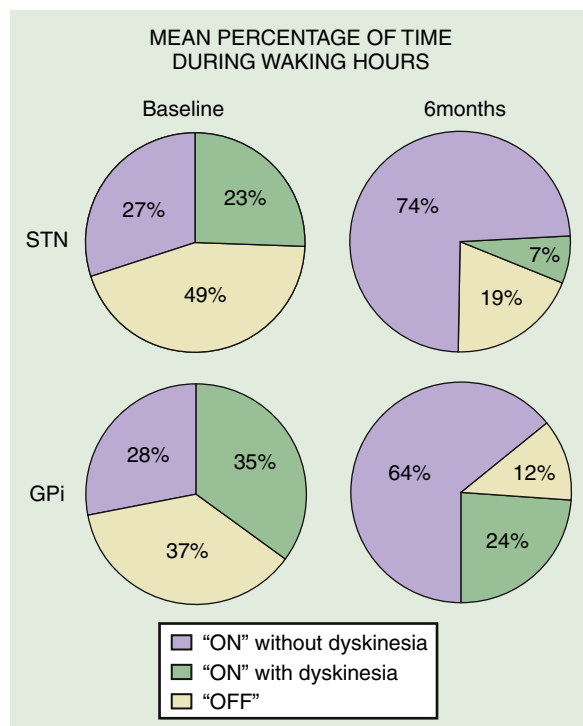


Fig. 7.4 Results of a multicenter trial of STN and GPi DBS. (Redrawn from Deep-Brain Stimulation for Parkinson's Disease Study Group. *N Engl J Med.* 2001;345:956–963.)

a large cerebral hemorrhage. This and other studies provide evidence for the conclusion that STN DBS is no better than levodopa, but it ameliorates levodopa-related motor complications and dyskinesias and “off” period dystonia. In a double-blind, crossover evaluation of STN DBS in 10 patients during practically defined “off” (medications stopped overnight), the mean motor UPDRS score improved from 43 to 26 ($P < 0.04$), and various timed tests (walking and tapping) also improved significantly ($P < 0.04$) (Rodriguez-Oroz et al., 2004). Open-label, 4-year follow-up also showed significant improvement in dyskinesia and levodopa reduction by half. In a 5-year follow-up of 11 patients treated with bilateral pallidal DBS, dyskinesias remained well controlled, but the initial benefit in “off” motor symptoms and fluctuations and ADLs gradually declined and the benefits were restored in 4 patients after replacement of the pallidal electrodes into STN (Volkman et al., 2004). In a study of 30 patients undergoing STN DBS, levodopa-induced complications based on UPDRS IV and during an acute levodopa challenge improved markedly after 1 year (both on and off stimulation) and still further at 5 years (Simonin et al., 2009). Furthermore, the peak-dose dyskinesia decreased significantly between 1 and 5 years, possibly related to a reduction in levodopa equivalent dose from 1323 ± 501 mg at baseline to 753 ± 451 mg at year 1, and 850 ± 555 mg at year 5. The DBS parameters at 5-year follow-up were voltage 2.92 ± 0.73 V, frequency 127 ± 28 Hz, and pulse 76 ± 14 μ s. These results are consistent with many other studies showing long-term benefits of STN DBS in PD (Wider et al., 2008), although there is a gradual emergence and progression of nondopaminergic symptoms such as falls, dysphagia, incontinence, and dementia (Merola et al., 2011). In a 10-year follow-up of 41 patients operated between 1996 and 2000 at the Toronto Western Hospital, 18 of whom were available for follow-up assessments, STN-DBS, as assessed by “blinded” rating of videos, still significantly improved the UPDRS II and IV, total motor score, resting and action tremor, and bradykinesia subscores with reduced levodopa equivalent daily dose compared with baseline (Castrìoto et al., 2011). Axial signs, however, showed progressive decline over that period despite reducing the frequency of stimulation to 60 Hz, as recommended by some investigators (Brozova et al., 2009).

Reduction of dopaminergic drugs as a result of STN DBS may unmask restless legs syndrome (Kedia et al., 2004). STN DBS, however, has been reported to improve restless legs syndrome in six patients in whom the syndrome accompanied PD (Driver-Dunckley et al., 2006). Bilateral STN DBS has been reported to produce about 78% improvement in the thoracolumbar angle of patients with PD-associated camptocormia (Sako et al., 2009; Jankovic, 2010). Other reports have suggested that spinal corrective surgery may provide a significant benefit to patients with PD-related camptocormia and kyphosis (Wadia et al., 2011).

Besides reducing the need for levodopa, bilateral STN DBS also reduces the need for other medications, including apomorphine (Varma et al., 2003). Moro and colleagues (2002) showed that although the duration and latency of levodopa response are well maintained in patients with chronic STN DBS, the magnitude of the short-duration response tends to decrease with time. Because improvements in dyskinesia usually require a reduction in levodopa dosage, unilateral STN DBS is impractical because the side of the body contralateral

to the unstimulated side would clearly worsen. Many investigators recommend bilateral STN DBS even in markedly asymmetrical PD (Kim et al., 2009). Furthermore, bilateral implantation during a single procedure is less inconvenient to the patient than a staged procedure, the neurophysiologic mapping may be facilitated by anatomic symmetry, and implantation of both stimulators can be performed under a single general anesthetic.

Bilateral STN DBS appears to be more effective than unilateral STN DBS in improving parkinsonism, but unilateral STN DBS may be appropriate for patients with asymmetrical parkinsonian symptoms, including a high-amplitude tremor (Kumar, Lozano, et al., 1999; Linazasoro et al., 2003; Sturman et al., 2004; Stover et al., 2005; Diamond, Shahed, Jankovic, 2007; Fishman et al., 2008). STN DBS has been shown to have a robust effect not only on levodopa-related motor complications, but also on the treatment of PD-related tremor (Diamond, Shahed, Jankovic, 2007). This marked benefit on tremor is also supported by marked improvement of postural and kinetic tremor with stimulation of the subthalamic area (Murata et al., 2003; Herzog et al., 2007; Hamel et al., 2007). Because bilateral STN DBS appears to be associated with less ataxia and dysarthria than VIM DBS (Pahwa et al., 2006), it may be considered the target of choice in patients with ET requiring bilateral stimulation (Diamond, Shahed, Jankovic, 2007).

Bilateral STN DBS greatly improves functioning and reduces levodopa-induced dyskinesias, probably by allowing a reduction in total levodopa dosage. STN DBS, however, may also somehow reverse the levodopa sensitization, because levodopa-induced dyskinesias seem to be markedly reduced after continuous bilateral STN stimulation even when the DBS is turned off (Bejjani et al., 2000). This may be due to the marked reduction in daily levodopa dose permitted by chronic STN DBS. Nutt and colleagues (2001b) suggested that the improvement in motor fluctuations produced by STN and GPi DBS is due to improvement in “off” disability rather than any effects on pharmacodynamics or pharmacokinetics of levodopa. Younger patients with levodopa-responsive PD are considered the best candidates for bilateral STN DBS (Charles et al., 2002; Welter et al., 2002). In a 2-year follow-up of patients with bilateral STN DBS, preoperative response to levodopa was found as the only predictor of a favorable outcome (Kleiner-Fisman et al., 2003). Washout effects of STN DBS vary among patients, but patients with longer duration of disease seemed to have faster washout after cessation of stimulation (Cooper et al., 2013).

In patients with prior pallidotomy, bilateral (not unilateral) STN DBS may be beneficial (Su and Tseng, 2001; Kleiner-Fisman et al., 2004). The mean firing frequency of STN on the side ipsilateral to the pallidotomy is lower than on the contralateral, intact side (Mogilner et al., 2002). In a randomized trial involving 34 patients with advanced PD the “off” UPDRS score improved significantly more after bilateral STN DBS compared with unilateral pallidotomy; “on” UPDRS motor and dyskinesia scores also improved more in the DBS group than in the pallidotomy group (Esselink et al., 2004).

Although bilateral STN DBS is clearly effective in improving the cardinal and other parkinsonian symptoms, the procedure does not necessarily improve all the symptoms, and as a result of progression of cognitive, speech, and other deficits

frequently associated with PD, the quality of life might not substantially improve in patients who exhibit these additional features (Hariz et al., 2000; Diamond and Jankovic, 2005), only about half of patients regain their employment, and many experience new marital and socioprofessional problems (Schuepbach et al., 2006). In one study, only young PD patients were found to have a significant improvement in their quality of life with STN DBS (Derost et al., 2007). Furthermore, preexisting personality disorders and psychiatric disorders might not necessarily improve with STN DBS and might actually worsen and further compromise the patient's quality of life (Houeto et al., 2002), but in carefully selected patients, mood, anxiety, apathy, and quality of life may improve with the procedure (Czernecki et al., 2005; Houeto et al., 2006). Normalization of bladder symptoms associated with PD-related detrusor hyperreflexia was demonstrated in a study of 16 patients with bilateral STN DBS (Seif et al., 2004).

Using the PD Quality of Life Questionnaire in 60 patients, Lagrange and colleagues (2002) showed improvements 1 year after bilateral STN DBS in all dimensions, including motor (+48%), systemic (+34%), emotional (+29%), and social (+63%). Other studies have demonstrated significant improvements in health-related quality of life in patients with advanced PD treated with bilateral STN DBS (Just and Ostergaard, 2002; Lagrange et al., 2002; Martinez-Martin et al., 2002). In another study, Lezcano and colleagues (2004a) applied the UPDRS, PDQ-39, and the scale of quality of life for caregivers (SQLC) in 11 PD patients 2 years after they had undergone bilateral STN DBS and found 62% improvement in PDQ-39 ($P < 0.001$) and 68% in SQLC ($P = 0.002$). In an 18-month follow-up of patients after bilateral implantation of STN DBS, sustained improvements were demonstrated in a variety of measures of HRQL (Siderow et al., 2006). A cost-effectiveness analysis suggests that DBS could be cost effective in treating PD quality of life, which improved 18% or more compared with best medical treatment (Tomaszewski and Holloway, 2001). In a European SPARK study the 6-month cost of PD decreased from about \$10,000 to \$1600 after bilateral STN DBS, largely because of marked reduction in medications (Fraix et al., 2006). In a 6-month study of 156 patients with advanced PD randomized to STN DBS or medical management, the German Parkinson Study Group (Deuschl et al., 2006) concluded that STN DBS was more effective than medical management. The baseline characteristics, including the mean age of the patients in each group (60.5 versus 60.8 years, respectively) was similar, but the mean PDQ-39 score, the primary endpoint, decreased from 41.8 to 31.8 in the DBS group (25% improvement) and increased from 39.6 to 40.2 in the medication group (no improvement). The PDQ-39 improvement in the DBS group was significant in the subscales for mobility, ADLs, emotional well-being, stigma, and bodily discomfort. The mean UPDRS III score during "off" time improved from 48.0 to 28.3 (41% improvement) with DBS, but remained unchanged in the medication group (46.8 versus 46.0) and improved during "on" time from 18.9 to 14.6 (23% improvement) in the DBS group, but remained unchanged in the medication group (17.3 versus 17.5). Although a total of 39 (50%) adverse events were reported in the DBS group compared with 50 (64%) in the medication group, there were significantly more serious adverse events

reported in the DBS group ($N = 10$, 12.8%), including three deaths, compared with the medication group ($N = 3$, 3.8%) ($P = 0.04$). A total of 255 patients were enrolled in a randomized controlled trial (RCT), designed to compare the effects of DBS (STN, $N = 60$, or GPi, $N = 61$) and "best medical therapy" ($N = 134$) after 6 months, at seven Veterans Affairs (The Parkinson's Disease Research, Education, and Clinic Center, PADRECC) and six university hospitals (Weaver et al., 2009). Patients treated with DBS gained a mean of 4.6 hours/day of "on" time without troubling dyskinesia compared with 0 hours/day for patients who received best medical therapy ($P < 0.001$) (Fig. 7.5). Furthermore, motor function improved by 5 or more points on the motor UPDRS in 71% of DBS and 32% of medical therapy patients. This was accompanied by improvements in the majority of PD-related HRQL measures and only minimal decrement in neurocognitive testing. The overall risk for experiencing a serious adverse event, however, was 3.8 times higher in the DBS group than in the medical therapy group (40% versus 11%). Although benefits associated with DBS extend beyond what can be achieved with medical therapy alone, selection of the appropriate patients and target and skills and experience of the DBS team must be considered before referring patients for this surgical treatment (Okun and Foote, 2009). It is also important when selecting candidates for surgery to carefully evaluate all the ethical aspects of DBS, the net benefit, and the long-term burden it may place on the patient and his or her caregiver, especially given the impaired cognition that can follow the implantation of the DBS (Farris et al., 2008). Only a few studies have objectively compared these two approaches (Okun and Foote, 2005; Okun et al., 2009; Albanese and Romito, 2011) (see Fig. 7.4). Before addressing this controversy, it is important to point out that GPi is a much larger

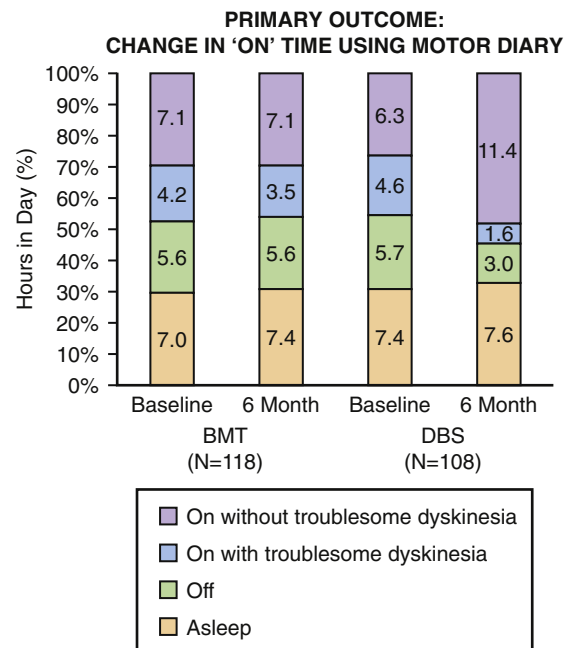


Fig. 7.5 Results of a multicenter trial comparing DBS (subthalamic nucleus [STN] or GPi, globus pallidus interna [GPi]) and best medical therapy. (Data from Weaver FM, Follett K, Stern M, et al.; CSP 468 Study Group: Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. *JAMA*. 2009;301:63–73.)

target than STN (500 mm³ versus 200 mm³) and therefore requires a greater density of stimulation. On the other hand, stimulation of the STN, because it is a smaller target, may lead to spreading of current from the intended sensorimotor area to potentially unwanted areas of the nucleus, such as the associative and limbic regions. This might account for a slightly higher frequency of cognitive and behavioral adverse effects with STN DBS (Anderson et al., 2005). Several studies have demonstrated greater antidyskinetic effects of GPi versus STN stimulation, and some studies have suggested that GPi DBS might be especially indicated in patients with a low threshold for dyskinesia (Minguez-Castellanos et al., 2005), and GPi is considered by many experts to be the desirable target for treatment of dystonia and other hyperkinetic movement disorders. The relative safety and efficacy of STN versus GPi DBS have been compared in a few studies (Burchiel et al., 1999; Anderson et al., 2005; Okun et al., 2009). Although Burchiel and colleagues (1999) found no difference between the two targets, their initial study had insufficient power to detect a difference between the two groups. In their subsequent study involving 23 patients with PD complicated by marked levodopa-related motor fluctuations and dyskinesias, the investigators concluded that there were no significant differences in the overall benefits, although levodopa was decreased more in the STN group and dyskinesia improved more in the GPi group (Anderson et al., 2005). Krause and colleagues (2001) reported results in 6 patients with PD treated with GPi DBS and 12 patients with STN DBS. They found that although GPi DBS was associated with a lower frequency of levodopa-related complications, there was no improvement in bradykinesia or tremor. STN DBS, on the other hand, improved all parkinsonian symptoms and was associated with a reduced daily dose of levodopa. The authors concluded that STN was “the target of choice” for patients with severe PD who have side effects from levodopa. In a retrospective analysis of 16 patients undergoing STN DBS versus 11 treated with GPi DBS, Volkman and colleagues (2001) showed that STN stimulation was associated with a 65% reduction in medication and required less electric power but required more intensive postoperative monitoring and was associated with a higher frequency of adverse effects related to levodopa withdrawal compared with GPi DBS. A retrospective study using MRI-guided STN DBS showed 52% improvement in the UPDRS and in levodopa-induced dyskinesia with very low frequency of adverse effects (Foltynie et al., 2011; Krack, 2011).

Several studies attempted to compare STN versus GPi as targets for DBS in PD. No difference between stimulation of the two targets on improvement of rigidity, strength, speed of movement execution, or movement initiation was found (Brown et al., 1999). For most effective results, the upper STN (sensorimotor part) and the subthalamic area containing the zona incerta, fields of Forel, and STN projections should be stimulated (Hamel et al., 2003). However, further controlled, randomized studies are needed to answer the question of which of the two methods is more effective and which patients should be considered the best candidates for either of the two procedures. In the COMPARE trial, 52 patients were randomized to unilateral STN or GPi DBS without any significant difference in outcomes except more worsening in letter verbal fluency in patients with STN DBS (Okun et al., 2009). In a follow-up analysis of the Veterans

Affairs Cooperative Studies Program (Weaver et al., 2009) outcomes for the STN and GPi DBS were analyzed after 24 months in 299 patients; there were no differences in mean changes in the motor (Part III) UPDRS between the two targets (Follett et al., 2010). Patients undergoing STN required a lower dose of dopaminergic agents than did those undergoing pallidal stimulation ($P = 0.02$) and visuomotor processing speed declined more after STN than after GPi stimulation ($P = 0.03$). On the other hand, there was worsening of depression after STN DBS but mood improved after GPi DBS ($P = 0.02$). Slightly more than half of the patients experienced serious adverse events, but there was no difference in the frequency of these events between the two groups. Based on these and other studies there is emerging evidence that GPi DBS may be particularly suitable for patients who may have troublesome dyskinesias and mild cognitive or behavioral impairment, whereas bilateral STN DBS may be the surgical choice for patients who are cognitively intact but in whom reduction in levodopa dosage is the primary goal. In the PD SURG trial, an ongoing randomized, open-label trial at 13 neurosurgical centers in the United Kingdom, 366 patients were randomly assigned to receive immediate surgery (DBS) and best medical therapy (183) or best medical therapy alone (183) (Williams et al., 2010). At 1 year, the mean improvement in PDQ-39 summary index score compared with baseline was 5.0 points in the surgery group and 0.3 points in the medical therapy group ($P = 0.001$), but there were 25 adverse events in the surgical group and only 14 events in the medical group (Williams et al., 2010). Furthermore, a meta-regression analysis of long-term effects of DBS on balance and gait suggested that GPi DBS may be more effective than STN DBS for patients with postural instability and gait disability (PIGD) (St. George et al., 2010). In a study of 133 patients, followed at the University of Florida, there was no statistical difference in the improvement in dyskinesia between STN and GPi (Oyama et al., 2012). In the NSTAPS study, 128 patients from five centers in the Netherlands, 65 of whom were assigned to GPi DBS and 63 to STN DBS (Odekerken et al., 2013). No statistically significant difference in either of the primary outcomes: mean change in weighted Academic Medical Center Linear Disability Scale (ALDS) between the two targets, but there was a more robust improvement in off-drug phase in the STN group compared with the GPi group in the mean change in UPDRS Motor Part and reduction in dopaminergic drugs. The authors suggested a slight advantage for STN in motor symptoms. Of the 128 patients initially enrolled, 90 completed the 3-year follow-up and found that “off” motor symptoms and functioning improve more after STN DBS than after GPi DBS (Class II evidence) with a similar risk for cognitive, mood, and behavioral complications (Odekerken et al., 2016).

In the first randomized clinical trial of DBS aimed to assess the safety and efficacy of bilateral constant-current stimulation of STN DBS 136 patients with moderately advanced PD were implanted with the constant-current device (Libra DBS, St. Jude Medical Neuromodulation Division, Plano, TX, United States) and were randomly assigned to receive immediate (101 patients) or delayed (35 patients) stimulation (Okun et al., 2012). An increase in “on” time was greater in the stimulation group than the control delayed group (4.27 hours versus 1.77 hours, difference 2.51 [95% CI, 0.87–4.16]; $P = 0.003$) and the UPDRS motor scores in

the off-medication state improved by 39% from baseline (24.8 versus 40.8) with stimulation. Among the most serious adverse events were infections (4%) and intracranial hemorrhage (3%); other side effects associated with STN DBS included dysarthria, fatigue, and paresthesias. Unfortunately, the subjects were not blinded after the randomization; and, therefore, the benefit in the control group could have been attributed to a placebo effect (surprisingly, there was no nocebo effect) despite the expected disappointment of control patients). The rationale for constant-current stimulation was that this method has the theoretical advantage over voltage-driven devices because the latter devices are susceptible to heterogeneity in tissue impedance. However, after a few weeks the electrode-tissue interface is stabilized and the electrode impedance remains relatively constant (Volkman, 2012).

DBS of the STN has been found to be effective in controlling not only parkinsonian tremor (Sturman et al., 2004), but also bradykinesia, gait difficulty, and freezing (Limousin et al., 1995; Allert et al., 2001; Faist et al., 2001; Stolze et al., 2001; Bakker et al., 2004; Ferraye et al., 2010; Moro et al., 2010) and handwriting (Siebner et al., 1999). In addition to improving limb signs and the cardinal signs of PD, bilateral STN DBS has been found to also improve axial parkinsonian symptoms, particularly arising from chair and gait (Bastian et al., 2003; Bakker et al., 2004), in addition to speech, neck rigidity, abnormal posture, "off" dystonia, balance, and postural instability (Maurer et al., 2003; Colnat-Coulbois et al., 2005; Nilsson et al., 2005; Shivitz et al., 2006), and sensory symptoms (Bejjani, Damier, et al., 2000; Lohr et al., 2002; Rocchi et al., 2002; Krystkowiak et al., 2003). Even sexual functioning has been shown to improve after STN DBS (Castelli et al., 2004). Using static posturography, Rocchi and colleagues (2002) found an improvement in postural sway with bilateral STN DBS but worsening with levodopa. Bilateral STN DBS has been reported to improve PD-related dysarthria in some studies (Gentil et al., 1999; Pollak, 1999). Other studies, however, have found that dysarthria, cognitive impairment, and postural instability fail to improve with STN DBS even in the same PD patient in whom the procedure improved the usual levodopa-responsive symptoms (Jarraya et al., 2003). STN or GPi DBS has been shown to improve gait velocity by increasing stride length with normalization of the gait pattern (Pahwa et al., 1997; Allert et al., 2001; Damier et al., 2001; Faist et al., 2001; Bastian et al., 2003). In one study, the "off" period cadence increased from 117 ± 18.9 steps per minute to 126 ± 9.4 steps per minute ($P < 0.05$) after GPi DBS (Volkman et al., 1998). In contrast, bilateral STN DBS increased stride length but not cadence (Allert et al., 2001; Faist et al., 2001). Other studies reported significant improvements in essentially all components of gait (Krystkowiak et al., 2003; Bakker et al., 2004). The possibility that chronic DBS interferes with STN's excitatory output has suggested to some experts a controversial role of this treatment as a neuroprotective strategy (Piallat et al., 1996; Henderson and Dunnett, 1998; Krack et al., 1998b). This notion is supported by the observation that ablation of STN attenuates the loss of dopamine neurons in rats exposed to the mitochondrial toxin 3-nitropropionic acid (3-NP) or the catecholamine toxin 6-hydroxydopamine (6-OHDA) (Nakao et al., 1999). A 20% to 40% preservation of SN neurons was observed with STN lesion of DBS using

MPTP monkeys as a model for PD (Wallace et al., 2007). The animal studies have led some investigators to argue that STN DBS may offer neuroprotection by reducing glutamate excitotoxicity and that performing the procedure early in the course of the disease might prevent motor disability and adverse reactions to levodopa (Mesnage et al., 2002; Schuepbach et al., 2007; Wallace et al., 2007).

There is growing interest in applying DBS earlier in the course of PD, partly supported by animal studies that provide a rationale for STN DBS as a potential neuroprotective strategy (deSouza et al., 2013). In one prospective study of 20 patients with early PD, randomized to either STN-DBS or medical therapy, the authors found that the quality of life measures improved 24% in the surgical group but not at all in the medical group and after 18 months the severity of parkinsonian motor signs off medication, levodopa-induced motor complications, and daily levodopa dose were reduced by 69%, 83%, and 57% in operated patients and increased by 29%, 15%, and 12%, respectively, in the group with medical treatment only ($P < 0.001$) (Schuepbach et al., 2006). The authors concluded that DBS "should be considered a therapeutic option early in the course of PD." The EARLYSTIM trial, which included patients with onset of levodopa-induced motor complications for only 3 years or less (Deuschl et al., 2013). In this 2-year trial, designed to assess the effects of DBS in early PD, 251 patients with PD and early motor complications (mean age, 52 years; mean duration of disease, 7.5 years) were randomized to STN DBS plus medical therapy versus medical therapy alone (Schuepbach et al., 2013). For the primary outcome of quality of life, the mean score for the DBS group improved by 7.8 points, and that for the medical-therapy group worsened by 0.2 points (between-group difference in mean change from baseline to 2 years, 8.0 points; $P = 0.002$). Furthermore, DBS was superior to medical therapy with respect to motor disability ($P < 0.001$), ADLs ($P < 0.001$), levodopa-induced motor complications ($P < 0.001$), and time with good mobility and no dyskinesia ($P = 0.01$). Serious adverse events occurred in 54.8% of the patients in the DBS group and in 44.1% of those in the medical-therapy group; serious adverse events related to surgical implantation or the neurostimulation device occurred in 17.7% of patients. The only three deaths in the trial were due to suicide, 2 patients in the DBS group and 1 in the medical-therapy group. Another randomized controlled trial aimed at assessing the usefulness of early STN DBS involved 30 subjects with relatively mild PD (Hoehn and Yahr stage 2 off medication), on medication 6 months or longer but 4 years or less, and without motor fluctuations or dyskinesias (Charles et al., 2014). They were randomized to optimal drug therapy (ODT) ($n = 15$) or DBS + ODT ($n = 15$). At 24 months after randomization the mean UPDRS total and Part III scores were not significantly different on or off therapy, but medication requirements in the DBS + ODT group were lower at all time points, with a maximal difference at 18 months. Two subjects in the DBS + ODT group suffered serious adverse events. Further studies are needed to determine the role of DBS in early stages of PD (Hacker et al., 2015).

The Vanderbilt group published a safety and feasibility study of early PD DBS before the onset of motor fluctuations. "DBS plus optimal drug therapy (DBS + ODT) subjects experienced a 50% to 80% reduction in the relative risk of

worsening after 2 years. The DBS + ODT group was improved compared with optimal drug therapy at 24 months. Total UPDRS, Part IV, and PDQ-39 scores significantly worsened in the ODT group after 2 years with no significant change in the DBS + ODT group" (Hacker 2015). In a small follow-up study this same group showed data to suggest that early DBS may possibly slow tremor progression (Hacker, 2018).

Effects of ablative surgery versus DBS on various parkinsonian features have not been adequately compared. In one prospective study, 13 patients with PD were randomized to pallidal stimulation versus pallidal ablation (Merello et al., 1999). Although the primary endpoint effects at 3 months on UPDRS and ADLs were "comparable," pallidal DBS had more beneficial effects on hand-tapping speed, whereas pallidotomy had more robust effect on levodopa-induced dyskinesias. However, additional blinded comparison studies of STN versus GPi DBS are needed before any definite conclusions about the relative effects of the two targets can be made. DBS electrodes are increasingly being used to make ablative lesions in the target areas (Raoul et al., 2003). GPe DBS might also provide benefits to patients with PD and with less delay than GPi DBS, although in one study, it was associated with slightly higher frequency of dyskinesia (20% versus 9%) (Vitek et al., 2004).

As with any procedure, appropriate selection of patients as candidates for DBS surgery is critical to ensure optimal outcome (Table 7.5). Screening tools for surgical candidates have been developed and validated (Okun, Fernandez, et al., 2004; Tan and Jankovic, 2013). Although traditionally PD patients with moderately advanced PD responsive to levodopa but who experience levodopa-related complications that could not be adequately managed medically, have been considered candidates for DBS, but there is growing interest in the role of DBS as a potential disease-modifying therapy in early stages of PD (Kahn et al., 2012). Many studies have demonstrated that patients with atypical parkinsonism, such as progressive supranuclear palsy, multiple system atrophy, or dementia with Lewy bodies, do not respond well to surgery and their symptoms may substantially worsen after surgery. Patients with atypical parkinsonism, such as multiple system atrophy, are poor candidates for surgery, and

STN DBS may aggravate speech, swallowing, and gait (Tarsy et al., 2003; Lezcano et al., 2004b; Shih and Tarsy, 2007).

The diagnostic inaccuracy improves with follow-up; thus, it is advisable to consider patients for surgery only when there is a considerable duration of symptoms (at least 5 years). This is reasonable considering the fact that most patients develop complications of fluctuations and dyskinesias, the chief indications for surgery, only after 5 to 6 years of levodopa therapy.

Besides GPi, GPe, and STN, other targets that are being explored for DBS treatment of PD include caudal part of the zona incerta (cZI) (Plaha et al., 2006, 2008a,b, 2011) and PPN (Hamani et al., 2007; Stefani et al., 2007). Several groups have reported that the most effective target for treatment of PD lies dorsal/dorsomedial to the STN (region of the pallidofugal fibers and the rostral zona incerta) or at the junction between the dorsal border of the STN and the latter. In a study of 35 patients with PD who underwent MRI-directed implantation of 64 DBS leads into the STN (17), dorsomedial/medial to STN (20), and cZI (27), the mean adjusted contralateral UPDRS III score with cZI stimulation was 3.1 (76% reduction) compared with 4.9 (61% reduction) in the group with target dorsomedial/medial to STN, and 5.7 (55% reduction) in the STN (P value for trend < 0.001) (Plaha et al., 2008a). There was a 93% improvement in tremor with cZI stimulation, but no improvement in dyskinesia scores and no change in levodopa dosage. The authors concluded that "High frequency stimulation of the cZI results in greater improvement in contralateral motor scores in PD patients than stimulation of the STN" (see Fig. 7.3). The authors also showed that rest tremor of PD can be induced by 5- to 40-Hz stimulation of cZI (Plaha et al., 2008a) and that PD tremor, ET, and other tremors may be markedly improved with low-voltage, high-frequency DBS of cZI (Plaha et al., 2008b, 2011). Bilateral DBS of cZI nucleus may be a better target for DBS treatment of ET because it appears to cause less disequilibrium (Plaha et al., 2011).

Pathologically proven case of cZI DBS provided evidence for effective treatment of PD symptoms with stimulation of this target (Guehl et al., 2008). Other targets when stimulated with high frequency shown to improve bradykinesia and other parkinsonian features include putamen (Montgomery et al., 2011).

Low-frequency (60 Hz) compared with the standard high-frequency (130 Hz) STN stimulation has been reported to benefit freezing (Moreau et al., 2008), but this PD symptom is usually refractory to both medical and surgical therapy. High-frequency STN DBS does not appear to provide additional benefit on freezing beyond levodopa (Ferraye et al., 2010). Although PPN DBS has been reported to provide improvement in gait in monkeys, targeting this brainstem nucleus for therapeutic purposes in patients with PD or other movement disorders associated with gait difficulty will be technically challenging (Jenkinson et al., 2006). PPN has been proposed as a potential therapeutic target in patients with gait and balance difficulties, including freezing (Nashatiazadeh and Jankovic, 2008; Strafella et al., 2008; Ferraye et al., 2010; Moro et al., 2010). Six patients with unsatisfactory pharmacologic control of axial signs such as gait and postural stability underwent bilateral implantation of DBS electrodes in the STN and PPN (Stefani et al., 2007). Clinical effects were evaluated 2 to 6 months after surgery in the off- and

Table 7.5 Selection of patients for deep brain stimulation

Parkinson disease (Pd) greater than 5 years (to allow for atypical features to emerge and assess response to dopaminergic therapy)
Select cases PD less than 5 years if younger and motor fluctuations
Dopaminergic responsiveness (>30% reduction in motor UPDRS)
There are select candidates who may fall short on the levodopa challenge (<30%)
Troublesome dyskinesias despite optimal medical therapy
Disabling medication responsive or resistant tremor
"Off" time
Exclude atypical and secondary parkinsonism
Exclude dementia and active depression
Exclude active untreated psychiatric issues (e.g., hallucinations, bipolar, anxiety, depression)
Few comorbidities
Realistic expectations
Magnetic resonance imaging with a clear surgical target and no contraindications

UPDRS, Unified Parkinson's Disease Rating Scale.

on-medication state, with both STN and PPN stimulation “on” or “off,” or with only one target being stimulated. Bilateral PPN-DBS at 25 Hz in off-medication produced an immediate 45% amelioration of the motor UPDRS subscale score, followed by a decline to give a final improvement of 32% in the score after 3 to 6 months. In contrast, bilateral STN-DBS at 130 to 185 Hz led to about 54% improvement. PPN-DBS was most effective on gait and postural items. In on-medication state, the association of STN and PPN-DBS provided a significant further improvement compared with the specific benefit mediated by the activation of either single target. Moreover, the combined DBS of both targets promoted a substantial amelioration in the performance of ADLs. The authors thought these findings indicate that in patients with advanced PD, PPN-DBS associated with standard STN-DBS may be useful in improving gait and in optimizing the dopamine-mediated “on” state, particularly in those whose response to STN only DBS has deteriorated over time and may also prove useful in disorders such as progressive supranuclear palsy. In another study, involving 6 patients with PD, unilateral PPN DBS was reported to reduce frequency of falls (Moro et al., 2010), but further studies are needed to confirm this initial finding. Patients with significant freezing of gait were not evaluated in this study, but were the subjects of other reports. In one patient, a 63-year-old man with PD-related freezing of gait, postural instability, and marked bradykinesia, PPN DBS resulted in 20% improvement in motor function, associated with increased rCBF in both thalami (Strafella et al., 2008). In a double-blinded study using objective spatiotemporal gait analysis in parkinsonian patients with severe gait freezing, caudal PPN DBS improved objective measures of gait freezing and Freezing of Gait Questionnaire scores, with bilateral stimulation more effective than unilateral (Thevathasan et al., 2012). At Baylor College of Medicine, we assessed the effects of PPN DBS in three patients. Patient 1, a 59-year-old man, underwent bilateral PPN DBS with noticeable improvement in his freezing of gait 2 and 6 weeks postoperatively, but the improvement was not subsequently sustained despite adjustments of stimulating parameters (Nashatiazedh and Jankovic, 2008). Patient 2, a 76-year-old man previously received unsuccessful bilateral GPi DBS, but had transient improvement in freezing after DBS of the right PPN. Patient #3, a 66-year-old man, underwent isolated right PPN but developed an increase in his Gait and Balance Scale score without noticeable improvement in freezing. In all 3 patients DBS setting adjustments were limited by blurry vision and balance problems. Further studies are needed before PPN-DBS can be routinely recommended for the treatment of gait and balance problems and freezing of gait. In a study of 6 patients with PD-related freezing of gait PPN-DBS resulted in modest improvements, with overall results described as “disappointing” (Ferraye et al., 2010). Combined PPN/cZI low-frequency stimulation produced a statistically significant improvement in axial signs as measured by the UPDRS III score compared with cZI stimulation alone, but there was no clinical effect of combined stimulation when patients were in an “off” state (Khan et al., 2012).

DBS safety and complications

STN stimulation, although usually well tolerated, may produce ballistic and choreic dyskinesia when the voltage is

increased above a given threshold, which is probably different from that produced by levodopa (Moro et al., 1999) (Video 7.6). Except for mild deficit in verbal memory and fluency, STN or GPi DBS does not appear to adversely affect cognitive performance (Pillon et al., 2000; Heo et al., 2008). In a study at Baylor College of Medicine, when 23 patients undergoing bilateral STN DBS were compared with 28 treated medically at 6 months after surgery, the DBS patients were found to have mild but significant declines in verbal recall and fluency and mild decline in frontostriatal cognitive measures, even when good motor outcome was achieved (York et al., 2008). When followed for 2 years, the STN DBS patients demonstrated significant impairments in verbal memory, oral information processing speed, and language (Williams et al., 2009). Additionally, one-third of the STN DBS patients declined on confrontational naming compared with none of the PD patients, and one-third of the STN DBS patients converted to PD dementia 2 years after STN DBS compared with none in the PD group. These results are consistent with the more recent reports on STN DBS that have found long-term deficits in multiple cognitive domains, including memory, attention, and frontostriatal functioning after STN DBS when more comprehensive neuropsychological measures were administered (Contarino et al., 2007). In one controlled study, 60 patients were randomly assigned to receive STN DBS and 63 to have best medical treatment. After 6 months, DBS-treated patients showed mild but significantly more evidence of impairments in executive function and verbal fluency, irrespective of the improvement in quality of life (Witt et al., 2008). In contrast, anxiety was reduced in the DBS group compared with the medication group. Based on data collected from 8 patients with advanced PD, mean age 56.5 years, during off-medication periods, significant declines in cognitive and motor function were found under modest dual-task conditions with bilateral but not with unilateral STN DBS (Alberts et al., 2008). Impaired performance in verbal fluency associated with STN DBS has been correlated with decreased rCBF in the left frontotemporal areas as measured by PET (Schroeder et al., 2003). Whereas many studies have concluded that cognitive function is unchanged with STN DBS (Tröster et al., 1997; Ardouin et al., 1999; Gerschlager et al., 1999; Vingerhoets et al., 1999; Pillon et al., 2000; Daniele et al., 2003), even after 3 years (Funkiewiez et al., 2004), or only slightly declined even after 5 years (Contarino et al., 2007), other studies have found declines in working memory and response inhibition performance (Hershey et al., 2004), impaired frontal executive function, particularly older patients, reduced verbal fluency, impaired naming speed, reduced selective attention, delayed verbal recall (Saint-Cyr et al., 2000; Woods et al., 2006). Although the presence of dementia is considered a contraindication to DBS, cognitive function apparently improved in a patient with PD dementia with bilateral stimulation of the nucleus basalis of Meynert and STN (Freund et al., 2009). Further studies, however, are necessary before this approach can be recommended for patients with PD and cognitive deficit. ●

Several studies have reported changes in mood and behavior after DBS. Emotional lability and psychiatric complications, found in about 9% of patients after STN DBS, have been found in one prospective study with a control group consisting of PD patients without DBS (Smeding et al., 2006). In another study, bilateral STN DBS was associated with moderate

Video 7.6 Deep brain stimulation–induced hemiballism.

improvement in tasks of prefrontal function and obsessive-compulsive behavior (Mallet et al., 2002; Mallet et al., 2008) but moderate deterioration in verbal memory and prefrontal and visuospatial function (Alegret et al., 2001). Whereas some patients have experienced euphoria, mania, infectious laughter, and hilarity with STN DBS (Krack et al., 2001; Kulisevsky et al., 2002), others have experienced depression and other mood changes, aggressive behavior (posteromedial hypothalamus), pseudobulbar crying (Okun, Raju, et al., 2004), and other psychiatric problems (Bejjani et al., 2002; Berney et al., 2002; Mayberg and Lozano, 2002), and some have noted improvement in psychiatric symptoms, particularly obsessive-compulsive disorder (Mallet et al., 2002; Mallet et al., 2008; Tye et al., 2009). STN DBS may occasionally lead to increased impulsivity, similar to pathologic gambling seen in patients treated with dopamine agonists, which possibly may be due to impaired ability to self-modulate decision processes and cognitive control (Frank et al., 2007; Stamey and Jankovic, 2008; Halbig et al., 2009; Rodriguez-Oroz et al., 2011).

The neuropsychological and neuropsychiatric issues of DBS have been of increasing interest and concern and have been the topic of several reviews (Parsons et al., 2006; Saint-Cyr and Albanese, 2006; Voon et al., 2006; Appleby et al., 2007; Heo et al., 2008; Witt et al., 2008; Le et al., 2009). A meta-analysis of 10 years of experience with DBS, has concluded that the prevalence of depression was 2% to 4%, mania 0.9% to 1.7%, emotional changes 0.1% to 0.2%, and suicidal ideation/suicide attempt 0.3 to 0.7% (completed suicide rate was 0.16%–0.32% over 2.4 years, compared with 0.02% annual suicide rate in the United States) (Appleby et al., 2007). In another study, hypomania was associated with STN DBS contacts located in the SN, mainly in its ventral part, and was mediated by activation of the anterior cingulate and medial prefrontal cortex (Ulla et al., 2011). Other studies have drawn attention to apathy (Le et al., 2009) and suicidal behavior as a potential hazard of STN DBS (Soulas et al., 2008; Voon et al., 2008). A survey of 75 DBS surgical centers representing four continents, 55 of which responded, indicated that of a total of 5311 patients, 24 (0.45%) completed and 48 (0.90%) attempted suicide (Voon et al., 2008). The mean interval after surgery for all events was 17.8 months (range 1–48 months for completed suicides, 0.25–100 months for attempts), and 75% of all events occurred within this interval. The suicide rate in the first postoperative year was approximately 10 times the expected rate, adjusted for age, gender, and country, and remained elevated at 4 years. The risk for suicide correlated with postoperative depression, single marital status, and impulse control disorder. Although the rate of suicide after epilepsy surgery is even higher (1%), according to the authors “the baseline suicide rate [among patients with epilepsy] is eight times higher than the general population, [whereas] baseline PD suicide rates range from the same to as much as ten times lower than [in] the general population.” Weintraub and colleagues (2013) published a follow-up study on suicide rates in the large Veterans Administration (VA) multicenter DBS study. Phase 1 of the VA study showed no suicide behaviors, and new-onset suicide ideation was rare (1.9% for DBS versus 0.9% for bone marrow transplant; Fisher’s exact $P = 0.61$). Rates of suicide and suicide symptoms were similar in STN and GPi DBS; however, the authors pointed out that several proxy symptoms were worse in the STN randomized group (Weintraub, 2013).

Transient mania also has been reported as an adverse effect of DBS, particularly involving the medial portion of the

STN (Raucher-Chene et al., 2008). Impulse control disorder (ICD) has been reported to both improve and worsen after STN DBS (Broen et al., 2011). In one study, 8 of 50 (16%) patients with PD undergoing DBS had current or a history of ICD, although 7 were also treated with dopamine agonists (Shotbolt et al., 2012). STN DBS has been found to also improve autonomic dysfunction, including orthostatic hypotension, associated with PD (Stemper et al., 2006). Rossi and associates (2017) performed a small subjective study of ICD in PD across both STN and GPi DBS. “Patients with ICDs preoperatively ($n = 14$, 37.8%) had significant improvement in QUIP scores at follow-up (6.00 ± 0.94 vs. 2.64 ± 0.98 , $p = 0.0014$, paired t -test). Improvement was not uniform across the cohort: 1 patient with ICD at baseline developed worsening symptoms, and 4 patients with no ICD preoperatively developed clinically significant ICDs postoperatively” (Rossi, 2017). Psychogenic tremor after DBS surgery for ET has been reported in one case (McKeon et al., 2008).

Hypophonia and dysarthria were reported to be the most frequent long-term effects of STN DBS (Romito et al., 2002). Dysarthria, observed as a side effect more with left than right STN DBS (Santens et al., 2003), may develop despite improved oral control of jaw, lips, and tongue movements (Pinto et al., 2003). Although some individual components of speech may improve with STN DBS, most studies have shown that speech either fails to improve or deteriorates with STN DBS (Klostermann et al., 2008). Several studies have now demonstrated a significant weight gain in patients with STN DBS (Montaurier et al., 2007). In one study, there was a 3.4 ± 0.6 kg body weight increase, associated with a significant decrease in energy expenditures, $-7.3 \pm 2.2\%$ in men and $-13.1 \pm 1.7\%$ in women ($P < 0.01$), associated with a gain primarily in fat-free mass in men and fat in women. In another study, 32.1% of patients showed about 15% increase in body weight and a mean BMI increase of 24.7 kg/m^2 in 1 year (Barichella et al., 2003). Whereas over half of patients initially considered to be DBS failures eventually had good results, 34% had persistently poor outcomes despite optimal management (Okun et al., 2005).

Several studies have addressed DBS-related hardware complications (Kenney et al., 2007; Baizabal Carvallo et al., 2011, 2012; Hariz, 2011). The frequency of intraoperative complications associated with implantation of DBS was found to be 4.2% (11 of 262), and during a 3-year follow-up the frequency of hardware-related complications was 13.9% (25 of 180) (Voges et al., 2006). A total of 319 patients underwent DBS implantation at Baylor College of Medicine, Houston, Texas over a 10-year period, 182 of whom suffered from medically refractory PD; the other patients had ET (113), dystonia (18), and other hyperkinetic movement disorders (6) (Kenney et al., 2007) (Table 7.6). Intraoperative adverse effects were rare: vasovagal response in 8 patients (2.5%), syncope in 4 (1.3%), severe cough in 3 (0.9%), transient ischemic attack in 1 (0.3%), arrhythmia in 1 (0.3%), and confusion in 1 (0.3%). Perioperative adverse effects included headache in 48 patients (15.0%), confusion in 16 (5.0%), and hallucinations in 9 (2.8%). The most serious intraoperative/perioperative adverse effects occurred in 4 (1.3%) patients with an isolated seizure, 2 (0.6%) patients with intracerebral hemorrhage, 2 (0.6%) patients with intraventricular hemorrhage, and 1 (0.3%) patient with a large subdural hematoma (Kenney et al., 2007). Long-term complications of DBS surgery included dysarthria (4.0%), worsening gait

Table 7.6 Safety data related to deep brain stimulation at Baylor College of Medicine and The Methodist Hospital

Of the 319 patients treated with deep brain stimulation (DBS) (Baylor/Methodist) between 1995 and 2005, 182 had Parkinson disease; the other patients had essential tremor (112), dystonia (19), and other hyperkinetic movement disorders (6)

Intraoperative adverse events (AEs) included vasovagal response in 8 patients (2.5%), syncope in 4 (1.2%), severe cough in 3 (0.9%), transient ischemic attack in 1 (0.3%), arrhythmia in 1 (0.3%), and confusion in 1 (0.3%)

Perioperative AEs included headache in 48 patients (15%), confusion in 16 (5%), and hallucinations in 9 (2.8%)

Intraoperative/perioperative AEs included isolated seizure in 4 patients (1.2%), intracerebral hemorrhage in 2 (0.6%), intraventricular hemorrhage in 2 (0.6%), and a large subdural hematoma in 1 (0.3%)

Persistent long-term complications of DBS surgery included dysarthria (4%), worsening gait (3.8%), cognitive dysfunction (4%), and infection (4.4%)

Revisions were required in 25 patients (7.8%) for the following reasons: loss of effect, lack of efficacy, infection, lead fracture, and lead migration

Hardware-related complications included 12 lead fractures and 10 lead migrations

Conclusions: Based on the 10-year experience, DBS has proven to be safe for the treatment of medically refractory movement disorders

From Kenney C, Simpson R, Hunter C, et al: Short-term and long-term safety of deep brain stimulation in the treatment of movement disorders. *J Neurosurg.* 2007;106:621–625.

(3.7%), cognitive decline (4.0%), and infection (4.4%). Hyperhidrosis has been reported in a single case as a complication of thalamic stimulation for ET (Diamond, Kenney et al., 2007). Revisions were completed in 25 (7.8%) patients for several reasons: loss of effect, lack of efficacy, infection, lead fracture, and lead migration. In addition to reviewing experience at Baylor College of Medicine, we summarized reports from 25 other centers and provided a guide and an algorithm on how to approach hardware-related complications (Baizabal et al., 2011). The reported rate of complications varied between 3.8% and 29% per electrode-year and included electrode misplacement or migration, lead fractures, infections, skin erosion, device malfunction, and other complications. Furthermore, 23.2% of patients required at least one visit to the emergency department (ED) for DBS-related complication. In one study of 100 patients who were implanted with a total of 191 STN DBS devices, there were 7 (3.7%) device infections, 1 cerebral infarct, 1 intracerebral hematoma, 1 subdural hematoma, 2 (1%) skin erosions, 3 (1.6%) periprocedural seizures, and 6 (3.1%) brain electrode revisions (Goodman et al., 2006). There were 13 (6.8%) patients with postoperative confusion and 16 (8.4%) had battery failures, but there were no surgical deaths or permanent new neurologic deficits. In another study of 60 patients who underwent 96 DBS-related procedures, followed over a period of 43.7 months (range 6–78 months), 18 (30%) developed 28 adverse events, requiring 28 electrodes to be replaced (Paluzzi et al., 2006a). The rate of adverse events per electrode-year was 8%. Hardware-related complications included 12 lead fractures and 10 lead migrations. In one study, 25.6% of all 215 patients with DBS presented to the ED at least once for various reasons, including neurologic (54.6%), such as headache (22.1%), change in mental status

(15.1%), and syncope (9.3%), followed by infections/hardware issues (27.9%), orthopedic/focal problems (10.5%), and medical issues (7%) (Resnick et al., 2010). Several other studies have addressed DBS-related complications (Morishita et al., 2010).

Knowledge and skills needed to prevent and troubleshoot problems, such as a nonideal initial DBS candidate, inadequate multidisciplinary team care, failure of perceived expectations, DBS procedural complication, hardware complication, suboptimal lead placement, programming, access to care, disease progression, and tolerance/habituation, are critical to the optimal response to DBS and to prevent potential “DBS failures” (Okun et al., 2008). Postoperative issues, including outcomes and complications, have been summarized in recent reviews (Deuschl et al., 2006; Kleiner-Fisman et al., 2006; Voges et al., 2007; Hariz, Rehnchrona et al., 2008; Videnovic et al., 2008).

Chronic stimulation appears to be well tolerated, and the risk for local gliosis is minimal (Caparros-Lefebvre et al., 1994; Haberler et al., 2000; Henderson et al., 2002; DiLorenzo et al., 2010, 2014), although more extensive damage has been rarely reported (Henderson et al., 2001). Vedam-Mai and colleagues examined gliosis in a postmortem study in 18 cases. “Microscopic evaluation revealed tissue reaction and astrocytic responses to the lead. Significant fibrosis was seen in $n = 2$ brains and prominent microglial response in $n = 1$. Mean gliotic collar measured from hematoxylin and eosin and glial fibrillary acidic protein (GFAP) staining was $122.5 \mu\text{m}$ and $162.5 \mu\text{m}$, respectively. Mean gliotic thickness at the DBS electrode lead tip was $119.13 \pm 64.29 \mu\text{m}$ for patients receiving DBS for 0 to 5 years, $127.85 \pm 94.34 \mu\text{m}$ for 5 to 10 years, and $111.73 \pm 114.18 \mu\text{m}$ for patients with DBS for longer than 10 years. Kruskal-Wallis one-way analysis of variance (ANOVA) revealed no statistically significant differences between DBS duration and amount of gliosis” (Vedam-Mai 2018). Electron microscopy examination of tissue adherent to the explanted electrode revealed foreign body multinucleate giant cell-type (some larger than $100 \mu\text{m}$) reaction, possibly representing a response to the polyurethane component of the DBS electrode (Moss et al., 2004). Very few studies have addressed the rate and type of complications associated with DBS. During a mean follow-up period of 33 months and the cumulative follow-up of 217 patient-years of 84 consecutive cases, Oh and colleagues (2002) found that 20 patients (25.3%) had 26 hardware-related complications involving 23 (18.5%) of the electrodes. These included 4 lead fractures, 4 lead migrations, 3 short or open circuits, 12 erosions and/or infections, 2 foreign body reactions, and 1 cerebrospinal fluid leak. In addition, the hardware-related complication rate per electrode-year was 8.4%.

Several studies have addressed the safety concerns related to performance of MRI scans in patients with implanted DBS devices. Standard and functional MRI scans have been performed in many patients with implanted DBS without significant complications (Jech et al., 2001; Tagliati et al., 2009) (Table 7.7). In a survey of medical directors of National Parkinson Foundation Centers of Excellence, data on MRI safety was available on 3304 PD patients with one or more DBS leads; DBS patients had MRI of other body regions. No complications were reported except in one case MRI of the brains was associated with an IPG failure with no neurologic sequelae (Tagliati et al., 2009). Diathermy treatment, which involved pulse-modulated radiofrequency to the maxilla, in

Table 7.7 Results of a safety survey on magnetic resonance imaging in patients with deep brain stimulation devices

- Investigators from 40 of 42 (95%) National Parkinson Foundation Centers of Excellence (COEs) completed the survey
- 23 (58%) reported that they were currently performing brain MRI in DBS patients; 3 (7.5%) had done it in the past
 - The 17 COEs currently not performing postoperative MRI for DBS listed the following reasons:
 - Industry guidelines and/or warning (53%)
 - Defer clinical decision to outside department (29%)
 - Liability/risk/safety (18%)
 - No active DBS program (18%)
 - No available MRI (12%)
 - Insurance and reimbursement concerns (6%)
 - A total of 3304 patients with PD with one or more DBS leads had a brain MRI scan, and 177 DBS patients had MRI of other body regions
 - In one case MRI was associated with an IPG failure without neurologic sequelae after IPG replacement. No other complications were reported.
 - Conclusions: These data provide evidence for a favorable risk-to-benefit ratio for brain MRI in patients with DBS implants. We suggest that the current safety guidelines be reexamined given this large and positive experience.

DBS, Deep brain stimulation; IPG, implantable pulse generator; MRI, magnetic resonance imaging; PD, Parkinson disease.
 From Tagliai M, Jankovic J, Pagan F, et al.; National Parkinson Foundation DBS Working Group. Safety of MRI in patients with implanted deep brain stimulation devices. *Neuroimage* 2009;47(Suppl. 2):T53–T57.

a 70-year-old patient with PD implanted with ITREL model 7424 in the STN resulted in permanent diencephalic and brainstem lesions and a vegetative state (Nutt et al., 2001a). This tragic complication probably resulted from induction of radiofrequency current and heating of the electrodes, leading to the edema surrounding the DBS electrode. Although no serious complications have been reported in women with implanted DBS during pregnancy or delivery (Paluzzi et al., 2006b), electrocautery during delivery by cesarean section should be used cautiously.

To improve the safety and efficacy of DBS, it is important to continue advancing our understanding of the mechanisms underlying DBS and to build on and improve DBS technology (e.g., develop directional electrodes, prolonging battery life, allow remote and “smart” programming).

After attending a workshop and reviewing the literature, an international consortium of experts issued the following consensus statement about DBS: (1) Patients with PD without significant active cognitive or psychiatric problems who have medically intractable motor fluctuations, intractable tremor, or intolerance of medication adverse effects are good candidates for DBS. (2) DBS surgery is best performed by an experienced neurosurgeon with expertise in stereotactic neurosurgery who is working as part of an interprofessional team. (3) Surgical complication rates are extremely variable, with infection being the most commonly reported complication of DBS. (4) DBS programming is best accomplished by a highly trained clinician and can take 3 to 6 months to obtain optimal results. (5) DBS improves levodopa-responsive symptoms, dyskinesia, and tremor; benefits seem to be long-lasting in many motor domains. (6) Subthalamic nuclei DBS may be complicated by increased depression,

apathy, impulsivity, worsened verbal fluency, and executive dysfunction in a subset of patients. (7) Both globus pallidus pars interna and subthalamic nuclei DBS have been shown to be effective in addressing the motor symptoms of PD. (8) Ablative therapy is still an effective alternative and should be considered in a select group of appropriate patients (Bronstein et al., 2011).

The multiple current source steering study known as the VANTAGE study was nonrandomized and prospective, and the implants were bilateral STN. The UPDRS III motor score improved 6 months after first lead implantation. There were 125 adverse events and the most frequent were dystonia, speech issues, and apathy. There was one case of infection, one migration, and one case of respiratory depression (Timmermann, 2015). A follow-up prospective randomized study was recently completed in the United States, and results are set to be published in the near future.

Deep brain stimulation for hyperkinetic and other disorders

Primary dystonia

GPI DBS also has been reported to be effective in patients with primary generalized dystonia (Krauss et al., 1999; Kumar, Dagher et al., 1999; Coubes et al., 2000; Tronnier et al., 2000; Brin et al., 2001; Krack and Vercueil, 2001; Muta et al., 2001; Vercueil et al., 2001; Albright, 2003; Coubes et al., 2004; Diamond et al., 2006; Vidailhet et al., 2005; Jankovic, 2006; Kupsch et al., 2006; Jankovic, 2007; Vidailhet et al., 2007; Kenney and Jankovic, 2008; Isaías et al., 2008; Isaías et al., 2009; Andrews et al., 2010), segmental dystonia (Wohrle et al., 2003), cervical dystonia (Bereznai et al., 2002; Krauss et al., 2002), blepharospasm–oromandibular (cranial) dystonia (Capelle et al., 2003; Foote et al., 2005; Vagefi et al., 2008), tardive dyskinesia (Eltahawy, Feinstein, et al., 2004; Lenders et al., 2005), and tardive dystonia (Trottenberg et al., 2001b; Trottenberg et al., 2005; Cohen et al., 2007; Sako et al., 2008; Gruber et al., 2009; Capelle et al., 2010). Vercueil and colleagues (2001) described 10 patients with bilateral GPI DBS; 5 had a major improvement, 2 had a moderated improvement, and 1 had a minor improvement after 14 months. They concluded that GPI DBS is much more effective than thalamic DBS for the treatment of dystonia. In a 2-year follow-up of 31 patients with primary generalized dystonia, Coubes and colleagues (2004) noted a mean improvement in the clinical and functional Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) of 79% and 65%, respectively. There was no difference in response between DYT1-positive and DYT1-negative patients, but the magnitude of improvement was greater in children than in adults. In a presentation during the seventh International Congress of Parkinson's Disease and Movement Disorders in Miami in November 2002, Coubes provided data on 68 patients with generalized dystonia, 78% with primary dystonia, 19 of whom were DYT1-positive, and 29% with secondary dystonia, treated with GPI DBS. The MRI-guided, single-tract, bilateral implantation showed an overall 80% improvement, and this was most robust in primary, DYT1 dystonias and in the pantothenate kinase-associated neurodegeneration cases. Primary dystonia clearly responds better than secondary dystonia to either pallidotomy or GPI DBS, although

patients with pantothenate kinase-associated neurodegeneration also experience marked improvement in their dystonia (Coubes, 2000; Eltahawy, Saint-Cyr, et al., 2004; Castelnau et al., 2005). Essentially all patients achieved steady state in 6 weeks. The improvement was particularly noticeable in the rapid ("ballistic") dystonic movements, pain, and bradykinesia, but there was no effect on the slow dystonia or associated bradykinesia. Except for implantable pulse generator infection in three patients and lead fracture and other lead problems in two patients, there were no other complications. The stimulating parameters were as follows: pulse rate was 450 μ s, frequency was 130 Hz, and amplitude was 0.8 to 1.6 V. In a prospective, multicenter study of 22 patients with generalized dystonia, 7 of whom had DYT1 mutation, the BFMDRS score improved after bilateral GPi DBS from a mean of 46.3 ± 21.3 to 21.0 ± 14.1 at 12 months ($P < 0.001$) (Vidailhet et al., 2005). A "blinded" review of the videos at 3 months showed improvement with stimulation from a mean of 34.63 ± 12.3 to 24.6 ± 17.7 . The improvement in mean dystonia motor scores was 51%, and one-third of the patients improved more than 75% compared with preoperative scores. In addition, there was a significant improvement in health-related quality of life as measured by the SF-36, but there was no change in cognition or mood. Although the sample was rather small, the authors were not able to find any predictors of response such as DYT1 gene status, anatomic distribution of the dystonia, or location of the electrodes. Patients with a phasic form of dystonia improved more than those with tonic contractions and posturing. The maximum benefit was not achieved in some patients until 3 to 6 months after surgery. In a 3-year follow-up, motor improvement observed at 1 year (51%) was maintained at 3 years (58%) and the authors concluded that "bilateral pallidal stimulation provides sustained motor benefit after 3 years" (Vidailhet et al., 2007). The improvement noted at a 3-year follow-up was sustained at 5-year assessment; the improvement from 6 months to 3 years (-5.7 points $\pm 8 \times 4$; -34% ; $N = 31$) was significant and sustained at the 5-year follow-up ($-4.3 \pm 10 \times 4$; 21% , $N = 32$). In a study involving French centers, bilateral DBS of ventral GPi was associated with a 42% reduction in the BFMDRS score whereas DBS of dorsal GPi resulted in less predictable effects (Houet et al., 2007). In a retrospective review of 40 patients with primary generalized dystonia who had been treated by bilateral GPi DBS followed for up to 8 years, the most important predictors of poor response was high preoperative FMDRS score, older age at surgery, and small GPi volume, but no significant correlation was found between the electrical parameters used and the mean motor scores (Vasques et al., 2009). In a meta-regression of individual patient outcomes Andrews and colleagues (2010) analyzed 157 papers reporting clinical outcomes of DBS for dystonia on 466 patients. They concluded that patients with primary forms of dystonia, myoclonus-dystonia, subtypes of hereditary degenerative dystonia and tardive dystonia have a greater than 50% mean improvement in dystonia severity after DBS and among patients with primary generalized dystonia, duration of symptoms ($P = 0.008$), lower baseline severity score ($P = 0.024$), and DYT1 positive status ($P = 0.002$) were all independently associated with a significantly higher percentage improvement from surgery. Kupsch and associates (2006) compared GPi DBS with sham stimulation in a clinical RCT of 40 patients with

primary segmental or generalized dystonia. The primary endpoint was the change from baseline to 3 months in the severity of symptoms, according to the movement subscore on the BFMDRS. Two investigators who were unaware of treatment status assessed the severity of dystonia by reviewing videotaped sessions. Three months after randomization, the change from baseline in the mean ($\pm$ standard deviation [SD]) movement score was significantly greater in the neurostimulation group (-15.8 ± -14.1 points) than in the sham-stimulation group (-1.4 ± -3.8 points, $P < 0.001$). Similar results were obtained in other centers (Krause et al., 2004).

Targeting the posteroventral GPi seems to provide the most robust benefits in patients with dystonia (Tisch et al., 2007; Kupsch et al., 2011). It is of interest that an ablative lesion or high-frequency stimulation of the GPi can both produce and improve dystonia, suggesting that it is the pattern of discharge in the basal ganglia rather than the actual location or frequency of discharge that is pathophysiologically relevant to dystonia (Münchau et al., 2000). In one patient, a 49-year-old woman with severe generalized dystonia, bilateral GPi DBS produced an immediate improvement in dystonia, which was associated with a reduction in PET activation in certain cortical motor areas that are usually overactive in dystonia (Kumar, Dagher, et al., 1999).

GPi DBS has been used chiefly in patients with generalized dystonia, but it also has been reported to improve cranial-cervical dystonia in selected cases (Ostrem et al., 2007; Blomstedt et al., 2008; Pretto et al., 2008; Markaki et al., 2010; Reese et al., 2011; Sako et al., 2011). Muta and colleagues (2001) described a 61-year-old woman with cranial dystonia manifested chiefly blepharospasm, facial grimacing, cervical dystonia, and spasmodic dysphonia who had previously failed to improve with bilateral thalamotomy had marked improvement in all aspects of her dystonia with bilateral GPi DBS, including complete resolution of blepharospasm and oromandibular dystonia. In a blinded review of videos of 13 patients with segmental dystonia of various causes and different distributions (4 with cranial dystonia), GPi DBS was associated with global subjective gains and notable objective improvement in 11 of 13, but the response was quite variable and unpredictable (Pretto et al., 2008). Although bilateral GPi DBS may improve symptoms of cranial-cervical dystonia, motor function in nondystonic body parts may worsen (Ostrem et al., 2007). In another study involving 12 patients with cranial dystonia (Meige syndrome) followed for up to 78 months after bilateral GPi DBS dystonia severity as assessed by the BFMDRS showed a mean improvement of 45% at short-term follow-up (4.4 ± 1.5 months; $P < 0.001$) and of 53% at long-term follow-up (38.8 ± 21.7 months; $P < 0.001$) (Reese et al., 2011). In 5 patients treated with GPi DBS for cranial dystonia the mean scores of BFMDRS and disability scales improved significantly by $84\% \pm 6.8\%$ (range, 75%–94%) and $89\% \pm 8.1\%$ (range, 80%–100%), respectively (Sako et al., 2011).

Bilateral GPi DBS also has been found effective in patients with cervical dystonia (Krauss et al., 1999; Kulisevsky et al., 2000; Parkin et al., 2001; Skogseid et al., 2012). In a report of 2 patients with cervical dystonia, bilateral GPi DBS produced more improvement in pain than in motor symptoms (Kulisevsky et al., 2000). Parkin and colleagues (2001) reported progressive improvement in pain and posture in three patients

with cervical dystonia. A prospective, single-blind, multicenter study assessing the efficacy and safety of bilateral GPi DBS in 10 patients with severe, chronic, medication-resistant cervical dystonia, found improvement in the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) severity score improved from a mean (SD) of 14.7 (4.2) before surgery to 8.4 (4.4) at 12 months postoperatively ($P = 0.003$) (Kiss et al., 2007). The disability and pain scores also improved, as did general health and physical functioning and depression scores. In a prospective study of 8 patients with cervical dystonia treated with bilateral GPi DBS for median (range) 30 (12–48) months, blinded rater TWSTRS severity score from videos improved from mean 25 (19–30) to 8 (4–23) ($P = 0.028$), a 70% score reduction (Skogseid et al., 2012). Also, the Disability and Pain scores improved by median 91% and 92%, respectively, and the SF-36 subdomain scores improved significantly. Although GPi has been traditionally considered the main target for DBS treatment of dystonia, bilateral STN DBS has been found to be effective in 4 patients with dystonia previously treated with bilateral pallidotomy (Fonoff et al., 2012).

The pattern of reoccurrence of segmental dystonia after discontinuation of GPi DBS was studied in 8 patients (Grips et al., 2007). Phasic dystonia appeared within a few minutes but the tonic form of dystonia reoccurred with a more variable delay. Some patients obtain optimal improvement with lower-than-usual stimulation frequency (80–100 Hz) (Alterman et al., 2007). GPi DBS is gaining acceptance as the surgical treatment of choice not only in adult patients with dystonia but also in children (Alterman et al., 2007). Several studies have shown that enhanced plasticity, as measured by paired associative stimulation using transcranial magnetic stimulation (TMS), occurs as a result of DBS in patients with dystonia and this phenomenon may be responsible for the delay in optimal clinical effects after DBS is turned on and for the observed worsening of dystonia after DBS is turned off (Ruge et al., 2011a,b).

Secondary dystonia

Although ablative or DBS procedures have been perceived to be less effective in secondary than in primary dystonia, surgical treatments also can be effective in patients with tardive dystonia, dystonic cerebral palsy, and certain hereditary degenerative diseases (Marks et al., 2011; Tierney and Lozano, 2012). Bilateral GPi DBS also has been reported to produce about 24.4% improvement in the Burke-Fahn-Marsden scale in adult patients with dystonia–choreoathetosis associated with cerebral palsy (Vidailhet et al., 2009). It also has been found helpful in patients with neurodegeneration with brain iron accumulation (Dusek et al., 2012), although not as much as in patients with primary dystonia (Timmermann et al., 2010). A small case series of GPi DBS for ADCY5 dystonia has been reported as showing mild to moderate benefits (Dy, 2016).

Tourette Syndrome

There has been increasing interest in DBS as a treatment of medically intractable or malignant Tourette syndrome (TS) (Cheung et al., 2007). Because of prior success with thalamic ablation in the treatment of severe TS reported in 1970 by Hassler and Dieckman, translated from French (Rickards et al., 2008), most investigators use the original report as a rationale for selecting the thalamus as the target

in ablative and DBS treatment of TS. In 1999, thalamic DBS was introduced for intractable TS, but since then, multiple targets have been used with relatively comparable results (Ackermans et al., 2008). In their series of 6 patients who participated in a prospective, randomized, double-blinded study of stimulation targeting the Cm-Spv-Voi complex, the authors found a statistically significant improvement in the YGTSS in the on-stimulation compared with the with off-stimulation state (Ackermans et al., 2011). Other thalamic targets include centromedian/parafascicular complex (CM/Pf) and ventralis oralis (Vo) (Porta et al., 2009; Savica et al., 2012). The improvement in the YGTSS was maintained at 1-year follow-up with a 49% improvement reported. No significant difference was seen in psychiatric comorbidities or neuropsychological testing, except a lengthening in the time needed to complete the color-word card of the Stroop test. A small pilot study involving only 5 subjects with TS, mean age of 34.4 (range, 28–39) years and a mean disease duration of 28.8 years, revealed only modest reductions in the YGTSS total score, but statistically significant improvements were observed in some secondary variables such as the Modified Rush Tic Rating Scale Score total score (Okun et al., 2013). Tic suppression was most robust when contacts were placed deep (ventral) in the bilateral centromedian thalamic region. Despite very limited data the authors conclude that that “Scheduled stimulation holds promise as a potential first step for shifting movement and neuropsychiatric disorders toward more responsive neuromodulation approaches.” Recently the International Tourette Syndrome Database and Registry published 1-year outcomes in *JAMA Neurology*. There were 185 patients and 171 analyzed. “Symptoms of obsessive-compulsive disorder were present in 97 of 151 patients (64.2%) and 32 of 148 (21.6%) had a history of self-injurious behavior. The mean (SD) total Yale Global Tic Severity Scale score improved from 75.01 (18.36) at baseline to 41.19 (20.00) at 1 year after DBS implantation ($P < .001$). The mean (SD) motor tic subscore improved from 21.00 (3.72) at baseline to 12.91 (5.78) after 1 year ($P < .001$), and the mean (SD) phonic tic subscore improved from 16.82 (6.56) at baseline to 9.63 (6.99) at 1 year ($P < .001$). The overall adverse event rate was 35.4% (56 of 158 patients), with intracranial hemorrhage occurring in 2 patients (1.3%), infection in 4 patients with 5 events (3.2%), and lead explanation in 1 patient (0.6%). The most common stimulation-induced adverse effects were dysarthria (10 [6.3%]) and paresthesia (13 [8.2%]) (Martinez-Ramirez-2018).”

The globus pallidus has been increasingly used as the target in patients with disabling tics because of the long-term experience with this target in the treatment of other hyperkinetic movement disorders, such as dystonia and levodopa-induced dyskinesia (Diederich et al., 2005). In a 16-year-old boy with disabling, medically intractable TS, bilateral GPi DBS resulted in 63% improvement in Yale Global Tic Severity Scale, 85% improvement in Tic Symptom Self Report, and 51% improvement in SF-36, a quality of life measure (Shahed et al., 2007). Furthermore, the patient was able to return to school. Martinez-Fernandez and associates (2011) reported their experience with five patients implanted in the GPi for TS; three patients were implanted in the posteroventral GPi, and two patients were implanted in the anteromedial GPi. Over a mean follow-up of 1 year, the mean YGTSS decreased by 29% from 77.8 to 54.2, and the mean YBOCS decreased from 16.3 preoperatively to 10.8 postoperatively, an improvement that was maintained at

last follow-up. They concluded that the anteromedial region of the GPi may result in the most optimal control of tics. Several other reports confirmed that GPi is an effective target for the treatment of TS (Dehning et al., 2008, 2011).

Although these observations must be confirmed by a controlled trial before DBS can be recommended even to severely affected patients, it suggests that stimulation of certain targets involved in the limbic striato-pallidal-thalamo-cortical system may be beneficial in the treatment of various aspects of TS. In TS, perhaps even more importantly than in other movement disorders, appropriate screening and accurate and comprehensive assessment of not only tics but also behavioral comorbidities are absolutely critical in patient selection for DBS (Mink et al., 2006).

Other Indications for DBS

The expanding use of DBS in the treatment of various disorders could provide insights into the pathophysiology of other disorders (Benabid et al., 2000). In addition to the hyperkinetic movement disorders already discussed, DBS may be useful in patients with severe chorea associated with Huntington disease. Bilateral GPi was found to control chorea and markedly improved the quality of life in a 60-year-old man with a 10-year history of Huntington disease (Biolsi et al., 2008).

In addition to VIM as a target for patients with disabling tremor, STN DBS also has been found to be useful in the treatment of severe proximal tremor (Kitagawa et al., 2000) and rest and postural tremor in PD (Sturman et al., 2004).

The observation that stimulation of the substantia nigra precipitates acute depression (Bejjani et al., 1999) or mania (Ulla et al., 2006) that resolves immediately when the DBS is turned off suggests that the nigrothalamic pathway may play an important role in bipolar disorder. Besides left SN stimulation (Bejjani et al., 1999), stimulation superior and lateral to the right STN also produced mood changes (dysphoria) (Stefurak et al., 2003). Stimulation of white matter adjacent to the subgenual cingulate region (Brodmann area 25), which is metabolically overactive in treatment-resistant depression, has been found to be effective in treating depression in four of six patients (Mayberg et al., 2005).

Other emerging applications of DBS include treatment of obsessive-compulsive disorder targeting chiefly the ventral anterior limb of the internal capsule and adjacent ventral striatum or STN (Gabriels et al., 2003; Nuttin et al., 2003; Greenberg et al., 2008; Mallet et al., 2008) and various pain disorders, including migraines and cluster headaches, eating disorders, and various cognitive and psychiatric disorders (Leone et al., 2003; Burdick and Foote, 2011; Hariz et al., 2013) (Table 7.8).

The future of DBS

Each year the DBS Brain Stimulation Think Tank convenes and discusses cutting edge therapies, neuroethics, novel approaches, and threats to the future of the field of neuromodulation. Several lead designs are being investigated, including segmented DBS leads, multiple current source shaping and changing the shape of DBS waveforms. Additionally, there are many “design considerations for DBS electrodes, improved sensors, neuronal signal processing, advancements in development and uses of responsive DBS

Table 7.8 Current and potential indications for deep brain stimulation

Suppression of tremor: Essential tremor, Parkinson disease, multiple sclerosis, Wilson disease, cerebellar outflow, posttraumatic Parkinson disease (bilateral STN, GPi, GPe, cZl, PPN)
• ↑ “On time” (without dyskinesias)
• Improves cardinal signs and dyskinesia
• Improves quality of “off”
• Improves quality of life; ↓ levodopa dosage
• Neuroprotective?
Dystonia
Tourette syndrome
Spasticity
Epilepsy
Pain, cluster headaches
Depression
Obesity
Addiction
Obsessive-compulsive disorder
cZl, caudal part of the zona incerta; GPe, globus pallidus externa; GPi, globus pallidus interna; PPN, pedunculopontine nucleus; STN, subthalamic nucleus.

(closed-loop systems), and policy issues arising in and from DBS research and applications in practice (Ramirez-Zamora 2018).”

Vagus nerve and other stimulation procedures

On the basis of the observation that vagus nerve stimulation has a nonspecific “calming” effect in treated patients with epilepsy and that it suppresses harmaline-induced tremor in rats (Handforth and Krah, 2001), a multicenter trial was conducted to study the effects of vagus nerve stimulation in patients with essential and parkinsonian tremor, but no meaningful benefit was demonstrated (Handforth et al., 2003). Encouraged by the initial reports of prefrontal rapid-rate, repetitive transcranial magnetic stimulation in PD and despite lack of effect in more recent studies (Ghabra et al., 1999), some investigators have tried extradural motor cortex stimulation using a quadripolar electrostimulator and reported bilateral benefits in PD motor signs and in dyskinesias (Canavero and Paolotti, 2000; Arle and Shils, 2008). In one study involving six patients with ET and five with PD, a four-contact electrode (Resume II model 3587, Medtronic, Inc., Minneapolis, MN) was positioned subdurally on the motor cortex, after identification of the area with direct monopolar cortical stimulation, tremor was improved in two of three patients with ET, but no improvement was observed in the five parkinsonian patients (Moro et al., 2011). The results of these preliminary studies, however, must be confirmed by a larger study before this procedure can be considered as a potential treatment in PD.

One potentially promising technique that is receiving growing attention is optogenetics (Kravitz and Kreitzer, 2011). With the discovery of channelrhodopsin-2 (ChR2), a protein that can mediate light-sensitive cation currents, optogenetics is increasingly used to study brain circuitry, and optogenetic approaches used to modulate neuronal activity with light are being explored as potential therapeutic strategies. It may eventually be possible to control expression of optogenetic proteins using activity-sensitive promoters for immediate early genes.

Brain grafting

Neurotransplantation using fetal nigral tissue as a treatment for PD was introduced after laboratory studies demonstrated that grafts of fetal dopaminergic neurons can survive for long periods in the host striatum, that they are capable of forming synapses with striatal neurons, and that they actually produce dopamine (Freed et al., 1992; Freeman et al., 1995; Collier and Kordower, 1998; Hauser et al., 1999; Lindvall, 1999). Ventral mesencephalic grafts into parkinsonian animal models have been found to improve not only parkinsonian features but also levodopa-induced dyskinesias (Lee et al., 2000). Initial results of clinical trials have been inconsistent, and only moderate improvement has been observed. The variable results have been thought to be due to differences in surgical methods, the age and the amount of donor tissue, methods of storage, the site of implantation, and the distribution of the tissue within the target region (Hauser et al., 1999). Controlled trials designed to determine the efficacy of fetal nigral transplantation are currently under way, but ethical concerns about the justification of sham operations, employed in these trials, have generated a lively controversy. Inclusion of sham surgery in design of clinical trials is, however, gaining increasing acceptance not only among investigators but also among patients, particularly those who are more educated (Frank et al., 2008). Fetal tissue is generally obtained from elective abortions at postgestational ages ranging between 6 and 9 weeks. The tissue must be screened for infections and is implanted stereotactically in the striatum. Commonly, the putamen is chosen as the target site, sometimes in combination with the caudate. The donor tissue may be delivered via several needle tracts, either unilaterally or bilaterally. Tissue of up to eight fetal donors are grafted per patient. Whether cyclosporine or other immunosuppressants are needed has not yet been determined.

Although the initial results were encouraging, subsequent controlled studies have failed to show any meaningful benefit from neuronal grafting, and in one study more than half of the implanted patients experienced "off" dyskinesias (Freed et al., 1992; Sawle et al., 1992; Spencer et al., 1992; Peschanski et al., 1994; Freeman et al., 1995; Wenning et al., 1997; Lindvall, 1998; Hauser et al., 1999; Lindvall, 1999; Freed, Greene, et al., 2001; Olanow, 2002; Mendez et al., 2005). Improvement is commonly noted between 1 and 3 months postoperatively. In single patients, functional improvement has been demonstrated up to 46 months postoperatively (Freed et al., 1992). Several patients were able to markedly reduce or even discontinue their dopaminergic drugs. Additional improvements have been noted after sequential bilateral transplantation (Hagell et al., 1999). [^{18}F]fluorodopa PET scans have demonstrated increased uptake after fetal transplants (Sawle et al., 1992; Freeman et al., 1995; Hauser et al., 1999), but this method has been challenged (Martin and Perlmuter, 1994). In one report, a patient received a unilateral fetal implant in 1989, with "gradual, major clinical improvement" over 3 years. Levodopa was withdrawn at 32 months, and immunosuppression was stopped at 64 months (Piccini et al., 1999). In the grafted putamen, the [^{11}C]-raclopride PET had normalized by 3 years with minor increases thereafter, and the untreated side showed gradual decline. Whereas the untreated side showed increased raclopride (D2) binding (indicative

of upregulation of receptors), the grafted side showed normal levels of binding. After administration of amphetamine, which promotes dopamine release, the untreated side showed no decrease in raclopride binding, while the grafted side had a decrease in binding (because of competition from dopamine) equivalent to nondiseased controls.

Freed, Greene, and colleagues (2001) reported the results of the first double-blind placebo-controlled trial of fetal graft transplantation for advanced PD. Forty patients, stratified by age into younger than 60 years and older than 60 years, with about a 7-year history of PD symptoms, were randomized to receive either four embryonic mesencephalons delivered via four needle passes to the left and right putamen or a sham operation (four drill holes to the forehead without dural penetration). After 1 year, the "sham" patients were given the option to be implanted and were then followed in an open-label manner; a total of 33 patients received an implant. Overall, there was no difference between the implanted and sham patients with respect to the primary outcome variable, a global rating by the patients (from -3, PD markedly worse, to +3, PD markedly improved). There was, however, a significant improvement in bradykinesia and rigidity, but only in the younger (younger than 60 years) patients. There was no improvement in freezing or motor fluctuations, and gait actually deteriorated. Although there were more adverse events in the implanted group, these were not considered directly related to the surgery. There was a marked placebo effect, sometimes lasting the whole year. Of the 20 implanted patients, 17 had evidence of fiber outgrowth from the transplanted tissue, as indicated by [^{18}F]fluorodopa PET scans, but there was no correlation between the PET results and the UPDRS, except in the younger patient group. In a 1-year follow-up, a blinded PET study showed that patient age did not affect viability of the implant, but only in the younger group was there significant correlation between [^{18}F]fluorodopa putaminal uptake and an improved UPDRS score for bradykinesia, though not tremor or rigidity (Nakamura et al., 2001). Most important, 5 of 33 patients who eventually received the implant experienced dyskinesias even during "off" periods, which correlates with increased F-dopa uptake on PET scans (Ma et al., 2002). GPi DBS improved these "run-away dyskinesias" in 3 of the 5 patients (Freed, Breeze, et al., 2001) and in other patients (Graff-Radford et al., 2006). In the second, National Institutes of Health-funded, controlled trial of fetal transplants, 34 patients were randomized to receive bilateral grafting into the posterior putamen of four or one fetal tissue per side or sham surgery (partial burr hole without penetration of the dura) (Olanow et al., 2003). All patients received immunosuppression for 6 months after surgery and were followed for 24 months. Of the 31 patients who completed the trial, 2 died during the trial and 3 died afterward from causes unrelated to the procedure. There was no significant overall treatment effect, but the patients with milder PD did show significant improvement ($P = 0.006$). PET results indicated a significant dose-dependent increase versus baseline in fluorodopa uptake, with no change in placebo patients and an approximate one-third increase in patients receiving four tissues. Despite these histochemical and imaging improvements, no significant differences were seen in clinical measures. Increase (worsening) from baseline in the UPDRS motor score while off medication was 9.4 for placebo, 3.5 for one tissue, and -0.72 for four tissues ($P = .096$ for

four versus placebo). Although treated patients improved for approximately 9 months, they then worsened. There was no difference between implanted and sham patients in “on” time without dyskinesias, total “off” time, ADLs scores, or levodopa dose required. No placebo patients but 13 of 23 (56%) treated patients developed off-medication dyskinesias. The authors concluded that “Fetal nigral transplantation currently cannot be recommended as a therapy for PD based on these results.” The off-medication dyskinesias emerged about 5 months after transplant with legs being more frequently affected in a stereotypic, repetitive manner, similar to the pattern observed in diphasic dyskinesias (Olanow et al., 2009). “Off” period dyskinesias were also reported in all 14 PD patients at a mean of 40 months after fetal transplants performed in Europe (Hagell et al., 1999). Many of these patients required GPi DBS, which markedly improved the “off” dyskinesias and levodopa dyskinesias (Herzog et al., 2008).

Limitations of both of the National Institutes of Health-sponsored studies have been reviewed (Winkler et al., 2005). Subsequent analysis suggested that younger patients and those with milder disease, particularly if immunosuppressed for more than 6 months, had more robust benefit. Both studies demonstrated a marked placebo effect and highlighted the need for controlled trials in assessing surgical interventions (McRae et al., 2004). Survival of the human grafts can be prolonged by administering the lazaroid tirilazad mesylate, a lipid peroxidation inhibitor, into the graft tissue (Brundin et al., 2000) or possibly by immunosuppression, although postmortem studies performed 3 to 4 years after implants found that the grafts are only mildly immunogenic to the host brain (Mendez et al., 2005). Serious neurologic complications of neurotransplantation have occurred in 1% to 2% of cases and may include intracerebral hemorrhage (Hauser et al., 1999). There is also a potential risk for transmission of infectious vectors.

Besides the in vivo evidence of graft survival, neuropathologic studies also provide evidence of graft survival and striatal reinnervation up to 16 years after transplantation of fetal mesencephalic tissue (Kordower et al., 1995, 2008a,b; Collier and Kordower, 1998; Morley and Duda, 2009). In one case, Lewy body-like inclusions that stained positively for alpha-synuclein and ubiquitin were found in nigral neurons grafted into the striatum 14 and 16 years earlier (Brundin et al., 2008; Kordower et al., 2008a,b; Li et al., 2010). These findings suggest that the disease can propagate from host to graft cells and have implications for future cell-based therapies (Braak and Del Tredici, 2008). Furthermore, there is no evidence that the grafted cells will innervate nondopaminergic regions that are known to be damaged in PD (Olanow et al., 2009). However, no microglial infiltration or any other pathologic changes were noted in five other patients who underwent fetal midbrain suspension grafts (Mendez et al., 2008). Later studies showed that alpha-synuclein is may be transported by endocytosis to neighboring neurons and forms Lewy-like inclusions (Desplats et al., 2009). Furthermore, there is some evidence that alpha-synuclein acts like a prion (Olanow and Prusiner, 2009; Angot et al., 2010; Goedert et al., 2010). Indeed, the propagation of synuclein pathology from caudal brainstem (Braak and Del Tredici, 2008) has been linked to oligomerization and propagation of beta-sheet, similar to prion, although it is not clear how the spread would skip

important brainstem structures such as the oculomotor nuclei, which are spared in PD.

Observations that cell division can occur in an adult brain have led to speculations that stem cell technology could be applied to neurodegenerative diseases, including PD (Barker, 2002; Bjorklund et al., 2002; Lunn et al., 2011). One of the most exciting areas of current research is the potential use of cultured, well-characterized stem cells or adult bone marrow cells, with the ability to generate neurons and glia, for therapeutic applications in PD. This interest has been fueled by the encouraging findings from clinical trials using fetal grafts into brains of PD patients (see later). It has become possible to generate central nervous system cells that express neuronal and glial properties by manipulating the tissue cultures with various cytokines and growth factors. When these progenitor cells are injected into an intact striatum, they acquire the characteristics of striatal cells (but when injected into a lesioned brain, they differentiate into glia). In one experiment, neuronal progenitor cells from a neonatal anterior subventricular zone were implanted in an adult rat with unilateral nigrostriatal denervation by 6-hydroxydopamine (6-OHDA) and were found to differentiate into neuronal phenotype as long as 5 months after implantation (Zigova et al., 1998). Rietz and colleagues (2001) found that a population of neuronal stem cells located in both ependymal and subventricular zones acts as a functional stem cell in vivo and has a potential to differentiate not only neuronal but also nonneuronal cells. Transplanting low-dose undifferentiated mouse embryonic stem cells into the rat striatum results in a proliferation and full differentiation into dopaminergic neurons (Bjorklund et al., 2002; Winkler et al., 2005). These studies suggest the possibility that in PD, the progenitor or stem cells can be eventually used to replace lost or degenerated cells. However, this enthusiasm must be tempered by the two negative studies of fetal transplants (see later) and the findings from animal studies that show that fetal transplants produce more robust motor and behavioral effects than transplanted embryonic stem cells. Other major limitations of stem cells are the lack of effect on nondopaminergic symptoms of PD and the potential for unregulated release of dopamine and cellular growth.

Many questions regarding fetal tissue grafting remain open, and the procedure should be viewed as experimental (Winkler et al., 2005). Ethical concerns on the use of fetal tissue have been raised. Selection criteria for neurotransplantation differ among investigators. It has not yet been determined which patients are the ideal candidates for these procedures. Because of logistical and ethical problems associated with harvesting human fetal mesencephalon, the use of other donor tissues has been explored. The implantation of autologous adrenal medulla into patient's striatum has been found to be helpful in about one-third of patients, but the limited benefits and the potential risks for complications have resulted in the cessation of these procedures (Jankovic et al., 1989). Porcine (pig) fetal mesencephalic transplants, however, are currently being investigated as a potential therapeutic intervention (Galpern et al., 1996; Deacon et al., 1997). In 12 patients with advanced PD who received embryonic porcine ventral mesencephalic tissue, Schumacher and colleagues (2000) found 19% improvement in total UPDRS 12 months after the surgery. There were no changes in the ¹⁸F-dopa PET scans. Preliminary results from a multicenter double-blind RCT of fetal porcine implants in

10 patients with PD have not produced encouraging results (Hauser et al., 2001). In addition to human embryonic tissue, other donor sources are currently being investigated, including retinal pigment epithelial cells (Spheramine) (Watts et al., 2003; Bakay et al., 2004). These cells, located in the inner layer of neural retina, produce dopamine. When attached to cross-linked gelatin microcarriers (Spheramine) and implanted stereotactically into the striatum, the cells have improved parkinsonian symptoms in rodents, nonhuman primates, and parkinsonian patients. A pilot open-label study of six patients showed 48% improvement in the UPDRS motor score 12 months after implantation (Bakay et al., 2004). An RCT conducted in selected centers in North America and Europe did not show any benefit, but the full report has not yet been published. In one patient, a 68-year-old man who underwent bilateral surgical implantation of 325,000 retinal pigment epithelial (RPE) cells in gelatin microcarriers (Spheramine) but died 6 months after surgery, a total of 118 cells (estimated 0.036% survival) were found associated with marked inflammation (Farag et al., 2009). In the final results of the Spheramine trial, of the 71 enrolled patients, 35 underwent cell transplantation and 36 sham surgery (Gross et al., 2011). There was no significant change in mean motor scores in the various variables and the overall rate of adverse events was similar in the two groups, surgery-related adverse effects were more frequent in the RPE group.

The use of immortalized neural progenitor cells in repair and as a source of trophic factors is also being investigated in many centers (Martinez-Serrano and Björklund, 1997). Other approaches include transplantation of polymer-coated xenografts, transfected mesencephalic neural cell lines, genetically engineered dopamine-producing fibroblasts, viral vectors modifying host cells by intrusion of the tyrosine hydroxylase gene, carotid body glomus cells, which also express the glial cell line-derived neurotrophic factor (Minguez-Castellanos et al., 2007). Alternative approaches also include the intraventricular or intraparenchymal infusion of neurotrophic factors such as the glial cell-derived neurotrophic factor (GDNF) (Gash et al., 1996). A multicenter study of this approach, however, was discontinued because of lack of efficacy.

Another approach, involving surgical gene delivery of adeno-associated virus-based vector encoding human neurturin (AAV2-NTN; also called CERE-120), has been tested in parkinsonian animals and is currently undergoing clinical trials. In the phase I study involving 12 patients with Hoehn and Yahr stage 3 to 4 PD neurturin (CERE-120) was infused into their putamen at doses of 1.3×10^{11} and 5.4×10^{11} , respectively (Marks et al., 2008). No adverse effects were observed, and there was 29% improvement in "off" total UPDRS, 36% reduction in the motor UPDRS, and a mean increase of 2.3 hours in "on" time without troublesome dyskinesia. There was no change in other secondary measures or the ^{18}F -L-DOPA PET, and there was no "off" dyskinesia. In a phase II multicenter, double-blind, sham-surgery controlled trial, 58 patients with advanced PD were randomly assigned (2:1) to receive either AAV2-neurturin (5.4×10^{11} vector genomes) (CERE-120) injected bilaterally into the putamen or sham surgery (Marks et al., 2011). There was no significant difference in the primary endpoint (a change in motor UPDRS after 12 months) in patients treated with AAV2-neurturin compared with control individuals). Serious adverse events occurred in 13 of 38 patients treated with AAV2-neurturin and 4 of 20 control individuals. Three patients in the AAV2-neurturin group

and two in the sham surgery group developed tumors. Another trial, currently in progress, is targeting not only the putamen but also the SN (Lewis and Standaert, 2011). The latter strategy is based on the hypothesis that neurturin will be transported from degenerating terminals to their cell bodies in the SN to the striatum, which was observed in MPTP primates. This hypothesis is supported by the postmortem findings in two brains of patients who participated in the previously described phase II trial with neurturin-immunostaining in the targeted striatum (15% of the putamen), but there was no evidence of expression in the SN (Bartus et al., 2011). Although targeting the SN with AAV2-neurturin is feasible (Bartus et al., 2013), the results of the study were disappointing (personal communication).

Unilateral injection of gene for the enzyme glutamic acid decarboxylase (GAD), which converts glutamate to GABA, with adeno-associated virus (AAV) into the STN of 12 patients with PD was reported to result in significant improvements in motor UPDRS scores ($P = 0.0015$), predominantly on the side of the body that was contralateral to surgery, noted at 3 months after the gene therapy and the effects persisted up to 12 months (Kaplitt et al., 2007). This was associated with a substantial reduction in thalamic metabolism measured by ^{18}F -fluorodeoxyglucose PET in the treated hemisphere. The authors concluded that "AAV-GAD gene therapy of the STN is safe and well tolerated by patients with advanced PD," suggesting that in-vivo gene therapy in the adult brain might be safe for various neurodegenerative diseases. Although this pilot, phase I study provides evidence for proof-of-principle, it is not clear how this strategy differs from STN stimulation or lesioning, also designed to inhibit impulses from hyperactive STN (Stoessl, 2007). In a double-blind, phase II, RTC of 66 patients assessed for eligibility, 21 randomly assigned to sham surgery and 16 to AAV2-GAD infusions were analyzed at the 6-month endpoint (LeWitt et al., 2011). The UPDRS score for the AAV2-GAD group decreased by 8.1 points (SD 1.7, 23.1%; $P < 0.0001$) and by 4.7 points in the sham group (1.5, 12.7%; $P = 0.003$); the AAV2-GAD group showed a significantly greater improvement from baseline in UPDRS scores compared with the sham group ($P = 0.04$). In addition to the relatively small magnitudes of improvement, the study raises some questions about methodology and conduct of the study, such as whether blinding is possible in patients who are awake during the procedure. Furthermore, of the 45 randomized subjects only 37 were analyzed; 6 from the active treatment arm and 2 from the sham group were excluded from the analyses because of missed surgical target or catheter/pump malfunction. Finally, one of the authors owns stock options in Neurologix, the funding source.

Other genes delivered surgically or via a vector, including genes for vesicular monoamine transporter-2 (VMAT-2) and aromatic L-amino acid decarboxylase (AADC) genes, are currently being investigated in preclinical and early clinical trials (Lee et al., 2006). Other gene-based therapies are being pursued in laboratories all over the world, such as ProSavin (Oxford Biomedica), have started in France, with experts confident of success, a lentivector system carrying AADC, tyrosine hydroxylase, and GTP-cyclohydrolase (<http://www.biomedica-usa.com>).

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Nonmotor problems in Parkinson disease

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Introduction

Although the motor symptoms of Parkinson disease (PD) dominate the clinical picture—and even define the parkinsonian syndrome—many patients with PD have other complaints that have been classified as *nonmotor* (Chaudhuri et al., 2006a), and several recent scales have been developed to quantify these symptoms (Chaudhuri et al., 2006b). The Unified Parkinson's Disease Rating Scale (UPDRS) has been recently modified by the Movement Disorders Society (MDS) to include more nonmotor features of PD (Goetz et al., 2007). These include fatigue, depression, anxiety, sleep disturbances, constipation issues, bladder dysfunction, and other autonomic disturbances (sexual, gastrointestinal), and sensory complaints. Sensory symptoms, including pain, may occur. Orthostatic hypotension (OH) can lead to syncope and in some cases cognitive issues. Behavioral and mental alterations include changes in mood, lack of motivation or apathy, slowness in thinking (bradyphrenia), and a declining cognitive capacity; these can lead to disability. In one survey of nondemented PD patients, nonmotor symptoms (NMS) were found to occur in the majority of patients (Table 8.1). Genetic and sporadic forms of PD have NMS (Kasten et al., 2010). NMS commonly occurs and can occasionally manifest early without the cardinal signs of PD (Langston, 2006). Lang (2011) used the term *premotor* for nonmotor symptoms that are part of PD but precede the motor symptoms. The idea of premotor or premanifest symptoms was born from the Braak hypothesis, which was discussed in Chapter 5. It has been hypothesized that PD (the pathologic processes of Lewy neurites) begins in the olfactory and autonomic nervous system approximately 20 years before the onset of the

motor symptoms of PD and that many nonmotor symptoms appear before the motor symptoms (Hawkes et al., 2010).

A large collaborative Italian study of more than 1072 patients with PD found that 98.6% of patients with PD reported the presence of NMS (Barone et al., 2009). The most common were fatigue (58%), anxiety (56%), leg pain (38%), insomnia (37%), urinary urgency and nocturia (35%), drooling of saliva (31%), and difficulties in maintaining concentration (31%). The mean number of NMS per patient was 7.8 (range, 0–32). NMS in the psychiatric domain were the most frequent (67%). The frequency of NMS increased with disease duration and PD severity.

Nonmotor symptoms often have an impact on quality of life more than motor symptoms. Helping patients with PD to cope with nonmotor difficulties is just as critical as manipulating therapy to provide control of their motor symptoms. In addition, antiparkinsonian drugs commonly induce unwanted nonmotor effects and can also aggravate a few of the nonmotor symptoms. For example, sensory “offs” (e.g., pain, anosmia, depression) are often underappreciated but are usually a greater source of discomfort than are motor “offs.” In this chapter, we cover nonmotor problems inherent to the disease and also nonmotor problems induced by PD medications. Finally, it is important to appreciate that the nonmotor symptoms increase in disability with the increasing duration of the disease.

Nonmotor symptoms are commonly the presenting PD complaint. In pathologically proven PD, 91 of 433 (21%) patients presented with nonmotor symptoms, of which the most frequent were pain (53%), urinary dysfunction (16.5%), and anxiety or depression (12%) (O'Sullivan et al., 2008). The presentation of nonmotor symptoms was

Table 8.1 Frequency of nonmotor symptoms in Parkinson disease

Symptom	Frequency (%)
Depression	36
Anxiety	33
Fatigue	40
Sleep disturbances	47
Sensory symptoms	63
No nonmotor symptoms	12

Data from Shulman LM, Taback RL, Bean J, Weiner WJ. Comorbidity of the non-motor symptoms of Parkinson's disease. *Mov Disord.* 2001;16:507–510.

associated with a delayed diagnosis of PD. PD patients with nonmotor symptoms were more likely to be misdiagnosed initially and were also more likely to have been referred to orthopedic surgeons or rheumatologists than neurologists. Comparing newly diagnosed patients with a control population, Miller and colleagues (2011) found a statistically significant higher number of autonomic and sensory symptoms present in the PD group, especially olfaction issues, urinary issues, drooling, constipation, and sensory complaints.

As PD evolves, nonmotor symptoms become more common and can become the dominant and most troublesome symptom(s) (Hely et al., 2005, 2008). In addition, medications to treat the motor symptoms of PD can cause nonmotor symptoms, including impulse control problems, confusion, hallucinations, and paranoid psychosis. Behavioral, mood, and cognitive problems can develop as complications of surgery for PD, such as deep brain stimulation (DBS) (Voon et al., 2006c), and these are covered in Chapter 7. These surgical complications can occur as a result of medication reduction or can occur de novo.

Nonmotor symptoms as a part of PD fit the pattern of the location of Lewy neurites described by Braak and colleagues (see review by Braak et al., 2006) and are presented in detail in Chapter 6. The Braak hypothesis as an early feature of PD is not uniformly accepted (Burke et al., 2008). As more PD specialists have been focusing on nonmotor symptoms, there has been a coincident increase in publications. Three reviews on this topic are recommended: Simuni and Sethi (2008), Lim and associates (2009), Chaudhuri and Schapira (2009), and Lang (2011).

We review updates on the evolving use of the term *prodromal PD* (Berg, 2015) and also on the nonmotor treatments of PD according to the MDS and other studies (Seppi, 2011). Finally, two prominent risk factors for mortality in PD are the nonmotor symptoms of psychosis and dementia and both will be reviewed (Forsaa et al., 2010).

Sensory symptoms

Pain

Many textbooks do not list pain and the other sensory complaints in Table 8.2 as a part of PD, and they may be erroneously omitted as symptoms of the disease (Snider et al., 1976; Koller, 1984; Goetz et al., 1986; Quinn et al., 1986; Ford et al., 1996; Ford, 2010). A constant, boring pain in the initially affected limb may be the first complaint. Aching in the shoulder and arm is also a common earlier symptom in

Table 8.2 Sensory symptoms in Parkinson disease

Pain
Paresthesias
Numbness
Burning
Akathisia
Restless legs syndrome
Hyposmia
Urgency to urinate

PD and may be incorrectly attributed to a bursitis or a frozen shoulder. When pain occurs in the hip or leg, it is often attributed to arthritis. That such pain is due to PD is most supported by the observation that there is relief with antiparkinsonian medication, though in many cases there may be only partial relief or even no relief. Once adequate dosing is achieved, whether or not mobility is restored, such pain may improve. Of course, patients with PD may also have coincidental joint disease, so if the pain persists, patients require appropriate investigation.

Another initial complaint, particularly in younger patients, may be painful dystonic foot cramps, especially on walking. Rarely, similar painful cramps may occur in the hands. An extended big toe or curling of small toes may be observed with the cramping. In surveys conducted in 2008, about two-thirds of patients experience chronic pain (Defazio et al., 2008; Nègre-Pagès et al., 2008).

When patients with PD develop motor fluctuations and dyskinesias, pain may become a major feature. Additionally, “off-period” dystonia may be frequently painful. This issue may manifest as early morning painful cramps, particularly affecting the feet (Melamed, 1979). Similar painful dystonic cramps may emerge during “off” periods and can be very distressing (Ilson et al., 1984). Some patients may experience more generalized excruciating pain during “off” periods, often a deep-seated aching, but sometimes accompanied by a superficial burning quality. In many cases, such pains disappear when the patient is switched “on” by appropriate medication. An “off-period” pain may be an indication for the use of rapidly acting water-soluble preparations of levodopa or apomorphine rescue injections.

Burning, numbness, and paresthesia

Other specific sensory symptoms, such as burning, numbness, and paresthesia, are less common in PD. Some patients may describe nonspecific paresthesia in the affected limbs; however, objective sensory signs are absent (Snider et al., 1976; Koller, 1984). A rare patient may have sensory complaints from levodopa therapy, unaccompanied by dystonia. Electroconvulsive therapy (ECT) has been reported in some cases as effective in alleviating the problem, though this would not be a first-line therapy. If parkinsonian pain occurs during an “off” or as a result of parkinsonism, one should first try to increase medications to avoid “offs.” (Sensory “offs” are considered later in this chapter.) If pain occurs during peak-dose dystonia, one needs to consider lowering the dose. If pain is secondary to levodopa or a dopamine agonist, one needs to reduce or eliminate the causal agent. Occasionally, the ergot dopamine agonists bromocriptine

and pergolide may cause a burning pain with inflammatory changes in the skin. This condition has been referred to as St. Anthony's fire. If this issue emerges, the agonist needs to be discontinued.

A recent review of pain by Jost and colleagues (2019) revealed that there is an appreciation for both nociceptive and neuropathic pain in PD. Data on drug therapy are limited and not specific. Medications used include dopaminergic drugs, opioids, nonopioid analgesics, anticonvulsives, antidepressants, and cannabinoids. Pain may be resistant to many of these therapies.

Akathisia

A more common sensory symptom is akathisia, or a sense of inner restlessness. This symptom may be focused on the legs with uncomfortable paresthesias and the need to move the legs to gain relief, in which the condition may be termed a true restless legs syndrome (RLS) (Lang, 1987). More often, there is a sense of generalized inner restlessness and discomfort, demanding walking for relief; akathisia is the more appropriate description (Lang and Johnson, 1987). Akathisia may be a presenting feature of PD. The symptoms of both restless legs and akathisia may respond to dopamine replacement therapy. Akathisia may also occur during the "off" period (Lang, 1994). It may be difficult for the patient and the clinician to distinguish between akathisia and RLS in select patients.

Akathisia probably occurs more often in PD than is commonly recognized. It can be a sensory complaint of the disease and also an adverse effect from levodopa. Lang and Johnson (1987) asked patients with PD specifically for complaints of restlessness and found that 86% had this subjective complaint. Most patients with PD who complained of an inner feeling of restlessness did not overtly manifest any signs such as moving about. From Lang and Johnson's study it was not clear whether akathisia represented an adverse effect from levodopa or was a feature of the disease. In most of their patients it appeared only after the introduction of antiparkinsonian drugs, but a small number had this symptom early in the course of PD, before receiving any medication. It is likely that levodopa and other antiparkinsonian agents may also contribute to this complaint. Restlessness has been reported to occur in patients with primary torsion dystonia after starting these drugs.

Restless legs syndrome

RLS is encountered frequently in patients with PD. In one study, 24% of patients with PD had RLS (Peralta et al., 2009). The symptoms are described in Chapter 23. Briefly, it consists of unpleasant crawling sensations in the legs, particularly when sitting and relaxing in the evening, and disappears on walking. Whether RLS is an epiphenomenon of PD, because both respond to dopaminergics, is not clear. Like PD, dopamine transporter binding is reduced in the striatum in sporadic RLS (Early et al., 2011). Sporadic and familial RLS respond to dopamine agonists and levodopa, but these drugs can cause augmentation, a worsening of the restless legs symptoms—more severe unpleasant sensations, occurring earlier in the day, and spread to involve other body parts. This raises the possibility that some cases of RLS in

patients with PD may be the result of dopaminergic medications used to treat PD. Fortunately, opioids are effective in treating RLS and periodic movements in sleep, whether in patients with PD or in sporadic and familial RLS (Hening et al., 1986; Kavey et al., 1988), and these can be used safely in PD. Propoxyphene 65 mg late in the day before the onset of symptoms is usually effective. Start with a half-tablet, and titrate up to two tablets if necessary. Other opioids such as oxycodone (Walters et al., 1993), tramadol (Lauerma and Markkula, 1999), and methadone (Silver et al., 2011) are effective without the augmentation problem. Finally, pregabalin and gabapentin have both been used to treat restless legs (Winkelmann, 2018).

Meta-analysis revealed that the prevalence of restless legs is higher in PD. It was also higher among patients who had previously received PD treatment (15%) than among drug-naïve patients (11%). Overall, the RLS prevalence was higher among PD patients than controls (odds ratio [OR], 2.86; 95% confidence interval [CI], 2.10–3.90; $P < 0.001$) (Yang, 2018).

Hyposmia

Decreased sense of smell is not a common PD complaint; however, if olfaction is tested, decreased smell is detected in most patients with PD. In one study, 45% of patients were functionally anosmic, 51.7% were hyposmic, and only 3.3% were normosmic (Haehner et al., 2009). This indicates that 96.7% of PD patients presented with significant olfactory loss compared with young normosmic subjects. This figure fell to 74.5% when adjusted to age-related norms.

Hyposmia often precedes the onset of motor symptoms (Ponsen et al., 2004; Haehner et al., 2007) and is now being studied to determine whether it can predict future PD. Hyposmia is more predictive than is executive dysfunction (Ponsen et al., 2009). One study indicated that hyposmia could predict PD in men up to 4 years before the onset of motor features (Ross et al., 2008), and an autopsy study showed that those with the greatest reduction of smell were more likely to have incidental Lewy bodies at autopsy (Ross et al., 2006). One problem is that hyposmia is not selective; it is decreased in other neurodegenerative disorders, including corticobasal degeneration (Pardini et al., 2009). Hyposmia has been associated with striatal dopamine deficiency (Wong et al., 2010) but showed a better correlation with decreased cholinergic activity in the cortical and limbic areas (Bohnen et al., 2010).

Autonomic dysfunctions: bladder and sexual problems

The listing in Table 8.1 does not include autonomic symptoms, but PD patients also frequently report these issues, such as gastrointestinal, urinary, cardiovascular, thermoregulatory, and sexual dysfunction compared with a control population. The greatest differences have been in the gastrointestinal and urinary domain (Verbaan et al., 2008). These symptoms were found to increase with age, disease severity, and medication use.

The autonomic dysfunctions in patients with PD can be segregated into urogenital problems and those that affect

Table 8.3 Autonomic dysfunction in Parkinson disease

Bladder problems
Sexual dysfunction
Hypotension
Gastrointestinal problems
Seborrhea
Sweating
Rhinorrhea
Abdominal bloating

other functions, such as blood pressure, the gastrointestinal tract, and the skin (Table 8.3). In this section, we discuss bladder problems in patients with PD.

The prevalence of bladder symptoms in PD is high; the most common complaint is nocturia followed by frequency and urgency (Fitzmaurice et al., 1985; Winge and Fowler, 2006). Of course, PD patients are usually of an age at which prostatic problems in men and stress incontinence in women can commonly occur. However, PD affects bladder control, owing to detrusor hyperreflexia. As a result, premature uninhibited bladder contractions cause frequency and urgency, and these symptoms can be particularly troublesome at night and during “off” periods. Araki and Kuno (2000) assessed voiding dysfunction in 203 consecutive PD patients and found that 27% had symptomatic voiding dysfunction. The severity correlated with the severity of PD and not with disease duration, age, or sex.

Prostatic outflow obstruction can add to the problem in males. Incontinence not explained by immobility when taken by the urge to micturate or by retention with overflow is not, however, a part of PD. True neurogenic incontinence in someone with parkinsonism suggests the possibility of a diagnosis of multiple system atrophy (MSA) (Stocchi et al., 1997). In this case, sphincter electromyographic studies may reveal signs of denervation resulting from involvement of Onuf’s nucleus in the sacral spinal cord.

The diagnosis of significant prostate enlargement in PD is difficult, and prostatectomy may not improve the symptoms and may in some cases lead to worsening. Prostatectomy should be considered only in those with proven outflow obstruction. A simple screening test in patients with PD is noninvasive ultrasonic estimation of postmicturition residual volume and simple mechanical measurement of urinary flow rate. If there is significant residual volume after urination (greater than 100 mL) or if flow rate is reduced, there may be bladder outlet obstruction and further investigation by more extensive urodynamic studies and other urologic testing is required. If there is no significant residual volume or reduction of flow rate, urinary frequency and urgency may be helped by a peripheral antimuscarinic drug such as oxybutynin (Ditropan; 5–10 mg at night or 5 mg three times a day). This approach is often not feasible in PD because it may worsen cognition. Fluid intake should be reduced at night. A tricyclic antidepressant with anticholinergic properties, such as amitriptyline, may help sleep not only through its sedative actions but also by reducing bladder irritability. This approach may also worsen cognition. Intranasal desmopressin (DDAVP) at night also may reduce nocturia.

Impotence in the male patient with PD causes distress to both partners (as do immobility and other problems in the

female patient). PD itself does not normally cause impotence, although this is a common early complaint in MSA. Loss of libido and failure to gain or sustain erections may have some other cause in this age group. Whether the issue is psychological, vascular, hormonal, or neurogenic, an appropriate investigation is warranted. Some antidepressant drugs, monoamine oxidase inhibitors (MAOIs), and antihypertensive medications can impair sexual performance. Failure of erection can be overcome by a variety of intrapenile or oral medications such as sildenafil (Viagra) (Zesiewicz et al., 2000). Sildenafil can be efficacious in the treatment of erectile dysfunction in both PD and MSA; however, it can unmask or exacerbate hypotension in MSA (Hussain et al., 2001). Parkinsonian symptoms are not affected, but a side benefit of reduced dyskinesias has been reported (Swope, 2000). Hypersexuality, particularly in males, is a rare and unacceptable side effect of dopamine replacement therapy in PD. Both levodopa and dopamine agonists have been reported as possible offenders, and, if this cause can be pinned down, it usually requires reduction of antiparkinsonian medication.

Levodopa itself can affect the bladder (Brusa et al., 2007). In dopa-naïve PD patients challenged with carbidopa/levodopa 50/200 mg, bladder overactivity (neurogenic overactive detrusor contractions) threshold and bladder capacity significantly worsened (32% and 22% of worsening, respectively). However, when the same patients were rechallenged after being on levodopa therapy for 2 months, there was improvement of bladder function. Compared with the values obtained earlier, bladder activity and capacity improved 93% and 33%, respectively. Furthermore, the sensation of bladder filling was reported to have a robust improvement of 120% over baseline.

Behavioral therapy has been considered as a potential treatment for bladder issues (Vaughan, 2019). A group of 53 participants were randomized, and 47 reported 8-week outcomes. Quality of life (-22.6 ± 19.1 versus -7.0 ± 18.4 , $P=0.048$) and bother (-12.6 ± 17.2 versus -6.7 ± 8.8 , $P=0.037$) improved significantly more with behavioral therapy. Although disappointing, this approach will likely be refined in future trials.

Other autonomic symptoms

Lewy body degeneration affects the autonomic nervous system in PD. Both sympathetic ganglion neurons and parasympathetic myenteric and cardiac plexi can be involved (Qualman et al., 1984; Kupsky et al., 1987; Wakabayashi et al., 1988). The postganglionic sympathetic nerves to the heart degenerate early and in a centripetal manner, with synuclein accumulation, not only in PD but also in persons with incidental Lewy bodies (Orimo et al., 2008). The loss of these sympathetic neurons is reflected in the reduced cardiac uptake of 123I-meta-iodobenzylguanidine (MIBG), a physiologic analog of norepinephrine, in patients with PD and with Lewy body dementia (DLB) (Oka et al., 2007a). In contrast, postganglionic sympathetic fibers remain intact in MSA, and so MIBG uptake is normal in MSA. Central autonomic nuclei, such as those of the hypothalamus and dorsal motor nucleus of the vagus, also can be affected in Lewy body degeneration (Eadie, 1963).

With *orthostasis*, control of blood pressure may be compromised by sympathetic failure with impaired vasoconstriction and inadequate intravascular volume. Faintness on standing (presyncope) and frank loss of consciousness on standing (postural syncope) can occur owing to OH. OH can also cause posturally induced fatigue and weakness, blurring of vision, and “coat-hanger” neck and shoulder aching. Hypotension also may occur postprandially because of gastrointestinal vasodilatation. Levodopa, dopamine agonists, and selegiline (Churchyard et al., 1999) may aggravate postural hypotension. Oka and colleagues (2007b) compared PD patients with and without OH and found a greater association with male gender, older age, longer disease duration, posture and gait instability phenotype, low Mini-Mental State Examination (MMSE) scores, and visual hallucinations. Cardiac MIBG uptakes were lower in patients with OH.

Prominent early symptoms of postural hypotension are, of course, one of the hallmarks of MSA, so such complaints may raise concern over the diagnosis of PD. The severity of postural hypotension in PD rarely is as severe as that seen in MSA. Nevertheless, treatment might be required. A selective peripheral dopamine antagonist such as domperidone sometimes helps, as does increasing fluid and salt intake, with head-up tilt at night, which may reduce nocturnal polyuria. Intranasal DDAVP (5–40 mcg at night) also reduces nocturnal polyuria but can cause hyponatremia. However, a small dose of fludrocortisone (0.1–0.5 mg) (to promote salt retention), or midodrine (ProAmatine) (a selective α -agonist) (2.5–5 mg three times daily), might be required to maintain adequate blood pressure. Pyridostigmine was found to improve OH, probably because of enhanced sympathetic ganglionic neurotransmission and a vagal shift in cardiac sympathovagal balance (Singer et al., 2006).

Gastrointestinal problems cause significant disability in PD (Edwards et al., 1991, 1992). Dysphagia is due partially to poor masticatory and oropharyngeal muscular control making it difficult to chew and propel the bolus of food into the pharynx and esophagus (Bushman et al., 1989; Edwards et al., 1994). Soft food is easier to eat, and antiparkinsonian medication may in some cases improve swallowing.

Parasympathetic failure may contribute to gastrointestinal problems in PD, causing delay in esophageal and gastric motility. A sense of bloating, indigestion, and gastric reflux are all common in PD (Edwards et al., 1992). Many factors contribute to delayed gastric emptying, including immobility, parasympathetic failure, constipation, and antiparkinsonian drugs (both anticholinergic and dopamine agonists). Levodopa is absorbed in the upper small bowel, so gastric stasis may slow or prevent levodopa assimilation, leading to “delayed-ons” and “no-ons” (dose failures) after single oral doses (either there is an excessive interval before the drug works, or it does not work at all).

Constipation is another frequent complaint in PD (Edwards et al., 1992, 1994; Kaye et al., 2006) and is multifactorial. Again, immobility, drugs, reduced fluid and food intake, and parasympathetic involvement prolonging colonic transit time may all contribute to issues. In addition, malfunction of the striated muscles of the pelvic floor because of the PD can make evacuation of the bowels difficult (Mathers et al., 1988, 1989). Constipation may exacerbate gastric stasis. Anticholinergic drugs should be stopped and physical exercise should be increased. The role of levodopa in causing

or in treating constipation is uncertain. This drug usually does not relieve the problem, and some patients think that it worsens the problem. Constipation is ameliorated by adequate fluid intake, fruit, vegetables, fiber, and lactulose (10–20 g/day) or also by the use of other mild laxatives. The following “rancho recipe” provided by Dr. Cheryl Waters has been found useful for many patients: Mix together 1 cup each of bran, applesauce, and prune juice; take two tablespoons every morning; the mixture can be refrigerated for 1 week, then should be discarded. Polyethylene glycol powder (marketed as MiraLax) can be effective to overcome constipation; the usual dose is 17 g/day dissolved in a glass of water at bedtime. Refractory constipation may be helped by apomorphine injections, which may also assist in defecation (Edwards et al., 1993; Merello and Leiguarda, 1994).

Pyridostigmine is also another option by enhancing parasympathetic tone that can aid peristalsis and help in the treatment of constipation. For patients who have *abdominal bloating* as a result of suppression of peristalsis when they are “off,” keeping them “on” with levodopa or other dopaminergics may be a beneficial strategy.

Excessive sebum (*seborrhea*) may be due to facial immobility more than overproduction. The greasy skin of PD contributes to seborrheic dermatitis and dandruff. Medicated soaps and shampoos help. Blepharitis also is common, due in part to reduced blinking. Artificial tears also can be helpful.

Excessive sweating can be a problem, particularly in the form of sudden drenching sweats (sweating crises). These seem to occur as part of an “off” phenomenon (Sage and Mark, 1995; Swinn et al., 2003; Pursiainen et al., 2007). Sweating can cause physical, social, and emotional impairment.

Excessive salivation (sialorrhea) is due more to failure to swallow saliva frequently than to overproduction (Bateson et al., 1973). Drooling of saliva can be helped by chewing gum (which also helps with dry mouth) or by using peripherally acting anticholinergic drugs, which are quaternary ammonium compounds that do not cross the blood-brain barrier. Two such compounds are glycopyrrolate and propanteline. The former was tested in a controlled clinical trial and found to be effective and safe therapy for sialorrhea in PD (Arbouh et al., 2010). If these are unsuccessful, intraparotid injections of botulinum toxin B can sometimes be effective in reducing salivary secretions and drooling (Lipp et al., 2003; Racette et al., 2003; Ondo et al., 2004). Chewing gum has also been found useful to increase swallow frequency, and chewing gum decreases the latency of swallowing in PD (South et al., 2010). These are common problems in advanced PD and contribute to weight loss.

Rhinorrhea is not infrequent in patients with PD and has been reported to occur in almost 50% (Friedman et al., 2008). Patients with PD with rhinorrhea were older and had a higher Hoehn and Yahr stage. Duration of disease was not different between those with and without rhinorrhea. Most patients with rhinorrhea reported that it worsened with eating.

Respiratory distress

Respiratory distress such as dyspnea can occur as a symptom of PD in some patients, including during the “off” period (Ilson et al., 1983). It can also occur as a complication of

dystonia, usually peak-dose dystonia (Braun et al., 1983), and with some dopamine agonists, particularly pergolide. Removing the offending drug is required. “Off” period dyspnea is difficult to treat, other than attempting to keep the patient “on.” Despite the sensation of dyspnea, oxygen saturation is not affected because the patient will have a voluntary sigh or transient deep breathing when feeling short of breath. Some forms of parkinsonism-plus syndromes may have an accompanying apnea that is life-threatening, such as postencephalitic parkinsonism (Strieder et al., 1967; Efthimiou et al., 1987), frontotemporal dementia (Lynch et al., 1994), MSA (Chester et al., 1988; Salazar-Grueso et al., 1988), Joseph disease (SCA3) (Kitamura et al., 1989), and other familial parkinsonian syndromes (Perry et al., 1990).

Difficulties at night and daytime sleepiness

Table 8.4 lists some of the sleep problems observed in PD. Patients often have troubled nights for many reasons (Factor et al., 1990; Askenasy, 1993; Van Hilten et al., 1994; Bliwise et al., 1995). The most common problem is difficulty with sleep maintenance (so-called sleep fragmentation). Frequent awakenings may be caused by tremor reappearing in the lighter stages of sleep, difficulty in turning in bed because of nocturnal akinesia as the effects of daytime administration of dopaminergic drugs wear off at night, and nocturia. In addition, periodic leg movements in sleep (sometimes associated with restless legs), fragmentary nocturnal myoclonus, sleep apnea, rapid eye movement (REM) sleep behavioral disorders (RBD; intense dream-like motor and behavioral problems), and parasomnias (nocturnal hallucinations and nocturnal wandering with disruptive behavior) may all disrupt sleep in PD. Reversal of the sleep rhythm with sundowning also is common in PD (Bliwise et al., 1995). Many of these conditions probably occur more frequently in PD than in other aged populations. As a result, PD patients and their caregivers face disrupted nights, which lead to poor quality of life and worse parkinsonism the next day. In fact, along with depression, poor sleep is a major factor in a PD patient’s assessment of having a poor quality of life (Karlsen et al., 1999b). Rating scales to assess the severity of sleep disturbances have been developed (Trenkwalder et al., 2011). A good night’s sleep reduces the severity of daytime parkinsonism, and many patients comment on sleep benefit, describing better mobility the morning after a restful night. Indeed, patients with marked sleep benefit might not require antiparkinsonian medication for some hours after they awaken, and some PD patients find that a daytime nap “charges the batteries.” It has been suggested that this phenomenon occurs more frequently in the young-onset PD patients with mutations in the *parkin* gene for they typically show sleep benefit (Elibol et al., 2000), though many experts have reported this phenomenon in other patients.

Another cause of disturbed sleep is the return of parkinsonian symptoms during the night after the last dose of medication has worn off. Nocturnal tremor and akinesia because of the PD and nocturia in the elderly can lead to sleep arousals. A simple treatment is redosing when awakening occurs. Depression, which is common in PD, can cause insomnia and is a major factor associated with nighttime sleep problems (Verbaan et al., 2008). Drugs administered to treat PD symptoms also can interfere with sleep.

PD pathologic processes can be associated with RBD and parasomnias, especially in patients with incipient or frank dementia. RBD, described initially by Schenck and colleagues (1986), is a condition in which there is lack of somatic muscle atonia, thus enabling such individuals to move while they dream (acting out their dreams). One animal model of REM sleep without atonia has shown that lesions of the perilocus coeruleus disrupt the excitatory connection to the nucleus reticularis magnocellularis in the descending medullary reticular formation and may disable the hyperpolarization of the alpha spinal motoneurons (Ferini-Strambi and Zucconi, 2000). The development of RBD may be an early marker for the later onset of PD (Schenck et al., 1996; Tan et al., 1996; Postuma et al., 2006).

RBD may precede or develop after PD. RBD is suspected of arising in the pons–medulla area of the brainstem, and therefore the Braak scheme would have RBD occurring before PD. In the survey of their PD patients, Scaglione and colleagues (2005) found that only 33% had RBD. Of these, PD preceded RBD in 73%, an average of 8 years before onset of RBD. In another study, RBD preceded PD in only 22% (De Cock et al., 2007). Postuma and colleagues (2009) followed patients with idiopathic RBD and found that the risk for developing any neurodegenerative disease (PD, DLB, MSA, or Alzheimer disease [AD]) was 17.7% by 5 years, 40.6% by 10 years, and 52.4% by 12 years. Only 14 of 93 developed PD. With longer follow-up, approximately 50% of idiopathic RBD cases will develop PD and the more severe the loss of atonia on baseline polysomnograms, the better the prediction of the development of PD (Postuma et al., 2010).

RBD is usually successfully treated with a bedtime dose of clonazepam (Schenck et al., 1987); 0.5 mg is often sufficient, but sometimes a higher dosage is required to obtain complete relief. This strategy may also lead to daytime somnolence and can contribute to falls, so the management needs to be tailored to individual patient needs.

The treatment of sleep disorders in PD is important. Attention to sleep hygiene by avoiding alcohol, caffeine, nicotine, and excessive fluid intake at night is helpful. Deprenyl (selegiline), which is metabolized to methamphetamine and amphetamine, should not be given at night. Treatment of depression also might be required. A sedative antidepressant, such as amitriptyline (10–25 mg at night), mirtazapine, or trazodone, can be very useful, not only to induce and maintain sleep, but also to reduce urinary frequency. A dose of a long-acting levodopa preparation before bed may improve nocturnal akinesia (Laihnien et al., 1987; Lees, 1987). However, levodopa administered at night may provoke excessive dreaming and disrupted sleep in some patients (Nausieda et al., 1982). A benzodiazepine, especially clonazepam, may lessen RBDs. A low dose of 0.5 mg at bedtime is usually effective. Propoxyphene is useful for periodic leg movements of sleep and restless legs (Hening et al., 1986). A small bedtime

Table 8.4 Sleep problems in Parkinson disease

Sleep fragmentation
REM sleep behavior disorder
Excessive daytime sleepiness
Altered sleep–wake cycle
Drug-induced sleep attacks

dose of clozapine (Rabey et al., 1995) or quetiapine may also be effective in improving sleep. For patients who have no problem falling asleep, but awaken in 2 to 3 hours, the short-acting hypnotic zolpidem may be useful when taken after the awakening. It helps the patient get back to sleep quickly and still be refreshed in the morning. Another option is redosing levodopa.

Excessive daytime sleepiness (EDS) occurs in about 15% of patients with PD and is associated with more severe PD and patients with cognitive decline (Tandberg et al., 1999). In one study, EDS was found in 50% of patients (Shpirer et al., 2006). EDS was determined by short sleep latency and sleep-onset REM periods. When studied with tests determining these two criteria, PD patients with EDS were found to correlate not with variables related to disease severity or to total sleep time or sleep stage percentages, but rather those related to primary impairments of waking arousal and REM-sleep expression (Rye et al., 2000). Dopamine agonists were more likely than levodopa to be associated with EDS (Ondo et al., 2001; Gjerstad et al., 2006). The antisoporific agent modafinil can sometimes be beneficial in overcoming EDS in patients with PD (Happe et al., 2001). Oxybate has been reported to reduce EDS (Ondo et al., 2008).

Some patients who sleep a lot during the day may also report a problem related to drowsiness after a dose of levodopa. This phenomenon is usually observed in patients with cognitive dysfunction. With post-levodopa drowsiness, patients can sleep during much of the day and are then awake at night. This altered sleep–wake cycle can make life unbearable for the caregiver, who requires adequate sleep at night. If a patient becomes drowsy after each dose of medication, this may possibly be a sign of overdosage. Reducing the dosage can in some cases improve this problem. Sometimes, substituting Sinemet CR for standard Sinemet will help because this provides for a slower rise in plasma and lower top end brain levels of levodopa.

If the patient's sleep problem has advanced to that of an altered sleep–wake cycle, it is important to shift the patient onto a sleep–wake schedule that fits with that of the rest of the household. To correct the problem, it might be necessary to use a combination of approaches. Efforts must be made to stimulate the patient physically and mentally during the day and to force the patient to remain awake; otherwise, he or she will not be able to sleep at night. At night, the patient should then be drowsy enough to be able to sleep. If this fails, it might be necessary to use stimulants in the morning and sedatives at night to reverse the altered state. This should be performed in addition to prodding the patient to remain awake during the day. Drugs such as methylphenidate and amphetamine are usually well tolerated by patients with PD. A 10-mg dose of either of these two drugs, repeated once if necessary, may be helpful. To encourage sleep at night, a hypnotic agent might be necessary in addition to using daytime stimulants. It should be noted that strong sedatives, such as barbiturates, are poorly tolerated by patients with PD. Milder hypnotics, such as benzodiazepines, are usually taken without difficulty. Short-acting benzodiazepines would be preferable, but if the patient awakens too early, a longer acting one might need to be used. Benzodiazepines may increase fall risk, and amphetamines have an associated cardiac risk. These should be discussed with patients and families before implementation.

Sleep attacks

Falling asleep while driving and without warning is a serious problem that has been encountered with dopaminergic agents; it seems more likely to occur with pramipexole and ropinirole, but is not limited to just these drugs (Frucht et al., 1999; Ferreira et al., 2000; Hoehn, 2000; Schapira, 2000). The decision about which dopamine agonist to place a patient on was discussed in Chapter 6. Once sleep attacks have occurred, the patient should not drive or the medication should be changed. Modafinil has been reported to be helpful in preventing some sleep attacks; however, over the years it has not been shown to be universally efficacious (Hauser et al., 2000). A review of the literature (Homann et al., 2002) showed that sleep attacks have been reported with all dopaminergic medications, including levodopa, with the greatest number associated with pramipexole and ropinirole. Unfortunately, not all reports refer strictly to sudden attacks without warning; some reports refer to falling asleep from drowsiness, so the interpretation is open to uncertainty. The most important issues are to keep patients and families safe and restrict driving.

Sleep issues are now commonly appreciated in PD patients and many recent reviews suggest that a reasonable treatment approach is referral to a sleep expert (Wade, 2018). One issue has been the lack of randomized controlled studies in this area. In addition, sleep apnea has been found to be very common in PD yet it can be challenging to treat even with conventional continuous positive airway pressure (CPAP). Drugs such as melatonin are also promising sleep aids, but recent study results have been negative (Gilat, 2019).

Sleep and deep brain stimulation of the pedunculopontine area

One consequence of the experimental DBS in the pedunculopontine (PPN) area has been an attempt to treat parkinsonian gait disorders, and the procedure may possibly affect sleep. Low-frequency stimulation of the PPN area increased alertness, whereas high-frequency stimulation induced non-REM sleep (Arnulf et al., 2010). The number of cases reported has been small, so these observations should be cautiously interpreted.

Fatigue

Although fatigue can be a symptom of sleepiness or depression, it is also a symptom that may be unassociated with these states. The clinician should probe the patient to distinguish between fatigue and sleepiness. In patients with PD, fatigue is often a complaint during the earliest phase of the disease, before motor symptoms, such as stiffness and slowness, become prominent. As these other features of PD develop, with their important contribution to disability, these become more of a complaint than does fatigue. But when patients are specifically asked, fatigue remains a common feature in PD. In a community study of elderly people in Norway, 44% of PD patients and 18% of healthy controls reported fatigue (Karlsen et al., 1999a). In a Japanese study involving 361 PD patients, fatigue was present in 41.8% and depression was not a contributing factor (Okuma et al., 2009).

In newly diagnosed patients with PD, fatigue was discerned in 36% and was less likely to worsen if the patient received levodopa compared with a placebo (Schifitto et al., 2008). Treating depression and daytime sleepiness would be helpful, but when fatigue is an independent symptom, no treatment has been found satisfactory. Despite the claimed benefit of amantadine in treating fatigue in multiple sclerosis, neither this drug nor the MAOI selegiline has been found particularly beneficial in treating fatigue in PD. Modafinil also has not been found beneficial in a small, controlled trial (Lou et al., 2009). Methylphenidate 30 mg/day has been reported to reduce fatigue in a controlled clinical trial (Mendonça et al., 2007) and in fatigue in patients with prostate cancer (Roth et al., 2010). Oxybate at bedtime also has been reported to help (Ondo et al., 2008) but may lead to confusion in PD. Friedman and colleagues (2007) published a thorough review of fatigue in PD. A small study showed that rasagiline may improve fatigue in PD, but a larger randomized study will be needed to confirm this result (Lim, 2015).

Depression, anxiety, and change in personality

Loss of motivation

It is common in patients with PD to have a change in personality (Table 8.5), and the change may precede motor symptoms, but usually the changes develop and worsen over the course of PD. Executives with decision-making tasks might find such duties difficult and may not be able to continue in their work. Passivity, dependency, and lack of motivation are often more troublesome for the spouse than for the patient. Lack of motivation, as it becomes more severe, may transform into apathy; and when apathy becomes more severe, in some cases abulia may emerge. Abulia is a severe form of both mental and motor apathy, with not only a loss of initiative and drive but also a general restriction of activities, including the reticence to speak. Abulia is a recognized clinical syndrome that has been described in association with caudate and prefrontal dysfunction. In its milder form (i.e., apathy), the loss of initiative, both mental and motor, is often commented on by the spouse or close relatives, who perceive a change in personality. Spouses particularly complain about the patient's lack of desire to socialize with friends and communicate freely. When the spouse wants to go out, dine, or meet with friends, the apathetic patient just wants to sit at home and not participate in these activities. Such alterations in activity may be a result of depression, but not infrequently there is no change in mood. A direct test for apathy and depression in patients with PD and dystonia (control group)

found no apathy in the absence of depression in the dystonic population, whereas apathy in the absence of depression was frequent in PD (29%) (Kirsch-Darrow et al., 2006). Evaluation in 175 untreated PD patients found 37% with depression, 27% with apathy, 18% with sleep disturbance, and 17% with anxiety (Aarsland et al., 2009b). Apathy does not respond to dopamine replacement therapy in the way the motor problems of PD do, nor to antidepressants, unless depression is present and is itself the cause of the apathy.

In one survey of 164 patients with PD, 52 (32%) met diagnostic criteria for apathy (Starkstein et al., 2009). Of these, 83% had comorbid depression and 56% had dementia. Of the 164 PD patients, 40 had neither depression nor dementia; only 5 (13%) of the 40 had apathy. One study found that apathy appears to be a predictive factor for dementia and cognitive decline over time (Dujardin et al., 2009). Some studies have suggested treatment with dopamine agonists and others with behavioral therapies. There remains no consensus on the best approaches to treat apathy. One approach has been the Parkinson's Active Living Program (PAM) (Butterfield, 2016). This behavioral treatment has shown promise to address PD-related apathy but will need further study.

Depression

Depression is common in PD, with at least one-third of patients exhibiting significant depressive symptoms in cross-sectional surveys (Brown et al., 1988; Dooneief et al., 1992). Anguenot and colleagues (2002) reported a higher number of PD patients having depression. The Geriatric Depression Scale was administered to subjects enrolled in clinical trials for early PD, and 28% were found to have some depression (Ravina et al., 2007); 40% did not require treatment. However, depression was a predictor of more impairment in activities of daily living and increased need for symptomatic therapy of PD. In another study, all patients with early PD were found to have executive dysfunction, and those with major depression also had episodic/working memory and language deficits (Stefanova et al., 2006).

However, it is often difficult to distinguish true depression from the apathy (abulia) associated with PD, especially in the presence of the characteristic expressionless face, bowed posture, and slowed movement, which resemble the psychomotor retardation of a primary depressive illness. The critical factor is whether the patient has a true disturbance of mood (dysphoria), with low spirits, loss of interest, bleak outlook, typical depressive sleep disturbance, paranoid ruminations, and sometimes suicidal thoughts. Schrag and colleagues (2007) evaluated a variety of depression rating scales and found many of them satisfactory for use and concluded that it is not necessary to develop new ones.

The reasons for depression in PD are debated. On the one hand, depressive symptoms are not surprising in vulnerable individuals who are faced with the disabilities and handicaps imposed by PD, with reduced activities and independence, and the prospects of a chronic incurable condition. Such reactive depression certainly contributes to the problem. But one study suggests that depression in PD is more strongly influenced by the patients' perceptions of handicap than by actual disability (Schrag et al., 2001). However, there is also the probability that the pathologic process of PD in itself might predispose to depression, especially that

Table 8.5 Personality and behavior in Parkinson disease

Depression
Fearfulness
Anxiety
Loss of assertive drive
Passivity
Dependency
Inability to make decisions
Loss of motivation, apathy
Abulia

involving serotonergic and noradrenergic systems, which have been implicated in the neurochemical basis of primary depressive illnesses. The substantia nigra is implicated by the report that DBS of this structure in a patient with PD induced acute severe depression (Bejjani et al., 1999).

The recognition and treatment of depression in PD is important because depression has a major impact on the overall disability imposed by the illness. In fact, depression carries a hazard ratio of 2.66 for increased mortality in PD (Hughes et al., 2004). Most antidepressant drugs can be used safely in PD. However, nonselective MAOIs are contraindicated in patients who are taking levodopa because of potential pressor reactions. There also have been concerns over the use of selective serotonin reuptake inhibitors (SSRIs), which in a few cases have been reported to interact with levodopa to induce the “serotonin” syndrome (confusion, myoclonus, rigidity, and restlessness) and to worsen PD symptoms. Despite these worries, many depressed patients with PD have been treated safely and successfully with SSRIs, for example, fluoxetine or paroxetine (20–40 mg/day). By enhancing serotonergic “tone” and thereby potentially inhibiting dopaminergic neurons in the substantia nigra, there is the potential, especially in the absence of dopaminergic drug treatment, that SSRIs may increase parkinsonian symptoms, but such events are rare (Jansen Steur, 1993; Jimenez-Jimenez et al., 1994; Richard et al., 1999; Ceravolo et al., 2000; Tesei et al., 2000). The traditional tricyclic antidepressants also can be employed, although their sedative and anticholinergic properties may be detrimental in elderly patients. A small double-blind trial comparing paroxetine, nortriptyline, and placebo in 52 patients with PD and depression was carried out over 8 weeks and showed that nortriptyline was superior to placebo but paroxetine was not (Menza et al., 2009). A clinical trial testing the efficacy of pramipexole found the drug to be superior to placebo in treating the depression of PD patients (Barone et al., 2010). A trial of the norepinephrine uptake inhibitor atomoxetine found it to be ineffective in treating depression in PD (Weintraub et al., 2010b).

If a severely depressed patient with PD fails to respond to antidepressant drug treatment, ECT can be used (Douyon et al., 1989). Indeed, ECT in itself can temporarily improve mobility in PD. Tranylcypromine, a noncompetitive inhibitor of types A and B MAO, is an effective antidepressant (Fahn and Chouinard, 1998) but cannot be administered in the presence of levodopa because of the likelihood of hypertension. One of the most important aspects to treatment of depression in PD is to involve a psychiatrist for comanagement and also to schedule frequent follow-up appointments to assess the dose and response to therapy.

The most important recent study on Parkinson and depression has been the National Institutes of Health (NIH) SAD PD trial. Subjects were randomized to receive an SSRI (paroxetine; $n = 42$), an SNRI (venlafaxine extended release [XR]; $n = 34$), or placebo ($n = 39$). Both paroxetine and venlafaxine XR significantly improved depression in subjects with PD. Both medications were generally safe and well tolerated and did not worsen motor function (Richard, 2012). Practitioners seeing PD patients should have a low threshold for diagnosis and management of depression but should keep in mind that many medication therapies may be useful and the key is in titration of dose and monitoring response.

Anxiety

Anxiety and panic can be major difficulties in PD (Stein et al., 1990). Many patients, even early in the illness, complain of loss of confidence. In particular, they fear social occasions and public display at work, and they tend to withdraw from outside life. In part, this is due to anxiety over their friends and acquaintances perceiving that they have PD, to their loss of mobility, and to their nonverbal emotional responses to social interactions. However, some also develop a generalized and disturbing anxiety state, which might require psychotherapy and anxiolytic drug treatment. Those in the more advanced stages of the illness may experience profound anxiety and even terror during “off” periods (Nissenbaum et al., 1987). Many practitioners will try to assess anxiety and classify it as “off”-period anxiety or alternatively “non-off” anxiety. In addition, most practitioners will try to assess whether the anxiety was premorbid before the diagnosis of PD and also will involve a psychiatrist for cotreatment.

Often, anxiety can be relieved by effective antiparkinsonian drug therapy, but if uncontrolled and pervasive, it might require an antidepressant, and if dysphoria is present, a benzodiazepine (e.g., lorazepam 0.52 mg three times a day) or buspirone. Anxiety and stress worsen tremor, and alprazolam 0.25 mg during those periods can provide relief. However, all of these drugs can increase confusion in those who are cognitively impaired. There has been recent interest in cannabinoids as treatments for anxiety, sleep, and pain; however, controlled studies will be required to assess this as a potential treatment.

Many patients have sensory or behavioral “off” periods, either accompanying or instead of a motor “off.” The behavioral symptoms can consist of depression, anxiety, dysphoria, and panic; the sensory symptoms consist mainly of pain or akathisia. These sensory or behavioral “offs” are most distressing to the patient. Whereas motoric “offs” represent insufficient dopaminergic tone in the neostriatum, the behavioral and sensory “offs” probably represent an insufficient dopaminergic tone in the limbic dopaminergic areas of the brain, such as the nucleus accumbens, amygdala, and cingulate cortex. Like motor “offs,” these sensory “offs” respond to dopaminergic medication. Keeping the patient “on” all the time would prevent these sensory “offs,” but this is a difficult task. It is not clear that DBS can overcome sensory “offs.” Often patients with sensory “offs” will take increasingly more levodopa to stay “on.” This can contribute to a possible dopamine dysregulation syndrome.

The treatment of anxiety in PD remains tricky, and practitioners should consider the risks and benefits of treatments and involve a psychiatrist. Although antidepressants may help in some cases, they may not be enough to improve quality of life. Some medications may be too sedating (benzodiazepines), and others may not be feasible (cognitive behavioral therapy). Newer treatments are needed, and several ongoing studies are addressing cannabinoids (Sawada, 2018).

Cognitive problems

As listed in Table 8.6, slowness of thinking (bradyphrenia) and trouble finding words (“tip of the tongue phenomenon”)

Table 8.6 Cognition and dementia in Parkinson disease

Bradyphrenia
"Tip of the tongue" phenomenon
Confusion
Dementia

are common in patients with PD. (Dementia is discussed in the next section.) About two-thirds of patients with early PD will show abnormalities of cognitive function on formal neuropsychological testing (Lees and Smith, 1983; Levin et al., 1989; Brown and Marsden, 1990; Cooper et al., 1991). In particular, such patients may show deficits in performance of tests that are sensitive to frontal lobe dysfunction (executive function), such as verbal fluency, the Wisconsin card sorting test, the Tower of London test and its variants, and tests of working memory. Poor performance on tests such as these suggests abnormalities of frontal lobe executive functions, which may be due to defective input from nonmotor basal ganglia regions (via the thalamus) into prefrontal cerebrocortical areas. Thus, some patients with early PD may exhibit a frontostriatal cognitive syndrome, which is sometimes rather inaccurately described as a subcortical dementia, in the absence of any major defects in language, episodic memory, or visuospatial functions. The pathologic substrate of such a frontostriatal cognitive syndrome in PD has been recently examined by many imaging studies. Dopamine deficiency in the nonmotor regions of the striatum, especially the caudate nucleus, may partially underpin this issue. The loss of dopamine projections from the midbrain ventral tegmental area to the frontal lobes, the loss of cortical cholinergic projections from the substantia innominata, the loss of cortical noradrenergic projections from the locus coeruleus, and the cortical Lewy body degeneration may collectively contribute to the issues.

The Montreal Cognitive Assessment (MoCA) was found to be a useful screening tool for cognitive dysfunction in PD and was shown to be more sensitive than the MMSE (Gill et al., 2008; Hoops et al., 2009). Using more formal neuropsychological testing in newly diagnosed PD patients and controls, Aarsland and colleagues (2009) found that 18.9% of patients had mild cognitive impairment, with a relative risk of 2.1 (e.g., 2 times the risk). Ultimately, most patients with PD have cognition problems and eventually dementia. In one study, 13 of 126 (10%) newly diagnosed cases of PD had developed dementia at a mean of 3.5 years from diagnosis, corresponding to an annual dementia incidence of 30.0 per 1000 person-years; rapid development of dementia was associated with the postural instability and gait disorder (PIGD) form of PD (Williams-Gray et al., 2007). Hely and colleagues (2005) reported cognitive decline in 84% and dementia in 48% of patients with PD for 15 years. By 20 years, 83% had dementia (Hely et al., 2008). The Hely results are presented in Tables 6.7 and 6.8. Aarsland and colleagues (2003), following patients for 8 years, found that by that time span, 78% had cognitive decline. In a Norwegian study in which PD patients were followed for 12 years, 60% had developed dementia, with dementia steadily increasing with age, reaching 80% to 90% by age 90 years (Buter et al., 2008).

One approach to determine the pathoanatomic correlates to cognitive decline is to measure the functional networks

detected by fluorodeoxyglucose positron emission tomography (FDG PET) scanning. Whereas the motor manifestations of PD have been linked to an abnormal covariance pattern involving basal ganglia thalamocortical pathways, a covariance pattern that correlated with impaired memory and executive functioning was found to be metabolic reductions in frontal and parietal association areas and relative increases in the cerebellar vermis and dentate nuclei (Huang et al., 2007). This network of PD cognitive pattern increased stepwise with worsening cognitive impairment (Huang et al., 2008).

The clinical question is to what extent such neuropsychological defects intrude into everyday life in patients with PD. In this context two clinical features of PD deserve further comment, namely bradyphrenia and abulia.

Bradyphrenia, or slowness of thought, occurs in many patients. For example, patients might comment on a slowing of mental processing and memory retrieval, and examination of neuropsychological test performance might show delay in deciding on choices, although the final decisions are correct. Finding the right word or the answer to a question may be slow. The "tip of the tongue" phenomenon refers to the patient's knowing the word he or she wants, but not being able to come up with it and say it at that moment, a problem that is often encountered in PD (Matison et al., 1982). Some patients with PD spontaneously volunteer the observation that they have less ability to deal with mental problems, particularly multiple tasks at the same time. However, the extent to which depression might contribute to such problems is controversial. The general concept of bradyphrenia could be considered in the wider issue of abulia.

The overall impression of cognitive dysfunction in nondemented patients with PD may be summarized as follows: (1) Many, but not all, patients with early PD exhibit subtle frontostriatal cognitive impairments, but, to begin with, these do not necessarily intrude into everyday life. (2) However, a substantial number of patients with early PD do complain of some cognitive changes, in particular a slowing of thought, a difficulty or delay in memory retrieval, and problems in handling multiple tasks. (3) Such cognitive impairments may be due to depression or when there is a change in mood, but often there is no dysphoria. One multicenter survey of nondemented PD patients revealed that 26% had mild cognitive impairment (Aarsland et al., 2010).

Unfortunately, these selective cognitive impairments do not seem to respond to dopamine replacement therapy. These issues may not respond to antidepressants, unless depression is present and is itself the cause of the slowness of thinking. It is important to assess and treat any concurrent depression. It also is important to review current drug therapy. Anticholinergics, amantadine, dopamine agonists, and even levodopa in excess may also possibly impair cognitive function, especially in the elderly PD patient.

Whether these cognitive difficulties are the precursor to frank dementia is uncertain, but obviously they raise concern. In practice, it is likely that a minority of patients with such complaints in the early stages of PD will progress to frank dementia. Possible risk factors for developing dementia are low serum epidermal growth factor (Chen-Plotkin et al., 2011), low cerebrospinal fluid (CSF) amyloid-beta (Siderowf et al., 2010), and severity of olfactory impairment (Stephenson et al., 2010). Many studies are now focusing on

determining the patterns and subtypes of disease that may be at greatest risk to develop dementia.

Dementia and confusion

Unfortunately, a sizable proportion of patients with PD eventually develop a multifocal, pervasive dementia. This typically occurs in elderly patients. Cross-sectional studies suggested that in those with PD aged over 65 years, some 20% will be demented, compared with some 10% of non-PD individuals in this age group (Brown and Marsden, 1984). Initial prospective longitudinal studies raised that up to 40% become demented as they age (Mayeux et al., 1990; Biggins et al., 1992; Hughes et al., 2000). Aarsland and colleagues (2001) found the incidence rate for dementia to be 95.3 per 1000 person-years, which is a 6-fold greater risk than that in non-PD individuals. Following PD patients over an 8-year period, Aarsland and colleagues (2003) found that 78.2% developed dementia and that hallucinations and akinetic-dominant or mixed tremor/akinetic PD had a potentially higher risk for dementia. Another study also found that dementia was more likely to occur in the PIGD category of patient than in the type presenting with tremor (Burn et al., 2006a). In fact, in studying the incidence of dementia, Alves and colleagues (2006) found that the tremor-dominant subtype did not develop dementia until those patients converted to the PIGD subtype. Other correlations for developing dementia are older age, greater severity and longer duration of PD, and male sex. However, looked at from the opposite perspective, most patients with PD, particularly the young, do not have dementia. Aarsland and colleagues (2004) followed the MMSE and found that the mean annual decline for PD patients was 1 point. However, a marked variation was found. In patients with PD and dementia, the mean annual decline was 2.3, which was similar to the decline observed in patients with AD. The MoCA was found to be more sensitive as a screening tool than the MMSE, but a positive screen using either instrument required additional assessment because of suboptimal specificity at the recommended screening cutoff point (Hoops et al., 2009). Additionally, some patients with testing indicative of mild cognitive impairment will possibly revert back to normal levels on follow-up testing.

It is bad enough to develop the debilitating and disabling problem of dementia, but what compounds this development is a frequent lesser response to levodopa therapy in controlling motor symptoms (Alty et al., 2009). In patients without dementia the “off” phase motor function worsened at a yearly rate of 2.2% of the maximum disability score, and the magnitude of the levodopa response was well preserved as the disease progressed. Typically, patients who developed motor fluctuations maintained better “on” phase motor function than non-fluctuators ($P = 0.01$). However, dementia was associated with worse “on” and “off” motor disability scores ($P < 0.001$), and a smaller levodopa response magnitude after 14 years ($P = 0.008$).

The MDS’s Task Force on Dementia developed a set of criteria for diagnosing dementia in patients with PD (Emre et al., 2007). PD dementia (PDD) is characterized by impairment in attention, memory, executive and visuospatial functions, and behavioral symptoms such as affective changes, hallucinations, and apathy are also frequent. The Task Force

proposed clinical diagnostic criteria for “probable” and “possible” PDD (Emre et al., 2007). It also proposed guidelines for assessing such patients (Dubois et al., 2007). Level 1 was for general clinicians, and Level 2 tests were for more sophisticated evaluations and even for clinical trials.

Concurrent AD, probably coincidental, obviously accounts for some of the dementia in PD (Boller et al., 1980). However, with the use of antisynuclein antibody stains to detect Lewy bodies, it has become apparent that widespread Lewy body degeneration is another common cause of dementia (Byrne et al., 1989), some say second in frequency to AD. In those with prior PD, this may follow the progression and spread of Lewy neurite distribution observed by Braak and colleagues (2003). PDD is now the term applied to those whose PD symptoms began at least 1 year before the onset of dementia. It is called dementia with Lewy bodies (DLB) (McKeith et al., 1996) when the dementia precedes or occurs within 1 year after onset of parkinsonian motor features (Lippa et al., 2007). Although there is a clear relationship between the duration of PD before the onset of dementia and key neuropathologic and neurochemical characteristics, there is a gradation of these differences across the DLB/PDD spectrum and the findings do not support an arbitrary cutoff between the two disorders (Ballard et al., 2006).

DLB may coexist with the pathologic changes of AD, particularly with amyloid plaques rather than neurofibrillary tangles. One hypothesis is that the two pathologic processes, Lewy body degeneration in the cerebral cortex and the cholinergic substantia innominata and AD change coexist by chance but summate to cause dementia. Another hypothesis is that the one predisposes to the other, and it is intriguing that alpha-synuclein is a component of both plaques (the nonamyloid component) and Lewy bodies. Whatever the pathogenic mechanism, this combination (which some have called the Lewy body variant of AD) is a common cause of dementia in PD. Pure DLB may possibly be less common. However, it has been shown pathologically that cortical Lewy bodies can be associated with cognitive impairment independent of AD-type pathologic findings (Mattila et al., 2000).

Thus, there are at least three common substrates for dementia in PD: AD, AD with Lewy bodies, and diffuse Lewy body disease (DLB). A fourth possibility is dementia with just the standard pathologic processes of PD (PDD), typically with Lewy bodies in the cerebral cortex. Whether such dementia in patients with PD occurs without the spread of Lewy bodies into the cortex is uncertain. In addition, all the other causes of dementia may occur in patients with PD, including cerebrovascular disease, rare degenerations such as frontotemporal dementia and Pick disease, cerebral tumors and other intracranial mass lesions, hydrocephalus, and metabolic, endocrine, and vitamin abnormalities. In one pathologic study, the Lewy body score was significantly associated with the rate of cognitive decline (Aarsland et al., 2005).

PDD shares identical clinical features with DLB; both entities can be distinguished from AD (Galvin et al., 2006). A personality trait that distinguishes DLB/PDD from AD is passivity (diminished emotional responsiveness, relinquished hobbies, growing apathy, and purposeless hyperactivity) (Galvin et al., 2007). Neuroimaging with the Pittsburgh compound B (PIB) ligand with PET can reveal the presence of fibrillar Abeta amyloid, which is present in patients with

PDD (Brooks, 2009; Burack et al., 2010). This finding is present in the absence of AD at autopsy.

Accordingly, the first step in assessment of a patient with PD who has dementia is to undertake the usual investigations for known causes, especially those that are treatable. Depression causing a pseudodementia also must be carefully assessed. Anticholinergic drugs in PD appear to hasten cognitive decline (Ehrt et al., 2010), and withdrawal of such agents could improve cognitive function.

Having excluded such symptomatic causes of dementia, the clinical picture may offer important clues as to the underlying degenerative condition causing the dementia. Prominent early memory difficulties with language, praxis, and visuospatial problems pointing to temporoparietal problems suggest AD. A variable, fluctuating course with prominent hallucinations (especially visual), confusion, and an unusual susceptibility to neuroleptics could indicate DLB (McKeith et al., 1996, 1999), that is, diffuse Lewy body disease. Prominent behavioral, speech, and memory difficulties could point to frontotemporal dementia or Pick's disease.

FDG PET scans were correlated with the dementia score on the UPDRS. A correlation was found with left limbic structures such as the cingulate gyrus, parahippocampal gyrus, and medial frontal gyrus (Wu et al., 2000).

Whatever the pathologic substrate of dementia in PD, the combination poses formidable management problems. These are similar to those discussed in the section entitled "Psychosis; hallucinations, and paranoia." The difficulty is to maintain mobility with adequate doses of antiparkinsonian medication without exacerbating the mental and behavioral problems. Behavioral disturbances, including verbal and physical aggression, wandering, agitation, inappropriate sexual behavior, uncooperativeness, and urinary incontinence, cause major difficulties. General structured care in a familiar environment is essential. Judicious use of daycare facilities and home assistants may be necessary. Drug therapy should be simplified, removing selegiline, anticholinergic agents, amantadine, and dopamine agonists. Depression might require specific treatment, preferably avoiding antidepressants with marked anticholinergic properties. Nocturnal sedation might require quetiapine, which provides both sedation and antihallucinatory effects. Clozapine does the same but requires weekly ascertainment for neutropenia. Other bedtime hypnotics, such as benzodiazepines and zolpidem, can be effective. Donepezil (Aricept), which provides modest benefit in AD, has been found also to provide modest benefit in cognition in those with PD who are demented without aggravating the motoric symptoms of PD (Aarsland et al., 2002; Ravina et al., 2005). Rivastigmine and other centrally active cholinesterase inhibitors were found to provide some improvement in apathy, anxiety, delusions, and hallucinations in patients with DLB (McKeith et al., 2000) and can improve dementia (Giladi et al., 2003). In a large multicenter, controlled clinical trial, rivastigmine was found to provide moderate improvement in dementia associated with PD (Emre et al., 2004). Memantine was found to be superior to a placebo in a couple of small studies (Aarsland et al., 2009a; Leroi et al., 2009). An evidence-based review of treatment of PD dementia and psychosis was conducted by the American Academy of Neurology (Miyasaki et al., 2006).

Dementia, with or without a frank confusional state, is the most common cause of final nursing home placement in

those with PD, and dementia shortens life expectancy (Goetz and Stebbins, 1993).

MDS experts have recently updated and addressed dementia classification in PD and also addressed the conversion of mild cognitive impairment to dementia (Saredakis, 2019; Hoogland 2019, Hoogland 2017). Recent failures of dementia drug trials have also led to a reassessment of needs of carers and patients (Goldman, 2018).

Compulsive behaviors

A large multicenter, cross-sectional evaluation of impulse control disorders (ICDs) assessed 3090 patients with PD (Weintraub et al., 2010a). The point prevalence estimates of four ICDs were 5.0% with pathologic gambling, 3.5% with hypersexuality, 5.7% with compulsive buying, and 4.3% with binge-eating. ICDs were more common in patients treated with a dopamine agonist than in patients not taking a dopamine agonist (17.1% versus 6.9%; OR, 2.72; $P < 0.001$). ICD frequency was similar for pramipexole and ropinirole (17.7% vs. 15.5%). ICDs have become a problem, particularly for young individuals on a dopamine agonist. A screening questionnaire for ICDs (the QUIP) has been validated (Weintraub et al., 2009).

In the category of compulsive behaviors, the most newsworthy has been *pathologic gambling* (Driver-Dunckley et al., 2003), which is now being more widely recognized. It is possibly related to dopaminergic stimulation in the mesolimbic system (Gschwandtner et al., 2001). Treatment of PD with a dopamine agonist increases the lifetime risk for a PD patient to have pathologic gambling from 3.4% to 7.2% (Voon et al., 2006a). In a PD clinic in Scotland, pathologic gambling occurred in 8% of patients on dopamine agonists (Grosset et al., 2006b). Patients with a younger age at PD onset, higher novelty seeking traits, and a personal or family history of alcohol use disorders were found to have a greater risk for pathologic gambling with dopamine agonists (Voon et al., 2007). Pathologic gambling is not limited to patients with PD on dopamine agonists. It has also been seen in patients with RLS with these drugs (Tippmann-Peikert et al., 2007). In a PET study of PD patients during gambling, those with pathologic gambling had greater decreases in radiopride binding in the ventral striatum during gambling (13.9%) than in control patients (8.1%), likely reflecting greater dopaminergic release (Steeves et al., 2009).

In a survey of other reward-seeking behaviors in 297 patients with PD, pathologic *hypersexuality* lifetime prevalence was 2.4%, and *compulsive shopping* was 0.7% (Voon et al., 2006b); combined with pathologic gambling data, the lifetime prevalence of these behaviors was found to be 6.1% and increased to 13.7% in patients on dopamine agonists. In another survey of 272 patients with PD, these compulsive behaviors were found to have occurred in 6.6% (Weintraub et al., 2006). Dopamine agonists and a history of ICD symptoms before PD onset were found to be risk factors.

Compulsive eating with weight gain has also been reported with dopamine agonist therapy, especially pramipexole (Kumru et al., 2006; Nirenberg and Waters, 2006). This is in contrast to the typical weight loss often seen in patients with PD. In one analysis, patients with PD were found to have lost

a mean of 7.7% of body weight over a mean of 13.1 years with PD (Uc et al., 2006).

The term *punding* has been used to describe an abnormal motor behavior in which there is an intense fascination with repetitive handling and examining of mechanical objects, such as picking at oneself, taking apart watches and radios, or sorting and arranging of common objects, such as lining up pebbles, rocks, or other small objects. Punding has been reported with levodopa (Fernandez and Friedman, 1999) and dopamine agonists (McKeon et al., 2007), including for the treatment of RLS (Evans and Stegeman, 2009).

A common form is repetitive cleaning/rearranging/ordering behaviors, which can be disabling. These have associated features of hypomania, occur during motor “on” periods, and often occur nocturnally (Kurlan, 2004). The repetitive behavior responds poorly to serotonin reuptake inhibitors, but may benefit from atypical antipsychotics (Kurlan, 2004). Punding, a term that was first used in amphetamine abusers, is considered a dopamine dysregulation disorder (Evans et al., 2004). This behavior would appear to be a form of compulsive disorder. In this age of technology, excessive use of the computer is a particular form of repetitive behavior reported to be caused by levodopa therapy (Fasano et al., 2006). Punding incidence is lower than other compulsive behaviors (Miyasaki et al., 2007).

In a small cross-over study, amantadine was found to reduce pathologic gambling (Thomas et al., 2010); however, two reviews of databases showed that pathologic gambling and other ICDs are more often associated with patients on amantadine (Weintraub et al., 2010c; Lee et al., 2011). Recently naltrexone was also tried as a therapy to address ICD but was not found to be efficacious (Papay, 2014).

Psychosis: hallucinations and paranoia

Criteria for diagnosing psychosis in PD and differentiating it from other causes of psychosis were established by an NIH working group (Ravina et al., 2007). These criteria were in the style of the *Diagnostic and Statistical Manual of Mental Disorders* IV-TR (Table 8.7).

Hallucinations occur in a significant proportion of those with PD, especially in elderly patients. In a community study in Norway, 10% of PD patients had hallucinations with insight retained, and another 6% had more severe hallucinations or delusions (Aarsland et al., 1999). Forsaa and colleagues (2010b) followed Norwegian PD patients over 12 years and found that 60% developed hallucinations or delusions, with an incidence rate of 79.7 per 1000 person-years. Risk factors were higher age at onset, dopaminergic dose, and RBD at baseline.

Psychotic features appear to be due to a complex interaction between the progressive and widespread pathologic processes of the illness (diffuse cortical Lewy body degeneration, concurrent Alzheimer plaques and tangles, and cortical cholinergic, noradrenergic, and serotonergic denervation), the unwanted effects of drugs (anticholinergics, levodopa, and dopamine agonists), and intercurrent illness (e.g., infections or metabolic disturbances).

Isolated visual hallucinations are fairly common (Naimark et al., 1996; Sanchez-Ramos et al., 1996). Auditory hallucinations are very uncommon (Inzelberg et al., 1998). Visual

Table 8.7 Proposed diagnostic criteria for PD-associated psychosis

Characteristic symptoms

Presence of at least one of the following symptoms (Criterion A)
(specify which of the symptoms fulfill the criteria):

Illusions
False sense of presence
Hallucinations
Delusions

Primary diagnosis

UK brain bank criteria for PD

Chronology of the onset of symptoms of psychosis

The symptoms in Criterion A occur after the onset of PD

Duration

The symptom(s) in Criterion A are recurrent or continuous for 1 month

Exclusion of other causes

The symptoms in Criterion A are not better accounted for by another cause of parkinsonism such as dementia with Lewy bodies; psychiatric disorders such as schizophrenia, schizoaffective disorder, delusional disorder, or mood disorder with psychotic features; or a general medical condition including delirium

Associated features (specify if associated):

With/without insight
With/without dementia
With/without treatment for PD (specify drug, surgical, other)

From Ravina B, Marder K, Fernandez HH, et al. Diagnostic criteria for psychosis in Parkinson's disease: Report of an NINDS, NIMH work group. *Mov Dis.* 2007;22(8):1061–1068.

hallucinations often take the form of familiar humans or animals, which the patients know are false (pseudohallucinations). Even when the hallucinations do not disturb the patient because the visual images are friendly and not frightening (benign hallucinations), these milder forms can worsen to a more malignant type of hallucination (Goetz et al., 2006). Such hallucinations may progress to a delusional paranoid state (often concerning infidelity) or a frank confusional state with impairment of attentiveness and disorientation. FDG PET revealed that PD patients with visual hallucinations have a reduced metabolic rate in the occipito-temporoparietal regions, sparing the occipital pole (Boecker et al., 2007).

When such symptoms occur, although antiparkinsonian drug therapy is the most likely cause, it is wise first to search for some intercurrent illness, such as a stroke or intracranial mass lesion, a chest or urinary infection, disturbance of electrolytes, renal or hepatic dysfunction, anemia, or endocrine dysfunction. Psychosis caused by antiparkinsonian medications can usually be counteracted by atypical antipsychotics, drugs that usually do not aggravate parkinsonism at a dosage that has a therapeutic benefit in treating the psychosis, namely quetiapine (Seroquel) and clozapine (Clozaril). Quetiapine appears to be effective only for milder psychosis, such as hallucinations, but not in more severe forms of psychosis, as demonstrated by its failure in controlled trials (Ondo et al., 2005; Kurlan et al., 2007; Rabey et al., 2007). Quetiapine had a clinical benefit similar to that of clozapine in one study (Merims et al., 2006). Because quetiapine does

not cause agranulocytosis and does not require blood count monitoring (Fernandez et al., 1999; Juncos et al., 2004), as does clozapine, it is practical to start therapy with quetiapine if the hallucinations are mild. A dose of 25 to 50 mg at night can often control confusion and psychosis without worsening the parkinsonism. Because of the potential for drowsiness, it is best initially to use a small dose of such drugs at night, thereafter gradually increasing the dose to that required to control the confusion without worsening the parkinsonism. The benefit of aiding sleep at night is an advantage, but try to avoid a dose that might extend the drowsiness to daytime. Quetiapine can be used as a hypnotic in older patients with PD to take advantage of suppressing the development of hallucinations in this susceptible population.

If quetiapine is ineffective or produces too much daytime drowsiness or other adverse effects, including worsening of parkinsonism, clozapine (Clozaril) should be tried next, starting with 12.5 mg at night to avoid daytime drowsiness and increasing the dose until benefit or adverse effects are encountered. It is more effective than quetiapine, but its use requires regular monitoring of blood counts to prevent the 1% to 2% risk for agranulocytosis (Scholz and Dichgans, 1985; Friedman and Lannon, 1990; Pfeiffer et al., 1990; Wolters et al., 1990; Kahn et al., 1991; Factor and Brown, 1992; Greene et al., 1993; Pinter and Helscher, 1993; Factor et al., 1994; Diederich et al., 1995; Rabey et al., 1995; Factor and Friedman, 1997; Ruggieri et al., 1997; Friedman et al., 1999; Pollak et al., 2004). In one open-label comparative trial, quetiapine and clozapine appeared equally effective; interestingly, both also reduced the severity of dyskinesias and controlled psychosis (Morgante et al., 2004). Further studies have revealed a failure of quetiapine to show benefit in randomized clinical studies (Chen, 2019), and clozapine has on the other hand been found to be an efficacious treatment for PD psychosis.

Other so-called atypical antipsychotics appear to be so designated for marketing purposes. Olanzapine can be effective but easily increases parkinsonism and so needs to be used in small doses to avoid a worsening of parkinsonism (Wolters et al., 1996; Friedman, 1998; Jimenez-Jimenez et al., 1998; Goetz et al., 2000); therefore, it is relegated to third choice. Risperidone more closely resembles a typical rather than an atypical antipsychotic and worsens PD. Aripiprazole has also worsened parkinsonism (Fernandez et al., 2004). A more thorough discussion of atypical antipsychotics is found in Chapter 19. Molindone, pimozide, or other relatively weak antipsychotics might also be considered but are rarely employed because they may worsen psychosis.

An alternative to atypical antipsychotics are the centrally active anticholinesterase drugs that are used in the treatment of dementia. They have been reported to have similar efficacy on psychosis as quetiapine (Van Laar et al., 2001; Bergman and Lerner 2002; Reading et al., 2002; Burn et al., 2006b).

If psychosis continues without adequate benefit from the antipsychotics, selegiline, anticholinergics, and amantadine should be withdrawn. The need for anxiolytics and antidepressants should be reconsidered. If the symptoms persist, dopamine agonists should be reduced or stopped. If necessary, the dose of levodopa should be tapered. However, more often than not, as drugs are reduced to improve the mental state, mobility deteriorates. A brittle balance is reached at which the patient either is mobile but confused, paranoid, or

hallucinating or is mentally clear but immobile. More dopamine replacement therapy is required to maintain mobility, but this causes a recurrence of the confusion and it is very difficult to achieve a compromise. In this situation, a limited drug holiday, withdrawing dopaminergic drugs for 1 to 2 days each week, might help dispel psychotoxicity, allowing a reasonable dose of medication to maintain mobility on other days. Sustained withdrawal of levodopa provokes unacceptable parkinsonism and, sometimes, particularly if the levodopa is withdrawn suddenly, a “neuroleptic” malignant syndrome (Friedman et al., 1985; Hirschorn and Greenberg, 1988). When it comes to balancing drug-induced psychosis and parkinsonism, keep in mind that intact mental function is more important than intact motor function.

The serotonin 5HT₃-receptor antagonist ondansetron blocks nausea and vomiting experienced with anticancer drugs. It has been reported to reduce hallucinations, paranoia, and confusion in PD (Zoldan et al., 1995). Of the 16 patients treated with 12 to 25 mg/day for up to 8 weeks, 15 showed moderate to marked improvement of visual hallucinations and paranoid delusions. There was no worsening of the parkinsonism. However, this was not replicated by Eichhorn and colleagues (1996), who failed to find benefit in most patients and found waning of benefit in the few for whom the drug was initially beneficial.

Finally, the serotonin inverse agonist pimavanserin has been shown to be effective in treatment of mild to moderate psychosis in PD and received FDA approval. This drug carries the same black box warning as other antipsychotics but because it does not block dopamine its potential advantage is that it may not worsen PD motor symptoms. In a 2019 review, participants in the pimavanserin group had a 5.79-point decrease in symptoms on the PD psychosis (SAPS-PD) scale compared with a 2.73-point decrease seen with placebo ($P < 0.001$) (Patel, 2019).

Quality of life

Measuring quality of life in 124 patients with PD, Schrag and colleagues (2000) showed that it significantly deteriorated with increasing disease severity, as measured by the PDQ-39, the EQ-5D, and the physical summary of the SF 36. The greatest impairment was seen in the areas related to physical and social functioning, whereas reports of pain and poor emotional adjustment had similar prevalence in patients with PD and the general population. The impairment of quality of life was seen in all age groups and was similar for men and women, but the differences between patients with PD and the general population were most marked in the younger patient groups.

From the quality of life survey of patients with PD conducted in Norway by Karlsen and colleagues (1999b), the three most important factors affecting quality of life were depression, sleep disorders, and a sense of low degree of independence. The first two were addressed in this chapter, and their prominence in quality of life indicates the importance of the nonmotor symptoms of PD. Independence would be affected by gait and balance disorders predominantly. Sexuality is part of quality of life, and patients with PD are more dissatisfied with their sexual functioning and relationship than controls (Jacobs et al., 2000).

Falls and fractures also affect quality of life. Compared with an equal number of age- and sex-matched non-PD subjects, PD patients were found to be at a 2.2-fold increased risk for fractures generally and a 3.2-fold greater risk for hip fractures specifically (Melton et al., 2006). Adjusting for age, the independent predictors of overall fracture risk in the PD subjects were female sex and dementia, both with hazard ratios (HRs) of 1.6. Interestingly, chronic depression was associated with a reduced risk (HR, 0.4). Perhaps depressed patients are more cautious in walking. Hip fractures were predicted by dementia (HR, 2.2). Sato and colleagues (2006, 2007) showed that the incidence of fractures could be reduced by treating with risedronate, ergocalciferol (Sato et al., 2007), and lendronate and vitamin D₂ (Sato et al., 2006).

Patients with PD tend to forget to take their medication or are late in the timing of a dose, which usually affects the patients with wearing-off. Erratic intake was shown to be an emerging and more common problem that is likely to affect motor control and quality of life adversely (Grosset et al., 2005). Electronic monitoring of tablet administration provides the most accurate methodology for determining accurate compliance (Grosset et al., 2006a). Improved quality of life might be better achieved with better compliance of timing of medication in those who are fluctuators.

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Atypical parkinsonism, parkinsonism-plus syndromes and secondary parkinsonian disorders

Chapter contents

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Introduction

Parkinsonism is a dominant or an important clinical feature in a large number of neurodegenerative disorders (Litvan et al., 2003; Wenning et al., 2011; Stamelou et al., 2013). Most patients who are referred to specialized movement disorder clinics with hypokinetic disorders are diagnosed clinically as having Parkinson disease (PD); others have a variety of parkinsonian disorders, including (in descending order of frequency, vascular parkinsonism (VP), progressive supranuclear palsy (PSP), multiple system atrophy (MSA), dementia with Lewy bodies (DLB), Parkinson disease dementia (PDD), and a variety of other of parkinsonian disorders (Mehanna and Jankovic, 2013; Armstrong and McFarland, 2019; Bhidayasiri et al., 2019) (Tables 9.1 to 9.3). Although parkinsonism, manifested chiefly by bradykinesia, is the unifying feature for all of these disorders, many patients have additional motor and nonmotor features. The term *extrapyramidal* is sometimes used in the literature to refer to these motor manifestations, but it is too vague and does not necessarily indicate that the pathologic condition is outside of the pyramidal system. Therefore the term *extrapyramidal* should be avoided in scientific writing and is essentially banned from use in movement disorder journals (Obeso, 2016).

The classification of parkinsonism is evolving but with improved understanding of pathologic and pathogenic mechanisms neurodegenerative disorders are now categorized as follows: (1) amyloidosis (e.g., Alzheimer disease [AD]), (2) synucleinopathies (e.g., PD, MSA, DLB), (3) tauopathies (e.g., PSP, corticobasal degeneration [CBD], and frontotemporal dementia [FTD]); (4) polyglutamine expansion diseases (e.g., Huntington disease [HD]), spinocerebellar ataxias (SCAs), and (5) prion diseases (e.g., Creutzfeldt-Jakob disease [CJD]) (Jankovic, 2008;

Ling et al., 2018; Armstrong and McFarland, 2019) (Fig. 9.1). Besides parkinsonian findings, patients with these disorders exhibit additional (“plus”) features; thus, they are also sometimes referred to as “parkinsonism-plus” disorders. It is well recognized that the pathologic changes that are hallmarks of alpha-synucleinopathies (PD, PDD, DLB, and MSA) begin years before a clinical diagnosis and may be initially associated with certain nonmotor conditions, such as constipation, anxiety, and rapid eye movement (REM) sleep behavior disorder (RBD) (Savica et al., 2018). During a follow-up of 461 patients with various synucleinopathies, patients with MSA had the highest risk for death, followed by those with DLB, PDD, and PD (Savica et al., 2017).

The epidemiology of these atypical parkinsonian disorders has not been well studied but a community-based study in north-east Scotland found the crude annual incidence to be 3.2 per 100,000 for VP, 1.7 for PSP, and 1.4 for MSA parkinsonism type (Caslake et al., 2014). Based on a review of medical records of the Rochester Epidemiology Project among 542 incident cases of parkinsonism, 389 (71.8%) had presumed synucleinopathies and 264 (48.7% of all cases) had PD (Savica et al., 2013). The most common tauopathy was PSP (16 cases, or 2.9% of all cases), 36 (6.6%) had drug-induced parkinsonism, 11 (2.0%) had VP, and 84 (15.5%) remained unspecified. The incidence rate of synucleinopathies was 21 and of tauopathies 1.1 per 100,000 person-years, and the rate increased steeply with age. Findings at brain autopsy confirmed the clinical diagnosis in 53 of 65 (81.5%) patients who underwent autopsy. In this chapter we review the most common categories of atypical parkinsonism. The topic of PD subtypes and juvenile parkinsonism is covered elsewhere in this book and in other reviews (Thenganatt and Jankovic, 2014; Mehanna and Jankovic, 2019; Niemann and Jankovic, 2019).

Table 9.1 Classification of parkinsonism**I. Primary (idiopathic) parkinsonism**

Parkinson disease

II. Multiple system degenerations (parkinsonism-plus)

Multiple system atrophy

Progressive supranuclear palsy

Corticobasal degeneration

Lytico-bodig or parkinsonism–dementia–ALS complex of Guam

Progressive pallidal atrophy (primary pallidal degeneration)

Parkinsonism–dementia complex

Pallidopyramidal disease (PARK15, *FBX07*)**III. Heredodegenerative parkinsonism**

Hereditary juvenile dystonia–parkinsonism

Autosomal dominant Lewy body disease

Huntington disease

Wilson disease

Hereditary ceruloplasmin deficiency

Neurodegeneration with brain iron accumulation

- Aceruloplasminemia
- Neuroferritinopathy
- Pantothenate kinase–associated neurodegeneration (PKAN)
- PLA2G6 associated neurodegeneration (PLAN)
- Fatty acid hydroxylase–associated neurodegeneration (FAHN)
- ATP13A2 mutation (Kufor–Rakeb disease) and lysosomal disorders
- Woodhouse–Sakati syndrome (WSS)

Spinocerebellar ataxia (SCA) types 2, 3, 6, 12, 17, 21

Frontotemporal dementia and other tauopathies (see [Table 9.3](#))

Progressive autosomal dominant parkinsonism with central hypoventilation, depression, apathy, and weight loss (Perry syndrome)

Gerstmann–Sträusler–Scheinker disease

Familial progressive subcortical gliosis

Lubag (X-linked dystonia–parkinsonism)

Familial basal ganglia calcification (bilateral striopallidodentate calcinosis; Fahr disease)

Mitochondrial cytopathies with striatal necrosis

Juvenile neuronal ceroid lipofuscinosis

Juvenile parkinsonism with neuronal intranuclear inclusions

Familial parkinsonism with peripheral neuropathy

Parkinsonian–pyramidal syndrome

Neuroacanthocytosis

Hereditary hemochromatosis

Fragile-X–associated tremor/ataxia syndrome (FXTAS)

Autosomal dominant striatal degeneration with dysarthria and gait disorder (5q13–5q14)

Progressive external ophthalmoplegia and parkinsonism associated with *POLG1* mutationSensory ataxic neuropathy dysarthria and ophthalmoparesis (SANDO) with parkinsonism and dystonia with *POLG1* mutation

Progressive encephalopathy with rigidity (with glycine receptor antibodies)

IV. Secondary (acquired, symptomatic) parkinsonism

Infectious: Postencephalitic, AIDS, SSPE, CJD, prion diseases

Immunologic and paraneoplastic: Voltage-gated potassium channel autoimmunity

Drugs: Dopamine receptor–blocking drugs (antipsychotic, antiemetic drugs), reserpine, tetrabenazine, α -methyl-dopa, lithium, flunarizine, cinnarizine, ecstasy (MDMA), cyclosporine ([Mintzer et al., 1999](#))Toxins: 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine, CO, Mn, Hg, CS₂, cyanide ([Rosenow et al., 1995](#)), methanol, ethanol, organophosphates ([Bhatt et al., 1999](#))

Vascular: Multi-infarct, Binswanger disease, Sjögren syndrome

Trauma: Pugilistic encephalopathy

Other: Parathyroid abnormalities, hypothyroidism, hepatocerebral degeneration ([Burkhard et al., 2003](#)), alcohol-induced coma and respiratory acidosis with bilateral pallidal lesions ([Kuoppamaki et al., 2005](#)), brain tumor, brainstem astrocytoma ([Cicarelli et al., 1999](#)), normal pressure hydrocephalus (NPH), noncommunicating hydrocephalus, syringomyelia, hemiparkinsonism–hemiatrophy, wasp sting, peripherally induced tremor and parkinsonism, and psychogenic**V. Juvenile parkinsonism (see [Table 9.4](#))**

AIDS, Acquired immunodeficiency syndrome; ALS, amyotrophic lateral sclerosis; CJD, Creutzfeldt–Jakob disease; MDMA, 3,4-Methylenedioxymethamphetamine; SSPE, subacute sclerosing panencephalitis.

Multiple system atrophy**Clinical features**

Historically, the first case that James Parkinson described in his 1817 “Essay on the Shaking Palsy” had associated autonomic features and might have been the first case of MSA ([Obeso et al., 2017](#)). First coined by Graham and Oppenheimer in 1969 ([Graham and Oppenheimer, 1969](#)), the term *multiple system atrophy* (MSA) describes a syndrome characterized clinically by parkinsonism, dysautonomia, and other features previously reported as Shy-Drager syndrome (SDS), striatonigral degeneration, and sporadic olivopontocerebellar atrophy (OPCA) ([Jellinger, 2014](#)). The term *Shy-Drager syndrome* is still occasionally used in the literature, particularly by some American clinicians, as a tribute to Dr. Shy, a neurologist from University of Pennsylvania and Columbia University, and Dr. Drager, a urologist at Baylor College of Medicine, who first drew attention to this disorder in 1960 ([Shy and Drager, 1960](#)). In their initial report, Shy and Drager described two men who presented with symptoms of orthostatic syncope, impotence, and bladder dysfunction.

They later developed parkinsonian features, including gait disturbance, mild tremor, dysarthria, constipation, and bowel and bladder incontinence. The term *striatonigral degeneration* (SND) was introduced in the 1960s by Adams, Van Bogaert, and Van de Eecken ([Aotsuka and Paulson, 1993](#); [Jellinger, 2014](#)). Dejerine and Thomas (1900) introduced the term *olivopontocerebellar atrophy* to describe a group of heterogeneous disorders characterized clinically by the combination of progressive parkinsonism and cerebellar ataxia and pathologically by neuronal loss in the ventral pons, inferior olives, and cerebellar cortex ([Berciano et al., 2006](#)). OPCA may be inherited, usually in an autosomal dominant pattern, but only the sporadic OPCAs are considered variants of MSA. Although considered a sporadic disease, families with a phenotype suggestive of autosomal recessive MSA have been described (Hara et al., 2007). It is possible, however, that these familial cases represent either some forms, yet to be identified, SCA, or familial OPCA.

A rating scale, the Unified Multiple System Atrophy Rating Scale (UMSARS), that assesses all important symptoms and signs of MSA has been developed and validated against

Table 9.2 Tauopathies

- Alzheimer disease
- ALS–parkinsonism–dementia
- Argyrophilic grain disease
- Chronic traumatic encephalopathy
- Corticobasal degeneration
- Diffuse neurofibrillary tangles with calcification
- Down syndrome
- Familial British/Danish dementia
- FTDP-17 (caused by MAPT mutations)
- Frontotemporal lobar degeneration (some caused by *C9ORF72* mutations)
- Gerstmann–Sträussler–Scheinker disease
- Guadeloupean parkinsonism
- Myotonic dystrophy
- Neurodegeneration with brain iron accumulation
- Niemann–Pick disease, type C
- Non-Guamanian motor neuron disease with neurofibrillary tangles
- Pick disease
- Postencephalitic parkinsonism
- Prion protein cerebral amyloid angiopathy
- Progressive subcortical gliosis
- Progressive supranuclear palsy
- SLC9A6-related intellectual disability
- Subacute sclerosing panencephalitis
- Tangle-only dementia
- White matter tauopathy with globular glial inclusions

Modified from Spillantini MG, Goedert M. Tau pathology and neurodegeneration. *Lancet Neurol.* 2013;12(6):609–622.

related rating scales, such as the Unified Parkinson's Disease Rating Scale and the International Cooperative Ataxia Rating Scale (Wenning et al., 2004). The UMSRAS Motor Examination score, which has been demonstrated to have satisfactory intrarater reliability (Krismer et al., 2012) seems to be the best outcome measure for future therapeutic trials (May et al., 2007).

The discovery by Papp and colleagues (1989) that the pathologic hallmark shared by all three disorders is the presence of filamentous alpha-synuclein-containing glial cytoplasmic inclusions (GCI) led to the recognition that these disorders are manifestations of the same pathologic process (Jellinger, 2014; Koga and Dickson, 2018). MSA has therefore been redefined as a sporadic, progressive, adult-onset synucleinopathy characterized clinically by autonomic dysfunction (MSA-A), parkinsonism (MSA-P), and cerebellar ataxia (MSA-C) (Gilman et al., 2008). According to the second consensus statement (Gilman et al., 2008), features that would argue against the diagnosis of MSA include age at onset older than 75 years, the presence of typical PD rest tremor, neuropathy, sporadic hallucinations, dementia, white matter lesions in MRI suggestive of multiple sclerosis, and a family history of ataxia or parkinsonism. MSA may be difficult to differentiate from PD associated with autonomic dysfunction (Palma and Kaufmann, 2014). Whereas autonomic symptoms often precede the onset of MSA, this is rarely the case in PD. Furthermore, in contrast to PD, cardiac neuroimaging often shows evidence of sympathetic denervation in PD whereas cardiac sympathetic function remains typically intact in MSA. Besides lack of tremor, the symmetrical onset of SND (MSA-P) is sometimes helpful in differentiating SND from PD. In a study comparing 16 patients with

pathologically proven MSA of the SND (MSA-P) variety with PD and PSP, a set of clinical criteria reliably differentiated MSA from PD but not from PSP (Colosimo et al., 1995). In addition to cerebellar and pyramidal signs and early instability with falls, the following features were more typically present in MSA than in PD: autonomic dysfunction (69% versus 5%), absence of rest tremor (87% versus 40%), rapid progression (mean disease duration 7.1 years versus 13.6 years), and poor or unsustained response to levodopa (31% versus 0%). In contrast to other reports, 43.7% of the MSA patients in this series had a symmetrical onset. Although earlier studies and the second consensus statement on MSA (Gilman et al., 2008) considered cognition to be relatively preserved in MSA, there is growing recognition that cognitive disturbances, particularly frontal-executive and visuospatial dysfunction and memory and frank dementia, may be present in patients with MSA (Stankovic et al., 2014). Clinicopathologic studies, however, found no differences in pathologic changes between MSA patients with ($n = 9$) and without ($N = 9$) cognitive impairment (Asi et al., 2014).

MSA should be considered in the differential diagnosis of adult-onset, sporadic parkinsonism, ataxia, and dysautonomia (Lin et al., 20014; Krismer and Wenning, 2017). The clinical features and natural history of MSA were analyzed in 100 cases with probable MSA, of which 14 were confirmed at autopsy (Wenning, Shlomo, et al., 1994). The population consisted of 67 men and 33 women, with a median age at onset of 53 years (range, 33–76). Autonomic symptoms were present at onset in 41% of the patients, but 97% developed autonomic dysfunction during the course of the disease. Impotence was the most frequent autonomic symptom in men, and urinary incontinence predominated in women. Some evidence of orthostatic hypotension (OH) was present in 68% of patients, but severe OH was noted in 15%. In contrast to PD and other parkinsonian disorders in which the latency to onset of OH is usually several years, patients with MSA usually develop symptomatic OH within the first year after onset of symptoms (Wenning et al., 1999), and urinary dysfunction may occur even earlier (Sakakibara et al., 2000a,b). In another study of 16 autopsy-proven cases of MSA, Litvan, Goetz, and colleagues (1997) identified early severe autonomic failure, absence of cognitive impairment, early cerebellar symptoms, and early gait problems as the best predictors of the diagnosis of MSA. In a study designed to validate the clinical criteria for MSA, Litvan, Booth, and colleagues (1998) found that the accuracy was best when at least six of the following eight features were present: sporadic adult onset, dysautonomia, parkinsonism, pyramidal signs, cerebellar signs, no levodopa response, no cognitive dysfunction, and no downward gaze palsy. Wenning and colleagues (1997) examined the clinical features of 203 pathologically proven cases of MSA reported in 108 publications. The male-to-female ratio was 1.3:1, dysautonomia was present in 74%, parkinsonism in 87%, cerebellar ataxia in 54%, and pyramidal signs in 49%. MSA-P patients had more rapid deterioration than MSA-C patients. In a study of 49 MSA cases (median age at onset, 56.1 years; 16 women) confirmed by autopsy at Mayo Clinic, symptoms at onset were autonomic in 50%, parkinsonian in 30%, and cerebellar in 20% of cases (Figuerola et al., 2014). The median was 8.6 (6.7–10.2) years; it was shorter in patients with early laboratory evidence of generalized autonomic failure (7.0

Table 9.3 Juvenile parkinsonism

Designation gene	Location	Clinical features*	Comments	Levodopa- response [†]	MRI	Striatal dopami- nergic imaging [‡]	Pathology
Autosomal recessive							
PARK- <i>Parkin</i>	6q26	Typical	Possible onset with dystonia	+ LID, MF	NL	ABNL	SNpc neuron loss, rare LB
PARK- <i>PINK1</i>	1p36.12	Typical		+ LID, MF	NL	ABNL	SNpc neuron loss, possible LB
PARK- <i>DJ1</i>	1p36.23	Typical		+ LID, MF	NL	ABNL	SNpc neuron loss, possible LB
PARK- <i>ATP13A2</i> (Kufor-Rakeb syndrome)	1p36.13	Atypical	Eye movement disorders, UMN, psychosis, dementia, facial-faucial-finger minimyoclonus	+ LID, MF, hallucinations	NL (early) or atrophy	ABNL	UN
PARK- <i>TH</i> (dopa-responsive dystonia)	11p15.5	Atypical	Often infantile onset, broad phenotype including dystonia	+ LID	NL	NL	NL, ± depigmentation SNpc
DYT/PARK- <i>PLA2G6</i>	22q13.1	Atypical	Depression, psychosis, dementia, UMN	+ LID, MF	NL or atrophy	ABNL	SNpc neuron loss, LB
PARK- <i>FBXO7</i>	22.q12.3	Atypical	UMN, dystonia, supranuclear gaze palsy	+ LID, MF, behavioral disturbance	NL or atrophy	ABNL	UN
PARK- <i>DNAJC6</i>	1p31.3	Typical or atypical	Isolated parkinsonism or parkinsonism with epilepsy, cognitive decline, dystonia, and UMN	+ LID, MF, behavioral disturbance	NL	ABNL	UN
PARK- <i>SYNJ1</i>	21q22.11	Atypical	Epilepsy in infancy, dystonia, cognitive decline, eye movement abnormalities	± LID	NL or atrophy	ABNL	UN
<i>PODXL</i>	7q32.3	Typical	Severe rigidity, rapid progression	+ LID	NL	UN	UN
DYT- <i>ATP7B</i> (Wilson disease)	13q14.3	Atypical	Progressive dysarthria, parkinsonism, and dystonia; Kayser-Fleischer rings; stigmata of hepatic dysfunction	±	T2 hyperintensity in BG, thalami, midbrain, and pons; global atrophy	ABNL	Cell loss, astrogliosis, and demyelination in BG, thalami, cerebellum, and brainstem
CHOR- <i>VPS13A</i> (chorea acanthocytosis)	9q21.2	Atypical	Chorea, dystonia, seizures, peripheral neuropathy	–	Caudate atrophy	ABNL (rare cases)	Neuronal loss and gliosis in BG (predominantly caudate)
NBIA/DYT- <i>PANK2</i> (PKAN)	20p13	Atypical	Upper motor neuron signs, dystonia, parkinsonism, chorea, eye movement abnormalities	–	“Eye of the tiger” sign (pallidal T2 hyperintensity surrounded by hypointensity)	ABNL (mild changes)	Pallidal iron accumulation and neuron loss
HSP/NBIA- <i>C19orf12</i> (MPAN)	19q12	Atypical	Upper motor neuron signs ≥ lower motor neuron signs, optic atrophy, cognitive decline, psychiatric disturbance, dystonia, parkinsonism	±	SN and pallidal T2 hypointensity (hyperintense pallidal “streaking” may lead to misdiagnosis of “eye of the tiger”/PKAN), cerebellar atrophy	ABNL	Pallidal and SN iron accumulation with neuron loss; widespread LB, LN

Table 9.3 Juvenile parkinsonism—Continued

Designation gene	Location	Clinical features*	Comments	Levodopa- response†	MRI	Striatal dopami- nergic imaging‡	Pathology
NBIA-COASY (CoPAN)	17q21.2	Atypical	Dystonic-spastic paraplegia, cognitive impairment, neuropathy, oromandibular dystonia	UN	Caudate/putaminal swelling and T2 hyperintensity, later T2 hypointensity in the GP with central hyperintensity (similar to “eye of the tiger”)	UN	UN
HSP-KIAA1840 (SPG11), HSP-ZFYVE26 (SPG15)	15q21.1, 14q42.1	Atypical	Spastic paraplegia, cognitive decline, peripheral neuropathy	±	Thinning of the corpus callosum, white matter hyperintensities (frontal horns; “ears of the lynx sign”)	ABNL	Spinal (± brainstem) corticospinal tract degeneration
PRTHD1	2p23.3	Atypical	Cognitive decline, later onset of parkinsonism ± UMN	+	NL	ABNL	UN
PARK-VPS13C (PARK23)	15q22.2	Atypical	Rapidly progressive, UMN, dementia	+	NL or atrophy	UN	Diffuse LB
Autosomal dominant							
PARK-SNCA	4q22.1	Typical	Juvenile onset rare (<1%), early dementia in some	+	NL or atrophy	ABNL	SNpc and LC neuron loss, LB, LN
22q11.2DS	22q11.2	Typical	History of seizures; neurodevelopmental disorders, dystonia, and psychiatric disorders may precede motor symptoms	+	NL	ABNL	SNpc and LC neuron loss, LB, LN
DYT/PARK-GCH1 (dopa-responsive dystonia)	14q22.2	Atypical	Dystonia marked, broad phenotype, rare AR phenotype	+	NL	NL	NL, ± depigmentation SNpc
DYT-ATP1A3 (rapid-onset dystonia-parkinsonism)	19q13.2	Atypical	Orobulbar and upper body dystonia, axial parkinsonism, rostrocaudal progression	–	NL	NL	Broad spectrum of changes, including mild depigmentation and neuronal loss in SNpc, absence of LB
CHOR-HTT (Huntington disease)	4q16.3	Atypical	Cognitive and behavioral disturbance; motor onset with parkinsonism and dystonia > chorea; seizures seen in 40%	± May worsen behavioral disturbance	Caudate and putamen atrophy, cerebellar atrophy often seen in juvenile patients, global cerebral atrophy	ABNL	Striatal (medium spiny neurons), pallidal, and cortical neurodegeneration, absence of LB
SCA-ATXN2, SCA-ATXN3	12q24.12, 14q32.12	Atypical	Ataxia and ocular symptoms, some cases may present with predominant parkinsonism	±	Pontocerebellar atrophy	ABNL	Pallidal, SNpc, and cerebellar neuron loss; LB (likely incidental)
NBIA/CHOR-FTL (neuroferritinopathy)	19q13.33	Atypical	Chorea, dystonia, tremor, and parkinsonism; low serum ferritin	±	Cavitation/cystic changes in GP and putamen, T2 hypointensity with central hyperintensity in putamen, GP (mimicking “eye of the tiger”), thalamus, and dentate nucleus	NL	Cerebral and cerebellar atrophy, BG cavitation and accumulation of iron and ferritin

Continued

Table 9.3 Juvenile parkinsonism—Continued

Designation gene	Location	Clinical features*	Comments	Levodopa- response [†]	MRI	Striatal dopami- nergic imaging [‡]	Pathology
X-linked							
DYT-PARK- <i>TAF1</i> (X-linked dystonia- parkinsonism, Lubag)	Xq13.1	Atypical	Triphasic with predominant dystonia at onset, parkinsonism also may be seen early	±	T2 hyperintense putaminal rim sign (all phases of disease), caudate and putaminal atrophy (combined dystonia- parkinsonism phase)	ABNL (may be normal in early disease)	Striatal neuron loss
NBIA/PARK- <i>WDR45</i> (BPAN)	Xp11.23	Atypical	Onset with intellectual disability, spasticity, and seizures followed by parkinsonism and/or dystonia	± LID	SN > GP T2 hypointensity and T1 SN hyperintense “halo” (neuromelanin)	ABNL	Iron accumulation (GP, SN), tau neurofibrillary tangles diffusely
<i>RAB39B</i>	Xq28	Atypical	Epilepsy, cognitive impairment, macrocephaly	±	GP and SN T2 hypointensity CT: BG calcifications	ABNL	SNpc neuron loss, LB, and LN; abundance of cortical LB

*Typical clinical features are bilateral (symmetrical or asymmetrical) parkinsonism (tremor, rigidity, bradykinesia). Atypical features are features atypical for Parkinson disease, such as (but not limited to): rapid progression, early/severe dysautonomia, early cognitive decline, prominent psychiatric symptoms, prominent nonparkinsonian phenomenology (e.g., dystonia or upper motor neuron signs), and levodopa-unresponsiveness.

[†]Levodopa-response: +, = significant improvement of parkinsonism; ±, minimal or inconsistent improvement of parkinsonism; –, no improvement of parkinsonism.

[‡]Position emission tomography (PET) using 6-[¹⁸F]fluoro-L-3,4-dihydroxyphenylalanine (FDOPA) or single-photon emission computed tomography (SPECT) using ¹²³I-ioflupane (N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane (FP-CIT)).

ABNL, Abnormal; BG, basal ganglia; GP, globus pallidus; LB, Lewy bodies; LID, levodopa-induced dyskinesias; LN, Lewy neurites; MF, motor fluctuations; NL, normal; SNpc, substantia nigra pars compacta; UMN, upper motor neuron signs; UN, unknown.

Modified from Niemann N, Jankovic J. (2019). Juvenile parkinsonism: Differential diagnosis, genetics, and treatment. *Parkinsonism Relat Disord.* 2019;67:74–89.

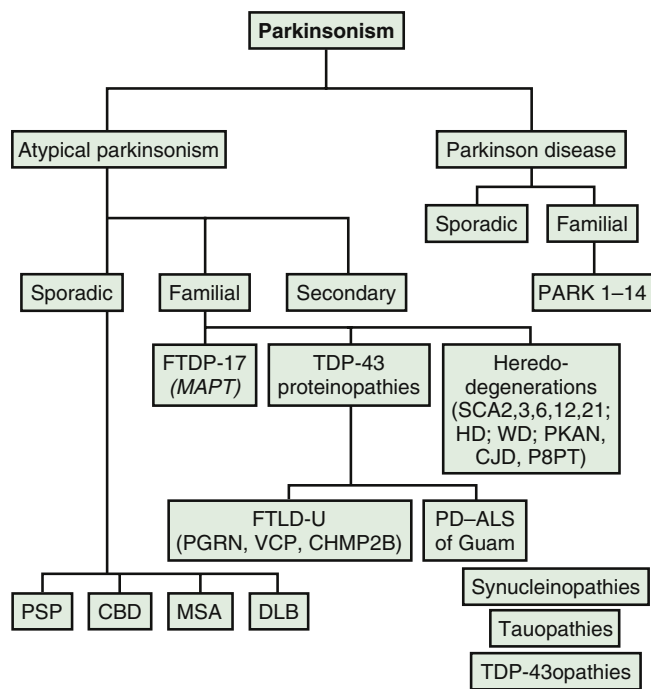


Fig. 9.1 Classification of parkinsonism. CBD, corticobasal degeneration; CJD, Creutzfeldt–Jakob disease; DLB, dementia with Lewy bodies; FDP-17, frontotemporal dementia and parkinsonism linked to chromosome 17; HD, Huntington disease; MSA, multiple system atrophy; P-D-ALS, parkinsonism–dementia–amyotrophic lateral sclerosis; PKAN, pantothenate kinase–associated neurodegeneration; PSP, progressive supranuclear palsy; TDP-43, TAR-DNA binding protein 43; WD, Wilson disease.

versus 9.8 years; $P=0.036$), and early requirement of bladder catheterization (7.3 versus 13.7 years; $P=0.003$) compared with those without these clinical features. Another factor that adversely influenced survival was older age at onset, but sex, phenotype, early development of gait instability, aid-requiring ambulation, orthostatic symptoms, neurogenic bladder, or significant anhidrosis did not necessarily indicate shorter survival. In a natural history study, 175 patients with probable MSA-P or MSA-C from 12 U.S. neurology centers specializing in movement or autonomic disorders, evaluated every 6 months for 5 years with the UMSARS, the Composite Autonomic Symptoms Scale (COMPASS), and other instruments, the mean age at study entry was 63.4 years (± 8.6), median survival from symptom onset was 9.8 years (95% confidence interval [CI], 8.8–10.7) and median survival from enrolment was 1.8 years (0.9–2.7) (Low et al., 2015). Patients with severe symptomatic autonomic failure at diagnosis progressed more rapidly than those without it, but there was no difference in prognosis between the two types of MSA. In another study from Mayo Clinic, a total of 685 patients were identified; 594 met criteria for probable MSA and 91 for possible MSA (Coon et al., 2015). The study found that the average age at onset was earlier in MSA-C (58.4 years) compared with MSA-P (62.3 years; $P < 0.001$); median disease duration from symptom onset to death was 7.51 years (95% CI, 7.18–7.78) and time from diagnosis to death was 3.33 years (95% CI, 2.92–3.59). A multivariate model retained the following unfavorable predictors of survival: (1) falls within 3 years of onset (hazard ratio [HR], 2.31; $P < 0.0001$), (2) bladder symptoms (HR, 1.96; $P < 0.0001$), (3) urinary

catheterization within 3 years of symptom onset (HR, 1.67; $P < 0.003$), (4) orthostatic intolerance within 1 year of symptom onset (HR, 1.28, $P < 0.014$), (5) older age of onset (HR, 1.02; $P = 0.001$); and (6) degree of autonomic failure as measured by a validated composite autonomic severity score (HR, 1.07; $P < 0.0023$).

Early development of autonomic dysfunction has been found to be an independent predictor of poor prognosis (Tada et al., 2007). It should be noted, however, that pure autonomic failure (PAF) might herald the onset not only of MSA but also of PD and DLB (Mabuchi et al., 2005; Kaufmann et al., 2017; Singer et al., 2017). In PAF, OH and sudomotor dysfunction followed by constipation are the typical initial symptoms, whereas in MSA, the initial presentation usually consists of urinary problems, followed by sudomotor dysfunction or OH, with subsequent progression to respiratory dysfunction (Mabuchi et al., 2005; Cortelli et al., 2019). A study of 115 patients with MSA showed that autonomic dysfunction, motor impairment, and depression were most closely related to poor outcome in measures of health-related quality of life (Schrag et al., 2006). Among 437 MSA patients evaluated in 19 centers in 10 European countries, the mean age at onset was 57.8 years and the mean disease duration of symptoms was 5.8 years; 68% were classified as parkinsonian type (MSA-P) and 32% as cerebellar type (MSA-C) (Kölsch et al., 2010). The investigators observed the following symptoms: dysautonomia 99%, erectile dysfunction 84% of males, parkinsonism 87%, symptomatic OH 75%, urinary incontinence 73%, cerebellar ataxia 64%, urinary retention 48%, hyperreflexia 43%, depression 41%, psychosis 6%, and dementia 4.5%. In one series of 29 autopsy-confirmed cases evaluated at the Mayo Clinic, rapid progression, early postural instability, poor levodopa responsiveness, symmetrical involvement, and progressive adrenergic and sudomotor failure, were highly predictive features of MSA (Iodice et al., 2012) (Fig. 9.2).

Movement disorders other than parkinsonism that are seen in patients with MSA include dystonia, myoclonus, hemiballism, and chorea, unrelated to dopaminergic therapy (Chen et al., 1992; Steiger et al., 1992; Salazar et al., 2000). Dystonia is relatively rare in MSA patients (Rivest et al., 1990; Marsili et al., 2019), but in one study, 46% of patients with MSA were found to have dystonia, particularly if anterocollis is considered a form of cervical dystonia (Boesch et al., 2002). Some investigators, however, think that the neck flexion, often associated with anterior sagittal shift, is due to disproportionately increased tone in the anterior neck muscles leading to secondary fibrotic and myopathic changes (van de Warrenburg et al., 2008). Although dystonia is frequently considered to be a cause of the MSA-associated anterocollis, the mechanism of progressive neck flexion, so characteristic of MSA, particularly MSA-P, may be multifactorial. In some cases, the neck flexion has been attributed to neck extensor weakness as part of “dropped head” syndrome associated with axial myopathy (Suarez and Kelly, 1992; Oerlemans and de Visser, 1998; Askmark et al., 2001), motor neuron disease (Gourie-Devi et al., 2003; Gilbert et al., 2010), or other causes. Neck flexion, however, is not unique to MSA and can be also seen in patients with otherwise typical PD (Djaldetti et al., 1999). In some cases of PD, more frequently than in MSA, the axial postural abnormality may lead to severe flexion of the trunk, the so-called bent spine syndrome, or

AUTOPSY-CONFIRMED MSA CASES: Mayo experience and role of autonomic tests.

- N = 29, 17 men
- Age at onset 57 ± 8.1 years
- Disease duration to death 6.5 ± 3.3 years

First evaluation at the Mayo Clinic

Clinical phenotype	No. of patients
MSA-P	18
MSA-C	8
PAF	2
PD	1

Autonomic dysfunction	% of patients
OI	75
Bladder dysfunction	89
Urinary incontinence	44.4
Urinary retention	26
Urinary frequency	18.5
Sweating dysfunction	40
Bowel dysfunction	77
Constipation	46
Fecal incontinence	27
Sexual dysfunction	64
REM BD	54
Sleep apnea	37
Nocturnal stridor	30

BD, Behavior disorder; MSA-C, multiple system atrophy with predominant cerebellar involvement; MSA-P, multiple system atrophy with predominant parkinsonism; OI, orthostatic intolerance; PAF, pure autonomic failure; PD, Parkinson's disease

TST = Thermoregulatory sweat test

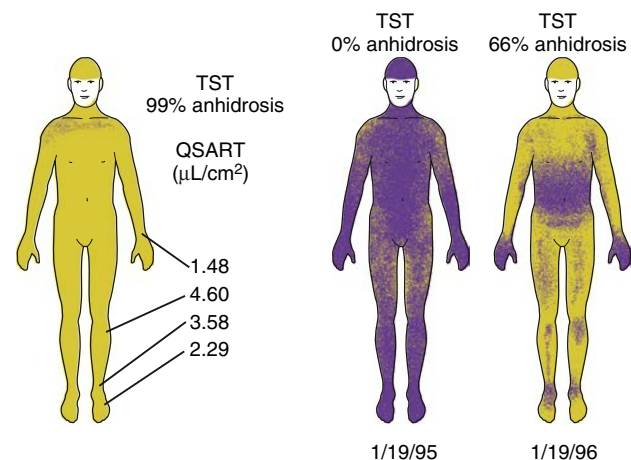


Fig. 9.2 Autonomic dysfunction in multiple system atrophy. (Modified from Iodice V, Lipp A, Ahlskog JE, et al. Autopsy confirmed multiple system atrophy cases: Mayo experience and role of autonomic function tests. *J Neurol Neurosurg Psychiatry* 2012;83[4]:453–459.)

camptocormia (Umapathi et al., 2002; Azher et al., 2005; Jankovic, 2010). Another abnormal posture frequently encountered in MSA is the “Pisa syndrome” manifested by leaning of the body to one side reminiscent of leaning tower of Pisa (Ashour et al., 2006) (Video 9.1). Besides anterocollis, another form of dystonia that is relatively frequently encountered in patients with MSA is facial and oromandibular dystonia associated with levodopa therapy, a typical form of levodopa-induced dyskinesia in patients with MSA. (Video 9.1)

In addition to action and stimulus-sensitive cortical myoclonus (Video 9.1), focal reflex myoclonus, induced by pinprick, may be seen in MSA patients (Clouston et al., 1996; Salazar et al., 2000). This form of myoclonus has a longer latency than that seen in patients with CBD (see later). In 9 of 11 patients with MSA and myoclonic tremulous movements, jerk-locked averaging technique showed premyoclonic potential, suggesting that the jerklike movements represent a form of cortical myoclonus (Okuma et al., 2005). Besides the classic motor signs, MSA is associated with a variety of oculomotor abnormalities, including sustained gaze evoked nystagmus, square wave jerks, slow and hypometric saccades, diminished vestibular-ocular reflex suppression, internuclear ophthalmoparesis, and reduced vertical gaze (Fabbrini et al., 2011; Waln and Jankovic, 2018). (Video 9.2)

Although dysautonomia is a cardinal feature of MSA, this neurodegenerative disorder should be differentiated from PAF, which has no central component (Coon, 2020). Autonomic dysfunction is essential for the diagnosis of MSA, and in many cases of MSA, autonomic failure, particularly

impotence, precedes other neurologic symptoms or signs by several years. In contrast to PD associated with dysautonomia, in which there is predominantly peripheral (ganglionic and postganglionic) involvement, including myocardial and sympathetic denervation, the peripheral autonomic system appears to be spared in MSA and the primary lesion is preganglionic (Lipp et al., 2009). In fact, some persistence of central autonomic tone might be responsible for the frequently observed supine hypertension in MSA (Parikh et al., 2002). MSA patients also have more autonomic symptoms at baseline and more progression to global anhidrosis, as demonstrated by the thermoregulatory sweat test, than patients with PD (Lipp et al., 2009; Iodice et al., 2012; Kimpinski et al., 2012). The “cold hands” sign, manifested by cold, dusky, violaceous appearance of the hands, is another characteristic feature of MSA (Klein et al., 1997). Some patients have the “cold feet” sign (Video 9.2). Liquid meal, consisting chiefly of glucose and milk, markedly reduces blood pressure in patients with MSA but not in those with PD (Thomaides et al., 1993) (Video 9.2). (Video 9.2)

Respiratory disturbance, including severe obstructive sleep apnea, and vocal cord paralysis with stridor may be found in more advanced stages of the disease (Cortelli et al., 2019), but respiratory insufficiency may be the presenting symptom of MSA (Glass et al., 2006). Inspiratory stridor as a result of the paradoxical movement of the vocal cords (also known as Gerhardt syndrome) has been described in MSA (Eissler et al., 2001). The observation that inspiratory stridor improves with botulinum toxin injections into the adductor laryngeal

Video 9.1 Multiple system atrophy (MSA).

Video 9.2 Multiple system atrophy (MSA).

muscles suggests that this symptom of MSA could be due to focal laryngeal dystonia (Merlo et al., 2002). The occurrence of nocturnal or daytime stridor carries a poor prognosis, particularly when it is associated with central hypoventilation (Silber and Levine, 2000). Occasionally, however, vocal cord abductor paralysis can be seen even in the initial stages of the disease, and it has been associated with nocturnal sudden death (Isozaki et al., 1996). In a study of 136 patients with MSA, stridor was diagnosed in 42 patients and 22 presented early stridor onset (Giannini et al., 2016). Patients with early stridor onset had a worse prognosis than those developing this symptom later and early stridor onset was an independent predictor for shorter survival; tracheostomy could control stridor, influencing disease duration.

Early diagnosis can be made by laryngoscopy during sleep. Hypoxemia with increased alveolar-arterial oxygen gradient, associated with laryngopharyngeal movements, however, has been demonstrated in MSA patients even during wakefulness (Shimohata et al., 2007). The presence of impaired hypoxic ventilatory response has helped differentiate MSA-C from idiopathic late-onset cerebellar ataxia (Tsuda et al., 2002).

Natural history

The natural history of MSA has been the subject of several studies. In contrast to the approximately 1.5% annual decline in Unified Parkinson's Disease Rating Scale (UPDRS) III noted in patients with PD (Jankovic and Kapadia, 2001), the average annual decline in MSA-P is 28.3% (Seppi et al., 2005). Most of the studies were based on pathologically proven cases; therefore, the prognosis in these series has been worse than otherwise predicted. On the basis of a meta-analysis of 433 reported cases of MSA, Ben-Shlomo and colleagues (1997) found survival to range from 0.5 to 24 years (mean: 6.2 years), and cerebellar features were associated with marginally better survival. In one study of 100 patients clinically diagnosed with probable MSA (14 of whom were pathologically confirmed), nearly half of all the patients were markedly disabled or wheelchair bound within 5 years after onset, and the median survival was 9.5 years (Wenning, Shlomo, et al., 1994). This is similar to the findings from a prospective study of 141 patients with moderately severe MSA (mean age at symptom onset 56.2 ± 8.4 years) who had a median survival of 9.8 years (95% CI, 8.1–11.4) (Wenning et al., 2013). Shorter survival was suggested by the parkinsonian variant of MSA and incomplete bladder emptying, and shorter symptom duration at baseline and absent levodopa response predicted rapid progression. In one retrospective study of 100 patients with MSA the mean survival was 8 years; disease onset before 55 years predicted longer survival in, but there was no difference in survival between, MSA-P or MSA-C, although the frequency of abnormal magnetic resonance imaging (MRI) findings was higher in the MSA-C group (Roncovic et al., 2014). In another study involving 22 patients followed prospectively with pathologically proven MSA, the median survival was 8.6 years for men and 7.3 years for women (Schrage et al., 2008). This is a rapidly progressive neurodegenerative disorder with death occurring usually within 7 to 8 years after the initial symptoms (Iodice et al., 2012; Wenning et al., 2013).

MSA patients usually die of aspiration, sleep apnea, or cardiac arrhythmia. Survival data and clinically relevant milestones, that is, frequent falling, cognitive disability,

unintelligible speech, severe dysphagia, dependence on wheelchair for mobility, the use of urinary catheters, and placement in residential care, were determined based on a retrospective chart review of pathologically confirmed cases of PSP (N = 110) and MSA (N = 42) (O'Sullivan et al., 2008). Patients with PSP had an older age of onset ($P < 0.001$) and reached their first clinical milestone earlier than patients with MSA ($P < 0.001$). Patients with PSP generally had a less favorable prognosis than those with MSA. Although some authors have suggested that the earlier and the more severe the involvement of the autonomic nervous system, the poorer the prognosis (Saito et al., 1994), this has not been confirmed by other studies (Ben-Shlomo et al., 1997).

Differential diagnosis

When patients present with parkinsonism alone, without other evidence of MSA, their MSA might be difficult to differentiate from PD during the first 6 years (Albanese et al., 1995). In one study, the following features were found to be the best predictors of MSA: dysautonomia, poor response to levodopa, speech or bulbar dysfunction, falls, and absence of dementia and levodopa-induced confusion (Wenning et al., 2000). As in PD, PSP, and other subcortical neurodegenerative disorders, the cognitive deficit in MSA consists chiefly of mild impairment of memory and executive functions, with prefrontal dysfunction more severe in patients with MSA-P than those with MSA-C (Kawai et al., 2008). Although pseudobulbar affect associated with emotional incontinence, also referred to as emotional expression disorder, is typically seen in patients with PSP, pathologic laughter and crying has been described in autopsy-proven cases of MSA, particularly the MSA-C type (Parvizi et al., 2007) and other neurodegenerative disorders, particularly amyotrophic lateral sclerosis. In one study, episodes of pseudobulbar crying or laughing were often induced by contextually appropriate emotional stimuli as a result of loss of inhibition in frontal neural systems that normally regulate emotion (Olney et al., 2011).

Several clinical studies have addressed the differentiation between MSA-P and other parkinsonian or ataxic disorders. A collection of "red flags" has been generated and validated as having high diagnostic specificity (Köllensperger et al., 2008; Stefanova et al., 2009; Iodice et al., 2012; Fanciulli and Wenning, 2015; Bhidayasiri et al., 2019; Fanciulli et al., 2019) (Table 9.4). The red flags were grouped into the following six categories: (1) early instability, (2) rapid progression, (3) abnormal postures (includes Pisa syndrome, disproportionate anterocollis, and/or contractures of hand or feet), (4) bulbar dysfunction (includes severe dysphonia with "squeaky" voice, dysarthria, and/or dysphagia), (5) respiratory dysfunction includes diurnal or nocturnal inspiratory stridor and/or inspiratory sighs, and (6) emotional incontinence (includes inappropriate crying and/or laughing). A combination of two of these six red flag categories were used as additional criteria for the diagnosis of probable MSA-P. In one study the clinical records of 203 patients with a clinical diagnosis of MSA were reviewed and the following red flags were considered in support of the diagnosis of MSA: orofacial dystonia, disproportionate anterocollis, camptocormia and/or Pisa syndrome, contractures of hands or feet, inspiratory sighs, severe dysphonia, severe dysarthria, snoring, cold hands and feet, pathologic laughter and crying, jerky myoclonic postural/action tremor

Table 9.4 Multiple system atrophy: red flags**Supportive features**

- Early instability (wheelchair within 5 years)
- Rapid progression
- Abnormal postures: Pisa syndrome, anterocollis and/or contractures
- Bulbar dysfunction: Early and severe dysphonia, dysarthria, dysphagia
- Respiratory dysfunction: Diurnal or nocturnal inspiratory stridor and/or inspiratory sighs
- Pseudobulbar affect (emotional incontinence): Inappropriate crying and/or laughing
- Two of the following six items needed for diagnosis of probable MSA-P*:
 - Early autonomic dysfunction
 - Myoclonus, jerky tremor
 - “Cold hands/feet” (Raynaud phenomenon)
 - REM sleep behavior disorder (in 70% of patients; the most common presentation)
 - Sleep apnea
 - Poor response to levodopa, orofacial dystonia

Features contrary to the diagnosis

- Age at onset older than 75 years, rest tremor, neuropathy, sporadic hallucinations, dementia, white matter lesions in MRI suggestive of MS, and a family history of ataxia or parkinsonism

*Kölschensperger M, Geser F, Seppi K, et al.; European MSA Study Group. Red flags for multiple system atrophy. *Mov Disord.* 2008;23:1093–1099.

MRI, Magnetic resonance imaging; MS, multiple sclerosis; MSA-P, multiple system atrophy–parkinsonian type; REM, rapid eye movement.

and polyminimyoclonus, and seven disability milestones (Miki et al., 2019). Of the 203 cases, 160 (78.8%) were correctly diagnosed in life and had pathologically confirmed MSA; the remaining 21.2% (43/203) had alternative pathologic diagnoses, including DLB (12.8%; $n = 26$), PSP (6.4%; $n = 13$), cerebrovascular diseases (CVD) (1%; $n = 2$), amyotrophic lateral sclerosis (ALS) (0.5%; $n = 1$), and cerebellar degeneration (0.5%; $n = 1$). More patients with MSA developed ataxia, stridor, dysphagia, and falls than patients with DLB; resting tremor, pill-rolling tremor, and hallucinations were more frequent in DLB. Autonomic dysfunction within the first 3 years from onset can differentiate MSA from PSP; patients with MSA had shorter latency to reach use of urinary catheter and longer latency to residential care than PSP patients.

Some features of MSA-C overlap with SCAs, particularly SCAs 2, 3, 7, 8, and 17 (Doherty et al., 2014; Lin et al., 2014). Also the fragile X–associated tremor/ataxia syndrome caused by permutations of the fragile X intellectual disability 1 gene (FMR1), and fragile X–associated tremor/ataxia syndrome may be a rare cause of MSA phenotype (Biancalana et al., 2005). Pathologically, there might be some similarities between the central disorders, including the presence of GCI in rare cases of SCA, but the spinal cord is usually more atrophied in SCA than in MSA. There are many other disorders that clinically resemble MSA, and careful diagnostic approach is required before the diagnosis is secure (Stamelou et al., 2013) (Fig. 9.3).

Epidemiology

The average annual incidence for MSA has been estimated to be three new cases per 100,000 person-years (Bower et al., 1997),

but other have estimated an incidence of 0.7 per 100,000 person-years (Bjornsdottir et al., 2013). The age-adjusted prevalence has been reported to vary between 3.4:100,000 (Bjornsdottir et al., 2013) and 4.4 per 100,000 (Schrage et al., 1999). MSA appears to be more common in men than in women, with symptoms first beginning in the sixth decade, although rare cases of MSA with onset before age 40 have been reported (Kim et al., 2012). Some studies have shown that, similar to PD, smoking is significantly less frequent in patients with MSA, and farming is an independent risk factor for MSA (Vanacore et al., 2005).

Neurodiagnostic studies

In addition to tests of autonomic function, patterns of plasma levels of catecholamines and their metabolites may be helpful in differentiating the various forms of autonomic failures. These studies are designed primarily to localize the site of autonomic impairment and include investigation of neurogenic bladder, sphincter electromyography (EMG), and other investigations designed to test the integrity of the autonomic nervous system. External anal sphincter EMG denervation was once thought to be a sensitive measure of anorectal dysfunction in MSA, but it does not differentiate MSA from PD or from many other neurodegenerative disorders (Tison et al., 2000). Although the peripheral sympathetic neurons are spared in MSA, there is some evidence that they lack the normal preganglionic activation (Parikh et al., 2002). Furthermore, the relatively well preserved sympathetic tone is probably responsible for the supine hypertension seen in many patients with MSA. In neurogenic OH, the rise in norepinephrine (NE) levels is minimal or absent despite a marked drop in blood pressure after either head-up tilt or an upright position. Clonidine has been found to increase growth hormone (GH) in normal controls, patients with PAF, and patients with PD but not patients with MSA (Kimber et al., 1997). In a study of 69 MSA patients, 35 PD patients, and 90 healthy controls, the GH response to arginine was found to be significantly lower in MSA patients compared with PD or healthy controls, a finding with over 90% sensitivity and specificity (Pellecchia et al., 2006). Whereas somatosensory, visual, and auditory evoked responses are often abnormal, motor evoked potentials are usually normal (Abele et al., 2000).

Sleep abnormalities have been documented in patients with MSA even before the onset of motor symptoms (Iranzo et al., 2010). A strong relationship between some form of RBD and subsequent MSA has been demonstrated by a number of other studies. Using video-polysomnography, RBD was observed in 43 of 49 (88%) patients with MSA, and in 81% bed partners reported some improvement in parkinsonian features during RBD episodes (Cohen et al., 2011). Obstructive sleep apnea in MSA is related to a thalamic cholinergic deficit, possibly owing to decreased pontine cholinergic projections.

Pharmacologically, MSA and PAF may be distinguished by supine and standing plasma NE levels. In PAF, both standing and supine NE levels are low, whereas in MSA, only the standing value is diminished. This is consistent with the notion that postganglionic sympathetic neurons are intact in MSA but their function is markedly impaired in PAF.

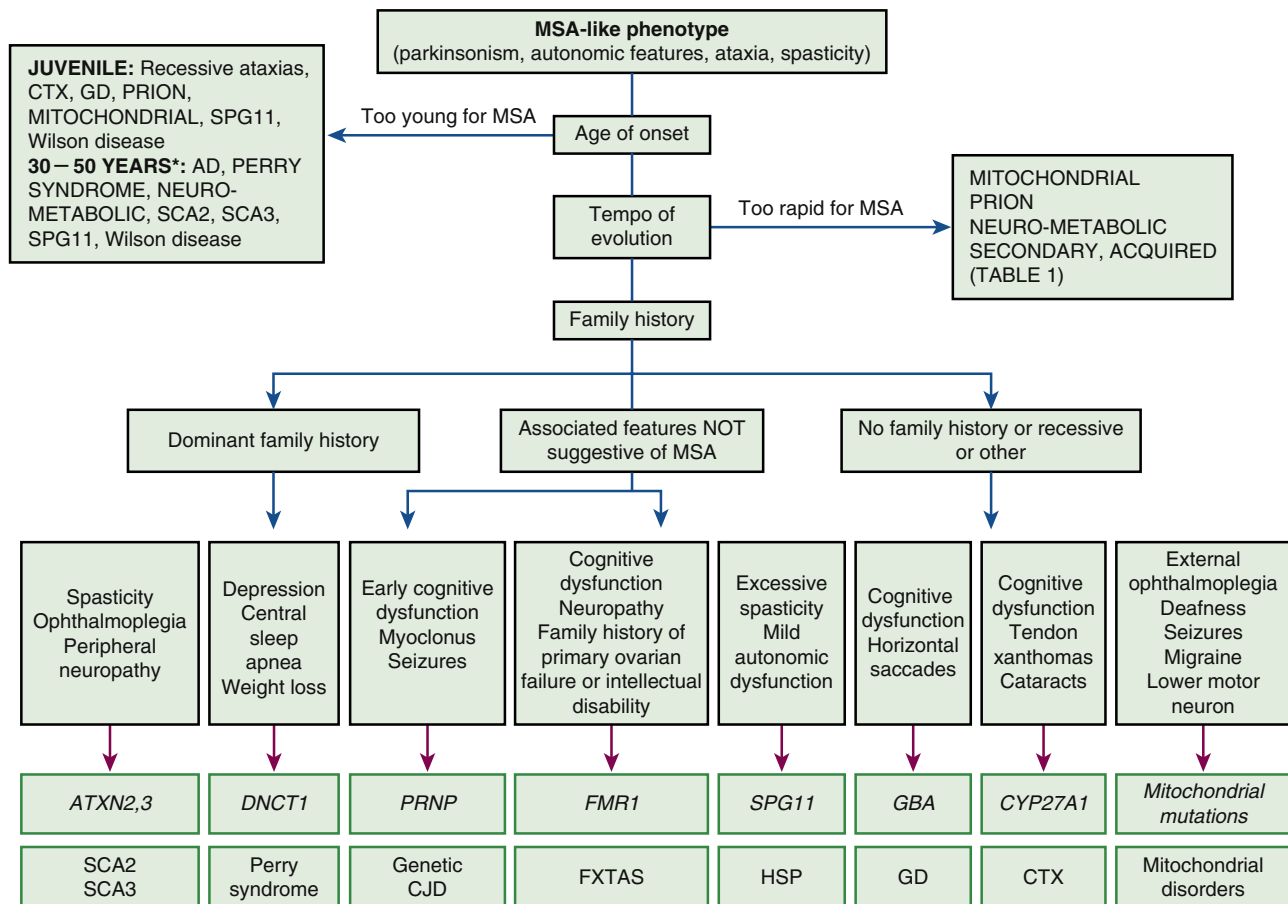


Fig. 9.3 Diagnostic approach to a patient presenting with a multiple system atrophy (MSA)-like phenotype. CJD, Creutzfeldt–Jakob disease; CTX, cerebrotendinous xanthomatosis; FXTAS, Fragile-X-associated tremor/ataxia syndrome; GD, Gaucher's disease; HSP, Hereditary spastic paraplegia; SPG11, spastic paraplegia. (Modified from Stamelou M, Quinn NP, Bhatia KP. "Atypical" atypical parkinsonism: New genetic conditions presenting with features of progressive supranuclear palsy, corticobasal degeneration, or multiple system atrophy—a diagnostic guide. *Mov Disord.* 2013;28[9]:1184–1199.)

Neuroimaging techniques, including MRI, transcranial sonography, functional imaging (positron emission tomography [PET] and single-photon positron emission tomography [SPECT]), and imaging cardiac sympathetic innervation, can be very helpful in differentiating MSA from other parkinsonian disorders, and neuroimaging criteria have been proposed (Brooks et al., 2009). MRI in patients with MSA sometimes reveals areas of decreased signal bilaterally in the posterolateral putamen on T2-weighted images. Although increased levels of iron may contribute to this hypointensity, reactive microgliosis and astrogliosis may also play an important role. In addition to striatal (putamen) hypointensity on T2-weighted MRI scans, a characteristic finding in patients with MSA, particularly MSA-P, is the slit-hyperintensity in the lateral margin of the putamen (Sitburana and Ondo, 2009). The combination of increased signal on T2 or fluid-attenuated inversion recovery (FLAIR) imaging in the lateral putamen (indicating iron deposition) and the slit hyperintensity at the posterolateral border of the putamen on T2-weighted images provides a sensitivity for MSA of 97% (von Lewinski et al., 2007) (Fig. 9.4A). Using diffusion-weighted imaging (DWI)-MRI, Schocke and colleagues (2002) found that regional apparent diffusion coefficients values are increased in the putamen of patients with

MSA, and this evidence of striatal degeneration apparently reliably differentiates MSA from PD. DWI imaging showing abnormal signal in the middle cerebellar peduncle is apparently relatively specific for MSA-C and is not seen in PSP or PD (Nicoletti et al., 2006; Paviour et al., 2007). Several studies have highlighted the "hot cross bun" sign in the pons as a characteristic feature of MSA (Sitburana and Ondo, 2009) (see Fig. 9.4B). This sign is best visualized by proton density-weighted imaging (PDWI) (Kasahara et al., 2012). Degenerated pontocerebellar tracts on diffusion tensor imaging (DTI) seems to correspond to the transverse portion of the hot cross bun sign (Fujimori et al., 2011). Another MRI sign that helps differentiate MSA from other parkinsonian disorders is the "zebra sign," which may reflect the degeneration of the upper motor neurons within the motor cortex because it is also observed in patients with ALS (Sugiyama et al., 2019). A diagnostic algorithm based on brain MRI has been proposed (Bhattacharya et al., 2002).

PET scanning has revealed decreased striatal and frontal lobe metabolism and a reduction in D2 receptor density in the striatum. In a study of 167 patients [^{18}F]fluorodeoxyglucose (FDG) PET was found to have high specificity and sensitivity in distinguishing among parkinsonian disorders (Tang et al., 2010).

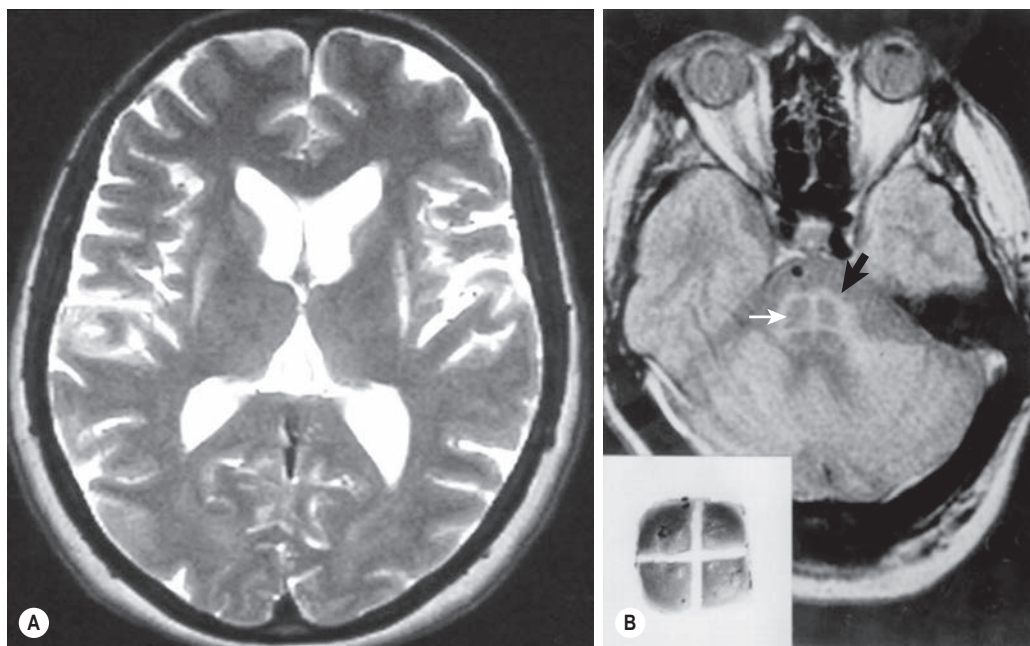


Fig. 9.4 (A) Magnetic resonance imaging of a 55-year-old woman with probable multiple system atrophy–parkinsonian type showing the linear hyperintensity along the lateral border of the putamen. (B) Hot cross bun sign (arrow and inset).

Besides neuroimaging, transcranial ultrasonography has been reported to provide high diagnostic yield in differentiating PD from atypical parkinsonian disorders. Brain parenchyma sonography was used in one study to differentiate PD from atypical parkinsonism, mostly MSA (Walter et al., 2003). The investigators found that 24 of 25 (96%) patients with PD exhibited hyperechogenicity, whereas only 2 of 23 (9%) patients with atypical parkinsonism showed a similar pattern. They concluded that brain parenchyma sonography might be highly specific in differentiating between PD and atypical parkinsonism. Sonographic studies in 102 patients with PD, 34 with MSA, and 21 with PSP found marked unilateral or bilateral hyperechogenicity in 89% of 88 patients with PD, 25% of 32 patients with MSA-P, and 39% of 18 patients with PSP (Behnke et al., 2005).

Neuropathology, neurochemistry, and pathogenesis

The spectrum of pathologic changes in MSA includes cell loss, gliosis, and demyelination in the striatum (caudate and putamen), substantia nigra (SN), locus coeruleus (LC), inferior olives, pontine nuclei, dorsal vagal nuclei, Purkinje cells of the cerebellum, intermediolateral cell columns, and Onuf nucleus of the caudal spinal cord. Involvement of at least three of these areas, including the putamen and SN, is required for the pathologic diagnosis of MSA (Ubhi et al., 2011; Jellinger, 2014).

Because the discovery by Papp and Lantos (Papp et al., 1989) of the characteristic histologic marker, the GCIs, there has been substantial improvement and clarification of MSA as a specific clinicopathologic entity (Jellinger, 2014). These inclusions, which represent the pathologic hallmark of MSA, are particularly concentrated in the oligodendroglia and have been found in all autopsied brains of patients previously classified as SDS, SND, and sporadic

OPCA. This shared pathologic feature strongly argues in support of the notion that these three disorders should be regarded as variants of the same disease entity, namely, MSA. GCI, argyrophilic, perinuclear inclusions, with a diameter varying from 4 to 20 μm , are found particularly in the oligodendroglia in the supplementary motor cortex, anterior central gyrus, putamen, pallidum, basal pons, and medullary reticular formation. They are composed of 20- to 30-nm straight tubules and contain ubiquitin, tau protein, alpha- and beta-tubulin, MAP-5, αB -crystallin, and alpha-synuclein. Several studies have documented the presence of alpha-synuclein in the GCI (Spillantini et al., 1998; Tu et al., 1998; Wakabayashi et al., 1998). Although very characteristic of MSA, GCIs have been rarely found in other disorders, such as CBD, PSP, and autosomal dominant SCA. Alpha-synuclein is selectively and extensively phosphorylated at serine 129, especially by casein kinase 1 and 2, in various synucleinopathies, including MSA (Fujiwara et al., 2002). Because of increasing evidence of dysregulation of myelin basic protein and p25 α , also called tubulin polymerization promoting protein, in MSA, there is an emerging notion that MSA represents an oligodendrogliaopathy (Wenning et al., 2008). A significant correlation has been found between the frequency of GCIs, severity of neuronal cell loss, and disease duration (Ozawa et al., 2004). Whereas in PD and DLB, alpha-synuclein forms neuronal inclusions called Lewy bodies, in MSA alpha-synuclein aggregates in glia and Lewy bodies are found in 10% of MSA cases (Ozawa et al., 2004). Several studies found biochemical, conformational, and other differences between alpha-synuclein strains in PD versus MSA (Strohäker et al., 2019; Yamasaki et al., 2019). One pathologic study of 100 MSA cases (46 men and 54 women) showed that GCIs might be contributing to neuronal damage in the MSA-C type more than the MSA-P type, suggesting the possibility of different mechanisms of cell death in the subtypes of MSA (Ozawa et al., 2004). In addition to

GCI, it is increasingly recognized that widespread neuronal inclusions are also important pathologic findings in brains of patients with MSA (Cykowski et al., 2015).

The fundamental pathologic changes in MSA-C, whether familial or sporadic, are a loss of Purkinje cells in the cerebellar cortex, particularly in the vermis, and degeneration of the olivopontine nuclei. In addition to cerebellar atrophy, SN degeneration and depigmentation, neuronal loss in other brainstem nuclei, and demyelination of corticospinal tracts and posterior columns are seen. The medial spiny neurons that give rise to both the direct pathway from the striatum to the globus pallidus internus (GPi) and the indirect pathway from the striatum to the globus pallidus externus (GPe) are affected. Gliosis, however, seems to be much more prevalent in the GPe than in the GPi. Upregulation of dopamine 1 (D1) receptors, determined by dopamine-stimulated adenylyl cyclase, has been demonstrated in brains of patients with PD compared with PSP and MSA ($n = 10$ each); it is actually reduced in MSA (Tong et al., 2004). In another study, the investigators analyzed 35 pathologically confirmed cases of MSA and confirmed a direct correlation between severity of disease and nigrostriatal cell loss (Wenning et al., 1995). Although marked degeneration in the olivopontocerebellar system, particularly the cerebellar vermis, was noted in 88% of the brains, the cerebellar pathologic findings did not correlate with the presence of cerebellar signs.

Cholinergic neurons in the pedunculopontine nucleus (PPN) and laterodorsal tegmentum and noradrenergic neurons in the LC were found to be markedly depleted in the brains of patients with MSA, whereas the serotonergic rostral raphe neurons are well preserved (Benarroch et al., 2013). Degeneration of the catecholaminergic neurons in the intermediate reticular formation of the rostral ventrolateral medulla seems to correlate well with autonomic failure in patients with MSA. Lewy bodies or neurofibrillary tangles (NFTs) are not common. Loss of arginine-vasopressin synthesizing neurons in the hypothalamic suprachiasmatic nucleus has been demonstrated in the brains of patients with MSA. Calbindin-D28k immunoreactivity in the striatal projection system is markedly decreased in the Purkinje cells of the cerebellum in patients with MSA (Wüllner et al., 2000). In the early stages of MSA-P, the medium spiny neurons staining for calbindin (localized to the matrix), but not those staining for calcineurin (localized striasomes), appear to be depleted first (Sato et al., 2007). Reduced calcium-binding capacity in these neurons might affect the bcl-2 family of proteins and lead to apoptosis of selected neuronal regions not only in PD but also in other neurodegenerative diseases, such as MSA. The small, myelinated fibers innervating the vocal cord are lost in nearly all patients with MSA, but when the large, myelinated fibers of the recurrent laryngeal nerve become affected, as is seen in some patients with MSA, vocal cord paralysis becomes evident and may be life-threatening (Hayashi et al., 1997).

The autonomic failure in MSA has been largely attributed to the depletion of sympathetic preganglionic neurons in the spinal intermediolateral cell column and its afferent medullary catecholaminergic and serotonergic neurons. In 12 MSA patients who had died within 3.5 years after disease onset, 4 died suddenly and 8 died as a result of established causes (Tada et al., 2009). The investigators found that the spinal intermediolateral and medullary catecholaminergic and

serotonergic systems were involved even in the early stages of MSA, and their degeneration may be responsible for sudden death in patients with MSA.

Diffuse degeneration of the white matter, particularly involving the central tegmental tract associated with vacuolation, has been an increasingly recognized pathologic feature of MSA (Armstrong et al., 2007). Other studies found evidence of apoptosis in the glia, but not neurons, of MSA brains (Probst-Cousin et al., 1998). Furthermore, microglial activation involving translocation of nuclear factor (NF)- κ B/Rel A to the nucleus was found to be particularly prominent in affected brain regions (Schwarz et al., 1998).

In addition to the typical findings in the brain, there is a marked loss of neurons in the lateral horns of the spinal cord, but these pathologic changes correlate poorly with dysautonomia. Substance P-like immunoreactivity was markedly decreased in laminae I + II of the fourth thoracic and third lumbar spinal cord segments in 10 of 11 SDS patients, and all had a decrease in small and large myelinated fibers in the fourth thoracic ventral roots. In addition to the central nervous system, alpha-synuclein pathologic findings can be demonstrated in other organs, including the enteric system. For example, alpha-synuclein findings were seen in a colonic biopsy sample of the enteric nervous system in 1 of 6 MSA patients and in 5 of 9 PD patients (Poulet 2012). Thus, although synuclein pathologic findings are less common in MSA than in PD, they may involve the entire enteric nervous system.

The cause of MSA is unknown, and genetic factors probably do not play an important role. Because MSA is classified as alpha-synucleinopathies, variations in the gene coding for alpha-synuclein (SNCA) were examined in a genome-wide association study (GWAS) of PD in 413 MSA cases and 3974 control subjects and the 10 most significant single nucleotide polymorphisms (SNPs) were then replicated in an additional 108 MSA cases and 537 controls (Scholz et al., 2009). The study found that SNPs at SNCA were associated with increased risk for the development of MSA at an odds ratio (OR) of 6.2 ($P = 5.5 \times 10^{-12}$). Although no gene mutations have been identified in several families with MSA phenotype, homozygous mutation and compound heterozygous mutations in the COQ2 gene was found in two multiplex families (The Multiple-System Atrophy Research Collaboration, 2013). In addition, a common variant (V343A) and other variants in COQ2 were found to be associated with sporadic MSA. The COQ2 gene encodes an enzyme that is essential for the biosynthesis of coenzyme Q10 and the authors suggested that "oral supplementation with coenzyme Q10 may be helpful in treating MSA, particularly for patients with susceptibility-conferring COQ2 variants." A GWAS performed on 918 patients with MSA of European ancestry and 3864 controls found no significant loci, although potentially interesting regions were identified, including SNPs in the genes *FBXO47*, *ELOVL7*, *EDN1*, and *MAP* (Sailor et al., 2016).

Although many studies have investigated the putative role of environmental toxins in the pathogenesis of idiopathic PD, the possible role of such toxins in MSA has received little attention. We reported on 10 patients whose clinical features were consistent with those of MSA and in whom toxins were suspected to play an etiologic role (Hanna et al., 1999). One patient with pathologically confirmed

MSA was exposed to high concentrations of various toxins, including formaldehyde, malathion, and diazinon. The other MSA patients had a history of heavy exposure to various agents, such as n-hexane, benzene, methyl-isobutylketone, and pesticides. The pathologic case revealed extensive advanced glial changes, including GCIs, which were seen particularly in the deep cerebellar white matter, brainstem, cortex (superior frontal, insula, and hippocampus), and putamen. Additionally, there was notable neuronal cell loss with depigmentation of the SN and LC. Although a cause-and-effect relationship cannot be proven, these cases suggest that environmental toxins could play a role in the pathogenesis of some cases of MSA. The inverse relationship between PD and smoking also has been found with MSA but not with PSP (Vanacore et al., 2000).

Although there is no experimental model of MSA, intraperitoneal injection of 3-acetylpyridine in rats produces neurochemical and histologic changes that are consistent with MSA-C (Deutch et al., 1989). In addition to causing degeneration of the nigrostriatal dopaminergic pathway, this neurotoxin causes degeneration of the climbing fibers, which normally originate in the inferior olive and terminate in the cerebellum. Another possible animal model of MSA is the “double lesion” rat model in which an initial 6-hydroxydopamine (6-OHDA) SN lesion is followed by a quinolinic acid-induced lesion in the striatum (Köllensperger et al., 2007). Transgenic mice overexpressing human wild-type alpha-synuclein in oligodendrocytes exhibit many of the features of MSA (Yazawa et al., 2005). The selective neuronal loss in a transgenic MSA mouse model has been attributed to deficiency of oligodendroglial glial-derived neurotrophic factor (GDNF) release (Ubhi et al., 2011). Another important finding is that tubulin polymerization promoting protein, also known as p25alpha, was shown to specifically accelerate oligodendroglial alpha-synuclein oligomer formation and to promote alpha-synuclein-positive GCI-like inclusions. Interestingly, cerebrospinal fluid (CSF) from patients with MSA seems capable of promoting in vitro alpha-synuclein fibril formation (Hirohata et al., 2011). Finally, there is growing evidence that MSA is caused by a human prion, different from the scrapie isoform of the prion protein (PrP^{Sc}), that causes CJD (Prusiner et al., 2015; Meissner et al., 2019).

Treatment

Despite marked involvement of the striatum, about two-thirds of patients with MSA do improve with levodopa, at least initially. In contrast to patients with PD, MSA patients often experience dyskinesias without concomitant improvement in motor functioning (Castro Caldas et al., 2017). The levodopa-induced dyskinesias that are seen in MSA patients seem to be more dystonic, often involving the face, rather than the choreic or stereotypic movements that are characteristically seen in patients with PD. Furthermore, MSA patients do not seem to notice a recurrence of parkinsonian symptoms until several days after levodopa withdrawal. Ataxia, present in patients with MSA-C, does not respond to pharmacologic therapy, and most patients with this type of MSA increasingly rely on a cane, walker, or wheelchair. The autonomic symptoms associated with MSA are treated similarly to dysautonomia associated with PAF or other disorders with

Table 9.5 Treatment of multiple system atrophy

- Parkinsonism: One-third respond to levodopa
- Orthostatic hypotension
 - Elastic stocking, leg-crossing and squatting
 - Correct volume depletion and anemia
 - Liberal salt
 - Fludrocortisone (mineralocorticoid alpha1 agonist; 0.1–0.5 mg/d)
 - Midodrine (a peripheral alpha1 agonist; 5–10 twice daily)
 - Droxidopa (L-threo-3,4-dihydroxyphenyl serine, 200–2000 mg/d)
 - Octreotide (a somatostatin analog; 100–1500 mcg/d subcut)
 - Other: Indomethacin, ibuprofen, pseudoephedrine, caffeine and dihydroergotamine, yohimbine, erythropoietin, and fipamezole (alpha2a, b, c antagonist)
- Treatment of supine hypertension
 - Reverse Trendelenburg position
 - Nighttime nitroglyceride
 - Clonidine patches
 - Pyridostigmine

subcut, subcutaneous.

prominent autonomic dysfunction (Mostile et al., 2009) (Table 9.5).

Levodopa not only can cause dyskinesia without motor improvement but frequently also exacerbates the already prominent symptoms of OH. The addition of liberal salt, fludrocortisone, and elastic stockings can improve standing blood pressures. However, parkinsonian patients have difficulty putting on elastic stockings, such as the Jobst stockings. In addition, physical maneuvers such as leg-crossing and squatting can alleviate orthostatic lightheadedness. In a double-blind, placebo-controlled study of 97 patients with various causes of autonomic failure, including 18 patients with MSA and 22 patients with PD, midodrine, a peripheral alpha-adrenergic agonist, was found to be effective in the treatment of OH (Jankovic, Gilden, et al., 1993). The safety and efficacy of midodrine were later confirmed by a larger controlled study involving a total of 171 patients with OH (Low et al., 1997). Wright and colleagues (1998) showed dose-dependent increases in standing systolic blood pressure with midodrine in patients with MSA. The most frequent side effects associated with the drug included piloerection, scalp pruritus, urinary retention, and supine hypertension. The effects of subcutaneous injections of octreotide, a somatostatin analog, were tested in a group of nine patients with MSA (Bordet et al., 1995). The drug improved OH and allowed patients to maintain an upright posture for a longer time compared with placebo. Because fludrocortisone and midodrine, particularly when combined with liberal salt intake, increase the risk for supine hypertension, patients should be instructed to place their beds in the reverse Trendelenburg position. The use of nighttime nitroglyceride or clonidine patches has been suggested for the treatment of supine hypertension, but these measures are not always successful. Although this modest improvement was attributed to a release of NE by octreotide during maintenance of erect posture, no increase in plasma NE levels could be demonstrated.

Other agents that are used to increase standing blood pressure include indomethacin, ibuprofen, pseudoephedrine and other sympathomimetics, caffeine and dihydroergotamine, yohimbine, and NE precursors, such as 3,4-dihydroxyphenylserine, also known as L-threo DOPS or droxidopa.

Droxidopa appears to increase NE in the brains of normal and NE-depleted animals, suggesting that it acts as an NE precursor. The drug may also act in the peripheral nervous system, as evidenced by increased heart rate and elevated blood pressure. In 32 patients (26 MSA, 6 PAF) with symptomatic OH, droxidopa (up to 300 mg twice daily) reduced the fall in systolic blood pressure during orthostatic challenge (by a mean of 22 ± 28 mm Hg) and 78% of the patients were considered clinically improved. There were no reports of supine hypertension (Mathias et al., 2001). Carbidopa may partially blunt the effects of droxidopa, but this does not appear to be clinically meaningful in patients with PD or MSA who also take carbidopa/levodopa (Kaufmann et al., 2003). In a large class I pivotal trial, patients with symptomatic OH because of PD, MSA, PAF, or nondiabetic autonomic neuropathy, there was a significant improvement (0.90 units, $P = 0.003$) with droxidopa in the Orthostatic Hypotension Questionnaire (OHQ) composite score compared with placebo (Kaufmann et al., 2014). Furthermore, the mean standing systolic blood pressure increased by 11.2 versus 3.9 mm Hg ($P < 0.001$) and mean supine systolic blood pressure by 7.6 versus 0.8 mm Hg ($P < 0.001$). Supine systolic hypertension (blood pressure greater than 180 mm Hg) was observed in 4.9% of droxidopa and 2.5% of placebo subjects.

Bladder problems, particularly urinary retention and incontinence, are relatively common and often troublesome manifestations of MSA (Scientific Committee of the First International Consultation on Incontinence, 2000). Increased urinary frequency because of overactive bladder is less common and often improves with 5 mg of antimuscarinic oxybutynin three to four times per day and 2 mg of tolterodine three times per day. The latter drug may be better tolerated because it has eight times less affinity for the salivary gland, thus having much lower frequency of dry mouth. Use of 0.4 mg of the alpha-blocker tamsulosin twice daily may be effective if the urinary frequency is associated with benign prostatic hypertrophy; this condition must be excluded before the use of antimuscarinic agents. Prazosin and moxisylyte are specific antagonists of bladder alpha-adrenergic receptors. In a controlled study in 49 patients, there was improvement in symptoms in 47.6% in the prazosin group and 53.6% in the moxisylyte group. Orthostatic hypotension was seen in about 23% in the prazosin group and 11% in moxisylyte group. More than 35% of patients had reduction in residual volume, and there was improvement in urinary urgency, frequency, and incontinence. The dosage used was 1 mg of prazosin and 10 mg of moxisylyte three times daily in an oral form (Sakakibara et al., 2000a,b). The combination of intravesical prostaglandin E2 and oral bethanechol chloride has been found to be of limited usefulness in treating urinary retention (Hindley et al., 2004). Sildenafil citrate has been found to be safe and effective in the treatment of erectile dysfunction associated with PD, but it may unmask OH in patients with MSA (Hussain et al., 2001; Farooq et al., 2008).

Constipation represents the most frequent gastrointestinal manifestations of MSA. Psyllium was found to increase stool frequency and weight but did not alter colonic transit or anorectal function. Other effective treatments for constipation include polyethylene glycol, bisacodyl, magnesium sulfate, and macrogol. Mosapride citrate, a novel 5HT₄ agonist and partial 5HT₃ antagonist, has been found to ameliorate

constipation in parkinsonian patients (Liu et al., 2005). Other drugs for constipation include lubiprostone, which locally activates intestinal ClC-2 chloride channels and increases intestinal fluid secretion without altering serum electrolyte levels, and tegaserod maleate, a novel selective serotonin receptor type-4 (5HT₄) partial agonist that stimulates upper gastrointestinal tract motility (Sullivan et al., 2006). Linaclotide may be another medication useful in the treatment of constipation associated with MSA (Rothstein and Friedenberg, 2013).

MSA is often associated with a variety of respiratory problems, shortness of breath, aspiration pneumonia, stridor, and sleep apnea (Mehanna and Jankovic, 2010). In a study of 20 patients with MSA, Iranzo and colleagues (2000) found vocal cord abduction dysfunction in 14 (70%); and in 3 of 3 patients, continuous positive airway pressure (CPAP) completely eliminated laryngeal stridor, obstructive apnea, and hemoglobin desaturation. In another study, CPAP effectively ameliorated nocturnal stridor in 13 patients with MSA (Iranzo et al., 2004). Tracheostomy or other airway restoration techniques sometimes must be performed in patients who have vocal cord abductor paralysis (Isozaki et al., 1996). Stridor has been reported to improve with botulinum toxin injections into the adductor laryngeal muscles (Merlo et al., 2002).

The following trials of drugs studied as potential disease-modifying agents were negative: riluzole, minocycline, rifampin (Low et al., 2014), and rasagiline (Poewe et al., 2015). In the latter study, 174 patients with clinically diagnosed MSA were randomized to rasagiline ($n = 84$) or placebo ($n = 90$) treatment. At week 48, patients in the rasagiline group had progressed by an adjusted mean of 7.2 (standard error [SE], 1.2) total UMSARS units versus 8 (1.1) units in those in the placebo group (not significant [NS]). The most common adverse events in the rasagiline group were dizziness (12%), peripheral edema (11%), urinary tract infections (11%), and OH (10%). Intravenous immunoglobulin has not been found to be effective in patients with MSA (Wenning et al., 2011). In one study, 33 patients with probable MSA-C were evaluated in a randomized clinical trial of mesenchymal stem cells administered via intra-arterial and intravenous routes (Lee et al., 2012). The study showed a modest but significant reduction in UMSARS II scores compared with the placebo. There were no serious adverse effects except for small ischemic lesions on MRI related to intra-arterial infusion. In another study involving 24 patients with MSA who received between 10 and 200 million adipose-derived autologous MSCs intrathecally the rate of progression (UMSARS total) was markedly lower compared with a matched historical control group (0.40 ± 0.59 versus 1.44 ± 1.42 points/month, $P = 0.004$) with an apparent dose-dependent effect (Singer et al., 2019).

Patients with MSA are not candidates for deep brain stimulation except when the goal is to relieve severe camptocormia or Pisa sign, but even in these situations, the surgical intervention is usually not completely beneficial (Lizarraga et al., 2019).

Progressive supranuclear palsy

Clinical features and natural history

First described by Steele, Richardson, and Olszewski (Steele et al., 1964; Williams et al., 2008) in 1964, PSP has become

a well-recognized, clinicopathologic entity that may overlap in some clinical and pathologic features with other tauopathies such as CBD and AD (Litvan, 1998b; Litvan et al., 2000; Golbe and Ohman-Strickland, 2007; Golbe et al., 2007; Houghton and Litvan, 2007; Azher and Jankovic, 2008; Josephs, 2017; Ling et al., 2018; Stamelou et al., 2019). Although the motor subscale of the UPDRS has been found to reliably assess most aspects of PSP (Cubo et al., 2000), the PSP Rating Scale (PSPRS) has been found to be sensitive to disease progression, increasing at a mean rate of about 1 point per month (Golbe and Ohman-Strickland, 2007). PSPRS, along with the Quality of Life Scale (Schrug et al., 2006), should be used in future clinical trials investigating novel therapeutic interventions.

Several diagnostic criteria for PSP have been proposed (Höglinger et al., 2017; Shoeibi et al., 2019). The application of National Institute of Neurological Disorders and Stroke (NINDS)-SPSP diagnostic criteria (Litvan, Agid, Calne et al., 1996) and other criteria improved the accuracy of initial clinical diagnosis only marginally. On the basis of an analysis of 103 pathologically confirmed consecutive cases of PSP, Williams and colleagues (2005) divided PSP into two categories: Richardson syndrome, characterized by the typical features described in the original report, and PSP-P, in which the clinical features overlap with PD and the course is more benign. The latter group, representing about a quarter of all patients with PSP (Williams et al., 2005), has fewer tau pathologic findings than the classic Richardson's syndrome (PSP-Richardson syndrome) (Williams et al., 2007; Williams et al., 2008; Williams and Lees, 2009). The mean 4R-tau/3R-tau ratio of the isoform composition of insoluble tangle-tau isolated from the pons was significantly higher in Richardson's syndrome (2.84) than in PSP-P syndrome (1.63). The PSP-P phenotype has better survival with longer disease duration and slower rate of disease progression than the classic PSP-RS phenotype.

Another subgroup of PSP that has been identified is the so called "frontal" PSP, representing about 20% of all PSP patients (Kaat et al., 2007). These patients initially present with behavioral and cognitive symptoms, with or without ophthalmoparesis, that then evolve into typical PSP. In a retrospective chart review of 100 patients with autopsy-confirmed PSP there was marked phenotypic heterogeneity with 24% presenting as the classic PSP-RS (Respondek et al., 2014). Besides PSP-Richardson syndrome, other subtypes of PSP included PSP with parkinsonism (PSP-P), PSP with pure akinesia with gait freezing (PSP-PAGF), PSP with CBS (PSP-CBS), PSP with predominant speech and progressive nonfluent aphasia (PSP-PNFA), PSP with predominant frontotemporal dysfunction (PSP-FTD), PSP with cerebellar ataxia (PSP-C), and PSP with primary lateral sclerosis (PSP-PLS) (Respondek and Höglinger, 2016).

The MDS criteria identified four functional domains (ocular motor dysfunction, postural instability, akinesia, and cognitive dysfunction) as clinical predictors of PSP (Höglinger et al., 2017). Within each of these domains, there are three clinical features that contribute different levels of diagnostic certainty. Specific combinations of these features define the diagnostic criteria, stratified by 3 degrees of diagnostic certainty (probable PSP, possible PSP, and suggestive of PSP); clinical clues and imaging findings represent supportive features. The overall sensitivity of the MDS-PSP criteria was

87.9% and specificity 85.7% (Ali et al., 2019), compared with 45.5% and 90.5%, respectively, for the NIH-PSP criteria (Litvan et al., 1996a,b). Another set of diagnostic criteria, that largely overlap with the MDS criteria have been proposed using data from a sample of 274 clinically diagnosed PSP patients participating in the Environmental Genetic PSP (ENGINE-PSP) case control study (Shoeibi et al., 2019).

Diagnosis of PSP should be considered in any patient with progressive parkinsonism, postural instability, and disturbance of ocular motility. The earliest and most disabling symptom of PSP usually relates to gait and balance impairment, as a result of which patients frequently fall and sustain injuries. The following factors significantly increase the risk for falls in patients with PSP: abnormal saccades, eyelid dysfunction, modified turning, bradykinesia, axial rigidity, neck dystonia, and postural stability, symptom duration, and overall disease severity (Bluett et al., 2016).

The average period from onset of symptoms to the first fall in PSP is 16.8 months, compared with 108 months in PD, 42 months in MSA, 54 months in DLB, and 40.8 months in VP (Williams et al., 2006). The marked instability is presumably a result of visual-vestibular impairment, axial rigidity, and bradykinesia. Using computerized posturography, certain measures of balance impairment can reliably differentiate between PSP and PD even in early stages of the disease (Ondo et al., 2000). In contrast to the short and shuffling steps, stooped posture, narrow base, and flexed knees that are typically seen in PD, PSP patients have a stiff and broad-based gait, with a tendency to have their knees (and trunk) extended and arms slightly abducted. Instead of turning en bloc, they tend to pivot, which further compromises their balance (Video 9.3). Some PSP patients may present with the syndrome of "pure freezing," also referred to by some as *motor blocks*, *gait ignition failure*, and *primary progressive freezing of gait*. This gait disorder is manifested chiefly by akinesia of gait associated with start-hesitation, freezing of gait, festination, and disequilibrium with frequent falling and in some cases this gait disorder may be not only the presenting symptoms feature but the only motor feature (Compta et al., 2007; Williams et al., 2007; Facheris et al., 2008; Williams and Lees, 2009). Patients with pure freezing may evolve into or eventually have neuropathologic evidence of PD, CBD, pallidonigrolusian degeneration (Ahmed et al., 2008; Wong et al., 2013), and diffuse Lewy body disease (Factor et al., 2006; Williams et al., 2007). In addition to PSP, frontal gait disorder may be the initial manifestation of AD and CBD (Rossor et al., 1999). Although the PSP may be associated with ataxia and the gait may appear ataxic, the patients usually do not exhibit prominent cerebellar findings. The uncompensated loss of postural reflexes and motor blocks (freezing) especially on turning, coupled with a peculiar lack of insight into the difficulties with equilibrium (possibly secondary to frontal lobe dysfunction), leads to frequent falling and slumping into the chair on an attempt to sit down. There is, however, emerging evidence for cerebellar abnormalities, both clinically and pathologically, in PSP (Kanazawa et al., 2009). Abnormal otolith-mediated reflexes may also contribute to the falls of PSP (Liao et al., 2008). Based on physiologic and functional imaging studies, there is growing support for the notion that vestibular thalamus is involved in postural instability associated with PSP (Zwergal et al., 2011), similar to thalamic astasia (Masdeu et al., 1988). Another feature of

Video 9.3 Progressive supranuclear palsy (PSP).

PSP is symmetrical or asymmetrical arm levitation (Barclay et al., 1999) which may be exaggerated arm abduction, the so-called gunslinger's walk, typical of PSP gait. ●

Gait and postural abnormalities are often later accompanied by impairment of speech (stuttering, stammering, and monotonous hypophonia without normal modulation), handwriting difficulty (micrographia), and eyelid motor disturbance (blepharospasm, apraxia of eyelid opening or closure, also referred to as eyelid freezing) (Jankovic, 1984a) and other neuro-ophthalmological signs (Waln and Jankovic, 2018). Although hand tremor, typically seen in PD, is usually not a feature of PSP, one pathologically proven case of PSP manifested with jaw tremor has been reported (Louis et al., 2013). In contrast to PD, PSP patients have small finger separation without progressive decrement on repetitive finger tapping, and have more severe micrographia (Ling et al., 2012). Although cognitive and psychiatric symptoms are well recognized in PSP, overall functional disability is more related to motor impairment (Duff et al., 2013). Loss of insight, particularly inability to accurately predict performance on future tasks (anticipatory awareness), is a common feature not only in PSP but also in patients with FTD and CBD (O'Keefe et al., 2007). This is often present even in the early stages of the disease and helps differentiate PSP from PD (Litvan, Mangone, et al., 1996).

Along with postural instability, supranuclear ophthalmoparesis typically manifests by paralysis of downgaze, the most important distinguishing sign of PSP (Litvan, Campbell, et al., 1997; Waln and Jankovic, 2018) (Video 9.4). The predictability of these two features with regard to the final pathologic diagnosis was confirmed by a clinicopathologic study of 24 autopsy-proven cases of PSP (Litvan, Agid, Jankovic, et al., 1996). About one-third of PSP patients complain of blurred vision, diplopia, and eye discomfort, but most eventually lose their ability to read or maintain eye contact. Involuntary persistence of ocular fixation is a typical, though rarely mentioned, feature of PSP. In addition to transient persistence of gaze on oculomotor testing, PSP patients often lag with their head turning behind turning of their body (presumably because they continue to fixate their gaze in primary position even though their body is making the turn). Other oculomotor abnormalities that are seen in patients with PSP include impairment of saccades, optokinetic nystagmus (OKN), and the presence of square wave jerks. In early stages of PSP, patients might have only mild limitation of voluntary downgaze and inability to converge, but slowing of horizontal and vertical saccades appears to be the earliest oculomotor sign of PSP (Video 9.5). Marked slowing of vertical compared with horizontal OKN, best noted when the OKN tape moves in an upward direction, demonstrates impairment of down-saccades. Indeed, slowing of vertical saccades, even in the presence of normal vertical saccade amplitude, was found to be one of the earliest signs of an autopsy-proven PSP (Hardwick et al., 2009). One study compared saccades, OKN, and other ophthalmologic signs in six patients with PSP compared with PD and normal control (Garbutt et al., 2004). All PSP patients showed (1) slowing of vertical saccade and quick phase of nystagmus; (2) square wave jerks, which were more frequent and larger during fixation; and (3) impaired vertical OKN. Deficient generation of the motor command by midbrain burst neurons has been suggested as the primary mechanism for the

slow vertical saccades (Bhidayasiri et al., 2001). Slowing of vertical saccades might help differentiate PSP from other parkinsonian disorders, including PD, MSA, and CBD, although some slowing of vertical saccades also can be seen occasionally in these parkinsonian disorders (Vidailhet et al., 1994; Rivaud-Péchoux et al., 2000; Bhidayasiri et al., 2001), including PD (Knapp et al., 2009). In addition to slow vertical saccades, bilateral impairment of the antisaccade task (the patient is instructed to look in the direction opposite to the visual stimulus) correlates well with frontal lobe dysfunction in PSP (Vidailhet et al., 1994) and other neurodegenerative and frontal lobe disorders (Condy et al., 2004; Munoz and Everling, 2004; Zee and Lasker, 2004). Abnormalities in antisaccades, which imply a dysfunction of the dorsolateral prefrontal cortex and the superior colliculus, often precede impairments in vertical and eye movements. The ophthalmoparesis can be overcome by the oculocephalic (doll eyes) maneuver (Videos 9.3, 9.4, 9.6), but with disease progression and brainstem involvement, vestibulo-ocular reflexes can be lost, suggesting additional nuclear involvement (Ishino et al., 1974). Another characteristic feature of PSP is the "round the houses" sign (Quinn et al., 1996). ●

Supranuclear ophthalmoparesis may occur in DLB (Daniel et al., 1995; Brett et al., 2002; Waln and Jankovic, 2018), CBD, postencephalitic parkinsonism and encephalitis lethargica (Vilensky et al., 2010a,b), prion disease, Wernicke encephalopathy, dorsal midbrain syndrome, paraneoplastic syndrome, progressive subcortical gliosis, Whipple disease (Jankovic, 1986; Simpson et al., 1995; Averbuch-Heller et al., 1999), Niemann-Pick and Gaucher diseases (Shulman et al., 1995; Uc et al., 2000), Kufor-Rakeb syndrome (PARK9; secondary to mutation in *ATP13A2* gene on chromosome 1p36) (Hampshire et al., 2001), stiff-person syndrome, primary pallidal degeneration, and other disorders (Calabrese and Hadfield, 1991).

Rigidity, bradykinesia, and hypertonicity of the facial muscles produce deep facial folds and a typical worried or astonished facial expression (Fig. 9.5). The worried appearance is partly due to contraction of the procerus (and possibly corrugator) muscle, the so-called procerus signs (Romano and Colosimo, 2001) (Videos 9.3, 9.4). Blepharospasm, the most common form of dystonia in PSP, is encountered in nearly a third of all patients with PSP; other frequently encountered eyelid abnormalities include "apraxia" of eyelid opening, eyelid closure, or both. Although some (Lepore and Duvoisin, 1985) have hypothesized that these lid abnormalities are due to involuntary supranuclear inhibition of levator palpebrae, others have drawn attention to the similarity of this disorder of eyelid motor control and the parkinsonian phenomenon of sudden transient freezing, hence suggesting the term *lid freezing* (Jankovic, 1995a). Other terms that are used to describe this condition include pretarsal blepharospasm (Elston, 1992) and focal eyelid dystonia (Krack and Marion, 1994). ●

Pseudobulbar symptoms in PSP patients are characterized chiefly by dysarthria, dysphagia, and pseudobulbar affect, also referred to as "emotional incontinence" or "emotional expression disorder" (Video 9.7). Speech in PSP is characterized by a spastic, hypernasal, hypokinetic, ataxic, monotonous, low-pitched dysarthria (Video 9.3, 9.6, 9.7). The speech rate may be slow or fast, and some patients have severe palilalia and stuttering. An "apraxia of phonation"

Video 9.4 Progressive supranuclear palsy (PSP).
Video 9.5 Progressive supranuclear palsy (PSP).
Video 9.6 Progressive supranuclear palsy (PSP).
Video 9.7 Progressive supranuclear palsy (PSP).



Fig. 9.5 Faces of progressive supranuclear palsy.

has been reported in one patient who was aphonic except during periods of excitement or during sleep. In contrast, some patients have almost continuous involuntary vocalizations, including loud groaning, moaning, humming, and grunting sounds. Progressive dysphagia causes most patients to modify their diet, and some eventually need a feeding gastrostomy to maintain adequate nutrition. As a result of chewing difficulties, inability to look down, and poor hand coordination, PSP patients are often described as “sloppy eaters.” ▶

Dystonia may be a feature in all forms of atypical parkinsonism (Marsili et al., 2019). In a review of dystonia in pathologically proven cases of PD, MSA, and PSP, Rivest and colleagues (1990) found dystonia to be an uncommon feature, noted in 15 of 118 (13%) cases. They regarded the frequently reported neck extension as a form of axial rigidity rather than dystonia. In another study, the increased neck muscle tone was thought to have features of both dystonia (tonic shortening reaction) and rigidity (antagonist muscle contraction indicative of increased tonic stretch reflex) (Tanigawa et al., 1998). Neck extension, although often noted in published reports, is actually an uncommon sign in PSP. Indeed, neck flexion, usually associated with MSA, can occasionally be seen in PSP (Daniel et al., 1995). In contrast to the typical presence of neck rigidity, truncal muscle tone is only slightly increased, and distal limbs may actually seem hypotonic (Tanigawa et al., 1998). In some patients, however, distal dystonia can be seen (Barclay and Lang, 1997). Although PSP is usually a symmetrical disorder, dystonia represents an occasional exception in that unilateral dystonia may be present, particularly in the more advanced stages of the disease. In one study of 83 patients with PSP, 38 (46%) had some form of dystonia, 22 (24%) had blepharospasm, 22 (27%) had limb dystonia, and 14 (17%) had axial dystonia (Barclay and Lang, 1997). Sometimes, spontaneous arm levitation, a well-recognized sign in CBD, is also seen in

patients with PSP and may be wrongly attributed to dystonia (Barclay et al., 1999).

In their original monograph, Steele, Richardson, and Olszewski (1964) indicated that mild dementia was present during early stages of the disease. Although some investigators have reported severe cognitive impairment in this population, others have attributed these deficits, at least in part, to poor visual processing (Daniel et al., 1995). In a Neuroprotection and Natural History in Parkinson Plus Syndromes (NNIPPS) study, a randomized, multicenter, double blind, placebo-controlled trial of riluzole that included 372 MSA and 311 PSP patients (with 94% diagnostic accuracy based on postmortem examination, cognitive impairment on the Dementia Rating Scale (DRS) was observed in 57% of the PSP group and 20% of the MSA group. On the Frontal Assessment Battery (FAB), impairment was observed in 62% of patients with PSP and 32% of those with MSA. Cognitive slowing, impairment of executive (goal-directed) functions, and subcortical dementia with deficits in tasks requiring sequential movements, conceptual shifts, and rapid retrieval of verbal knowledge are typically present in patients with PSP (Litvan, Paulsen, et al., 1998). The apathy, with or without depression, and other hypoactive behaviors that are typically seen in PSP have been attributed to a dysfunction in the frontal cortex and associated circuitry (Litvan, Paulsen, et al., 1998). This is in contrast to HD, in which behaviors such as agitation, anxiety, and irritability have been related to hyperactivity of the medial and orbitofrontal cortical circuitry. Sparing of olfactory function in PSP, in contrast to that in PD, is another clinical difference between the two neurodegenerative disorders (Doty et al., 1993). Litvan, Mega, and colleagues (1996) studied the neuropsychiatric aspects of PSP in 22 patients and found that apathy occurred in 91%, disinhibition in 36%, dysphoria in 18%, anxiety in 18%, and irritability in fewer than 9%. Another sign of frontal lobe dysfunction in PSP is the

“applause sign” (signe de l’applaudissement), which probably represents a perseveration of automatic behavior (Dubois et al., 2005) (Video 9.8). This sign, characteristically present in patients with PSP (but also present in some patients with FTD with parkinsonism and CBD), is manifested by persistence (perseveration) of clapping after the patient is instructed to clap consecutively three times as quickly as possible. In a study of patients with various neurologic disorders evaluated at Baylor College of Medicine, the applause sign was present in 77.8% of 9 patients with CBD, 53.9% of 13 patients with MSA, 52.6% of 19 patients with PSP, 20% of 10 patients with HD, and 12.5% of 24 patients with PD (Wu et al., 2008). Although the test differentiated patients with CBD from those with PD ($P < 0.005$) and HD ($P < 0.005$), it failed to discriminate patients with PSP from other parkinsonian groups, but had a 100% specificity in distinguishing parkinsonian patients from normal subjects. Another study also showed no difference in applause sign when comparing PSP with FTD and FTD with AD (Luzzi et al., 2011).

After idiopathic PSP, the most common cause of PSP is a multi-infarct state. Multi-infarct or vascular PSP can be difficult to differentiate clinically from the more common idiopathic variety (Winikates and Jankovic, 1994; Mehanna and Jankovic, 2013). In addition to a much higher frequency of stroke risk factors and abnormal imaging studies, the vascular PSP patients are more likely to have asymmetrical and predominantly lower body involvement, cortical and pseudobulbar signs, dementia, and bowel and bladder incontinence (Winikates and Jankovic, 1994). The concept of vascular PSP is supported by the observation that up to 81.0% of patients with clinically diagnosed PSP have hypertension (Ghika and Bogousslavsky, 1997; Rabadia et al., 2019). A clinicopathologic study of four patients who were clinically diagnosed with PSP but found to have vascular PSP at autopsy showed that vascular PSP is characterized by asymmetrical signs, falls within 1 year of onset, and vascular lesions on MRI (Josephs et al., 2002). One cause of vascular PSP is cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) as a result of mutations in *NOTCH3* gene (Erro et al., 2013). Other reported causes of secondary PSP include exposure to organic solvents (McCrack et al., 1989), paraneoplastic syndrome (Jankovic, 1985), mesencephalic tumor (Siderowf et al., 1998), autoimmune disease (e.g., anti-IgLON5) (Gaig et al., 2017), surgery on the aorta (Mokri et al., 2004; Nandipatti et al., 2013), and other rare and often unsubstantiated causes.

The natural history of PSP has been addressed in several studies. In one longitudinal study involving 43 patients, 60.5% died after a median survival of 7.1 years (2.2–18) (dell’Aquila et al., 2013). Early dysphagia and early cognitive impairment are predictors of poor prognosis (Glasmacher et al., 2017). Richardson syndrome (compared with PSP–Parkinsonism phenotype), older age at onset (older than 63 years), early dysphagia, and early cognitive deficits were predictors of shorter survival (dell’Aquila et al., 2013). The relentlessly progressive course leads to death, usually from aspiration, within 10 years of onset in the majority of cases. In one clinicopathologic study of 24 patients with PSP, the median survival from onset was 5.6 years, and this was shorter in men and in patients who experienced falls during the first year of symptoms and with early dysphagia or supranuclear palsy (Litvan, Mangone, et al., 1996; Litvan, 2003).

In another clinicopathologic study involving 16 cases of PSP, Birdi and colleagues (2002) found the mean survival to be 8.6 years (range, 3–24), and the mean age at death was 72.3 years (range, 60–89). In a review of 187 cases, those with early bulbar features had around 5 years less life expectancy than did those who had no or late bulbar features (Nath et al., 2003). Similar to other series, the median survival in this study was 5.7 years. Because this figure is based on deceased cases, it might be too pessimistic because slowly progressive cases are still being followed. In another study of 50 PSP patients, Goetz and colleagues (2003) found the median survival from the onset of first symptom to be 7.9 years (6.5 years in the 21 patients who were followed to death). In addition to the short survival, PSP is associated with many symptoms that have a serious impact on the quality of life (Schrage et al., 2006). Overall, the median latency from onset to chairbound state is 5 years and to death is 7 years (Golbe and Ohman-Strickland, 2007). In a report of 37 studies presenting findings on 6193 patients (1911 PSP), early dysphagia and early cognitive symptoms were identified as unfavorable predictors of survival (Glassmacher et al., 2017).

Epidemiology

About 6% of all parkinsonian patients who are evaluated in a specialized clinic fulfill the clinical criteria for PSP. On the basis of a medical record review of the Rochester Epidemiology Project, the average annual incidence rate has been estimated to be 1.1 to 5.3 new cases per 100,000 person-years (Bower et al., 1997; Stamelou et al., 2019). The prevalence, after age adjustment to the U.S. population, has been estimated to be 1.39 per 100,000 (Golbe et al., 1988). In a review of computerized records of 15 general practices in and around London, Schrage and colleagues (1999) found an age-adjusted prevalence for PSP of 6.4 per 100,000. In other studies carried out in the United Kingdom, the prevalence of PSP ranged from 1 to 6.5 per 100,000 (Nath et al., 2001). Similar to the European studies, a prevalence of 5.82 per 100,000 has been reported in Yonago, Japan (Kawashima et al., 2004).

Like PD, PSP occurs more often in men, but its onset at a mean age of 63 years, is about 10 years later than the typical onset of PD. Although no well-designed epidemiologic studies have been performed in PSP, one case-control study found that PSP patients were more likely to live in areas of relatively sparse population (Davis et al., 1988). Another study by the same investigators failed to identify any risk factors, except for low likelihood of completing at least 12 years of education that would differentiate patients with PSP from a matched control population (Golbe et al., 1996).

Neurodiagnostic studies

There is no blood or CSF test that can diagnose PSP but CSF neurofilament light (NFL) protein is elevated in PSP and other atypical parkinsonian disorders compared with PD and healthy controls (Boxer et al., 2017; Stamelou et al., 2019). Blood levels of NFL correlate with CSF levels and they are more elevated in atypical parkinsonism than in controls and patients with PD (Hansson et al., 2017; Marques et al., 2019).

Electrophysiologic studies have been helpful in documenting other abnormalities, such as sleep difficulties and seizures. One study showed marked reduction in percentage of

Video 9.8 Progressive supranuclear palsy (PSP).

REM sleep in patients with PSP (Montplaisir et al., 1997). The same study also showed frontal electroencephalogram (EEG) slowing in patients with PSP. In a review of 62 patients seen over a 9-year period, Nygaard and colleagues (1989) noted seizures in 7 patients and suggested a higher than expected frequency of seizures in this population. Although not reported by others, the relatively high frequency of seizures reported by Nygaard and colleagues (1989) might have been secondary to cortical infarcts. Abnormalities in motor and frontal sensory evoked potentials have been found in 8 of 13 patients with the clinical diagnosis of PSP (Abbruzzese et al., 1991).

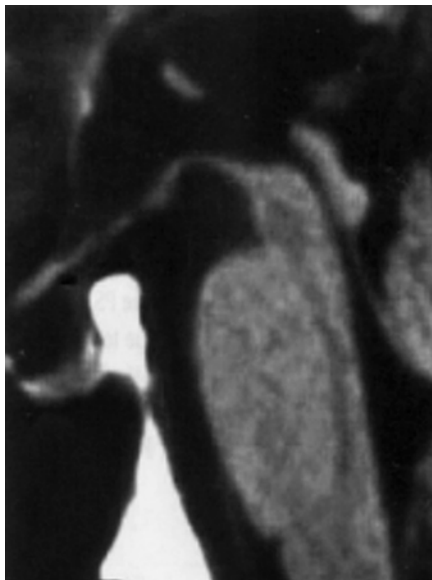
The typical findings on computed tomography (CT) or MRI scans of patients with PSP include generalized and brain-stem, particularly midbrain, atrophy (Whitwell et al., 2017). Measuring the anteroposterior diameter of the suprapontine midbrain, Warmuth-Metz and colleagues (2001) found that in contrast to PD patients (mean 18.5 mm), PSP patients had a significantly lower diameter (13.4 mm) on axial T2-weighted MRI, and as a result the authors concluded that this finding reliably differentiates between PD and PSP and recommended that this evaluation “should be incorporated into the diagnostic criteria for PSP.” In another study, using midsagittal MRI, the average midbrain area of patients with PSP was 56 mm², which was significantly smaller than that of patients with PD (103 mm²) or MSA-P (97.2 mm²), and this parameter, particularly the ratio of the area of the midbrain to the area of the pons, was found to reliably differentiate among the three disorders (Oba et al., 2005). Other studies have established the utility of using the ratio of pons to midbrain diameter to differentiate between various PSP disorders and other parkinsonian syndromes (Longoni et al., 2011; Massey et al., 2013). On the midsagittal view of the MRI, as a result of atrophy of the rostral midbrain tegmentum, the most rostral midbrain, the midbrain tegmentum, the pontine base, and the cerebellum appear to correspond to the bill, head, body, and wing, respectively, of a hummingbird

(Kato et al., 2003) or penguin (Oba et al., 2005; Sitburana and Ondo, 2009) (Fig. 9.6). The “hummingbird sign” was demonstrated in all 8 MRI scans of PSP patients but not in any of the 12 scans of PD patients or 10 scans of normal controls (Kato et al., 2003). The “morning glory sign,” a peculiar MRI finding of midbrain atrophy with concavity of the lateral margin of the midbrain tegmentum, resembling the lateral margin of the morning glory flower, is observed in patients with PSP (Adachi et al., 2004). MRIs in patients with PSP, MSA, and other parkinsonian syndromes have been associated with putaminal hypointensity on T2-weighted MRI, but this finding is less consistently noted in PSP than in the other parkinsonism-plus syndromes. In one study, PSP could be differentiated from MSA by the presence of marked atrophy and hyperintensity of the midbrain and atrophy of the frontal and temporal lobes. The “eye of the tiger” sign on brain MRI, typically associated with neurodegeneration with brain iron accumulation type 1 (NBIA1), also has been reported in PSP. PSP is associated with dorsal midbrain atrophy and as a result of degeneration of superior colliculi, the floor of the third ventricle is flattened on sagittal MRI images.

With DTI and voxel-based morphometry in PSP, Padovani and associates (2006) provided evidence of both gray and white matter degeneration even in early stages of PSP. Voxel-based morphometry in 15 patients with clinically proven PSP and 14 with CBD showed distinct patterns of atrophy that differentiated between the two disorders with 93% accuracy (Boxer et al., 2006). Whereas CBD patients had a marked asymmetrical (L > R) pattern of atrophy involving premotor cortex, superior parietal lobules, and striatum, PSP was characterized by atrophy of the midbrain, pons, thalamus, and striatum. Indeed a systematic review and meta-analysis of studies that evaluated DTI in various parkinsonian disorders identified different patterns of distribution that allowed the abnormal neuroimages to be categorized as PD, PSP, or MSA (Cochrane and Ebmeier, 2013). Using diffusion-weighted MRI (DWI-MRI), Seppi and colleagues (2003) were able to

The birds and flowers of PSP

Hummingbird or penguin sign



Morning glory sign

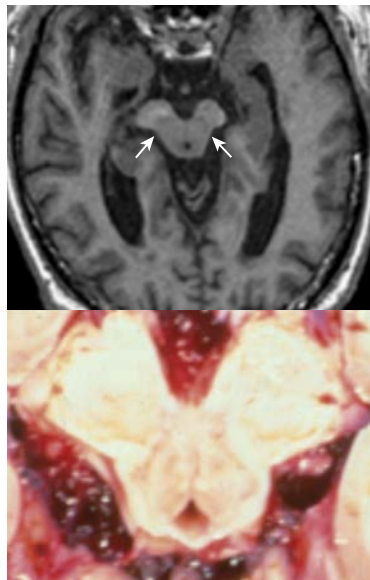


Fig. 9.6 Magnetic resonance imaging signatures of progressive supranuclear palsy.

differentiate between PSP and PD with 90% sensitivity and 100% specificity, but this technique could not differentiate between PSP and MSA. Degeneration predominantly affecting brainstem, association, and commissural fibers was demonstrated in a study of 20 patients with probable PSP and 20 age- and sex-matched healthy controls (Whitwell et al., 2011). Compared with controls, PSP patients showed abnormal diffusivity predominantly in the superior cerebellar peduncles, body of the corpus callosum, inferior longitudinal fasciculus, and superior longitudinal fasciculus in patients with PSP. Furthermore, fractional anisotropy values in the superior cerebellar peduncles correlated with disease severity, inferior longitudinal fasciculus correlated with motor function, and superior longitudinal fasciculus correlated with severity of saccadic impairments. A magnetic resonance parkinsonism index (MRPI) greater than 13.55 is more predictive of evolving clinically unclassifiable parkinsonism into PSP than clinical features (Morelli et al., 2011). The MRPI is calculated by multiplying the pons area–midbrain area ratio (P/M) by middle cerebellar peduncle (MCP) width–superior cerebellar peduncle (SCP) width ratio (MCP/SCP) ($[P/M] \times [MCP/SCP]$). Although MRPI has adequate utility in supporting the diagnosis of PSP–Richardson syndrome and differentiating it from both PD and healthy controls, it has low sensitivity and specificity profile in differentiating PSP-P from PD (Picillo et al., 2020).

Stroke risk factors and a multi-infarct state on CT or MRI have been noted in patients with PSP with a higher frequency than in those with PD (Mehanna and Jankovic, 2013). One cause for a subgroup of PSP might be small vessel disease producing subcortical ischemia with reduction of regional cerebral blood flow, cerebral hypometabolism, and a multi-infarct state.

PET scans have revealed decreased metabolic activity in the caudate, putamen, and prefrontal cortex, but the earliest sign of PSP appears to be decreased glucose metabolism in the midbrain (Mishina et al., 2004). In one study, ^{18}F DOPA uptake was markedly reduced in the caudate and the anterior and posterior putamen of PSP patients (Brooks et al., 1990). In contrast, the uptake was reduced only in the posterior putamen in PD patients. Similarly, dopamine transporter (DAT), imaged by ^{11}C -WIN PET, showed a relatively uniform reduction involving the entire striatum, whereas patients with PD had involvement chiefly of the posterior putamen (Ilgin et al., 1999). F-dopa and F-deoxyglucose PET were abnormal in 5 (33%) individuals among 15 subjects at risk for familial PSP even though they did not (yet) exhibit any symptoms (Piccini et al., 2001). Using ^{11}C -raclopride as a D2 ligand, Brooks and colleagues (1992) showed a 24% reduction in D2 density in the caudate and a 9% reduction in the putamen of patients with PSP. The marked reduction in postsynaptic D2 receptor density probably explains the poor response of PSP to levodopa. Using ^{123}I]β-CIT SPECT, Pirker and colleagues (2000) showed marked reduction of striatal binding in PD, PSP, MSA, and CBD, but the pattern of abnormality (reduction in overall binding and asymmetry) did not allow a differentiation between the various disorders. Using the receptor ligand ^{18}F altanserin, PET scans in 8 patients with PSP showed upregulation of 5-HT_{2A} receptors in the SN and to a lesser degree in the striatum, compared with 13 controls, and these changes significantly correlated with the UPDRS III and PSP-Rating Scale (Stamelou et al., 2009).

In addition to measuring metabolism, neurotransmitters, and receptors, PET technology has advanced to the point of measuring depositions of tau protein. ^{18}F FDDNP is a ligand that can be used to image by PET hyperphosphorylated tau fibrillar aggregates (Kepe et al., 2013). In 15 patients in whom this PET scan was used, ^{18}F FDDNP binding was demonstrated in subcortical areas (e.g., striatum, thalamus, subthalamic region, midbrain, and cerebellar white matter) with progressive involvement as disease severity increased. These findings provide evidence that PET ^{18}F FDDNP imaging is a sensitive tool to detect tau fibrillar aggregates in PSP and may serve as a biomarker for disease progression.

In addition to imaging studies, analysis of the CSF may also be helpful in evaluation of patients with PSP. One study, for example, found a low ratio of light (33 kDa) to heavy (55 kDa) tau protein in the CSF of patients with PSP, which differentiated (without any overlap) this group from other tauopathies such as AD, CBD, and FTD and from synucleinopathies such as PD and DLB (Borroni et al., 2008; Ling et al., 2018). This finding had an 87% sensitivity and 86% specificity and was validated against MRI voxel-based morphometry of brainstem gray matter.

Neuropathology, neurochemistry, and pathogenesis

The motor, neurobehavioral, and neuro-ophthalmic findings in patients with PSP reflect marked neuronal degeneration in the basal nucleus of Meynert, pallidum, subthalamic nucleus (STN), superior colliculi, mesencephalic tegmentum, SN pars compacta (SNpc) and SNpr, LC, red nucleus, reticular formation, vestibular nuclei, cerebellum, and spinal cord (Steele et al., 1964; Jellinger and Bancher, 1993; Hardman et al., 1997a,b; Kanazawa et al., 2009; Kovacs et al., 2020). In addition, in contrast to PD, both the GPi and GPe are markedly affected in PSP, and this may contribute to thalamic inhibition and some of the parkinsonian features (Hardman and Halliday, 1999a,b). Along with the degeneration of the SNpc and the PPN, the glutamatergic caudal intralaminar thalamic nuclei are involved in both PSP and PD (Henderson et al., 2000). The importance of PPN in gait abnormalities, including freezing, is demonstrated by the occurrence of these symptoms after a stroke in this brainstem region (Kuo et al., 2008). In addition there is a widespread loss of A10 dopamine neurons, clearly more severe than in PD (Murphy et al., 2008). Atrophy of the superior cerebellar peduncle has been found to be a frequent finding in the brains of patients with PSP, and this correlates with the duration of the disease (Tsuboi et al., 2003b). In one pathologic study, marked atrophy of the GPi differentiated PSP from PD and DLB. CBD and tau-positive inclusion bodies have been demonstrated in the Purkinje cells of patients with PSP, particularly when associated clinically with ataxia (Kanazawa et al., 2009). Although bladder dysfunction has not been considered a prominent feature in patients with PSP, the finding of neuronal loss in the Onuf nucleus in patients with PSP suggests that bladder function should be carefully evaluated in patients with PSP (Scaravilli et al., 2000).

Based on a workshop sponsored by the National Institutes of Health, the following neuropathologic criteria were proposed: (1) high-density NFTs and neuropil threads in the basal ganglia and brainstem and (2) tau-positive astrocytes or their

processes in areas of involvement (Hauw et al., 1994; Litvan, Agid, et al., 1996). Using rather crude pathologic criteria, De Bruin and Lees (1994) demonstrated that the clinical manifestations of PSP can vary considerably. They reviewed 90 cases reported in the literature between 1951 and 1992 that met the criteria of subcortical neurofibrillary degeneration and exclusion of other recognized nosologic entities. There were 51 men and 34 women (in 5 cases, the sex was not specified), with an average age at onset of 62 years and mean age at death of 67 years. The most common symptoms were unsteady gait (70.7%), stiffness (67.4%), slurred speech (67.4%), falls (60.6%), dysphagia (57.3%), and blurring of vision (21%). Vertical gaze palsy was the most common sign but was noted in 68.5% of all cases, followed by bradykinesia in 67.4%, dysarthria in 67.4%, rigidity in 58.4%, axial dystonia in 48.3%, segmental dystonia in 20.2%, and tremor in 16.8%.

Microscopic examination reveals NFTs, granulovacuolar degeneration, gliosis, and rare Lewy bodies (Steele et al., 1964; De Bruin and Lees, 1994). One pathologic study showed no evidence of increased Lewy bodies in PSP (Tsuboi et al., 2001). The NFTs in PSP differ from those seen in AD and other neurodegenerative disorders in that PSP tangles consist of 15-nm straight tubules rather than 20- to 24-nm-wide paired helical filaments (PHFs) (Jellinger and Bancher, 1993; Dickson, 1997). PHFs are composed of the microtubule-associated protein tau (MAPT) in a hyperphosphorylated state. In contrast to the other neurodegenerative diseases with tau pathologic processes, such as AD, Pick disease, CBD, and the parkinsonism-dementia complex of Guam, which are characterized by flame-shaped NFTs, the NFTs in PSP are predominantly of the globose type. The tau-containing astrocytic inclusions ("tufted astrocytes") are more common in the basal ganglia and the brainstem of PSP, whereas they are more common in the cortex of brains of CBD. Tau inclusions in PSP oligodendrocytes are described as "coiled bodies."

Several clinicopathologic studies have attempted to establish criteria that separate PSP from other, related disorders. In 60 cases of patients clinically diagnosed with PSP, 47 (78%) of which were pathologically proven, false-positive diagnoses included PD combined with cortical Lewy body pathologic findings or AD, MSA, CBD, Pick disease, motor neuron disease (Gilbert et al., 2010), cerebrovascular disease, and FTD.

Pathologically documented cases of PSP without ophthalmoparesis have been reported (Davis et al., 1985; Daniel et al., 1995). When PSP patients with ophthalmoparesis were compared with those without ophthalmoparesis, no differences in the pathologic findings of the two groups were noted and there was no correlation between the severity of clinical symptoms and degenerative changes (Daniel et al., 1995). In another pathologic study, brains of patients with PSP who had gaze palsy had 2-fold greater loss of neurons in the substantia nigra reticulata (SNr) (Halliday et al., 2000). Because SNr projects to the superior colliculi, degeneration of SNr might contribute to the limitation of eye movements.

The clinical and pathologic overlap between PSP, CBD, and AD provides evidence that these disorders are closely related, although the absence of amyloid deposits in PSP and CBD suggests a clear difference between the two disorders and AD (Feany and Dickson, 1996; Litvan et al., 1999; Rossor et al., 1999; Boeve, Lang, et al., 2003; Wakabayashi et al., 2004; Galpern and Lang, 2006; Kouri et al., 2011; Ling et al., 2014).

Among 180 cases of clinically diagnosed PSP that came to autopsy, 137 (36%) met the pathologic criteria for PSP (Josephs and Dickson, 2003). The other diagnoses included CBD, MSA, DLB, and CJD. The following features were seen more frequently in non-PSP cases than in PSP cases: tremor, psychosis, early dementia, asymmetrical findings, absence of H1 haplotype, and presence APOE ϵ 4. The various disorders can be differentiated by a careful histologic examination. For example, the tau in NFTs of AD shows marked ubiquitin immunoreactivity, whereas the NFT-tau from PSP does not (Flament et al., 1991; Shin et al., 1991). Cdk5, a kinase that is physiologically involved in the phosphorylation of tau protein, is overexpressed in PSP brains (Borghi et al., 2002). PSP and CBD also overlap with FTD in clinical, pathologic, biochemical, and genetic aspects (Boeve, Lang, et al., 2003). Tuft-shaped astrocytes seem to be more indicative of PSP than CBD with prominent tuft-shaped astrocytes in the precentral gyrus and premotor cortex, caudate, putamen and globus pallidus, red nucleus, and superior colliculus in PSP brains (Hattori et al., 2003). Another pathologic evidence of overlap between PSP and CBD is the abundance of pathologic tau in the white matter in both disorders (Zhukareva et al., 2006). In one study there appeared to be more tau burden pathologic findings in cortical regions away from the basal ganglia, suggesting that PSP-CBS is a "cortical" PSP variant, which also seems to have less severe neuronal loss in the dorsolateral and ventrolateral subregions of the SN and more severe microglial response in the corticospinal tract than in classic PSP (Ling et al., 2014).

The histopathologic features of PSP also overlap closely with those of postencephalitic parkinsonism (Litvan et al., 1998; Vilensky et al., 2010a,b) and the parkinsonism-dementia complex of Guam, but the pallidum and the STN are usually spared in the former, and the cortex seems to be more involved in the latter. Rarely, cases with clinical presentation nearly identical to that of PSP have been reported to have the pathologic picture of pallidonigrolusian atrophy (PNLA) (Ahmed et al., 2008; Wong et al., 2013). Of 400 cases of PSP, 8 (2%) were found to have pathologic features of PSP, and PNLA is now considered a rare variant of PSP, with the latter usually presenting at a younger age, with gait and handwriting abnormalities in early stages, and having slower progression (Ahmed et al., 2008). In 25 cases of pathologically proven PNLA the mean age at onset was 54.3 ± 14.3 years and average duration of disease was 7.9 ± 5.8 years (Wong et al., 2013). In addition to gait or balance disturbance, seen essentially in all cases, chorea was encountered in 20% and 36% had coexistent motor neuron disease. Besides extensive gliosis, many brains showed iron-positive pigments in the pallidonigrolusian system, and p62-positive glial inclusions without evidence of tauopathy.

Although tau pathology is the most characteristic feature of PSP it is typically combined with other pathological abnormalities (Jecmenica et al., 2020). In one study, only 8% of 101 patients presented with pure PSP pathology; other copathologies included AD (84%), argyrophilic grains (58%) in combination with other proteinopathies or cerebrovascular disease (Kovacs et al., 2020). In another study, 54% of pathologically proven cases of PSP had coexistent AD and PD, providing evidence for overlap between these neurodegenerative disorders (Gearing et al., 1994). Calbindin-D28k

immunoreactivity, normally found in the medium-sized neurons and neuropil of the striatal matrix, globus pallidus (GP), and SNpr, is reduced in the GP of patients with PSP (and in striatum and SNpr of patients with SND). This finding suggests that calcium cytotoxicity might play a role in the marked neuronal degeneration that is found in these structures.

PSP and CBD also share pathologic tau doublet (64 and 69 kDa) and the predominance of 4R tau isoforms with argyrophilic grain disease (AGD). This sporadic neurodegenerative disease, which accounts for about 5% of all cases of dementia, is manifested by late-onset episodic memory loss and progressive dementia along with personality changes, irritability, agitation, delusions, and apathy. Neither clinical nor neuroimaging features can reliably differentiate between AGD and AD, and the diagnosis of AGD is based on autopsy findings. Pathologically, aggregated tau proteins are found in limbic structures in the shape of distinct argyrophilic grains and coiled bodies (Tolnay et al., 2002; Liang et al., 2005; Ferrer et al., 2008). Because of overlap in pathologic features with not only PSP and CBD, but also AD and other neurodegenerative diseases, questions have been raised whether AGD represents a distinct entity. Argyrophilic grains are present in 4% to 9% of adult brains and the incidence increases with age. Besides aging, oxidative stress appears to play a critical role in the development of the pathologic changes, including activation of tau kinases, which facilitate tau hyperphosphorylation in some neurons. The abnormal tau apparently binds to p62 and, after ubiquitination, aggregates, forming grains and tangles. Thrombin, which accumulates in the grains, has been thought to facilitate tau truncation, which further increases oxidative stress and contributes to the toxicity.

Molecular misreading of the ubiquitin-B (UBB) gene results in a dinucleotide deletion in ubiquitin-B mRNA, which in turn leads to accumulation of the mutant protein ubiquitin-B+1 in AD, Pick disease, FTD, PSP, and AGD, but not in synucleinopathies (PD or MSA) (Fischer et al., 2003) (see Fig. 9.1). This finding provides evidence that the ubiquitin-proteasome system is impaired in these tauopathies and that ubiquitin-B+1 protein serves as a marker for these diseases. Unique haplotype in 17q21, found in 16% of Spanish and American PSP patients but not in any of the controls, provides further evidence that PSP is a form of a tauopathy (Pastor et al., 2004). Better understanding of the molecular pathways that are altered in various neurodegenerative disorders could be helpful in differential diagnosis based on postmortem examination of brain tissue.

Tsuboi and colleagues (2003a) showed that APOE ϵ 4 is a risk factor for AD-type pathologic features in PSP. Some brains of patients with Guam parkinsonism–dementia complex also contain deposits of the TDP-43 protein (transactive response DNA binding protein 43 kDa), which binds ubiquitin, suggesting that a common pathogenic mechanism through conformational changes in this protein links this disease with FTDP, ALS, and related neurodegenerative diseases.

The marked reduction in striatal D2 receptors in PSP, demonstrated by PET studies, also has been documented in postmortem studies (Ruberg et al., 1993). In contrast to the D2 receptors, the striatal D1 receptors are spared (Pascual et al.,

1992). Biochemical studies show that in addition to degeneration of the nigrostriatal dopaminergic system, the cholinergic and GABAergic systems seem to be particularly affected. Cholinergic neurons have been found to degenerate in the Edinger–Westphal nucleus, the rostral interstitial nucleus of Cajal (possibly contributing to the extensor nuchal rigidity), the medial longitudinal fasciculus (contributing to vertical gaze palsy), the superior colliculus, and the PPN. Autoradiographic study of 18 brains of patients with pathologically confirmed PSP showed marked reduction in M2 and M4 receptors in the posterior striatal cholinergic interneurons and a reduction of M4 receptors on medium spiny projection neurons, confirming marked cholinergic dysfunction in PSP compared with DLB ($n = 45$), AD ($n = 39$), and normal controls ($n = 50$) (Warren et al., 2007). Using the technique of an in situ hybridization of GAD₆₇ messenger RNA, Levy and colleagues (1995) demonstrated 50% to 60% reduction in the number of neurons expressing GAD₆₇ messenger RNA in the caudate nucleus, ventral striatum, and both segments of the GP in three brains of patients with PSP. They suggest that the marked destruction of the basal ganglia output nuclei might explain the poor response to dopaminergic therapy in this disorder.

The most striking neurochemical abnormalities found in PSP brains are a marked reduction in striatal dopamine, dopamine receptor density, choline acetyltransferase activity, and loss of nicotinic, rather than muscarinic, cholinergic receptors in the basal forebrain (Ruberg et al., 1993). Normal dopamine levels in the nucleus accumbens suggest that the mesolimbic system is relatively spared. Because of the relative sparing of the mesocorticolimbic dopaminergic system in contrast to the severe degeneration of the mesostriatal system, some investigators have suggested that the primary site of pathologic findings in PSP is the striatum and that the changes observed in the SN are simply a result of a retrograde degeneration (Ruberg et al., 1993). The cholinergic neurons are, however, also markedly affected and may be primarily involved in PSP. The cholinergic innervation of the thalamus is particularly affected in PSP, and this finding helps to differentiate PSP from PD (Shinotoh et al., 1999). In addition, reduction in acetylcholine vesicular transporter has been found to differentiate PSP from other types of neurodegenerative disorders (Suzuki et al., 2002). Suzuki and colleagues (2002) were able to correlate reductions in acetylcholine vesicular transporter and choline acetyltransferase activity in the striatum of postmortem brains of patients with PSP, but choline acetyltransferase was also significantly reduced in the inferior frontal cortex. Glutamate has been found to be increased in the striatum, pallidum, nucleus accumbens, and occipital and temporal cortex. In contrast to PD, glutathione was found to be increased in the SN of PSP patients (Perry et al., 1988). The observation that multiple neurotransmitters, particularly dopamine and acetylcholine, are affected in PSP suggests that PSP is not a primary neurotransmitter disease but a disorder in which multiple subpopulations of neurons degenerate for yet unknown reason.

The cause of PSP is unknown, but oxidative damage, mitochondrial dysfunction, and abnormal protein (e.g., tau) processing have received the most attention (Albers and Augood, 2001) (Fig. 9.7). Decreased rates of adenosine

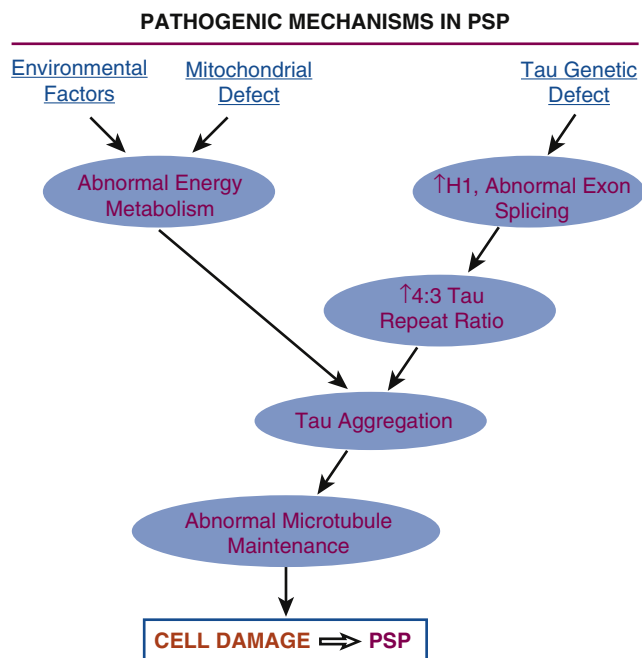


Fig. 9.7 Presumed pathogenesis is progressive supranuclear palsy (PSP).

triphosphate production were found in a preliminary study of muscle mitochondria function in patients with PSP, suggesting impaired mitochondrial respiratory chain activity in PSP (Di Monte et al., 1994). Further support for mitochondrial defect in PSP was later provided by additional studies. Using cytoplasmic hybrid (cybrid) lines expressing mitochondrial genes, Swerdlow and colleagues (2000) found a 12.4% decrease in complex I activity ($P < 0.005$) in cybrid cells but no change in complex IV activity. Cybrid cells also had significantly increased levels of several antioxidant enzymes. This study suggests a mtDNA-encoded electron transport chain enzyme defect in PSP. Further evidence for a defect in mitochondrial oxidative metabolism is the finding of significantly reduced levels of phosphocreatine and Mg^{++} and increased levels of adenosine diphosphate (ADP) and inorganic phosphate using phosphorus magnetic resonance spectroscopy of the brain and calf muscle in five PSP patients (Martinelli et al., 2000). Using proton magnetic resonance spectroscopic imaging, Tedeschi and colleagues (1997) found a reduced ratio of N-acetylaspartate to creatine-phosphocreatine in the brainstem, centrum semiovale, and frontal and precentral cortex and N-acetylaspartate/choline in the lentiform nucleus in patients with PSP. Based on the hypothesis that exposure to chemicals such as complex I mitochondrial enzyme inhibitors could increase the risk for PSP, the ENGINE-PSP, a multicenter case-control study, found that that living in an agricultural area is a potential risk factor for PSP and having a college degree is protective (Litvan et al., 2016).

Research into mechanisms and treatment of PSP has been hampered by paucity of suitable animal models. Rats that are exposed systemically and chronically to annonacin, a lipophilic mitochondrial complex I inhibitor extracted from tropical fruit plants, have been shown to produce neurodegeneration resembling PSP, providing further evidence of mitochondrial dysfunction in PSP (Champy et al., 2004; Stamelou et al., 2019). Another potential animal model of

PSP is a transgenic mouse (TgT34) that overexpresses wild-type human tau (T34 tau isoform) driven by the astrocyte-specific glial fibrillary acidic protein promoter (Forman et al., 2005). These transgenic mice accumulate tau in astrocytes, similar to what occurs in PSP, leading to focal neuronal degeneration. Another potential animal model of PSP is the JNPL3 mouse, in which the human four-repeat tau with the P301L mutation is expressed resulting in a severe phenotype within 5 to 6 months but without motor defects (Lewis et al., 2000).

Although PSP is considered a sporadic disorder, familial cases of PSP phenotype have been reported (Jabbari et al., 2019). The supranuclear ophthalmoparesis, however, was not well documented in many of the familial cases, and the presence of atypical features, such as early cognitive decline in the family reported by Brown and colleagues (1993) and the relatively early age at onset (53 years) in the de Yebenes and colleagues (1995) kindred suggested that these families had a neurodegenerative disorder that was distinct from idiopathic PSP. Furthermore, no linkage to the tau gene (*MAPT*) has been identified in any of these families, although linkage to 1q31.1 has been demonstrated in one large Spanish family (Ros et al., 2005). In a comprehensive epidemiologic-genetic study, 33% of individuals with PSP were found to have at least one first-degree relative with dementia or parkinsonism and 12 families with PSP were identified (5 cases were pathologically confirmed), but the intrafamily phenotype was very variable, the P301L *MAPT* mutation was identified in only one patient, and there were other limitations in obtaining the family and medical information (Kaat et al., 2009). Homozygous mutations, such as deletion at codon 296 in the *MAPT* gene, was identified in one atypical case of PSP (Ferrer et al., 2003). The presence of subhaplotype overrepresented in individuals with PSP increases the risk for the disease. Of the two haplotypes that span an area that contains the *MAPT* gene, H1 haplotype and its H1c subhaplotype are disproportionately present in patients with PSP; the less common variant, the H2 haplotype, appears to be protective. There are several *MAPT* H1 subhaplotypes that have been identified as risk factors for PSP and for severity of the disease (Heckman et al., 2019). The H1 and H2 haplotypes influence the risk for not only PSP but also CBD.

Several studies have drawn attention to abnormal phosphorylation of tau proteins as an important mechanism of neurodegeneration in PSP. Tau exon 10 + 16 mutation in the tau gene (*MAPT*, IVS10, C-U, +16) was found in a case of young-onset (age 40 years) PSP phenotype with neuropathologic features of FTD (Morris et al., 2003). Tau is phosphorylated by serine, threonine, and tyrosine kinases, and this phosphorylation might lead to abnormal aggregation. There is growing support for the notion of altered regulation of tau gene expression in PSP (Rademakers et al., 2005). All three have neurologic functions. MOBP is a protein associated with myelin, STX6 is involved in membrane recycling, and EIF2AK3 is involved in translating RNA to protein and it signals cells to stop making proteins when abnormal proteins start to accumulate inside cells. In another GWAS study, involving 152 CBD cases and 3311 controls, and 67 CBD cases and 439 controls in a replication stage, an association was found with *MAPT* at 17q21 (which codes for tau protein) at and with MOBP at 3p22 (which

codes for myelin-associated oligodendrocyte basic protein) and concluded that CBD and PSP share a genetic risk factor at these two loci (Kouri et al., 2015; Stamelou et al., 2019). Genes coding for protein kinase R-like endoplasmic reticulum kinase (*PERK*; *EIF2AK3*) may also increase the risk for PSP. Another gene implicated in the pathogenesis of PSP is *CXCR4*, whose product participates in microglial activation, which correlates with tau pathologic findings in PSP. Posttranslational hyperphosphorylation increases the propensity of tau to aggregate and hinders its interaction with microtubules (Stamelou et al., 2019).

The relationship between abnormalities in tau and PSP is described in detail in the section on tauopathies (Ling et al., 2018). It should be noted that tau pathology is also increasingly recognized not only in the classic tauopathies but also in PD (Pan et al., 2021). In addition to tau pathology the role of microglial activation in the pathogenesis of PSP and other neurodegenerative disorders is receiving growing attention from many researchers (Alster et al., 2020).

Treatment

Although in the early stages mild improvement in parkinsonian symptoms may be noted with levodopa or dopamine agonists (e.g., pergolide, pramipexole), most PSP patients fail to reach and maintain any meaningful improvement with these drugs (Jankovic, 1983; Weiner et al., 1999). The most likely reason is that in PSP, there is a marked loss of the post-synaptic receptors, particularly the D2 receptors, secondary to the loss of the postsynaptic striatal neurons. Idazoxan, an experimental potent and selective α_2 presynaptic inhibitor that increases NE transmission, was shown in a double-blind crossover study to improve motor function in nine PSP patients (Ghika et al., 1991). Physostigmine has been shown to have variable clinical effects on cognitive deficits (Blin et al., 1995). Furthermore, PSP patients have been found to be unusually sensitive to cholinergic blockade with anticholinergic drugs (Litvan et al., 1994); therefore, these drugs should be avoided in patients with PSP. On the other hand, the cholinergic drug donepezil has not been found to be beneficial in a placebo-controlled trial of 21 patients with PSP, and it might actually worsen motor function (Litvan, Phipps, et al., 2001). Other drugs, including methysergide and amitriptyline, although anecdotally reported to be beneficial, have been generally disappointing (Newman, 1985). Besides amitriptyline and serotonin uptake inhibitors, dextromethorphan/quinine (DM/Q) has been used to treat involuntary emotional expression disorder, or pseudobulbar affect, also known as emotional lability or incontinence (Panitch et al., 2006; Rosen and Cummings, 2007; Pioro et al., 2010). Zolpidem, a gamma-aminobutyric acid (GABA) agonist and a short-acting hypnotic drug, was found to improve moderately voluntary saccadic eye movements and motor function in a small ($n = 10$) group of patients with PSP compared with placebo (Daniele et al., 1999). Blepharospasm, with or without eyelid freezing, and other forms of focal dystonias, can be effectively treated with botulinum toxin injections (Jankovic, 2004) (Video 9.9). Electroconvulsive therapy, although helpful in some patients with PD, markedly exacerbated motor and mental symptoms in one patient with PSP. Cricopharyngeal myotomy is almost never performed, but severe dysphagia in advanced stages of the disease often necessitates the placement a feeding

gastrostomy. There is no evidence, however, that tube feeding prevents aspiration (Finucane et al., 1999). ●

Only symptomatic therapy has been used thus far, albeit with disappointing results, but it is hoped that better understanding of the pathogenesis of neuronal degeneration in PSP will lead to more effective, hypothesis-driven therapeutic interventions. It is possible, for example, that because cross-linking of tau protein by transglutaminase stabilized tau filaments into NFTs, inhibitors of transglutaminase may prevent the formation of NFTs and may have a neuroprotective effect on the disease (Zemaitaitis et al., 2000). Glycogen synthase kinase-3 (GSK-3 β) (also known as tau protein kinase I) phosphorylates tau on multiple sites that regulate microtubule stability and function. This enzyme has been found to be overexpressed in tau deposits of PSP brains, and it has been postulated that hyperphosphorylation of tau leads to formation of NFTs, which triggers neurodegenerative processes, such as inflammation, apoptosis, impaired axonal transport, reduced synaptic plasticity, and inhibition of long-term potentiation, and that inhibition of GSK-3 may potentially prevent PSP-related neurodegeneration (Tolosa et al., 2014). For example, drugs such as lithium and valproic acid that inhibit abnormal phosphorylation of the tau protein by blocking the enzyme glycogen synthase kinase (GSK-3 β ; also known as tau protein kinase I) might possibly exert neuroprotective effects (Chen et al., 1999). Lithium has been found to induce phosphorylation of the serine 9 residue of GSK-3 β , inhibiting tau phosphorylation on the PHF-1 epitope, and, therefore, this GSK-3 β inhibitor may have neuroprotective properties in various tauopathies, including PSP. Besides GSK-3, lithium also inhibits inositol monophosphatase and the proteasome, protects cultured neurons against A β toxicity, prevents NFT accumulation, and causes downregulation of tau proteins by reducing tau mRNA (Rametti et al., 2008). By limiting tau phosphorylation, valproate would be expected to prevent the disturbed microtubule function, disrupted intracellular protein trafficking, formation of NFTs, and neuronal death. Valproate might also prevent elevations of intracellular calcium, increase levels of the antiapoptotic protein Bcl-2, act as a histone deacetylase inhibitor (which might interfere with apoptosis), and inhibit GSK-3 β (Phiel et al., 2001; Qing et al., 2008). In the Tau Restoration on PSP (TAUROS) study, a double-blind, placebo-controlled, randomized trial of tideglusib, a GSK-3 inhibitor, 146 PSP patients with mild to moderate PSP were enrolled and randomized to receive once-daily 600 mg tideglusib, 800 mg tideglusib, or placebo (ratio, 2:2:1) (Tolosa et al., 2014). No significant differences were detected in the primary or secondary endpoints at week 52 between placebo and either dose of tideglusib. Other kinase inhibitors, such as noscavine and olomoucine, might also play a role as potential therapeutic strategies in PSP (Boxer et al., 2017).

Because of some evidence of mitochondrial complex I dysfunction in PSP (Di Monte et al., 1994), mitochondrial enhancers, such as coenzyme Q10, have been studied in PSP. One randomized, placebo-controlled, phase II trial involving 21 patients with PSP showed slight but significant improvements in the scores of the total PSP Rating Scale and Frontal Assessment Battery in the group treated with a nanoparticulate emulsion of complex I dysfunction in PSP (Di Monte et al., 1994), mitochondrial enhancers, such as lipophilic emulsion, nanoQuinon (5 mg/kg) compared with

Video 9.9 Progressive supranuclear palsy (PSP).

placebo (Stamelou et al., 2008). This was accompanied by a significant reduction in ADP on magnetic resonance spectroscopy (MRS) in the occipital lobe and right basal ganglia. These encouraging findings from the initial study must be confirmed by a larger, phase III clinical trial. Another drug, methylene blue (Urolene Blue), an old drug used for the treatment of urinary tract infections, thought to prevent formation of tangles in AD at doses of 60 mg three times a day of methylthioninium chloride, may be potentially helpful in PSP. It is not clear whether the drug acts as a kinase inhibitor, but it has been shown to increase mitochondrial complex IV and have a variety of antioxidant properties (Atamna et al., 2008). Another drug that is currently being investigated in PSP is davunetide, an analog of vasoactive intestinal peptide that enhances the synthesis of the activity-dependent neuroprotective protein, of which davunetide is a fragment (also known as NAP), administered as a nasal spray. In pre-clinical studies, this neurotrophic factor promoted microtubule stability, reduced tau phosphorylation, stimulated neurite elongation and synapse formation, and prevented toxicity from amyloid beta peptides (Shiryaev et al., 2009). However, in a double-blind, parallel group, phase II/III trial involving 313 patients randomly assigned to davunetide or placebo, 241 (77%) of whom completed the study, no differences were found between davunetide and placebo groups in the effects on the PSPRS or any other outcome measures (Boxer et al., 2014). The phase II PASSPORT study of gosuranemab (BIIB092), a humanized monoclonal antibody that targets N-terminal tau, failed to meet the primary endpoint, as measured by the PSPRS at week 52. Various other strategies designed to prevent the accumulation or enhance the clearance of misfolded tau protein, including intravenous administration of UCB0107, a recombinant humanized IgG4P monoclonal antibody with specificity for human tau (NCT04185415), are currently in development.

Deep brain stimulation of the PPN provided only partial and transient improvement in two patients (Hazrati et al., 2012).

Corticobasal degeneration

Clinical features and natural history

In 1968, Rebeiz and colleagues (1968) reported 3 patients of Irish descent with parkinsonism, myoclonus, supranuclear palsy, and apraxia who were found at autopsy to have "corticodentatonigral degeneration with neuronal achromasia." Cerebellar deficit is not a feature of the disorder, and, therefore, the term was changed to *corticobasal ganglionic degeneration* and later to *corticobasal degeneration* (Mahapatra et al., 2004). The initial reports of CBD were based on clinicopathologic characteristics. Subsequently, the term corticobasal syndrome (CBS) has been suggested as more appropriate in order to draw attention to the marked clinical heterogeneity and to emphasize that CBD pathologic features may be encountered in PSP, FTD, speech apraxia, primary progressive aphasia (PPA), and the posterior cortical atrophy syndrome (Kouri et al., 2011; Josephs et al., 2013; Mesulam et al., 2013). The most striking features of CBD include marked asymmetry of involvement; focal rigidity and dystonia with or without contractures (Fig. 9.8); and hand, limb, gait, and speech apraxia (Video 9.10). Although



Fig. 9.8 Dystonia in corticobasal degeneration (CBD). Among 66 patients with CBD 59% had dystonia and of those, 92% had arm dystonia as noted in this woman with CBD. (Reproduced from Vanek Z, Jankovic J. Dystonia in corticobasal degeneration. *Mov Disord.* 2001;16:252–257.)

one of the most asymmetrical neurodegenerative disorders, a symmetrical form of CBD has been described (Hassan et al., 2010). This series of 5 pathologically proven patients, however, had many atypical features, such as absence of limb dystonia, myoclonus, apraxia, or alien hand, and 40% had positive family history, suggesting the possibility of a disorder other than CBD, despite its pathologic overlap with typical CBD. Some patients with CBD manifest coarse rest and action tremor, and cortical-type focal myoclonus (Video 9.1). In some cases, cognitive decline may precede these classic features (Bergeron et al., 1998). Other cortical features include cortical sensory deficit, language and speech alterations (Özsancak et al., 2000), frontal lobe symptomatology, depression, apathy, irritability, and agitation (Litvan, Cummings, et al., 1998; Lee et al., 2011). In some clinics, particularly those specializing in dementia, frontal lobe involvement, rather than parietal or basal ganglia, may be the presenting symptoms of CBD (Lee et al., 2011). In one study, the authors compared three published diagnostic criteria for clinically diagnosed CBD in a group of 40 consecutive patients (22 men, mean age 67 years) with focal cortical syndrome characterized by apraxia and parkinsonism, and found that 30 patients (75%) satisfied all three criteria (Mathew et al., 2012). They proposed their own diagnostic criteria (the Cambridge criteria) which include not only the motor and sensory features but also cognitive features, especially speech and language impairment, frontal executive dysfunction, and visuospatial deficits. ►

The asymmetrical onset differentiates CBD from most other neurodegenerative disorders, and some patients who have

Video 9.10 Corticobasal degeneration (CBD).

been categorized as having “asymmetrical cortical degenerative syndrome” (Caselli et al., 2000) might have CBD. In a study of 14 patients with pathologically confirmed CBD, Wenning and colleagues (1998) found that asymmetrical hand clumsiness was the most common presenting symptom, noted at onset in 50% of the patients. At the time of the first neurologic visit, about 3 years after onset, the following signs were present: unilateral limb rigidity (79%), bradykinesia (71%), ideomotor apraxia (64%), postural imbalance (45%), unilateral limb dystonia (43%), and cortical dementia (36%). The mean age at onset was 63 ± 7.7 years; the mean duration of symptoms from onset to death was 7.9 ± 0.7 years (range, 2.5–12.5). Patients with early bradykinesia, frontal syndrome, and two of the following three—tremor, rigidity, and bradykinesia—had a poor prognosis. These clinical features are similar to those described earlier by Rinne and colleagues (1994), who reviewed 36 patients (20 women and 16 men), with a mean age at onset of 60.9 ± 9.7 years (range, 40–76). In patients reported by Riley and colleagues (1990), the mean age at onset was 60 years (range, 51–71), and men were more commonly affected than women (3:2). Two patients died 7 and 10 years after disease onset. In a series of 147 cases collected from eight centers, the following features were most common: parkinsonism (100%), higher cortical dysfunction (93%), dyspraxia (82%), gait disorder (80%), dystonia (71%), tremor (55%), myoclonus (55%), alien limb (42%), cortical sensory loss (33%), and dementia (25%) (Kompoliti et al., 1998). In one clinicopathologic study, the presence of varying combinations of early frontal-lobe type behavioral symptoms, nonfluent language disturbance, orobuccal apraxia, and utilization behavior were predictive of CBD rather than AD pathologic findings (Shelley et al., 2009).

The typical features of CBD can be categorized into movement disorders (akinesia, rigidity, postural instability, limb dystonia, cortical myoclonus, and postural/intention tremor) and cortical signs, such as cortical sensory loss, apraxias (ideational and ideomotor) (Video 9.10), the alien limb phenomenon (Video 9.11), and cognitive features (speech and language impairment, frontal executive dysfunction, and visuospatial deficits) (Riley et al., 1990; Rinne et al., 1994; FitzGerald et al., 2007; Brainin et al., 2008; Mathew et al., 2012; Bhidayasiriet et al., 2019). The alien hand syndrome occurs not only in CBD but also other disorders, including strokes involving the genu or anterior rostrum of the corpus callosum and the contralateral frontomedial cortical and subcortical regions (Brainin et al., 2008). Ideomotor apraxia, possibly secondary to involvement of the supplementary motor area and characterized by not knowing “how to do it” (as opposed to not knowing “what to do” in ideational apraxia), is the most typical form of apraxia (Leiguarda and Marsden, 2000; Zadikoff and Lang, 2005; Wheaton and Hallett, 2007; Leiguarda et al., 2014). This apraxia may improve with tactile stimulation, such as the use of the appropriate tool (Graham et al., 1999). Using the De Renzi ideomotor apraxia test, Soliveri and colleagues (2005) compared limb apraxia in patients with CBD ($n = 24$) and PSP ($n = 25$). They found that “awkwardness errors,” conceptually appropriate but clumsily executed actions because of fine finger motility, were the most common apraxic error in patients with CBD, followed by spatial errors, characterized by incorrect orientation or trajectory of the arm, hand, or digits in space or in

relation to the body. Sequence errors, incorrect sequences of actions or inappropriate repetition of movements, were least impaired in CBD. The order of impairment was reversed in patients with PSP. Overall, apraxia, particularly ideational or limb-kinetic apraxia, was more frequent and more severe in patients with CBD than in those with PSP, in whom ideomotor apraxia appears more common. Limb contractures, often preceded by the alien hand phenomenon, are more common in this condition than in the other parkinsonism-plus syndromes (Leiguarda and Marsden, 2000). This anterior or motor alien hand syndrome must be differentiated from sensory or posterior syndrome associated with a lesion in the thalamus, splenium of corpus callosum, and temporal-occipital lobe (Hakan et al., 1998). The new consensus CBD criteria were applied to patients with pathologic features consistent with those of CBD and those considered CBD mimics without confirmatory pathologic findings (Alexander et al., 2014). This study addressed two questions: whether the criteria identified CBD pathology and what clinical criteria distinguished CBD from CBD mimics. Of 19 patients with confirmed CBD pathologic features, 9 were diagnosed as probable CBD at presentation, and 12 of 19 were diagnosed by death. This was similar to using the previous criteria and thus did not improve diagnostic accuracy. Of 14 patients without CBD pathologic features, 14 met criteria for probable or possible CBD using new diagnostic criteria. Thus, the new criteria identified a broader spectrum of phenotypes for CBD but had a low specificity for clinical diagnosis. No clinical features distinguished the CBD group and CBD mimics.

In autopsy-proven cases of CBD, the following were found to be the best predictors of the diagnosis of CBD: limb dystonia, ideomotor apraxia, myoclonus, and asymmetrical akinetic-rigid syndrome with late onset of gait or balance disturbance (Litvan, Agid, Goetz, et al., 1997; Wenning et al., 1998). In some cases of CBD, the alien hand phenomenon is associated with spontaneous arm levitation and tactile avoidance, tactile pursuit, or both, each in the opposite limb (FitzGerald et al., 2007). Arm levitation also has been described in PSP, another feature overlapping these two disorders (Barclay et al., 1999). In a study of 66 patients diagnosed with CBD, 39 (59%) had dystonia (Vanek and Jankovic, 2001). In a clinicopathologic study, dystonia was present in 37.5% of 296 cases of CBD (Stamelou et al., 2012).

Neurologic examination often reveals asymmetrical apraxia; oculomotility disturbance, particularly manifested by impaired convergence and vertical and horizontal gaze palsy; bulbar impairment; focal myoclonus; mirror movements; hyperreflexia; or Babinski sign, but no ataxia. In contrast to PSP, the vertical saccades are only slightly impaired in CBD and usually involve only upward gaze. Furthermore, there is a marked increase in horizontal saccade latency in CBD, which correlates well with an apraxia score (Vidailhet et al., 1994).

Focal myoclonus, usually involving one arm, present at rest and exacerbated by voluntary movement or in response to sensory stimulation, resembles typical cortical myoclonus but differs in several features. In contrast to the typical reflex cortical myoclonus, which is characterized by long latency (50 ms in the hand), enlarged somatosensory evoked responses (SEPs), and cortical discharge preceding the movement, the reflex myoclonus associated with CBD is usually not associated with enlarged SEP and has a shorter latency

Video 9.11 Corticobasal degeneration (CBD).

from stimulus to jerk (40 ms) (Thompson et al., 1994). This suggests that the characteristic short-latency reflex myoclonus in CBD represents enhancement of a direct sensoricortical pathway, whereas the more typical reflex cortical myoclonus involves abnormal sensorimotor cortical relays (Strafella et al., 1997).

Using transcranial magnetic stimulation, Valls-Solé and colleagues (2001) found evidence of enhanced excitability or reduced inhibition in the motor area of the hemisphere contralateral to the alien hand sign in patients with CBD. [^{18}F]FDG PET scans in patients with CBD and upper limb apraxia showed marked hypometabolism in the superior parietal lobule and supplementary motor area (Peigneux et al., 2001). In another study of a 70-year-old right-handed man who had alien hand syndrome-related right parietal infarction, functional MRI identified selective activation of contralateral primary motor cortex (M1), presumably released from conscious control by intentional planning systems (Assal et al., 2007). In addition to parkinsonian, aphasia, neuropsychological, and oculomotor deficits, patients with CBD may also present as having progressive spasticity (Hasselblatt et al., 2007).

Although considered by some as “the most common presentation” of CBD (Grimes et al., 1999), in our experience, dementia is a late feature of CBD and semantic memory is usually well preserved (Graham et al., 2003a,b; Murray et al., 2007). This also has been suggested by a clinicopathologic study of 15 patients with CBD followed longitudinally. Despite the persistence of apraxia, impaired executive functioning, and worsening language performance, memory remained relatively preserved (Murray et al., 2007). CBD-type syndrome, however, may be the main clinical manifestation of AD (Chand et al., 2006), and some patients with clinical presentation consistent with FTD have been found to have CBD at autopsy (Mathuranath et al., 2000).

There are three PPA syndromes: (1) Progressive nonfluent aphasia (PNFA), characterized by effortful speech with agrammatism and speech apraxia; (2) semantic PPA or semantic dementia (SemD), which involves fluent speech with loss of word and object meaning; and (3) logopenic progressive aphasia (LPA), characterized by word-finding pauses, moderate anomia, and impaired repetition of sentences (Kertesz et al., 1994; McMonagle et al., 2006; Rohrer et al., 2008; Mendez, 2010; Gorno-Tempini et al., 2011; Grossman, 2012; Teichmann et al., 2013). Agrammatic PPA is characterized by syntactic deficits often accompanied by a motor speech disorder that causes distortion of word sounds; logopenic PPA is characterized by word-finding difficulties and anomia, often accompanied by phonologic errors, but the distinction between motor speech and phonologic deficits is often difficult. In a study of 13 cases of PPA, selected on the basis of their underlying pathologic findings, all 6 with FTD pathologic features (PPA-FTD) were tau positive and had agrammatic forms of PPA whereas the other 7 underlying AD PPA (PPA-AD) were largely logopenic in type (Kielb et al., 2016). The investigators found significant effects for effortless learning, which was essentially the free recall of the three words and shapes immediately after copying them; those with amnesic AD and PPA-AD were equally impaired on the effortless recall of words and much worse than patients with PPA caused by FTL degeneration. Patients with semantic PPA were not included in this study because

most of them are associated with TDP-43 pathologic features (Hodges, 2016).

Based on analysis of 267 pathologically confirmed CBD cases, 4 CBD phenotypes emerged: CBS, frontal behavioral-spatial syndrome (FBS), nonfluent/agrammatic variant of primary progressive aphasia (naPPA), and PSP syndrome (PSPS) (Armstrong et al., 2013). Criteria for the diagnosis of “probable CBD” include insidious onset and gradual progression for at least 1 year, age at onset 50 years or older, no similar family history or known tau mutations, and a clinical phenotype of probable CBS or either FBS or naPPA with at least 1 CBS feature. The diagnosis of “possible CBD” includes similar criteria, but there are no restrictions on age or family history; tau mutations and less rigorous phenotype fulfillment are allowed. Some patients with PPA present as having the “foreign accent syndrome” (Luzzi et al., 2008). In one study of 10 patients with PPA who were followed prospectively until they became nonfluent or mute, Kertesz and Munoz (2003) found that at autopsy, all had evidence of FTD: CBD in 4, Pick body dementia in 3, and tau and synuclein negative ubiquitinated inclusions of the motor neuron disease in 3. In another clinicopathologic study involving 52 patients, 25 met one of the 3 PPA classifications (13 logopenic, 8 nonfluent/agrammatic, and 4 semantic); the others had aphasic syndromes that could not be classified (Harris et al., 2013). In 13 patients with PPA studied at the Mayo Clinic, 5 (61%) evolved into a PSP-like syndrome and apparently none into CBD (Josephs et al., 2014).

PPA is sometimes confused with the syndrome of slowly progressive anarthria that is seen in the late anterior opercular syndrome (see later), but in the latter syndrome, there is no associated language or cognitive deficit. Imaging studies have shown that PPA is often associated with atrophy in the left frontotemporal region, and other areas such as the fusiform and precentral gyri and intraparietal sulcus are activated, possibly as a compensatory neuronal strategy (Sonty et al., 2003). These and other studies provide evidence that PPA is related to dissociation for grammatical and working memory aspects of sentence processing within the left frontal cortex. Patients presenting with nonfluent PPA, early severe dysarthria, relatively selective white matter atrophy at presentation, and a greater rate of change in the brainstem measured by longitudinal imaging may suggest underlying PSP rather than CBD (Santos-Santos et al., 2016).

Maurice Ravel, the well-known French composer, was thought to have PPA, which later evolved to right hand apraxia and other features of CBD (Amaducci et al., 2002). Another patient with PPA, a scientist with an interest in visual arts, became fascinated with Ravel’s *Bolero* and during the evolution of her own PPA, transformed the musical elements of the piece into visual form (“transmodal art”) (Seeley et al., 2008). Despite severe degeneration in the left inferior frontal-insular, temporal, and striatal regions, this new creativity was associated with increased gray matter volume and hyperperfusion in her right posterior neocortex on various neuroimaging studies. This form of synesthesia has been described in a variety of disorders, present to a variable degree in up to 4% of normal individuals (Simner, 2007), but also has been found in patients with thalamic lesions (Ro et al., 2007) and new or increased creativity has been reported in patients with temporal lobe lesion, PD, FTD,

and other neurodegenerative disorders (Pollak et al., 2007; Griffiths, 2008; Mesulam et al., 2008).

Neuropsychological testing in patients with CBD typically shows deficits in frontal-striatal-parietal cognitive domains, including attention/concentration, executive functions, verbal fluency, praxis, language, and visuospatial functioning. Patients also exhibit impaired graphesthesia and may present with visuospatial dysfunction (Tang-Wai et al., 2003). This profile depends on which hemisphere is primarily affected. In one study of 55 patients, CBD was divided into "motor onset" (N = 19) and "cognitive onset" (N = 36) and found that language is more impaired in the latter, but there was no correlation between side of atrophy or motor impairment and the severity of language dysfunction (McMonagle et al., 2006).

There are many neurodegenerative disorders whose phenomenology overlaps with CBD (Williams and Lees, 2009). CBD is probably most frequently confused with PSP, chiefly because of the overlapping oculomotor findings. The CBD patients, however, have much more marked asymmetry in their motor deficits, less severe ophthalmoparesis, and more prominent apraxia and myoclonus. The neuropsychological studies show a pattern of deficits that is different from that seen in PSP or AD. When 21 patients with CBD were compared with a group of patients with AD, the CBD patients performed significantly better than the AD patients on tests of immediate and delayed recall of verbal material, whereas the AD patients (with or without parkinsonian symptoms) performed better on tests of praxis, finger-tapping speed, and motor programming (Massman et al., 1996). The CBD and AD groups all displayed prominent deficits on tests of sustained attention/mental control and verbal fluency and exhibited mild deficits on confrontation naming. The CBD patients endorsed significantly more depressive symptoms on the Geriatric Depression Scale. In addition to an overlap with PSP, behavioral variant of FTD, PPA, CBD cases may also present with the posterior cortical atrophy syndrome (PCAS). Also known as the Benson syndrome, PCAS typically manifests by disturbance in visual perception, Balint syndrome, Gerstmann syndrome, visual agnosia, and alexia. Characterized pathologically by atrophy of the occipitoparietal cortices, PCAS is typically seen in the setting of AD and CJD.

The full spectrum of clinical features typically seen in CBD also can be present in patients with documented Pick disease, but the latter disorder is usually dominated by cognitive, behavioral, and language disturbances, including PPA and semantic dementia (Kertesz and Munoz, 2003). Families with clinical features of Pick disease and the pathologic picture of CBD have been described (Brown et al., 1996). In contrast, apraxia and parkinsonism, if present, are usually late findings in Pick's disease, whereas personality changes, aggressive behavior, disinhibition, cognitive deficits, elements of Klüver-Bucy syndrome, and other features of FTD are common. In a clinicopathologic study of 18 patients followed over a 15-year period, patients with anarthria had a tauopathy, the agrammatics had a ubiquitin-positive, TDP-43 proteinopathy, those with typical SemD had a ubiquitin-positive TDP-proteinopathy, and those with atypical SemD had either CBD or AGD (Deramecourt et al., 2010). In one clinicopathologic study of 33 patients clinically diagnosed

with PPA, CBD and PSP accounted for 12% each (all tauopathies, 36%), of all cases; others included AD (40%), FTD-U (18%) and other causes (Xiong et al., 2011).

Another disorder that progresses rapidly to a nonambulatory state and muteness is motor neuron disease-inclusion body dementia (MND-ID) (Kleiner-Fisman et al., 2004). This entity, a subtype of FTD, which is confirmed only pathologically, usually begins in the patient's midforties and shares some features of CBD. Typically, the patients have early dysphagia suggestive of bulbar palsy but without fasciculations. Pathologically, the brains show severe caudate atrophy, with intracytoplasmic inclusions that stain with antibodies against heavy and light subunits of neurofilaments and against ubiquitin.

Neurodiagnostic studies

Asymmetrical frontoparietal atrophy helps differentiate CBD from PSP (Sitburana and Ondo, 2009). Hyperintensity in the subcortical white matter in the Rolandic region on FLAIR images with asymmetrical atrophy in the cerebral peduncle and atrophy in the midbrain tegmentum also have been described as typical MRI findings in patients with CBD (Koyama et al., 2007). Marked asymmetry of the motor pathways (corticospinal and transcallosal fibers) in CBD also can be demonstrated by diffusion tensor tractography using MR DTI (Boelmans et al., 2009). Despite these reported abnormalities, no specific neuroimaging picture of CBD has emerged, and there is no correlation between antemortem MRI and pathologically confirmed CBD (Josephs et al., 2004). Whereas widespread atrophy on MRI is indicative of a pathologic diagnosis of FTLD-TDP or AD, more focal atrophy predominantly involving the premotor and supplemental motor area is indicative of CBD or PSP pathologic features (Whitwell et al., 2010). Another radiographic abnormality that is occasionally encountered in CBD is the "eye of the tiger" sign on brain MRI, characteristically seen in NBIA1 (Molinuevo et al., 1999). CBD phenotype also has been described in patients with basal ganglia calcification, similar to Fahr disease (Manyam et al., 2001; Warren et al., 2002; Oliveira et al., 2004).

PET scans in patients with CBD show reduced [^{18}F]fluorodopa uptake in the caudate and putamen and markedly asymmetrical cortical hypometabolism, especially in the superior temporal and inferior parietal lobe (Sawle et al., 1991; Blin et al., 1992). In one study, [^{123}I]β-CIT SPECT showed marked asymmetry in reduced striatal binding in patients with CBD, similar to PD, but this did not allow reliable differentiation among PD, PSP, MSA, and CBD (Pirker et al., 2000).

Neuropathology, neurochemistry, and pathogenesis

Pathologic features in CBD include neuronal degeneration in the precentral and postcentral cortical areas, degeneration of the basal ganglia, including the SN, and the presence of achromatic neural inclusions seen not only in the cortex, but also in the thalamus, STN, red nucleus, and SN (Lowe et al., 1992). These ballooned neurons, characterized by perikaryal swelling, dispersion of Nissl substance, eccentrically located nucleus, cytoplasm vacuolation, and achromasia, show

strong diffuse cytoplasmic immunoreactivity with anti- α B crystallin, a protein that is homologous with the small cell stress proteins. They also show weak, diffuse immunoreactivity with antiubiquitin (not present in swollen neurons in infarcted brain). Although ballooned neurons are not specific for CBD and have been found in Pick disease, PSP, AD, FTD, AGD, and CJD, tau-containing distal astrocytic processes producing “astrocytic plaques” have been suggested by Feany and Dickson (1996) to be a distinctive pathologic feature of CBD. These cortical plaques, which are amyloid- and microglia-negative, represent clusters of miliary-like tau-positive structures within the distal processes of the astrocytes. Abnormal phosphorylation of tau is not specific for CBD; it can be seen in a variety of neurodegenerative disorders. Tau immunostains usually show granular neuronal deposits, neuropil threads, and glial inclusions. In addition, NFTs and Pick bodies, spherical cortical intraneuronal inclusions, are usually present in the cortical areas but, in contrast to Pick disease, not in the hippocampus. Another characteristic finding of CBD is the presence of corticobasal inclusions, which consist of round, fibrillary or homogeneous basophilic tau-positive inclusions that displace cellular pigment into the periphery, similar to globose neurofibrillary tangles seen in PSP (Kertesz et al., 2009). Neuronal inclusions in CBD are found predominantly in cortical pyramidal and nonpyramidal neurons and may have a distinctive perinuclear, coiled filamentous appearance. In addition to the different distribution, the Pick bodies of Pick disease and the Pick-like bodies of CBD have distinct staining characteristics. Whereas Pick bodies are strongly argentophilic with Bodian and Bielschowsky stains but negative with the Gallyas stain, the Pick-like bodies of CBD stain with Gallyas stain but are not strongly argentophilic. Furthermore, typical Pick bodies usually do not stain with the antitau antibody 12E8, which detects phosphorylation at SER 262/356, although the CBD inclusions are recognized by the 12E8 antibody. Astrocytic plaques, different from thorn-shaped astrocytes that are typically seen in PSP, are also typically present in the brains of patients with CBD. In addition, coiled bodies, ubiquitin-negative, tau-immunoreactive inclusions, and oligodendroglial inclusions that consist of filaments coiled around a nucleus and extend into the proximal part of the cell process are also typically present in CBD. These inclusions are found not only in CBD, but also in PSP and Pick disease; they are particularly numerous in CBD and PSP. Some have suggested that because of the clinical and pathologic overlap between CBD and PSP they should be lumped as CBD/PSP along with PPA and FTD in the “Pick complex” (Sha et al., 2006).

The apparent overlap in clinical and pathologic features between CBD, PSP, and Pick disease needs clarification (Schneider et al., 1997; Kouri et al., 2011). Asymmetrical parietofrontal cortical degeneration was the most consistent pathologic abnormality in reported autopsy series. One of the most important studies addressing the clinical and pathologic overlap between CBD and PSP was based on 35 cases from the Queen Square Brain Bank, in which there were 21 clinically diagnosed cases of CBS and 19 pathologically diagnosed as CBD (Ling et al., 2010). Of 19 pathologically confirmed CBD cases, 5 had been diagnosed correctly in life (sensitivity, 26.3%). All had a unilateral presentation, clumsy useless limb, limb apraxia, and myoclonus, 4 had cortical sensory impairment and focal limb dystonia, and 3

had an alien limb. Of CBD cases, 8 had been clinically diagnosed as PSP, all of whom had vertical supranuclear palsy, and 7 had falls within the first 2 years. Of 21 cases with CBS, 5 had CBD (positive predictive value of 23.8%); 6 others had PSP pathologic findings, 5 had AD, and the remaining 5 had other nontau pathologic conditions. Forty-two percent of CBD cases presented clinically with a PSP phenotype and 29% of CBS cases had underlying PSP pathologic features. The authors suggested the term “CBD–Richardson syndrome” for the overlap cases and concluded that CBD “is a discrete clinicopathologic entity but with a broader clinical spectrum than was originally proposed.” In another pathologic series, of 10 consecutive autopsied patients who had CBS (mean age $\pm$ standard deviation, 67.9 ± 9.3 years; male-to-female ratio, 6:4), 3 had CBD, 3 had PSP, 3 had AD, and 1 had atypical four-repeat tauopathy (Ouch et al., 2013).

A relationship among CBD, Pick disease, and PSP is suggested by the presence of ballooned neurons and nigral basophilic inclusions, which are usually present in all three disorders. Although these disorders are clinically and pathologically similar, there are some distinguishing pathologic features. Although parietal Pick disease has been reported, the vast majority of pathologically documented Pick cases exhibit degenerative changes predominantly in the frontotemporal distribution with “knife-edge” atrophy of the gyri. In addition, ballooned neurons and Pick bodies, strongly argentophilic and homogeneously ubiquitinated intraneuronal inclusions, are typically present in the Pick disease. However, neither of the two histologic hallmarks is absolutely required for the neuropathologic diagnosis of Pick disease (Growdon and Primavera, 2000).

Neurochemical studies in CBD have been sparse. Dopamine concentration was reduced in the CBD brains throughout the striatum and SN compared with age-matched controls (Riley et al., 1990). AD-like CSF tau-to- α -beta ratio pattern was found in 20% of patients with CBD (Borrioni et al., 2011).

The potential link among CBD, PSP, and FTD is the growing number of reports with overlapping phenotype associated with mutations in the *MAPT* and *progranulin* (*PRGN*) genes (Passov et al., 2011; Kouri et al., 2014). In a cohort of 109 autopsy-confirmed cases of CBD, *MAPT* mutations were found in 4.6% of CBD patients compared with 1.2% of controls (Kouri et al., 2014). In addition, TDP-43 inclusions, characteristic of frontotemporal lobar degeneration with ubiquitin-positive inclusions (FTLD-U), may be seen in brains of patients with all three disorders (Espay et al., 2011). In a report of two 70-year-old women with rapidly progressive severe postural instability, parkinsonism, oculomotor dysfunction, and frontal-predominant dementia with language impairment and pseudobulbar palsy, TDP-43-positive neuronal intracytoplasmic inclusions were found in the primary motor cortex, granule cell layer of the hippocampus, and several cranial and spinal cord nuclei (Espay et al., 2011). The clinical features of CBD, including PPA, have been described in two cases with LRRK2 G2019S mutation (Chen-Plotkin et al., 2008), but this mutation has not been described in other, even familial, cases of CBD.

The pathogenesis of CBD is not well understood. One study showed that the inheritance of the tau H1/H1 haplotype is associated with the severity of motor function but not age at onset and cognition and that there was a trend toward

shortened survival in the H1/H1 group of CBD patients (Litvan et al., 2010). In one pair of siblings with clinicopathologic phenotype of CBD and extensive bilateral T1-weighted hyperintensities and T2-W hypointensities in basal ganglia and thalamus, whole exome sequencing showed mutations in *MRS2* and *ZHX2* genes, but the significance of this finding is unknown (Fekete et al., 2013). A systematic genetic analysis of *MAPT* in 10 pathologically confirmed CBD cases identified a novel mutation in MAPT, in exon 13, p.N410H (Kouri et al., 2014). Functional analysis demonstrated that this mutation interfered with tau homeostasis.

Parkinsonism and pyramidal signs associated with speech and orofacial apraxia slowly progressing to anarthria and muteness without other language or cognitive deficits should suggest the possibility of late anterior opercular syndrome (Broussolle et al., 1996; Bakar et al., 1998). This syndrome resembles Foix–Chavany–Marie syndrome, also known as Worster–Drought syndrome (Christen et al., 2000), which is characterized by bilateral facioglossopharyngomasticatory paresis (pseudobulbar palsy) associated with bilateral lesions in the frontal and parietal opercula. The anterior opercular syndrome is a severe form of pseudobulbar palsy in which patients with bilateral lesions of the perisylvian cortex or subcortical connections become completely mute. These patients can follow commands involving the extremities but not the cranial nerves; for example, they might be unable to open or close their eyes or mouth or smile voluntarily, yet they smile when amused, yawn spontaneously, and even utter cries in response to emotional stimuli. The syndrome is usually seen in patients who have had multiple strokes, but rare cases of progressive disease, as in the syndrome of primary progressive anarthria, may occur. A related cheiro-oral syndrome (sensory disturbance in one hand and the ipsilateral oral corner) has been associated with rostral brainstem lesions. Similar to CBD, imaging studies usually show markedly asymmetrical (L more than R) cortical atrophy and reduced metabolism, especially involving the posteroinferior frontal lobe, particularly the operculum (the cerebral cortex and subcortical white matter covering the insula). One of our patients with this syndrome also exhibited pseudobulbar palsy, vertical ophthalmoparesis, and postural instability similar to that of PSP. Supranuclear ophthalmoparesis has been described in some previously reported cases of the anterior opercular syndrome. Some of the cases that came to autopsy showed focal frontal (particularly left opercular) cortical atrophy with spongiform changes in layers II and III and SN degeneration without Lewy bodies. Although this syndrome is considered to be due to some yet-unknown neurodegeneration, phenotypically similar cases have been documented to be due to CBD, herpes simplex encephalitis (McGrath et al., 1997), cortical infarcts, trauma, meningitis, benign epilepsy of childhood with Rolandic spikes, and developmental dysplasia (Weller, 1993).

Treatment

To date, no effective treatment has been found, although myoclonus may improve with clonazepam, and painful rigidity and dystonia may improve with botulinum toxin injections (Vanek and Jankovic, 2001). Dopaminergic drugs are rarely, if ever, effective. Although levodopa rarely provides any improvement in patients with CBD (Kompoliti et al., 1998), levodopa-induced dyskinesia has been

reported in rare autopsy-proven cases (Frucht et al., 2000). Rehabilitation has been reported to improve ideomotor apraxia after stroke, but it is not known whether similar strategies improve apraxia associated with CBD (Hanna-Pladdy et al., 2003). Currently, lithium, a GSK-3 β inhibitor, and davunetide, a neuroprotective peptide that stimulates microtubule assembly and reduces tau phosphorylation, are being evaluated as potential disease-modifying therapies in patients with CBD.

Parkinsonism—dementia syndromes

Dementia with Lewy bodies

Also referred to variably as diffuse Lewy body disease, senile dementia of Lewy body type, major neurocognitive disorder with Lewy bodies (NCDLB) (DSM-5), and Lewy body variant of AD, DLB has emerged as the second most common cause of degenerative dementia in the elderly. Although it is usually a sporadic disorder, few families with DLB have been described (Tsuang et al., 2002). Consensus guidelines for the clinical and pathologic diagnosis of DLB have been proposed (McKeith et al., 1996; Hohl et al., 2000; Lopez et al., 2002; McKeith et al., 2005, 2017; Barrett and Armstrong, 2017). These criteria have been reformulated by the Consortium on DLB by adding the presence of extrapyramidal signs (McKeith et al., 1996; Mega et al., 1996). In addition to progressive cognitive decline, two of the following criteria are required for the diagnosis of probable DLB (one for a “possible” diagnosis): (1) fluctuating cognition with pronounced variations in attention and alertness; (2) recurrent, typically well-formed, visual hallucinations; and (3) motor features of parkinsonism. Supportive features, not required for the diagnosis, include repeated falls, syncope, transient loss of consciousness, neuroleptic sensitivity, systematized delusions, and hallucinations in other modalities. Using these clinical criteria in 18 cases of pathologically diagnosed AD, the authors found 100% specificity with high interrater reliability (Mega et al., 1996). In a review of 31 pathologically proven cases of DLB, Louis and colleagues (1997) found that the presence of myoclonus, absence of rest tremor, no response to levodopa, or no perceived need to treat with levodopa was highly predictive of the diagnosis of DLB. RBD has been described at onset in a group of patients with DLB (Boeve et al., 1998), and RBD and depression were added as additional features supportive of the diagnosis of DLB during the second DLB workshop (McKeith et al., 1999). The revised diagnostic criteria gave increased weight to the presence of RBD and to ¹²³I-MIBG myocardial scintigraphy (McKeith et al., 2017). There is an ongoing debate whether cognitive decline and psychotic symptoms must occur at least 1 year before onset of motor symptoms to support the diagnosis of DLB (Boeve et al., 2016; Postuma et al., 2016). But the most recent consensus opinion is that “the 1-year rule is here to stay” (Barrett and Armstrong, 2017). Despite increased efforts to refine the diagnostic criteria, about 20% of DLB diagnoses are incorrect (Rizzo et al., 2018).

DLB, still considered by some as a variant of AD or an overlap between AD and PD, is now a well-recognized clinicopathologic entity (McKeith et al., 1996, 2005; Mega et al., 1996; Litvan, MacIntyre, et al., 1998; Verghese et al., 1999; Lopez et al., 2002; Pompeu and Growdon, 2002; Galvin et al., 2006). Differentiation of AD and DLB on clinical

findings alone can be difficult, but the following features are significantly more frequent in DLB than in AD and serve to differentiate the two disorders: cognitive fluctuations, visual and auditory hallucinations, depression, sleep disturbance, agitation, delusions, and abnormal EEGs were more common in the DLB than in the AD patients (Galvin et al., 2006). Fluctuations, particularly when associated with disturbed arousal and disorganized speech, are very characteristic of DLB and serve to differentiate it from AD (Ferman et al., 2004).

DLB and PDD (see later), however, share identical clinical features, and some argue that DLB represents the most common form of PDD, accounting for 38% of pathologic cases of PDD; PD-AD was seen in 32% (Galvin et al., 2006). The presence of visual hallucinations is the strongest positive predictor of the diagnosis of DLB (Tiraboschi et al., 2006). Visual hallucinations in DLB seem to correlate with the presence of Lewy bodies in the temporal lobe (Harding et al., 2002). Indeed, the presence of hallucinations should suggest Lewy body pathologic processes because non-Lewy body parkinsonism is only infrequently associated with hallucinations.

Besides hallucinations, another characteristic feature of DLB is the presence of sleep disturbances. The RBD Screening Questionnaire (RBDSQ) seems to be a sensitive instrument that captures most of the characteristics of RBD (Stiasny-Kolster et al., 2007). In a study of 15 patients (14 men) diagnosed at Mayo Clinic with RBD, all had clear histories of dream enactment behavior and 10 had RBD confirmed by polysomnography; the neuropathologic diagnoses were DLB in 12 patients (neocortical in 11 and limbic in 1) and MSA in 3 patients (Boeve, Lang, et al., 2003). The clinical and pathologic literature, therefore, suggests that when associated with a neurodegenerative disorder, RBD tends to occur in certain disorders (e.g., DLB, PD, and MSA) and rarely if ever occurs in others (e.g., PSP, CBD, AD, FTD). In another study, the authors showed that in the setting of dementia or parkinsonism, the presence of RBD often reflects synucleinopathy (Boeve, Silber, et al., 2003).

Differentiation between DLB and the other parkinsonism-plus syndromes, particularly PSP, can be particularly difficult when a patient with parkinsonism and dementia is also found to have oculomotor disturbance, as has been noted in some patients with DLB (Lewis and Gaweel, 1990). OH and other autonomic symptoms can be seen in DLB; however, this disorder may at times be difficult to differentiate from MSA (Thaisethawatkul et al., 2004). In contrast to AD, in which urinary incontinence usually occurs late in the course of the dementia, urinary incontinence may precede severe cognitive decline in DLB (Del-Ser et al., 1996).

Using voxel-based morphometry, patients with DLB were found to have more cortical atrophy on MRI than patients with PDD, thus arguing that the two disorders are two separate subtypes of Lewy body disease (Beyer et al., 2007). Medial temporal lobe atrophy (MTA) on MRI failed to differentiate between DLB and AD, although the latter had more severe MTA (Barber et al., 1999).

Parkinson's disease dementia

PDD is defined as cognitive impairments that include cognitive and motor slowing, executive dysfunction, and impaired

memory retrieval, which results from heterogeneous involvement of several distinct neural dopaminergic and nondopaminergic networks (Gratwicke et al., 2015). In a clinical-neuropathologic study of 92 PD patients who developed dementia compared with 48 who remained cognitively normal, severity of cortical Lewy body pathologic findings correlated with dementia ($P < 0.001$), with an OR of 4.06 (95% CI, 1.87–8.81) (Irwin et al., 2012). Significant dementia occurs in 30% of patients with PD, a 6-fold increase over the risk for dementia in non-PD controls (Emre et al., 2007; Aarsland et al., 2008). This risk for dementia increases during the course of the illness, reaching 80%, and with estimated incidence ranging from 2.7% per year at ages 55 to 64 to 13.7% per year at ages 70 to 79 (Braak et al., 2005; Galvin et al., 2006; Aarsland et al., 2008). Patients with PD have nearly twice the risk for developing dementia as controls (Marder et al., 1995), and siblings of demented PD patients have an increased risk for AD (Marder et al., 1999). Poor performance on tests of verbal fluency appears to be predictive of incipient dementia in patients who are in early phases of PD (Jacobs et al., 1995). Cognitive decline seems to be more prominent in patients with older onset and the postural instability with dysfunctional gait form of PD (Jankovic et al., 1990; Thenganatt and Jankovic, 2014).

Cognitive impairment is common in parkinsonian disorders, and characteristic psychological profiles can differentiate PD from atypical parkinsonian syndromes (Galvin et al., 2006; Lipka et al., 2007; Aarsland et al., 2008). Clinical diagnostic criteria for possible and probable PDD have been formulated, but it is not clear how sensitive and specific these criteria are in differentiating PDD from DLB (Emre et al., 2007). Diffuse Lewy body disease is the most common pathologic finding in patients with PD who later developed dementia (Apaydin et al., 2002), and the density of the cortical Lewy bodies correlates well with the severity of dementia (Hurtig et al., 2000). Braak and colleagues (Braak et al., 2005), however, attribute cognitive decline in PD to "the cumulative effects of the progressive PD pathology," although cognitively impaired PD patients also had a greater degree of AD pathologic findings than did those who were cognitively unimpaired.

The relationship of PDD to AD and other dementing disorders such as DLB has not yet been well defined (Arvanitakis et al., 2019). Although some investigators suggest that clear clinicopathologic separation is possible between the three disorders, the differences in neuropathologic and neurochemical characteristics suggest that there is a continuum and that the disorders are difficult to differentiate clinically and pathologically (Ballard et al., 2006; Lipka et al., 2007). Significant alpha-synuclein pathologic features are the main pathologic findings in the brains of patients with PD and dementia, coexistent pathologic factors, such as tau and amyloid-beta, are common (Smith et al., 2019). Although longer duration of PD symptoms appears to be associated with fewer AD pathologic findings and less cortical alpha-synuclein, the cholinergic deficit is more severe, probably because of Lewy body pathologic processes in the nucleus basalis of Meynert present in both PDD and DLB (Ballard et al., 2006; Lipka et al., 2007). Extrapyramidal signs have been reported in about one-third of patients with AD (Clark et al., 1997; Wilson et al., 2003). Pathologically, the parkinsonian signs in AD correlate best with the presence of NFTs rather than Lewy bodies in the SN (Liu et al., 1997)

and with the presence of iron in the SN (Brar et al., 2009). Other studies have shown that AD patients with parkinsonism have PD-like pathologic features in their SN (Burns et al., 2005). In a prospective clinicopathologic study by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD), 16 (20.5%) of the 78 cases of AD had coexistent PD pathologic findings (Hulette et al., 1995). About 15% to 45% of patients with AD develop parkinsonism, and the presence of such motor impairment markedly increases the burden on the patient and increases the cost of patient care (Murman et al., 2003). Except for tremor, parkinsonian and other motor signs increase during the course of AD (Scarmeas et al., 2004). A neuropathologic study compared AD patients with and without parkinsonism, but without pathologic findings consistent with idiopathic PD (Horvath et al., 2014). Parkinsonism in AD was associated with cell loss in the SN and the putamen. Neuronal tau pathologic features were less striking NfT density in the SN but not the putamen, correlating with parkinsonism.

Several risk factors have been identified for PD-AD coexistence. Apolipoprotein E4 (APOE4) genotype (OR, 4.19; 95% CI, 1.28–13.75; $P = 0.018$) was found to be an important risk factor, and 28.6% of all PD cases had sufficient pathologic findings for comorbid AD, of whom 89.5% were demented. In addition to the gene mutation in 21q21.2 that produces mutant APP and is responsible for early-onset AD, mutations in other genes (e.g., 1q41, 12p, 14q24.3, and 19q13.2) affect the formation of A β . Currently, the most sensitive and specific biologic markers for AD are reduced levels of A β 42 amyloid protein and sulfatide and increased levels of tau and phosphorylated tau in the CSF. Using PET with radiolabeled Pittsburgh compound-B (^{14}C -PIB) in 10 patients with PD, 12 with PDD, 13 with DLB, and 41 age-matched controls, amyloid load was significantly increased in over 80% of DLB subjects, but amyloid pathologic findings were infrequent in PDD (Edison et al., 2008a,b). These findings were confirmed by other (Gomperts et al., 2008) but not all studies (Rowe et al., 2007). Several genetic markers have been identified in patients with the combination of parkinsonism and dementia, including overexpression of alpha-synuclein as a result of multiplication of SNCA (Ross et al., 2008) and high beta-amyloid load associated with the APOE genotype (Lashley et al., 2008). Similar to PSP, H1/H1 is also associated with PDD (Goris et al., 2007).

Many disorders that resemble AD–parkinsonism clinically but can be differentiated from pure AD only at autopsy. These include not only DLB, as discussed previously, but also Pick disease, CJD, and sporadic or familial progressive subcortical gliosis. Autosomal dominant subcortical gliosis, with prominent white matter changes on MRI and at autopsy, may manifest as FTD (Swerdlow et al., 2009; Arvanitakis et al., 2019).

Parkinsonism–dementia complex of Guam and French West Indian Islands

The combination of parkinsonism, dementia, and motor neuron disease was first noted in a population of Guam, where it is known as *lytico-bodig* (Hirano et al., 1961), and the associated dementia is known among the Chamorros, the native inhabitants of Guam, as *Mariana dementia* (Galasko et al., 2002). Guam dementia is more common than the

parkinsonian–dementia complex and is strongly associated with age and low education (Galasko et al., 2007). In a review of 363 Chamorro and 3 Filipino immigrants with this disease, men were affected twice as frequently as women, but no differences in age of onset (57 years) or death (62 years) were seen between the sexes (Zhang et al., 1990). Besides parkinsonism, supranuclear ocular motility disorder has been reported in all 37 patients in one series (Lepore et al., 1988) (Video 9.12). Patients with parkinsonism usually present later than those with ALS, possibly because patients presenting with motor neuron disease do not survive long enough to develop extrapyramidal symptoms (Zhang et al., 1990; Gilbert et al., 2010). Environmental cause of PDACG is suggested not only by its restricted geographic distribution but also by its declining incidence (Galasko et al., 2007). They suggest that the rapid decline in incidence of these disorders in Guam strongly supports the role of environmental factors in their pathogenesis. ●

The neurotoxins methyl-azoxymethanol β -D-glucoside (cycasin) and β -N-methylamino-L-alanine (BMAA), compounds that are found in the cycad plant and are thought to be in high concentrations in flour made from this plant, produce a similar spectrum of neurologic decline in rats and other animals (Shen et al., 2010). However, an analysis of BMAA content in cycad flour suggests that BMAA normally consumed by the inhabitants of the endemic areas was not sufficient to produce neurologic toxicity. Cox and Sacks (2002) hypothesized that the consumption of flying foxes by the Chamorro people might have generated sufficiently high cumulative doses of plant neurotoxins (Banack and Cox, 2003; Cox et al., 2003). The Chamorro eat flying foxes (*Pteropus mariannus*) boiled in coconut cream in ceremonial feasts. The bats eat the seeds of cycad trees (*Cycas micronesia*), which contain BMAA. Flying foxes, like the disease, are now rare. Other epidemiologic evidence supports the association between the Guamanian syndrome and the picking, processing, and eating of foods by young adults containing flour called *fadang* made from the seeds of a plant, *Cycas cicalalis*, that contains cycasin and BMAA (Borenstein et al., 2007).

Pathologically, PDACG resembles AD more than PD. There is growing evidence that tau and alpha-synuclein affect each other, which might explain the overlap in clinical and pathologic features of the two types of neurodegenerative disease (Lee et al., 2004). Some patients with ALS–dementia–parkinsonism of Guam (ADPG) have been found to have both tau and synuclein inclusions. Tau-containing NFTs are present, particularly in the hippocampus and other brain and spinal cord areas. In addition, beta-amyloid protein-containing NFTs have been identified in the brains of patients with PDACG. Immunohistochemical studies of autopsied brains of patients with PDACG showed marked reduction in the number of dopaminergic neurons in both the lateral and medial SN. Despite marked reduction of nigrostriatal dopamine concentration, the striatal output system is well preserved, and glutamate, GABA, choline acetyltransferase, and serotonin are spared. No *C9orf72* expansions have been found in ALS-PDC in Chamorros (Dombroski et al., 2013). Two endoplasmic reticulum-associated protein, chaperone binding immunoglobulin protein/glucose-regulated protein and phosphorylated (activated) stress sensor protein kinase

Video 9.12 Lytico-bodig disease.

have been found to accumulate in the brains of patients with Guamanian parkinsonism–dementia (Verheijen et al., 2019).

Another geographically determined PSP-like disorder was described in 1999 by Caparros-Lefebvre and colleagues (1999) on the Caribbean island of Guadeloupe. The case-control survey found that the disease is associated with the use of two indigenous plants (*Annona muricata*; synonyms: soursop, corossol, guanbana, graviola, and sweetsop) that contain the mitochondrial complex I and dopaminergic neuronal toxins reticuline, corexime, and annonacin (Hoglinger et al., 2003; Lannuzel et al., 2018). In addition, custard apple is considered to be one of the foods containing annonaceous benzyltetrahydroisoquinoline (TIQ) alkaloids that might be responsible for the neurotoxicity leading to these geographically specific tauopathies (Steele et al., 2002), associated in some cases with unusual asymptomatic retinopathy (Jano-Edward et al., 2002). Patients with the Guadeloupean tauopathy usually have levodopa-resistant parkinsonism, tremor, rest and action myoclonus, subcortical dementia, and ophthalmoparesis with predominant cortical dysfunction demonstrated by various neurophysiologic studies (Apartis et al., 2008). About a third of parkinsonian patients in Guadeloupe had typical PD, one-third had a PSP-like syndrome, and one-third had parkinsonism–dementia complex. The PSP-like syndrome differs from the typical PSP in that the majority have tremor and hallucinations and half have dysautonomia. A similar clinical syndrome has been reported in Afro-Caribbean and Indian immigrants in England who regularly consumed imported Annonaceae products (Chaudhuri et al., 2000).

The Guadeloupean parkinsonism is categorized as a PSP-like tauopathy, although no mutation of the tau gene has been found (Caparros-Lefebvre et al., 2002; Steele et al., 2002). Although the tau gene failed to show any mutations, an analysis of insoluble protein extracted from the brain of one of the affected family members showed a 60-, 64-, 68-kDa triple, suggesting that this disorder might be a variant of a tauopathy. Although mutations in the tau gene have been identified, the tau gene might be a modifying gene because of linkage disequilibrium between PDACG and certain tau polymorphisms. It has been postulated that the high prevalence of atypical parkinsonism resembling PSP on the island of Guadeloupe is related to consumption of Annonaceae fruit and teas that contain high levels of mitochondrial complex I inhibitors such as benzyl-TIQs (reticuline) and tetrahydroprotoberverine (coreximine). In addition to Guam and Guadeloupe, another geographic area where ALD–dementia–parkinsonism complex has been identified is the Kii peninsula of Japan.

Frontotemporal dementias and other tauopathies

Frontotemporal lobar degeneration (FTLD), also known as frontotemporal degeneration (FTD), consists of three subtypes: (1) behavioral variant of FTD (bvFTD), SemD, and PNFA (Piguet et al., 2011; Kertesz et al., 2010a; Kertesz et al., 2010b; Spillantini and Goedert, 2013; Irwin, 2016; Josephs, 2017; Ling et al., 2018). The overall prevalence of FTD has been estimated to be 16%, but it is the most common cause of presenile dementia, equal in prevalence to AD in patients

younger than 65 years and accounting for more than 3% of those with dementia onset after 70 years. The age at onset is usually in the sixth and seventh decade, but the symptoms can begin as early as age 27 and as late as age 75. The family history suggests autosomal dominant inheritance.

The FTDs, along with PSP, CBD, PPA, Pick disease, and other neurodegenerative disorders, are examples of a group of neurologic disorders that are referred to as tauopathies (Sha et al., 2006; Snowden et al., 2007; Ling et al., 2018). The prototype tauopathy is an inherited parkinsonism–dementia disorder, initially described as the Wilhelmsen–Lynch disease (disinhibition–dementia–parkinsonism–amyotrophy complex), linked by Lynch and colleagues in 1994 to a locus on 17q21–q22 (Lynch et al., 1994). Another family with autosomal dominant parkinsonism–dementia was later described by Muentert and colleagues (1998). Clinically, the affected individuals in the latter family had a young-onset, rapidly progressive, levodopa-responsive parkinsonism and mild dysautonomia, later associated with dementia. Some members of the family had isolated postural tremor, phenomenologically identical to essential tremor. Pathologically, the brains showed features similar to those of primary PD. Subsequently other families with the hereditary parkinsonism–dementia have been described, and the disorder is now referred to as *frontotemporal dementia and parkinsonism linked to chromosome 17* (FTDP-17) (Morris et al., 2001; Seelaar et al., 2011; Spillantini and Goedert, 2013). In a study of nine British families with pathologically and genetically proven FTD, disinhibition was the most common presenting symptom, followed by frontal dysexecutive symptoms, apathy, impairment of episodic memory, and depression (Janssen et al., 2002). Subsequently, essentially all patients develop personality and behavioral changes, memory impairment, language deficits, ritualistic behavior, hyperphagia, hyperorality, parkinsonism, and neuroleptic sensitivity. Semantic dementia, a term coined by Snowden and associates in their description of patients with fluent PPA and impaired word comprehension, is one of the main features of FTD (Hodges and Patterson, 2007).

Although FTD is heterogeneous in its presentation, typical clinical features include personality changes (withdrawal, apathy, depression, aggressive and addictive behavior, alcoholism, excessive craving of sweets, childishness, apathy, loss of empathy, abulia, Klüver–Bucy syndrome, hypersexuality, and other evidence of disinhibition), defective executive functions (e.g., drawing to command), language deficits eventually leading to muteness, seizures, pyramidal signs, and amyotrophy. Parkinsonian features include bradykinesia, rigidity, and gait difficulty, but there is usually no tremor and no response to levodopa. Reduction in striatal DAT correlates with the severity of parkinsonian symptoms (Rinne et al., 2002). Stereotypies, such as rubbing and self-injurious behavior, similar to those seen in patients with autism and intellectual disability, are also characteristically seen in patients with FTD (Mendez et al., 2005; Ondo et al., 2012). Many other movement disorders are associated with FTD (Baizabal-Carvallo and Jankovic, 2016).

The following diagnostic criteria for FTD were formulated by an international group of clinical and basic scientists (McKhann et al., 2001):

1. The development of behavioral or cognitive deficits manifested by either:

- a. Early and progressive change in personality, characterized by difficulty in modulating behavior, often resulting in inappropriate responses or activities, or
- b. Early and progressive changes in language, characterized by problems with expression or severe naming difficulty and problems with word meaning.
2. The deficits in 1a and 1b cause significant impairment in social or occupational functioning and represent a significant decline from previous level of functioning.
3. The course is characterized by gradual onset and continuing decline in function.
4. Other causes are excluded.

The various tauopathies not only have in common genetic abnormalities in the tau gene (see later) but also overlap in neuropathologic abnormalities (Munoz et al., 2003; Seelaar et al., 2011; Ling et al., 2018). Clinicopathologic studies have shown that FTDs that are manifested chiefly by behavioral symptoms and semantic dementia have a broad specific range of pathologic changes, whereas those associated with motor neuron disease have predominantly ubiquitinated inclusions; parkinsonism and apraxia are associated with corticobasal pathologic features, and nonfluent aphasia predicted Pick bodies (Hodges et al., 2004; Piguet et al., 2011).

Although 6-[¹⁸F]-fluoro-L-dopa (FDOPA) PET is usually normal in patients with motor neuron disease (ALS), SPECT studies have shown that parkinsonism in these patients correlates with decreased blood flow in the frontotemporal areas suggesting that the parkinsonism in these patients is due to cortical lesions rather than nigrostriatal damage (Hideyama et al., 2006).

Pathologic changes in AD have been well characterized: Neuritic plaques containing beta-amyloid protein have been demonstrated in both sporadic and familial AD; and NFTs consist of the PHF tau. The NFTs in AD are found predominantly in the hippocampus, but extrapyramidal signs are more likely associated with the presence of NFTs in the SN. About one-third of patients with AD also have both cortical and SN Lewy bodies at autopsy; essentially all patients with PD have Lewy bodies in the cortex. Patients with DLB, however, seem to have a greater neuronal loss in the SN, substantia innominata, and LC and have lower cortical choline acetyltransferase levels than do the AD patients. In addition to the diffuse distribution of Lewy bodies throughout the basal forebrain, brainstem, and hypothalamus, the lack of NFTs in DLB helps differentiate it from AD. In contrast to PD, no reductions in DAT sites, tyrosine hydroxylase, and D2 autoreceptors were found in the SN of patients with AD or AD-parkinsonism (Murray et al., 1995). The brains of patients with pure AD, however, have a loss of DAT sites in the nucleus accumbens, and those with AD-parkinsonism had additional loss particularly in the rostral caudate and putamen. Because bradykinesia and rigidity, but not tremor, are usually the chief parkinsonian features of AD-parkinsonism, the observed biochemical alterations are consistent with the hypothesis that the presence of tremor correlates with dopamine depletion in the caudal, rather than rostral, caudate nucleus. The pathologic findings suggest that in AD-parkinsonism, the loss of dopaminergic striatal terminals is not simply a reflection of nigral dopaminergic neuronal loss.

The tauopathies are neurodegenerative disorders manifested pathologically by neuronal and glial inclusions consisting of hyperphosphorylated, insoluble tau (Ling et al.,

2018). The mutated tau presumably prevents proper binding to the microtubules, which could either destabilize the microtubules, interfering with axoplasmic transport, or lead to an excess of free-floating, toxic tau. All the identified mutations appear to destabilize the self-aggregating stem loop structure at the exon 10 splice site, leading to overproduction of four-repeat (rather than three) isoforms of tau (Morris et al., 1999). The four-repeat tau is insoluble, and it aggregates to form neuronal and glial inclusions. These inclusions contain “twisted ribbon” filaments rather than the PHFs and straight filaments that are typically observed in AD. In contrast, missense mutations outside exon 10, which affect all tau isoforms, result in neuronal inclusions that consist of both three- and four-repeat tau, with morphology similar to that of AD. In addition to the abnormal tau, brains of patients with FTDP-17 have pronounced frontotemporal atrophy, neuronal loss, gliosis, granulovacuolar degeneration, and cortical spongiform changes. Silver-positive, spheroidal enlargements of the presynaptic terminals have been found within the neuropil of the vulnerable regions (Zhou et al., 1998). These neuropil spheroids are immunopositive cytoskeletal proteins, including tau, and probably represent dystrophic changes associated with retrograde degeneration. In a study of 90 brains with clinically diagnosed FTD, tauopathies were found in 46%, frontotemporal lobar degeneration with ubiquitin-positive inclusions in 29% (often associated with motor neuron disease), and AD in 17% (Forman et al., 2006).

Treatment of dementia-parkinsonism

Although the parkinsonian features might improve with dopaminergic therapy, there is little that one can do to improve the cognitive deficit. In one study, donepezil at 5 and 10 mg/day produced significant cognitive, behavioral, and global improvements in DLB patients that lasted at least 12 weeks, reducing caregiver burden at the highest dose (Mori et al., 2012). Rivastigmine inhibits not only acetylcholinesterase but also butyrylcholinesterase, which, in contrast to its relative absence in normal brain, accounts for 40% of cholinergic activity in the cortex and 60% in the hippocampus in AD brains. In a randomized, double-blind, placebo-controlled, multicenter study of 120 patients with probable DLB, McKeith and colleagues (2000b) found the drug to be safe and to effectively ameliorate apathy, anxiety, delusions, and hallucinations. The efficacy of cholinesterase inhibitors in DLB has been attributed to relative preservation of cortical muscarinic M1 receptors. In addition to the usual side effects of cholinesterase inhibitors, such as nausea, vomiting, anorexia, and weight loss, four patients noted emergent tremor without a significant worsening of UPDRS.

Hallucinations, a frequent complication of dopaminergic drug therapy, may be controlled with clozapine, but potentially serious side effects, including agranulocytosis, require weekly monitoring of the white blood cells (Chacko et al., 1993). Olanzapine, another atypical neuroleptic, has been reported to exert an antipsychotic effect similar to that of clozapine but without the risk for agranulocytosis (Wolters et al., 1996). In several studies, however, olanzapine was associated with exacerbation of parkinsonian motor disability (Ondo et al., 2002). Quetiapine fumarate, a dibenzothiazepine that blocks not only D1 and D2 receptors but also 5HT_{1A} and 5HT₂ receptors, also has been found to have a

beneficial effect in PD patients with hallucinations described previously with the other atypical neuroleptics (Fernandez et al., 1999). Indeed, quetiapine is our drug of choice for psychosis in patients with PD, followed by clozapine and olanzapine.

Although DLB patients might not respond as well to levodopa as do those with typical PD, many do obtain satisfactory improvement with levodopa and benefit from chronic treatment (Bonelli et al., 2004). Cholinesterase inhibitors have demonstrated robust superiority to placebo treatment across multiple randomized double-blind placebo-controlled clinical trials, including in studies of rivastigmine and donepezil (Ikeda et al., 2015). Pimavanserin, a selective 5HT_{2A} inverse agonist/antagonist, approved by the U.S. Food and Drug Administration for treatment of hallucinations and delusions associated with PD, may be effective also in the treatment of dementia-related psychosis associated with other neurodegenerative disorders (Cummins et al., 2018). In one study, pimavanserin was found to be more clinically useful than quetiapine in patients with DLB-related psychosis (Horn et al., 2019).

Heredodegenerative parkinsonism

Parkinsonism may be an associated or the dominant clinical feature in some heredodegenerative disorders (see Table 9.1). Most of these disorders are discussed elsewhere, particularly in Chapters 5 and 12. In addition to a growing number of monogenetic disorders associated with parkinsonism, some disorders are primarily categorized as dystonias with associated parkinsonism. For example, an X-linked dystonia–parkinsonism (XDP, DYT3 [MIM 314250]) seen almost exclusively in male adults with maternal roots from the Philippine island of Panay may in addition to dystonia (intermittent twisting referred to as *Lubag* and sustained posturing referred to as *Wa-eg*) and parkinsonism with bradykinesia and shuffling gait (referred to as *Sud-sud*), manifest a wide spectrum of movement disorders. These include tremor, myoclonus, chorea, and myorhythmia. Linkage analyses and linkage disequilibrium studies have assigned the disease locus to a 260-kb interval on Xq13.1, and five disease-specific sequence changes were described in the multiple transcript system (MTS) in the DYT3 critical region. A disease-specific SVA (short interspersed nuclear element, variable number of tandem repeats, and Alu composite) retrotransposon insertion related to reduced neuron-specific expression of the TATA-binding protein–associated factor 1 gene (TAF1) was reported in some DYT3 patients (Deng et al., 2008). An X-linked four-repeat tau parkinsonism and spasticity has been reported in five males in a three-generation family (Poorkaj et al., 2010).

Neurodegeneration with brain iron accumulation

Our understanding of the NBIA syndrome continues to grow as a result of discoveries of new genetic mutations causing this phenotype. In addition to the core syndromes of pantothenate kinase–associated neurodegeneration (PKAN, NBIA1) and PLA2G6-associated neurodegeneration (PLAN, NBIA2), several other genetic causes have been identified

(including FA2H, C19orf12, ATP13A2, CP, and FTL) (Dusek et al., 2012; Schneider et al., 2012; Hayflick et al., 2018). The clinical, imaging, and even pathologic features of NBIA also may overlap with those of other diseases, including spastic paraplegias, leukodystrophies, and neuronal ceroid lipofuscinosis. The pathologic findings, in addition to iron accumulations, may include Lewy bodies, neurofibrillary tangles, and other pathologic hallmarks of apparently distinct neurodegenerative disorders such as PD and AD (see also Chapter 15).

NBIA1, formerly known as Hallervorden–Spatz disease, is an autosomal recessive disorder characterized by dystonia, parkinsonism, dementia, and brain iron accumulation (Thomas and Jankovic, 2003; Dusek et al., 2012; Schneider et al., 2012, 2013). Because of Julius Hallervorden's terrible past and his shameless involvement in active euthanasia during World War II (Shevell, 2003), the eponym carrying his name has been replaced by the new term NBIA1. Characterized by childhood-onset progressive rigidity, dystonia, choreoathetosis, spasticity, optic nerve atrophy, and dementia, NBIA1 can present as an adult-onset parkinsonism–dystonia–dementia syndrome (Jankovic et al., 1985). Linkage analyses initially localized the *NBIA1* gene on 20p12.3–p13; subsequently, 7–base pair deletion and various missense mutations were identified in the coding sequence of gene *PANK2*, which codes for pantothenate kinase (Hayflick et al., 2003), hence the term pantothenate kinase–associated neurodegeneration. Pantothenate kinase is an essential regulatory enzyme in coenzyme A biosynthesis. It has been postulated that, as a result of phosphopantothenate deficiency, cystein accumulates in the GP of brains of patients with NBIA1. It undergoes rapid auto-oxidation in the presence of nonheme iron, which normally accumulates in the GPi and SN, generating free radicals that are locally neurotoxic. Interestingly, atypical subjects were found to be compound heterozygotes for certain mutations for which classic subjects were homozygous. Most, but not all, patients with the NBIA1 phenotype have mutations in the *PANK2* gene (Thomas and Jankovic, 2003). On the basis of an analysis of 123 patients from 98 families with NBIA1, Hayflick and colleagues (2003) found that classic Hallervorden–Spatz syndrome was associated with *PANK2* mutation in all cases and one-third of atypical cases (late-onset, slowly progressive disorder characterized by palilalia, dysarthria, dystonia, perseverative behavior and movements, freezing, and dementia) had the mutations within the *PANK2* gene. Those who had the *PANK2* mutation were more likely to have dysarthria and psychiatric symptoms, and all had the typical “eye-of-the-tiger” abnormality on MRI with a specific pattern of hyperintensity within the hypointense GPi.

Another disorder that can cause NBIA is the Kufor–Rakeb syndrome (PARK9), caused by mutations in the *ATP13A2* gene on chromosome 1p36 (Hampshire et al., 2001; Schneider et al., 2012). These rare cases usually present with early-onset behavioral disturbances and levodopa-responsive, asymmetrical, dystonia; akinetic-rigid parkinsonism with pyramidal signs; and eye movement abnormalities. Although they usually do not have typical tremor at rest, they may exhibit a “jerky,” myoclonic tremor, particularly involving the face and fingers. Brain MRI revealed generalized atrophy and putaminal and caudate iron accumulation bilaterally.

Adult-onset, levodopa-responsive dystonia–parkinsonism, a variant of NBIA, has been categorized as PARK14

(Paisán-Ruiz et al., 2008). Inherited in an autosomal recessive fashion, this subtype of NBIA is due to mutations in the *PLA2G6* gene, located on chromosome 22q13.1, which encodes a calcium-independent phospholipase A2 enzyme that catalyzes the hydrolysis of glycerophospholipids. *PLA2G6*-associated neurodegeneration (PLAN) is an early childhood-onset syndrome with axial hypotonia, spasticity, bulbar dysfunction, ataxia, levodopa-responsive parkinsonism, dystonia, and dementia with frontotemporal lobar atrophy, sometimes, but not always, associated with MRI changes indicative of iron deposition in GP and SN (Kurian et al., 2008; Yoshino et al., 2010). Previously diagnosed as infantile neuroaxonal dystrophy, a form of NBIA (NBIA2) and in the past referred to as Karak syndrome, PLAN may have a wide phenotypic spectrum with or without iron on brain imaging (Paisán-Ruiz et al., 2008, 2010; Yoshino et al., 2010). The dystonia-parkinsonism syndrome occurs when arginine is replaced by glutamine in both copies of the gene, but when it is replaced by tryptophan either the classic infantile neuroaxonal dystrophy or more insidious NBIA will develop, but there is marked phenotypic variability even within the same family. One mechanism that both PANK2 and PLAN share may be an abnormality in the deacetylation-reacetylation cycle of repair to polyunsaturated fatty acids damaged by reactive oxidative species resulting in secondary damage to the inner mitochondrial membrane, rich in these fatty acids. Regression of symptoms after 6 months of iron chelation with deferiprone has been reported in some patients with NBIA (Forni et al., 2008). Another form of NBIA, which can be inherited as either autosomal recessive or autosomal dominant neurodegenerative disorder, mitochondrial membrane protein-associated neurodegeneration (MPAN) is caused by pathogenic sequence variants in *C19orf12* (Gregory et al., 2019). This disorder may be manifested by levodopa-responsive parkinsonism and levodopa-induced dyskinesia (Savitt and Jankovic, 2019).

Other disorders that are associated with abnormal brain iron accumulation include PD, MSA, AD, HD, human immunodeficiency encephalopathy, neuroferritinopathy (caused by a mutation in the gene coding for ferritin light polypeptide on chromosome 19q13.3) (Curtis et al., 2001; Ondo et al., 2010), aceruloplasminemia (caused by mutations in the gene coding ceruloplasmin (Miyajima et al., 2002; Nittis and Gitlin, 2002), and various inborn errors of metabolism (Sedel et al., 2008). A novel mutation in the ferritin light chain gene was reported in a French Canadian family with Dutch ancestry manifested chiefly by atypical postural instability with dysfunctional gait, parkinsonism with blepharospasm and oromandibular dystonia, and putaminal hyperintensity on T2-weighted MRI (Mancuso et al., 2005).

Juvenile parkinsonism

Juvenile parkinsonism refers to a group of parkinsonian disorders with onset at or before age 21 years (Niemann and Jankovic, 2019); young-onset parkinsonism starts in the range of 21 to 40 years (Mehanna and Jankovic, 2019). Juvenile parkinsonism may be a manifestation of idiopathic or genetic (usually autosomal recessive) forms of PD, often characterized by prominent gait and balance difficulties, dystonia, and improvement after sleep, or it may be a manifestation of one of many hereditodegenerative forms of

parkinsonism (Paviour et al., 2004). Many juvenile cases of parkinsonism are caused by one of many *Parkin* mutations (PARK2). Lewy body pathologic findings are extremely rare in cases of juvenile parkinsonism. The syndrome of juvenile- or early-onset, progressive parkinsonism has been gradually expanding with the advances in neurogenetics. Juvenile parkinsonism, often characterized by prominent gait and balance difficulties, dystonia, and improvement after sleep, may occur sporadically or as an autosomal recessive disorder. One form of juvenile parkinsonism, neuronal intranuclear inclusion disease (NIID), also known as neuronal intranuclear hyaline inclusion disease (Espay et al., 2010), is a rare disorder that may manifest as a childhood- or adult-onset neurodegenerative disease involving central, peripheral, and autonomic nervous system. It manifests by asymmetrical onset, levodopa-responsive parkinsonism, levodopa-induced dyskinesia, gaze-evoked nystagmus, early-onset dysarthria and dysphagia and oculogyric crises, chorea, dystonia, ataxia, nystagmus, oculogyric deviations, pyramidal signs, seizures, intellectual disability, dementia, and dysautonomia (manifested by gastrointestinal pseudoobstruction) (Josephs, 2011). At autopsy, there are widespread neuronal, eosinophilic, hyaline intranuclear inclusions, immunoreactive for ubiquitin, that also can be found on rectal biopsy, and neuronal depletion in the SN, LC, and, to a lesser extent, the frontal cortex, and inclusions were particularly prominent in these areas (O'Sullivan et al., 2000; Lai et al., 2010). Hyaline intranuclear inclusions can be found in the brain and in rectal, sural nerve, or skin biopsy samples (Sone et al., 2011).

The syndrome of juvenile-onset or early-onset progressive parkinsonism has been gradually expanding with the advances in neurogenetics. One such syndrome, associated with pyramidal tract signs and previously referred to as pallido-pyramidal or parkinsonian-pyramidal syndrome, has been found to be due to mutation in the F-box only protein 7 gene (*FBXO7*) on chromosome 22q12–13 has been classified as PARK15 (DiFonzo et al., 2009; Deng et al., 2013). Both homozygous and compound heterozygous mutations have been identified, suggestive of autosomal recessive inheritance. This parkinsonism-pyramidal syndrome is differentiated from PD by additional symptoms besides parkinsonism, such as spasticity. In addition to ATP13A2, *PLA2G6*, *FBXO7*, spatacsin mutations can cause early-onset levodopa-responsive parkinsonism with pyramidal signs (Paisán-Ruiz et al., 2010). Another form of juvenile onset, levodopa-responsive parkinsonism is Chediak-Higashi syndrome, a rare autosomal recessive disorder caused by mutations in the lysosomal trafficking regulator gene, *LYST*, or *CHS1* (Bhambhani et al., 2013). There are many other causes of juvenile parkinsonism (see Table 9.2).

Genetic proteinopathies

The human gene that encodes MAPT occupies over 100 kb on chromosome 17q21 and contains 16 exons (Ling et al., 2018). Tau is a low-molecular-weight protein that has a number of functions, including stabilization of polymerization of microtubules in the brain, facilitating axonal transport, and contributing to cytoskeletal stability. In tauopathies, the normally soluble tau protein becomes hyperphosphorylated and forms ordered filamentous assemblies; these deposits

of filamentous tau are the characteristic pathologic features of tauopathies (Ling et al., 2018). Alternative splicing of tau mRNA from 11 of the 16 exons produces six tau isoforms ranging in size from 352 to 441 amino acids. These three- and four-carboxy-terminal tandem repeat forms are further differentiated by tau isoforms without (0N) or with either 29 (1N) or 58 (2N) amino acid inserts located on the N-terminal half; an additional 31 amino acid insert is located on the C-terminal half. Inclusion of the latter, which is encoded by exon 10 of the tau gene, gives rise to the three isoforms with four microtubule-binding repeats each; the other three isoforms have three repeats each. Although all six tau isoforms are found in the abnormal filaments in AD, only four-repeat tau isoforms are found in PSP and CBD, and there is a preponderance of three-repeat isoforms in Pick disease. Splicing, a process in which introns are excised and the remaining exons are joined together to generate mRNA, is regulated in part by unique proteins, such as the neuro-oncologic ventral antigen 1 (NOVA-1) (Dredge et al., 2001). The six major tau protein isoforms that are found in the normal adult brain are generated by alternative splicing of exons 2, 3, and 10; exons 9 to 12 encode four microtubule-binding domains that are imperfect repeats of 31 or 32 amino acid residues. Exon 10 encodes the second of four microtubule-binding domains in the C-terminal half of the protein. Alternative splicing of exon 10 generates isoforms with either four or three microtubule-binding domains; the inclusion of exon 10 results in isoforms with four repeats, and the exclusion of exon 10 results in three repeats. Mutations in the splice-donor site of exon 10 lead to increased incorporation of exon 10 and therefore an increase in levels of four-repeat tau. The presence of three or four microtubule-binding repeats in the C-terminal region depends on whether E10 is spliced out or in (Spillantini and Goedert et al., 2013). Brains of patients with FTD have tau aggregates in degenerating neurons and glia with overproduction of tau isoforms with four microtubule-binding repeats. Thus, instead of the normal 1:1 ratio of the three-repeat and four-repeat isoforms, the brains of patients with FTD have an increased proportion of exon 10+ mRNA and a corresponding increase in the proportion of four-repeat tau.

The role of tau in neurodegeneration is unknown, but one hypothesis suggests that the hyperphosphorylated tau loses its affinity for microtubules and becomes resistant to proteases, thus leading to aggregation. Tau is also the main component of NFTs, and tau pathologic findings are observed in neurons, C4d-positive oligodendrocytes, and glial fibrillary acidic protein-positive and CD44-positive astrocytes. Another hypothesis suggests that under oxidative conditions, the cysteine 322 residue on tau forms intermolecular bridges between tau proteins. Growing evidence indicates that mRNA for a tau protein isoform that contributes to NFTs is overexpressed in brainstem of patients with PSP but not patients with AD (Chambers et al., 1999). The unifying theme of all of these tauopathies is that the mutated tau cannot interact with microtubules, thus inappropriately freeing the mutant tau, resulting in an accumulation of the aberrant tau.

There are only two common extended haplotypes, H1 and H2, that cover the entire tau gene. The H1 haplotype extends beyond the outer edges of *MAPT* and displays considerable variability, whereas the H2 haplotype is relatively conserved and seems to play a protective role in both PSP and CBD

(Kalineri et al., 2009). Both H1 and H1/H1 are also overrepresented in CBD compared with controls, strongly supporting the conclusion that PSP and CBD are genetically and pathologically related, suggesting a common pathogenic mechanism involving tau dysfunction, although other risk factors must be present to explain the divergent clinical and pathologic presentation (Houlden et al., 2001). The observation that the haplotype that is overrepresented in PSP is the common tau haplotype present in a homozygous form in about 55% of normal white individuals suggests that the tau gene is a susceptibility gene for PSP but that other genetic and environmental factors must play an important role in the pathogenesis of this neurodegenerative disorder. Some studies, however, failed to demonstrate that the H1 haplotype has a major influence on the biochemical or pathologic phenotype of PSP (Liu et al., 2001), and neither H1/H1 nor A0/A0 genotype predicts the prognosis of PSP (Litvan et al., 2001). An extended tau haplotype (H1), known to be associated with PSP, has been found to interact with the $\epsilon 2$ allele of APOE to increase the risk for FTD (Verpillat et al., 2002).

A GWAS study of 1114 individuals with PSP (cases) and 3247 controls (stage 1) followed by a second stage in 1051 cases and 3560 controls found significant signals ($P < 5 \times 10^{-8}$) associated with PSP risk at STX6, EIF2AK3, and MOBP (Höglinger et al., 2011). In addition, two independent variants in *MAPT* affecting risk for PSP, one of which influences *MAPT* brain expression, were confirmed. The genes implicated encode proteins for vesicle-membrane fusion at the Golgi-endosomal interface, for the endoplasmic reticulum unfolded protein response, and for a myelin structural component.

FTDP-17 joins a growing list of tauopathies such as AD, Pick disease, PSP, CBD, ALS-dementia complex (lytico-bodig disease of Guam), pallidopontonigral degeneration, Niemann-Pick disease type C, Gertmann-Sträussler-Sheinker (GSS) disease with tangles, prion protein amyloid angiopathy, familial multiple-system tauopathy, hereditary-dysphasic-disinhibition-dementia, familial progressive subcortical gliosis, and neuronal intermediate filaments inclusion disease. Only a small percentage of these patients, however, have an autosomal dominant disorder. One of the earliest such families identified was a large American family with pallidopontonigral degeneration (Wszolek et al., 1995).

About 40% of FTDs are of genetic origin and 60% are sporadic; there are a growing number of FTD cases attributed to specific mutations in the *MAPT* gene (Morris et al., 2001; Josephs, 2008; Spillantini and Goedert, 2013; Siuda et al., 2014). The majority of testing for the various mutations in the *MAPT* gene is done on a research basis, but information about commercially available testing can be found at <http://www.genetests.org>.

Expression of human tau containing the most common FTD mutation (P301L) in transgenic mice results in motor and behavioral deficits similar to those in human tauopathies, along with formation of NFTs and Pick body-like neuronal inclusions in the amygdala, hippocampus, brainstem, cerebellum, and basal ganglia (Lewis et al., 2000; Piguet et al., 2011; Ling et al., 2018). Further studies in humans and in mouse and *Drosophila* models of tauopathies will undoubtedly provide greater insight into the phenotypic variability of tauopathies and clarify the question of whether the observed tau aggregates are the cause or the result of

neurodegeneration (de Silva and Farrer, 2002). Even though genetically engineered mice that make no tau seem healthy, an animal model that reproduces neuronal tau pathologic features is now available. These transgenic mice of human tau with four tubulin-binding repeats (4R) containing three missense mutations associated with FTD-17, G272V, P301L, and R406W develop intracellular filaments composed of hyperphosphorylated 4R tau mainly concentrated in the apical dendrites and distributed in the cortex, hippocampus, and basal forebrain (Lim et al., 2001). This and other models (Lewis et al., 2000) can be used to study the effects of oxidative stress or toxins to clarify the role of tau pathologic processes in neurodegeneration.

Although mutations in the *MAPT* gene on chromosome 17q21 account for many of these diseases, similar phenotypes have been attributed to mutations in other genes such as *p97* (also known as valosin-containing protein) on chromosome 9p21-p12 and *CHMP2B* (charged multivesicular body protein 2B) on pericentromeric region of chromosome 3 (Skibinski et al., 2005; Parkinson et al., 2006), and *progranulin* (*PRGN*) on chromosome 17q21 (1.5 Mb centromeric of *Tau*) (Boeve, 2010; Spillantini and Goedert, 2013). Mutations in exons 9, 10, 12, and 13 of *MAPT* are associated with prominent dementia, whereas intronic and exonic mutations are associated with overproduction of four-repeat tau and predominant parkinsonism-plus phenotype. The various *MAPT* mutations do not reliably predict the presenting symptoms, such as disinhibition, loss of initiative, obsessive-compulsive behavior, or mutism. Additional studies are needed to explain the intrafamilial variation or differences in genotype.

In addition to abnormalities in the tau gene, FTD has been associated with mutations in the gene for progranulin (*PGRN*), which is located 1.7 Mb centromeric to the tau gene at 17q21.31. The function of the gene product is not fully understood, but it appears to act as a growth factor involved in cell proliferation and repair (Boeve et al., 2006; Masellis et al., 2006; Snowden et al., 2006; Davion et al., 2007; Siuda et al., 2014). *PGRN* also mediates proteolytic cleavage of TDP-43, a ubiquitin-binding protein, and mutations (or siRNA suppression) of *PGRN* result in caspase-dependent accumulation of TDP-43 fragments that can be inhibited with caspase inhibitor treatment (Zhang et al., 2007). Plasma and CSF levels of progranulin have been found to be nearly 4-fold reduced in affected and unaffected subjects with *PGRN* mutations, and low (75% reduction) plasma progranulin levels may be used as a screening tool for *PGRN* mutations (Ghidoni et al., 2008; Finch et al., 2009; Sleegers et al., 2009). However, in addition to FTD, progranulin levels may be decreased in some patients with PD (Rodríguez-Rodríguez et al., 2013).

Families with *PGRN* mutations have clinical features indistinguishable from those of other cases of FTD, including hereditary dysphasic disinhibition dementia (HDDD) (Mukherjee et al., 2006); PPA, which may evolve into CBD (Mesulam et al., 2008; Passov et al., 2011); and other abnormalities such as parkinsonism, stuttering dysarthria, oculomotor abnormalities, orolingual dyskinesia (Wider et al., 2008), and apraxic agraphia (Passov et al., 2011). Pathologically, they are similar to Pick disease but differentiated by the presence of cytoplasmic and intranuclear ubiquitin inclusions and AD pathologic features in areas other than the frontal lobes without tau pathologic findings (FTLD-U).

In addition to ubiquitin, tau, and synuclein pathologic features, some brains of patients with *PGRN* mutations also stain with antibodies to the TDP-43 protein (TAR-DNA binding protein 43) (Leverenz et al., 2007). The TDP-43 proteinopathies are now recognized to represent a continuum of clinical and pathologic syndromes with various phenotypes ranging from FTDL-U to motor neuron disease (Geser et al., 2009; Gilbert et al., 2010). Other genes in which mutations have been associated with FTD include those coding for *CHMP2B*, *DJ-1*, and other proteins, such as valosin, synuclein, TDP-43, and prion protein. The nuclear protein TDP-43 has been found in both FTD and ALS inclusion, providing a biochemical link between the two neurodegenerative disorders (Neumann et al., 2006). In addition to *MAPT*, *PGRN*, and *CHMP2B*, the other gene associated with FTD is valosin-containing protein gene (*VCP*) (Tolnay and Frank, 2007). The identification of TDP-43 as the major disease protein in the pathologic processes of both FTLD with ubiquitin inclusions and ALS provides the first molecular link for these diseases. TDP-43 is the pathologic substrate of neuronal and glial inclusions in frontotemporal lobar degeneration with ubiquitin-positive inclusions (FTLD-U) and in ALS (Neumann et al., 2007). Mutations in the progranulin gene (*PGRN*) have been shown to cause familial FTLD-U, but there is no evidence that it plays a genetic role of PD (Nuytemans et al., 2008). The relationship between progranulin and TDP-43 and their respective roles in neurodegeneration is unknown. Suppression of *PGRN* expression with small interfering RNA leads to caspase-dependent accumulation of TDP-43 fragments that can be inhibited with caspase inhibitor treatment. The results suggest that abnormal metabolism of TDP-43 mediated by progranulin may play a pivotal role in neurodegeneration. Brains of patients with CBD apparently show TDP-43 inclusions, but these are not seen in brains of patients with clinically diagnosed PSP. Mutations in the abundant fused in sarcoma (*FUS*) gene may cause not only ALS-type syndrome but also a variety of stereotypies (Deng et al., 2014).

Another form of FTLD, caused by hexanucleotide expansions mutation in the chromosome 9 open reading frame 72 (*C9orf72*) may cause dementia, parkinsonism, CBD, ataxia (Khan et al., 2012; Cooper-Knock et al., 2013; Lindquist et al., 2013) and a variety of sleep disorders, including fatal familial insomnia, agrypnia excitata (inability to sleep associated with a generalized motor and autonomic overactivity), and oneiric stupor episodes (peculiar motor behavior such as simple or complex automatic gestures mimicking daily life activities) (Guaraldi et al., 2011). Based on the presence of more than 30 repeats, the expansion in the *C9orf72* was detected in 9.3% of patients with ALS, 5.2% of patients with FTLD, and 0.7% of patients with PD (Xi et al., 2012). Although the *C9orf72* gene accounts for a relatively large proportion of ALS and FTD, some of these disorders are associated with parkinsonism, and in one study of 1446 parkinsonian patients, 5 carried *C9orf72* expansions; 3 with typical PD and 1 each with PSP and CBD (Lesage et al., 2013).

Rapidly progressive autosomal dominant parkinsonism with central hypoventilation, depression, apathy, weight loss, supranuclear gaze palsy, and poor response to levodopa, referred to as Perry syndrome, has neuropathologic features similar to those of PD but without Lewy bodies (Wider and

Wszolek, 2008; Richardson et al., 2020). TDP-43-positive neuronal inclusions, dystrophic neurites and axonal spheroids in a predominantly pallidonigral distribution, sparing the neocortex and motor neurons, were demonstrated in autopsied brains of patients with this autosomal dominant neurodegenerative disorder (Wider et al., 2008). This genetic disorder has been found to be caused by mutations in the CAP-Gly domain of dynactin (encoded by the *DCTN1* gene) and resulting in impaired microtubule binding and formation of intracytoplasmic inclusions (Farrer et al., 2009; Araki et al., 2014; Chung et al., 2014; Felicio et al., 2014). Another family with *DCTN1* gene mutation but PSP-like and FTDP phenotype was subsequently identified (Caroppo et al., 2014; Richardson et al., 2020). Dynectin codes for dynein, which is involved in multiple basic cellular functions, such as mitosis, autophagy, and structure of endoplasmic reticulum and Golgi, but also in neuron-specific functions in particular retrograde axonal transport, implicated increasingly as the origin of PD pathologic processes (Eschbach and Dupuis, 2011).

Several neurodegenerative diseases, including AD, FTD, and PD, are due to accumulation of intermediate filaments characterized pathologically by neuronal intermediate filament inclusions. In one family with a novel late-onset dementia-parkinsonism associated with neuronal inclusions by hematoxylin and eosin stain, the cause was found to be a heterozygous c.149T>G (p.Leu50Arg) missense mutation in the gene encoding the protein kinase A type I-beta regulatory subunit (PRKAR1B) (Wong et al., 2014). A family carrying a heterozygous 6.4-Mb duplication of the *SNCA* locus with a phenotype of FTD and late-onset pallidopyramidal syndrome was reported (Kara et al., 2014).

Secondary parkinsonism

Parkinsonism, the clinical syndrome that is manifested chiefly by tremor, bradykinesia, rigidity, and postural instability may be the sole manifestation of a disorder, such as PD, it may be a component of a more complex disorder such as one of the multiple-system degenerations or hereditodegenerations, or it may result from pharmacologic, physiologic, or pathologic abnormalities with different causes (see Table 9.1). Although the “secondary” parkinsonian disorders are produced by different mechanisms, they all seem to produce parkinsonian symptoms by interfering with normal dopaminergic production or transmission. Only the most important secondary types of parkinsonism are reviewed here.

Infections

An exposure to an infectious agent, such as the one (or more) responsible for the 1917 to 1928 pandemic of encephalitis lethargica (von Economo encephalitis), has been long recognized as a cause of parkinsonism (Krusz et al., 1987; Calne and Lees, 1988; Dale et al., 2004). Indeed, encephalitis lethargica or postencephalitic parkinsonism was once thought to be the primary cause of PD (Litvan et al., 1999e; Vilensky et al., 2010a,b). The clinical presentation often involved fever, somnolence, ophthalmoplegia, and CSF lymphocytic pleocytosis (50–100 lymphocytes). About 40% of

the affected individuals died during the acute illness. Parkinsonism occurred in 50% of the survivors within 5 years and 80% within 10 years. In addition to the typical parkinsonian features, which were usually levodopa responsive, there were many other neurologic and movement disorders that helped differentiate this postencephalitic syndrome from idiopathic PD. The accompanying features included oculogyric crises, blepharospasm, palilalia, and various hyperkinesias such as dystonia, chorea, tics, and hiccups.

The pathologic findings of the acute disorder consisted chiefly of midbrain and periventricular inflammation. The delayed-onset movement disorder was characterized by marked depletion of neurons in the SN and NFTs in the residual neurons (Litvan et al., 1999e). No virus was ever documented as the cause of postencephalitic parkinsonism, but there has been a reemergence of interest in the influenza A virus as a possible etiologic agent. This virus displays preferential tropism to the brainstem (especially the nigral neurons), cerebellum, and limbic system and produces changes (e.g., phosphorylation of cytoskeletal proteins and alterations in intermediate filaments) that could lead to the formation of Lewy bodies (Takahashi and Yamada, 1999). The mechanism of the latency between the acute illness and the subsequent development of parkinsonism has never been elucidated. The syndrome of postencephalitic parkinsonism, however, serves as a model for other delayed-onset movement disorders (Saint Hilaire et al., 1991; Scott and Jankovic, 1996; Vilensky et al., 2010a,b).

Sporadic cases of postencephalitic parkinsonism have been reported since the 1917 to 1928 pandemic (Howard and Lees, 1987; Vilensky et al., 2010a,b). Japanese encephalitis not only may involve the cortex, thalamus, brainstem, and spinal cord, but in some cases may be associated pathologically with predominant involvement of the SN and clinically with otherwise typical parkinsonism (Pradham et al., 1999). West Nile encephalitis has been associated with tremor, myoclonus, and parkinsonism during the acute illness, with complete recovery in some patients, but persistent parkinsonism resulting from SN damage has been reported (Bosanko et al., 2003; Sejvar et al., 2003).

Poststreptococcal acute disseminated encephalomyelitis (PSADEM), a poststreptococcal disorder that may include parkinsonism and dystonia, has been described in association with the anti-basal ganglia antibodies (Dale et al., 2001). Laboratory investigation suggested a poststreptococcal cause in that antistreptolysin O (ASO) titer was elevated in 65% of patients and Western immunoblotting showed that 95% of the patients had autoantibodies reactive against human basal ganglia antigens, compared with 2% to 4% of these antibodies in controls ($n = 173$, $P < 0.0001$). One case that was examined at autopsy showed striatal encephalitis with periventricular B- and T-lymphocytic infiltration. The methodology of the study and the specificity of the antibodies, however, have been questioned (Vincent, 2004). Other infectious causes of parkinsonism include human immunodeficiency virus (HIV) and associated infections (Nath et al., 1987).

Some infections are followed by autoimmune disorders, but most autoimmune forms of parkinsonism are related to some specific antibodies that are part of a paraneoplastic syndrome. This group of disorders is reviewed elsewhere in this volume and in prior reviews (Baizabal-Carvallo and Jankovic, 2018).

Prion diseases

Although parkinsonism is not a common feature of CJD, this diagnosis should be considered in patients with rapidly progressive dementia and parkinsonism (Heath et al., 2011; Davidson and Knight, 2014). The elegant studies of Prusiner and his collaborators have drawn attention to a group of disorders known as prion diseases, and because of their growing scientific importance as well as their potential impact on public health, Prusiner was awarded the 1997 Nobel Prize for Medicine (Prusiner, 2001; Glatzel et al., 2005). These transmissible spongiform encephalopathies, some of which are associated with parkinsonian features, consist of four conditions: (1) CJD and its variant (see later), (2) kuru (Kompoliti et al., 1999), (3) GSS disease, protease-sensitive prionopathy (PSP^r), and (5) familial or sporadic fatal insomnia. CJD can manifest with rapidly progressive parkinsonism, often accompanied by dementia, myoclonus, and gait disorder. In a series of 232 cases of sporadic CJD, cognitive decline was present in 100%, myoclonus in 78%, cerebellar signs in 71%, pyramidal signs in 62%, and extrapyramidal signs, including parkinsonism, in 56% (Brown et al., 1994). Prominent amyotrophy is also occasionally present in patients with CJD (Worrall et al., 2000).

Although various forms of prion disease are presumably the result of core molecular changes involving the prion protein, PrP, with the formation of PrP^{Sc}; the exact mechanisms of neuronal dysfunction and neuronal death in prion disease remain uncertain. Loss of PrP^C function or toxicity from aggregated PrP^{Sc} do not seem to be the main pathogenic mechanisms. There is increasingly more evidence that oligomeric protein species formed as intermediates between PrP^C and PrP^{Sc} are more likely to be toxic and that PrP^C itself may have a pathologic role. There is also growing support for the possibility that unfolded protein response initiated by increasing levels of misfolded proteins, mediated by phosphorylation and activation of eIF2 α , which terminates the synthesis of cellular proteins, including synaptic proteins (Moreno et al., 2012). This mechanism may have important implications for other protein misfolding diseases, including PD.

Several diagnostic tests can be helpful in confirming the premortem diagnosis of CJD. Periodic EEG is present in about 60% of all sporadic cases, but this pattern is rarely present in familial cases. Periodic complexes are relatively specific for CJD, with a 9% false positive rate (Steinhoff et al., 2004). On the basis of a study involving 300 cases of sporadic CJD the authors proposed a classification of six phenotypic variants with a variable degree of rapidly progressive dementia, myoclonus, ataxia, insomnia, and typical EEG (Parchi et al., 1999). The new variant CJD, caused by bovine spongiform encephalopathy prions, differs dramatically from the more common sporadic form in that the patients' age is usually in the twenties, about three or four decades earlier than that in the sporadic disease, and many patients present with prominent affective symptoms, including dysphoria, irritability, anxiety, apathy, loss of energy, insomnia, and social withdrawal. Evidence of focal cortical syndrome, such as alexia without agraphia, may be the presenting feature of CJD (Adair et al., 2007). Symptoms that are typically seen in the sporadic disease, such as cognitive impairment, dysarthria, gait abnormalities, and myoclonus, are late features.

Diagnostic criteria for sporadic CJD include immunohistochemistry with antibodies against the prion protein (Kretzschmar et al., 1996). Several studies have shown that the presence of 14-3-3 protein in the CSF improved the diagnosis of CJD (Aksamit, 2003). Although the sensitivity of this test may be as high as 97% and its specificity may be as high as 87% (Lemstra et al., 2000; Castellani et al., 2004), particularly in the classic variety of sporadic CJD, some studies have found the sensitivity to be as low as 53% (Geschwind et al., 2003). CSF tau-protein assay by enzyme-linked immunosorbent assay (ELISA), already readily available in routine laboratories, has been found to have a 92% positive predictive value in diagnosing CJD; 74 of 77 patients with probable CJD had a tau-protein level greater than 1300 pg/mL, whereas 2 of 28 patients with AD had such high levels, and the percentage was even lower in other dementias (Otto et al., 2002). Using ELISA to measure tau protein and Western blot to detect 14-3-3 protein, Hamlin and colleagues (Hamlin et al., 2012) found tau and 14-3-3 proteins to be closely correlated, but tau was a better marker for the diagnosis of CJD than 14-3-3 protein. Some studies showed that the 14-3-3 test does not differentiate between CJD and other neurodegenerative disorders associated with dementia (Burkhard et al., 2001). False positive results include stroke, meningoencephalitis, vasculitis, paraneoplastic disorders, FTD, and AD (Chapman et al., 2000).

In addition to the positive 14-3-3 immunoassay, over 70% of patients with the new variant of CJD (nvCJD) who were homozygous for methionine at codon 129 of the prion protein gene had bilateral pulvinar high signal on MRI, also referred to as "hockey stick sign" (Will et al., 2000). In patients with rapidly progressive dementia in addition to positive 14-3-3 CSF protein, the presence of distinctive MRI (increased signal intensity on FLAIR or restricted pattern DWI-MRI) is often detected in cerebral cortex, caudate, or putamen. DWI-MRI has the highest sensitivity for the detection of signal intensity abnormalities in CJD. Increased signal intensity is typically seen bilaterally in the striatum, thalamus, and cortex (cortical ribbon) (Mendez et al., 2003; Shiga et al., 2004; Geschwind et al., 2007). In an analysis of 19 reported cases of CJD with DWI-MRI lesions, CSF protein 14-3-3 was negative in 6 cases and positive in 2 others (Mendez et al., 2003). The authors concluded that "multifocal cortical and subcortical hyperintensities confined to gray matter regions in DWI-MRI may be a more useful noninvasive diagnostic marker for CJD than CSF protein 14-3-3." Furthermore, high T2-weighted signal in the basal ganglia correlated with valine (VV) or methionine valine (MV) codon 129 genotypes (Meissner et al., 2004). Real-time quaking-induced conversion (RT-QuIC) testing of CSF and of nasal brushings from olfactory epithelium has been found to be highly diagnostic of sporadic CJD (Orrú et al., 2014). In addition, using the protein misfolding cyclic amplification (PMCA) technique to amplify minute quantities of PrP^{Sc}, this misfolded protein can be detected in the urine of patients with vCJD with high sensitivity and specificity (Moda et al., 2014).

The National Prion Disease Pathology Surveillance Center at Case Western Reserve University offers, free of charge, a variety of diagnostic tests, including Western blots on frozen brain tissue to detect protease-resistant PrP, immunohistochemical tests for PrP on fixed tissue, analysis of DNA

extracted from blood or brain tissue for PRNP, and analysis of CSF for 14-3-3 protein. Parchi and colleagues (1999) classified the six types of CJD according to homozygosity or heterozygosity of M and V at codon 129 of the prion protein gene: The MM1 and MV1 correlate with the phenotype of classic sporadic CJD (rapidly progressive dementia with periodic EEG), whereas others are more atypical, with slower progression and young age at onset (VV1) or ataxia (MV2 and VV2). Using solid-state binding matrix to capture and concentrate disease-associated prion proteins coupled with direct immunodetection of surface-bound material investigators think they have developed a blood test that, based on 15 samples from patients with CJD, showed an assay sensitivity for variant CJD of 71.4% (95% CI, 47.8–88.7) and a specificity of 100% (95% CI, 97.8%–100%) (Edgeworth et al., 2011).

There are many potentially treatable disorders misdiagnosed as CJD. In 1106 brain autopsies, 352 (32%) were negative for prion disease; AD (n = 154) and vascular dementia (n = 36) were the most frequent diagnoses (Chitravas et al., 2011); 71% of patients had potentially treatable diseases. Clinical findings included dementia (42 cases), pyramidal (n = 20), cerebellar (n = 14), or extrapyramidal (n = 12) signs; myoclonus (n = 12); visual disturbance (n = 9); and akinetic mutism (n = 5); a typical EEG occurred only once. Neuropathologic diagnoses included immune-mediated disorders (n = 26), neoplasia (n = 25, most often lymphoma), infections (n = 14), and metabolic disorders (n = 6).

The prion diseases are caused by abnormal processing of a normal cellular constituent, the PrP, which is normally encoded by a gene on the short arm of chromosome 20 (Prusiner, 2001). When the normal PrP^C protein, which has an alpha-helical structure, undergoes a conformational change to a beta-pleated structure, the resulting abnormal PrP^{Sc} (Sc = scrapie) isoform leads to development of the disease. There is growing evidence that the fundamental process in prion propagation involves seeded aggregation of misfolded host proteins. The molecular strain characteristics of nvCJD are clearly different from those of previously recognized human prion strains, but it closely resembled those seen in bovine spongiform encephalopathy. None of the patients with nvCJD had mutations in the *PRNP* gene, but all so far reported have been methionine homozygotes at codon 129.

Mutations in the prion protein gene (*PRNP*) have been found not only in patients with CJD, but also in fatal familial insomnia and GSS disease, manifested by autosomal dominantly inherited progressive ataxia and dementia (Panegyres et al., 2001). For example, in GSS disease, *PRNP* mutations were found in codons 102, 117, 198, and 217, whereas in fatal familial insomnia, a *PRNP* mutation is present in codon 178. Detection of pathologic PrP^{Sc} in the olfactory epithelium in nine patients with sporadic CJD but not in any controls suggests that the olfactory pathway might be the route of infection by the prions; this finding suggests that olfactory biopsy might be of diagnostic importance (Zanusso et al., 2003).

There is no treatment for CJD, but there might be some rationale for using the antimalarial drug quinacrine because of its protease resistance of PrP peptide aggregates, although there is little hope that this drug will significantly alter the natural course of the fatal disease (Barret et al., 2003). Improved understanding of the molecular mechanisms of

prion diseases may eventually lead to effective therapies, but current therapeutic strategies do not seem to offer meaningful improvements in the symptoms or progression of the disease (Stewart et al., 2008).

Drugs

Although drug-induced parkinsonism is one of the most common forms of parkinsonism, it is not commonly encountered in movement disorder clinics. Parkinsonian symptoms and findings, often indistinguishable from those seen in patients with PD, may be evident within the first few days of neuroleptic therapy; nearly all cases become evident within 3 months after initiation of treatment (Jankovic, 1995; Shin and Chung, 2012; Factor et al., 2019). In addition, chronically treated patients may develop parkinsonian findings when the dose of a neuroleptic is increased. The prevalence of neuroleptic-induced parkinsonism has been reported to range from 10% to 60% of patients treated with antipsychotics. Advanced age, female sex, and possibly genetic predisposition, such as the presence of essential tremor, have been identified as potential risk factors. About one-third of all patients referred to a movement disorder clinic with drug-induced movement disorders, such as tardive dyskinesia, have parkinsonian findings (Jankovic, 1995). Although two-thirds of all patients recover within 7 weeks after stopping the offending drug, the symptoms may persist for more than 18 months. In one study, 11% of patients who recovered from neuroleptic-induced parkinsonism were later found to have the characteristic pathologic findings of PD at autopsy (Rajput et al., 1982). This suggests that parkinsonism that persists even after the offending drug is withdrawn may represent subclinical, latent PD. This is supported by another clinicopathologic study from the same investigators in which brains from seven drug-induced parkinsonism patients were examined and two had autopsy evidence of underlying PD, one had mild SN neuronal loss without Lewy bodies, and the others had no identifiable cause for their parkinsonism (Shuaib et al., 2016). The authors concluded that reversal of parkinsonism after discontinuing offending drugs does not indicate absence of underlying pathologic processes and that neuroleptics can unmask preclinical PD in patients with insufficient SN damage for the disease to manifest clinically.

In a study of 20 patients with drug-induced parkinsonism, 11 had abnormal β -CIT SPECT scans suggesting underlying nigrostriatal deficiency and that even though the patients were taking neuroleptics, their parkinsonism may have been the result of exacerbation of underlying PD (Lorberboym et al., 2006).

Besides the neuroleptics, many other drugs may cause parkinsonism, including valproate, lamotrigine, zonisamide, vigabatrin, and other anticonvulsants (Jamora et al., 2007; Zadikoff et al., 2007). In addition, certain cardiac drugs, such as amiodarone, may cause parkinsonism.

Toxins

Our knowledge of the mechanisms and treatment of parkinsonism has expanded dramatically as a result of the discovery

that the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydro pyridine (MPTP) can induce parkinsonism. MPTP can produce parkinsonism in animals (particularly primates) and humans that can be clinically indistinguishable from idiopathic PD. In contrast to PD, which affects chiefly the putamen, however, MPTP impairs dopaminergic function in both the caudate and putamen (Snow et al., 2000). Several other toxins can cause parkinsonism, but only carbon monoxide and manganese are reviewed here.

Carbon monoxide exposure can result in acute intoxication, which is associated with about a 35% mortality rate, progressive akinetic-mute state, or delayed-relapsing encephalopathy (Sohn et al., 2000). The latter syndrome usually develops after a 3-week recovery period. The delayed relapsing type of carbon monoxide sequelae is characterized by slow, short-stepped gait, start-hesitation, freezing, body bradykinesia, and rigidity but little or no tremor. In addition, these patients often develop akinetic mutism and other peculiar behaviors. They usually do not improve with levodopa. Delayed-onset parkinsonism has been documented not only after carbon monoxide poisoning, but also after anoxia, trauma, and other brain injuries (Bhatt et al., 1993; Scott and Jankovic, 1996; Li et al., 2000).

Because certain metals, such as iron, copper, and manganese, can facilitate oxidative reactions, there is growing interest in these transitional metals in the pathogenesis of neurodegenerative disorders (see earlier discussion about NBIA). Manganese was first reported to cause a parkinsonian syndrome in 1837, only 20 years after James Parkinson described the disease that now bears his name (Calne et al., 1994; Jankovic, 2005). Since that time, there have been many reports of manganese intoxication causing psychiatric problems ("manganese madness"), usually followed in a few months by motor symptoms. These consist of dystonia, parkinsonism, retropulsion, and a characteristic gait called cock-walk, which is manifested by walking on the toes with elbows flexed and the spine erect. There is usually no tremor, and the motor deficits rarely improve with levodopa therapy. Manganese intoxication has been reported in miners, smelters, welders, workers involved in the manufacture of dry batteries, chronic accidental ingestion of potassium permanganate, and incorrect concentration of manganese in parenteral nutrition. Welders with PD were found to have their onset of PD on the average 17 years earlier than a control population of PD patients, suggesting that welding, possibly by causing manganese toxicity, is a risk factor for PD (Racette et al., 2001). Besides welding and manganese mining, manganese toxicity may occur with long-term parental nutrition. Although it has been postulated that manganese causes parkinsonism because of pallidal damage, some studies, including β -CIT SPECT scans, indicate a presynaptic form of parkinsonism associated with a reduction in striatal DAT (Kim et al., 2002). Manganese intoxication has been suggested as a possible cause of some of the neurologic abnormalities and abnormal MRI imaging (abnormal signal hyperintensity in the GP and SN on T1-weighted images) associated with chronic liver failure (Racette et al., 2005; Sitburana and Ondo, 2009). The abnormal imaging studies and the lack of response to levodopa are consistent with the pathologic findings in humans and experimental primates of marked neuronal loss and gliosis in the GP and SNr. The associated marked

accumulation of iron and aluminum suggests that oxidant stress plays an important role in manganese neurotoxicity. One piece of evidence that has been used to link welding with manganese-induced parkinsonism are the occasional reports of increased T1 basal ganglia signal on MRI of the brain (Josephs et al., 2005). In one report from the Mayo Clinic, eight male career welders with such MRI findings exhibited parkinsonism (three patients), myoclonus and limited cognitive impairment (two patients), vestibular-auditory dysfunction (two patients), and minor subjective cognitive impairment, anxiety, and sleep apnea (one patient) (Josephs et al., 2005). The broad spectrum of clinical manifestations, however, argues against a direct cause-and-effect relationship.

In contrast to PD, fluorodopa PET scans are normal in patients with manganese parkinsonism (Lu et al., 1994), and raclopride (D2 receptor) binding is only slightly reduced in the caudate but is normal in the putamen (Shinotoh et al., 1997). β -CIT SPECT scans, however, may be abnormal, indicating degeneration of presynaptic dopaminergic terminals in some patients with manganese parkinsonism (Kim et al., 2002). Despite a growing number of publications, there is little evidence that welding causes manganese-induced parkinsonism or PD (Jankovic, 2005; Kiebertz and Kurlan, 2005; Mortimer et al., 2012). Based on a meta-analysis of 16 studies the authors concluded that "welding and manganese exposure are not associated with increased PD risk" (Mortimer et al., 2012).

In addition to environmental causes of manganese intoxication, there have been an increasing number of genetic causes of parkinsonism-dystonia syndrome associated with cirrhosis and polycythemia, such as mutations in the *SLC30A10* on chromosome 1q41-q42 (Quadri et al., 2012; Tuschl et al., 2012), resulting in an autosomal recessive disorder of abnormal metabolism of manganese. These discoveries have enormous implications for the diagnosis and treatment of these disorders because chelation therapy with calcium sodium edetate and oral iron can completely reverse the neurologic deficit. Furthermore, some patients thought to have environmentally induced hypermagnesemia may instead have this genetic disorder or be genetically susceptible to develop manganese toxicity.

Other toxins, such as certain hydrocarbons (Pezzoli et al., 2000) and organophosphates (Bhatt et al., 1999), have been implicated in the pathogenesis of parkinsonian syndromes. Many of the cases are complicated by legal issues; therefore, it is not always easy to prove a cause-and-effect relationship. If the parkinsonian syndrome occurs in a cluster, it is more likely that the putative toxin is responsible.

Vascular parkinsonism

Parkinsonism resulting from strokes or other vascular causes can mimic idiopathic neurodegenerative disorders, such as PD or PSP (Mehanna and Jankovic, 2013). In a systematic review of 25 articles, patients with VP were older, with a shorter duration of illness; presented with symmetrical gait difficulties; were less responsive to levodopa; and were more prone to postural instability, falls, and dementia (Kalra et al., 2010). Pyramidal signs, pseudobulbar palsy, and incontinence were more common in VP, but tremor is rarely present. Structural neuroimaging was abnormal in 90% to 100%

of vascular cases, compared with 12% to 43% of PD cases. In contrast to PD, there is usually no abnormality in presynaptic striatal DATs as measured by SPECT in VP. Winikates and Jankovic (1999) compared a group of patients who satisfied the clinical, radiographic, or pathologic criteria for VP with a group of patients with PD to determine which clinical variables differentiate these two forms of parkinsonism. Patients with VP were older, were more likely to present with gait difficulty than with tremor, and were less likely to respond to levodopa than were patients with PD. Vascular patients were also significantly more likely to have predominant lower body involvement, postural instability, and a history of falling, dementia, corticospinal findings, incontinence, and pseudobulbar affect. Lower body parkinsonism, a condition in which upper body motor function is relatively preserved and gait is markedly impaired, has previously been linked to multiple lacunar infarctions (Fitzgerald and Jankovic, 1989). A clinicopathologic study of 17 patients concluded that vascular disease per se can cause parkinsonism without invoking coexistent neurodegenerative disease (Zijlmans et al., 2004a). In one study, frontal leukoaraiosis was associated with increased rate of axial and total MDS-UPDRS scores and with elevated systolic blood pressure, suggesting that cardiovascular risk factors may contribute to axial motor features in PD (Kotagal et al., 2014).

Binswanger disease, a form of leukoencephalopathy caused by hypoxia-ischemia of distal watershed periventricular territories associated with aging, hyperviscosity, and increased fibrinogen levels (Roman, 1999; Rosenberg et al., 2015), can rarely present as levodopa-responsive parkinsonism (Mark et al., 1995). Alternatively, about 10% of patients with small deep infarcts and white matter lesions have been found to have a parkinsonian syndrome (van Zagten et al., 1998). In a series of 28 cases with pathologically confirmed VP, the vascular cases were older, but only 39% apparently had concomitant cognitive decline or dementia, which is much less than the 80% frequency reported in clinical series (Glass et al., 2012). There is growing evidence that cerebral microinfarcts that may not be detected by conventional structural MRI can be responsible for the gait abnormalities of lower body parkinsonism (Buchman et al., 2011; Smith et al., 2012; Buchman et al., 2013). The Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Cohort (RUN DMC) study was designed to investigate the relationship between baseline cerebral small vessel disease and the risk for incident parkinsonism using different MRI and DTI measures (van der Holst et al., 2015). In this prospective cohort study, during a follow-up of mean 5.2 years in duration of 501 elderly participants with CVD and de novo parkinsonism developed in 20 participants, 15 (3%) of whom were diagnosed with VP. The 5-year risk for (any) parkinsonism was increased for those with a high white matter hyperintensity volume (hazard ratio [HR], 1.8 per standard deviation [SD] increase; 95% CI, 1.3–2.4) and a high number of lacunes (HR 1.4 per number increase; 95% CI, 1.1–1.8) at baseline. For VP, this risk was also increased by the presence of microbleeds (HR, 5.7; 95% CI, 1.9–16.8) and a low gray matter volume (HR, 0.4 per SD increase; 95% CI, 0.2–0.8). Thus, cerebral small vessel disease, especially a high white matter hyperintensity volume and a high number of lacunes, was associated with incident parkinsonism. The authors concluded “Our findings favor a role of cerebral small vessel

disease in the etiology of parkinsonism.” One of the limitations of the study was that parkinsonism was diagnosed by direct neurologic examination in 10 of the 398 patients who had follow-up at 5 years. The rest of the patients were diagnosed indirectly through medical records review. In a cross-sectional study comparing 15 patients with VP (8 [53.3%] men; aged 75.7 ± 10.4 years) with 30 patients with PD (17 [56.7%] men; aged 67.3 ± 7.5 years), patients with VP typically presented with a sudden onset of parkinsonism (80%) and a rapidly progressive clinical course (53.3%) (Vale et al., 2015). In addition, they were more likely to have lower body parkinsonism ($P < 0.001$), postural instability ($P = 0.003$), freezing of gait ($P < 0.001$), falls ($P < 0.001$), urinary incontinence ($P < 0.001$), and pyramidal signs ($P < 0.001$), and 80% fulfilled diagnostic criteria for probable vascular dementia. VP was also associated with brain MRI changes, such as multiple lacunar infarcts (66.7%) or extensive white matter disease (26.7%).

In a study of 2500 persons participating in the Religious Orders Study or the Memory and Aging Project who participated in annual motor assessments before autopsy, brains from 850 deceased participants (mean age at death 88.5 years) were examined (Buchman et al., 2013). In over 60% of cases there was evidence of microvascular pathologic features and the majority had no observed macroinfarcts. In one study of 158 patients, poor response to levodopa was associated with greater frequency of symmetrical onset of motor symptoms, worst disease severity, absence of dyskinesia, and greater number of vascular risk factors (Antonini et al., 2012). Striatal DAT density on ^{123}I -FP-CIT SPECT was normal in 48 (30.4%) and abnormal in 110 (69.6%) patients and patients with normal DAT binding showed higher vascular load at MRI. The authors concluded that “Multiple cerebral vascular lesions modify clinical presentation and severity in patients with parkinsonism and this is underlined by specific risk factors primarily hypertension. Striatal DAT assessment is helpful in identifying patients where therapy benefit is less likely.”

Many of the concepts behind VP have been challenged by Vizcarra and colleagues (2015), arguing that the diagnosis of VP cannot be made without pathologic confirmation, but they did not consider the possibility of cerebral microinfarcts as described previously (Buchman et al., 2011; Buchman et al., 2013; Van Veluw et al., 2017). Perivascular spaces (also known as Virchow–Robin spaces), involved in the physiologic drainage of interstitial fluid into perivascular and subarachnoid space and in the lymphatic drainage systems, have been found to be associated with aging, vascular risk factors, vascular diseases, and vascular cognitive impairment and a host of neurodegenerative disorders, including parkinsonism (Rundek et al., 2019).

Others have argued that pathologic findings may not be the gold standard for the diagnosis of VP because there are no accepted pathologic diagnostic criteria for VP and cases that reach autopsy might not be representative of the general population and are likely to include unusual cases (Korczyn, 2015). Furthermore, MRI might be more sensitive than pathologic examination in identifying white matter lesions and can be used to quantify the damage (including changes in normal-appearing white matter) because it is conducted while patients are alive, and provides a view of the whole brain rather than the selective samples used for microscopic

autopsy examinations. In a study of 42 consecutive parkinsonian patients with diffuse leukoaraiosis, but no basal ganglia vascular lesions, 20 (48%) had coexisting striatal dopaminergic deficit as demonstrated by [^{18} F] FP-CIT PET studies (Lee et al., 2015). Those with coexisting dopaminergic deficit (and presumed PD) had asymmetrical onset, greater rigidity and resting hand tremor, better response to levodopa, and less prominent lower body parkinsonism compared with parkinsonian patients with isolated leukoaraiosis. Several studies have linked evidence of cerebral small vessel diseases as demonstrated by 3-tesla MRI with gait disorders (Kim et al., 2016; Werring and Camicioli, 2016; Schwartz et al., 2018; Wardlaw et al., 2019).

It is possible that some of the familial forms of VP represent the entity CADASIL, an autosomal dominant arteriopathy associated with stroke and dementia, caused by mutations in the Notch3 gene on chromosome 19p13.2 (Chabriat et al., 2009). Because of multiple mutations, patients who are suspected to have this syndrome should first be screened for mutations in exons 4, 5, and 6, and if the tests are negative, a skin biopsy should be carried out searching for thickened basal lamina distorted by irregular deposits of granular osmophilic material, coupled with MRI T2 scanning (Markus et al., 2002). VP also has been described in moyamoya (Tan et al., 2003). Based on “a blinded evaluation” of MRI scans in 20 patients with PD “visible arterial compression of the cerebral peduncle” was noted in 74% of cases compared with 5% of 20 age-matched controls (Jannetta et al., 2011). One patient apparently improved after vascular decompression. These observations must be confirmed by other, well-designed, controlled studies.

About a third to half of patients with VP respond to levodopa (Demirkiran et al., 2001), but those with vascular lesions in or close to the nigrostriatal pathway are more likely to improve with levodopa (Zijlmans et al., 2004b). Some patients with VP have a transient improvement in their gait after removal of 35 to 40 mL of CSF (Ondo et al., 2002).

Trauma

Traumatic brain injury (TBI) is one of the major sources of morbidity and mortality, affecting about 2% of the U.S. population with long-term disabilities. Although no definite link between trauma and PD can be established, there is convincing evidence for the concept of posttraumatic parkinsonism (Jankovic, 1994; Krauss and Jankovic, 2012). Parkinsonism is a rare complication of a single trauma to the head unless the injury is severe enough to result in a comatose or vegetative state or causes a penetrating injury to the brainstem or subdural hematoma with compression of the brainstem. However, parkinsonism is a well-recognized sequela of repeated head trauma, such as is seen in the “punch-drunk” syndrome, or pugilistic dementia, in boxers. In addition to typical parkinsonian symptoms, other neurologic consequences of boxing include dementia, paranoia, loss of inhibitions, and bradyphrenia. One of the reasons for the initial underrecognition of boxer’s parkinsonism and other progressive neurologic problems has been the long latency, lasting several years or even decades between cessation of competitive boxing and the development of neurologic symptoms and signs. The evidence indicates that it is the number of bouts (and presumably repetitive subconcussive blows) rather than the number

of knockouts that correlates best with the development of chronic brain damage. A study of 86 amateur boxers found no evidence of cognitive impairment, suggesting that only a small minority of boxers have brain damage (Butler et al., 1993). In addition to dementia, TBI can be associated with parkinsonism (Shively et al., 2012).

Chronic traumatic encephalopathy (CTE), initially described in boxers, is increasingly recognized in other sports, particularly football, hockey, and soccer players and in military personnel (McKee et al., 2013; Baugh et al., 2014; Gandy et al., 2014). At autopsy, brains of patients with CTE typically show global atrophy, with thinning of the corpus callosum and enlarged ventricles and cavum septum pellucidum. In addition, brains from patients with CTE show NFTs that tend to aggregate in the medial temporal cortex, hippocampus and parahippocampal gyrus, thalamus, mammillary bodies, amygdala, hypothalamus, and SN. In contrast to AD, NFTs in CTE concentrate in the superficial layers II and III and there is a paucity of neuritic plaques in CTE (Shively et al., 2012). In a cohort of 85 subjects with histories of repetitive mild TBI evidence of CTE was found in 68 subjects and included focal perivascular epicenters of NFTs in the frontal neocortex, severe tauopathy affecting widespread brain regions, multifocal axonal varicosities and axonal loss in deep cortex and subcortical white matter, and TDP-43 immunoreactive inclusions and neurites (McKee et al., 2013). Clinical features included poor concentration, depression, explosivity and short-term memory loss, executive dysfunction, and cognitive impairment. CTE was the sole diagnosis in 43 cases (63%); 8 were also diagnosed with motor neuron disease (12%), 7 with AD (11%), 11 with Lewy body disease (16%), and 4 with frontotemporal lobar degeneration (6%).

Most of the blows to the head that boxers sustain result in rotational (angular) acceleration, which can cause not only subdural hematoma, petechial hemorrhages, and diffuse axonal injury to the long fiber tracts but also injury to the medial temporal cortex and rostral brainstem, particularly the SN. Marked neuronal degeneration, especially in the lateral and intermediate cell groups, depigmentation, gliosis, and NFTs have been well documented in the SN of boxers’ brains. Although initial pathologic studies of brains of boxers with dementia pugilistica emphasized the presence of numerous NFTs without plaques, subsequent reexamination of the brains with immunocytochemical methods has provided evidence that the beta-amyloid protein present in brains of patients with AD is also present in the boxers’ brains and that dementia pugilistica and AD share common pathogenic mechanisms (Roberts et al., 1990). One study showed increased severity of neurologic deficits in boxers with the APOE ϵ 4 allele, suggesting that genetic predisposition may play a role in the neurologic impairments associated with chronic TBI (Jordan et al., 1997).

Parkinsonism can result not only from injury to the central nervous system but also from peripheral trauma (Cardoso and Jankovic, 1995). In 21 patients, the onset of the movement disorder began within 2 months after injury; in 6 patients, the tremor started 3 to 5 months after the trauma, and the onset was delayed by 1 year in 1 patient. The mean age at onset of the movement disorder was 46.5 ± 14.1 years. Among the parkinsonian patients, high-dose levodopa failed to ameliorate the symptoms in 4 of the 10 patients and the others had only modest improvement. None of the

patients achieved spontaneous remission; in 19 patients, the movement disorder worsened or remained unchanged. PET scans showed decreased fluorodopa uptake in the striatum of 3 patients who were tested, and the raclopride binding in the striatum was symmetrical and slightly increased in 2 of the 3 patients. The postsynaptic nature of peripherally induced parkinsonism is suggested by poor response to levodopa and deep brain stimulation (Baizabal-Carvallo and Jankovic, 2016). Although it is possible that the parkinsonism in these patients occurred by chance alone, the young age at onset, the anatomical and temporal relationship to severe local injury, and the atypical clinical and pharmacologic features suggest that peripherally induced parkinsonism should be added to the growing list of peripherally induced movement disorders.

Hemiparkinsonism–hemiatrophy

Hemiparkinsonism–hemiatrophy syndrome is a rare form of secondary parkinsonism that begins usually in the third or fourth decade; it is characterized by unilateral body atrophy and ipsilateral parkinsonian findings, dystonia, slow progression, and poor response to levodopa (Wijemanne and Jankovic, 2007). Contralateral cortical hemiatrophy is usually present, and there is often a history of perinatal asphyxia or other perinatal injury (Scott and Jankovic, 1996; Wijemanne and Jankovic, 2007). In contrast to a presynaptic involvement in PD, PET studies have provided evidence of presynaptic and postsynaptic nigrostriatal dopaminergic dysfunction in patients with hemiparkinsonism–hemiatrophy syndrome (Przedborski et al., 1994). One patient with hemiparkinsonism–hemiatrophy was found to have a mutation in the *parkin* gene on chromosome 6 (Pramstaller et al., 2002).

Normal pressure hydrocephalus

Normal pressure hydrocephalus (NPH) should be considered in the differential diagnosis of all patients with progressive gait disturbance and other parkinsonian features (Klassen and Ahlskog, 2011). Although this disorder has been recognized for long time, it continues to be quite controversial and there is no consensus on its diagnosis or treatment (Saper, 2016). The American Academy of Neurology Practice Guidelines provided the following conclusions and recommendations (Halperin et al., 2015). *Conclusions:* Shunting is possibly effective in idiopathic NPH (iNPH) (96% chance of subjective improvement, 83% chance of improvement on timed walk test at 6 months) (3 class III). Serious adverse event risk was 11% (1 class III). Predictors of success included elevated Ro (1 class I, multiple class II), impaired cerebral blood flow reactivity to acetazolamide (by SPECT) (1 class I), and positive response to either external lumbar drainage (1 class III) or repeated lumbar punctures. Age may not be a prognostic factor (1 class II). Data are insufficient to judge efficacy of radionuclide cisternography or aqueductal flow measurement by MRI. *Recommendations:* “Clinicians may choose to offer shunting for subjective iNPH symptoms and gait (Level C). Because of significant adverse event risk, risks and benefits should be carefully weighed (Level B). Clinicians should inform patients with iNPH with elevated Ro and their families that they have an increased chance of

responding to shunting compared with those without such elevation (Level B). Clinicians may counsel patients with iNPH and their families that (1) positive response to external lumbar drainage or to repeated lumbar punctures increases the chance of response to shunting, and (2) increasing age does not decrease the chance of shunting being successful (both Level C).”

Because the CSF pressure is not always normal and the disorder seems to be quite heterogeneous in terms of age at onset and clinical presentation, the term *chronic hydrocephalus* has been proposed (Bret et al., 2002). The gait and parkinsonian features associated with NPH include short steps, wide base, stiff legs, start-hesitation, and freezing (“magnetic gait”). In contrast to other parkinsonian disorders associated with freezing, the gait of patients with NPH usually does not improve with visual clues. In addition to the characteristic gait disturbance, the NPH patients frequently exhibit bradykinesia, flexed posture, loss of postural reflexes, cognitive decline, and urinary incontinence. In contrast to PD, patients with NPH have near normal leg function in supine and sitting positions, and they tend to have less tremor. Some patients with NPH may later develop PD, suggesting that the clinical features of NPH were actually the initial manifestation of underlying PD. Shunting may be considered for patients with NPH in whom gait disturbance precedes mental impairment and the mental impairment is of recent origin and mild. Other predictors of favorable outcome after shunting include a known cause of NPH, absence of white matter lesions on MRI, a substantial clinical improvement after CSF tap, 50% occurrence of B-wave on intracranial pressure recording, and resistance to CSF outflow of at least 18 mm Hg/mL/min during CSF infusion test. In a retrospective study of 41 patients at the Mayo Clinic who underwent an invasive diagnostic procedure for evaluation of suspected NPH between 1995 and 2003, 13 ultimately received shunts (Klassen and Ahlskog, 2011). Definite gait improvement was documented in 75% at 3 to 6 months after shunt placement, but it dropped to 33% at 3 years. Patients with cognitive impairment, urinary incontinence, or postural instability experienced little or no sustained benefit. The complications rate was 33%, and 1 patient died during the perioperative period. Additionally, 5 of 12 patients were later found to have an alternative diagnosis. External lumbar drainage of CSF (~25 mL every 3 hours except at night over 72 hours) was investigated in 15 patients, 7 of whom improved in gait and 6 in attention (Lenfeldt et al., 2012). Despite a median drain volume of 470 mL (range, 160–510 mL), the mean ventricular size was reduced by 4.2% and the ratio of volume contraction to drain volume was 0.9%. The authors concluded that the clinical improvement in patients with NPH is related to the continued CSF drainage rather than the reduction in ventricular volume. Thus, 20 mL extraction is easily replaced in about 3 hours, consistent with the accepted CSF production of 15 to 20 mL/h.

Patients with short history, a known cause of hydrocephalus, predominant gait disorder, and imaging studies suggestive of hydrodynamic hydrocephalus without cortical atrophy and without white matter involvement, are considered the best candidates for shunting, and 50% to 70% experience substantial improvement after surgery. In one study of 55 patients treated with shunting for NPH, the improvement was sustained during the mean follow-up of 5.9 ± 2.5

years, with gait and cognitive function improving the most (Pujari et al., 2008). NPH is sometimes difficult to differentiate from VP or subcortical arteriosclerotic encephalopathy (SAE) (Mehanna and Jankovic, 2013). Furthermore, hypertension, white matter lesions, diabetes mellitus, and other vascular factors probably contribute to the pathophysiology of NPH (Jaraj et al., 2016).

Obstructive hydrocephalus, with or without aqueductal stenosis, can also result in parkinsonism that may respond to levodopa (Jankovic et al., 1986; Racette et al., 2004). Most patients with disabling symptoms of hydrocephalus-associated parkinsonism require ventriculoperitoneal shunting. Despite aggressive marketing directly to patients by various companies promoting their shunting devices (e.g., Codman), NPH is actually quite uncommon and even well-selected patients do not always obtain satisfactory results from shunting. In an open-label randomized, delayed-treatment trial (SINPHONI-2) involving 93 patients in Japan, lumboperitoneal shunt surgery was thought to be beneficial for patients with iNPH (Kazui et al., 2015).

The entity of NPH has been increasingly challenged, and some have expressed doubt about the existence of this disorder (Saper et al., 2017). In one study initial diagnosis of idiopathic NPH persisted in 32% of patients at 36 months, with revised diagnoses of AD, DLB, and PSP confirmed in over 25% of the cases (Espay et al., 2017). In a Japanese family with several members expressing the clinical features of NPH whole-exome sequencing identified a loss-of-function variant in *CFAP43*, which encodes cilia- and flagella-associated protein (Morimoto et al., 2019). Thus, this suggests another mechanism for the clinical phenotype of NPH.

Other secondary parkinsonian disorders

It is beyond the scope of this review to discuss all other causes of parkinsonism. Brain tumors and gliomatosis cerebri, even when they spare basal ganglia, may cause parkinsonism (Krauss et al., 1995; Cicarelli et al., 1999; Pohle and Krauss, 1999; Tagliati et al., 2000). Familial basal ganglia calcification (bilateral striopallidodentate calcinosis, or Fahr disease) is another diagnosis that should be considered in any patient with parkinsonism unresponsive to levodopa, ataxia, and personality changes (Manyam et al., 2001; Warren et al., 2002; Oliveira et al., 2004; Wang et al., 2012). The basal ganglia, cerebellar, paraventricular, and cortical calcification may be missed on MRI and may not become apparent until a CT scan of the head is obtained (Kozic et al., 2009). Mutations in *SLC20A2*, encoding the type III sodium-dependent phosphate transporter 2 (PiT2) in the idiopathic basal ganglia calcification families, implicate altered phosphate homeostasis in the cause of this disorder (Wang et al., 2012).

Other causes of parkinsonism include central pontine and extrapontine myelinolysis (Seiser et al., 1998), wasp sting (Leopold et al., 1999), Sjögren syndrome (Walker et al., 1999), and others. There is growing interest in paraneoplastic and other autoimmune causes of neurodegeneration resulting in atypical forms of parkinsonism (Golbe et al., 1989; Baizabal-Carvallo and Jankovic, 2018). For example, the clinical spectrum of voltage-gated potassium channelopathies (VGKCs) with autoantibodies detected in the blood, neurons, glia, and muscle, include parkinsonism, tremor, myoclonus, and chorea (Tan et al., 2008). Other features

of this paraneoplastic syndrome include cognitive impairment, seizures, dysautonomia, peripheral neuropathy, and the presence of certain cancers. Antiphospholipid syndrome has been associated with chorea and other movement and neurologic disorders, including parkinsonism (Huang et al., 2008).

Parkinsonism, frontal dementia, peripheral neuropathy, neurogenic bladder, and upper motor neuron signs have been described in adult polyglucosan body disease (Robertson et al., 1998). A growing number of mitochondrial disorders have been described with a broad phenotype, including parkinsonism. These include the *POLG1* mutation syndromes that may also include sensory ataxic neuropathy, dysarthria, and ophthalmoparesis (SANDO), intellectual disability, epilepsy, migraines, dementia, dystonia, focal myoclonus, and liver disease (Hudson et al., 2007; McHugh et al., 2010). The symptoms and liver failure may be markedly exacerbated by valproate. Inherited in an autosomal recessive or dominant mitochondrial pattern, the disease, referred to also as Alpers syndrome, is due to mutations in *POLG1*, a nuclear gene that encodes for the catalytic subunit of the mtDNA polymerase gamma, essential for mtDNA replication (Milone and Massie, 2010). A single point mutation in mitochondrial 12SrRNA has been reported to be associated with parkinsonism, deafness, and neuropathy (Thyagarajan et al., 2000). Encephalopathy and parkinsonism have been reported in children with leukemia who have been treated with bone marrow transplantation, amphotericin, immunosuppressants, and total body irradiation (Mott et al., 1995).

Rarely, functional (psychogenic) causes have been implicated in the pathogenesis of parkinsonism (Lang et al., 1995; Jankovic, 2011; Pareés et al., 2013; Baizabal-Carvallo et al., 2019a,b; Thenganatt and Jankovic, 2019). In addition to typical PD-related symptoms, functional (psychogenic) parkinsonism often exhibits abrupt onset, typically in response to a stressful event, followed by fluctuating course, early disability, bilateral shaking and slowness, nondecremental slowness when performing repetitive movements, voluntary resistance against passive movement without cogwheel rigidity, distractibility, generalized and “give-way” weakness, stuttering speech, bizarre gait, and a variety of behavioral, sexual, and other motor and nonmotor symptoms. Levodopa-related motor complications do not occur even in the setting of chronic, high-dose therapy. In some cases the differentiation between PD and functional (psychogenic) parkinsonism is very difficult, and in those cases the response to placebo (e.g., powerful suggestion when applying a tuning fork to a tremulous limb, or administration of carbidopa without levodopa) may be helpful (Jankovic, 2011). The mechanism of functional (psychogenic) parkinsonism and other psychogenic movement disorders is unknown, but some have proposed a pivotal role for “self-directed attention” (Pareés et al., 2013). A comprehensive, multidisciplinary assessment of patients with psychogenic parkinsonism, when combined with insight-oriented psychotherapy, physiotherapy, and treatment of comorbid depression, is often helpful, although the prognosis for this group of disorders remains relatively poor.

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Tremors

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Introduction

Tremor is a rhythmic, oscillatory movement produced by alternating or synchronous contractions of antagonist muscles. It is the most common form of involuntary movement, but only a small fraction of those who shake seek medical attention. Indeed, in one epidemiologic study of normal controls, 96% were found to have clinically detectable postural tremor and 28% had a postural tremor of “moderate amplitude” (Louis, Ottman, et al., 1998).

Tremors can be classified according to their phenomenology, distribution, frequency, or cause (Hallett, 1991; Lou and Jankovic, 1991a; Bain, 1993; Deuschl, Bain, et al., 1998; Jankovic, 2000; Deuschl et al., 2001; Jankovic and Lang, 2008; Deuschl and Elble, 2009; Elble and Deuschl, 2011; Elias and Shah, 2014). Phenomenologically, tremors are divided into two major categories: rest tremors and action tremors (Table 10.1). Rest tremor is present when the affected body part is fully supported against gravity and not actively contracting; rest tremor is diminished or absent during voluntary muscle contraction and during movement. Action tremors occur with voluntary contraction of muscles, and they can be subdivided into postural, kinetic, task-specific or position-specific, and isometric tremors. Postural tremor is evident during maintenance of an antigravity posture, such as holding the arms in an outstretched horizontal position in front of the body. Some parkinsonian patients exhibit postural tremor that emerges after a latency of a few seconds. This tremor, referred to here as reemergent tremor, probably represents a rest tremor that has been “reset” during posture holding (Jankovic et al., 1999) (Fig. 10.1). The relationship of this reemergent tremor to the typical rest tremor is supported by the observation that this reemergent repose tremor shares many characteristics with the typical rest tremor;

it has the same 3- to 6-Hz frequency, and it also responds to dopaminergic therapy (Video 10.1). Rarely, postural tremor occurring after a brief (2- to 4-second) latency can be seen even without observable rest tremor (Louis, Pullman et al., 2008). Kinetic tremor can be seen when the voluntary movement starts (initial tremor), during the course of the movement (dynamic tremor), and as the affected body part approaches the target, such as while performing the finger-to-nose or the toe-to-finger maneuver (terminal tremor, also called intention tremor). Task-specific tremors occur only during, or are markedly exacerbated by, a certain task, such as while writing (primary handwriting tremor) (Video 10.2), while speaking or singing (voice tremor) (Rosenbaum and Jankovic, 1988; Soland et al., 1996a), or while smiling (Schwingenschuh et al., 2009). Besides writing, task-specific tremors may be triggered during other activities, such as while playing golf, particularly when putting (Video 10.3). Position-specific tremors occur while holding a certain posture (e.g., the “wing-beating” position or holding a spoon or a cup close to the mouth). One example of a task- or position-specific tremor is the tremor that occurs in performing the dot test (“dot approximation test”), during which the subject, seated at the desk with elbow elevated to a 90-degree shoulder abduction, is asked to hold the tip of the pen as close to a dot on a horizontal paper as possible without touching the dot. Patients with essential tremor (ET) or other action tremors usually exhibit exacerbation of the tremor during this specific task. A variant of this tremor occurs in performing the modified finger-nose-finger test, during which the subject stands in front of a paper mounted on a wall and is asked to mark the center of the drawn target and to make a mark with a felt-tipped pen five times (Louis, Applegate, et al., 2005). Isometric tremor occurs during a voluntary contraction of muscles that is not accompanied by

Video 10.1 Reemergent tremor.

Video 10.2 Task-specific tremor.

Video 10.3 Task-specific tremor.

Table 10.1 Categorization of tremors

Rest	Action		
	Postural	Kinetic	Miscellaneous
• Parkinsonian – Parkinson disease (PD) – Secondary – P-plus • ET variants • Midbrain • Myorhythmia	• Physiologic • Enhanced physiologic – Stress – Endocrine – Drugs, toxins • Essential tremor • Orthostatic • Other position-specific tremors • PD (reemergent) • Dystonic • Cerebellar • Myorhythmia • Cortical • Neuropathic • Fragile X-associated tremor/ataxia syndrome (FXTAS)	• Cerebellar – Multiple sclerosis – Stroke – Degenerative – Wilson disease – Drugs, toxins • Midbrain • Task-specific • Cortical	• Idiopathic • Psychogenic • Other involuntary rhythmic movements – Convulsions – Myoclonus – Asterixis – Nystagmus – Fasciculations – Clonus

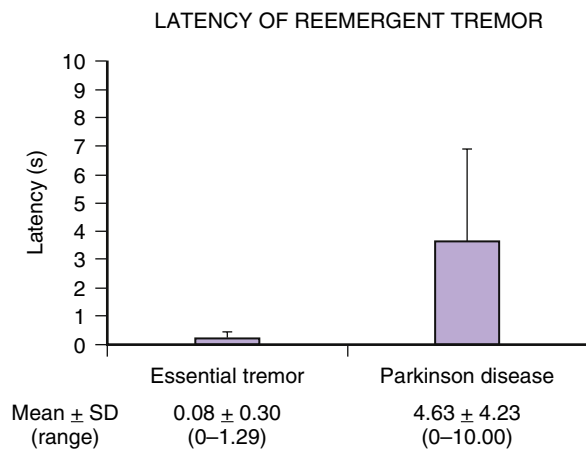


Fig. 10.1 Rest tremor of Parkinson disease reemerges after a latency when arms are outstretched or in a wing-beating position. (Jankovic J, Schwartz KS, Ondo W. Re-emergent tremor of Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 1999;67:646–650.)

a change in position of the body part, such as maintaining of a tightly squeezed fist or while standing (e.g., orthostatic tremor; see later). ●

Tremors also can be classified according to their anatomic distribution—for example, head, tongue, voice, and trunk. Some patients describe “internal tremor,” found in 32.6% of patients with Parkinson's disease (PD) and 54.5% of those with ET (Cochrane et al., 2015). Orolingual tremors include physiologic, essential, task- and position-specific, dystonic, orthostatic, parkinsonian, palatal (also termed palatal myoclonus), drug-induced, hereditary, and psychogenic (Erer and Jankovic, 2007; Kenney et al., 2007; Silverdale et al., 2008). Because of the complexity of limb tremors, it is best to describe them according to the joint about which the oscillation is most evident—for example, metacarpal-phalangeal joints, wrist, elbow, and ankle tremor. In most tremors, the frequency ranges between 4 and 10 Hz, but the cerebellar tremors may be slower, with a frequency of 2 to 3 Hz. The “slow” tremors (frequency: 1–3 Hz) are sometimes referred

to as myorhythmia and are usually associated with brainstem pathologic processes (Masucci et al., 1984; Tan et al., 2007; Baizabal-Carvallo et al., 2015; Ure et al., 2016). The “fast” tremors (frequency: 11–20 Hz) may be distinct tremor disorders, such as orthostatic tremor, or may represent harmonics of other tremors. The clinical characteristics of tremors provide the most important clues to their cause (Table 10.2).

Assessment of tremors

There have been many attempts to quantitate tremor, but it is not apparent whether electromyographic (EMG), accelerometric, or other methods of measuring tremor correlate with the clinical rating scales (Maetzler et al., 2013; Pulliam et al., 2014). Indeed, one study suggested that assessments of spirometry and handwriting correlated better with overall functional tremor-related disability than did the electrophysiologic methods (Bain et al., 1993). However, because the physiologic measurements and the clinical ratings were not performed simultaneously and because of other technical problems, interpretation of the study was challenging. Elble and colleagues (1996) described the use of a digitizing tablet in quantification of tremor during writing and drawing. Although relatively good intertrial correlations were obtained with this method, the tablet failed to capture the speed of writing or the amount of effort exerted by the patient who during the task was trying to control the tremor while simultaneously writing. One study found high interobserver reliability using a diagnostic protocol for ET (Louis, Ford, Bismuth, 1998). The investigators also found high specificity and sensitivity of a screening questionnaire compared with the physician's examination in patients with definite and probable ET, but actual examination of the subjects was necessary to detect mild ET (Louis, Ford, Lee, Andrews, 1998). In another study, the authors concluded that when a limited number of tests was available in large epidemiologic surveys, a test such as the finger-nose maneuver may be used to screen populations for ET, whereas to exclude normal subjects, the spiral drawing test, water

Table 10.2 Classification and differential diagnosis of tremors

A. Rest tremors	
1. Parkinson disease (PD)	(3) Drugs: Beta-agonists (e.g., theophylline, terbutaline, epinephrine), dopaminergic drugs (levodopa, dopamine agonists), stimulants (amphetamines), psychiatric drugs (lithium, neuroleptics, tricyclics), methylxanthines (coffee, tea), valproate, amiodarone, cyclosporine, interferon
2. Other parkinsonian syndromes	(4) Toxins: Hg, Pb, As, Bi, Br, alcohol withdrawal
a. Multiple system atrophies (SND, SDS, OPCA)	c. Essential tremor
b. Progressive supranuclear palsy	(1) Autosomal dominant
c. Cortical-basal-ganglionic degeneration	(2) Sporadic
d. Parkinsonism–dementia–ALS of Guam	d. Postural tremor associated with
e. Diffuse Lewy body disease	(1) Dystonia
f. Progressive pallidal atrophy	(2) Parkinsonism
	(3) Myoclonus
	(4) Hereditary motor-sensory neuropathy (Roussy–Levy)
	(5) Kennedy syndrome (X-linked spinobulbar atrophy)
3. Heredodegenerative disorders	e. PD and other parkinsonian syndromes
a. Huntington disease	f. Tardive tremor
b. Wilson disease	g. Midbrain (rubral) tremor
c. Neuroacanthocytosis	h. Cerebellar hypotonic tremor (titubation)
d. Neurodegeneration with brain iron accumulation 1 (NBIA1)	i. Neuropathic tremor: Motor neuron disease, peripheral neuropathy, peripheral nerve injury, reflex sympathetic dystrophy
e. Gerstmann–Sträussler–Scheinker disease	
f. Ceroid lipofuscinosis	
4. Secondary parkinsonism	2. Kinetic (intention, dynamic, termination) tremors
a. Toxic: MPTP, CO, Mn, methanol, cyanide, CS ₂	a. Cerebellar disorders (cerebellar outflow): Multiple sclerosis, trauma, stroke, Wilson disease, drugs, and toxins
b. Drug-induced: Dopamine receptor–blocking drugs (reserpine, tetrabenazine), dopamine-depleting drugs (reserpine, tetrabenazine), lithium, valproate, amiodarone, flunarizine, cinnarizine	b. Midbrain lesions
c. Vascular: Multi-infarct, Binswanger disease, lower body parkinsonism	3. Task- or position-specific tremors
d. Trauma: Pugilistic encephalopathy, midbrain injury	a. Handwriting
e. Tumor and paraneoplastic	b. Orthostatic
f. Infectious: Postencephalitic, fungal, AIDS, subacute sclerosing panencephalitis, Creutzfeldt–Jakob disease	c. Other (e.g., occupational) task-specific tremors
g. Metabolic: Hypoparathyroidism, chronic hepatic degeneration, mitochondrial cytopathies	
h. Normal pressure hydrocephalus	4. Isometric
5. Severe essential tremor (ET)	a. Muscular contraction during sustained exertion
6. Midbrain (rubral) tremor	
7. Tardive tremor	C. Miscellaneous tremors and other rhythmic movements
8. Myorhythmia	1. Myoclonus: Rhythmical segmental myoclonus (e.g., palatal), oscillatory myoclonus, asterixis, minipolymyoclonus
9. Spasmus nutans	2. Dystonic tremors
	3. Cortical tremors
	4. Epilepsia partialis continua
	5. Nystagmus
	6. Clonus
	7. Fasciculation
	8. Shivering
	9. Shuddering attacks
	10. Head bobbing (third ventricular cysts)
	11. Aortic insufficiency with head titubation
B. Action tremors	
1. Postural tremors	
a. Physiologic tremor	
b. Enhanced physiologic tremor:	
(1) Stress-induced: Emotion, exercise, fatigue, anxiety, fever	
(2) Endocrine: Hypoglycemia, thyrotoxicosis, pheochromocytoma, adrenocorticosteroids	

MPTP, 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

pouring test, or arm extension test may be preferable (Louis et al., 1999a). In a study in which 54 Archimedes spirals were drawn using a digitizing tablet by nine ethanol-responsive patients with ET before and after the administration of ethanol, computerized scores correlated with visual ratings ($P < 0.0001$) and quantitative ratings provided better sensitivity than visual rating when recording the overall effects of an ethanol challenge ($P < 0.05$) (Haubenberger et al., 2011). A performance-based test for ET has been validated and compared with other measures of tremor (Louis et al., 1999b). Although this performance-based test was thought to objectively assess functional capacity in patients with ET, the test was cumbersome to perform because it required a variety of

props, such as a milk carton, a glass, a soup spoon, a bowl, a saucer, a wallet, coins, an electrical socket, a thread and needle, a strip of buttons, and a telephone. Using another instrument, the modified Klove-Matthews Motor Steadiness Battery and the Nine-Hole Steadiness Tester, Louis, Yousefzadeh, and colleagues (2000) showed that these portable instruments provided a reliable and valid means of collecting objective quantitative data on tremor severity. A Tremor Disability Questionnaire was developed and found to reliably correlate with multiple measures of tremor severity (Louis, Barnes, et al., 2000). Another screening instrument for ET, consisting of 7 items and a spiral drawing, has been found to have 70.5% sensitivity, 68.2% specificity, and 64.9% positive

predictive value (Lorenz et al., 2008). A simple, user-friendly clinical tool, with a higher sensitivity, specificity, and predictive value is needed to assess tremors in the clinic and in the field. A teaching videotape for assessment of ET was developed to improve the uniform application of the Washington Heights-Inwood Genetic Study of Essential Tremor (Louis, Barnes et al., 2001). Using a clinical evaluation (interview and videotaped examination) and an electrophysiologic evaluation (quantitative computerized tremor analysis using accelerometry and EMG), Louis and Pullman (2001) found a very high concordance rate between the two methods in 51 of 54 (94%) subjects, suggesting that using either technique would result in a similar diagnosis. Although not yet validated, the Unified Tremor Rating Assessment developed by the Tremor Research Group has been used in a number of clinical therapeutic trials (Bain, 1993; Jankovic et al., 1996). The other scale that has been used in several tremor studies is the Fahn-Tolosa-Marin Tremor Rating Scale (TRS) (Fahn et al., 1993). Although the inter-rater reliability of this scale has been shown to be relatively poor, there has been good consistency, with an average Spearman correlation of 0.87, when the same rater repeatedly assesses the tremor (Stacy et al., 2007). Using the TRS, Putzke and associates (Putzke et al., 2006) showed that the total score increased by about 2 points during prospective follow-up of patients with ET over a mean of 3.6 years and that older age, longer duration of disease, and asymmetrical onset of tremor was associated with increased tremor severity.

Another tremor rating scale, The Essential Tremor Rating Scale (TETRAS), developed by the Tremor Research Group (TRG), has been validated against the TRS (Elble et al., 2008, 2012). TETRAS comprises two subscales, the Activities of Daily Living (ADL) subscale and the Performance subscale. The TETRAS Performance has been shown to be a valid scale with excellent inter-rater and intrarater reliabilities (Elble et al., 2012). One study on temporal fluctuations in ET over 6 hours has demonstrated a good correlation of a quantitative motor assessment system with TETRAS for upper limb tremor, a subset of the TETRAS Performance scale (Mostile et al., 2012). Using accelerometry as a measure of tremor in 15 ET patients after a single oral ethanol dose calculated to reach 0.05 g/dL breath alcohol content, significant correlation was found between the accelerometry data TETRAS results with the calculated minimum detectable change of TETRAS of 8.9%. This demonstrated sensitivity to change of the scale for assessing effects of a therapeutic intervention (Voller et al., 2014). In general, the minimum detectable change for an individual is about 50% of baseline, but when comparing groups, a 30% change is considered by most experts as significant.

The existing five tremor severity scales (the Fahn-Tolosa-Marin Tremor Rating Scale, the Bain and Findley Clinical Tremor Rating Scale, the Bain and Findley Spirography Scale, the Washington Heights-Inwood Genetic Study of Essential Tremor Rating Scale, and the Tremor Research Group Essential Tremor Rating Assessment Scale), one ADL/disability scale (the Bain and Findley Tremor ADL Scale), one quality-of-life scale (the Quality of Life in Essential Tremor Questionnaire), and one screening instrument (the Washington Heights-Inwood Genetic Study of Essential Tremor Rating Scale, version 1) have been evaluated, and all have been found useful in assessing tremor. However, "a more

comprehensive analysis of sensitivity to change in order to judge their utility in clinical trials and individual patient assessments" has been recommended (Elble et al., 2013).

The TETRAS has been found to correlate with quantitative assessments using the Kinesia (CleveMed) system (Mostile et al., 2010; Heldman et al., 2011; Pulliam et al., 2014). Any assessment of tremor must take into account minute-to-minute and hour-to-hour amplitude variability (Koller and Royce, 1985; Mostile et al., 2012), and potential provocations, such as voluntary isometric contraction in the case of action tremors and walking and counting backward in the case of rest tremor (Raethjen et al., 2008). In one study, a maximal 23% absolute variation in tremor amplitude was found in patients with ET, TETRAS, quantitative motor assessment system (QMAS), and videos were used to record tremor amplitude every 2 hours for 6 hours (Mostile et al., 2012). There also has been an emerging wearable technology that uses accelerometers and other sensors coupled with computers to quantitate tremors and other movement disorders (Maetzler et al., 2013).

Rest tremors

Diagnosis

Rest tremor is most typically present in patients with PD, although 19% of ET patients have rest tremor (Cohen et al., 2003). In one study, all 34 patients with pathologically proven cases of idiopathic (Lewy body) parkinsonism demonstrated typical rest tremor sometime during the course of their illness (Rajput et al., 1991). Although this study suggests that parkinsonian patients who do not exhibit rest tremor probably do not have idiopathic parkinsonism (PD), another study, involving 100 pathologically proven cases of PD, found that 32% of all patients apparently never manifested tremor during the course of their disease (Hughes et al., 1993). Although rest tremor in PD typically involves the hands or legs, it may also involve the face and jaw. In one study 28 of 559 (5%) patients with PD had facial tremors and these tremors responded to levodopa in 46% of patients (Rossi et al., 2016). Facial tremors, such as lip, chin and jaw tremor can be the initial early sign of PD (Erer and Jankovic, 2007).

Several studies have suggested that the natural course of PD is in part related to the presence or absence of tremor (Jankovic et al., 1990; Hughes et al., 1993; Helmich et al., 2012, 2013). Tremor-dominant PD may be associated with earlier age at onset, less cognitive decline, and slower progression than the type of PD that is dominated by postural instability and gait difficulty (PIGD) (Jankovic et al., 1990). Clinicopathologic correlations are needed to answer the question as to whether the tremor-dominant form and the PIGD-dominant form represent different diseases or merely variants of one disease, namely, PD. In support of the former is the finding that 27% of patients with the PIGD form of idiopathic parkinsonism had Lewy bodies at autopsy (Rajput et al., 1993). In another clinicopathologic study, Hirsch and colleagues (1992) demonstrated that patients with PD and prominent tremor have degeneration of a subgroup of midbrain (A8) neurons, whereas this area was spared in PD patients without tremor. This observation supports the hypothesis that differential damage of subpopulations

of neuronal systems is responsible for the diversity of phenotypes seen in PD and other parkinsonian disorders. It is unclear whether the occasional patients with long-standing unilateral tremor and minimal or no other parkinsonian findings have a benign form of PD, as is suggested by positron emission tomography (PET) scans that have revealed low fluorodopa uptake in the contralateral putamen (Brooks et al., 1992), or whether this condition represents a separate disease entity. In contrast to patients with the PIGD form of PD, patients with tremor-dominant PD have increased metabolic activity in the pons, thalamus, and motor-association cortices (Antonini et al., 1998). When rest tremors involve the fingers, hands, lips, jaw, and tongue in the same individual, they share a common frequency, suggesting that they may be of central origin (Hunker and Abbs, 1990). This pattern, however, changes during sleep in that non-rapid eye movement (REM) sleep transforms the alternating tremor that is typically seen in the awake patient into subclinical repetitive muscle contractions of variable frequency and duration during sleep stages I to IV, and the tremor disappears during REM sleep (Askenasy and Yahr, 1990).

Rest tremor has other causes in addition to PD and related parkinsonian disorders (Table 10.3). Patients with severe ET

Table 10.3 NIH Essential Tremor Consortium diagnostic criteria for essential tremor

Definite

1. Bilateral arm tremor with 2+ amplitude rating in at least one arm and 1+ in the other arm
or
2. Predominant cranial-cervical tremor with 2+ amplitude rating and 1+ rating in at least one arm. The head tremor is rhythmical, without directional preponderance, and without asymmetry of cervical muscles
3. Exclude obvious secondary causes of tremor: For example, physiologic, drug-induced, Charcot-Marie-Tooth (CMT), chronic inflammatory demyelinating polyradiculoneuropathy (CIPD), Parkinson disease (PD) (coexistent dystonia is allowed, but coexistent PD is not)

Probable

1. 1+ arm tremor bilaterally
or
2. Isolated cranial-cervical tremor with 2+ amplitude rating
or
3. Convincing history of ET
4. Exclude obvious secondary causes of tremor: For example, physiologic, drug-induced, CMT (coexistent dystonia is allowed; coexistent PD is allowed if there is a convincing history of preexisting ET)

Possible

1. Isolated 1+ cranial-cervical tremor
2. Task/position specific hand/arm tremor
3. Unilateral arm tremor
4. Orthostatic tremor

Tremor rating: 0, none perceived; 1, slight (barely noticeable); 2, moderate, noticeable, probably not disabling (<2-cm excursions); 3, marked, probably partially disabling (2–4 cm excursions); 4, severe, coarse, disabling (>4 cm excursions).

Participants in the July 1996 NIH meeting: J. Beach, S. B. Bressman, M. F. Brin, D. De Leon, L. Goldfarb, M. Hallett, J. Jankovic, W. Koller, D. Mirel, K. Wilhemssen. From Brin MF, Koller W. Epidemiology and genetics of essential tremor. *Mov Disord.* 1998;13(Suppl. 3):55–63.

may have tremor at rest and prominent kinetic tremor. It is not known whether the ET patients with rest tremor have associated PD, whether they later develop other features of PD, or whether the rest tremor is a feature of ET (Jankovic, 1989; Shahed and Jankovic, 2007).

Some patients with lesions in the cerebellar outflow pathways, particularly in the superior cerebellar peduncle near the red nucleus, in addition to postural and kinetic tremor, also have tremor at rest, probably because of an interruption of the nigrostriatal pathway (Remy et al., 1995; Baizabal-Carvallo et al., 2015). In 1904, Gordon Holmes described a syndrome characterized by a low-frequency rest tremor (less than 4.5 Hz), which was accentuated by posture and intentional movements. Because isolated lesions in the red nucleus are not tremorogenic and animal and clinicopathologic studies have shown that this tremor typically resulted from lesions of adjacent structures (involving cerebellothalamic and nigrostriatal tracts) the term “Holmes tremor” is preferred rather than “rubral” tremor. Holmes tremor is characterized by a large and irregular (2–5 Hz) amplitude tremor often affecting predominantly proximal upper extremities (Raina et al., 2016). The exact pathophysiology remains unknown, but this tremor has been described in patients with lesions involving the cerebello-thalamo-cortical and dentato-rubro-olivary pathways and is often associated with dysfunction in the nigrostriatal pathway. This predominantly unilateral tremor may be associated with other neurologic signs, such as ataxia, bradykinesia, and ophthalmoplegia. It is often associated with midbrain pathologic conditions, such as multiple sclerosis, stroke, tumor, or arteriovenous malformation (Lee et al., 2008). In one series of 29 patients, the most common causes were vascular (48.3%) and the median latency from lesion to tremor onset was 2 months (Raina et al., 2016). The affected arm or leg may possibly be ataxic and may be associated with third nerve palsy (Benedikt syndrome) (Video 10.4). Holmes tremor is most often caused by trauma, stroke, multiple sclerosis, and Wilson disease (Lou and Jankovic, 1993; Krauss et al., 1995; Miwa et al., 1996; Alarcon et al., 2004). Strokes involving the posterior circulation may involve the thalamus, producing slow (1- to 3-Hz) rest and postural tremors, sometimes referred to as myorhythmia (Masucci et al., 1984; Cardoso and Jankovic, 1996; Miwa et al., 1996; Baizabal-Carvallo et al., 2015). Holmes tremor rarely responds to any medical therapy; however, wrist weights, levodopa, dopamine agonists, amantadine, propranolol, clonazepam, isoniazid, and levetiracetam (Fellazzo et al., 2008) may be effective in reducing the amplitude of this often disabling tremor. Several case reports and small series of patients with positive benefits have been treated with deep brain stimulation (DBS), although the results on proximal tremor are often not robust (Raina et al., 2016).

Myorhythmia is a slow (1- to 3-Hz) frequency, continuous or intermittent, relatively rhythmic movement that is present at rest but may persist during activity (Masucci et al., 1984; Cardoso and Jankovic, 1996). It may be associated with palatal myoclonus, and it disappears with sleep. Except for the slower frequency, the presence of flexion-extension rather than the typical supination-pronation pattern, and the absence of associated parkinsonian findings, myorhythmia resembles a parkinsonian tremor. In the cases that were examined at autopsy, the sites of maximum pathologic findings involved chiefly the brainstem (particularly the

Video 10.4 Cerebellar outflow tremor.

substantia nigra [SN] and the inferior olive) and the cerebellum. The causes of myorhythmia include brainstem stroke, cerebellar degeneration, Wilson disease, and Whipple disease (Masucci et al., 1984; Tison et al., 1992; Cardoso and Jankovic, 1996).

Palatal myoclonus, sometimes referred to as palatal tremor, has some features of tremor, but in contrast to tremor, which is produced by alternating or synchronous contractions of antagonist muscles, the palatal movement is produced by rhythmical contractions of agonist muscles; thus, the term *myoclonus* has been preferred by many experts despite the arguments raised against this nosology (Zadikoff et al., 2006). Because of its rhythmicity many experts also refer to it as a tremor and thus we will include it in this chapter. Palatal myoclonus, a form of segmental myoclonus, manifests as rhythmical contractions of the soft palate resulting from acute or chronic lesions involving the Guillain-Mollaret triangle, which includes the circuit of the dentate nucleus and red nucleus via the central tegmental tract with connections to the inferior olivary nucleus. Symptomatic palatal myoclonus (SPM) usually persists during sleep, whereas essential palatal myoclonus (EPM) is frequently associated with an earclicking sound and disappears with sleep. In EPM the muscle agonist is the tensor veli palatini, which opens the Eustachian tube and is innervated by the trigeminal nerve. In the SPM, the palatal movement is due to contractions of the levator veli palatine, innervated by the facial nucleus and nucleus ambiguus. When the tensor muscle contracts, as in EPM, the entire soft palate moves, whereas only the edges of the soft palate move when the levator muscle contracts in the SPM. Symptomatic, but not essential, palatal myoclonus is often associated with hypertrophy of the inferior olive (Goyal et al., 2000). SPM has been associated with a variety of lesions involving the brainstem and some neurodegenerative disorders such as Alexander disease (Pareyson et al., 2008).

Treatment with neuroleptics can also result in persistent tremor, referred to as tardive tremor (Stacy and Jankovic, 1992). This rest, postural, and kinetic tremor, with a frequency of 3 to 5 Hz, is aggravated by, and persists after, neuroleptic withdrawal and improves after treatment with the dopamine-depleting drug tetrabenazine. The tremor may be accompanied by other tardive movement disorders, including akathisia, chorea, dystonia, myoclonus, and stereotypy. There is usually no family history or other explanation for the tremor.

Spasmus nutans is characterized by the triad of nystagmus; abnormal head position; and irregular, multidirectional head nodding that disappears during sleep. This condition is self-limited, and often a familial condition is first noted between the ages of 4 and 12 months, and it usually disappears within a year or two. Another oculomotor cause of head tremor is "head-shaking nystagmus" seen in patients with lateral medullary infarction (Choi et al., 2007). The 2- to 3-Hz horizontal head shaking has been postulated to result from unilateral impairment of nodulouvarial inhibition of the multisensory rotation estimator (velocity storage).

Pathophysiology

The pathophysiology of rest tremor is not well understood, but emerging data suggest primary involvement of the

cerebello-thalamo-cortical circuit in the generation of this tremor. This circuit rather than pallidal or other basal ganglia or thalamic neurons fires in synchrony with ongoing resting tremor in PD (Timmerman et al., 2003; Helmich et al., 2012, 2013). Although the rest tremor appears to be generated in the cerebello-thalamo-cortical loop, it is likely that the rest tremor is triggered by a pacemaker autorhythmic activity in the thalamus or basal ganglia (Helmich et al., 2012, 2013). According to the proposed "dimmer-switch model" of parkinsonian tremor "depletion of pallidal dopamine (and possibly serotonin) causes pathologic activity in the striato-pallidal circuit that triggers—through the motor cortex—tremor-related activity in the cerebello-thalamo-cortical circuit" (Helmich et al., 2012, 2013). This striato-pallidal activity can emerge only under rest conditions when the basal ganglia are not involved in voluntary movement; therefore, the classic PD tremor can be observed both at rest and during fixed postural holding (reemergent tremor) (Jankovic et al., 1999). By simultaneous recording of local field potentials from the subthalamic nucleus (STN) in 11 patients with PD, Hirschmann and colleagues (2013) showed increased local field potential power at individual tremor frequency and decreased cortical power in the beta band (13–30 Hz). These findings demonstrate a direct relationship between the synchronization of cerebral oscillations and tremor frequency.

Treatment

The treatment of rest tremors is similar to that of parkinsonism (Jankovic and Marsden, 1998; also see Chapter 6). Secondary and potentially curable causes should be excluded, particularly when there are associated features to suggest disorders other than PD (see Table 10.3). Anticholinergic and dopaminergic drugs provide the most effective relief of rest tremors; however, because of side effects anticholinergics are rarely used. Clozapine, an atypical neuroleptic that does not significantly exacerbate parkinsonism but can in rare cases lead to potentially serious side effects such as agranulocytosis, has been shown to be effective in the treatment of parkinsonian tremor (and ET) (Bonuccelli et al., 1997; Friedman et al., 1997; Ceravolo et al., 1999). Ethosuximide, an anticonvulsant that blocks low-threshold Ca^{++} conductance in the thalamus, has been shown to reduce tremor in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) monkeys and potentiate the effects of a D2 agonist (Gomez-Mancilla et al., 1992). However, ethosuximide was found ineffective in a pilot study of six PD patients with drug-resistant tremor (Pourcher et al., 1992). Mirtazapine (Remeron), a novel antidepressant that enhances noradrenergic and serotonergic transmission and acts as a presynaptic α_2 , 5HT₂, and 5HT₃ receptor antagonist, has been reported to improve rest tremor (Pact and Giduz, 1999). Other drugs reported to have a possible beneficial effect in patients with ET include mirtazapine, clozapine, sodium oxybate, dimethoxymethyldiphenyl-barbituric acid (T-2000), and carisbamate (Lyons and Pahwa, 2008). High-amplitude parkinsonian tremors and rest tremors caused by disorders other than PD usually do not improve with pharmacologic therapy.

In some cases, botulinum toxin (BTX) injections in the involved muscles produce a satisfactory reduction in the tremor amplitude (Jankovic and Schwartz, 1991; Jankovic et al., 1996; Hou and Jankovic, 2002). A multicenter,

randomized, double-blind, controlled trial confirmed the results of an earlier study (Jankovic et al., 1996) that BTX injections produce significant reduction in the postural hand tremor of ET and modest functional improvement (Brin et al., 2001). By avoiding injections of the forearm extensor muscles there can in many cases be a prevention of finger extensor weakness, which is a relatively frequently reported complication (Pacchetti et al., 2000).

Ventral lateral thalamotomy, particularly involving the ventral intermediate nucleus of the thalamus (VIM) was considered the neurosurgical treatment of choice for disabling, drug-resistant tremors until the later 1980s, when the ablative procedure fell out of favor compared with high-frequency thalamic DBS (Benabid et al., 1991; Fox et al., 1991; Jankovic, Cardoso, et al., 1995; Flora et al., 2010). Although effective in a majority of cases, tremor and/or ataxia worsen in about 20% of patients, and there can be considerable risk for contralateral hemiparesis, hemianesthesia, ataxia, speech disturbance, and other potential complications. Unilateral thalamic lesions are, however, still excellent therapy especially when carefully placed into the target. The risks of lesions are compounded when the procedure is performed bilaterally. Thalamic DBS has become the surgical treatment of choice for patients with disabling tremors (Deiber et al., 1993; Benabid et al., 1996; Ondo et al., 2001; Pahwa and Koller, 2001; Pahwa et al., 2006) (see Chapter 7). DBS targeting the STN has been reported to be effective not only in the treatment of PD tremor but also in ET (Diamond et al., 2007; Blomstedt et al., 2010). Bilateral caudal zona incerta nucleus has been suggested as a better target for DBS treatment of ET because it appears to cause less disequilibrium or tolerance (Plaha et al., 2011). The long-term benefits of DBS of the caudal zona incerta in ET are increasingly being recognized (Fyttagoridis et al., 2012). Some patients who have failed to respond to VIM DBS have had a modest improvement when they were reoperated and the stimulating electrode was placed in the caudal zona incerta (Blomstedt et al., 2011). There have been several small studies with zona incerta DBS showing improvements similar to those with VIM DBS (Martinez, 2018). The U.S. Food and Drug Administration (FDA) has achieved approval for focused ultrasound therapy for ET (Elias et al., 2016), and the outcomes have been correlated to lesion location (Boutet, 2018).

Recently 76 patients were treated with magnetic resonance imaging (MRI)-guided focused ultrasound therapy for ET. Subjects were assigned 3:1 to ultrasound thalamotomy or to a sham group. The primary outcome for the study was the between-group difference in the change from baseline to 3 months in hand tremor. Hand-tremor scores improved more in the ultrasound group (18.1 points versus 9.6). The between-group difference was 8.3 points. The improvements were reported as maintained at a 1-year and later at a 2-year second follow-up study. Gait issues were reported in 36% and sensory changes in 38%. Limitations of the ultrasound procedure include skull thickness that may prevent treatment predictability of lesion size and lesion location. Additionally, this procedure should be applied only unilaterally to prevent the occurrence of pseudobulbar speech and swallowing issues (Elias, 2016; Boutet, 2018; Chang, 2018).

DBS has been proposed for chronic treatment of parkinsonian, essential, and other tremors. Using high-frequency (100 Hz or greater) stimulation, with the tip of a monopolar

electrode implanted stereotactically in the VIM contralateral to the disabling tremor, Benabid and colleagues (1991) noted “complete relief” of contralateral tremor in 27 of 43 (63%) thalami that were stimulated and “major improvement” in 11 (23%). The series included 26 patients with PD and 6 with ET, 7 of whom had been previously treated with thalamotomy. The benefit of thalamic stimulation was maintained for up to 29 months (mean follow-up, 13 months). The results were similar in their subsequent report of long-term effects of chronic VIM stimulation in 117 patients, 74 of whom had bilateral implantation (Benabid et al., 1996). The most robust tremor suppression was noted in patients with PD ($n = 80$), but patients with ET ($n = 20$) also benefited, although 18.5% deteriorated with time. Dysarthria and ataxia still occurred, but the patients were able to adjust the intensity of stimulation to ameliorate these side effects, though at the expense of increased tremor. Nevertheless, the investigators thought that the reversible nature of the side effects was the chief advantage of DBS over the permanent lesion produced by thalamotomy. To compare thalamic DBS with thalamotomy, Schuurman and colleagues (2000) conducted a prospective, randomized study of 68 patients with PD, 13 with ET, and 10 with multiple sclerosis. They found that the functional status improved more in the DBS group than in the thalamotomy group, and tremor was suppressed completely or almost completely in 30 of 33 (90.9%) patients in the DBS group and in 27 of 34 (79.4%) patients in the thalamotomy group. Although one patient in the DBS group died after an intracerebral hemorrhage, DBS was associated with significantly fewer complications than was thalamotomy. This procedure may also be advantageous in elderly patients and when bilateral effects are desirable (Blond et al., 1992). We found that bilateral thalamic DBS was more effective than unilateral DBS in controlling bilateral appendicular and midline tremors of ET and PD, and thalamic DBS did not seem to improve meaningfully any parkinsonian symptoms other than tremor (Ondo, Almaguer, et al., 2001). In addition, we found that VIM DBS produces modest improvement, rather than tremor augmentation as previously suggested, in ipsilateral tremor in patients with ET (Ondo, Vuong, et al., 2001). A review of long-term efficacy of VIM DBS in 39 patients (20 with PD and 19 with ET) showed that the benefits may be maintained for at least 6 months (Rehncrona et al., 2003). DBS has been found to be safe and effective in patients followed for up to 10 years with hardware complications rate of 23% of patients over that period of observation (Baizabal-Carvallo et al., 2014). In one of our patients, minimal foreign body reaction and gliosis around the electrodes was found 12 years after implantation, the longest reported follow-up with autopsy examination after DBS, supporting the long-term safety of DBS (DiLorenzo et al., 2010). One emergent issue in the field has been worsening of tremor suppression over time. Favilla and associates (2012) evaluated this issue and concluded that disease progression (tremor and ataxia) were the main factors influencing worsening over time. The importance of this study is that much of the literature may overstate tolerance, which is a relatively rare effect.

In addition to improving distal tremor associated with PD and ET, VIM DBS can effectively control ET head tremor, which usually does not respond to conventional therapy (Koller et al., 1999). Other midline tremors, such as voice,

tongue, and face tremor, also may improve with unilateral VIM DBS, although additional benefit can be achieved with contralateral surgery (Obwegeser et al., 2000). The risk for local gliosis with chronic stimulation of the thalamus is minimal (Caparros-Lefebvre et al., 1994; DiLorenzo et al., 2010; DiLorenzo et al., 2014). Unfortunately, thalamic stimulation does not appear to be as effective in patients with predominantly kinetic and axial tremors, and it does not improve other parkinsonian features such as bradykinesia, rigidity, and levodopa-related motor complications. Furthermore, although VIM DBS is very effective in improving PD tremor, when performed bilaterally it is often associated with dysarthria and postural and gait abnormality (Pahwa et al., 2006), as a result of which STN has been suggested as a more appropriate target in PD patients with severe tremor (Limousin et al., 1998; Benabid et al., 2000; Diamond et al., 2007; Fishman, 2008) and even in patients with severe ET (Blomstedt et al., 2010). The mechanism of action of DBS is unknown, but “jamming” of low-frequency oscillatory inputs has been suggested as a possible mechanism for the antitremor effects of DBS. Regional cerebral blood flow, measured by PET scan, demonstrated that tremor suppression was associated with decreased cerebellar blood flow and, presumably, decreased synaptic activity in the cerebellum (Deiber et al., 1993). The biology of DBS effects has been clarified, though there are still many uncertainties. DBS has neurophysiologic, neurochemical, neurovascular, neurogenic, and neuro-oscillatory effects (Okun, 2012, 2015). Which effects are most important to tremor suppression is debated; however, a 2008 paper in *Nature Medicine* showed adenosine as important to tremor suppression (Bekar, 2008).

In 1992, Laitinen of Stockholm, Sweden, reported the results of 90 pallidotomies in 86 patients with severe PD (Laitinen et al., 1992). The external, posteroventral portion of the medial globus pallidus internus (GPi) was the intended target for the stereotactically placed lesion. Nearly all patients had “marked improvement in tremor and akinesia.” In addition, some patients apparently also noted improvement in their gait, speech, and pain. Only two patients suffered permanent visual field defect, and one had “minor stroke with hemiparesis.” Several pallidotomy series have since confirmed the beneficial effects of pallidotomy on various parkinsonian symptoms, including tremor (Jankovic and Marsden, 1998). These results provide support for the notion that surgical or chemical lesions of these structures may have a therapeutic value not only in controlling tremor but also in improving bradykinesia (Bergman et al., 1990; Aziz et al., 1991). Although some investigators (Subramanian et al., 1995) have suggested that posteroventral pallidotomy is as effective as thalamotomy in controlling parkinsonian tremor, others (Dogali et al., 1995) think that pallidotomy provides only partial relief of tremor.

Postural tremors

Diagnosis and clinical features

Physiologic tremor

Normal and enhanced physiologic tremors are the most common forms of postural tremor, but they rarely require medical attention. Postural tremors are clinically similar despite different causes. In contrast to ET, the frequency of

physiologic tremor can be slowed by mass loading (Elble and Koller, 1990). Indeed, there appear to be two components to physiologic tremor: variable frequency (peak 8 Hz), which is dependent on loading, and consistent frequency (peak 10 Hz), which is independent of peripheral influence. The latter suggests central origin of the tremor, as is presumed the case in ET. Thus, the amplitude of ET is less dependent on the position of the tested limb than is the amplitude of other postural tremors, including physiologic tremors (Sanes and Hallett, 1990).

Essential tremor

Although the term *essential* implies necessary or desirable, it actually means that there is no known cause and the term is synonymous with *idiopathic*. The term *essential tremor* did not gain regular and widespread use until a century or so after its initial use in 1874 by Pietro Buresi, a professor of medicine at the University of Siena, Italy (Louis et al., 2008). He coined the term *tremore semplice essenziale* or “simple essential tremor” when he described the case of an 18-year-old man suffering from severe tremor of the arms when engaged in voluntary movement. He also described head tremor. In the past, the modifier “benign” was used (“benign ET”) to indicate favorable prognosis of ET, even though it is now well accepted that ET can produce marked physical and psychosocial disability (Busenbark et al., 1991; Jankovic, 2000; Sullivan et al., 2004; Louis, 2005; Benito-Leon and Louis, 2006; Elble et al., 2006; Elble and Deuschl, 2011; Elble, 2013). Although the amplitude of ET tends to increase with age, the tremor frequency decreases with age (Elble et al., 1994; Elble, 2000b). The International Classification of Disease–10th Revision–Clinical Modification (ICD-10-CM) assigned a specific diagnostic code for ET: G250, essential tremor).

Epidemiology

Meta-analysis of epidemiologic studies has observed that the prevalence of ET to range between 0.01% and 20.5%, but the pooled prevalence is 0.9%; the prevalence in people 65 years and older is 4.6% and may be as high as 21.7% in people 95 years and older; the prevalence is higher in males than females (Louis and Ferreira et al., 2010). There are many other estimates (Haerer et al., 1982; Louis et al., 1995; Louis, Ford, Pullman, et al., 1998; Dogu et al., 2003) such as 5.5% in people over the age of 40 years (Rautakorpi et al., 1982) and 14% in people 65 years or older (Moghal et al., 1994) (Table 10.4). In one epidemiologic study, 108 of 1056 (10%) nondemented individuals in upper Manhattan, age 65 or older, reported “shaking” (Louis et al., 1996). Neurologic examination confirmed rest tremor in 8.3% and action tremor in 17.6%, and the prevalence of PD and ET was estimated to be 3.2% and 10.2%, respectively. One of the earliest epidemiologic studies of ET in a U.S. population was based on a large-scale morbidity survey conducted in a rural, biracial Mississippi county (Copiah County) (Haerer et al., 1982). The overall prevalence ratio was 414.6 per 100,000 (0.4%) inhabitants. In a door-to-door survey of people age 40 years or older in Mersin Province, Turkey, the prevalence of ET was found to be 4% (Dogu et al., 2003). In another population-based survey, involving 5278 subjects age 65 years or older in central Spain who were followed for a median of 3.3 years,

Table 10.4 Prevalence and incidence of essential tremor**Prevalence**

- 0.4%–5.5%: Community-based studies
- 14% in people 65 years or older
- 4%: A door-to-door survey of people 40 years or older in Mersin Province, Turkey

Incidence

- 616/100 000 person-years: A population-based study of 5278 subjects 65 years or older in central Spain followed for a median of 3.3 years
- 64/83 (77.1%) incident cases had not been previously diagnosed, and 4 (4.8%) were taking antitremor medications

the adjusted annual incidence was determined to be 616 per 100,000 person-years; 64 of the 83 (77.1%) incident cases had not been previously diagnosed, and only 4 (4.8%) were taking antitremor medications (Benito-Leon et al., 2005). In yet another population-based study of northern Italian adults in which all participants were examined and classified by movement specialists using rigorous diagnostic criteria, tremors comprised the most common category of movement disorders, followed by restless legs syndrome (RLS) (Wenning et al., 2005). These epidemiologic studies provide strong evidence that the prevalence and incidence of ET are higher than was previously recognized. In a longitudinal, prospective, population-based study, ET has been found to be associated with increased mortality at an estimated risk ratio of 1.59 (95% confidence interval [CI] = 1.11–2.27; $P = 0.01$) (Louis et al., 2007). In contrast, a study of tremor phenomenologically similar to ET in the elderly found a lower mortality rate in tremor patients compared with controls (Deuschl et al., 2015). This is similar to the findings of increased longevity in affected parents of ET patients (Jankovic, Beach, 1995).

Diagnosis and Clinical Features

Although ET was described as early as the nineteenth century (Dana, 1887; Louis, 2010), there is still considerable controversy about the diagnostic criteria (Chouinard et al., 1997; Louis, Ford, Lee, et al., 1998; Jankovic, 2000; Louis, 2010; Quinn et al., 2011). In one study of 71 patients, 37% diagnosed with ET based on the criteria for ET adapted from the consensus statement of the Movement Disorders Society (Deuschl et al., 1998) were misdiagnosed, usually either as PD or dystonia (Jain et al., 2006). This is partly because of a lack of a disease-specific marker for ET. No specific pathologic changes indicative of PD were noted in 20 brains of ET patients that were examined at autopsy (Rajput et al., 2004). However, this study was fundamentally flawed, because all patients who were selected for the study had a diagnosis of ET at the time of death and patients who started with ET and later developed PD would have been excluded (Jankovic, 2004). The controversy about the possible association of ET and PD should be clarified once the genetic basis and pathophysiology of ET are understood. Until then, the operational diagnostic criteria must rely on the presence of typical clinical characteristics. The presence or absence of certain clinical

Table 10.5 Proposed classification of essential tremor**A. Definite essential tremor****1. Inclusions**

- Bilateral postural tremor with or without kinetic tremor involving hands or forearms, which is visible and persistent and is long-standing in duration (>5 years)
- Tremor involving body parts other than the upper limbs may be present, the tremor may be asymmetrical, amplitude may fluctuate, and the tremor might or might not produce disability

2. Exclusions

- Neurologic signs, except for Froment sign
- Causes of enhanced physiologic tremor
- Concurrent or recent exposure to tremorgenic drugs
- Direct or indirect trauma to the central and peripheral nervous systems
- Historical or clinical evidence of psychogenic origins of tremor
- Convincing evidence of sudden onset or evidence of stepwise deterioration

B. Probable essential tremor**1. Inclusions**

The same as for definite ET, but the tremor may be confined to body parts other than hands and the duration is greater than 3 years

2. Exclusions

- Primary orthostatic tremor, which is an isolated, high-frequency (14–18 Hz), bilaterally synchronous leg tremor on standing or voluntary contraction of leg muscles
- Isolated voice, tongue, or chin tremors
- Position- and task-specific tremors

C. Possible essential tremor**1. Inclusions**

- Type 1:** Satisfy criteria for definite or probable ET but exhibit other recognizable neurologic disorders, such as:
 - (1) Parkinsonism, dystonia, myoclonus, peripheral neuropathy, or restless legs syndrome
 - (2) Other neurologic signs of uncertain significance not sufficient to make a diagnosis of a recognizable neurologic disorder, such as mild extrapyramidal signs (hypomimia, decreased arm swing, and mild bradykinesia)
- Type 2:** Monosymptomatic and isolated tremors of uncertain relationship to ET. This includes position- and task-specific tremors, such as occupational tremors (primary writing tremors); primary orthostatic tremor; isolated voice, chin, tongue, and leg tremor; and unilateral postural hand tremor

2. Exclusions

Same as points 2a–f for definite ET

Members of the Tremor Research and Investigation Group: M. Brin, C. Contant, R. Elble, L. Findley, J. Jankovic, W. Koller, P. LeWitt, A. Rajput.

From Findley LJ, Koller WC. Definitions and behavioural classifications. In: Findley LJ, Koller WC (eds): Handbook of Tremor Disorders. New York, Marcel Dekker, 1995, pp 1–5.

characteristics may be used to categorize ET into “definite,” “probable,” and “possible” (Table 10.5). The diagnostic criteria may be used or modified according to specific needs. For example, for genetic linkage studies, only “definite” ET may be acceptable, whereas in studies that are designed to explore the clinical spectrum of ET, including associated features, the “possible” ET category might be more appropriate (see Table 10.3). Family history, alcohol sensitivity, and propranolol responsiveness, although characteristic of ET, should not

be considered necessary for the diagnosis. Although in one study 46% of patients exhibited alcohol sensitivity (some with rebound worsening the following day), the investigators found no reliable predictors of response to alcohol (Hopfner et al., 2015). More recently, core and secondary criteria were proposed to facilitate a practical approach to the diagnosis of ET (Elble, 2000a). Core criteria include bilateral action tremor of the hands and forearms (but not rest tremor), absence of other neurologic signs, except for the Froment sign (a “cogwheel” phenomenon on passive movement of the affected limb with voluntary movement of the contralateral limb), and isolated head tremor without signs of dystonia.

The tremor of ET is typically a postural or kinetic tremor with frequency varying between 4 and 10 Hz. Although the frequency of the tremor is relatively constant in a particular individual, the amplitude may vary and in some cases may be suppressed by mental concentration and distraction (Koller and Biary, 1989; Kenney et al., 2007). A review of the clinical features in 350 consecutive patients who were referred to the Movement Disorders Clinic at Baylor College of Medicine and diagnosed with ET has shown that although tremor is clearly the most troublesome symptom, it is not necessarily the only symptom in patients with ET (Lou and Jankovic, 1991b) (see Tables 10.2 and 10.5). This is supported by the reports of well-studied families in which some members have typical ET, whereas others have dystonia, parkinsonism, or a combination of all three disorders (Jankovic et al., 1997; Farrer et al., 1999; Bertoli-Avella, 2003; Yahr et al., 2003; Spanaki and Plaitakis, 2009). One multigenerational family, 36 members in five generations, had an admixture of ET, PD, and dystonia (Yahr et al., 2003). Two brothers, twins, with ET and PD had the classic pathologic features of PD at autopsy. The authors concluded, “This unusual set of clinical and pathologic circumstances can hardly be attributed to chance occurrence and raises the question of a specific genetic mutation and/or clustering, which may link ET with PD.” In a study of the first-degree relatives of 303 PD probands and 249 controls from Crete, ET was present in the relatives of PD patients more often than in those of controls (odds ratio [OR], 3.64; $P < 0.001$) and the risk was even greater (OR, 4.48) when the affected proband had tremor-dominant or mixed PD (Spanaki and Plaitakis, 2009). Twelve subjects had both ET and PD phenotypes. The authors concluded that “in certain families ET and PD are genetically related probably sharing common hereditary predisposition.” In another large, autosomal dominant family from Arkansas consisting of 138 individuals, 65 of whom were examined, various members manifested slowly progressive, levodopa-responsive PD, ET, RLS, depression, or a combination of these disorders (Puschmann et al., 2011). PET showed reduced presynaptic dopamine function typical of sporadic PD in a patient with PD and ET, but not in persons with ET or RLS and neuropathologic examination revealed pallidonigral pigment spheroid degeneration with ubiquitin-positive axonal spheroids; TDP43-positive pathologic findings in the basal ganglia, hippocampus, and brainstem; and only sparse Lewy bodies. No gene mutation has been identified.

Retrospective chart review at the Neurological Institute (NI) of New York showed that 56.7% versus 33.3% ($P < 0.001$) of 210 PD compared with 210 Parkinson-plus syndrome

patients had kinetic tremor on examination and patients with PD were more likely to have a diagnosis of ET assigned by an NI neurologist (5.3% versus 0.0%; OR, 12.85; 95% CI, 1.66–99.8; $P = 0.001$) (Louis and Frucht, 2007). Patients with PD were 3 to 13 times more likely to have diagnoses of ET than were patients with Parkinson-plus syndromes, thus confirming “the link between ET and PD, and possibly, between ET and Lewy body disease.” In another large family, originally from Cuba, with parkinsonism and ET, the parkinsonism was linked to a marker on chromosome 19p13.3–q12, but it did not cosegregate with ET (Bertoli-Avella, 2003). Other gene mutations associated with PD have not been found in patients with ET alone (Deng et al., 2006a). In a small study, a locus on chromosome 5 was linked to ET (Hicks et al., 2016).

Using a combination of whole exome sequencing and targeted resequencing in three ET families, a missense mutation in the *TENM4* gene was found to segregate in an autosomal dominant fashion in an ET family and other gene mutations were identified in ET patients (Hor et al., 2015). The mutant protein was found to mislocalize and induce defects in axon guidance, confirming a dominant-negative mode of action for these mutations. A *Tenm4* knock-out mouse was found to display an ET phenotype.

The clinical heterogeneity of ET suggests that there may be different subtypes. Indeed, Louis, Ford, and colleagues (2000) found that patients with older onset (older than 60 years) and those without head tremor progressed more rapidly than did patients with young-onset tremor and those with head tremor. They also later found that head tremor was present four times more frequently in women than in men (Louis et al., 2003; Hardesty et al., 2004). The same investigators also studied 51 ET cases with head tremor and found that 14 (27.5%) had “no-no” tremor, 9 (17.6%) had “yes-yes” tremor, and 28 (54.9%) had a mixed tremor (Robakis and Louis, 2016). The authors noted that mixed and “yes-yes” patients were older ($P = 0.004$) and had a longer tremor duration ($P = 0.018$) than “no-no” cases and the latter group had a higher tremor severity in the arms than the “yes-yes” and “no-no” cases ($P = 0.04$). Using the medical records linkage system of the Rochester Epidemiology Project, the authors identified ET patients who also had an autopsy report and found that women with ET were six times more likely to develop head tremor than were men (Hardesty et al., 2004). The presence of jaw tremor, seen in 7.5% to 18.0% of patients with ET, has been found to be associated with older age at onset, more severe action tremor in the arms, and the presence of head and voice tremor (Louis et al., 2006). In a study of 34 patients with voice tremor, 93% were women and the voice tremor typically began in the seventh decade (62.9 ± 15.0 years) (Sulica and Louis, 2010). More than a third had tremor in a first-degree relative, and more than a quarter reported a beneficial effect of ethanol. In this study, 11 (32.3%) were aware of an arm tremor and 10 (29.4%) had been misdiagnosed as having spasmodic dysphonia. Only 56% of treated patients found BTX helpful, and the response was often incomplete. Jaw tremor was also significantly associated with rest tremor, suggesting that some patients with ET and jaw tremor may convert to PD. Besides ET and PD, jaw tremor may be a manifestation of dystonia (Schneider and Bhatia, 2007). Lower extremity tremor in ET is usually mild or asymptomatic (Poston et al., 2009).

The ongoing debate as to whether ET is a monosymptomatic or heterogeneous disorder or phenotypic manifestations of multiple entities will probably not be resolved until disease-specific physiologic, genetic, or other biologic markers are identified (Schrag et al., 2000; Elble, 2002; Jankovic, 2002; Elble et al., 2006; Deuschl and Elble, 2009; Louis, 2009). One hypothesis is that the various nonmotor signs linked to ET (Chandran and Pal, 2012; Chandran et al., 2012) could be secondary to “abnormal neuronal oscillation” (Deuschl and Elble, 2009), but this would not explain the heterogeneous presentation of ET. In addition, the proposed classification of ET into “hereditary” (unequivocal family history), “sporadic” (no immediate family member with ET), and “senile” (onset after age 65) is too artificial and not easily applicable.

Some studies have suggested that there is an association between ET and parkinsonism (Jankovic et al., 1997; Yahr et al., 2003; Shahed and Jankovic, 2007; Fekete and Jankovic, 2011; Thenganatt and Louis, 2012a), but other studies have not found a link (Adler et al., 2011) (Fig. 10.2). Differentiation between ET and PD is critical particularly in early stages because ET has been found to be erroneously treated with anti-PD in 12.4% of 402 community cases reevaluated by a movement disorder specialist (Meara et al., 1999). Postural tremor, similar to ET, has been reported to occur in as many as 93% of patients with PD and to correlate with the ipsilateral rest tremor but not with age at onset or disease duration (Louis, Levy, et al., 2001). Furthermore, in 22 patients with PD with family history of ET, 90% (20 of 22) had tremor-predominant subtype of PD, suggesting that “these patients have inherited a genetic susceptibility factor for tremor, which affects the motor phenotype of PD” (Hedera et al., 2009). Phenomenologically similar to ET, the postural tremor of PD has been linked by some investigators to coexistent ET (Geraghty et al., 1985; Jankovic, 1989; Jankovic et al., 1997; Jankovic 2000). Others, however, think that the coexistence of the two disorders simply “represents a chance occurrence of two common diseases” (Pahwa and Koller, 1993). On the basis of an analysis of 678 patients

diagnosed as having ET, some by movement disorder specialists and others by private practice neurologists, 6.1% were found to have concomitant PD and 6.9% had coexisting dystonia (Koller et al., 1994). The authors concluded that “the frequency of PD in ET is more than would be reported in the general population.” In a longitudinal, population-based study of The Neurological Disorders in Central Spain (NEDICES) of 3813 people (mean age 73.4 ± 6.6 years), after a median of 3.3 years, 12 (5.8%) of 207 ET cases developed parkinsonism compared with 56 (1.6%) of 3606 controls, with adjusted relative risk (RR) of 3.47 (95% CI, 1.82–6.59; $P < 0.001$) (Benito-Leon et al., 2009). Six (3.0%) of 201 ET cases developed incident PD versus 24 (0.7%) of 3574 controls with adjusted RR of 4.27 (95% CI, 1.72–10.61; $P = 0.002$). The authors concluded that “patients with ET were four times more likely than controls to develop incident PD during prospective follow-up.”

The coexistence of ET and PD may be difficult to recognize because once a patient develops PD, the postural tremor is usually attributed to the disease, and it is therefore difficult to diagnose ET in a patient who already has symptoms of PD (Shahed and Jankovic, 2007; Louis, 2009; Thenganatt and Louis, 2012a) (see Fig. 10.2). Although rest tremor may be observed in patients with advanced ET, it may also be the initial manifestation of coexistent PD (Shahed and Jankovic, 2007; Fekete and Jankovic, 2011). The “postural tremor” that is seen in many patients with PD may represent an enhanced physiologic tremor (Forssberg et al., 2000), coexistent ET (Geraghty et al., 1985; Jankovic, 1995), or a reemergent classic rest tremor (Jankovic et al., 1999) with the same frequency and clinical characteristics as the typical rest tremor. This reemergent tremor is also often exacerbated during walking. In contrast to ET, which is seen immediately when patients outstretch their arms, the reemergent tremor of PD usually appears after a latency of several seconds (Jankovic et al., 1999). Furthermore, this PD-related tremor often responds to levodopa, whereas the postural tremor of ET does not (Kulisevsky et al., 1995). It is actually this action tremor that seems to correlate with motor disability rather

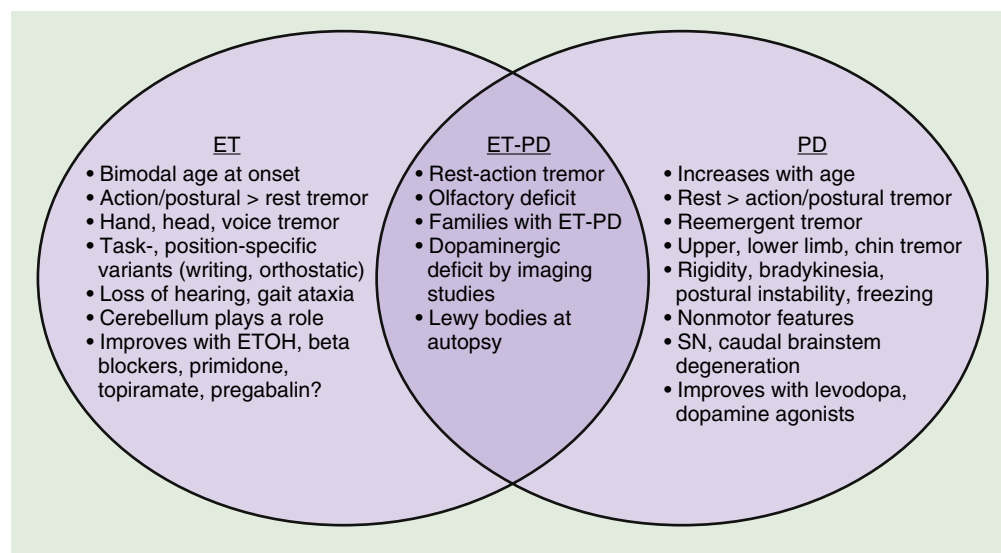


Fig. 10.2 Overlap between and differentiation of essential tremor and Parkinson disease. ETOH, Ethanol; SN, substantia nigra. (Modified from Shahed J, Jankovic J. Exploring the relationship between essential tremor and Parkinson's disease. *Parkinsonism Relat Disord* 2007;13:67–75.)

than the typical rest tremor, which correlates chiefly with social handicap (Zimmermann et al., 1994). The clinical characteristics, however, may not always reliably differentiate between the two types of postural tremor (Henderson et al., 1995). Furthermore, reemergent tremor may be observed in patients without obvious rest tremor (Louis and Dhawan, 2008).

In addition to clinical overlap, there may be a genetic link between ET and PD. We found a higher frequency of the 263–base pair (bp) allele of the NACP-Rep1 polymorphism not only in patients with PD (OR, 3.86) but also in patients with ET (OR, 6.42) but not in patients with Huntington disease, supporting a genetic link between PD and ET (Tan et al., 2000). Further evidence that ET and PD may be related is the observation that patients with ET have an olfactory deficit that is similar, although milder, than that noted in patients with PD (Louis et al., 2002; Louis and Jurewicz, 2003; Djaldetti et al., 2008). In one study, however, there was no difference in the results of olfactory testing between ET patients and controls (Shah et al., 2008). We and others (Gimenez-Roldan and Mateo, 1991) have noted that patients with ET seem to have a higher propensity toward neuroleptic-induced parkinsonism than do patients without ET, although a formal epidemiologic study is needed to confirm this clinical observation. To examine an ET-PD relationship, we described 22 patients with childhood-onset ET who later developed PD (Shahed and Jankovic, 2007). Of 11 patients reporting asymmetrical ET, PD symptoms began on the same side as the more severe ET tremor in 10 (90.9%, $\chi^2 = 0.66$; $P = 0.024$), with 68.2% reporting change in tremor as their first PD manifestation. These findings, supported by another study (Tan et al., 2006), suggest that in some patients, childhood ET evolves into adult tremor-dominant PD, explaining the coexistence of ET and PD within the same patient and family.

It has been postulated that ET-related gene mutations may predispose some patients to subsequent development of PD. In a study of 53 patients with the ET-PD combination, compared with 53 PD and 150 ET patients, the side of the greatest initial ET severity corresponded to the side of the greatest PD severity (Minen et al., 2008). In another study involving 13 patients who presented originally with asymmetrical postural tremor and no rest tremor for at least 10 years (mean, 19.2 years) and were initially diagnosed with ET, all patients subsequently developed evidence of PD (Ray Chaudhuri et al., 2005). The onset of levodopa-responsive PD was manifested by rest tremor for a mean of 2.5 years before final presentation in the clinic. Furthermore, 5 patients who had β -CIT single-photon emission computed tomography (SPECT) all showed reduced uptake in the contralateral striatum. It is not clear whether these patients with a long-standing history of asymmetrical postural tremor have PD at onset, whether patients with unilateral postural tremor (isolated tremor) or asymmetrical postural tremor (atypical ET) who later develop PD represent an overlap between ET and PD, or whether this type of postural tremor is an early marker for PD (Grosset and Lees, 2005).

In a population-based study (981 first-degree relatives of 162 patients with PD and of 838 first-degree relatives of 147 controls), the risk for ET was significantly increased for relatives of patients with onset of PD ($P = 0.006$) (Rocca et al., 2007). Additionally, in a referral-based sample (981

first-degree relatives of 162 patients with PD and of 838 first-degree relatives of 147 controls), the risk for ET among relatives increased with younger onset of PD in patients ($P = 0.001$) and was higher in relatives of PD patients with the tremor-predominant or mixed form compared with relatives of patients with the akinetic-rigid form and in men compared with women. The authors concluded that “these findings suggest that PD and ET may share familial susceptibility factors.” In a case-control study of 600 subjects evaluated for tremor, ET was significantly more frequent in patients with PD (12/204, 5.9%) compared with diseased controls (2/206, 1%) and healthy controls (1/190, 0.5%) (Tan et al., 2008). The authors concluded that “PD patients were 5 to 10 times more likely to have ET compared with diseased and healthy control.” The observation of significant overlap in association between variants in LINGO1 and ET and PD (see later) provides support for the genetic association between the two common movement disorders (Vilariño-Güell et al., 2009; Annesi et al., 2011; Deng et al., 2012). Using exome sequencing analysis, a novel p.R377W mutation was identified in one patient, a member of a large French-Canadian family with ET in the fused in sarcoma (*FUS*) gene, thought to be pathogenic (Rajput et al., 2013). Another variant, Met392Ile, in the *FUS* gene, has been found to increase susceptibility of ET among ethnic Chinese (Wu et al., 2013). Other *FUS* gene variants have been identified in patients with ET (Deng et al., 2014).

In addition to genetic factors, there may be environmental factors that determine the occurrence of ET and its relationship to PD. For example, heavy cigarette smoking has been associated with lower risk for PD and ET (Louis et al., 2008). Although some studies have concluded dementia is more frequent in patients with ET than controls (Bermejo-Pareja et al., 2007) and one study reported the adjusted odds ratios to vary between 1.64 and 1.84 (Thawani et al., 2009), a relationship between ET and Alzheimer disease has not been established (Elble et al., 2007).

The possibility of additional cochlear involvement in ET is supported by the observation of high occurrence of partial or complete deafness in patients with ET (Ondo et al., 2003). Among 250 patients with ET, 42 (16.8%) patients wore hearing aids, compared with 2 of 127 (1.6%) PD patients and 1 of 127 (0.8%) controls ($P < .0001$). Pure tone audiometry demonstrated age-dependent higher frequency loss among patients with ET compared with the general population. High risk for hearing loss among patients with ET has been confirmed by other studies (Benito-Leon et al., 2007; Yilmaz et al., 2015). The combination of ET, sensorineuronal hearing loss, and early graying has been suggested to be a unique disorder, separate from Waardenburg syndrome (Karmody et al., 2005).

Although mental functioning is usually intact in patients with ET, detailed testing of cognitive performance has found some subtle abnormalities on tests of verbal fluency, naming, mental set-shifting, verbal working memory, and other tests of cognitive function (Benito-Leon et al., 2006a) and elderly patients with ET may possibly have an increased risk for dementia over those without ET (Benito-Leon et al., 2006b). Furthermore, depression has been found to occur in about a third of patients with ET, almost as frequently as in PD (Lombardi et al., 2001; Miller et al., 2007; Chandran et al., 2012). These deficits have been interpreted as suggesting

involvement of frontocerebellar circuits. In a cross-sectional study of personality, patients with ET were found to have a tendency to have increased levels of pessimism, fearfulness, shyness, anxiety, and easy fatigability, but none of these traits correlated with the severity of the tremor (Chatterjee et al., 2004). Another study indicated that ET patients have higher harm avoidance scores, particularly anticipatory worry and pessimism, and fatigability and asthenia than controls (Thenganatt and Louis, 2012b).

ET appears to be a heterogeneous disorder, as is suggested by multiple gene loci that have so far been identified and by the frequent association with other disorders, such as parkinsonism, dystonia, and myoclonus (Jankovic et al., 1997; Jankovic, 2002; Yahr et al., 2003; Deng et al., 2006b; Shahed and Jankovic, 2007; Fekete and Jankovic, 2011; Kühlenbäumer et al., 2014) (see Fig. 10.2). Postmortem studies of patients with ET have not provided evidence for nigrostriatal pathologic features in ET, but patients who had a diagnosis of PD at time of death (even though ET might have preceded the onset of PD) would have been excluded from these clinicopathologic studies (Jankovic, 2004; Rajput et al., 2004; Fekete and Jankovic, 2011). Furthermore, there is indirect evidence suggesting nigrostriatal impairment in some patients with ET. We found that relatives of patients with PD have at least a 2.5 times higher (those with the combination of ET-PD: 10 times higher) frequency of tremor than did normal controls, providing additional support for the association of ET and PD (Jankovic, Beach, et al., 1995). Similarly, a 4-fold increase in prevalence of isolated tremor among relatives of patients with PD compared with controls was found by Payami and colleagues (1994). Interestingly, among 196 twins with postural or kinetic tremors, Tanner and colleagues (2001) found that 137 had PD or had a twin with PD. About 19% of patients with ET have a rest tremor that has the clinical and physiologic characteristics of PD tremor (Cohen et al., 2003). However, when nine brains of patients who exhibited advanced ET and upper extremity rest tremor (without any other evidence of parkinsonism) were examined with alpha-synuclein staining, only two had Lewy bodies in the dorsal vagus nucleus and locus ceruleus, but none had Lewy body-containing neurons and/or Lewy neurites in the basal ganglia (Louis et al., 2011). Although this pathologic study suggested that rest tremor in patients with ET was not associated with PD pathologic features, 19 of 24 (80%) patients with ET and rest tremor without other parkinsonian features had abnormal dopamine transporter (DAT) uptake on DaTscan, particularly in the putamen (De Verdal et al., 2011). Another DaTscan study found “a significant presynaptic dopaminergic deficit” in patients with ET compared with normal volunteers, although the pattern of deficit was more diffuse, involving not only the putamen but also the caudate (Gerasimou et al., 2012).

Although the relatively frequent coexistence of ET and dystonia supports the notions that there is a pathogenetic link between the two disorders, linkage analysis has excluded the dystonia (*DYT1*) gene on chromosome 9 in hereditary ET (Conway et al., 1993; Dürr et al., 1993). This suggests that the genes for these two disorders are on separate loci or that the relationship between the two disorders is physiologic rather than genetic, though this does not exclude the possibility of linkage to other genetic disorders. Münchau and

colleagues (2001) studied 11 patients with classic ET and compared them to 19 patients with cervical dystonia and arm tremor. They found that the latency of second agonist burst during ballistic wrist flexion movements was later in ET patients than in those with arm tremor associated with cervical dystonia. Furthermore, the latter group had a greater variability in reciprocal inhibition than did the ET group. Patients with normal presynaptic inhibition had onset of their arm tremor simultaneously with onset of their cervical dystonia (mean age, 40 years), whereas patients with reduced or absent presynaptic inhibition had an earlier age at onset (mean, 14 years), and the interval between the onset of the tremor and the onset of cervical dystonia was longer (mean, 21 years). This suggests that the mechanisms of arm tremor in patients with ET and cervical dystonia may be different. The association among ET, dystonia, and PD is suggested by reports of families with manifestations of these three disorders in different or same members of the families (Jankovic et al., 1997; Yahr et al., 2003).

ET-like tremor has been described in patients with hereditary myoclonus and with hereditary motor-sensory neuropathy (sometimes referred to as Roussy-Levy syndrome) (Cardoso and Jankovic, 1993). ET-like tremor occurs in other genetic diseases, the study of which may provide important insights into possible genetic heterogeneity in families with clinically similar tremor. ET also may be associated with higher than expected frequency with RLS (Ondo and Lai, 2006). The validity and meaning of such associations, however, are disputed, and the controversies are not likely to be resolved until a disease-specific marker (e.g., an ET-linked genetic locus) is identified. A diagnostic marker for ET would also help resolve the question as to whether site-, position-, and task-specific tremors, such as primary handwriting tremor and orthostatic tremor, are distinct entities or whether these tremors represent clinical variants of ET (Rosenbaum and Jankovic, 1988; FitzGerald and Jankovic, 1991; Britton et al., 1993; Danek, 1993; Soland et al., 1996a; Sander et al., 1998; Hai et al., 2010) (see Table 10.1). It is still not clear whether primary writing tremor is a variant of ET, a type of focal dystonia such as writer's cramp, or a separate nosologic entity (Hai et al., 2010; Quinn et al., 2011).

Epidemiology

Epidemiologic studies indicate that up to 5% of the adult population have ET, and 5% to 30% of adults with ET report symptom onset during childhood (Ferrara and Jankovic, 2009). Childhood-onset ET is usually hereditary, begins at a mean age of 6 years, and affects boys three times as often as girls. In a study of 39 patients with childhood-onset ET, a mean age at onset of 8.8 ± 5.0 years, and a mean age at evaluation of 20.3 ± 14.4 years, we found that some had their initial symptoms as early as infancy (Jankovic et al., 2004). A family history of tremor was noted for 79.5% of the patients. Eighteen (46.2%) patients had some neurologic comorbidity, such as dystonia, which was noted in 11 (28.2%) patients. Only 24 (61.5%) patients were treated with a specific anti-tremor medication; 5 of the 12 patients who were treated with propranolol experienced improvement. Other studies of childhood-onset ET also found male preponderance and paucity of head tremor (Louis, Dure et al., 2001; Tan et al., 2006). Some investigators have suggested that “shuddering

attacks" of infancy might be the initial manifestation of ET (Vanasse et al., 1976; Kanazawa, 2000).

Imaging

Imaging studies have been helpful in providing insight into the mechanism of ET and its relationship to PD. Many of the structural imaging studies, such as MRI, diffusion tensor imaging (DTI), voxel-based morphometry, T2*-relaxometry on MRI, and other techniques, provide growing support for the notion that ET is a neurodegenerative disorder (Bhalsing et al., 2013). A 10% to 13% reduction in ^{18}F -dopa uptake in the striatum of patients with ET compared with controls (Brooks et al., 1992) suggests a physiologically important compromise of the dopaminergic system in patients with ET (Jankovic et al., 1993). Furthermore, ^{18}F -dopa uptake constants (K_i) in 5 of 32 asymptomatic relatives of patients with PD who had isolated postural tremor were reduced on average by 23% ($P < 0.001$) (Piccini et al., 1997). The mean K_i for the other 27 asymptomatic relatives was decreased by 17% ($P < 0.001$). Using ^{123}I -IPT SPECT to image the striatal DAT, Lee and colleagues (1999) found the mean bilateral uptake in 9 patients with isolated postural tremor (ET) to be slightly lower than that in normal control subjects (3.60 versus 3.80), but this did not reach statistical significance. Six other patients in whom rest tremor developed 4 to 18 years (mean, 11.5 ± 6.7) after the onset of postural tremor without other parkinsonian features, however, had a significant reduction in the DAT compared with normal controls (2.61 versus 3.83, $P < .05$) but lower than PD patients (1.97 contralateral and 2.35 ipsilateral). They concluded that some patients with postural tremor may acquire rest tremor in association with mild SN neuronal loss. Although the majority of ET patients have normal DAT SPECT, some cases may start with isolated postural tremor, phenomenologically identical to ET, who later develop PD. In one study the mean latency between the onset of asymmetrical postural tremor and PD was 19.2 years whereas the mean latency between onset of rest tremor was 2.5 years (Chaudhuri et al., 2005). In one study of 61 subjects presenting with "isolated atypical tremors defined as unilateral either postural, resting or mixed" followed at baseline and at mean 28.4 ± 7.2 months with ^{123}I -FPCIT SPECT, those ($N = 25$) with normal baseline scan had only tremor at follow-up and of the 36 with abnormal baseline scan 23 (64%) developed PD and the remaining patients had only tremor (presumably ET) (Ceravolo et al., 2008). They suggested that term "isolated tremor with dopaminergic presynaptic dysfunction" is used for the patients with unilateral or asymmetrical tremor with abnormal DAT SPECT. Whether the use of ^{123}I -FPCIT SPECT in differentiating ET from PD is cost effective or not is not clear, although one Italian study suggested some cost-savings when using this diagnostic tool (Antonini et al., 2008). In one study, FP-CIT SPECT showed that the pattern of dopaminergic loss over time is different between ET and PD, but both disorders exhibit impairment of DAT in the caudate nucleus (Isaias et al., 2010). Although this and other imaging studies reported by the same group (Isaias et al., 2008) provide important insights into the selective caudate dopaminergic deficit as a possible link between the two common disorders, some studies have reported that DAT SPECT remains normal over time in patients with mixed tremor (a combination of postural and rest tremor)

(Arabia et al., 2010). Because medial SN (that predominantly projects to the caudate nucleus) is particularly involved in the tremor-dominant PD and is associated with more caudate loss of DAT, it is possible that tremor-dominant PD and ET share a selective dopaminergic loss in the caudate nucleus. This, in turn, may lead to a dysfunction of the caudate-thalamic pathway and disinhibition of the thalamic autorhythmic pacemakers, clinically expressed as tremor. Indeed, β -CIT SPECT, which mainly reflects serotonin transporters, is lower in the thalamus of patients with tremor-dominant PD compared with those with nontremor PD (Caretti et al., 2008). DAT scanning was approved by the FDA in 2011 to differentiate ET from parkinsonism, but importantly DAT cannot make a specific diagnosis of parkinsonism.

In addition to thalamus, the caudate also projects to the inferior olive and cerebellum, both implicated in the pathophysiology of ET and supported by growing evidence of cerebellar pathologic features in ET. Using 3-tesla (T) MRI, Gallea and associates (2015) found that relative to the healthy controls, ET patients exhibited less gray matter in lobule VIII of the cerebellum and less effective connectivity between each cerebellar cortex and the ipsilateral dentate nucleus. Furthermore, the supplementary motor area in patients with ET exhibited (1) more gray matter, (2) a lower amplitude of low-frequency fluctuation of the blood oxygenation level-dependent signal, (3) less effective connectivity between each supplementary motor area and the ipsilateral primary motor hand area, and (4) a higher probability of connection between supplementary motor area fibers and the spinal cord. The structural and functional changes observed in the supplementary motor area are thought to be compensatory because this area presumably attempts to reduce tremor in the motor output by reducing its communication with M1 hand areas and by directly modulating motor output via its corticospinal projections. This is further supported by functional MRI and electrophysiologic studies demonstrating impaired connectivity in the cerebello-dentato-thalamic and cerebello-cortical pathways (Buijink et al., 2015).

The clinical overlap between ET and PD undoubtedly contributes to the 10% to 15% frequency of patients diagnosed with mild PD who have scans without evidence of dopaminergic deficit (SWEDDs) (Schneider et al., 2007; Bain et al., 2009; Schwingenschuh et al., 2010; Stoessl, 2010). Using logistics regression and receiver operating characteristic with area under the curve as the primary outcome measure of DTI, performed with 3-T units, identified relatively specific patterns of abnormalities that reliably differentiated between PD and ET (Prodoehl et al., 2013). PET imaging studies have suggested that a decrease in GABA receptors in the cerebellum leads to disinhibition of cerebellar output pathways (Paris-Robidas et al., 2012). Review of imaging studies in ET has concluded that they "provide support for the presence of cerebellar degeneration in ET" (Louis et al., 2014). In one study, 39 ET patients with and without parkinsonian features and 13 healthy controls underwent detailed examination by a movement disorders neurologist and DaTScans, analyzed by two independent radiologists "blinded" to the clinical diagnosis using semi-quantitative calculation of striatal binding ratios in different volumes of interests (Waln et al., 2015). The study found evidence of minimal dopaminergic deficit in the caudate nucleus of ET patients. Although this pattern is different from that of PD, in which the putamen

is more involved than the caudate, it suggests that some ET patients have a predisposition to develop PD.

A relationship between ET and nigral degeneration is supported by the finding of hyperechogenicity of SN on midbrain sonography in 16% of 44 ET patients compared with 3% of 100 controls and 75% of 100 patients with PD (Stockner et al., 2007). Although not demonstrated by all studies (Dopee et al., 2008; Budisic et al., 2008), the slightly increased hyperechogenicity of SN on midbrain sonography provides further support for the notion that some ET patients may later develop parkinsonism.

Orthostatic tremor

Orthostatic tremor, first described by Heilman in 1984 (Heilman, 1984), is a fast (14–16 Hz) tremor, involving mainly the legs and trunk, but cranial muscles also may be involved (Köster et al., 1999) (Video 10.5). The latter observation suggests that supraspinal mechanisms play a role in the pathophysiology of orthostatic tremor. This is further supported by the finding of high intermuscular coherence between both sides, providing evidence that the tremor originates from a common site (Lauk et al., 1999), and a high degree of EMG coherence between right and left muscle groups. This is in contrast to ET or PD tremors, in which there is no such left/right coherence, and these tremors are probably generated by more than one oscillator (Raethjen et al., 2000). Some authors have suggested that coherent high-frequency tremor in the legs may be a normal response to perceived unsteadiness when standing still and that orthostatic tremor may be an exaggeration of this response (Sharott et al., 2003). Others have postulated that orthostatic tremor merely unmasks 16-Hz central oscillators involved in postural tremor (McAuley et al., 2000; Muthuraman et al., 2013). Although there is robust evidence for supraspinal origin of orthostatic tremor (Muthuraman et al., 2013), the spinal cord may also serve as the generator of the tremor as suggested by the presence of a 16-Hz tremor in a man with complete paraplegia (Norton et al., 2004). The tremor is present chiefly on standing; orthostatic tremor also may be precipitated by isometric contraction of the upper limbs and facial and jaw muscles (Boroojerdi et al., 1999; Köster et al., 1999). This suggests that the generation of orthostatic tremor is more likely related to isometric force control rather than to regulation of stance. Orthostatic tremor is often associated with a feeling of unsteadiness and calf cramps, relieved by sitting or a supine position. Fung and colleagues (2001) postulated that “the sensation of unsteadiness arises from a tremulous disruption of proprioceptive afferent activity from the legs.” The leg cramps are presumably caused by a high-frequency (tetanic) contraction of the calf muscles. The muscle contraction can be “heard” by auscultating over the thigh or calf and listening for the characteristic thumping sound (Brown, 1995). ●

The pathophysiology of orthostatic tremor is not well understood, but some have suggested that it is a variant of ET. In support of the association between ET and orthostatic tremor is the relatively high occurrence of postural tremor, phenomenologically identical to ET, and the presence of family history of tremor in the majority of patients with orthostatic tremor (FitzGerald and Jankovic, 1991). In addition to ET, orthostatic tremor has been associated with

many other disorders, such as PD, progressive supranuclear palsy, RLS, dementia with Lewy bodies, dystonia, and cerebellar ataxia, but it is not clear whether the association is pathophysiologically linked or merely coincidental (Gerschlagler et al., 2004; Mestre et al., 2012). In one series of 26 cases of orthostatic tremor, with a median age at onset of 61 years and a median diagnostic delay of 4.5 years, orthostatic tremor-plus accounted for 8 cases (30.8%). In 18 (72%) cases the disorder was progressive and became refractory to medical therapy (Mestre et al., 2012). Furthermore, PET findings indicative of bilateral cerebellar (and contralateral lentiform and thalamic) dysfunction, similar to those observed in ET, also have been reported in patients with orthostatic tremor (Wills et al., 1996). Some studies have also suggested that there is a dopaminergic deficit in orthostatic tremor. Leg tremor, phenomenologically similar to orthostatic tremor, may be the initial manifestation of PD, particularly because of the parkin mutation (Kim and Lee, 1993; Deng et al., 2006b). Some patients with orthostatic tremor respond to levodopa (Wills et al., 1999) and dopamine agonists (Finkel, 2000). Furthermore, [¹²³I]FP-CIT SPECT showed evidence of marked reduction of DAT in patients with orthostatic tremor (Katzenschlagler et al., 2003).

Tremor that is present predominantly or only on standing, but usually of much lower frequency than the classic orthostatic tremor, also can be seen in other conditions, including parkinsonism, ET, head trauma, pontine lesions, and other disorders (Gabellini et al., 1990; Benito-Leon et al., 1997). In contrast to ET, orthostatic tremor does not respond to the conventional anti-ET medications, but usually improves with clonazepam and gabapentin (Rodrigues et al., 2006). In one study, 5 of 9 patients with orthostatic tremor benefited from levodopa (Wills et al., 1999). In a review of 41 patients with orthostatic tremor, Gerschlagler and colleagues (2004) found that 24 (58%) patients had associated postural arm tremor and 10 (25%) had “orthostatic tremor plus”; 6 (15%) patients had parkinsonism. The response to medications was generally poor, but some, particularly those with associated parkinsonism, responded to dopaminergic therapy. In the largest series of patients with orthostatic tremor, evaluated at Baylor College of Medicine Parkinson’s Disease Center and Movement Disorders Clinic, 89% of the 45 patients had primary orthostatic tremor and 5 patients had “orthostatic tremor plus,” including 3 with associated parkinsonism (Yalho and Ondo, 2014). Interestingly, 78% of all patients had postural hand tremor and 51% had a family history of hand tremor, suggesting a possible relationship with ET. Whether dopamine agonists and other antiparkinsonian treatments, including thalamotomy and VIM or STN/GPi DBS, will provide benefit to patients with orthostatic tremor remains to be determined. VIM DBS may be an effective treatment for patients with medically resistant orthostatic tremor (Espay et al., 2008; Guridi et al., 2008; Yalho and Ondo, 2011). Espay and colleagues published an international multicenter series of VIM DBS for orthostatic tremor that overall revealed possible mild benefits (Merola, 2017). Chronic spinal cord stimulation has been reported to be effective in 2 patients with medically intractable orthostatic tremor (Krauss et al., 2006).

The age at onset for ET showed a bimodal distribution with peaks in the second and sixth decades (Lou and Jankovic, 1991b). This was evident in both genders and

Video 10.5 Orthostatic tremor.

in patients with and without dystonia and parkinsonism. Patients with early-onset (<30 years) ET had significantly more hand involvement, were more likely to have associated dystonia, and were more likely to improve with alcohol than were those with later onset (>40 years) ET ($P < 0.05$). There were no significant differences in any clinical variables between patients with and those without a family history of tremor. Patients with older onset ET, sometimes also referred to as “senile tremor,” tended to have more rapid progression and more degenerative pathologic process than the younger onset patients (Louis ED, Faust PL, Vonsattel JP et al., 2009a). The relative lack of important differences among subgroups (early versus late onset, familial versus sporadic, mild versus severe, low versus high frequency) suggests that ET represents a single disease entity with a variable clinical expression. This conclusion is supported by a study by Koller and colleagues (1992). In their clinical and physiologic study of 61 patients, they found a frequency below 7 Hz in 79% of the patients, a positive family history in 72%, an amelioration with alcohol in 75%, an amelioration with primidone in 71%, and an amelioration with propranolol in 46%. Because no significant correlations could be found to suggest any particular grouping, they concluded that “essential tremor cannot be classified into subtypes.” In a study of 1137 tremor patients, 978 of whom had definite or probable ET, two subgroups were identified according to age at onset: early onset (24 years or younger, $n = 317$) and late onset (46 years or older, $n = 356$) (Hopfner et al., 2016). Although early-onset patients more frequently reported a positive family history and alcohol sensitivity of the tremor, tremor progression was significantly faster in the late-onset patients.

Dystonic Tremor

Several studies have addressed the relationship among ET, dystonia, and dystonic tremor. In one study of 463 patients from 97 kindreds with autosomal dominant mode of inheritance, “pure” ET was present in 79% of cases and focal or segmental dystonia in 21% cases (Hedera et al., 2010). The authors concluded that “familial ET associated with dystonia may represent a distinct subtype of ET.” Thus, there may be several types of tremors that may be initially misdiagnosed as either ET or PD: (1) ET with rest tremor, (2) dystonic tremor, and (3) “benign tremulous parkinsonism” manifested by predominant rest tremor, minimal bradykinesia, frequent family history of tremor, and modest response to levodopa (Josephs et al., 2006; O’Suilleabhain et al., 2006; Deeb et al., 2016). At autopsy, most of these patients had nigral pathologic findings that were qualitatively similar to those seen in idiopathic PD, but less severe (Selikhova et al., 2013). The patients with this form of parkinsonism respond well to VIM and STN DBS (Savica et al., 2011). Although the majority of patients with ET and rest tremor have normal DAT imaging with [^{123} I][β]-CIT and SPECT) or DaTscan, indicating that the rest tremor does not necessarily indicate underlying PD, many have increased R2 recovery components of the blink reflex, which is characteristic of dystonia (Nistico et al., 2012). This finding has been interpreted as evidence that the rest tremor associated with ET is a form of dystonic tremor, a conclusion supported by the presence of “subtle dystonia” in 36% of the ET cases. Using a magnetic search coil system to measure head movements in 14 subjects with cervical dystonia, investigators identified

two distinct types of oscillatory head movements: a relatively large-amplitude and jerky, irregular pattern (dystonic tremor) and a smaller amplitude with a more regular and sinusoidal pattern resembling ET; some subjects had a mixture of both (Shaikh et al., 2015). Reported tremor prevalence has ranged from 16.7% (Defazio et al., 2013) to 55.5% (Erro et al., 2014) of patients with adult-onset primary dystonia in one study. In another study, 46% of 273 patients with cervical dystonia had tremor (Rubio-Agusti et al., 2013).

In addition to dystonic tremor, patients with dystonia frequently have postural ET-like tremor present in body parts distal to the dystonia, and they have a higher than expected family history of postural tremor (Chan et al., 1991; Jankovic et al., 1991; Deuschl et al., 1997; Jankovic and Mejia, 2005; Schneider et al., 2007). Asymmetrical dystonic hand tremor may be initially misdiagnosed as PD-related tremor and, along with rest tremor associated with ET, may be responsible for SWEDDS (Schneider et al., 2007; Bain et al., 2009; Schwingenschuh, 2010; Stoessl, 2010; Erro et al., 2015). When 25 tremulous SWEDDS patients were compared with 25 tremor-dominant PD patients, the former group lacked true bradykinesia, they had evidence of dystonia and head tremor, whereas reemergent tremor, true fatiguing or decrement, good response to dopaminergic drugs, and presence of nonmotor symptoms favored PD (Schwingenschuh et al., 2010). Whether the hand tremor that is seen in about 25% (10%–85%) of patients with cervical dystonia represents an enhanced physiologic tremor, ET, dystonic tremor, or some other form of postural tremor is unknown (Jankovic et al., 1991; Deuschl et al., 1997; Schiebler et al., 2011). Although the frequency of ET and the limb tremor in patients with cervical dystonia are similar, the tremor amplitude in patients with dystonia is smaller and the tremor is more irregular, suggesting that the two types of tremors, although similar, arise from different types of oscillators (Shaikh et al., 2008). An analysis of ET patients from two large population-based studies and one large clinic-based cohort revealed no cases of pure head tremor in 583 patients (Louis and Dogu 2009). Therefore patients with pure head tremor probably should not be regarded as definite ET. Head tremor is observed in about 18% of population-based cases of ET and in 37% of a clinical sample of ET (Louis and Dogu, 2009). Secondary criteria include long duration (longer than 3 years), a positive family history, and a beneficial response to alcohol (Mostile and Jankovic, 2010). Another feature, seen in about a third of patients with ET is mirror movements (Louis et al., 2009), more typically observed in patients with focal dystonia (Sitburana et al., 2009). Red flags that indicate a diagnosis other than ET, such as unilateral tremor, present in only 4.4% of cases of ET (Phibbs et al., 2009), leg tremor, rigidity, bradykinesia, rest tremor, gait disturbance, focal tremor, isolated head tremor with abnormal posture (head tilt or turning), sudden or rapid onset, and drug treatment that may cause or exacerbate tremor. Thus, head tremor is usually a manifestation of ET or cervical dystonia; it is almost never seen in PD unless there is coexistent ET (Roze et al., 2006; Gan et al., 2009). In contrast to ET-related head tremor, which usually resolves when patients lie down, dystonic head tremor tends to persist in the supine position. In one study, supine head tremor persisted in 5 of 60 (8.3%) ET patients compared with 13 of 19 (68.4%) cervical dystonia cases ($P < 0.001$) (Agnew et al., 2012).

Some isolated site-specific tremors, such as those involving the head and trunk (Rivest and Marsden, 1990) and some task- or position-specific tremors, might actually represent forms of dystonic tremor (Elble et al., 1990; Jedynek et al., 1991; Bain et al., 1995; Elble et al., 2013). A series of 8 patients with facial dystonic tremor of irregular, 3- to 5-Hz frequency, have been described (Erro et al., 2014).

Dystonic tremor is typically irregular and position sensitive, and when the patient is allowed to move the affected body into the position of the maximal “pull,” the tremor often ceases; this is the so-called null point (Video 10.6, 10.7). Some patients with dystonic tremor present with asymmetrical rest hand tremor and decreased arm swing, which may initially lead to misdiagnosis of the tremor as PD (Jankovic and Mejia, 2005; Schneider et al., 2007; Bain, 2009). Although there is some overlap between primary writing tremor and dystonic writer’s cramp, the former is not usually associated with an excessive overflow of EMG activity into the proximal musculature, and the reciprocal inhibition of the median nerve H-reflex on radial nerve stimulation is normal (Bain et al., 1995; Modugno et al., 2002). The latter two features are typical of dystonia, and their presence in patients with task-specific tremors suggests that despite the absence of overt dystonia, these tremors represent forms of focal dystonia (Rosenbaum and Jankovic, 1988; Soland et al., 1996a). The overlap with primary handwriting tremor is supported by the observed activation of brain areas on functional magnetic resonance imaging (fMRI) that are commonly activated in ET and dystonic writer’s cramp. Other causes of postural tremor include midbrain (rubral) lesions. In a study of six patients with midbrain tremors, PET studies indicated dopaminergic striatal denervation, supported by markedly decreased fluorodopa uptake in the ipsilateral striatum (Remy et al., 1995). This nigrostriatal denervation, however, was not accompanied by striatal dopamine receptor supersensitivity, and the density of striatal D2 receptors did not change. Furthermore, the density of DAT is the same as that in normal controls (Antonini et al., 2001). Another form of postural tremor with bilateral high-frequency (14-Hz) synchronous discharges was reported in a patient with sporadic olivopontocerebellar atrophy (Manto et al., 2003). Patients with tremulous cervical dystonia are more likely to have involvement of the arms and a positive family history compared with nontremulous dystonia (Rubio-Agusti et al., 2013).

Treatment of dystonic tremor is challenging because there is no universally effective treatment, but the following drugs have been reported to have a modest benefit: anticholinergics, tetrabenazine, clonazepam, beta-blockers, primidone, and BTX, and levodopa is often efficacious in tremor associated with dopa-responsive dystonia (Fasano et al., 2014). Patients who continue to have troublesome dystonic tremor despite optimal medical therapy and BTX chemodenervation may benefit from DBS of the GPi, thalamus, or STN. Recent cohort-based evidence suggests that when tremor is the disabling feature in the setting of dystonia, VIIM DBS is the most reliable target (Morishita, 2010).

Genetics

A family history of tremor has been reported in 17% to 100% of patients with ET (Busenbark et al., 1996; Louis and Ottman, 1996). The reason for such a large discrepancy is

that unless all the symptomatic and asymptomatic members of the family are examined, the number of affected relatives will be underascertained (Jankovic et al., 1997; Louis et al., 1999b). Tremor in relatives is often wrongly attributed to aging, stress, nervousness, PD, alcoholism, or an associated illness or medications. In a study of 169 relatives of 46 ET patients, 12 (7.5%) were diagnosed as having probable or definite ET, but only 2 were reported by probands to have tremor (sensitivity: 16.7%); only 1 of 136 normal relatives were reported to have tremor (specificity: 99.3%) (Louis et al., 1999b). In other studies, the investigators found that 23% of elderly individuals had ET, and relatives of ET patients were five times more likely to develop the disease than was a control population (Louis, Ford, Frucht, et al., 2001), and first-degree relatives were more likely to have tremor compared with relatives of controls than were second-degree relatives (Louis, Ford, Frucht, Ottman, 2001). Factors that were associated with more accurate reporting were female informant, increased tremor severity, sibling relationship, and higher level of education. In a comprehensive study of 20 index patients with hereditary ET and their 93 first-degree relatives and 38 more distant relatives, Bain and colleagues (1994) examined 53 definite and 18 possible cases. Similar to the findings of Lou and Jankovic (1991a), the investigators found a bimodal distribution and autosomal dominant inheritance with nearly complete penetrance by the age of 65 years. In contrast to some previous studies, they found no cases of dystonia, PD, task-specific tremors, or primary orthostatic tremors, but migraine headaches occurred with a higher than expected frequency of 26%. About 50% were alcohol-responsive, but there was marked heterogeneity of responsiveness between and within families (Mostile and Jankovic, 2010). In contrast, a study of 252 members in four large kindreds with ET, three of the kindreds had a total of 41 members with the combination of ET and dystonia, and 2 had associated parkinsonism (Jankovic et al., 1997). Besides the one kindred with “pure” ET without any associated disorders (Jankovic et al., 1997), we subsequently studied 216 individuals of another large kindred with “pure” ET. The observation of earlier age at onset in successive generations suggests the phenomenon of anticipation, although the relatively small number of subjects and the possibility of ascertainment bias preclude any definite conclusions. Because ET is so common in the general population, bilineal transmission is not rare, and the amplitude of tremor appears to be greater in the children than in either affected parent (Rajput and Rajput, 2006). The younger the age at onset of ET, the higher the frequency of positive family history. In one study, 91% of cases with onset before the age of 20 years had a family history of tremor (Louis and Ottman, 2006).

Although the genetic origin of ET is widely recognized, the gene or genes responsible for ET have eluded intensive search by several groups of investigators (Deng et al., 2007; Jimenez-Jimenez et al., 2013) (Table 10.6). A genome scan of 16 ET Icelandic families containing 75 affected relatives with “definite” ET identified a marker for the familial ET gene, FET1 or ETM1, on chromosome 3q13 (Gulcher et al., 1997). An analysis of a large Czech American family established linkage to a locus ETM2 on chromosome 2p22–p25 (Higgins et al., 1997). Two of our families with “pure” ET and one with ET–parkinsonism–dystonia also mapped to the same locus (Higgins et al., 1998). On the basis of

Video 10.6 Dystonic tremor.

Video 10.7 Dystonic tremor.

Table 10.6 Review of genetic studies in essential tremor**ETM1- 3q13.1**

16 Icelandic families, 75 relatives with definite ET

ETM2-2p24.1

Linkage in 3 pure ET families and 1 ET–parkinsonism dystonia

6p22.3-24.1

Linkage in 2 ET families

D3 receptor gene (*DRD3*): 3q13.3

Ser9Gly variant associated with increased risk and younger age

Other Potential Candidate Genes

HS1 binding protein (HS1BP)

Solute carrier family 1 (glial high-affinity glutamate transporter) member 2 (SLC1A2)

Microtubule associated protein 2 (MAPT)

Methylenetetrahydrofolate reductase (NAD(P)H)(MTFHR)

Alpha-2 macroglobulin (A2M)

Cytochrome P450, family 2, subfamily C, polypeptide 19 (CYP2C19)

Cytochrome P450, family 2, subfamily C, polypeptide 9 (CYP2C9)

Cytochrome P450, family 2, subfamily C, polypeptide 8 (CYP2C8)

Alcohol dehydrogenase 4 (class II) pi polypeptide (ADH2)

Glutathione S-transferase pi 1 (GSTP1), paraoxonase 1 (PON1)

Gamma-aminobutyric acid (GABA) receptor genes

Fused in sarcoma/translated in liposarcoma (FUS/TLS)

Synuclein, alpha (non-A4 component of amyloid precursor) (SNCA)

Leucine-rich repeat kinase 2 (LRRK2)

Glucosidase, beta, acid (GBA)

Microtubule-associated protein tau (MAPT)

studies of genetically diverse populations of ET, the locus has been narrowed to 2p24.1 with a candidate interval to a 192-kilobase interval between the loci *etm1231* and *APOB* (Higgins et al., 2004). A missense mutation (828C→G) in the *HS1BP3* gene was identified in two American families with ET and was absent in 150 control samples (300 chromosomes) (Higgins et al., 2005, 2006). The 828C→G mutation causes a substitution of a glycine for an alanine residue in the HS1BP3 protein (A265G), which is normally highly expressed in motor neurons and Purkinje cells and regulates the Ca⁺⁺/calmodulin-dependent protein kinase activation of tyrosine and tryptophan hydroxylase. Studies in our own population of patients with ET and suitable controls, however, have led us to conclude that the variant might not be pathogenic for ET and might simply represent a polymorphism in the *HS1BP3* gene (Deng et al., 2005). A linkage to 6p23 with a lod score ranging from 1.265 to 2.983 was identified in two ET families, but further studies are needed to determine whether this merely represents a susceptibility locus or whether this gene region contains a causative gene (Shatunov et al., 2006). Variants in the coding region of the D3 receptor gene (*DRD3*), localized on 3q13.3, have been found to be associated with ET in some families and in a case-control study (Lucotte et al., 2006). In a genome-wide scan involving families from France and North America, Ser9Gly variant in the *DRD3* gene was found to increase dopamine affinity 4- to 5-fold and produce a gain-of-function abnormality as demonstrated by increased cyclic adenosine monophosphate dopamine-mediated response and prolonged

mitogen-associated protein kinase (MAPK) signal (Jeaneteau et al., 2006). *DRD3*Gly was found to be associated with an increased risk for and age at onset of ET in Spanish (Garcia-Martin et al., 2009) and French populations (Lorenz et al., 2009). This variant, however, has not been found in the majority of Asian (Tan et al., 2007) or Italian (Vitale et al., 2008) patients with ET, and some have argued against the role of *DRD3* gene in the pathogenesis of ET (Blair et al., 2008). Not all families map to the three known loci (ETM1, ETM2, or the 4p locus) (Kovach et al., 2001); thus, it is likely that familial tremor has marked not only phenotypic but also genetic heterogeneity and that additional gene loci will be identified in the near future. Furthermore, models other than autosomal dominant, including interaction between susceptibility genes and environmental risk factors should be considered (Ma et al., 2006).

Several studies have suggested a role for *LINGO1* variants in ET (Deng et al., 2012). When the genome-wide scan of 452 ET patients was compared with that of 14,378 controls, a marker in intron 3 of the *LINGO1* gene on chromosome 15q24.3 was found to be significantly associated with ET (Stefansson et al., 2009). In several large European and American populations, the odds ratios for carriers of one G allele averaged 1.55, with $P = 10^{-9}$. Odds increased to 2.4 for carrying two G alleles. Based on this and the prevalence of the allele, the population attributable risk for the variant was 20%. Another study involving North American population demonstrated a significant association between *LINGO1* rs9652490 and ET ($P = 0.014$) and PD ($P = 0.0003$) again suggesting that variations in *LINGO1* can increase risk for ET and provide evidence of a genetic link between ET and PD (Vilariño-Güell et al., 2009, 2010). Furthermore, a slightly higher frequency of the allele G of *LINGO1* marker rs9652490 was found in ET patients of Asian origin (Tan et al., 2009). Furthermore, pooled analysis revealed that the variant increased the risk in both familial and sporadic forms of ET among Asians (Wu et al., 2011). Other studies, however, have found no association between single nucleotide polymorphisms in *LINGO1* and ET (Lorenzo-Betancor et al., 2011a) but concluded that *LINGO1* rs11856808 *LINGO1* may increase the risk for PD (Lorenzo-Betancor et al., 2011b). *LINGO1* may be potentially pathogenic because it has been implicated in axon regeneration, and when mutated it may be responsible for fusiform swellings of Purkinje cell axons, similar to those found in autopsied brains of patients with ET (Yu et al., 2012). The SNP rs7033345 in the *LINGO2* gene, a member of LRR gene family, has been found to be associated with PD and ET and rs10812774 with ET among Asians (Wu et al., 2011). Protein levels of *LINGO1*, but not *LINGO2*, were found to be increased in the cerebellar cortex of ET patients compared with controls (Delay et al., 2014).

Using the Affymetrix Genome-Wide SNP Array, a two-stage genome-wide association study was conducted in a total of 990 subjects and 1537 control subjects from Europe to identify an intronic variant of the main glial glutamate transporter (*SLC1A2*) gene to be associated with ET (Thier et al., 2012). The *SLC1A2* variant also has been associated with ET in a Chinese population (Tan et al., 2013). Although the glutamatergic system has been implicated in the pathogenesis of ET, further studies are needed before it can be concluded that mutations in *SLC1A2* cause ET.

Another marker for ET has been mapped to chromosome 4p14–16.3 (MIM 168601) in a family with autosomal dominant PD (Farrer et al., 1999, 2004). This family, however, was later found to have alpha-synuclein gene (SNCA) triplication, and this SNCA triplication segregated with parkinsonism but not the postural tremor (Singleton et al., 2003). This suggests that the postural tremor is a coincidental finding. Subsequent studies have found no evidence that SNCA genetic variants increase the risk for ET (Ross et al., 2011). Using exome sequencing in a large ET family FUS p.Gln290* mutation was identified as the cause of ET in this family (Merner et al., 2012). Further screening of large and varied ET populations is needed to determine the frequency of the mutation and the associated phenotype.

In 1935, Minor (1935), a Russian neurologist, not only stated that “the older one is, the more likely one displays tremor (ET),” but also suggested “that a factor for longevity was also contained in the tremor gamete.” In support of the latter hypothesis, he offered the description of 51 cases of “hereditary tremor” associated with longevity. The longevity was based on patients’ parents and grandparents usually being older than 70 years. His control group consisted of 11 cases of parkinsonism in which “no example of longevity was found out.” However, the author did not state who in the ET families had tremor, and he did not provide details on his parkinsonian patients (clinical features, ages of the subjects and relatives), and normal controls were not examined. Supporting the clinical observation that patients with ET live longer than a control population, Jankovic, Beach, and colleagues (Jankovic, 1995) found that parents of patients with ET who had tremor (presumably ET) lived on the average 9.2 years longer than did parents without tremor. The association of familial tremor with significantly increased longevity suggests that familial tremor confers some antiaging influence. Alternatively, patients with ET might have an underlying personality trait that encourages dietary, occupational, and physical habits that promote longevity. Furthermore, the small amounts of alcohol to calm the tremor might prolong life, and, finally, the tremor itself might be viewed as a form of exercise that would have long-standing beneficial effects on general health (Mostile and Jankovic, 2010). In addition, some data suggest that wine consumption before the onset of tremor reduces the risk for ET; the subjects drinking more than 3 glasses of wine per day had 86% lower risk for ET (Nicoletti et al., 2011). Despite the overwhelming evidence that ET is of genetic origin, some researchers have suggested that environmental factors might also play a role, particularly because concordance among monozygotic twins is 60% (Louis, 2001; Tanner et al., 2001). However, in another study involving 92 twins with ET from the Danish twin registry, the concordance rate was 93% among monozygotic twins and 29% among dizygotic twins when the Tremor Research and Investigation Group consensus criteria were used (Lorenz et al., 2004).

Treatment

In designing protocols to study the effects of a therapeutic intervention on tremor-related functional impairment and on the mean amplitude (and frequency) of tremor, it is important to take into account the marked intraindividual and interindividual and diurnal variations in physiologic and

pathologic tremors (van Hilten et al., 1991; Deuschl et al., 2011). Factors such as anxiety, caffeine or alcohol intake, drugs, and even temperature (Lakie et al., 1994) can affect hour-to-hour variations in the amplitude of tremor. Caffeine, a nonselective adenosine receptor antagonist, can trigger or exacerbate tremor and the observed marked increase in the DBS-induced release of adenosine triphosphate from local astrocytes, which metabolizes to adenosine, has been suggested as one possible mechanism of DBS in suppression of tremor (Bekar et al., 2008).

Even without specific triggers or exacerbating factors, the ET amplitude may vary by 30% to 50% from hour to hour (Koller and Royse, 1985). The antitremor drugs exert their ameliorating effects by reducing tremor amplitude without any effect on tremor frequency. Reduction of tremor amplitude, however, does not always translate into improvement in function. There are currently no uniformly accepted ET rating scales, but the Unified Tremor Rating Assessment developed by the Tremor Research and Investigation Group (Jankovic et al., 1996; Ondo et al., 2000) and the Tremor Rating Scale developed by the Tremor Research Group (Tintner and Tremor Research Group, 2004) have been used in several studies.

The treatment of postural tremor depends largely on its severity; many patients require nothing more than simple reassurance. Most patients who are referred to a neurologist, however, have troublesome tremors that require pharmacologic or surgical treatments (Ondo and Jankovic, 1996; Bain, 1997; Lyons et al., 2003; Deuschl et al., 2011) (Fig. 10.3). The large-amplitude and slow-frequency postural tremors usually do not respond to any pharmacologic therapy. Because alcohol reduces the amplitude of ET in about two-thirds of patients for about 3 hours (Knudsen et al., 2011), some use it regularly for its calming effect and some use it prophylactically—for example, before an important engagement at which the presence of tremor could be a source of embarrassment. Although evidence concerning the risk for alcoholism among ET patients is contradictory, regular use of alcohol to treat ET is inadvisable (Mostile and Jankovic, 2010). One epidemiologic, prospective, population-based study in central Spain involving 3285 elderly participants, 76 of whom developed incident ET, concluded that baseline alcohol consumption was associated with substantially higher risk for developing ET (Louis et al., 2009). They suggested that the alcohol may be in part responsible for the cerebellar toxicity associated with ET. Although the authors dismiss the possibility that the participants who developed incident ET between the baseline and follow-up evaluations had preclinical ET at baseline, because they answered “no” when asked at baseline whether their arms or legs shook, many patients deny having tremor before the onset of alcohol consumption but validation by other family members often confirms that they had tremor before alcohol. Furthermore, family members of ET patients sometimes consume alcohol without being aware that it “calms” their tremor. Arguing against alcohol as contributing to the cause of ET is also the observation that many patients with ET never drink alcohol (Mostile and Jankovic, 2010).

The mechanism by which alcohol reduces tremor (effective blood level is less than 30 mg%) is unknown, but it is thought to act centrally, because infusion of alcohol into the brachial artery of a tremulous arm is ineffective

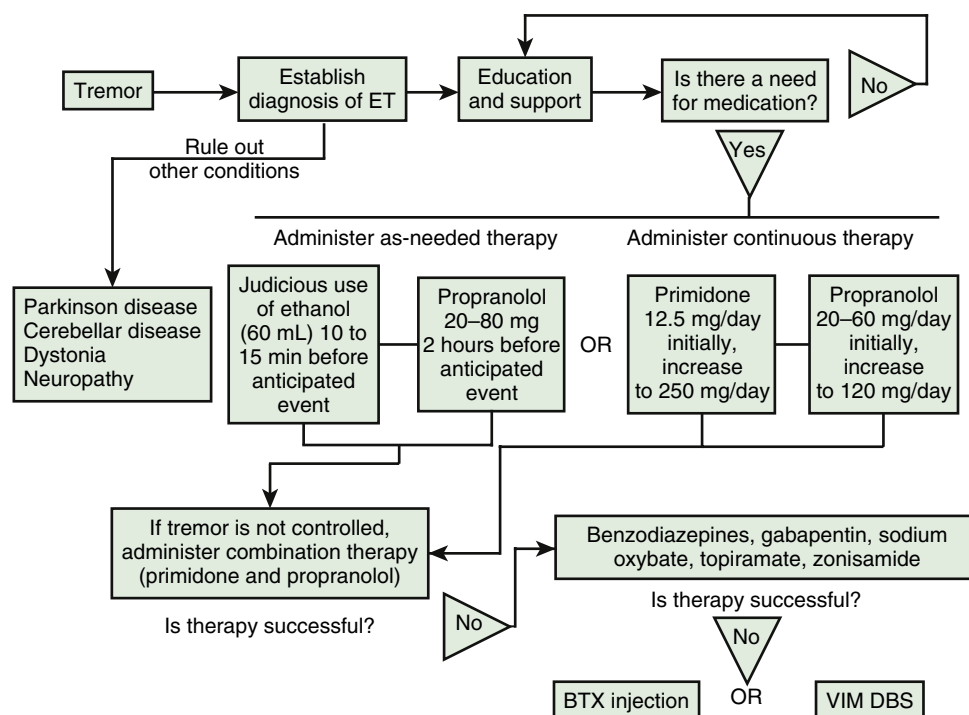


Fig. 10.3 Therapeutic algorithm in essential tremor.

(Growdon et al., 1975). Furthermore, the amplitude of the central but not peripheral components of ET is decreased after alcohol consumption (Zeuner et al., 2003a). Alcohol is known to affect multiple neurotransmitters, and it might stabilize neuronal membranes by potentiating GABA receptor-mediated chloride influx (Mostile and Jankovic, 2010). A pilot trial ($n = 12$) of 1-octanol, a food additive approved by the FDA that was previously demonstrated to suppress harmaline tremor (see later), found that it significantly decreased amplitude of ET for about 90 minutes after oral dose of 1 mg/kg (Bushara et al., 2004). The benefits and tolerance (except for unusual taste) of this drug were demonstrated in an open-label trial at doses up to 64 mg/kg (Shill et al., 2004). A single 4-mg/kg dose of octanoic acid was found not to be effective in reducing postural tremor in patients with ET at 80 minutes (primary outcome) but was effective after 180 minutes (Haubenberger et al., 2013).

Treatment of ET and other action tremors is not optimal. In a survey of 261 patients with ET, about a third who had been prescribed medication for tremor had discontinued the therapy and another third of cases with severe tremor had stopped medication (Louis et al., 2010). Propranolol, a beta-adrenergic blocker, remains the most effective drug for the treatment of ET and enhanced physiologic tremors, but other beta-blockers may also ameliorate postural tremor (Caccia et al., 1989; Calzetti et al., 1990; Koller et al., 2000) (Table 10.7). Propranolol is less effective in head tremor than hand tremor (Calzetti et al., 1992). Although a central mechanism of action has been suggested for this group of drugs, some beta-blockers exert potent antitremor activity even though they are not lipid soluble and hence do not cross the blood-brain barrier. This suggests that the therapeutic effect of beta-blockers may be mediated, at least in part, by the peripheral beta-adrenergic receptors (Guan and Peroutka, 1990). The major side effects of propranolol and, to a lesser degree, other beta-blockers include fatigability, sedation, depression, and sexual

Table 10.7 Evidence-based recommendations for treatment of essential tremor (Quality Standards Subcommittee of the American Academy of Neurology)

- Propranolol and primidone reduce limb tremor (Level A)
- Alprazolam, atenolol, gabapentin (monotherapy), sotalol, and topiramate (Level B)
- Propranolol reduces head tremor (Level B)
- Clonazepam, clozapine, nadolol, and nimodipine (Level C)
- Botulinum toxin A in limb, head, and voice tremor (Level C)
- Chronic DBS and thalamotomy (Level C)
- Surgical treatment of head and voice tremor and the use of gamma knife thalamotomy (Level U)

impotence. A critical review of 42 articles, based on controlled trials, concluded that despite the conventional wisdom, “there is no significant increased risk of depressive symptoms and only small increased risk of fatigue and sexual dysfunction” associated with beta-blocker therapy (Ko et al., 2002). These drugs are contraindicated in the presence of asthma, second-degree atrioventricular block, and insulin-dependent diabetes. Contrary to traditional recommendations, they may be used safely in patients with stable congestive heart failure resulting from left ventricular systolic dysfunction (Packer et al., 1999). The efficacy of sotalol, a nonselective beta-antagonist, in reducing ET is comparable to that of propranolol and atenolol, even though both atenolol and sotalol have very low lipid solubility and therefore act mainly through peripheral mechanisms (Leigh et al., 1983). Arutinolol, an alpha- and beta-blocker that is used as an antiobesity drug, was found to be as effective as propranolol in a randomized crossover study (Lee et al., 2003).

The antitremor effect of primidone has been confirmed by several open trials and placebo-controlled studies (Koller and Royse, 1986). By starting primidone at a very low dose

(25 mg at bedtime), the occasional idiosyncratic acute, toxic side effects (nausea, vomiting, sedation, confusion, and ataxia) can be prevented. Because there is little or no correlation between blood levels and tremolytic effects, the daily dosage should be gradually increased over a period of several weeks until the optimal therapeutic response is achieved. Dosages above 250 mg/day are only rarely necessary. The antitremor effect of primidone is largely attributed to the parent compound rather than to its metabolites, phenylethyl-malonamide or phenobarbital (Sasso et al., 1991). In one study (Koller et al., 1986), primidone alone was found to decrease tremor more than did propranolol alone, but a combination of the two drugs might be more efficacious than either drug alone. In a double-blind, placebo-controlled, crossover study, Gorman and colleagues (1986) found that both propranolol and primidone significantly reduced tremor compared with placebo. There is no evidence that either one of these primary anti-ET drugs is more efficacious than the other, but acute adverse effects with primidone and chronic side effects of propranolol limit therapy. The combination of the two drugs might be more efficacious than monotherapy (Koller and Royse, 1986). Although the benefits are usually maintained, the dosages might have to be increased after the first year to sustain the antitremor effectiveness. A double-blind study of 87 patients with ET, however, showed that low doses of primidone (250 mg/day) were as effective as or more effective than high doses (750 mg/day) (Serrano-Duenas, 2003).

In addition to beta-blockers and primidone, the benzodiazepine drugs, such as diazepam, lorazepam, clonazepam, and alprazolam (Gunal et al., 2000), and barbiturates, also may have some ameliorating effects on ET or its variants (Ondo and Jankovic, 1996). In a double-blind, crossover, placebo-controlled study, 22 patients with ET received in random order alprazolam, acetazolamide, primidone, and placebo for 4 weeks, each separated by a 2-week washout period. The study demonstrated that alprazolam was superior to placebo and equipotent to primidone, whereas there was no statistically significant difference between acetazolamide and placebo (Gunal et al., 2000). The mean effective daily dose of alprazolam was 0.75 mg, and no troublesome side effects were reported by the patients who took alprazolam. Clonazepam was shown to be ineffective in controlling ET in one double-blind study, but at a mean dose of 2.2 mg/day it improved kinetic tremor (Biary and Koller, 1987). Methazolamide (Neptazane), a sulfonamide that is used in the treatment of glaucoma, was reported to be effective in the treatment of ET (Muentner et al., 1991). Of 28 patients, 10 apparently achieved moderate to complete relief of their tremor. The average maintenance dose was 129 mg/day, and reported side effects included sedation, nausea, epigastric discomfort, and paresthesias. Aplastic anemia, the most feared complication, did not occur during the 6-month (10 weeks to 29 months) follow-up. The beneficial effects of methazolamide suggested by this open trial, however, could not be confirmed by a double-blind controlled study (Busenbark et al., 1993). Although our personal experience with this drug has been disappointing, we have found that up to 10% to 20% of patients who were previously unresponsive to other antitremor treatments note a marked improvement in their tremor with methazolamide. Flunarizine, a calcium channel blocker, was reported to improve ET in 13 of 15

patients (Biary and Deeb, 1991). This drug, however, is not available for use in the United States, and it can produce parkinsonism and tardive dyskinesia. Another calcium channel blocker, nimodipine at 120 mg/day, was found to improve ET in 8 of 15 patients who completed a double-blind, placebo-controlled trial (Biary et al., 1995). Anecdotally, fenofibric acid (Trilipix), a lipid-regulating agent, has been reported to also improve ET.

Despite some encouraging results with gabapentin based on pilot studies, subsequent double-blind controlled studies showed mixed results (Louis, 1999), ranging from no benefit (Pahwa et al., 1998) to modest improvement (Ondo et al., 2000) to a marked benefit comparable to that obtained with propranolol (Gironell et al., 1999). Topiramate, a broad-spectrum anticonvulsant, also has been reported to reduce ET in a double-blind, placebo-controlled trial at 400 mg/day dose (Connor, 2002). Although well tolerated, topiramate may cause paresthesias and weight loss and may adversely affect cognition (Thompson et al., 2000). Some patients who are unresponsive to conventional treatments do improve even with low-dose (50 mg/day) topiramate (Gatto et al., 2003). In a multicenter, double-blind, placebo-controlled trial involving 208 patients (topiramate, 108; placebo, 100) the final visit score (last observation carried forward) was lower in the topiramate group than with placebo ($P < 0.001$) (Ondo et al., 2006). Mean percentage improvement in overall TRS scores was 29% with topiramate at a mean final dose of 292 mg/day and 16% with placebo ($P < 0.001$), and topiramate was associated with greater improvement in function and disability ($P = 0.001$). The most common adverse effects were paresthesias (28%), weight loss (22%), and taste perversion (19%), but only the following adverse effects resulted in discontinuation of the drug: paresthesia (5%), nausea (3%), concentration/attention difficulty (3%), and somnolence (3%). Overall, adverse events were treatment limiting in 31.9% of topiramate patients and 9.5% of placebo patients. Thus, this multicenter study showed that topiramate was effective in the treatment of ET with acceptable tolerability profile. In a pilot, open-label, crossover trial designed to compare zonisamide and arotinolol in 14 patients with ET using the Fahn-Tolosa-Marin's clinical rating scale at baseline and 2 weeks after administration of each drug, both drugs were found to have significant and equal antitremor effect, but zonisamide was more effective for voice, face, tongue, and head tremors (Morita et al., 2005). In a subsequent double-blind, placebo-controlled trial involving 20 patients with ET, zonisamide failed to provide any improvement in clinical rating scales, although it reduced tremor by accelerometry (Zesiewicz et al., 2007). Zonisamide was, however, found to be more effective than propranolol in the treatment of isolated head tremor (Song et al., 2008). One study showed that 200 mg/day seemed to be the optimal dose for zonisamide in the treatment of ET (Handforth et al., 2009). Levetiracetam, another antiepileptic, was shown to have a significant antitremor effect in one double-blind, placebo-controlled trial at 1000 mg as a single dose (Bushara et al., 2005), but not in other studies (Handforth and Martin, 2004; Ondo et al., 2004; Elble et al., 2007). Pregabalin has been found effective in a pilot, double-blind, placebo-controlled trial (Zesiewicz et al., 2007), but not in another double-blind, placebo-controlled trial (Ferrara et al., 2009).

Mirtazapine has been reported to improve rest tremor (Pact and Giduz, 1999), but in a double-blind, placebo-controlled trial, the drug was not found to exert a significant benefit in ET (Pahwa and Lyons, 2003). Finally, clozapine has been found to be effective in selected drug-resistant patients with ET (Ceravolo et al., 1999). Gabapentin (Onofrij et al., 1998). Despite earlier reports, amantadine has not been found effective in patients with ET in a randomized, placebo-controlled trial, and in some patients actually exacerbated the postural tremor (Gironell et al., 2006). Sodium oxybate, a salt of gamma-hydroxybutyrate (GHB) may suppress tremor in a manner similar to alcohol (Frucht et al., 2005). AST-915 was formerly referred to as "AST-914 metabolite," manufactured by Manhattan Pharmaceuticals, has been studied in a randomized, double-blind, placebo-controlled, crossover design study involving 18 subjects with ET with reported benefits using accelerometry to test the central tremor component at various time-points after treatment. Nonpharmacologic treatments include helpful tips from occupational therapists on how to compensate for tremors that interfere with ADLs. Liftware (<http://www.liftware.com>), which includes stabilizing handle and utensil attachment such as spoon or fork, has been found helpful for some patients in whom tremor interferes with eating.

Clonazepam has been found to be the most effective drug in the treatment of orthostatic tremor, but levodopa (Wills et al., 1998), primidone, phenobarbital, and gabapentin have also been reported to be useful (Cabrera-Valdivia et al., 1991; FitzGerald and Jankovic, 1991). Most patients, however, do not obtain a satisfactory response to pharmacologic therapy and often resort to walking or sitting down after a few minutes. Some patients with orthostatic tremor carry with them stools in case standing becomes too uncomfortable (see <http://www.sportseat.com>). SAGE-217, a novel neuroactive steroid that acts as a modulator of synaptic and extrasynaptic GABAA receptor subtypes, is currently being tested as once-daily oral medication in patients with ET (<https://www.sagerx.com/programs-research/>).

Other treatment modalities for postural tremors include injections of BTX into muscles that are involved in the production of the oscillatory movement and various surgical approaches. In one open trial of BTX treatment, 67% of 51 patients with various disabling tremors noted at least some improvement (Jankovic and Schwartz, 1991). The average duration of improvement was 10.5 weeks, and side effects were chiefly related to local muscle weakness; 40% of 42 patients who were injected in the neck muscles to control head tremor and 60% of 10 patients who were injected in the forearm muscles to control hand tremor improved. Other studies have demonstrated the usefulness of BTX in the treatment of hand tremor (Trosch and Pullman, 1994). A double-blind, placebo-controlled trial has demonstrated a mild to moderate efficacy of BTX injections in patients with severe hand ET (Jankovic et al., 1996) and in patients with ET involving the head (Pahwa et al., 1995; Wissel et al., 1997). In a small, randomized, crossover trial of onabotulinumtoxinA in 23 patients with disabling tremor in 33 upper limbs related to multiple sclerosis, there was a significant improvement after active treatment compared with that after placebo at 6 and 12 weeks after injection in the Bain score for tremor, writing, Archimedes spiral drawing, drinking from a cup, and the 9-hole peg test (Van Der Walt et al., 2012). There

was, however, no improvement in the quality of life as measured by the Quality of Life in ET Questionnaire (QUEST). Treatment was complicated by transient weakness, noted in 42.2% of patients treated with BTX, compared with 6.1% of patients treated with placebo ($P = 0.0005$).

Although in one study, only 20% to 30% of patients with voice tremor were found to benefit from vocal cord injections of BTX, a majority of patients benefited from a subjective reduction in vocal effort that might have been attributable to reduced laryngeal airway resistance (Warrick et al., 2000). In another study involving 27 patients with adductor spasmodic dysphonia and vocal tremor and in four patients with severe vocal tremor alone, a significant improvement in various acoustic measures were observed after thyroarytenoid and interarytenoid BTX injections and less tremor was demonstrated in 73% of the paired comparisons (Kendall and Leonard, 2011). Although 67% of the patients with spasmodic dysphonia and vocal tremor wished to continue to receive BTX injections, only one patient with severe vocal tremor wished to continue with injections. BTX also may be effective in primary writing tremor, although a specially designed writing device might be a simpler and at least as effective treatment (Espay et al., 2005).

Peripheral deafferentation with anesthetic is currently being reexplored as a potential treatment of focal dystonia and tremor (Rondot et al., 1968; Pozos and laizzo, 1992; Kaji et al., 1995). An injection of 5 to 10 mL of 0.5% lidocaine into the target muscle not only improved focal dystonia, but also reduced the amplitude of the postural tremor. This short effect (<24 hours) can be extended for up to several weeks if ethanol is injected simultaneously (Kaji, personal communication). In a study of 10 patients with ET, Gironell and colleagues (2002) reported a transient (<1 hour) improvement in tremor after transient magnetic stimulation of the cerebellum.

The neurosurgical treatments, including DBS, that were discussed in the section on rest tremors also may be efficacious in patients with action hand tremors (Benabid et al., 1991; Blond et al., 1992; Deiber et al., 1993; Jankovic, Cardoso, et al., 1995; Koller et al., 1997), head tremors (Koller et al., 1999), and even task-specific tremors (Racette et al., 2001). It is of interest that cerebellar lesions can abolish ET, but it is unlikely that this observation will lead to surgically induced cerebellar lesions as a therapeutic modality in patients with ET (Dupuis et al., 1989). On the other hand, chronic cortical stimulation has been reported to improve contralateral action tremor (Nguyen et al., 1998). The observation that muscimol, a gamma-aminobutyric acid-A [GABA(A)] agonist, injection into the VIM thalamus improved tremor in patients with ET suggests that GABA agonists might be useful in the treatment of ET (Pahapill et al., 1999). On the basis of the observation that vagus nerve stimulation has a nonspecific calming effect in treated epileptics and that it suppresses harmaline-induced tremor (see later) in rats (Handforth and Kral, 2001), a multicenter trial was conducted to study the effects of vagus nerve stimulation in patients with essential and parkinsonian tremor, but no meaningful benefit was demonstrated (Handforth et al., 2003). Whether cortical stimulation will play a role in the future treatment of ET is not clear, but some preliminary reports suggest that this may potentially be an alternative to DBS (Moro et al., 2011). More recently, "focused ultrasound," a thermal ablation technique,

has been investigated using ExAblate Neuro, an investigational device manufactured by InSightec, Ltd. (<https://www.insightec.com/products/exablate-neuro/overview>) to target thalamus in the treatment of disabling tremor (Elias et al., 2013; Lipsman et al., 2013). The results have shown effectiveness in treatment of rest, postural, and action tremor in the setting of ET (Elias, 2016).

Kinetic tremors

Diagnosis

Kinetic tremor is typically associated with lesions or diseases that involve the cerebellum or its outflow pathways. The term *kinetic tremor* more accurately describes the oscillation occurring with limb movement than does the classic term *intention tremor*, which is ambiguous because it implies tremors that are present when “contemplating, initiating, performing, or completing a movement” (Lou and Jankovic, 1993). It is important to recognize that kinetic tremor is not simply a consequence of cerebellar ataxia (Diener and Dichgans, 1992), hypotonia, dysmetria, or dysdiadochokinesia but that the different motor disorders may coexist, often causing severe functional disability (Sabra and Hallett, 1984). Although kinetic tremor was traditionally considered a predominantly proximal tremor, using wrist (distal) or whole-arm (proximal) visually guided tracking in patients with multiple sclerosis showed a major frequency component at 4 to 5 Hz, most of the action tremor being distal rather than proximal (Liu et al., 1999).

In addition to this action, kinetic tremor patients with cerebellar lesions often exhibit postural tremors and titubation. The term *titubation* simply refers to a rhythmic oscillation of the head or trunk, presumably caused by hypotonia of the axial muscles. Kinetic cerebellar outflow tremor might be a component of the thalamic ataxia syndrome characterized in addition to the tremor by contralateral ataxia, hemisensory loss, and transient hemiparesis caused by a lesion in the mid to posterior thalamus involving the dentato-rubro-thalamic and ascending sensory pathways (Solomon et al., 1994). Kinetic terminal and postural tremors have been reported to result from repetitive transcranial magnetic stimulation, possibly by interfering with cerebellar inflow to the motor cortex (Topka et al., 1999). Although kinetic tremors are more difficult to assess than are ET or PD tremors, by using handwriting, spirals, and other tests, objective assessments of kinetic tremors, such as those seen in multiple sclerosis, can be reliably obtained (Alusi et al., 2000). In a study of 100 patients with definite multiple sclerosis, Alusi, Worthington, and colleagues (2001) found 58 with tremor, but it was symptomatic in 38 and incapacitating in 10. The authors concluded that multiple sclerosis tremors are usually related to involvement of the cerebellum.

Treatment

Some causes of tremor, such as alcohol withdrawal, phenytoin, lithium, amiodarone, and valproate toxicity (Nouzeilles et al., 1999) and cerebellar tumors and abscesses are specifically treatable. Tremor and ataxia in such cases can resolve after the underlying cause is removed. Some kinetic tremors can be reduced by attaching weights to the wrist, but this

method provides only limited improvement in function (Aisen et al., 1993).

No drugs have been shown to reduce cerebellar tremor satisfactorily and reproducibly, but the application of wrist weights before eating may enable the patient feed to himself or herself. Primidone, used in ET, has been found to be effective in 10 patients with multiple sclerosis and cerebellar tremor at doses that were gradually increased from 31.5 mg/day to 750 mg/day based on the Activity of Daily Living scale and the Fahn Tremor Rating Scale at 6 and 12 weeks (Naderi et al., 2012). Isoniazid was initially thought to improve cerebellar, postural tremor more than kinetic tremor (Sabra and Hallett, 1984), but the results of a double-blind trial were disappointing (Hallett et al., 1991). Sechi and colleagues (1989) reported that carbamazepine was effective in the treatment of cerebellar tremor, possibly by reducing hyperactivity in thalamic neurons. A group of 10 patients, 7 with multiple sclerosis and 3 with cerebrovascular disease, were followed for 2 to 24 months. All patients improved on a clinical rating scale and by accelerometric recording when given carbamazepine, 400 to 600 mg/day. There was no improvement with placebo. Trelles and colleagues (1984) reported that cerebellar kinetic tremor secondary to multiple sclerosis and olivopontocerebellar degeneration responded to clonazepam treatment at a daily dose of 8 to 15 mg. Alcohol not only improves ET, but also may improve tremor associated with multiple sclerosis (Hammond and Kerr, 2008). Glutethimide, a piperidinedione derivative with sedative and anticholinergic effects, also has been reported to be effective at doses of 750 to 1250 mg/day in action tremors, including ET, cerebellar tremors, and midbrain tremors (Aisen et al., 1991). The encouraging results from this open trial await confirmation by properly designed controlled studies. Even if it is found to be effective, however, the potential side effects of glutethimide, including respiratory depression, aplastic anemia, and physical and psychological dependence, will limit its usefulness. Buspirone, a serotonin (5-hydroxytryptamine_{1A}) agonist was reported to be useful in some patients with mild cerebellar ataxia, but placebo-controlled study is needed before it can be concluded that this drug is effective in cerebellar ataxia or tremor (Lou et al., 1995). Baker and colleagues (2000) found that cannabinoids control tremor in a mouse model of multiple sclerosis, but the effects of tetrahydrocannabinol in patients with cerebellar outflow tremor are unknown. Levetiracetam has been found to be effective in rare cases (Ferlazzo et al., 2008). As noted earlier, BTX has been found to be effective in some patients with cerebellar-outflow tremor secondary to multiple sclerosis (Van Der Walt et al., 2012).

Stereotaxic thalamotomy has been reported to successfully relieve kinetic tremor in patients with multiple sclerosis and other causes (Andrew, 1984). Radiofrequency lesions in the VIM seem to provide the best control of tremor with the lowest risk for neurologic deficit (Speelman and Manen, 1984; Nagaseki et al., 1986; Alusi, Aziz et al., 2001), although thalamic DBS also has been reported to be useful in selected patients with cerebellar-outflow tremor because of multiple sclerosis or other causes (Whittle et al., 1998; Montgomery et al., 1999). A National Institutes of Health trial published in *Lancet Neurology* suggested that leads placed in both the VIM and Voa-Vop may be a reasonable approach for the kinetic tremor of multiple sclerosis (Oliveria, 2017).

A report of the Quality Standards Subcommittee of the American Academy of Neurology, based on a review of evidence-based publications, published the following practice parameters related to therapies for ET. Propranolol and primidone reduce limb tremor (Level A); alprazolam, atenolol, gabapentin (monotherapy), sotalol, and topiramate are probably effective in reducing limb tremor (Level B); propranolol reduces head tremor (Level B); clonazepam, clozapine, nadolol, and nimodipine possibly reduce limb tremor (Level C); BTX type A may reduce limb, head, and voice tremor, but this treatment is limited by potential adverse effects (Level C); chronic DBS and thalamotomy are highly efficacious but potentially risky procedures (Level C); and there is insufficient evidence to support or refute the use of pregabalin, zonisamide, or clozapine as treatment for ET (Level U) (Zesiewicz et al., 2011) (see Table 10.7). Another evidence-based review concluded that there is a level B recommendation for onabotulinumtoxinA for the treatment of ET, but there was insufficient evidence to support or refute (level U) treatment of ET with other products (Hallett et al., 2013). Largely because of poor efficacy and tolerability, there is nearly 50% rate of noncompliance with medical therapy (Louis, 2015), and some patients require surgical treatment, including DBS or focused ultrasound thalamotomy (Elias et al., 2013; Lipsman et al., 2013).

Pathophysiologic mechanisms of rest and action tremors

Our understanding of mechanisms that are involved in generation of tremors has been facilitated by the development of neurophysiologic and other quantitative techniques such as EMG recordings and uniaxial and triaxial accelerometers and by the application of computer technology to analyze the frequency spectra and other tremor-related physiologic variables (Elble and Koller, 1990; Gresty and Buckwell, 1990; Elble et al., 1994; Louis, Dure, et al., 2001). A frequency of 6 Hz is usually the maximum rate of oscillation produced by a voluntary effort. During a voluntary contraction, motor units usually start firing at 8 Hz, and tetanic fusion frequency is reached at 15 to 20 Hz. Different parts of the human limb have mechanical characteristics (inertia and stiffness) that determine its natural resonant frequency. Such frequency is inversely related to the mass of the body part: finger, 25 Hz; wrist, 9 Hz; and elbow, 2 Hz (see Table 10.7).

A growing body of evidence supports the notion that central oscillators are important in the generation of physiologic and pathologic tremors (Pare et al., 1990; Plenz and Kitai, 1999; McAuley and Marsden, 2000; Brown, 2003; Gatev et al., 2006) (see Table 10.7). Using microelectrode recordings in awake or decerebrate monkeys who have been curarized and whose limbs were deafferented by sectioning C2 to T4 dorsal roots, Lamarre (1984) demonstrated spontaneous 3- to 6-Hz rhythmic discharges in the ventral thalamus and 7- to 12-Hz activity in the olivocerebellar system. Deafferenting the thalamus by a lesion in the ventromedial tegmentum of the midbrain facilitates synchronization of thalamic neurons, which is ultimately expressed as a spontaneous, 3- to 6-Hz, parkinsonian rest tremor. The amplitude of these discharges and associated tremors is markedly enhanced by the tremorgenic drug harmaline. Harmaline-induced tremor is

currently considered the most reliable animal model of ET because it generates both postural and kinetic tremors. It has been postulated that harmaline induces release of glutamate and acts as a potent reversible monoamine oxidase inhibitor. These and possibly other pharmacologic effects of harmaline result in facilitating low-threshold calcium conductance with resultant oscillatory activity of the olivocerebellar system, and eventual coupling and synchrony in the inferior olivary nucleus. Ethanol reduced harmaline-induced tremor, and possibly ET, by dysynchronizing the olivary discharges, in part by decreasing glutamate (Manot and Laute, 2008). There are two types of harmaline-induced tremors, both of which appear to originate in the inferior olivary nucleus: an 8- to 12-Hz tremor in normal animals (analogous to physiologic tremor) and a 6- to 8-Hz tremor in monkeys with lesions in the dentate nucleus. Single-unit recordings from patients with parkinsonian tremors showed that neurons in the thalamic ventral nuclear group show rhythmic activity that correlated with EMG activity. Some, but not all, of these cells responded to somatosensory activity, indicating the importance of peripheral modulation (Lenz et al., 1994). In addition to the thalamus, there are other subcortical nuclei—particularly the STN and external globus pallidus (GPe)—that contain neuronal populations that produce synchronized oscillating bursts at 0.4, 0.8, and 1.8 Hz in a cell-culture environment (Plenz and Kitai, 1999). In addition to the low-frequency (less than 10 Hz) oscillations, there are 11- to 30-Hz and greater than 60-Hz oscillatory activities within the subthalamopallidal-thalamocortical circuit (Brown, 2003). In PD, synchronized oscillatory activity in the 10- to 50-Hz band (often termed beta-band), prevalent in the basal ganglia thalamocortical circuit may be important in mediating certain parkinsonian features, including bradykinesia and tremor, can be reduced by dopaminergic treatments (Gatev et al., 2006). Furthermore, there is evidence that as a result of dopaminergic deficiency, the normal independent firing of pallidal neurons changes to both low-frequency (4–7 Hz) and high-frequency (10–16 Hz) oscillatory activity, which also can be recorded from the STN, and these oscillations often correlate with arm tremor (Bergman et al., 1998). This pacemaker could be responsible for the generation of tremor under pathologic conditions such as dopaminergic deficiency in Parkinson disease (PD). Therefore, surgical treatments of PD, such as lesion or stimulation of the GPi or STN, might act by desynchronizing the oscillatory basal ganglia-thalamocortical network activity. Such microelectrode-guided stereotactic operations in PD allow for single-cell recordings in the globus pallidus, thalamic nuclei, and other subcortical structures, leading to hypotheses about the normal and abnormal function of the basal ganglia. One such study, for example, found tremor-locked cells in the center median-parafascicular complex of the thalamus with low-threshold calcium spike-type bursts in the central lateral nucleus and paralamellar division of mediodorsal nucleus of the thalamus (Magnin et al., 2000).

Intracellular recordings from brainstem sections have demonstrated that neurons in the inferior olive have spontaneous oscillatory activity (Llinas, 1988; Kepler et al., 1990; Bevan et al., 2002). The autorhythmic properties of these neurons make this brainstem nucleus a prime candidate as a neuronal generator for tremor. In the olivary neurons, low-threshold Ca^{++} conductance at the somatic membrane

enables these neurons to generate action potentials (low-threshold spike) even at subthreshold depolarization. A fast-action potential, generated by Na^+ current into the cell body, is followed by a slow, high-threshold Ca^{++} spike that activates prolonged (80–100 ms) K^+ -mediated hyperpolarization. This is followed by an abrupt rebound response, generated by low-threshold Ca^{++} conductance, often large enough to generate a second, Na^+ -dependent, action potential, and the cycle repeats itself. In addition to the olivary nucleus, there are other areas of the brain, particularly the STN and globus pallidus, that display spontaneous rhythmic activities. In the STN neurons, voltage-gated Na^+ channels inactivate slowly during the depolarizing phase of the oscillation. In addition, Ca^{++} -dependent K^+ current is activated by Ca^{++} entry through high-voltage Ca^{++} channels that open briefly during each Na^+ action potential (Bevan et al., 2002). Harmaline enhances normal hyperpolarization, which is terminated by Ca^{++} influx and rebound excitation, leading to rhythmic activation of the neurons. Besides harmaline, many toxins can produce tremors in animals and provide useful models for the study of tremors (Wilms et al., 1999). Microelectrode-guided single-cell recordings in patients with PD showed that the average firing rate in the GPi was 91 ± 52 Hz and that in the globus pallidus externus (GPe) was 60 ± 21 Hz (Magnin et al., 2000). In addition, rhythmic, low-threshold calcium spike bursts are often recorded in the pallidum and medial thalamus; some, but not all, are synchronous (in phase) with the typical rest tremor. It has been postulated that the low-threshold calcium spike bursts contribute to rigidity and dystonia by activating the supplementary motor area.

Physiologic tremor is present in all humans. It is an asymptomatic oscillation of a body part, resulting from a complex interaction between local mechanical-reflex mechanisms and central oscillators (McAuley and Marsden, 2000) (Fig. 10.4). The mechanical-reflex component is determined partly by the ballistocardiogram, mechanical properties of the muscle, motor neuron firing characteristics, stretch reflex and muscle spindle feedback, supraspinal influences, and state of activation of the muscle beta receptors (Marsden, 1984). The frequency of this component is inversely proportional to the mass and stiffness of the limb; thus, increasing the external mass load decreases the tremor frequency (Elble and Koller, 1990). Besides this variable-frequency component, which is determined largely by the mechanical properties of the oscillating body part, spectral analyses of normal physiologic tremor show another, generally smaller, component with a relatively consistent frequency peak at about 10 (8–12) Hz. This 10-Hz frequency component is independent of peripheral influence, and it persists even after deafferentation, suggesting that this component of physiologic tremor is centrally generated. Supraspinal influence on physiologic tremor is supported by the observation that the loss of visual input when eyes are closed reduces or abolishes this tremor. The amplitude of physiologic tremor is determined largely by the degree of synchronization of motor unit discharges, modulated by muscle spindle Ia afferents. This process is exaggerated during anxiety, exercise, fatigue, and other conditions that are known to enhance peripheral beta-adrenergic activity, and it may result in a visible tremor called enhanced physiologic tremor (see Table 10.2).

In most pathologic tremors, such as the rest or reemergent tremor of PD (Jankovic et al., 1999), the central oscillators

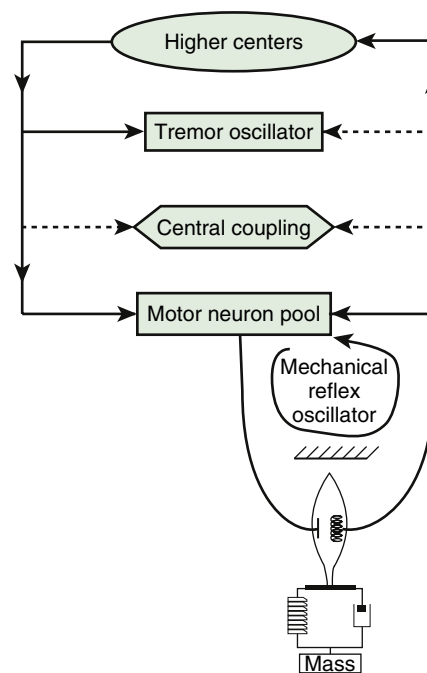


Fig. 10.4 Central and peripheral mechanisms of tremors.

are thought to drive the tremor, and the peripheral mechanisms are thought to merely modify or modulate its amplitude (Marsden, 1984; Britton et al., 1992a). Magnetic brain stimulation can also modify certain pathologic tremors, providing further evidence that these tremors are centrally generated (Britton et al., 1993). The motor pathways that are involved in transmission of signals from these central generators are not well understood. Inhibition of tremor by lesions in the basal ganglia outflow nuclei and in the thalamus suggests that these subcortical nuclei are involved in the pathophysiology of tremors. In parkinsonian states, as a result of nigrostriatal dopamine depletion, excessive GABA-mediated inhibition of the GPe within the indirect striato-pallidal pathway leads to a disinhibition of the STN and enhanced glutamate-mediated excitatory drive to the basal ganglia output nucleus (GPi) (DeLong, 1990). This increased drive from the output nuclei is reinforced by reduced inhibitory input to the GPi through the direct pathway. The typical 3- to 6-Hz rest tremor of PD possibly results from increased inhibition of the thalamic neurons that normally suppress the oscillators or from hyperpolarization of the oscillator neurons. In PD, the increased inhibitory output from the GPi leads to deafferentation of the thalamus, particularly the reticular nucleus, and synchronization of local neuronal networks with intrinsic properties to spontaneously discharge (Lamarre, 1984; Huntsman et al., 1999). This spontaneous bursting is transmitted via the thalamocortical-spinal circuitry to the motor neurons in the spinal cord, causing synchronization of motor unit discharges, ultimately expressed as an oscillatory movement.

Pathophysiology of parkinsonian tremor

In support of the role of the thalamus in the generation of parkinsonian rest tremor is the observation that the ventral thalamus of patients with PD contains a population of

neurons that fire spontaneously and rhythmically and that their firing frequency correlates relatively well with the frequency of tremor, recorded by EMG in the contralateral limb (Lenz et al., 1988). Furthermore, a lesion in the nucleus VIM or electrical stimulation of the nucleus, DBS, abolishes contralateral rest tremor (Kelly et al., 1987; Benabid et al., 1991, 1996; Hubble et al., 1997; Koller et al., 1997; Ondo et al., 1998; Limousin et al., 1999). That parkinsonian tremor is centrally driven is supported by the observation that complete paralysis of extensor forearm muscles as a result of radial nerve palsy actually increased the amplitude of the tremor without changing its frequency (Pullman et al., 1994). Volkmann and colleagues (1996) used magnetoencephalography to study parkinsonian resting tremor, and on the basis of these studies, they concluded that the typical 3- to 6-Hz parkinsonian tremor is generated by the same central mechanisms that are involved in voluntary rapid alternating movements. They proposed the following sequence of events for typical parkinsonian rest tremor: increased inhibitory output from GPI → hyperpolarization and activation of low-threshold calcium conductance in the anterior ventrolateral nucleus (VLa) → 5 to 10 ms → activation of the lateral premotor and motor cortex → 25 to 30 ms → EMG activity → 100 ms → activation of the central sulcus (reafferent input from muscle spindle to area 3a) → second activation of the somatosensory cortex by the antagonist contraction. The study of pacemaker neuronal networks as well as fast and slow oscillations within the basal ganglia circuitry will undoubtedly provide important insights into the pathophysiology of rhythmical involuntary movements such as tremors (Plenz and Kitai, 1999; Ruskin et al., 1999). Using ^{11}C -DASB PET as a marker of serotonin transporter binding in 12 patients with tremor-predominant, 12 with akinetic-rigid PD, and 12 healthy controls, reductions in ^{11}C -DASB in the caudate, putamen, and raphe nuclei significantly correlated with postural but not rest tremor in patients with PD, suggesting that serotonergic dysfunction plays a role in generation of postural tremor in PD (Loane et al., 2013). In contrast, a postmortem and imaging study using ^{123}I -FP-CIT, a marker of striatal dopamine and the brainstem serotonin system, found reduced raphe serotonin transporter availability correlating with rest tremor in 345 patients with early, drug-naïve PD (Qamhawi et al., 2015).

Pathophysiology of essential tremor

It has been suggested that the postural tremor of ET arises from spontaneous firing of the inferior olivary nucleus, which drives the cerebellum and its outflow pathways via the thalamus to the cerebral cortex and then to the spinal cord (Deuschl and Elble, 2000). In contrast to physiologic tremor, the frequency of ET does not decrease with mass loading, indicating a primary role of central mechanisms in ET (Elble and Koller, 1990). On the other hand, local cooling may significantly reduce the amplitude of ET, without changing its frequency (Lakie et al., 1994). Abnormal triphasic pattern with a delayed second agonist burst and other kinematic problems in response to a ballistic movement further support impaired cerebellar function in patients with ET (Koster et al., 2002). In one study, 25% of ET patients were found to have moderate or severe kinetic tremor and other elements of cerebellar dysfunction (Deuschl et al., 2000). In

addition, impaired eyeblink conditioning in patients with ET has been used as evidence of functional disturbance in the olivocerebellar circuits (Kronenbuerger et al., 2007). MRI scans, including diffusion-weighted imaging, have found no abnormalities associated with ET (Martinelli et al., 2007). Using a 3-T MRI in 19 ET patients (mean age 69.8 ± 9.4 years) and 20 age- and gender-matched controls, ET patients with severe tremor had significantly more white matter changes in the midbrain, both occipital lobes, and right frontal lobe, and gray matter changes bilaterally in the cerebellum (Benito-Leon et al., 2009). DTI MRI showed microstructural abnormalities in the dentate nucleus and superior cerebellar peduncle in patients with ET, providing further support of neurodegenerative pathologic processes of cerebellar structures in ET (Nicoletti et al., 2010). In a study of 24 patients with ET and 25 age-matched healthy controls, using a 3T MRI scanner, the investigators found increased brain iron accumulation in ET patients, particularly in the globus pallidus (Novellino et al., 2013).

The involvement of the olivocerebellar-thalamocortical circuitry in ET is supported by changes in the cerebellar blood flow as measured by PET during inhalation of C^{15} -labeled oxygen (Jenkins et al., 1993). Using this technique, the authors compared the cerebellar and cerebral blood flow in patients with ET and normal controls. They found that when the control subjects were holding one arm outstretched (in the absence of tremor), there was increased blood flow in the contralateral sensorimotor cortex and the supplementary motor area. In contrast, unilateral postural arm tremor in patients with ET was associated with markedly increased blood flow to *both cerebellar hemispheres*; in both premotor cortices; and to the contralateral striatal, thalamic, and sensorimotor cortex (but not the supplementary motor area). Passive and voluntary flexion–extension movements of the wrist significantly increased the blood flow only in the ipsilateral cerebellum. The investigators suggested that the increased flow in the cerebellum reflected increased activity of neurons involved in generation of tremor and that ET was due to oscillation within the olivocerebellar pathways, relayed by way of the thalamus and motor cortex to the spinal cord. Using a higher resolution camera, the investigators were additionally able to demonstrate bilateral midbrain activation in the region of the red nuclei during tremor, but there was no change in the activity of the inferior olive either at rest or during postural tremor (Wills et al., 1994). Additional evidence of increased activation of the cerebellum and red nucleus in ET has been provided by functional MRI studies (Bucher et al., 1997). The preponderance of evidence, based on PET and functional MRI studies, indicates that the inferior olive probably does not play an important role in the generation of ET. This is in contrast to one previous study that indicated the involvement of the inferior olive in ET, suggested by the finding of glucose hypermetabolism during activation (finger-to-nose) of tremor in patients with ET (Dubinsky and Hallett, 1987). The absence of activity in the inferior olive and the bilateral overactivity of cerebellar-rubral-thalamic connections suggest that the tremor generator for ET is located in the cerebellum rather than the inferior olive. This conclusion is further supported by the finding of abnormal bilateral overactivity of cerebellar connections, as measured by rCBF determined by PET with ^{15}O -labeled water, in patients with primary writing tremor and primary

orthostatic tremor (Wills et al., 1995, 1996). Other MRI studies have shown that cerebellum exhibited less gray matter in lobule VIII and less effective connectivity between each cerebellar cortex and the ipsilateral dentate nucleus. Changes in the cerebellum and supplementary motor area were inter-related (Gallea et al., 2015). The demonstration by magnetic resonance spectroscopy of reduced ratios of N-acetyl-L-aspartate to creatine and N-acetyl-L-aspartate to choline in the cerebellum of patients with ET compared with controls provides additional evidence for cerebellar dysfunction in ET (Pagan et al., 2003).

Cerebellar pathologic features, including loss of Purkinje cells, also have been described in some brains of patients with ET (Louis et al., 2006; Axelrad et al., 2008; Louis and Vonsattel, 2008; Kuo et al., 2011; Louis et al., 2011; Babij et al., 2013; Grimaldi and Manto, 2013; Louis et al., 2013); this finding has not been replicated by others (Rajput and Rajput, 2011; Rajput et al., 2011), and thus there is no consensus on cerebellar pathologic features in ET (Jellinger, 2014). It is of interest that in one patient with severe ET that began at age 45 and no parkinsonian features at the time of her death at age 91 years had Lewy bodies localized to the locus coeruleus, providing further evidence of a connection between ET and Lewy body disease (Louis, Honig et al., 2005). In one of the largest clinicopathologic studies, involving 33 ET and 21 control brains, 8 (24.2%), brains were found to have Lewy bodies in the brainstem, mainly in the locus coeruleus, and these patients were older than those ET cases without Lewy bodies (Louis et al., 2007). The major pathologic changes, however, were observed in the cerebellum, particularly marked reduction in the number of Purkinje cells and 7-fold increase in Purkinje cell torpedoes (Louis, Faust, Vonsattel et al., 2009b). Other findings included degeneration of the dentate nucleus, Purkinje cell heterotopias, and dendrite swellings, also confirmed by subsequent studies (Yu et al., 2012). In another study involving brains from 49 ET cases and 39 controls, thickened axonal profiles, axonal recurrent collaterals and branched axons were much more frequently observed on the axons of Purkinje cells with torpedoes versus Purkinje cells without torpedoes, but some of these changes could have been compensatory (Babij et al., 2013). Lewy body ET cases were older than ET cases without Lewy bodies. In another report the investigators found that brains of patients with ET had decreased climbing fiber–Purkinje cell synaptic density, more climbing fibers extending to the outer portion of the molecular layer, and more climbing fiber–Purkinje cell synapses on the thin Purkinje cell spiny branchlets (Lin et al., 2014). Increased cerebellar gliosis and depletion of pigmented neurons in locus coeruleus and SN (of which three had Lewy bodies) were found in a prospective study of 24 subjects enrolled in the Sun Health Research Institute and Body Donation Program (Shill et al., 2008). In a subsequent study, presumably based on the same pathologic cases, they found no difference in the putamenal tyrosine hydroxylase concentration between the ET cases (91.7 ± 113.2 ng/mg) and controls (96.4 ± 102.7 ng/mg) and concluded that “This study provides neurochemical support that ET does not appear to be preclinical PD.” In a subsequent autopsy study involving 23 ET subjects, there was no difference in striatal tyrosine hydroxylase or locus coeruleus dopamine beta-hydroxylase between ET and control brains, but parvalbumin, a marker of GABAergic neurons, was significantly

decreased in the pons in the region of the locus coeruleus of ET subjects versus controls, suggesting of a possible role for reduced GABAergic function in ET (Shill et al., 2012). The authors concluded that “The hypothesis that ET represents early PD was not supported, as striatal dopaminergic markers were not reduced compared with control subjects.” The data, however, do not support the conclusion for several reasons. First, the mean age in the pathologic series was 86.2 years, and mean duration of tremor was 11.1 years and 19 of 24 (79%) had a duration of 8 years or less. Although the authors do not provide the mean age at onset, based on their demographic data, the mean age at onset of ET in their population was about 75 years, which is 50 years later than the usual mean age at onset of ET of 25 years (Louis, Hernandez et al., 2013). It is likely, therefore, that most of the patients in the pathologic series of Shill and associates (2008) had “senile tremor” rather than typical ET (Deuschl, 2012). Furthermore, patients with prior history of a movement disorder, including those with parkinsonian features, were excluded; thus, by definition, clinical, pathologic, or biochemical evidence of PD could not be demonstrated in this selected ET population.

Cerebellar dysfunction in ET is also suggested by abnormalities in tandem gait, noted in 50% of ET patients (Singer et al., 1994; Stolze et al., 2001; Fasano et al., 2010; Louis et al., 2010, 2012), and by mild postural instability (Henderson et al., 1996; Overby et al., 1996). Although ataxic gait is rare, some ET patients exhibit a slightly slow or cautious pattern of walking (Kronenbueger et al., 2009). This gait ataxia improves with alcohol at blood level of 0.45% (Klebe et al., 2005). Alcohol has been found to suppress cerebellar synaptic overactivity in patients with ET, which in turn increases afferent input to the inferior olive (Boecker et al., 1996).

Posturographic analysis in patients with ET showed that balance control is only minimally impaired in ET, but patients with head tremor and longer disease duration may have slightly reduced postural stability (Bove et al., 2006). ET patients also show eye movement abnormalities indicative of cerebellar dysfunction, such as impaired smooth pursuit initiation and pathologic suppression of the vestibular-ocular reflex time constant by head tilts (otolith dumping) (Helmchen et al., 2003). Further evidence of cerebellar involvement in ET is suggested by a delay in second agonist EMG burst during rapid wrist movements (Britton et al., 1994). That the cerebellum might be involved in ET is also supported by the report of a 71-year-old man with ET in whom postural tremor disappeared on the right side after an ipsilateral cerebellar infarct (Dupuis et al., 1989). Besides the cerebellum, lesions in the frontal lobe, thalamus, and pons have been reported to markedly improve or completely abolish ET (Dupuis et al., 2010). Because the amplitude of ET can be substantially reduced by thalamic lesions or thalamic stimulation (Benabid et al., 1991) and close correlation has been demonstrated between thalamic neuronal activity and forearm EMG in patients with ET (Hua et al., 1998), it is likely that the thalamus also plays an important role in the generation or transmission of ET. Despite the reported evidence of cerebellar dysfunction in patients with ET, voxel-based morphometry shows no reduction in cerebellar gray matter volume (Daniels et al., 2006).

In addition to proposed cerebellar involvement in ET, there is some evidence that cerebral cortex plays a role in

the generation of ET (McAuley, 2001). Using simultaneous electroencephalogram (EEG)-EMG recordings, Hellwig and colleagues (2001) showed significant corticomuscular coherences in five of nine patients with ET. This is in contrast to a previous study that used magnetoencephalography (Halliday et al., 2000). That study found that in contrast to PD rest tremor, which is associated with marked disruption to the organization of the descending motor signals, there was no coherence between the magnetoencephalogram and EMG in patients with ET. However, the interpretation of the study that primary motor cortex does not contribute to the generation or maintenance of ET has been challenged because of possible insensitivity of the method (Elble, 2000c). The limitations of the various methods that were used in these studies have been pointed out by McAuley (2001), who also noted that EEG-EMG coherence does not necessarily establish cortical origin of the tremor (McAuley, 2001). Some patients with ET have abnormal vibration-induced illusion of movement, suggesting abnormal sensorimotor processing (Frima and Grunwald, 2005).

Rarely, postural tremor that occurs during sustained isometric muscle contraction can be a manifestation of cortical reflex myoclonus (Toro et al., 1993). This cortical tremor, also referred to as familial cortical myoclonic tremor with epilepsy (FCMTE), has been reported in many Japanese and European families (van Rootselaar et al., 2005) and in patients with spinocerebellar ataxia type 6 (SCA6) (Bour et al., 2008). Another term for this autosomal dominant disorder, characterized by a triad of cortical tremor, multifocal myoclonus, and generalized tonic-clonic seizures, is familial adult myoclonic epilepsy (FAME) (Crompton et al., 2012). Other acronyms used in the literature to describe this disorder include: ADCME, BAFME, Crt Tr, FCMT, FCMTE, FCTE, FEME, FMEA, and HTE (Sharifi et al., 2012). Typically starting in adolescence (median age, 15 years; age range, 4–60 years) with fine hand tremor, later associated with proximal myoclonus in about 80% of patients and generalized tonic-clonic seizures in 15%, has neurophysiologic features of cortical reflex myoclonus. Sometimes associated with cognitive decline and a family history suggestive of ET, this “cortical tremor,” with or without seizures, generally has a benign course and markedly improves with anticonvulsants (Okuma et al., 1998; van Rootselaar et al., 2005). It is characterized physiologically by an 8- to 15-Hz, synchronous, agonist-antagonist, EMG burst lasting less than 50 ms (10–50 ms). The condition shares neurophysiologic features with myoclonus, including giant somatosensory evoked responses and C-reflexes, and it responds well to anticonvulsants such as clonazepam, primidone, and valproate but not to beta-blockers (Okuma et al., 1998). The EMG pattern can be influenced by transcranial magnetic and electrical stimulation but not by peripheral nerve stimulation; therefore, the rhythmic movement is thought to arise from central, possibly cortical, generators. Jerk-locked back-averaging revealed a positive EEG wave 15 ms preceding the EMG burst of the wrist extensor muscle (Okuma et al., 1998). In contrast to ET, strong corticomuscular and intermuscular coherence in the 8- to 30-Hz range was demonstrated in patients with familial cortical myoclonic tremor with epilepsy (van Rootselaar et al., 2006). The syndrome of autosomal dominant cortical tremor, myoclonus, and epilepsy has been linked to three genetic markers, on 8q24, 5p15.31-p15 (Depienne et al., 2010),

and the FAME2 (OMIM 607876) has been mapped to 2p11.1–q12.2 (Striano et al., 2005; Crompton et al., 2012). Exome sequencing in a consanguineous Egyptian family with autosomal recessively inherited focal epilepsy, neuropsychiatric features, borderline cognitive level, and myoclonus found a homozygous deletion (c.503_503delG) leading to a frameshift in the coding region of *CNTN2*, which encodes contactin 2 (Stogmann et al., 2013). The interpretation that the *CNTN2* mutation is pathogenic, however, has been challenged because FCMTE is an autosomal dominant disorder with a typical electrophysiologic signature of cortical reflex myoclonus (i.e., giant somatosensory evoked potentials, premyoclonus cortical spikes detected by the jerk-locked back-averaging, etc.), not found in the Egyptian family (Striano et al., 2013). Cortical myoclonic tremor usually responds well to antimyoclonic drugs, such as clonazepam, valproate, and levetiracetam, but can be exacerbated by other anticonvulsants, such as carbamazepine, lamotrigine, and gabapentin, sometimes resulting even in refractory, life-threatening status epilepticus. Autopsy studies have shown evidence of cerebellar degeneration with Purkinje cell changes similar to those observed in SCA 6 (Sharifi et al., 2012).

Other abnormalities that are found in patients with ET include high blood levels of beta-carboline alkaloids. Interestingly, these endogenous compounds, also found in plant-derived foods, increase the synchrony of neuronal firing in the inferior olive and cause tremor in experimental animals and humans. Some investigators have suggested that a loss of GABA_A receptors may impair signaling by cerebellar Purkinje cells and cause tremor, as has been demonstrated in mice in which the gene coding for the GABA_A receptor alpha1 subunit has been knocked out (Jankovic and Noebels, 2005; Kralic et al., 2005). Mutations in the coding region of the *GABRA1* gene, however, do not seem to be a major genetic cause of ET (Deng et al., 2006c; Thier et al., 2011). Although the genetic studies have not produced much evidence for the role of GABA in ET, postmortem studies have demonstrated a decrease in GABA_A (35% reduction) and GABA_B (22%–31% reduction) receptors in the dentate nucleus of the cerebellum from individuals with ET compared with controls or individuals with PD (Paris-Robidas et al., 2012). The authors proposed that “a decrease in GABA receptors in the dentate nucleus results in disinhibition of cerebellar pacemaker output activity, propagating along the cerebello-thalamo-cortical pathways to generate tremors.” Evidence of reduced GABAergic innervation was also found in the locus coeruleus in one postmortem study (Shill et al., 2012). Thus far, no evidence of an association between GABA receptor and transporter genes has been found in patients with ET (Garcia-Martin et al., 2011a,b; Thier et al., 2011), but many investigators still think that disturbed GABA-mediated neuronal inhibition plays an important role in tremorogenesis.

Clinicoanatomic correlations indicate that kinetic tremor is usually associated with lesions in the cerebellar outflow pathways (Lou and Jankovic, 1993). Lesions of the dentate nucleus or the superior cerebellar peduncle proximal to the decussation correlate with kinetic tremor ipsilateral to the side of the lesion, whereas lesions that are distal to the decussation result in kinetic tremor contralateral to the side of the lesion (Carrea and Mettler, 1955). Lesions in the cerebellar hemisphere tend to produce kinetic tremors with a variable frequency ranging from 5 to 11 Hz; high brainstem lesions

are usually associated with tremor frequency in the range of 5 to 7 Hz; and lower brainstem lesions produce faster tremors, ranging from 8 to 11 Hz (Cole et al., 1988). In contrast, the frequency of classic midbrain (red nucleus) tremor is relatively slow, at 2 to 3 Hz. In one study of patients with multiple sclerosis, two types of action tremors were identified. One group of patients had pure kinetic tremor with a frequency of 5 to 8 Hz and an EMG burst duration of 75 to 100 ms; the other group had coexisting kinetic and postural tremor. In contrast to kinetic tremor, postural tremor had a slower (2.5–4 Hz) frequency and a higher amplitude with a longer burst duration (125–200 ms) (Sabra and Hallett, 1984). The postural tremor was thought to result from a lesion in the cerebellar outflow pathway. Cerebellar kinetic tremor is associated with errors in timing and amplitude of the EMG activities of agonists and antagonists (Flament and Hore, 1986; Hore and Flament, 1986). The important role of peripheral reflex mechanisms in the pathogenesis of cerebellar kinetic tremor is supported by the observation that the character of the tremor can be altered by mechanical loading to the tremulous limb (Sanes et al., 1988) and by improvement in writing after 3 to 5 minutes of compressive ischemia of the affected arm (Dash, 1995). Lakie and colleagues (2004) showed that reduction of tremor by ischemia may be due to an accumulation of interstitial potassium in the muscle. The frequency of the tremor can be increased by increasing the spring stiffness and decreasing the mass.

Other tremors

Fragile X-associated tremor/ataxia syndrome

Other causes of kinetic tremor, phenomenologically similar to ET, include premutation in the fragile X gene (*FMR1*) (Hagerman et al., 2001; Berry-Kravis et al., 2003; Jacquemont et al., 2003, 2004; Leehey et al., 2003; Hagerman and Hagerman, 2004, 2008; Amiri et al., 2008). Whereas normal individuals have about 30 CGG repeats in the *FMR1* gene, the carriers of this permutation syndrome have 55 to 200 repeats. The *FMR1* CGG repeat length has been found to predict motor dysfunction in permutation carriers (Leehey et al., 2008). In addition to the ET-like tremor, frequently affecting the head, and ataxia, this fragile X-associated tremor/ataxia syndrome (FXTAS) is also associated with mild cognitive impairment with frontal executive deficit, dementia, parkinsonism, dysautonomia, erectile dysfunction, peripheral neuropathy, and generalized brain atrophy, regardless of family history (Berry-Kravis et al., 2007) (Table 10.8). FXTAS may also, rarely, occur in females with a similar phenotype but early menopause because of ovarian failure and a propensity for autoimmune conditions (Winarni et al., 2012). One of our patients with severe FXTAS-associated tremor improved markedly with thalamic DBS (Ferrara et al., 2008). Unusual bilateral T2 middle cerebellar hyperintensities have been identified on MRI in some cases (Leehey et al., 2003). Overexpression and central nervous system toxicity of the fragile-X mental retardation gene, *FMR1*, mRNA has been thought to cause this FXTAS (Jacquemont et al., 2006; Berry-Kravis et al., 2007; Hagerman and Hagerman, 2008). In a clinical, morphologic, and neurophysiologic study of 22 patients with FXTAS, a total of 86% had tremor and 81% peripheral neuropathy (Aparitis et al., 2012). In addition to middle

Table 10.8 Clinical features of fragile X-associated tremor/ataxia syndrome (FXTAS)

- 55–200 CGG repeats (*FMR1* premutation)
- Essential tremor-like postural tremor
- Kinetic tremor
- Mild cognitive impairment with frontal executive deficit
- Ataxia
- Parkinsonism (multiple system atrophy)
- Erectile dysfunction
- Peripheral neuropathy
- Premature ovarian failure
- Magnetic resonance imaging: Bilateral T2 middle cerebellar peduncle hyperintensities

cerebellar peduncle hyperintensities, found in 64%, hyperintensity of corpus callosum splenium was noted in 68%. Despite prior findings of normal DAT SPECT scans (Ceravolo et al., 2005), 47% of patients in this study had an abnormal (¹²³I)-ioflupane SPECT.

Although some features overlap with those of multiple system atrophy, FXTAS is a rare cause of multiple system atrophy (Biancalana et al., 2005). Postmortem studies on brains of four elderly permutation carriers showed eosinophilic intranuclear inclusions in both neuronal and astrocytic nuclei throughout the brain, particularly involving the hippocampus (Greco et al., 2002). Subsequent neuropathologic studies of patients with FXTAS showed (1) cerebral and cerebellar white matter disease with spongiosis in the middle cerebellar peduncles, (2) astrocytic pathologic findings with enlarged inclusion-bearing astrocytes, and (3) intranuclear inclusions in the brain and spinal cord, including the cranial nerve nucleus XII (Greco et al., 2006). The number of inclusions seems to correlate with the number of CGG repeats (Cohen et al., 2006). The inclusions contain a variety of proteins, such as RNA binding proteins, but ubiquitinated proteins represent only a small portion of all the proteins, suggesting that breakdown of proteasomal degradation is not the main mechanism of the inclusions (Iwahashi et al., 2006). It has been postulated that premutation RNA is responsible for the observed neurodegeneration (Orr, 2004). Marked loss of Purkinje cells in the cerebellum, Purkinje axonal torpedoes, and Bergmann gliosis were also found. SCA12, a rare autosomal dominant ataxia, may also manifest with ET-like tremor before other signs of ataxia become evident. This form of ataxia has been associated with CAG repeat expansion in the *PPP2R2B* gene (5q31–33) coding for protein phosphatase PP2A (Fujigasaki et al., 2001). The frequency of fragile X premutation, even in patients with tremor, parkinsonism, and ataxia, is so low that it is not cost-effective to routinely test for it even in an enriched movement disorders population (Arocena et al., 2004; Deng et al., 2004; Tan et al., 2004). Interestingly, the location of the CAG repeat expansion in the 5' region is similar to that of the CGG repeat in *FMR1*, in which an expansion results in CpG hypermethylation and disruption of transcription, resulting in the fragile X phenotype.

Neuropathic tremors

Tremor has been described in patients with various types of peripheral neuropathy (Said et al., 1982; Shahani, 1984).

Distal postural tremor was noted in patients with chronic relapsing and dysgammaglobulinemic polyneuropathies (Bain et al., 1996) and immunoglobulin M (IgM)-monoclonal gammopathy (Ahlskog et al., 2012). The amplitude was not related to the severity of weakness or proprioceptive sensory loss, and propranolol improved the tremor in some patients. Hereditary motor and sensory neuropathy is associated with tremor, clinically similar to ET, in nearly half of cases (Cardoso and Jankovic, 1993). The frequent association between tremor caused by peripheral nerve injury and reflex sympathetic dystrophy suggests that the sympathetic nervous system contributes to the pathogenesis of peripherally induced tremor (Jankovic and Van der Linden, 1988; Deuschl et al., 1991; Jankovic, 1994; Cardoso and Jankovic, 1995).

Tremors caused by trauma or stroke

Tremor can also occur after severe or even minimal head trauma (Biary et al., 1989; Goetz and Pappert, 1992; Jankovic, 1994; Krauss et al., 1985). Biary and colleagues (1989) described seven patients who developed postural and kinetic tremors involving various body parts up to several weeks after mild head injury without loss of consciousness. Ipsilateral predecussational dentatohalamic lesion was involved in the majority (56%) of 25 instances of severe post-traumatic tremor in 19 patients, followed by involvement of the contralateral predecussational dentatohalamic pathway (28%), dentate nucleus (4%), and thalamus (4%); no lesion was identified by neuroimaging in 2 (8%) patients (Krauss et al., 1995). Clonazepam was effective in reducing tremor in 3 patients, and propranolol was effective in 1. Posttraumatic midbrain tremor may improve with anticholinergic and dopaminergic drugs (Samie et al., 1990), but in general, this tremor only rarely responds satisfactorily to drug therapy. Many of our patients with posttraumatic tremors have benefited from VIM thalamotomy; additional patients may benefit from thalamic stimulation (Broggi et al., 1993). In addition to trauma, a variety of tremors can occur after ischemic or hemorrhagic strokes (Ferber and Gerwig, 1993; Miwa et al., 1996).

Trauma can also cause injury to the peripheral nerves, producing a form of neuropathic tremor, which was discussed earlier. Traumatic neck injury may cause cervical radiculopathy, which may be associated with a postural tremor in the ipsilateral arm (Hashimoto et al., 2002). Loading and ischemic nerve block reduced the frequency of the tremor, suggesting a role of the mechanical reflex mechanism and stretch reflex loop in this peripherally induced tremor.

Psychogenic tremor

One of the most challenging tasks in the diagnosis of tremors is differentiating between psychogenic and neurogenic tremors (Kenney et al., 2007) (Table 10.9). Koller, Lang, and colleagues (1989) provided the following diagnostic criteria useful in the diagnosis of psychogenic tremors: (1) abrupt onset, (2) static course, (3) spontaneous remission, (4) difficulty in classifying (various combinations of rest, postural, and kinetic tremors), (5) selective disability, (6) changing amplitude and frequency, (7) unresponsiveness to anti-tremor drugs, (8) increasing of tremor with attention, (9) lessening of tremor with distractibility, (10) responsiveness

Table 10.9 Distinguishing psychogenic from essential tremor

- A “blinded” rater evaluated video segments of subjects using a standardized protocol.
- N = 33 subjects with ET (56.8 ± 17.0 years) and 12 with psychogenic tremor (42.5 ± 11.0 years).
- Patients with psychogenic tremor were significantly more likely to have a history of sudden onset ($P = 0.03$), spontaneous remissions ($P = 0.03$), and shorter duration of tremor ($P = 0.001$).
- Family history of tremor was significantly more common in the ET group ($P = 0.001$).
- A moderate to marked degree of distraction with alternate finger tapping ($P = 0.01$) and mental concentration on serial 7s ($P = 0.01$) was more common in psychogenic tremor.
- Suggestibility with a tuning fork ($P = 0.04$) and exacerbation with hyperventilation ($P = 0.06$) seemed predictive of psychogenic tremor.
- Entrainment was not different in the two groups.

Data from Kenney C, Diamond A, Mejia N, et al. Distinguishing psychogenic and essential tremor. *J Neurol Sci.* 2007;263:94–99.

to placebo, (11) absence of other neurologic signs, and (12) remission with psychotherapy (Video 10.8). Deuschl, Köster, and colleagues (1998) found the following features particularly characteristic of psychogenic tremor: sudden onset and variable (rarely remitting) course, coactivation sign (fluctuations in muscle tone and in tremor during passive movements), and absent finger tremor. Although overt signs of hysteria were often lacking, evidence of depression and psychosomatic conditions were common. In another study of 70 patients with psychogenic tremor, 73% had an abrupt onset, and 46% had their maximal disability at onset (Kim et al., 1999). Additional features that were found helpful in confirming the diagnosis of psychogenic tremor included spread from a focal onset to generalized tremor, variability, and entrainment. To determine clinical features that reliably distinguish psychogenic tremor and ET, Kenney and colleagues (Kenney et al., 2007) used clinical data and “blinded” rating of videos of 45 patients with these two tremor types. Patients with psychogenic tremor were significantly more likely to relay a history of sudden onset, spontaneous remissions, and shorter duration of tremor. Family history of tremor was significantly more common in the ET group. A moderate to marked degree of distraction with alternate finger tapping and mental concentration on serial 7s, suggestibility with a tuning fork, and exacerbation with hyperventilation were predictive of psychogenic tremor. ●

Electrophysiologic studies are sometimes helpful in differentiating organic tremor from psychogenic tremor (McAuley et al., 1998). Using accelerometry, Zeuner and colleagues (2003b) demonstrated that in contrast to essential and parkinsonian tremor, patients with psychogenic tremor showed larger tremor frequency changes and higher individual variability while tapping. In one study, patients with psychogenic tremor reported significantly more of the waking day with tremor compared with patients with organic tremor ($83.5\% \pm 14.0\%$ of the waking day versus $58.0\% \pm 19.0\%$ of the waking day; $P < 0.01$), despite having almost no tremor recorded by actigraphy (Pareés et al., 2012).

Longitudinal studies are needed to determine the natural history of psychogenic tremors. In one study, a 6-year follow-up of 64 patients with unexplained motor disorders,

Video 10.8 Psychogenic tremor.

3 were later found to have an organic diagnosis (Crimlisk et al., 1998). In the Parkinson's Disease Center and Movement Disorders Clinic at the Baylor College of Medicine, psychogenic tremor is the most common of all psychogenic movement disorders, accounting for 4.1% of all patients (Jankovic and Thomas, 2006). Clinical information was obtained on 228 of 517 (44.1%) patients, who were followed for a mean of 3.4 ± 2.8 years. Among the 127 patients who were diagnosed with psychogenic tremor, 92 (72.4%) were women, the mean age at initial evaluation was 43.7 ± 14.1 years, and the mean duration of symptoms was 4.6 ± 7.6 years. The following clinical features were considered characteristic of psychogenic tremor: abrupt onset (78.7%), distractibility (72.4%), variable amplitude and frequency (62.2%), intermittent occurrence (35.4%), inconsistent movement (29.9%), and variable direction (17.3%). In the majority of patients, some precipitating event could be identified before the onset of tremor, including personal life stress (33.9%), physical trauma (23.6%), major illness (13.4%), surgery (9.4%), or reaction to a medical treatment or procedure (8.7%). Coexistent organic neurologic disorder was present in 37% of patients with psychogenic tremor; psychiatric comorbidities included depression in 50.7% and anxiety in 30.7%. Evidence of secondary gain was present in 32.3%, including maintenance of a disability status in 21.3%, pending compensation in 10.2%, and litigation in 9.4%. Improvement in tremor, reported on a global rating scale at last follow-up by 55.1%, was attributed chiefly to "effective treatment by physician" and "elimination of stressors." On the basis of the analysis of data in this largest longitudinal study of patients with psychogenic tremor, we have concluded that the accurate diagnosis not only is based on exclusion of other causes but also is dependent on positive clinical criteria, the presence of which should avoid unnecessary investigation.

Miscellaneous Tremors

There are many other causes of tremors. In a review of "unusual tremor syndromes" the following entities were discussed: the review includes FXTAS, SCA12, tremors caused by autosomal recessive cerebellar ataxias, myorhythmia, isolated tongue tremor, Wilson disease, slow orthostatic tremor, peripheral trauma-induced tremor, tardive tremor and rabbit syndrome, paroxysmal tremors (hereditary chin tremor, bilateral high-frequency synchronous discharges, head tremor, limb-shaking transient ischemic attack), bobble-head doll syndrome, spasms nutans, and shuddering attacks (Ure et al., 2016). Rare tremors generally present with an action tremor and a variable combination of postural and kinetic components with resting tremors less frequently seen. The phenomenology of myorhythmia is still vague, and a clinical definition is proposed. The recognition of these entities should facilitate the correct diagnosis and guide the physician to a prompt intervention. One of the most common causes of tremors are certain drugs, such as antipsychotics, amiodarone, cyclosporine, lamotrigine, lithium, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), valproate, and other drugs (Morgan and Sethi, 2005). In one study of 707 patients treated with amiodarone,

2.8% had some neurotoxic effects, including de novo tremor and exacerbation of ET, gait ataxia, peripheral neuropathy, and cognitive impairment (Orr and Ahlskog, 2009). These side effects correlated with duration of exposure and were not always reversible. The bobble-head doll syndrome is a form of slow (2–30 Hz) oscillatory movement that is usually associated with cystic enlargement of the third ventricle, suprasellar arachnoid cysts, aqueductal stenosis, and other lesions involving the third ventricle (Goikhman, 1998; Bhat-tacharyya et al., 2003; Hagebeuk et al., 2005). "Head bobbing" has been described in animals, particularly in birds, as a rhythmic forward and backward movement of their heads when they walk (Necker et al., 2007). Hereditary chin tremor, or hereditary geniospasm, is an autosomal dominant disorder characterized by recurrent episodes of chin tremor (Soland et al., 1996b; Erer and Jankovic, 2007) (Video 10.9). Usually a benign condition with a peak in the mid-twenties (although it may be persistent in men), this condition has been mapped to a marker on chromosome 9q13–q21 (Jarman et al., 1997). Some investigators have suggested that "isolated generalized polyoclonus" may manifest as "whole body tremulousness" and that some of the cases are drug-induced (e.g., SSRI) or the result of an autoimmune disorder (McKeon et al., 2007). Genetic phenocopies of ET include FXTAS, Kennedy syndrome, SCA12, hereditary neuropathies, Klinefelter (XXY) syndrome (Harlow et al., 2008), Jacob syndrome (XYY) (Bardsley et al., 2016), and the 48,XXYY syndrome, which is also associated with gait ataxia, dysarthria, and nystagmus (Tartaglia et al., 2009). Kennedy syndrome, or Kennedy disease, also known as spinal and bulbar muscular atrophy, has an adult (or rarely childhood) onset caused by a trinucleotide (more than 38 CAG repeats) expansion in exon 1 of the androgen receptor gene on the long arm of chromosome X (Sperfeld et al., 2002; Finsterer and Soraru, 2016). In addition to postural tremor similar to ET, present in up to a third of the patients, there are many other motor and nonmotor manifestations, including progressive muscle weakness, cramps, fasciculations/twitching, dysarthria, dysphagia, or gynecomastia, myalgia, easy fatigability, exercise intolerance, polyneuropathy, hyper-CKemia, undermasculinized genitalia, scrotal hypospadias, microphallus, laryngospasm, or oligospermia. Many of the miscellaneous tremor disorders are approached with similar pharmacologic and surgical approaches as the other more classic disorders (Ramirez-Zamora, 2016). ▶

Appendix

International Essential Tremor Foundation (IETF)

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References available on Expert Consult:
www.expertconsult.com

Video 10.9 Hereditary chin tremor.

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Dystonia: Phenomenology, classification, etiology, pathology, biochemistry, and genetics

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In the course of the last 5 years I have repeatedly observed an affliction, whose meaning and classification caused great difficulties. When examining the first cases I was trying to decide between a diagnosis of hysteria, and idiopathic bilateral athetosis; but then I soon realized that neither of these diagnoses was appropriate, and that this was a new condition, or at least a new type of condition. The disease has something quite unique; namely the severe tonic cramps, particularly in the neck, head and the proximal sections of the extremities. The unique "torqued" gait is practically pathologic. The prognosis is bad. All therapeutic attempts are as of yet unsuccessful. During my efforts to delineate the methodology of the disease through an incisive name, I have selected the titles dysbasia lordotica progressiva and dystonia musculorum deformans and would prefer the latter.

Hermann Oppenheim, 1911
From his description of generalized dystonia

Historical highlights

Before the twentieth century, there are several suggestions in paintings, texts, and sculpture that dystonia was noted as far back Hippocrates and Celsus (Newby, Thorpe et al., 2017). In 1908, Schwalbe published his dissertation on a family with three affected children who are now recognized to have had primary generalized dystonia. An English translation of Schwalbe's paper is available (Truong and Fahn, 1988). Three years later Oppenheim (1911) described the same disorder in

four patients and coined the word "dystonia" to indicate that in this disorder, there would be hypotonia on one occasion and tonic muscle spasms on another, usually but not exclusively elicited on volitional movements. Oppenheim called this syndrome by two different names: "dystonia musculorum deformans" and "dysbasia lordotica progressiva." The first name relates to the spasms and to the postural deformities that develop in these children; the second name emphasizes the dromedary gait and the progressive nature of the illness. Oppenheim described muscle spasms; bizarre walking with bending and twisting of the torso; rapid, sometimes rhythmic jerking movements; and progression of symptoms leading eventually to sustained fixed postural deformities.

Oppenheim, however, failed to recognize the inherited nature of the disorder, which was emphasized by Flatau and Sterling (1911) later that year; they suggested the name "progressive torsion spasm," which perhaps would have been the preferred one, according to the full syndrome recognized today. The word "dystonia," however, was immediately adopted by neurologists and has been used to describe both a distinctive motor phenomenology and a clinical syndrome in which these motoric features are present. Over time, different meanings were used for "dystonia" (for historical details, see Fahn et al., 1987). The early observers described dystonia as a specific disease entity, but by the next decade, dystonia was recognized to be a feature in other neurologic disorders, such as Wilson disease and cerebral palsy, and after encephalitis. Soon, dystonia as a specific entity (today known as primary dystonia) was lost. It was Herz (1944a,b,c) who, in a masterful series of three papers, resurrected torsion dystonia as a specific neurologic entity and its presence within other neurologic diseases, described the motor phenomenology

and compared the duration of its contractions with those of chorea and athetosis, and used the analysis of cinematography to distinguish these differences in various movement disorders and showed the characteristic simultaneous contractions of agonist and antagonist muscles in dystonia.

Another major pioneer in dystonia was Zeman (1970), who, along with his colleagues (Zeman et al., 1959, 1960; Zeman and Dyken, 1967), carried out the first epidemiologic study, emphasized the autosomal dominant pattern of inheritance, described the focal dystonias as *formes frustes* of generalized dystonia, and found the pathologic anatomy to be normal in primary torsion dystonia (PTD). The disparate varieties of focal dystonias were not linked as focal dystonias until Marsden placed them together (1976). Still, patients with dystonia, both generalized and focal, were often considered to be hysterical, that is, to have a psychogenic disorder and not an organic one, as Lesser and Fahn (1978) pointed out, often with tragic consequences, as described in the book by Cooper (1976). Better awareness of the organic nature of dystonia, both generalized and focal (for torticollis and writer's cramp were often considered hysterical), began to come about with the holding and publication of the first international symposium on dystonia (Eldridge and Fahn, 1976). The final proof came with the discovery of the gene locus for Oppenheim dystonia (Ozelius et al., 1989) and the discovery that dystonia in the Ashkenazi Jewish population was inherited in an autosomal dominant pattern (Bressman et al., 1989).

Other important events in the development of our understanding of dystonia are the formation of the Dystonia Medical Research Foundation in 1976, the creation of four international symposia on dystonia with their subsequent publications (Eldridge and Fahn, 1976; Fahn et al., 1988, 1998b, 2004), and the investigations of clinical and molecular genetics that are leading to the discovery of the mutated genes and clarifying the classification and clinical features of the dystonias (Bressman et al., 1989, 1994a; Ozelius et al., 1989, 1997; Nygaard et al., 1993; Ichinose et al., 1994). The advances in genetics have led to a better etiologic classification of the dystonias (Fahn et al., 1998a) and to the labeling of many of the dystonias using a "DYT" classification. Reviews covering the historical aspects are available, to which the reader is referred for more details than are provided in this chapter (Fahn, 1984a; 1989a, 1990; Fahn and Marsden, 1987; Fahn et al., 1987, 1988; Rothwell and Obeso, 1987; Tsui and Calne, 1995; Jankovic and Fahn, 1998; Nemeth, 2002; Stacy, 2007; Breakefield et al., 2008; Newby, Thorpe et al., 2017). A collection of historical photographs related to dystonia also has been published (Goetz et al., 2001).

Phenomenology of dystonic movements

Dystonia is a disorder that is diagnosed clinically. There are no clinically available diagnostic laboratory or imaging tests to confirm the diagnosis. Nor are there validated diagnostic criteria that can be applied. The diagnosis depends entirely on the recognition of the clinical features. Isolated (primary dystonia) usually begins by affecting a single part of the body; this is *focal dystonia* (Video 11.1). Adult-onset focal dystonias are much more common than generalized dystonias (Fahn, 1986; Marsden, 1986) (Table 11.1). Dystonia is often initiated or worsened by voluntary action and associated with

Table 11.1 Distribution of dystonia by body parts

	No.	Percentage
Focal	1230	50
Segmental	837	34
Generalized	383	16
	2450	100

Data from the Center for Parkinson Disease and Other Movement Disorders, Columbia University Medical Center, New York City, NY.

overflow muscle activation. (Albanese, Bhatia et al., 2013). Young-onset generalized isolated (primary) dystonia is frequently associated with a genetic mutation (see next section). Dystonia is a dynamic disorder and rarely a fixed posture. Dystonia may appear on some actions and not others. For example, walking forward may enhance a foot dystonia that disappears when walking backward (Video 11.2). Dystonia is a chronic disorder but may fluctuate over time. Remissions do occur, have been assessed using a meta-analysis (Mainka, Erro et al., 2019), and are most frequent in cervical dystonia in which up to 12% may have complete remission and 4% a partial remission. Blepharospasm has a reduced remission rate, with 15% having complete and 6% partial remissions. These occurred approximately 4 to 5 years after onset, but recurrence rates were high, with approximately 64% having a relapse. A younger age of onset was associated with more frequent remissions (Mainka, Erro et al., 2019). ▶

Generalized dystonia is defined as representing a combination of segmental crural dystonia (i.e., both legs or legs plus trunk) plus involvement of any other area of the body (Videos 11.3 to 11.6). Isolated generalized dystonia rarely begins in adulthood. The typical clinical picture is onset as a focal dystonia in the limb of a child or adolescent. The dystonia worsens in the affected area and over years typically spreads to involve the body and becomes generalized dystonia. Although isolated generalized dystonia is motorically disabling, cognitive impairment is not a feature unless there is an underlying neurologic disorder. However, psychological disturbances are frequent in dystonia, including sleep disturbance, anxiety, depression and fatigue. Suicidal ideation was recently reported to affect up to 32% of patients, mostly those with generalized dystonia. ▶

Rarely, children and adolescents with primary and secondary dystonia can develop a crisis of sudden marked increase in the severity of dystonia, which has been called *dystonic storm* (Dalvi et al., 1998) and *status dystonicus* (Manji et al., 1998). Status dystonicus is a medical emergency. It can cause rhabdomyolysis and myoglobinuria, with a threat of death by renal failure (Jankovic and Penn, 1982; Paret et al., 1995). Status dystonicus may be triggered by several factors. One of the most frequent triggers is an infection. Other causes include malfunctioning of deep brain stimulation (DBS), adjustment of medications, surgical procedures, and metabolic disorders. However, up to one-third of patients will not have an identifiable precipitating factor. The dystonia storm may last up to 2 weeks, and the mortality is approximately 10%. The treatment of status dystonicus initially involves making the appropriate diagnosis. Medications are often used first, including tetrabenazine and anticholinergic

Video 11.1 Blepharospasm.

Video 11.2 Dystonia of leg, with active voluntary movement.

Video 11.3 Generalized dystonia.

Video 11.4 Generalized dystonia.

Video 11.5 Generalized dystonia that evolved into a fixed posture.

Video 11.6 Generalized dystonia with inability to walk or crawl.

Table 11.2 Distribution of focal dystonias

Type of dystonia	No.	Percentage
Cervical dystonia	447	44.4
Spasmodic dysphonia	257	25.5
Blepharospasm	140	13.9
Right arm	96	9.5
Oromandibular	31	3.1
Left arm	20	2.0
Left leg	6	0.6
Trunk	5	0.5
Right leg	4	0.4
Total	1006	100

Data from the Center for Parkinson Disease and Other Movement Disorders, Columbia University Medical Center, New York City, NY.

agents. Sedation is often required, which may be achieved with propofol, benzodiazepines or anesthesia. DBS also has been successfully used to treat the symptoms. Early recognition and treatment are imperative. Intensive care monitoring is often necessary (Lumsden, King et al., 2017; Ruiz-Lopez and Fasano, 2017; Arshad, Ahmad et al., 2018; Lumsden and Allen, 2018; Garone, Graziola et al., 2019; Rajan, Kaas et al., 2019).

Focal dystonia may affect different regions of the body (Table 11.2). *Focal dystonia* indicates that only a single area of the body is affected. Dystonia of the eyes is called blepharospasm. Blepharospasm is typically an adult-onset disorder. The facial muscles involved usually include the orbicularis oculi, procerus, and corrugator muscles. Blepharospasm is an involuntary blinking, narrowing, or closing of the eyes. Although usually symmetrical, asymmetry of eye closure can occur. Blepharospasm may have at onset a feeling of discomfort or grittiness in the eyes. It varies in severity and in severe cases may cause functional blindness. The spasms may be triggered by reading, bright light, and wind. Stress usually worsens the symptoms. Some patients may have alleviating maneuvers, such as touching the side of the face, yawning, or reading. Blepharospasm is a heterogeneous disorder that varies among individuals. It may remain focal, or it may spread to involve the lower face and jaw (craniofacial dystonia) (Defazio, Conte et al., 2017; Defazio, Hallett et al., 2017).

Cervical dystonia (formally spasmodic torticollis) is a focal dystonia involving the neck muscles, causing a turning, tilting, or flexion of the head and neck (Video 11.7). Cervical dystonia rarely consists of only a single head movement and is a complex disorder in which multiple postures may be present. Often shoulder movements are included, with shoulder elevation, or rotation. Cervical dystonia is frequently associated with pain in the neck region, and the pain may be more disabling than the movement. Cervical dystonia more frequently affects women than men (2–3 to 1). Over half are noted to have a head tremor, and in many there is an associated hand tremor. The onset of symptoms is usually in the mid-forties. Although most remain focal,

approximately a third will develop more extensive spread of the dystonia to laryngeal muscles and arm (Albanese, Di Giovanni et al., 2019, 2019).

Oromandibular dystonia affects the muscles of the jaw, with involuntary jaw opening, deviation, or closing. A summary of clinical data from 240 patients indicates that the age of onset is typically in the 50s, with a 2:1 female predominance compared with men. In this study, lingual dystonia was present in approximately 27% of the patients, and most had associated segmental or generalized dystonia. Frequently, oromandibular dystonia is an isolated dystonia, with no identifiable underlying cause (Slaim, Cohen et al., 2018). Jaw closing dystonia may be the most frequent form of oromandibular dystonia (Comella, 2018). Severe jaw closing dystonia impairs speech and eating. The forced closure may cause trauma to the tongue and cheeks. The most frequently involved muscles are the masseter and medial pterygoids. Jaw opening dystonia is less common. The forced jaw opening is often painful and results in abnormal speech. The muscles frequently involved include the medial pterygoids and digastric. Jaw deviation is the least common form, but may be combined with either jaw opening or closing. Typically the pterygoid muscles contracting asymmetrically underlie this movement. In addition to the mechanical difficulties with feeding and speech, the social implications of oromandibular dystonia can be significant.

Laryngeal dystonia (spasmodic dysphonia) is a rare, task-specific dystonia that is triggered by speech. The most frequent is the adductor type, in which the voice is strained and effortful. There are intermittent breaks in vowels while speaking, and the symptoms may be reduced during whispering. Abductor laryngeal dystonia is characterized by intermittent breathy breaks particularly during ongoing speech. Both abductor and adductor types of laryngeal dystonia demonstrate normal structure and symmetry of the vocal cords during otolaryngoscopy but demonstrate the dystonic contractions during speech. Muscular tension dysphonia is characterized by a continuous strained voice quality that occurs consistently during speech. There are no breaks in the voice, and on direct examination there is a continuous supraglottic compression. Finally, the vocal tremor type of spasmodic dysphonia demonstrates oscillation of the voice particularly with sustained expression of vowels. This type of dysphonia is characterized by bobbing of various structures, including the vocal cords, tongue, and pharynx (Blitzer, 2010; Whurr and Lorch, 2016; Ludlow, Domangue et al., 2018; Patel, Kabagambe et al., 2019).

Lingual dystonia involves the tongue. Tongue movements may be lateral or vertical, and many involve tongue protrusion. It can be part of a segmental dystonia, most frequently jaw, lower face, and craniofacial dystonia with blepharospasm (Slaim, Cohen et al., 2018). It can be seen as a part of other neurologic disorders, such as neuroacanthocytosis, where it manifests as a feeding dystonia with the tongue involuntarily pushing food out of the mouth. It is also seen in neurodegenerative diseases and has been described associated with corticobasal syndrome (Giza, Katsarou et al., 2015; Abraham, Taragin et al., 2015).

Limb dystonia can involve the upper and lower extremities. In childhood-onset dystonia, the disorder frequently begins in the foot or leg. Approximately 50% will subsequently spread to become generalized dystonia. Limb dystonia is

Video 11.7 Cervical dystonia.

Table 11.3 Distribution of segmental dystonias

Type of dystonia	No.	Percentage
Segmental cranial	167	42.8
Cranial + brachial	56	14.4
Cranial + axial	14	3.6
Segmental brachial	83	21.3
Segmental axial	31	7.9
Segmental crural	13	3.3
Multifocal	26	6.7
	390	100

Data from the Center for Parkinson Disease and Other Movement Disorders, Columbia University Medical Center, New York City, NY.

often action and posture dependent. As an example, at rest there may be no abnormal movements, but with assuming a posture with outstretched arms, the dystonic movements become manifest as a twisting, turning, extension, or flexion of the fingers, hand, or arm. Limb dystonia is often a task-specific dystonia. One that is common is called writer's cramp, in which there is dystonic posturing of the hand and the fingers but restricted to the specific action of writing. (Video 11.8), playing a musical instrument (musician's cramp) (Video 11.9), chewing (Video 11.10), and speaking, including auctioneering (Scolding et al., 1995). Often, these task-specific dystonias produce occupational disability—for example, musicians usually no longer can play their instrument professionally. Robert Schumann's career as a pianist was impaired, probably because of musician's cramp (de Yebenes, 1995). Musician's cramp and other occupational cramps can occur in any part of body that is engaged in repetitive, highly skilled tasks (Altenmüller and Jabusch, 2010). Embouchure (the pattern of lip, jaw, and tongue muscles used to control the flow of air into a mouthpiece) dystonia has been seen in horn and woodwind players (Frucht and Estrin, 2010). Patients with embouchure dystonia can be separated into several groups, including embouchure tremor, involuntary lip movements, and jaw closure (Frucht et al., 2001). The dystonia can spread to other oral tasks, often producing significant disability. Musician's dystonia, like other focal dystonias (discussed later in the section on pathophysiology of primary dystonia), is associated with increased sensorimotor activation (Haslinger et al., 2010). Focal *task-specific tremors* might be a form of focal dystonia rather than a manifestation of essential tremor (ET) (Soland et al., 1996b). Several reviews of musician's cramps were presented at an international symposium on dystonia (Brandfonbrener and Robson, 2004; Charness and Schlaug, 2004; Frucht, 2004; Jabusch and Altenmüller, 2004; Pesenti et al., 2004). ▶

Focal dystonia can spread to involve two or more contiguous body parts and are then referred to as segmental dystonia. These are described in Table 11.3.

Comparisons of the focal dystonias

The most common primary focal dystonia seen in a movement disorder clinic is cervical dystonia (torticollis), followed by dystonias affecting cranial musculature, such as

blepharospasm and spasmodic dysphonia (Table 11.4). The frequency of each of these in a community setting has not been firmly established and would require examination of each person, given the lack of diagnostic criteria. It may be that writer's cramp is the most common in the general population. Much of this would depend on the ethnicity and other factors of the population being assessed.

The most common primary segmental dystonia involves the cranial structures, and these are commonly referred to as cranial-cervical dystonia and sometimes as Meige syndrome (Tolosa and Klawans, 1979; Tolosa et al., 1988a) (Table 11.5). Details of cervical dystonia have been reviewed (Dauer et al., 1998).

Much less common than action dystonia or overflow dystonia is the reverse phenomenon. This is the presence of dystonia at rest that improves with voluntary movement and is also called *paradoxical dystonia* (Fahn, 1989c). With paradoxical dystonia the patient is usually observed moving the affected or nonaffected body part. The patient does this to obtain relief of the dystonia. When the paradoxical dystonia involves the trunk, the observer can easily mistake the patient's moving about as being caused by restlessness or akathisia, which is the most common differential diagnosis (Video 11.11). ▶

Hemidystonia is characterized by dystonia involving half of the body. In a patient with hemidystonia, there is often an underlying lesion (Narbona et al., 1984; Marsden et al., 1985; Pettigrew and Jankovic, 1985). A review of hemidystonia (Chuang et al., 2002) found that the most common causes were stroke, trauma, and perinatal injury; the mean age of onset was between 20 and 26 years; the mean latency from insult to dystonia was between 2.8 and 4.1 years, the longest latencies occurring after perinatal injury; and basal ganglia lesions were identified in 48% to 60% of the cases, most commonly involving the putamen. When there is a delay by a few years between time of insult and time of onset of dystonia, the condition is named delayed-onset dystonia (Burke et al., 1980).

As with other basal ganglia disorders, psychiatric comorbidity is common in dystonia, with some estimates being as high as 91% of patients with cervical dystonia. These include depression, anxiety, and social phobia. These psychological disorders are seen in any of the focal or generalized dystonias (Zurowski, McDonald et al., 2013; LeDoux, Vemula et al., 2016; Berman, Junker et al., 2017). In myoclonus dystonia, additional reports of psychiatric abnormalities, particularly obsessive-compulsive disorder (OCD) have been reported (Timmers, Smit et al., 2019). In addition to the psychological aspects of dystonia, there is evidence that dystonia also may be involved in sleep disturbances (Eichenseer, Stebbins et al., 2014).

The association of dystonia with tremor has been debated (Elble, 2013a,b) (Video 11.12). Tremor is an involuntary, rhythmic, oscillatory movement of a body part. One of the features that has been used to distinguish tremor from dystonic tremor is the regularity of the movement. Tremor appears as a regular oscillation, whereas dystonic tremor is often noted to be irregular and jerky in nature. Tremor, similar to dystonia, has been classified according to a consensus statement from the task force on tremor from the International Parkinson Disease and Movement Disorder Society. Similar to dystonia, this classification has two axes: clinical features and cause (Bhatia, Bain et al., 2018). Tremor can be present at rest, with posture, or with action. Essential tremor

Video 11.8 Writer's cramp.

Video 11.9 Musician's cramp.

Video 11.10 Action focal dystonia of the jaw when chewing.

Video 11.11 Truncal dystonia relieved by dancing or running.

Video 11.12 Postural tremor of the arms associated with dystonia of the arms.

Table 11.4 Comparisons of common focal dystonias

Feature	Blepharospasm	Dysphonia	Cervical dystonia	Hand dystonia
Prevalence per million	17–133	11–59	23–130	3.8–80
Predominant gender	Female	Female	Female	Male
Age at onset, mean	55.7	43	40.7	38
% Spread by 5 years	58	9–19	12–35	13
Sensory trick	Yes	No	Yes	Yes
Task specificity	No	Yes	No	Yes
Possible risk factors	Dry eyes, irritation	Sore throat	Neck-trunk trauma	Repetitive task

Modified from Defazio G, Berardelli A, Hallett M. Do primary adult-onset focal dystonias share aetiological factors? *Brain*. 2007;130(Pt 5):1183–1193.

Table 11.5 Distribution of segmental dystonias

Type of dystonia	No.	Percentage
Segmental cranial	167	42.8
Cranial + brachial	56	14.4
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Segmental brachial	83	21.3
Segmental axial	31	7.9
Segmental crural	13	3.3
Multifocal	26	6.7
	390	100

Data from the Center for Parkinson Disease and Other Movement Disorders, Columbia University Medical Center, New York City, NY.

is an isolated postural and action tremor without additional neurologic findings, including dystonia. In this paradigm, if there is a dystonic posturing, it is no longer considered isolated tremor despite the overlap between the two disorders. The prevalence of tremor in dystonia has been varied and reported in up to 60% of dystonia patients. (Hvizdosova, et al., 2020). Tremor is most strongly associated with body region involved by dystonia, and dystonia duration and severity (Shaikh and Beylergil, 2020, Vu et al., 2021). studies demonstrate that isolated tremor in the absence of dystonia do not have the same abnormalities as tremor associated with dystonia (Defazio, Conte et al., 2015). Head tremor at onset in patients with CD may suggest cerebellar involvement with axial cerebellar findings and superior vermis atrophy (Mahajan et al., 2020). ▶

One of the classic features of dystonia is the sensory trick, also referred to as the geste antagoniste or alleviating maneuver. This is defined as a voluntary touch or posture that reduces the severity of dystonia (Video 11.13). Historically, the effect of the sensory trick was described by Brisaud and his students in the nineteenth century, although it had been described previous to this in anecdotal reports (Poisson, Krack et al., 2012, Broussolle, Laurencin et al., 2015). Sensory tricks are mostly described in association with cervical dystonia, although they are common in other focal dystonias, such as blepharospasm (Kilduff, Casswell et al., 2016). Approximately 42% of patients with cervical

dystonia, most of whom are treated with botulinum toxin, report a sensory trick in one series and up to 90% in a different series. The most commonly described sensory tricks are a touch to the neck, cheek, and chin. The effect of the sensory trick was robust, with approximately a 70% improvement that lasted during the application of the maneuver and was present for a few seconds after discontinuation. The sensory trick was not as effective when performed by another person, and approximately 14% of cervical dystonia patients noted improvement if they visualized or imagined doing the sensory trick (Filip, Sumec et al., 2016). The efficacy of the sensory trick has been reported by some to be maximal early in the disorder (Benadof, Cisneros et al., 2019). Others have found no association of trick efficacy with duration of cervical dystonia or baseline severity (Patel, Hanfelt et al., 2014). The presence of a sensory trick has been suggested as one of the diagnostic clues that the diagnosis is dystonia (Defazio, Albanese et al., 2019). Neurophysiologic evidence suggests that sensory tricks reduce the abnormal facilitation seen in dystonia (Ramos, Karp et al., 2014). Functional MRI studies have shown that there are differences in functional connectivity between cervical dystonia patients with a trick versus those without, and implicate the cerebellum (Sarasso et al., 2020). The sensory trick may provide clues to the underlying pathophysiology of dystonia (Counihan and Martino 2020). Clinically, the use of sensory tricks as a treatment has not been well evaluated, although in some patients optimizing a sensory trick may improve symptoms in a practical sense. For example, writer's cramp may be improved using ancillary devices or altered posture during handwriting (Video 11.14). Cervical dystonia may improve with the use of a scarf. The presence of an sensory trick may significantly benefit sleep-related quality of life in cervical dystonia patients (Benadof, Cisneros et al., 2019). ▶

Classification

The definition of dystonia was first formulated by a committee organized by the Dystonia Medical Research Foundation and led by Stanley Fahn. The definition was as follows:

Dystonia is a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements, or abnormal postures.

Fahn, 1988

Video 11.13 Truncal dystonia relieved temporarily by placing a hand on the back of the head.

Video 11.14 Retrocollis dystonia relieved by touching the back of the head.

Table 11.6 Classification of dystonia

1. By age at onset
 - A. Early onset: ≤ 26 years
 - B. Late-onset: > 26 years
2. By distribution
 - A. Focal
 - B. Segmental
 - C. Multifocal
 - D. Generalized
 - E. Hemidystonia
3. By cause
 - A. Primary (also known as idiopathic) dystonia
 - B. Dystonia-plus
 - C. Secondary dystonia (environmental insult)
 - D. Heredodegenerative dystonia (usually manifests as dystonia-plus)
 - E. A feature of another neurologic disease (e.g., dystonic tics, paroxysmal dyskinesias, Parkinson disease, progressive supranuclear palsy)

To emphasize the twisting quality of the abnormal movements and postures, the term *torsion* is placed in front of the word *dystonia*. This twisting characteristic and the patterned movement are features that distinguish dystonic movements from those of other dyskinesias, such as chorea, and distinguishes dystonic postures from other syndromes of increased muscle tone, such as rigidity, stiff-person syndrome, and neuromyotonia (Fahn, 1999). The four consistent and predominant features of dystonic contractions were described as (1) relatively long duration (compared with myoclonus and chorea), although short-duration contractions can occur in dystonia; (2) simultaneous contractions of agonists and antagonists; (3) resulting in a twisting of the affected body part; and (4) continual contractions of the same muscle groups. Dystonia was classified as primary with dystonia as the sole manifestation, which could be hereditary or sporadic; secondary with additional neurologic, genetic, or environmental causes; and psychological, arising from non-physical conditions. Using this definition, dystonia was further classified according to the age of onset, distribution in body regions, and cause (Fahn, 1988 (Table 11.6)).

Classification by age at onset is useful because there are different implications for underlying genetic mutations and prognosis based on this feature. Age of onset may be the most important single factor related to prognosis of primary dystonia (Marsden et al., 1976; Fahn, 1986; Greene et al., 1995). When dystonia begins at a young age (26 years or younger), it is likely to begin in the limb, often the leg, and will usually spread to other body areas and in most cases become generalized (Greene et al., 1995) (Video 11.15). When dystonia begins at an older age (older than 26 years), it typically will begin in one body area, usually the upper body, with some spread to adjacent body areas but typically not evolve into generalized dystonia (Bressman, 2004) (Video 11.7). ►

Subsequently, the Dystonia Medical Research Foundation, the Dystonia Coalition and the European Dystonia Cooperation in Science and Technology organized a consensus committee to further delineate the phenomenology and propose a modification of the classification scheme for dystonia. The revised definition of dystonia was as follows:

Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned, twisting and may be tremulous.

The committee proposed a new classification system that consisted of two axes (Albanese, 2013) (Fig. 11.1). The term *primary dystonia* was abandoned in favor of *isolated dystonia*, in which dystonia is the only motor feature besides tremor. If additional findings such as parkinsonism, ataxia, or myoclonus was present, the terminology used was combined dystonia. Axis I focused on the clinical characteristics of dystonia. Age of onset was divided into onset in infancy (birth to 2 years), childhood (3–12 years), adolescence (13–20 years), early adulthood (21–40 years), and late adulthood (older than 40 years). Body distribution included focal (single body region affected), segmental (two or more contiguous body regions affected), multifocal (two noncontiguous body areas affected) and generalized (trunk and at least two other sites involved, with or without leg involvement), and hemidystonia (dystonia restricted to one body side). Temporal pattern included persistent (severity stable throughout the day), action-specific (dystonia occurring only with a particular activity or task), diurnal fluctuations (discernible circadian variations in dystonia), and paroxysmal (sudden episodes of dystonia with return to preexisting neurologic status).

Axis II focused on underlying cause. There are two components of this axis. The *presence or absence of nervous system* pathologic features is the basis of the first component and is classified as degeneration (progressive structural abnormality), static lesions, (nonprogressive neurodevelopmental anomalies or acquired lesions), and no evidence of degeneration or structural lesion. The second component describes whether the dystonia is inherited or acquired. In the inherited forms, a genetic origin is identified through testing for specific gene mutations. Acquired dystonia is used for dystonia resulting from a known specific cause, including drugs, infections, brain injury, toxins, and vascular or neoplastic causes. Finally, idiopathic dystonia is used when there is no discoverable cause for the dystonia; this is further subdivided into sporadic or familial.

This classification system is appropriate for adults but also has been found to be relevant in children and adolescents (Lumsden, Gimeno et al., 2016).

Although this new definition and classification system was designed to be more relevant to the clinical features of dystonia, the variable interpretation of its components has been an obstacle to its general use. Some investigators think that the use of this system could lead to ambiguity (van Egmond, Contarino et al., 2019).

A review of currently available literature showed that approximately 60% were using the classification correctly from 2013 to 2018 (Sasikumar, Albanese et al., 2019).

Epidemiology

Epidemiologic studies (Table 11.7) of dystonia are hampered by the lack of diagnostic criteria and laboratory confirmation. It often goes undiagnosed if the clinician or patient is not familiar with the clinical features. Hence epidemiologic studies are often based on clinical records and searching for diagnostic codes in patient databases. Zeman and colleagues

Video 11.15 Generalized torsion dystonia.

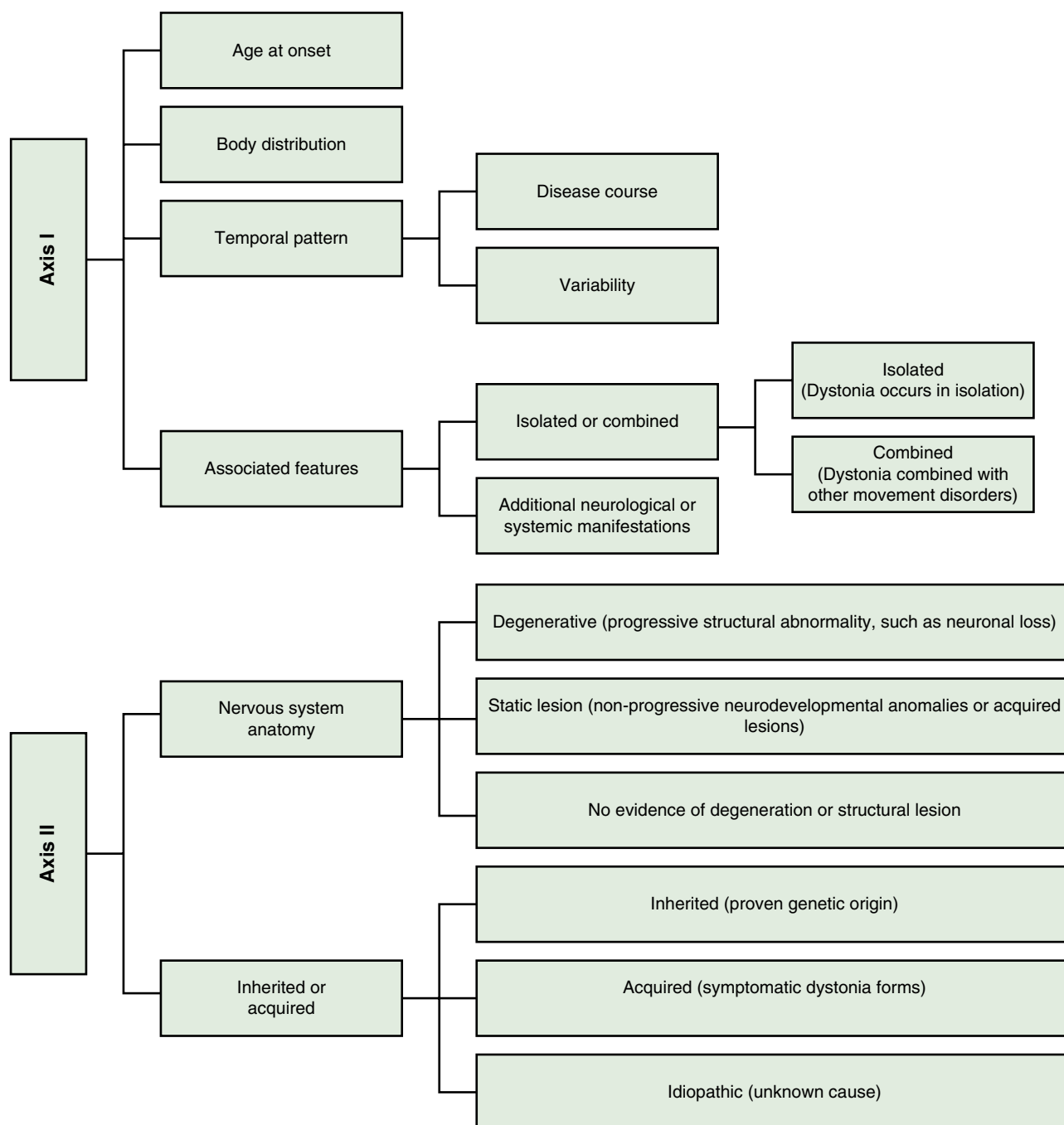


Fig. 11.1 Classification of dystonia (Albanese A, Bhatia K, Bressman SB, Delong MR, Fahn S, Fung VS, et al. Phenomenology and classification of dystonia: A consensus update. *Mov Disord.* 2013;28[7]:863–873.)

(Zeman and Dyken, 1967; Zeman et al., 1959, 1960) carried out the first epidemiologic study in dystonia in the population of the state of Indiana and emphasized the autosomal dominant pattern of inheritance in PTD. They considered only generalized dystonia to be PTD and viewed other types as formes frustes. Today, those other forms are viewed as focal and segmental dystonia and part of the spectrum of PTD. An epidemiologic study of PTD in the population living in Rochester, Minnesota, found the prevalence of generalized PTD to be 3.4 per 100,000 population and the prevalence of focal dystonia to be 30 per 100,000 (Nutt et al., 1988). In a study

of dystonia by Israel, Zilber, and colleagues (1984) estimated the prevalence of generalized dystonia among Jews of Eastern European ancestry to be 1 per 15,000 or 6.8 per 100,000, which is double the prevalence in the general population of Rochester. However, the analysis by Risch and colleagues (1995) indicates that the frequency in the Ashkenazim is much higher (between 1/6000 and 1/2000), and they suggest that the Ashkenazi population with PTD descends from a limited group of founders of the DYT1 mutation. These investigators also have traced the origin of the mutation to the northern part of the historic Jewish Pale of Settlement

Table 11.7 Prevalence of primary torsion dystonia

Authors	Population	Prevalence	Remarks
Zeman and Dyken (1967)	Indiana	1/200,000	Essentially a white, non-Jewish population Generalized dystonia only
Zilber et al. (1984)	Israel: Jews of Eastern Europe Afro-Asian Jews	1/15,000 1/117,000	Generalized dystonia only Generalized dystonia only
Nutt et al. (1988)	Generalized dystonia Focal dystonia	1/29,400 1/3,400	Olmsted County, Minnesota From Mayo Clinic records
Risch et al. (1995)	New York area, Ashkenazi Jewish	Disease 1/6,000; gene 1/2,000	Based on cases seen at Columbia University Medical Center
Nakashima et al. (1995)	Focal dystonia	1/16,129	Japan
Duffey et al. (1998)	General dystonia Focal dystonia	1/62,000 1/8,000	North of England survey
Warner et al. (2000)	Generalized and segmental dystonia Focal dystonia	1/28,500 1/8,500	European consortium survey
Defazio et al. (2001)	Blepharospasm	1/7,519	Puglia region, southern Italy
Pekmezovic et al. (2003)	Focal dystonia, cervical dystonia	1/8,929	Belgrade, Serbia
Le et al. (2003)	Focal and segmental dystonia	1/3,534	Europeans in Oslo, Norway
Matsumoto et al. (2003)	Focal dystonia	1/9,900	Kyoto, Japan
Bradley et al. (2003)	Blepharospasm	Incidence: 1.2/100,000/y	Olmsted County, Minnesota
Sugawara et al. (2006)	Generalized dystonia Focal dystonia	1/147,000 1/900	Akita Prefecture, Japan
Fukuda et al. (2006)	Focal dystonia	1/7,300	Tottori Prefecture, Japan
Asgeirsson et al. (2006)	Focal dystonia Segmental dystonia Multifocal dystonia Generalized dystonia	1/3,077 1/32,258 1/44,667 1/333,333	Iceland
Das et al. (2007)	Focal dystonia (mostly limb)	1/2,038	Kolkata, India
Frédéric et al. (2007)	DYT1 (TOR1A) mutations in newborns	Incidence: 1/12,000/y	Hérault, France
Marras et al. (2007)	Cervical dystonia, multiethnic population	Incidence: 1.07/100,000/y	Northern California

(Lithuania and Byelorussia), approximately 350 years ago. In Japan, the DYT1 mutation was looked for in 178 patients with various forms of dystonia and was found in 6 (3.4%) (Matsumoto et al., 2001) and phenotypically resembled Oppenheim dystonia seen in other populations.

In Japan the prevalence rate of focal dystonias was found to be 6.12 (Nakashima et al., 1995), 10.1 (Matsumoto et al., 2003), 13.7 (Fukuda et al., 2006), and 14.4 (Sugawara et al., 2006) per 100,000 population, all of which are considerably lower than the 30 per 100,000 found by Nutt and associates (1988) in Rochester, Minnesota. The prevalence of focal limb dystonia in India was higher, 49.06 per 100,000 (Das et al., 2007). In the north of England, the prevalence of focal dystonias was found to be 12 per 100,000, and the prevalence of generalized dystonia was found to be 1.6 per 100,000 (Duffey et al., 1998). A European consortium of investigators published their findings of 11.7 per 100,000 for focal dystonia and 3.5 per 100,000 for segmental and generalized primary dystonias (Warner et al., 2000). A survey of primary blepharospasm in the Puglia region of southern Italy found a prevalence of 13.3 per 100,000 (Defazio et al., 2001). The incidence rate

of primary blepharospasm was found to be 1.2 per 100,000 population per year in Olmsted County, Minnesota (Bradley et al., 2003). Incidence for cervical dystonia was higher in white individuals (1.23/100,000 per year) than in persons of other ethnicities (0.15/100,000 per year) (Marras et al., 2007). Using electronic medical records followed by chart review in a multiethnic population followed through the Kaiser Permanente health care maintenance organization consisting of 3 million members, Marras and colleagues estimated the minimum incidence of cervical dystonia to be 0.80 per 100,000 person years. The incidence was higher in white individuals and 2.5 times higher in women than in men. The duration between onset of symptoms to diagnosis was 4 to 5 years (Marras, Van den Eeden et al., 2007, LaHue, Albers et al., 2019). In a smaller study, the delay from symptom to diagnosis was approximately 7 years, with patients being evaluated by a mean of three physicians before diagnosis (Bertram and Williams, 2016).

In Belgrade the prevalence rate for focal, segmental, and multifocal dystonia was 13.6 per 100,000 population (Pekmezovic et al., 2003). It was almost twice as common

Table 11.8 Genetic classification of combined dystonia

Classification	Chromosome, gene mutation, gene product	Pattern of inheritance	Onset	Distribution, additional features
DYT3-PARK-TAF1	Xq TAF1	XR	A	Parkinsonism Filipinos (Lubag) mosaic striatal gliosis
DYT4-TUBB4A	19p13.3-p13.2 <i>TUBB4</i> (β -tubulin 4a)	AD	C, A	Whispering dysphonia, cranial, cervical, limb, hobby horse gait disorder, facial atrophy, ptosis, edentulous
DYT5a-PARK-GCH1	14q22.1 <i>GCH1</i> /GTP Cyclohydrolase I	AD	C	Dopa-responsive dystonia, diurnal fluctuation, gait disorder, parkinsonism, myoclonus, spasticity
DYT5b- PARK-TH	11p15.5 Tyrosine hydroxylase	AR	C	Dopa-responsive dystonia, gait disorder, parkinsonism, myoclonus, spasticity
DYT11-SGCE	7q21.3 <i>SGCE</i> ϵ -Sarcoglycan	AD	C	Myoclonus–dystonia, alcohol-responsive, obsessive-compulsive disorder, drug addiction
DYT12-PARK-ATP1A3	19q13.2 ATP1A3 Na ⁺ /K ⁺ -ATPase	AD	C, A	Rapid-onset dystonia–parkinsonism, cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss syndrome (CAPOS), alternating hemiplegia of childhood
DYT15	18p11	AD	C	Myoclonus–dystonia
DYT16-PRKRA	2q31.2 PRKRA	AD	C	Predominantly lower limb, axial, oromandibular, and laryngeal dystonia, parkinsonism, unresponsive to levodopa
DYT26	22q12 KCTD17	AD	C, A	Myoclonus–dystonia, cranial-cervical
DYT28	19q13.2 KMT2B	AD	C	Cranial-oromandibular-cervical-laryngeal, generalized, onset in leg, developmental delay, bulbous nose, elongated face, microcephaly, short stature, oculomotor apraxia, galloping tongue, open mouth, risus sardonius
DYT29	1p35.3 MECR	AR	C	Generalized, optic atrophy and basal ganglia abnormalities

A, Adult onset; C, childhood onset.

(25.4/100,000 population) in Oslo (Le et al., 2003). Gender appears to play a role in both the prevalence and the age at onset of focal dystonia, with women being more at risk and having an earlier age at onset for writer's cramp but men having an earlier age at onset for cervical dystonia, blepharospasm, and laryngeal dystonia (Epidemiologic Study of Dystonia in Europe [ESDE] Collaborative Group, 1999; Marras et al., 2007).

The prevalence of primary focal dystonia in the Faroe Islands was higher than in most studies at 602 per million, with the most common subtype of cervical dystonia (Joensen, 2016).

Genetics: isolated and combined dystonia

Isolated dystonia consists of familial and nonfamilial (sporadic) types. Although most patients with torsion dystonia have a negative family history for this disorder, the presence of other affected family members allows the family to be investigated in terms of localizing the abnormal gene(s) for dystonia. In primary dystonia, the only neurologic abnormality is the presence of dystonic postures and movements, with the exception of tremor that can resemble ET and can even be ET in some individuals. There is no

associated loss of postural reflexes, amyotrophy, weakness, spasticity, ataxia, reflex change, abnormality of eye movements, disorder of the retina, dementia, or seizures except where they may be the result of a concomitant problem such as a complication from a neurosurgical procedure undertaken to correct the dystonia or the presence of some other incidental neurologic disease. Because many of the secondary dystonias have these neurologic findings, the presence of any of these findings in a patient with dystonia immediately suggests that one is dealing with a secondary dystonia, a dystonia-plus syndrome, or a hereditodegenerative disorder (Table 11.8). However, the absence of such neurologic findings does not necessarily exclude the possibility of a secondary dystonia, which may rarely manifest as a pure dystonia.

Genetics: isolated dystonia (Table 11.9)

The phenotypes of Oppenheim dystonia (also known as DYT1 dystonia) was characterized in the Ashkenazi Jewish population when detection of individuals with the DYT1 mutation became possible because of the identification of the special genetic haplotype around the *DYT1* gene in this population (Bressman et al., 1994a). The mean ($\pm$ standard deviation [SD]) age at onset of symptoms is 12.5 $\pm$

Video 11.16 Onset of Oppenheim dystonia involving a leg.

Video 11.17 Worsening of dystonia over time.

Table 11.9 Genetic classification of isolated dystonias

Classification	Chromosome, gene mutation, gene product	Pattern of inheritance	Onset	Distribution, additional features
DYT1-TOR1A	9q34, GAG deletion, missense mutations, <i>TOR1A</i> /TorsinA	AD	C	Distal limbs, generalized Penetrance: 30% AJ, 70% NJ
DYT2	1p35.1 <i>HPCA</i> /hippocalcin	AR	C	Upper limbs, cranial-cervical, generalized, Spanish gypsies, Sephardic Jews
DYT6-THAP1	8q21–22 <i>THAP1</i>	AD	A, C	Cervical, cranial, brachial, German American Mennonite-Amish
DYT7	18p	AD	A	Cervical, cranial, spasmodic dysphonia, hand tremor
DYT13	1p36.13–32	AD	A, C	Cranial-cervical and upper limb
DYT17	20p11.22-q13.12	AR	C	Cervical dystonia, dysphonia, segmental, generalized
DYT21	2q14.3-q21.3	AD	A	Late-onset
DYT23	9q34.11, <i>CIZ1</i>	AD	A	Cervical
DYT24-ANO3	3, <i>ANO3</i>	AD	C, A	Cranial-cervical-laryngeal, tremor, myoclonus
DYT25-GNAL	18p, <i>GNAL</i>	AD	A	Cervical > cranial > arm > laryngeal
DYT27	2q37.3 <i>ATP1A2</i> , <i>COL6A3</i>	AR	C, A	Cranial-cervical, upper limbs, and trunk

A, Adulthood; AD, autosomal dominant; AJ, ***; AR, autosomal recessive; C, childhood; NJ, ***.

8.2 years. In 94% of patients, symptoms begin in a limb (arm or leg equally) (Videos 11.16 and 11.17); rarely the disorder starts in the neck (3.3%) or larynx (2.2%). Even in the non-Jewish population the same gene is responsible for most cases of early-onset and limb-onset PTD (Kramer et al., 1994). Over time, as diagnostic laboratory examinations for DYT1 have become available, some variations of the phenotype have been observed (Edwards et al., 2003). The phenotype varies from generalized to focal dystonia even in the same family as has been reported in two large families with proven *DYT1* gene mutation (Opal et al., 2002; Kostić et al., 2006). The proband of this family died with a dystonic storm, and other family members carrying the same mutation either were asymptomatic or displayed dystonia that was focal, segmental, multifocal, or generalized in distribution. One family member had onset of her dystonia at age 64 years. ▶

Several families with adult-onset familial torticollis have been reported, with one of them (Family K in northwest Germany) mapped to chromosome 18p; this locus being designated DYT7 (Leube et al., 1996). Investigation of more families and of apparently sporadic cases of torticollis from this region showed that most have inherited the same mutation as Family K from a common ancestor and, in fact, owe their disease to autosomal dominant inheritance at low penetrance (Leube et al., 1997a,b). However, subsequent information from these authors now questions whether their findings are incorrect (Klein et al., 1998b; Leube and Auburger, 1998). Other families with torticollis have been excluded from the chromosome 18p region and from DYT1 (Bressman et al., 1996; Cassetta et al., 1999; Jarman et al., 1999).

Cervical-cranial predominant dystonia is another form of autosomal dominant primary dystonia; it has been seen

in non-Jewish families that do not link to DYT1 (Bressman et al., 1994b, 1996; Bentivoglio et al., 1997). The site of onset is usually in the neck, which continues to dominate, but dystonia often spreads to involve the cranial structures as well, and occasionally the arm. Onset may be in childhood (Bentivoglio et al., 1997) or adulthood (Bressman et al., 1994b).

Two unrelated consanguineous Brazilian families with early-onset dystonia–parkinsonism were found to have a mutation in the *PRKRA* gene for protein kinase, interferon-inducible double-stranded RNA-dependent activator (Camargos et al., 2008). Onset began with abnormal gait and leg pain around age 12 years. Later the upper body became involved with dysphagia, spasmodic dysphonia, torticollis, upper limb dystonia, and opisthotonus. Orofacial dystonia and facial grimacing were prominent features. Some patients also had bradykinesia, one with tremor. Subsequently, a deletion in this gene was discovered in a German boy, whose dystonia began in the legs and became generalized (Seibler et al., 2008).

Genetic Combined Dystonia (see Table 11.8)

Several genetic forms of combined dystonia have been described, including DYT3, DYT4, DYT5, DYT11, DYT12, DYT15, DYT16, and DYT26. It is beyond the scope of this chapter to describe all of these dystonias in detail, but we highlight in the following section some of the most common and important forms. Lubag (X-linked dystonia–parkinsonism, XDP, DYT3)

The gene causing lubag (*DYT3*) was reported to involve a multiple transcript system (Nolte et al., 2003) (see Table 11.2). It was not initially possible to say which mutant protein (and there may be up to six from this mutation) is actually responsible for the disease. However, Makino and

colleagues (2007) have subsequently found the mutation for lubag to be in the *TAF1* gene.

This form of dystonia is inherited as an X-linked recessive trait. This is present in males from the island of Panay in the Philippines (Lee et al., 1976; Fahn and Moskowitz, 1988; Kawarai et al., 2017). The disease can begin with either dystonia or parkinsonism; with progression, parkinsonism develops eventually, even in those who had dystonia earlier (Lee et al., 1991). Pure parkinsonism has been considered a more benign phenotype (Evidente et al., 2002). The symptoms may begin in the big toe with abnormal movements. Dystonia typically spreads from the limbs to axial musculature. Some patients with older onset may have focal dystonia involving the tongue and jaw (Videos 11.18 and 11.19). The families with this disorder refer to the condition as *lubag* ("twisting" in Filipino). Female heterozygotes have been reported to manifest mild dystonia or chorea (Waters et al., 1993b). Evidente and colleagues (2004) reported eight more affected women. Six of the eight had parkinsonism, and only one had dystonia. The initial symptom was focal tremor or parkinsonism in four, chorea in three, and focal dystonia (cervical) in one. Seven of eight patients had slow or no progression of their symptoms and required no treatment. The patient with disabling parkinsonism was responsive to carbidopa/levodopa. ●

With the aid of molecular genetics for identification, the phenotype has been extended to also include tremor, myoclonus, chorea, and myorhythmia (Evidente et al., 2002). Deoxyglucose and fluorodopa positron emission tomography (PET) scans show decreased metabolism in the striatum and no or little decrease of dopa uptake (Eidelberg et al., 1992).

The abnormal gene that causes lubag has been localized near the centromere of the X chromosome at Xq13.1 (Kupke et al., 1990, 1992; Wilhelmsen et al., 1991; Graeber et al., 1992; Haberhausen et al., 1995; Makino et al., 2007) and has been given the designation *DYT3*. The gene involves a multiple transcript system (Nolte et al., 2003). The mutation has been identified in the coding portion of DNA (i.e., an exon). However, this region of DNA is extremely complex, with genes being made from both strands and multiple different RNAs (each encoding a different protein product) being made from each strand. Thus, although the investigators appear to have identified a specific mutation, they were not able to say which mutant protein (and there may be up to six from this mutation) is actually responsible for the disease. Subsequently, Makino and colleagues (2007) reported that it is the *TAF1* gene in this region that is particularly affected and its decreased function is likely the primary factor resulting in the disease.

The pathologic process of lubag has been reported (Altrochi and Forno, 1983; Waters et al., 1993a). The neostriatum shows astrocytosis in a multifocal or mosaic pattern, because of islands of normal striatum sharply demarcated by gliotic tissue. The lateral part of the putamen was most severely gliotic, and the astrocytosis in this region was confluent rather than mosaic-like. The gliotic areas also exhibited neuronal loss involving both large and small populations in the putamen. In the body and head of the caudate nucleus, the gliosis was less extensive and neuronal loss was equivocal. The tail of the caudate was also affected, showing a mild diffuse astrocytosis and loss of nerve cells. No areas of striatum seemed to

be spared. The myelinated fiber bundles in the caudate and putamen were thinned in affected foci. The brainstem was normal. In particular, there were no Lewy bodies or neurofibrillary tangles. In addition to the pathologic observations in the two Filipino men, a very similar pathologic finding was reported in a non-Filipino youth with progressive generalized dystonia with marked orolingual and pharyngeal involvement (Gibb et al., 1992) and in a non-Filipino man with a combination of psychiatric symptoms, craniocervical dystonia, bulbar dysfunction, and parkinsonism (Factor and Barron, 1997). The similar pathologic and clinical features of dystonia suggest that lubag might be present in other populations beside Filipinos. An Italian family with a mutation on the *DYT3* gene could be another case (Fabbrini et al., 2005). Lubag is now a confirmed neurodegenerative disorder and deserves much more intensive study. The mechanism of its pathogenesis might shed light on normal basal ganglia function and lead to a better understanding of the pathophysiologic mechanisms underlying dystonia and parkinsonism.

Toward that end, Goto and associates (2005) found that with the dystonia phenotype, the striosomes in the striatum are severely depleted, and the matrix compartment of the striatum is relatively spared. But as the disease progresses and the matrix becomes involved, the clinical features become parkinsonian. This suggests that dystonia may result from an imbalance in the activity between the striosomal and matrix-based pathways.

Treatment is not satisfactory, but antimuscarinics and clonazepam appear to be somewhat helpful, as does zolpidem (Evidente, 2002). Bilateral DBS in the globus pallidus internus (GPi) has been reported to be of benefit (Evidente et al., 2007; Patel et al., 2014; Brüggemann et al., 2019).

Dopa-responsive dystonia

Classic dopa-responsive dystonia

Segawa and colleagues (1976) described a syndrome of dystonia in children that has a diurnal pattern. The children may be relatively free of dystonic movements and postures in the morning and be severely afflicted in the late afternoon, evening, and night (Videos 11.20, 11.21, and 11.22). Segawa and colleagues (1976) called this disorder hereditary progressive dystonia with diurnal variation; they also mentioned that it responds to levodopa. Independently, Allen and Knopp (1976) described a form of childhood hereditary dystonia that had features of parkinsonism that showed sustained control by levodopa and anticholinergic medication. This was the same disorder. ●

Over time, several clinical features have been distinguished as highlighting this disorder: (1) Many patients with onset of dystonia in childhood have features of parkinsonism, including rigidity, bradykinesia, flexed posture, and loss of postural reflexes. (2) The disorder usually, but not exclusively, begins in childhood with a presentation of a peculiar gait, namely a tendency to walk on the toes (Wijemanne and Jankovic, 2015). (3) The disease can begin in infancy, thus resembling cerebral palsy (Nygaard et al., 1994) (Videos 11.23 and 11.24), and there has been a report of a neonatal onset of rigidity, tremor, and dystonia (Nardocci et al., 2003) (Video 11.25). (4) When the disorder begins in adulthood,

Video 11.18 Lubag causing severe oromandibular dystonia.

Video 11.19 Lubag with parkinsonism and lingual dystonia.

Video 11.20 A patient with dopa-responsive dystonia (DRD) in the morning.

Video 11.21 Same patient as in Video 11.20 with dopa-responsive dystonia (DRD), now at night.

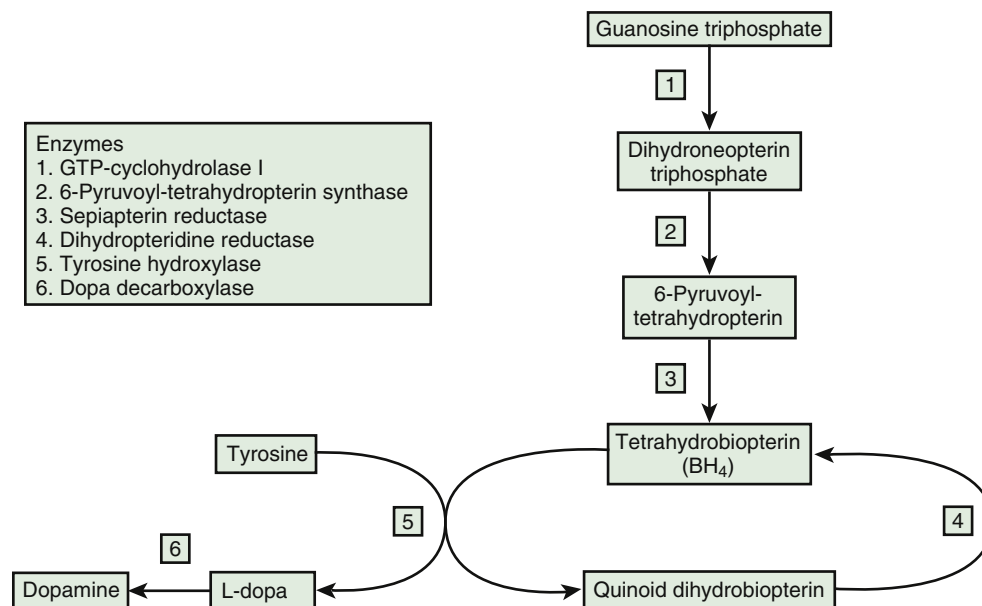
Video 11.22 A patient after treatment with levodopa.

Video 11.23 Dopa-responsive dystonia (DRD) manifesting in infancy.

Video 11.24 Same patient as in Video 11.23 after treatment with levodopa.

Video 11.25 Mother of a patient with dopa-responsive dystonia (DRD) who presents with parkinsonism.

Fig. 11.2 Metabolic pathway for the synthesis of tetrahydrobiopterin.



it can manifest as a focal dystonia of arm, neck, or cranium or manifest as parkinsonism, mimicking Parkinson disease (PD) (Nygaard et al., 1992). (5) The patients respond remarkably well to low-dosage levodopa. (6) Not all patients with childhood-onset dystonia have the diurnal fluctuation pattern. (7) Writer's cramp can be brought out with continued writing (Deonna et al., 1997). (8) Cerebellar signs have also been seen, with response to levodopa (Chaila et al., 2006). The term *dopa-responsive dystonia* (DRD) appears to be the preferred label for this disorder (Nygaard, 1989; Nygaard et al., 1990), because response to levodopa is the consistent finding, and the term also highlights the appropriate treatment. Moreover, the term *hereditary progressive dystonia* could apply to many genetic forms of dystonia, and certainly to the more virulent Oppenheim dystonia. ▶

If levodopa therapy is delayed for a great many years, patients still respond to low doses of levodopa (Harwood et al., 1994) (Video 11.26). Even if the onset is in adulthood presenting as parkinsonism, and resembling PD, it responds to low doses of levodopa and without adverse effects of response fluctuations (Nygaard et al., 1992; Harwood et al., 1994). Long-term treatment with levodopa does not cause the wearing-off phenomenon. Worsening of dystonia does not occur until 29 hours or more after levodopa withdrawal; the subjective feeling of wearing-off that is experienced by patients with DRD might be from one of the nonmotor effects of levodopa, such as mood elevation (Dewey et al., 1998). ▶

DRD is inherited in an autosomal dominant pattern and needs to be recognized because it is so easily treated. The gene causing DRD was mapped to chromosome 14q by Nygaard and associates (1993) and identified by Ichinose and colleagues (1994) as the gene for the enzyme GTP cyclohydrolase I (GCH), the rate-limiting enzyme in the biosynthesis of tetrahydrobiopterin (BH4) (Fig. 11.2), which is the cofactor of monoamine-synthesizing enzymes TH for dopamine and norepinephrine and tryptophan hydroxylase for serotonin (and also phenylalanine hydroxylase). The genetic designation DYT5 has been assigned to this form of dystonia (Wijemanne and Jankovic, 2015) (see Table 11.1). Clinically, only

dystonia and parkinsonism are manifested. Approximately 40% to 50% of patients with DRD have no known mutations (Furukawa and Kish, 1999). *GCH1* point mutations occur in approximately 54% of DRD patients and deletions in 8% (Zirn et al., 2008). Different families have different mutations on the same *GCH* gene (Hirano et al., 1995; Ichinose et al., 1995; Bandmann et al., 1996; Furukawa et al., 1996; Ichinose and Nagatsu, 1997; Jarman et al., 1997; Thony and Blau, 1997; Furukawa et al., 1998b; Steinberger et al., 1998; Tamaru et al., 1998), and spontaneous mutations have been identified. The multiple mutations are scattered over the entire coding region for the six exon-containing *GCH* gene (Yoshino et al., 2018).

Phenylalanine hydroxylase also requires the cofactor BH4 for its activity, and homozygous mutations and compound heterozygous mutations have been found in the *GCH* gene to cause the rare autosomal recessively inherited form of hyperphenylalaninemia (Thony and Blau, 1997; Furukawa et al., 1998a). Such mutations are therefore clinically similar to the compound heterozygous or homozygous mutations spread over all six exons encoding 6-pyruvoyl-tetrahydropterin synthase, which manifests as an autosomal recessively inherited variant of hyperphenylalaninemia, along with a deficiency of dopamine and serotonin. Hyperphenylalaninemia may be mild and go undetected neonatally; the child can develop dystonia later in childhood, along with developmental delay and seizures. The condition is treatable with levodopa, 5-hydroxytryptophan, and tetrahydrobiopterin (Demos et al., 2005). The other autosomal recessive pterin deficiency disorders also respond to levodopa, and they often have developmental delay, oculogyria, and dysautonomic features. Sepiapterin reductase deficiency appears to be fairly common in Malta (Neville et al., 2005; Wijemanne and Jankovic, 2015). Although dystonia can respond to levodopa, cognitive impairment does not.

In some pedigrees with DRD a mutation in the *GCH* gene has not been found. This fact, plus the multiple mutations in the *GCH* gene that have been discovered so far, indicated that genetic testing will not be an easy method to

Video 11.26 Untreated dopa-responsive dystonia (DRD) with onset in childhood, now an adult.

Table 11.10 Differential features between juvenile parkinsonism, dopa-responsive dystonia, and primary torsion dystonia

Clinical feature	Juvenile PD	DRD	Childhood PTD
Age onset	Rare <8 years	Infancy to 12 years	Uncommon <6 years
Gender	Predominantly male	Predominantly female	Equal
Initial sign	Foot dystonia or PD	Foot, leg dystonia, gait disorder	Arm or leg dystonia
Dystonia	At onset	Throughout	Throughout
Diurnal	Perhaps	Sometimes	No
Sleep benefit	Yes	Sometimes	No
Bradykinesia	Present	Present	No
Pull test	Abnormal	Abnormal	Normal
Gait	Abnormal	Abnormal	Abnormal if leg or trunk are affected
Anticholinergic response	Yes	Yes	Yes
Dopa responsive	Yes	Yes	No, or mild
Dopa dosage	Moderate to high	Very low	High
"Off" episodes	Fluctuations	Stable	Unknown
Dyskinesias	Prominent	With high-dose dopa	Unknown
Fluorodopa PET	Decreased	Normal or borderline	Normal
β-CIT SPECT	Decreased	Normal	Normal
CSF HVA	Decreased	Decreased	Normal
CSF neopterin	Moderately decreased	Markedly decreased	Normal
Phenylalanine test	Normal	Abnormal	Normal
Prognosis	Progressive	Plateaus	Usually worsens

β-CIT), [2beta-carboxymethoxy-3-beta-(4-[¹²³I]iodophenyl)tropane]; CSF, cerebrospinal fluid; DRD, dopa-responsive dystonia; HVA, homovanillic acid; PD, Parkinson disease; PET, positron emission tomography; PTD, primary torsion dystonia; SPECT, single-photon emission computed tomography.

determine the presence of the molecular defect. [Ichinose and Nagatsu \(1997\)](#) found that GCH activity in lymphocytes was decreased to less than 20% of the mean value of healthy controls and in unaffected carriers was 37%. The enzyme had normal activity in juvenile parkinsonism. These authors suggest that assay of GCH in blood cells might become a useful biochemical marker for the gene defect. A deficiency of neopterin is found in cerebrospinal fluid (CSF), but this is also reduced in juvenile parkinsonism ([Niemann and Jankovic, 2019](#)).

PET scans for 6-[¹⁸F]-fluoro-L-dopa (FDOPA) uptake and dopamine transporter (DAT) are normal, whereas those for the D2 receptor show increased binding, reflecting supersensitivity ([Rinne et al., 2004](#)). Network analysis, using fluorodeoxyglucose (FDG) PET, shows that DRD has a unique metabolic architecture that differs from that of other inherited forms of dystonia ([Asanuma et al., 2005a](#)). The characteristic features are increases in metabolism in the dorsal midbrain, cerebellum, and supplementary motor area (SMA) and reductions in motor and lateral premotor cortex and in the basal ganglia.

There has been a report of a patient with DRD who had a remission ([Di Capua and Bertini, 1995](#)), which perhaps should not come as a surprise because not every carrier of the mutation has symptoms. In fact, affected females outnumber affected males by a ratio of approximately 4:1 ([Ichinose and Nagatsu, 1997](#)). This ratio has been explained by the observation that males have a higher GCH activity normally, so missing one of the two genes by a mutation may still leave sufficient enzyme intact to avoid symptoms. There is also a report that selective serotonin reuptake inhibitor antidepressants reversed the benefit from levodopa therapy ([Mathen et al., 1999](#)).

The phenotype of DRD is not always easily distinguished from juvenile parkinsonism ([Mehanna and Jankovic, 2019](#); [Niemann and Jankovic, 2019](#)); features that help in the differential diagnosis are presented in [Table 11.10](#). Fluorodopa

PET scanning reveals a normal or modest reduction of dopa uptake ([Sawle et al., 1991](#); [Nygaard et al., 1992](#); [Snow et al., 1993](#); [Turjanski et al., 1993](#)), in contrast to the marked reduction in juvenile parkinsonism. A similar result is seen with β-CIT SPECT ([Jeon, 1997](#); [Naumann et al., 1997](#)) or other DAT ligands ([Huang et al., 2002](#)). Another important difference is that long-term treatment with levodopa in DRD is not associated with the motor complications that are seen with levodopa therapy in juvenile (and adult) PD ([Nygaard et al., 1991, 1992](#); [Harwood et al., 1994](#)).

An early sign of DRD in neonates may be difficulty with feeding, including vomiting, rigidity, and opisthotonus ([Chiang et al., 2007](#)). One unusual phenotypic expression is myoclonus, which occurred in one kindred and preceded the dystonia and bradykinesia ([Leuzzi et al., 2002](#)). Molecular genetics investigation found a missense mutation in exon 6 of the *GCH1* gene. Another phenotype of DRD is adult-onset oromandibular dystonia and no obvious family history of dystonia, which was found in one individual who had a mutation of *GCH* and who responded positively to treatment with levodopa ([Steinberger et al., 1999](#)). An adult with exercise-induced limb and trunk dystonia and with diurnal variation was found to respond to levodopa ([Regula et al., 2007](#)).

The first report of the pathologic findings of a case of DRD-GCH type revealed decreased neuromelanin in the substantia nigra (SN), but otherwise normal nigral cell counts and morphology ([Rajput et al., 1994](#)). Biochemically, this patient had reduced concentrations of dopamine and its metabolite, homovanillic acid (HVA), in both the caudate and putamen. Furukawa and his colleagues (1999) carried out more extensive postmortem biochemistry in two patients with typical DRD. One had two *GCH* mutations, but the other had no mutation in the coding region of this gene. Striatal bipterin and neopterin levels were markedly reduced. Both had severely reduced (less than 3%) TH protein levels and normal concentrations of dopa decarboxylase protein, DAT,

and vesicular monoamine transporters. The authors suggested that the reduction of TH protein might be explained by reduced enzyme stability/expression consequent to congenital BH4 deficiency.

A second autopsy report of DRD was on a patient with a presumed different genetic locus, chromosome 14q13, and called DYT14 by Grotzsch and colleagues (2002). An autopsy in the elderly proband revealed a normal number of cells in the SN and locus coeruleus (LC), which is typical of DRD and not PD, and there was a decrease in neuromelanin. No Lewy bodies were seen. These pathologic features are typical for DRD. Subsequently, more careful and thorough genetic analysis revealed that this family had a deletion in *GCH1*, so was just another pedigree with DYT5 dystonia (Wider et al., 2008). Deletions are harder to detect, and care must be made to search for them (Gasser, 2008).

In addition to the genetic types described in this section, some patients with focal dystonias, including familial cases, might respond to levodopa therapy. A report of two families with a total of four members with childhood-onset cervical dystonia, all of whom had an excellent response to levodopa, illustrates this point (Schneider et al., 2006c). Genetic testing on these patients showed that they did not have any of the genetic types discussed in this section. It is possible that these cases may represent new forms of DRD.

Intracortical inhibition of the primary motor cortex was studied in DRD patients and found to be normal, in contrast to adult-onset focal dystonia (see later discussion in the section on pathophysiology) (Hanajima et al., 2007). It is difficult to explain why loss of striatal dopamine in PD produces parkinsonian features whereas such a loss in DRD produces predominantly dystonic features. Using a transgenic mouse model for DRD, Sato and colleagues (2008) showed that dopamine loss is mainly anteriorly in the putamen, affecting the striosomes. They propose that in PD, the major loss of dopamine is in the posterior putamen, affecting mainly the matrix, and that this differential loss results in the different phenomenology between the two disorders (Fig. 11.3).

Tyrosine hydroxylase deficiency

TH deficiency is usually a more serious form of dopa-responsive dystonia and is transmitted as an autosomal recessive disorder. The presence of dystonia and parkinsonism in infancy is the clinical clue that this disorder should be suspected. Biochemical analysis of CSF will provide some evidence, but ultimately testing for the gene mutation is required to establish the diagnosis. Decreased CSF concentrations of HVA and 3-methoxy-4-hydroxyphenylethylene glycol, with normal 5-hydroxyindoleacetic acid CSF concentrations, are the biochemical hallmark of TH deficiency.

At least 10 different point mutations have now been discovered in the human TH gene, and more are being reported (Knappskog et al., 1995; Lüdecke et al., 1995, 1996; van den Heuvel et al., 1998; de Rijk-van Andel et al., 2000; Jansen et al., 2000; Swaans et al., 2000; Furukawa et al., 2001; Giovannelli et al., 2007). Many of the reports are in Dutch families. The clinical features range from a mild syndrome of juvenile DRD to more severe parkinsonism, dystonia, and oculogyric crises (all three representing dopamine deficiency) and also ptosis, miosis, oropharyngeal secretions, and postural hypotension (all representing norepinephrine

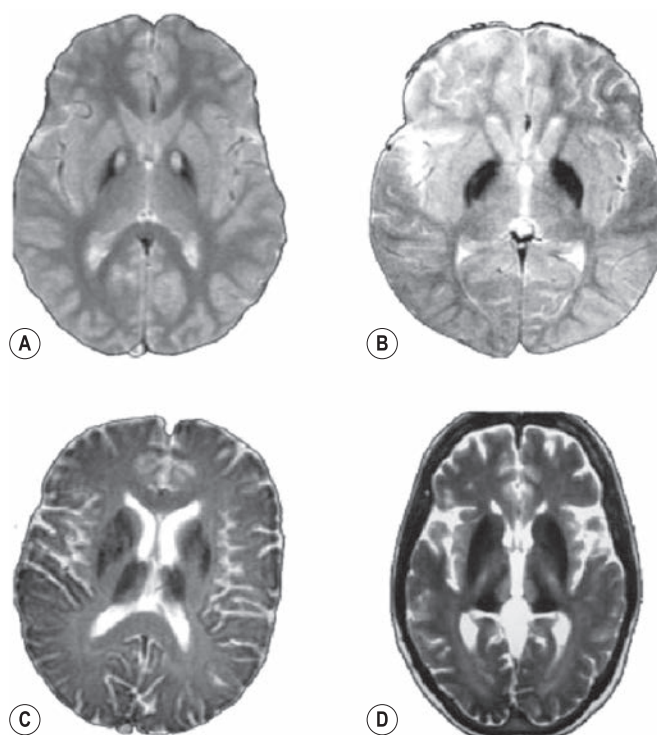


Fig. 11.3 Images of four neurodegenerations with iron accumulation. (A) Pantothenate kinase-associated neurodegeneration (PKAN). Note the eye-of-the-tiger sign in the globus pallidus. (B) Infantile neuroaxonal dystrophy (INAD). (C) Neuroferritinopathy. (D) Aceruloplasminemia.

deficiency). In the most severe form, the infant was virtually immobile, rigid, drooling saliva, with a tremor in tongue and hands. She responded dramatically to levodopa. The severity appears to be associated with the amount of loss of TH activity. Genetically, there can be homozygous mutations to heterozygous mutations. Compound heterozygotes have presented as spastic paraparesis, with a complete or very good response to levodopa (Furukawa et al., 2001; Giovannelli et al., 2007). Some patients with a mild form of the disorder live a normal life with a response to low-dose levodopa, into adulthood. One reported problem is hypersensitivity to levodopa (Grattan-Smith et al., 2002). Hoffmann and colleagues (2003) reported four patients with TH deficiency and emphasized that most patients with this disorder have an encephalopathy that is not predominantly dystonia, but rather a progressive, often lethal encephalopathic disorder, which can be improved but not cured by levodopa. The DRD of TH deficiency can be as responsive to levodopa, as is DYT5 with *GCH* involvement. Schiller and colleagues (2004) report sustained benefit and excellent response to levodopa even when treatment was delayed for 20 years. Most patients with TH deficiency can be successfully treated with levodopa.

A review of the literature and a report of 36 cases of TH deficiency divides the disorder into two phenotypes: an infantile-onset, progressive, hypokinetic-rigid syndrome with dystonia (type A) and a complex encephalopathy with neonatal onset (type B) (Willemssen et al., 2010). The HVA concentrations and the ratio of HVA to 5-hydroxyindoleacetic acid in CSF correlate with the severity of the phenotype.

A phenylalanine-loading test has been recommended as a means to distinguish between DRD with *GCH* deficiency and

that with TH deficiency (Hyland et al., 1997). In the former, phenylalanine is not metabolized rapidly and the blood levels remain elevated for a prolonged period. In TH deficiency, this test would be normal. One other potential method of differentiating GCH-deficient DRD from other DRDs or juvenile parkinsonism is the exquisite sensitivity to centrally acting anticholinergics. Some of the trihexyphenidyl responders reported by Fahn (1983) had responded to small doses, such as 6 mg/day. These patients were subsequently determined to have DRD. When trihexyphenidyl was first reported for the treatment of PD, some papers pointed out that small doses could have a dramatic benefit in some children with dystonia (Comer, 1952; Burns, 1959). These children had diurnal fluctuations of their dystonia. Jarman and colleagues (1997) screened some of their patients with responsiveness to anticholinergics and found that some had a GCH mutation.

Myoclonus–dystonia

Myoclonic movements were mentioned early in the description of the phenomenology of dystonia. Although lightning-like movements can occur in Oppenheim dystonia, they also can be seen in a distinct autosomal dominant disorder. Both conditions have unfortunately been called myoclonic dystonia, and in both, the myoclonic jerks can respond to alcohol. It has been recommended that when myoclonic jerks are part of Oppenheim dystonia, it should be referred to as dystonia with lightning-like jerks or myoclonic dystonia (Quinn et al., 1988). The autosomal dominant myoclonus–dystonia that is a distinct entity has been mapped to chromosome 7q21, and the mutated gene has been identified as the gene for ϵ -sarcoglycan (Zimprich et al., 2001; Asmus et al., 2002). The report of a mutation in the gene for the dopamine D2 receptor in a single family (Klein et al., 1999) has now been recognized to most likely represent a polymorphism (Klein et al., 2000a). This family has since been found to have genetic linkage to 7q21–q31 like the other families (Klein et al., 2000b). Whether myoclonus–dystonia is an entity separate from hereditary essential myoclonus (Fahn and Sjaastad, 1991; Quinn, 1996) remains to be determined through genetic studies. At least one family originally published as familial essential myoclonus has been reported to have a mutation in the ϵ -sarcoglycan gene and thus has myoclonus–dystonia (Korten et al., 1974; Foncke et al., 2006).

The onset can be in childhood or adulthood. Age at onset is highly associated with gender; the median age of onset for girls is 5 years versus 8 years for boys (Raymond et al., 2008). The myoclonus and dystonia are located predominantly in the arms and neck (Videos 11.27 and 11.28), and the symptoms tend to plateau after a period of progression (Kyllerman et al., 1990). There is clinical heterogeneity, and leg involvement can occur (Nardocci et al., 2008). OCD and alcohol dependence are not uncommon in individuals who carry the gene (Saunders-Pullman et al., 2002; Hess et al., 2007). Psychiatric problems also include substance abuse, anxiety/panic/phobic disorders, and psychosis (Doheny et al., 2002). Cognitive testing showed impaired verbal learning and memory in one family, impaired memory in the second family, and no cognitive deficits in the third family. In a large Dutch family, there was no cognitive deficit,

nor OCD, but there was depression and anxiety with panic attacks (Foncke et al., 2009). ●

In SCGE mutation carriers, there is hyperresponsiveness in contralateral inferior parietal cortical areas, ipsilateral premotor and primary somatosensory cortex, and ipsilateral cerebellum during the motor task compared with healthy control subjects (Beukers et al., 2010). This is similar to that in DYT1 and DYT6 dystonia and points to a disorganized sensorimotor integration.

There is markedly reduced penetrance if the parent carrying the mutation is the mother (penetrance about 5%–10%), whereas if the father carries the mutation, the penetrance is about 90%. This pattern of phenotypic expression of myoclonus–dystonia is called maternal imprinting. As Asmus and Gasser (2004) explained, if the mutated allele is inherited from the father, inactivation of the maternal allele as a result of imprinting leads to complete ϵ -sarcoglycan deficiency and hence to the development of clinical symptoms. If, on the other hand, the mutated allele is inherited from the mother, the intact paternal allele is sufficient to sustain ϵ -sarcoglycan function. Making the inheritance pattern more complicated is one report of reduced penetrance in which the mutated gene was inherited from the father (Muller et al., 2002). Deletions in the maternal allele and point mutations of the SCGE gene occur, and these can cause phenotypic variations, depending on the size of the deletion, with the largest deletion causing a split-hand/split-foot malformation and sensorineural hearing loss (Asmus et al., 2007).

Another gene locus has been found for one family with myoclonus–dystonia on chromosome 18p11 (Grimes et al., 2002). In a study of Dutch families with myoclonus–dystonia, 7 of 31 patients had carried a mutation in the ϵ -sarcoglycan gene (Gerrits et al., 2006). In one large Dutch family, originally published as essential myoclonus (Korten et al., 1974), the onset of myoclonus can be delayed as late as 75 years (Foncke et al., 2006), and although emphasis was made that the myoclonus was mainly distal in the arms in contrast to an assumption that myoclonus is usually proximal in this disorder, our personal experience is that myoclonus is commonly distal.

A phenotype similar to myoclonus–dystonia has been encountered with the SCA14 mutation (Foncke et al., 2010). Two independent studies searched for mutations in the ϵ -sarcoglycan gene in patients with familial and sporadic myoclonus–dystonia and did not find any (Han et al., 2003; Valente et al., 2003). This finding, plus the report of one family having a mutation on a different chromosome, 18p11 (DYT15), provides additional evidence for genetic heterogeneity in myoclonus–dystonia.

Two unrelated consanguineous Brazilian families with early-onset dystonia–parkinsonism were found to have a mutation in the *PRKRA* gene for protein kinase, interferon-inducible double-stranded RNA-dependent activator and it has been labeled as DYT16 (Camargos et al., 2008).

DYT17 is the designation given to a large consanguineous Lebanese family in which three sisters had PTD beginning with torticollis at ages 14, 17, and 19 years, spreading to segmental and generalized in one of the sisters (Chouery et al., 2008). DYT21 is an autosomal dominant family from northern Sweden with adult onset manifesting combinations of focal, segmental, and generalized dystonia (Holmgren et al., 1995; Norgren et al., 2011). Other gene abnormalities associated with myoclonus–dystonia include DYT15 and DYT26

Video 11.27 Myoclonus–dystonia in a boy.

Video 11.28 Myoclonus–dystonia in the father of the previous boy.

Rapid-onset dystonia–parkinsonism

Rapid-onset dystonia–parkinsonism (RDP) (DYT12) is an autosomal dominant movement disorder characterized by sudden onset of persistent dystonia and parkinsonism, generally during adolescence or early adulthood (Dobyns et al., 1993). Symptoms evolve over hours or days and generally stabilize within a few weeks, with slow or no progression. Members of a family who are wide apart in age may develop symptoms around the same time. Further follow-up of the original family revealed two members to have a more gradual progression of their disorder over 6 to 18 months. One of them experienced a rapid progression of symptoms 2 years after an initial stabilization of his condition. The phenotype, therefore, shows considerable variability (Brashear et al., 1996). Two other, seemingly unrelated, kindreds were subsequently reported (Brashear et al., 1997; Pittock et al., 2000). Variability occurs within a kindred, with some members in a kindred becoming stable after their worsening and others having fluctuating worsening or even improving over time (McKeon et al., 2007).

Now that the gene responsible for RDP has been discovered (de Carvalho Aguiar et al., 2004), it is possible to test a wide clinical spectrum of dystonia and determine the expanded phenotype (Brashear et al., 2007). The mutation is in the *ATP1A3* gene responsible for the alpha3 subunit of Na-K-ATPase. The phenotype of 36 affected individuals from 10 families included abrupt onset of dystonia with features of parkinsonism, a rostrocaudal gradient, and prominent bulbar findings. Other features found in some mutation carriers included common reports of triggers, minimal or no tremor at onset, occasional mild limb dystonia before the primary onset, lack of response to dopaminergic medications, rare abrupt worsening of symptoms later in life, stabilization of symptoms within a month, and minimal improvement overall. Tremor at onset of symptoms, a reversed rostrocaudal gradient, and significant limb pain excluded a diagnosis of RDP. A positive family history is not required.

Although there is little or no response to levodopa or dopamine agonists, a low concentration of HVA in the CSF in patients has been reported (Brashear et al., 1998). PET studies indicate no loss of dopaminergic nerve terminals in RDP (Brashear et al., 1999), suggesting that this disorder results from a functional deficit rather than being a neurodegenerative disease. An autopsied case revealed no neurodegeneration (Pittock et al., 2000). These findings suggest RDP is a neurochemical rather than a neurodegenerative disorder. DBS has not been helpful (Kamm et al., 2008).

The *ATP1A3* gene for RDP is on chromosome 19q13 (Kramer et al., 1999). Functional studies and structural analysis of the protein suggest that these mutations impair enzyme activity or stability. This finding implicates the Na⁺-K⁺ pump, a crucial protein that is responsible for the electrochemical gradient across the cell membrane. The authors suggest that the rapid onset that is seen in the disorder is related to an inability to “keep up with a high demand for ion transport activity” in response to stressful situations. However, there is genetic heterogeneity because one large family with the RDP phenotype was found not to have a mutation in the *ATP1A3* gene (Kabakci et al., 2005). Although most patients have been of European descent, at least one Asian (Korean)

Table 11.11 Clues that dystonia is secondary

1. History of possible etiologic factor (e.g., head trauma, peripheral trauma, encephalitis, toxin exposure, drug exposure, perinatal anoxia)
2. Presence of neurologic abnormality (e.g., dementia, seizures, ocular, ataxia, weakness, spasticity, amyotrophy)
3. Presence of false weakness or sensory examination findings or other clues of psychogenic cause (see Table 11.18)
4. Onset of rest instead of action dystonia
5. Early onset of speech involvement
6. Hemidystonia
7. Abnormal brain imaging
8. Abnormal laboratory workup

has been reported and with the typical phenotype (Lee et al., 2007).

Now that at least one gene for RDP has been found, genetic analysis can be carried out in dopa-nonresponsive parkinsonism. After being stable for 2.5 years, one patient thought to have Parkinson disease developed overnight oromandibular dystonia and more severe parkinsonian symptoms; he was found to have a missense mutation in the *ATP1A3* gene (Kamphuis et al., 2006).

Several other genetic forms of combined dystonia have been described over the past few years. Dystonia, designated as DYT28 dystonia, caused by loss-of-function mutations in *KMT2B* gene was first described in 2016 (Zech et al., 2016; Meyer et al., 2017). This is a childhood-onset dystonia usually starting in the legs and gradually becoming generalized with prominent cervical, cranial, and laryngeal dystonia. Also facial elongation and risus sardonicus have been reported in some of the cases. Marked improvement has been noted with DBS. The haploinsufficiency of *KMT2B* appears to be associated with disordered histone modification and transcriptional deregulation.

Dystonia with underlying cause

Dystonia may arise from multiple different underlying causes, both genetic and nongenetic. Table 11.11 provides some of the clues that suggest that dystonia is not isolated.

Neurodegenerations with brain iron accumulation (Table 11.12)

The gene for autosomal recessive neurodegeneration with brain iron accumulation type 1 (NBIA) (formerly known as Hallervorden–Spatz syndrome) has been identified as pantothenate kinase (PANK2) (Zhou et al., 2001; Hartig et al., 2006; Valentino et al., 2006). In 49 families with typical phenotype and magnetic resonance imaging (MRI) for NBIA, Hayflick and colleagues (2003) found that all had the PANK2 deficiency; in another 49 families with an atypical phenotype, 17 had the enzyme deficiency. In another study, looking at 10 families with MRI findings positive for iron accumulation, only 4 were found to have a mutation on *PANK2* (Thomas et al., 2004). The presence of a mutation in the *PANK2* gene was associated with younger age at onset and a higher frequency of dystonia, dysarthria,

intellectual impairment, and gait disturbance. Parkinsonism was seen predominantly in adult-onset patients, whereas dystonia seemed to be more frequent in the earlier onset cases. In the most comprehensive study, involving 72 patients with NBIA, 48 (67%) were found to have a *PANK2* mutation (Hartig et al., 2006). No strict correlation between the “eye-of-the-tiger” sign and *PANK2* mutations was found. Not all patients with *PANK2* deficiency have the eye-of-the-tiger sign on MRI; there is a report of one child whose eye-of-the-tiger sign disappeared on the MRI scan over time (Baumeister et al., 2005). Although the eye-of-the-tiger sign is very characteristic of *PANK2* mutation, it also may be seen in patients with other NBIA syndromes, such as neuroferritinopathy and aceruloplasminemia and in corticobasal degeneration and progressive supranuclear palsy (Kumar et al., 2006).

Another iron-accumulating dystonia presenting as infantile neuroaxonal dystrophy (NBIA2) can also manifest in older individuals, including adult-onset dystonia-parkinsonism with pyramidal tract signs and ataxia. When it manifests in adults, it can be without iron accumulation (Kurian et al., 2008; Paisán-Ruiz et al., 2009, 2010). It is the result of mutations in a phospholipase gene, *PLA2G6*,

and has been labeled PARK14 and NBIA2 and also called PLAN. Its pathologic findings can show widespread Lewy bodies and hyperphosphorylated tau (Paisán-Ruiz et al., 2010).

Neurodegeneration with brain iron accumulation type 3 is also called neuroferritinopathy. Chinnery and colleagues (2007) studied a large pedigree. Symptoms began in adulthood, and manifested first as chorea in 50%, lower limb dystonia in 42.5%, and parkinsonism in 7.5%. Serum ferritin levels were low in the majority of males and postmenopausal females, but within normal limits for premenopausal females. Brain MRI was abnormal on all affected individuals and one presymptomatic carrier. A gradient echo brain MRI identified all symptomatic cases.

A fourth neurodegeneration with brain iron accumulation (NBIA4) is aceruloplasminemia, an autosomal recessive disorder affecting the ceruloplasmin gene. NBIA is also seen with a mutation in the fatty acid hydroxylase gene (*FA2H*) manifested with ataxia, spasticity, and dystonia and referred to as FAHN (Kruer et al., 2010). It was originally referred to as a leukodystrophy and as part of the hereditary spastic paraparesis syndromes (Edvardson et al., 2008; Dick et al., 2010). McNeill and colleagues (2008) evaluated gradient and fast spin echo MRI scans and showed that the pattern of hypointensities from accumulated iron and hyperintensities differ in the four subtypes of hereditary neurodegenerations with brain iron accumulation, namely pantothenate kinase-associated neurodegeneration (PKAN), neuroferritinopathy, infantile neuroaxonal dystrophy (INAD), and aceruloplasminemia (Table 11.13; see Fig. 11.3).

Other combined dystonias

Tardive dystonia

Tardive dystonia is the most common form of symptomatic dystonia seen at the Movement Disorders Center at Columbia University Medical Center (Table 11.14). It can manifest exactly like PTD, but there is often accompanying classic tardive dyskinesia or tardive akathisia, which establishes the diagnosis. One form of clinical presentation seems more common in tardive dystonia. Many patients have retrocollis and extension of the elbows with internal rotation of the shoulders and flexion of the wrists. Tardive dystonia is a persistent dystonia as a result of a complication of drugs that block dopamine receptors. Clinical features of tardive dystonia are discussed in detail in Chapter 17.

Table 11.12 Neurodegenerations with brain iron accumulation

Condition or acronym	Synonym	Gene	Chromosome
PKAN	NBIA1	<i>PANK2</i>	20p13
PLAN	INAD, NBIA2, PARK14	<i>PLA2G6</i>	22q12
FAHN	SPG35	<i>FA2H</i>	16q23
Aceruloplasminemia		<i>CP</i>	3q23
Neuroferritinopathy		<i>FTL</i>	19q13
Kufor-Rakeb	PARK9	<i>ATP13A2</i>	1p36
SENDA syndrome		?	?

PKAN, pantothenate kinase–associated neurodegeneration; *PANK2*, pantothenate kinase 2; PLAN, *PLA2G6*-associated neurodegeneration; INAD, infantile neuroaxonal dystrophy; *PLA2G6*, phospholipase A2; SPG, spastic paraplegia; *FA2H*, fatty acid 2-hydroxylase; CP, ceruloplasmin; FAHN, fatty acid hydroxylase neurodegeneration; *FTL*, ferritin light chain; SENDA, static encephalopathy of childhood with neurodegeneration in adulthood.

From Schneider SA, Bhatia KP. Three faces of the same gene: *FA2H* links neurodegeneration with brain iron accumulation, leukodystrophies, and hereditary spastic paraplegias. *Ann Neurol*. 2010;68(5):575–577.

Table 11.13 Imaging features of neurodegenerations with iron accumulation

PKAN (n = 26)	Neuroferritinopathy (n = 21)	INAD (n = 4)	Aceruloplasminemia (n = 10)
T2*: Eye-of-the-tiger sign in GP in all Hypointensity of SN (80%); dentate (20%)	T2*: Hypointensity of dentate (95%), SN (81%), cerebral cortex (71%), GP (38%), putamen (28%), thalamus (19%), CN (14%) Hyperintensity as a confluent area between GP and putamen in 52%	T2*: Hypointensity of GP, SN, and dentate in all No eye-of-the-tiger sign	T2*: Hypointensity of GP, SN, putamen, CN, dentate, thalamus, and cerebral cortex in all Cerebellar cortex in 50% of cases

CN, Cranial nerve; GP, globus pallidus; SN, substantia nigra.

Data from McNeill A, Birchall D, Hayflick SJ, et al. T2* and FSE MRI distinguishes four subtypes of neurodegeneration with brain iron accumulation. *Neurology*. 2008;70(18):1614–1619.

Table 11.14 Common causes of torsion dystonia

Cause	No.
Primary	1762
Tardive dystonia	184
Birth injury	83
Psychogenic	64
Peripheral trauma	51
Head injury	39
Stroke	27
Encephalitis	24
Miscellaneous	164
Total	2398

Acute dystonic reactions

Acute dystonic reactions can occur from drugs that block dopamine receptors; these reactions are widely recognized and easily treated with antihistaminics and anticholinergics. Acute dystonia also has been reported with exposure to domperidone (Bonuccelli et al., 1991), amitriptyline (Ornadel et al., 1992), fluoxetine (Dave, 1994), clozapine (Kastrup et al., 1994; Thomas et al., 1994), and dextromethorphan (Graudins and Fern, 1996). Because domperidone is a peripherally acting dopamine receptor blocker, the acute dystonic reaction suggests that some of the drug entered the central nervous system (CNS), at least in the affected patient, who had polycystic ovary syndrome. Amitriptyline would ordinarily not be expected to produce such a reaction; the clinical description is that typical for acute dystonia after a neuroleptic, but no such drug was known to have been taken by the patient.

The so-called atypical antipsychotic drugs have been shown to have less risk for causing acute dystonic reactions. In one study evaluating a population of patients consecutively admitted to a psychiatric intensive care unit, 1337 cases were treated with antipsychotics (Raja and Azzoni, 2001). The authors observed 41 cases (3.1%) of acute dystonic reactions. Four occurred with risperidone monotherapy, one with olanzapine, and one with quetiapine. The remaining cases were with medications labeled as typical antipsychotics.

Serotonergic agents have also been reported to induce acute dystonic reactions (Lopez-Aleman et al., 1997; Madhusoodanan and Brenner, 1997; Olivera, 1997). Serotonergic agents, such as fluoxetine, can inhibit dopaminergic neurons in the substantia nigra, worsening parkinsonism (Baldessarini and Marsh, 1992). This might somehow be related to the development of the dystonic reaction. How clozapine induces an acute dystonic reaction is unknown; it could relate to binding to the D2 receptor, the D4 receptor, or the 5HT₂ receptor.

Posttraumatic dystonia

A large number of injuries to the nervous system can result in secondary dystonia (see Table 11.10). Head trauma and

peripheral trauma, including dental procedures (Schrage et al., 1999), can induce generalized and segmental dystonia and focal dystonia, respectively. Neck trauma can result in cervical dystonia, and in one child, also camptocormia (Shuper et al., 2007). Retrocollis is more commonly associated with tardive dystonia, but also can be the result of head or neck trauma (Papapetropoulos et al., 2007a). Delayed-onset focal dystonia can follow electrical injury (Lim and Seet, 2007). Trauma may provoke the onset of PTD in an individual who carries the gene for this disorder (Fletcher et al., 1991c). Segmental axial dystonia was described with a closed head injury with small areas of encephalomalacia, including the caudate nucleus (Jabbari et al., 1992).

Other combined dystonias

Cervical dystonia can sometimes be secondary to lesions in the CNS, such as lacunar infarction in the putamen (Molho and Factor, 1993), and to lesions in the upper cervical spinal cord (Klostermann et al., 1993; Cammarota et al., 1995), including syringomyelia (Hill et al., 1999). Torticollis has been reported to occur after electrocution (Colosimo et al., 1993) and in moyamoya disease (Yasutomo et al., 1993). Strokes can occasionally lead to delayed-onset hemidystonia. Perhaps in this category is the primary antiphospholipid syndrome, an immune-mediated vascular disorder that has been found to result in hemidystonia in children (Angelini et al., 1993). Sjögren syndrome, also considered an autoimmune disorder, has been associated with dystonia (van den Berg, et al., 1999). X-linked agammaglobulinemia can result in a fatal dementing, dystonia-parkinsonism syndrome (Papapetropoulos et al., 2007b).

Encephalitis, usually from severe equine encephalitis, results in permanent dystonia. The common Asian encephalitis known as Japanese encephalitis can cause severe dystonia (Kalita and Misra, 2000; Murgod et al., 2001). Occasionally, dystonia can be psychogenic in origin (see Chapter 27), and it is reasonable to consider psychogenic dystonia as one of the many causes of secondary dystonia. Sometimes psychogenic dystonia occurs after trauma. When associated with pain, it may be diagnosed as reflex sympathetic dystrophy or complex regional pain syndrome, but many of the patients have a psychogenic mechanism (Ochoa, 1999); this syndrome also has been called causalgia-dystonia (Bhatia et al., 1993a).

Clues that dystonia might be secondary (Tables 11.15 and 11.11)

In examining patients with dystonia, there are some clues in the history and neurologic examination that would suggest to the clinician that the patient's dystonia is secondary rather than primary.

Other movement disorders in which dystonia can be present

There are some movement disorders, including PD and Parkinson-plus syndromes, dystonic tics, and paroxysmal dyskinesias, in which dystonia is present, but that are not typically classified as dystonia (Table 11.16). Hypnogenic dystonia is commonly a manifestation of frontal lobe epilepsy

Table 11.15 Selected causes of secondary dystonia

1. Perinatal cerebral injury
 - a. Athetoid cerebral palsy
 - b. Delayed-onset dystonia
 - c. Pachygyria
2. Encephalitis, infectious and postinfectious
 - a. Reye syndrome
 - b. Subacute sclerosing leukoencephalopathy
 - c. Creutzfeldt–Jakob disease
 - d. HIV infection
3. Head trauma
4. Thalamotomy and thalamic lesions
5. Lenticular nucleus lesions
6. Primary antiphospholipid syndrome
7. Focal cerebral vascular injury
8. Arteriovenous malformation
9. Hypoxia
10. Brain tumor
11. Multiple sclerosis
12. Brainstem lesion, including pontine myelinolysis
13. Posterior fossa tumors
14. Cervical cord injury or lesion, including syringomyelia
15. Lumbar canal stenosis
16. Peripheral injury
17. Electrical injury
18. Drug-induced
 - a. Levodopa
 - b. Dopamine D2 receptor–blocking agents
 - (1) Tardive dystonia
 - (2) Acute dystonic reaction
 - c. Ergotism
 - d. Anticonvulsants
19. Toxins: Mn, CO, carbon disulfide, cyanide, methanol, disulfiram, 3-nitropropionic acid, wasp sting (Leopold et al., 1999)
20. Metabolic: Hypoparathyroidism
21. Immune encephalopathy: Sjögren syndrome, multiple myeloma, Rasmussen syndrome
22. Psychogenic
23. Creutzfeldt–Jakob disease (Hellmann and Melamed, 2002)
24. Familial basal ganglia calcifications, gene on 14q (Geschwind et al., 1999)
25. Familial basal ganglia calcifications, gene not on 14q (Wszolek et al., 2006)
26. Autosomal recessive
 - a. Wilson disease (can also present with tremor or parkinsonism) gene: Cu-ATPase located at 13q14.3
 - b. Niemann–Pick type C (dystonic lipidosis) (sea-blue histiocytosis) defect in cholesterol esterification; gene mapped to chromosome 18
 - c. Juvenile neuronal ceroid-lipofuscinosis (Batten disease)
 - d. GM1 gangliosidosis (Kobayashi and Suzuki, 1981; Campdelacreu et al., 2002)
 - e. GM2 gangliosidosis
 - f. Metachromatic leukodystrophy
 - g. Lesch–Nyhan syndrome (Jinnah et al., 2006)
 - h. Homocystinuria (Sinclair et al., 2006)
 - i. Glutaric acidemia
 - j. Triosephosphate isomerase deficiency
 - k. Methylmalonic aciduria
 - l. Hartnup disease
 - m. Ataxia telangiectasia
 - n. Friedreich ataxia (Hou and Jankovic, 2003)
 - o. Neurodegeneration with brain iron accumulation type 1 (formerly called Hallervorden–Spatz syndrome), renamed as pantothenate kinase–associated neurodegeneration (PKAN) (Hayflick et al., 2003)
 - p. Neurodegeneration with brain iron accumulation type 2, infantile neuroaxonal dystrophy (PLA2G6 mutation) (PARK14)
 - q. Neurodegeneration with brain iron accumulation type 3, aceruloplasminemia
 - r. Neurodegeneration with brain iron accumulation (FAHN) (FA2H mutation)
 - s. Neuroacanthocytosis
 - t. Neuronal intranuclear hyaline inclusion disease
 - u. Hereditary spastic paraplegia with dystonia
 - v. Sjögren–Larsson syndrome (ichthyosis, spasticity, intellectual disability) (Cubo and Goetz, 2000).
 - w. Ataxia–amyotrophy–intellectual disability–dystonia syndrome (Wilmschurst et al., 2000)
 - x. Biotin-responsive basal ganglia disease (SLC19A3 mutation) (Debs et al., 2010)
27. Probable autosomal recessive a. Progressive pallidal degeneration
28. Mitochondrial
 - a. Leigh disease
Genes: nuclear and mitochondrial DNA
 - b. Leber disease
Gene: mitochondrial DNA
 - c. Other mitochondrial encephalopathies (Sudarsky et al., 1999)
29. Associated with parkinsonian syndromes
 - a. Parkinson disease
 - b. Progressive supranuclear palsy
 - c. Multiple system atrophy
 - d. Cortical-basal ganglionic degeneration

Modified from Fahn S, Bressman SB, Marsden CD. Classification of dystonia. In: Fahn S, Marsden CD, DeLong MR, eds. Dystonia 3. Advances in Neurology, vol. 78. Philadelphia, PA: Lippincott-Raven, 1998, pp. 1–10, with more recent additions.

Table 11.16 Other movement disorders in which dystonia may be present

- A. Tic disorders with dystonic tics
- B. Paroxysmal dyskinesias with dystonia:
 - Paroxysmal kinesigenic dyskinesia
 - Paroxysmal nonkinesigenic dyskinesia
 - Paroxysmal exertional dyskinesia
 - Benign infantile paroxysmal dyskinesias
- C. Hypnogenic dystonia (sometimes these are seizures)

(Sellal et al., 1991; Meierkord et al., 1992; Montagna, 1992). In addition, there are many disorders in which dystonia is secondary to an underlying pathologic condition (see Table 11.15).

Pseudodystonia is not neurologically based dystonia and is not classified as dystonia but can be mistaken for dystonia because of sustained postures. The pseudodystonias are listed in (Table 11.17):

Perhaps the most difficult form of dystonia to diagnose is *psychogenic dystonia*, which can occur in up to 5% of children presenting with what otherwise appears to be primary dystonia. Clues suggesting a psychogenic cause are false (give-way)

Table 11.17 Pseudodystonias

1. Sandifer syndrome
2. Stiff-person syndrome
3. Isaacs syndrome
4. Satoyoshi syndrome
5. Rotational atlanto-axial subluxation
6. Soft tissue nuchal mass
7. Bone disease
8. Ligamentous absence, laxity, or damage
9. Congenital muscular torticollis
10. Congenital postural torticollis
11. Juvenile rheumatoid arthritis
12. Ocular postural torticollis
13. Congenital Klippel–Feil syndrome
14. Posterior fossa tumor
15. Syringomyelia
16. Arnold–Chiari malformation
17. Trochlear nerve palsy
18. Vestibular torticollis
19. Seizures manifesting as sustained twisting postures
20. Inflammatory myopathy
21. Torticollis from arteriovenous fistula at craniocervical junction

weakness, false sensory findings, inconsistent movements with changing patterns of involvement, incongruent movements not fitting with typical organic dystonia, self-inflicted injuries, deliberate slowness of movement, and multiple types of abnormal dyskinesias that do not fit into a single organic cause (Fahn and Williams, 1988). Table 11.18 lists the clinical situations that provide clues that the clinician might be encountering a psychogenic movement disorder.

Pathophysiology

A major characteristic of dystonic movements is the presence of sustained simultaneous contractions of agonists and antagonists (Herz, 1944a; Yanagisawa and Goto, 1971; Rothwell and Obeso, 1987). There are also contractions of adjoining and distant muscles, so-called “overflow,” particularly during a voluntary movement. In addition, rhythmic contractions frequently occur on voluntary movement referred to as dystonic tremor. None of these physiologic features is specific for dystonia.

It appears that an underlying propensity to excess movement is a loss of inhibition in the CNS (Hallett, 2009, 2011). The loss of inhibition can be demonstrated at spinal, brainstem, and cortical levels. In regard to the spinal level, in limb dystonia, there is an abnormality of reciprocal inhibition between antagonist muscles. Stimulating the radial nerve with muscles at rest produces three periods of inhibition in median nerve innervated muscles. The second phase of reciprocal inhibition is much reduced or even absent in affected limbs in dystonia (Nakashima et al., 1989) (Panizza, Hallett et al., 1989). This has been interpreted as evidence for reduced presynaptic inhibition of muscle afferent input to the inhibitory interneurons as a result of defective descending motor control, although there also could be abnormalities in local spinal circuits. Reduced reciprocal inhibition is also seen during voluntary movement in patients with limb dystonia (Valls-Sole and Hallett, 1995). Increasing muscle spindle activity by the

Table 11.18 Clues suggesting psychogenic dystonia (see also later chapter)

- A. Clues relating to the movements
 1. Abrupt onset
 2. Inconsistent movements (changing characteristics over time)
 3. Incongruous movements and postures (movements do not fit with recognized patterns or with normal physiologic patterns)
 4. Presence of additional types of abnormal movements that are not consistent with the basic abnormal movement pattern or are incongruous with a known movement disorder, particularly:
 - Rhythmical shaking
 - Bizarre gait
 - Deliberate slowness carrying out requested voluntary movement
 - Bursts of verbal gibberish
 - Excessive startle (bizarre movements in response to sudden, unexpected noise or threatening movement)
 5. Spontaneous remissions
 6. Movements decrease or disappear with distraction
 7. Response to placebo, suggestion or psychotherapy
 8. Presence as a paroxysmal disorder
 9. Dystonia beginning as a fixed posture
 10. Twisting facial movements which move the mouth to one side or the other (NOTE: Organic dystonia of the facial muscles usually do not move the mouth sideways)
- B. Clues relating to the other medical observations
 1. False weakness
 2. False sensory complaints
 3. Multiple somatizations or undiagnosed conditions
 4. Self-inflicted injuries
 5. Obvious psychiatric disturbances
 6. Employed in the health profession or in insurance claims
 7. Presence of secondary gain, including continuing care by a “devoted” spouse
 8. Litigation or compensation pending

tonic vibration reflex maneuver induced dystonic postures or movements typical of those seen during writing in 11 of 15 patients with writer’s cramp, but not in normal individuals (Kaji et al., 1995). Cooling the affected limb in writer’s cramp has been shown to reduce the dystonia and improve writing performance (Pohl et al., 2002), and this effect might be due to damping of spindle input. The cutaneous EMG silent period during isometric contraction is one exception. In both primary brachial dystonia and limb dystonia, the duration of the silent period was significantly prolonged (Pullman et al., 1996; Espay, Morgante et al., 2006).

At the brainstem level, some physiologic reflexes, such as blink reflexes, have been found to be abnormal in primary cranial and cervical dystonias (Berardelli et al., 1985; Tolosa et al., 1988b). The R1 and R2 blink responses have increased amplitude and duration. This finding implies excess physiologic excitatory drive in the midbrain region. A sensory trick that reduced blepharospasm was found to decrease the R2 blink response, implying that tricks might operate by increasing inhibition (Gomez-Wong et al., 1998). Blepharospasm has been studied in some detail, recording EMGs simultaneously from both orbicularis oculi (OO) and levator palpebrae superioris (LPS) (Aramideh et al., 1994). Some patients had contractions only of the OO and simultaneous reciprocal inhibition of LPS; others had combined simultaneous contractions of both OO and LPS; and others had gradual cessation of LPS inhibition along with OO contraction (combination

of blepharospasm, LP motor impersistence); a fourth group had a combination of blepharospasm and involuntary LP inhibition; a fifth group had involuntary inhibition of LPS activity, without any dystonic discharges in OO ("apraxia of eyelid opening"). Krack and Marion (1994) suggest that this so-called apraxia of lid opening is actually a dystonic phenomenon with difficulty in modulating antagonist muscles.

There is a loss of inhibition with increased excitability also at the cortical level (Udupa and Chen, 2019). The excitability of the motor cortex was studied in 11 patients with task-specific dystonia and 11 age-matched controls by delivering transcranial magnetic stimuli at different stimulus intensities (Ikoma et al., 1996). With increasing stimulus intensity, the increase in the motor evoked potentials in the flexor carpi radialis muscles was greater in patients than in normal subjects, suggesting that cortical motor excitability is increased in dystonia. A fundamental abnormality is a loss of short intracortical inhibition (SICI), which represents function of the inhibitory interneurons in the motor cortex (Ridding, Sheean et al., 1995; Thirugnanasambandam, Khera et al., 2015). This is demonstrated with paired-pulse transcranial magnetic stimulation (TMS). A first pulse conditions the cortex, and the second pulse is a test stimulus for the excitability at that exact time. At very short intervals, from 2 to 4 ms, there is inhibition, called SICI, and at longer intervals, like 10 to 15 ms, there is facilitation, called short intracortical facilitation (SICF). In dystonia, there is a loss of the inhibition but normal facilitation. There are many other cortical circuits that can be probed using clinical neurophysiologic techniques, and they generally show the same abnormality of loss of inhibition (Quartarone and Hallett, 2013; Pirio Richardson, Altenmuller et al., 2017; Udupa and Chen, 2019).

The loss of inhibition has a functional consequence of loss of surround inhibition in the cerebral cortex (Hallett, 2004; Sohn and Hallett, 2004). Surround inhibition, or lateral inhibition, sharpens the motor command by inhibiting muscles or movements not desired. Surround inhibition is considered to be facilitated by the basal ganglia with the direct pathway promoting the desired movement and the indirect pathway inhibiting undesired movements (Mink, 1996). A major contributor to the loss of surround inhibition is the failure of SICI (Beck, Richardson et al., 2008).

In addition to the obvious motor abnormalities in dystonia, there are some subtle sensory abnormalities. These include abnormal spatial discrimination, including two-point discrimination, and temporal discrimination (Conte, Defazio et al., 2019). Physiologic investigation of such abnormalities shows a failure of short latency inhibition within the sensory cortex (Tinazzi, Priori et al., 2000; Tamura, Matsushashi et al., 2008). Thus, there is a similar abnormality of short latency inhibition in motor and sensory systems, and this suggests an abnormality of inhibitory interneurons, likely gamma-aminobutyric acid (GABA) interneurons. Temporal discrimination abnormality is particularly sensitive for identifying patients with either focal or generalized dystonia, even in nonmanifesting gene carriers and relatives of patients with focal dystonia (Fiorio et al., 2007; Hutchinson, Kimmich et al., 2013).

There is a second important pathophysiological process, in addition to loss of inhibition, abnormal plasticity. There is a clinical sense for this given, for example, how dystonia can appear years after a stroke and how it might take many

months for DBS to reach an optimal effect. Also, motor learning is slower than normal (Ghilardi, Carbon et al., 2003). A physiologic measure of this abnormal plasticity is paired associative stimulation (PAS) (Stefan, Kunesch et al., 2000). PAS is a process similar to how long-term potentiation (LTP) is produced in animal models, and it shares properties of LTP. A shock to the median nerve is followed at about 25 ms by a TMS to the motor cortex. This produces two inputs to the motor cortex in near simultaneity, and that can strengthen synapses. After multiple paired stimulations, the excitability of the motor cortex is enhanced as demonstrated by an increase in size of the motor evoked potential. In patients with dystonia, the PAS effect is more than normal and spreads more widely to surrounding muscles (Quartarone, Bagnato et al., 2003; Quartarone and Hallett, 2013). The latter effect is further confirmation of the failure of surround inhibition in the motor cortex. An enhancement of plasticity is not necessarily good, because plasticity is supposed to stay within a homeostatic range, and, indeed, it has been demonstrated that the homeostatic principle is also violated in dystonia (Kang, Terranova et al., 2011).

A monkey model of focal dystonia uses abnormal plasticity by training long periods of continuous use of a limb, perhaps similar to the repetitive use in writing that leads to writer's cramp. This resulted in abnormal motor control and posturing. Associated with this was a finding of receptive fields in the sensory cortex that were 10 to 20 times larger than normal (Byl et al., 1996). This led to studies in patients with focal hand dystonia using functional MRI (fMRI), PET, electroencephalography (EEG), and magnetoencephalography, all of which showed that receptive fields were increased in size (Bara-Jimenez, Catalan et al., 1998; Meunier, Garnerio et al., 2001; Nelson, Blake et al., 2009; Catalan, Ishii et al., 2012). The receptive fields were not only large but were also disorganized, with finger representations sometimes out of order. These studies also raised a question as to whether these abnormalities were produced by activity or whether they were endophenotypic, because similar abnormalities were seen in the asymptomatic hand in patients with unilateral focal dystonia.

Given that there are sensory abnormalities and motor abnormalities, the question arises as to whether the motor abnormality might be a consequence of the sensory abnormality (Hallett, 1995). This seems less likely, however, than having both independently abnormal. Regardless, and not surprisingly, there is abnormal sensorimotor integration. One way of studying this is with the contingent negative variation (CNV), in which sensory stimuli trigger specified movements. In patients with writer's cramp, the CNV of the right hand had less magnitude than the left hand (Ikeda et al., 1996). In a subsequent study of writer's cramp, this group showed normal CNV for neck movements, but decreased in both hands (Hamano, Kaji et al., 1999). Conversely, in patients with cervical dystonia, the CNV for neck movements was abnormal, but normal for hand movements (Kaji, Ikeda et al., 1995). In another type of study dealing with sensory and motor interactions, somatosensory evoked potentials are reduced in amplitude during movement and even in the premovement period of a reaction time. Patients with writer's cramp had reduced gating in the premovement period (Murase, Kaji et al., 2000).

An interesting phenomenon in dystonia is the sensory trick. Given the important sensory-motor interactions, this

might not be surprising, but the exact physiology remains unknown (Patel, Jankovic et al., 2014; Ramos, Karp et al., 2014; Conte, Defazio et al., 2019; Sarasso, et al., 2020).

Whether many of these physiologic alterations are epiphenomena or part of the underlying pathophysiology is unclear, and Espay and colleagues (2006) made the situation more complex when they found analogous abnormalities in functional dystonia. One possibility is that these abnormalities are those associated with dystonia regardless of cause. Another is that a prolonged abnormal posture can lead to some of the abnormalities. Physiologic abnormalities were also seen in patients with fixed dystonia (Avanzino et al., 2008) perhaps supporting the latter idea. On the other hand, abnormal plasticity is not seen in functional dystonia (Quartarone, Rizzo et al., 2009), and this does indicate a physiologic difference.

Surgery for DBS has given the opportunity to record neural activity in patients with dystonia. Although the “rate theory” of basal ganglia pathophysiology would hypothesize that the neuronal activity in the GPi might be slow, the evidence is actually only marginal. The most obvious abnormality is irregular bursts that sometimes can be seen to correlate with dystonic movements (Zhuang, Li et al., 2004). In some recordings there is an abnormal rhythm found in the local field potential at alpha or theta frequency and this might arise from the bursting (Scheller, Lofredi et al., 2019).

Another theme of pathophysiology is a consideration of the role of the cerebellum. As will be noted below, most of the thinking about the pathophysiology of dystonia has been related to the basal ganglia. New evidence, both from animal models and human physiology suggests that the cerebellum plays a crucial role (Shakkottai, Batla et al., 2017; Bologna and Berardelli, 2018). For example, electrophysiologic studies in patients with cervical dystonia and focal hand dystonia using eyeblink conditioning reflex found differences between the patients and healthy controls (Teo et al., 2009). Eyeblink conditioning is mediated via the olivocerebellar pathway; this suggests that the cerebellum may play a role in dystonia. It is likely important in this regard that there are strong interconnections between the basal ganglia and cerebellum (Bostan, Dum et al., 2018).

A brief summary of the pathophysiology of dystonia is presented in Table 11.19, in part, taken from Berardelli and colleagues (1998), Hallett (2009), Quartarone and Hallett (2013), and Pirio Richardson and associates (2017). Briefly, dystonia is characterized by two main pathophysiologic abnormalities: “reduced” excitability of inhibitory systems at many levels of the CNS and “increased” plasticity of neural connections (Quartarone et al., 2009). The involvement of so many regions of the brain in the pathophysiology has led to the idea that dystonia is a network disorder (Latorre et al., 2020).

Pathoanatomy

Hints about the possible anatomical substrate for dystonia of unknown cause and even for many of the genetic causes (“primary” dystonia) come from dystonia produced by overt focal lesions (“secondary” dystonia). In this latter situation, lesions are frequently found in the basal ganglia, perhaps most frequently in the putamen (Burton et al., 1984). In an MRI study of eight patients with secondary unilateral

Table 11.19 Highlights of pathophysiology of torsion dystonia

1. Reduced and irregular neuronal firing rate in the internal and external segments of the globus pallidus
2. Reduced pallidal inhibition of the thalamus with consequent overactivity of medial and prefrontal cortical areas and underactivity of the primary motor cortex during movements
3. Cortical abnormalities:
 - a. Reduced preparatory activity in the electroencephalogram before the onset of voluntary movements
 - b. Enhanced premotor and supplementary motor cortical excitability
 - c. Reduced primary motor cortex activity
 - d. Enlarged, overlapping cortical sensory fields in focal dystonias (Nelson et al., 2009; Hallett, 2009)
 - e. Disorganized sensorimotor integration
 - f. Increased plasticity (Quartarone et al., 2006, 2009)
4. Loss of surround inhibition
5. Reduced spinal cord and brainstem inhibition is seen in many reflex studies (long-latency reflexes, cranial reflexes, and reciprocal inhibition)
6. Co-contraction and overflow of electromyographic activity of inappropriate muscles is characteristic
7. Reduced inhibition and increased plasticity are seen in unaffected muscles of patients with focal dystonia. Thus, they are thought to be primary abnormalities rather than secondary to dystonic muscle contraction. However, patients with psychogenic dystonia have the same abnormalities of short and long interval intracortical inhibition (SICI and LICI), cortical silent period, and spinal reciprocal inhibition as patients with primary dystonia (Espay et al., 2006; Quartarone et al., 2009). Although psychogenic dystonia shows similar cortical inhibition, plasticity (paired associative stimulation) is abnormally high only in the organic group, whereas there is no difference between the plasticity measured in psychogenic patients and healthy controls (Quartarone et al., 2009). Synaptic plasticity in the motor cortex is induced by repetitive transcranial magnetic stimulation (TMS). Increased plasticity is measured as an increased response to TMS. The finding of reduced cortical inhibition also occurs in psychogenic dystonia and implies that central nervous system inhibition may follow the abnormal usage of a limb or other affected body part and not necessarily be the cause or the epiphenomenon.

dystonia, lesions associated with dystonic spasms were located in the putamen posterior to the anterior commissure in all patients and extended variably into the dorsolateral part of the caudate nucleus, the posterior limb of the internal capsule, or the lateral segment of the globus pallidus (Lehericy et al., 1996). Lesions in the pallidum also can result in dystonia, often with parkinsonism (Munchau et al., 2000b). In fact, lesions can involve not only the basal ganglia, but also connections to and from these nuclei, such as the thalamus and the cortex (Marsden et al., 1985). In imaging studies of dystonia developing after a stroke, focal lesions were seen in the striatopallidum and in different parts of the thalamus (Karsidag et al., 1998; Krystkowiak et al., 1998). A characteristic dystonic tremor after a stroke is commonly localized to the thalamus by imaging studies (Cho and Samkoff, 2000).

However, one should not assume that the basal ganglia and its direct connections are always the site of physiologic pathologic processes in primary dystonia. It has been shown, for example, that the rostral brainstem (Jankovic and Patel, 1983; Kulisevsky et al., 1993), pontine tegmentum (Aramideh et al., 1996), and thalamus (Miranda and Millar, 1998)

can be pathologically damaged in some cases of secondary blepharospasm. Lesions from stroke, multiple sclerosis, and encephalitis have all been seen. Additional cases and a meta-analysis of the literature found 48 cases in total with lesions in the thalamus ($n = 12$), lower brainstem ($n = 11$), basal ganglia ($n = 9$), cerebellum ($n = 9$), midbrain ($n = 7$), and cortex ($n = 1$) (Khooshnoodi, Factor et al., 2013). A survey of secondary cervical dystonia found that structural lesions were most commonly localized to the brainstem and cerebellum, and fewer cases were in the cervical spinal cord and basal ganglia (LeDoux and Brady, 2003). A technique called “lesion network mapping” was applied to 39 cases found in the literature, with lesions in cerebellum, brainstem, and basal ganglia (Corp, Joutsa et al., 2019). The lesions could be mapped into a single network characterized with stronger connections, positive to the cerebellum and negative to the somatosensory cortex.

Turning now to primary dystonia, there have been few pathologic studies. The cases up to 1970 were reviewed by Zeman (1970), who also added his own cases; he concluded that whereas environmental causes leave their mark with alterations in the basal ganglia, the hereditary forms are without tangible pathologic abnormalities detectable by light microscopy. He thought that the earlier reports of positive findings could be explained as nonspecific alterations or as artifacts resulting from the agonal state before death.

Zweig and colleagues (1988) described the histology of the brainstem in four patients with primary dystonia. Two of them started in childhood or adolescence. One case had numerous neurofibrillary tangles (NFTs) in the LC, along with mild neuronal loss and extracellular neuromelanin. There were rare neurofibrillary tangles in the SN pars compacta (SNc), pedunculopontine nucleus (PPN), and dorsal raphe. There was no consistency of histologic findings in the cases. Bhatia and colleagues (1993b) found no abnormalities in a patient with orofacial dystonia and rest tremor.

McNaught and colleagues (2004) used special stains for a combination of ubiquitin, torsinA, and lamin in four brains of patients with Oppenheim dystonia (DYT1). Inclusions were present in the perinuclear region within brainstem cholinergic and other neurons in the PPN, cuneiform nucleus, and griseum centrale mesencephali. No inclusions were detected in the SNc, striatum, hippocampus, or selected regions of the cerebral cortex. McNaught and colleagues (2004) also noted tau/ubiquitin-immunoreactive aggregates in pigmented neurons of the SNc and LC. When this technique was applied to six adult-onset dystonia brains, the results were negative (Holton et al., 2008). Subsequent investigations of seven brains with DYT1 by Paudel and colleagues (2014) found no pathologic finding. In another study of six brains (four of which likely overlapped with those of Paudel and colleagues) that used all the stains that McNaught had used also found no pathologic features (Pratt, Mente et al., 2016). Moreover, cholinergic abnormalities were also sought with choline acetyltransferase (ChAT) staining, and none were found. It seems reasonable to conclude that there are no histologically identifiable hallmarks of primary generalized dystonia, at least DYT1 dystonia.

There are some pathologic studies of isolated cervical dystonia of unknown cause. Six brains were studied by Prudente and associates (2013). Although some of the brains showed that the SN had frequent ubiquitin-positive intranuclear inclusions known as Marinesco bodies, the only finding

that the authors deemed consistent was that the cerebellum showed patchy loss of Purkinje cells. Another study was done of eight brains focused on ChAT staining (Mente, Edwards et al., 2018). No abnormality was found in the putamen, but there was a marked loss in the PPN (in the six cases in which PPN was available for study) that could not be explained by cell loss or gliosis. More work is needed to replicate the findings in both of these studies.

There have been a large number of volumetric studies in dystonia of various types looking for where relevant lesions might be. The studies generally are inconsistent and suggest that most are underpowered and subject to type I errors. Some of these studies are noted here. In primary cervical dystonia, an increase in gray matter density bilaterally in the motor cortex and in the cerebellar flocculus and unilaterally in the right GPi was found by using voxel-based morphometry (Draganski et al., 2003). Voxel-based morphometry in patients with blepharospasm showed gray matter increase in the putamina bilaterally and decrease in the left inferior parietal lobule (Etgen et al., 2006). In writer's cramp, voxel-based morphometry found decreased gray matter in the hand area of the contralateral primary sensorimotor cortex and bilateral thalamus, and cerebellum (Delmaire et al., 2007). Obermann and colleagues (2007) evaluated voxel-based morphometry in patients with blepharospasm and cervical dystonia. They found that blepharospasm subjects had increased gray matter in the caudate head and cerebellum bilaterally and a decrease in the putamen and thalamus bilaterally. In cervical dystonia, they found increased gray matter in the thalamus, caudate head bilaterally, superior temporal lobe, and left cerebellum, whereas gray matter was decreased in the putamen bilaterally. One study assessed patterns of voxel-based morphometry in different types of primary dystonia: generalized dystonia, cervical dystonia, and focal hand dystonia and in age- and gender-matched controls. There was a common pattern of gray matter changes, namely gray matter volume increases bilaterally in the GPi, nucleus accumbens, and prefrontal cortex, and unilaterally in the left inferior parietal lobe (Egger et al., 2007). A voxel-based morphometry study showed a significant bilateral increase in gray matter in the hand representation area of primary somatosensory and, to a lesser extent, primary motor cortices in 36 patients with unilateral focal hand dystonia compared with 36 controls (Garraux et al., 2004). The presence of anatomical changes in the perirolandic cortex for the unaffected hand and the affected hand suggested to the investigators that these disturbances might be, at least in part, primary. A meta-analysis including 199 patients and 247 controls over different focal dystonias found gray matter volume to be greater in the caudate, postcentral cortex (BA2, 3, 40) and primary motor cortex and smaller in the thalamus and putamen (Zheng, Pan et al., 2012). More recent summaries of neuroimaging findings can be found in some reviews (Lehericy, Tijssen et al., 2013; Jinnah, Neychev et al., 2017; Simonyan, 2018). Using a deep learning algorithm with 392 patients who had three types of focal dystonia, it was possible to identify an abnormal pattern that was highly accurate in classifying patients from controls (Valeriani and Simonyan 2020). Abnormal areas were in corpus callosum, anterior and posterior thalamic radiations, inferior fronto-occipital fasciculus, and inferior temporal and superior orbital gyri.

Biochemistry

Some changes have been reported on postmortem biochemical analysis. Hornykiewicz and colleagues (1986) examined the biochemistry of the brain in two patients with childhood-onset generalized primary dystonia, and Jankovic and colleagues (1987) studied a single case of adult-onset primary cranial segmental dystonia. There were changes in norepinephrine, serotonin, and dopamine levels in various regions of brain. It is not clear which, if any, of these alterations is related to the pathophysiology of dystonia. In a patient with symptomatic dystonia as a result of neuroacanthocytosis, de Yebenes and colleagues (1988) found large increases in norepinephrine in caudate, putamen, globus pallidus, and dentate nucleus. Again, it is not clear whether norepinephrine is related to dystonia. More neurotransmitter studies need to be carried out.

A biochemical study investigating copper proteins in generalized dystonia found Wilson protein (ATP7B) and ceruloplasmin were increased in the lentiform nuclei in two patients with focal dystonia and reduced in the patient with generalized dystonia, and Menkes protein (ATP7A) was reduced in all three patients (Berg et al., 2000). Genetic analysis, however, has failed to find an alteration in the genes for the Menkes protein, the Wilson protein, or the intracellular copper chaperone, ATOX1, in patients with primary focal dystonia (Bandmann et al., 2002). In another biochemical study, plasma concentration of homocysteine was elevated in patients with generalized dystonia compared with age- and sex-matched controls (Muller et al., 2000).

In a study of platelet mitochondria, Benecke and colleagues (1992) found a defect in complex I in patients with primary dystonia, most of whom had cervical dystonia (DYT7). However, Reichmann and colleagues (1994) could not replicate this. Schapira and colleagues (1997) found that platelet complex I activity is normal in familial dystonia (including DYT1 dystonia) but is decreased in cervical dystonia.

Neuroimaging

As pointed out in the previous section, anatomical MRI can be used to try to define regions of the brain that might be abnormal. Using diffusion tensor MRI (DTI), the microstructure of white matter pathways can be assessed. Tract tracing also can be done, giving information about the connectivity between brain regions. DTI has been assessed in DYT1 mutation carriers and control subjects. Axonal integrity was found to be reduced in the subgyral white matter of the sensorimotor cortex of DYT1 carriers, and the changes were greater in manifesting than in nonmanifesting carriers (Carbon et al., 2004a). In a subsequent study, both DYT1 and DYT6 dystonic patients and nonmanifesting DYT1 carriers were evaluated. Both groups of dystonic patients had a significant reduction in fractional anisotropy in the pontine brainstem in the vicinity of the left superior cerebellar peduncle and bilaterally in the white matter of the subcortical sensorimotor region (Carbon et al., 2008b). Nonmanifesting DYT1 carriers showed only a slight reduction of fractional anisotropy compared with controls. Further analysis in DYT1 revealed reduced integrity of the proximal cerebello-thalamo-cortical

fiber tracts in both manifesting and nonmanifesting mutation carriers (Argyelan et al., 2009). In these subjects, reductions in cerebellothalamic connectivity correlated with increased motor activation responses, indicative of loss of inhibition at the cortical level. Nonmanifesting mutation carriers had an additional area of fiber tract disruption in the distal part of the tract, and clinical penetrance seemed to be determined by the difference in connectivity measured at proximal and distal sites. This team suggests that these circuit abnormalities are neurodevelopmental (Niethammer, Carbon et al., 2011).

DTI in patients with primary cervical dystonia and in patients with blepharospasm also has been carried out (Fabbrini et al., 2008). There were regional differences in patients with cervical dystonia and healthy controls, but no difference between patients with blepharospasm and controls.

FDG PET can evaluate focal magnitudes of metabolic activity. Eidelberg and colleagues (1995) evaluated FDG PET in 11 patients with predominantly right-sided DYT1 dystonia and 11 age-matched controls. They found that global and regional metabolic rates were normal, but the Scaled Subprofile Model analysis of the combined groups of patients and controls revealed a significant topographic profile characterized by relative bilateral increases in the metabolic activity of the lateral frontal and paracentral cortices, associated with relative covariate hypermetabolism of the contralateral lentiform nucleus, pons, and midbrain and decreased metabolism in the thalamus. Subject scores for this profile correlated significantly with Fahn–Marsden disease severity ratings. They subsequently called this the torsion dystonia-related pattern (TDRP). These findings were in contrast to PD, in which both lentiform nucleus and thalamus show increased metabolism. The presence of lentiform-thalamic metabolic dissociation suggests that in DYT1 dystonia hyperkinetic movements may arise through excessive activity of the direct putamino-pallidal pathway.

Eidelberg and colleagues in further studies with FDG PET found the TDRP in nonmanifesting DYT1 carriers (Eidelberg et al., 1998). They found a similar pattern in patients with blepharospasm (Hutchinson et al., 2000) and in patients with DYT6 (Trost et al., 2002). However, in other in patients with cervical dystonia, the pattern was broken because there was thalamic hypermetabolism (Galardi et al., 1996). The pattern was also broken in DYT6 patients who showed hypometabolism of the putamen (Carbon et al., 2004c).

PET can also be used to measure blood flow and can therefore be used to assess focal areas of brain active with tasks. Tempel and Perlmutter (1993) did such a study in patients with writer's cramp. Subjects had blood flow scans at rest and during vibration of either the affected or unaffected hand. Vibration produced a consistent peak response in the primary sensorimotor area and SMA, both contralateral to the vibrated hand. Both responses were significantly reduced approximately 25% in patients with writer's cramp whether the affected or unaffected hand was vibrated. This indicates that patients with unilateral writer's cramp have bilateral brain dysfunction. These investigators performed an analogous study in patients with blepharospasm (Feiwell et al., 1999) and found decreased blood flow in the primary sensorimotor cortical area, both ipsilateral and contralateral to the side of facial stimulation.

With movement in patients with idiopathic generalized dystonia, blood flow increased excessively in premotor cortex and SMA (Playford et al., 1998). Similar findings were seen in DYT1 manifesting, but not nonmanifesting, patients (Carbon et al., 2010). Such findings might well correlate with excessive movement in these patients. Blood flow PET has now largely been replaced by fMRI, and results with this technique will be discussed later.

PET also can be used to study neurotransmitters. Fluorodopa PET revealed mild reduction of uptake or normal uptake in different patients with hereditary generalized dystonia (Playford et al., 1993). Fluorodopa PET also shows a decrease of dopamine storage in patients with two focal dystonias, writer's cramp (Berman, Hallett et al., 2013), and spasmodic dysphonia (Simonyan, Berman et al., 2013).

Although there were some early contrary findings, PET scans using a ligand to bind to striatal dopamine D2 receptors shows decreased binding in the putamina (Perlmutter et al., 1997a; Todd and Perlmutter, 1998; Carbon et al., 2004b, 2009; Asanuma et al., 2005b). Interestingly, after the injection of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) into baboons, the animals transiently developed ipsilateral turning and contralateral hemidystonia involving arm and leg. This transient dystonia preceded hemiparkinsonism and corresponded temporally with a decreased striatal dopamine content and a transient decrease in D2-like receptor number (Perlmutter et al., 1997b). The animal model is consistent with the importance of the D2 findings in patients as being relevant in the genesis of dystonic movements. A caveat about decreased D2 receptors is one study with a highly selective D2 ligand that did not show a decrease, and the authors suggested that the apparent decrease with other ligands might be due to a decrease of D3 receptors that also bind other D2 ligands (Karimi, Moerlein et al., 2011).

Simonyan and associates (2013) looked at dopamine release in patients with spasmodic dysphonia using a special raclopride method, in which binding is measured at rest and then with action. With action, there should be dopamine release; then dopamine will compete with raclopride for binding, and the decreased binding will be a measure of the released dopamine. D2 binding was down at rest, and then dopamine release was also down with speaking but not with writing. Berman, and colleagues (2013) similarly studied patients with writer's cramp, found D2 receptors down at rest, but then decreased dopamine release with writing and not with speaking. The specificity of deficient dopamine release just related to the affected body part is certainly interesting.

Simonyan and associates (2017) also studied D1 receptor binding, and in both spasmodic dysphonia and writer's cramp, there is an increase in binding. Considering the D1 findings together with the D2 findings is suggestive of overactivity of the direct pathway and underactivity of the indirect pathway.

The physiologic findings of loss of inhibition suggested a possible abnormality of GABA function, and it is possible to assess GABA with neuroimaging. Levy and Hallett (2002) used magnetic resonance spectroscopy (MRS) to reveal GABA levels and found them decreased in sensorimotor cortex and lentiform nuclei contralateral to the affected hand in

patients with writer's cramp. Unfortunately, this could not be confirmed with a more sensitive MRS technique (Herath, Gallea et al., 2010). GABA MRS is likely not good enough to measure possible low levels in the brain. Another way of assessing GABA function is PET using flumazenil; this ligand binds to the GABA receptor. Several studies have now shown abnormalities in various types of dystonia typically decrease, but there are some increases (Garibotto, Romito et al., 2011; Berman, Pollard et al., 2018; Gallea, Herath et al., 2018).

Functional connections in brain can be studied with fMRI. A number of studies have been done at rest, which allows study of resting state networks. These studies show variable results but have been done on different patient populations and generally have had small numbers leading to possible type I errors. However, some areas are often found to be abnormal. In relation to patients with focal hand dystonia, most commonly writer's cramp, one study found a decrease in parietal-dorsal premotor connectivity (Delnooz, Helmich et al., 2012), another found decreased activity in the default mode network and SMA (Mohammadi, Kollewé et al., 2012), another a decline in the sensorimotor network and basal ganglia (Hinkley, Sekihara et al., 2013), and another a decrease in several connections from primary motor and sensory cortices, including to the basal ganglia (Dresel, Li et al., 2014). A larger group with multiple types of focal dystonias was subjected to graph theory analysis (Battistella, Termsarasab et al., 2017). This study found abnormalities in basal ganglia-thalamus-cerebellar networks, premotor area, sensorimotor area, and parietal area. A study with 58 patients with focal dystonias concluded that the critical abnormalities were in focal connections between basal ganglia and sensorimotor cortex or basal ganglia and parietal area, but not in whole brain network abnormality (Norris et al., 2020). Resting state connectivity studies also can be used to discriminate patients from controls (Battistella, Fuertinger et al., 2016). Another interesting finding from such studies in patients with laryngeal dystonia is that loss of connectivity between the sensorimotor area and parietal area correlates with the polygenic risk score for developing the disorder (Putzel, Battistella et al., 2018).

Functional activation can be examined during motor tasks. Although different tasks are done in each experiment, some common themes emerge. Studies are sometimes done in the asymptomatic hand of patients with focal hand dystonia. Although not itself dystonic, this has the advantage that dystonia will not develop during the task and complicate the analysis. Moreover, as the physiologic studies have shown, there are abnormalities in the asymptomatic limb. In one example of this, subjects learned a complex finger sequence (Zeuner, Knutzen et al., 2015). The anterior part of the right putamen showed decreased activity. In a study of the symptomatic hand in patients with task-specific writer's cramp, patients and controls did both writing and other tasks, looking for the isolated abnormality relating to writing in writer's cramp (Gallea, Horovitz et al., 2016). A specific abnormality was found—depressed activity and connectivity between parietal and ventral premotor areas. A nonspecific abnormality for all tasks was also found—depressed activity in the putamen. Similar themes were seen in resting state data reported earlier. Moreover, the abnormality in the connectivity between parietal and premotor areas can also be found in EEG studies

both at rest and during movement (Jin, Lin et al., 2011). In patients with writer's cramp, an LTD-like rTMS stimulation of the dorsal inferior parietal lobule could normalize their abnormal parietal-motor cortex interaction and their abnormal ventral premotor-motor cortex interaction, given further evidence to the importance of the parietal-motor interaction (Merchant et al., 2020). In an EEG study of writer's cramp, there was a task specific abnormality of alpha-coherence

between the bilateral sensorimotor regions only during writing (Thirugnanasambandam et al., 2020). This latter finding again indicates that there might well be an extended network of changes in dystonia (Conte et al., 2020).

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Treatment of dystonia

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Introduction

Despite paucity of knowledge about the cause and pathogenesis of dystonic disorders, the symptomatic treatment of dystonia has markedly improved, particularly since the introduction of botulinum toxin (BoNT). In most cases of dystonia, the treatment is merely symptomatic, designed to improve posture and function and relieve associated pain. In rare patients, however, dystonia can be so severe that it can produce not only abnormal postures and disabling dystonic movements, sometimes compromising respiration, but also muscle breakdown and life-threatening hyperthermia, rhabdomyolysis, and myoglobinuria. In such cases of dystonic storm or status dystonicus, proper therapeutic intervention can be life-saving (Jankovic and Penn, 1982; Jankovic, 2006, 2009a, 2013; Mariotti et al., 2007; Fasano et al., 2012; Thenganatt and Jankovic, 2013).

With advances in the understanding of the pathophysiology of dystonia, novel therapeutics are being developed and clinical trials must be appropriately designed to assess the safety and efficacy of the therapeutic intervention (Galpern et al., 2013). The assessment of various therapeutic interventions in dystonia is problematic for the following reasons: (1) Dystonia and its effects on function are difficult to quantitate, and thus most trials use crude clinical rating scales, many of which have not been properly evaluated or validated; (2) dystonia is a syndrome with different causes, anatomic distributions, and heterogeneous clinical manifestations producing variable disability; (3) some patients, perhaps up to 15%, may have spontaneous, albeit transient, remissions; (4) many studies have used dosages that may have been insufficient or too short a duration to provide benefit; (5) the vast majority of therapeutic trials in dystonia are not double-blind, placebo-controlled; and (6) most studies, have small sample sizes (Lindeboom et al., 1996).

The selection of a particular choice of therapy is guided largely by personal clinical experience and by empirical trials (Greene et al., 1988, 1995; Jankovic, 1997, 2004a, 2006, 2007, 2009, 2013; Brin, 1998; Albanese et al., 2006) (Table 12.1). An evidence-based review concluded that except for BTX in cervical dystonia and high-dose trihexyphenidyl in young patients with segmental and generalized dystonia (level A, class I-II), none of the methods of pharmacologic intervention have been confirmed as being effective according to evidence-based criteria (Balash and Giladi, 2004). The patient's age, the anatomic distribution of dystonia, and the potential risk for adverse effects are also important determinants of choice of therapy. The identification of a specific cause of dystonia, such as drug-induced dystonias or Wilson disease (Svetel et al., 2001), may lead to a treatment that is targeted to the particular cause. It is therefore prudent to search for identifiable causes of dystonia, particularly when some atypical features are present. The diagnostic approach to patients with dystonia is based on being aware of the multiple causes of torsion dystonia, which are covered in Chapter 11 and in other reviews (Fahn et al., 2011; Phukan et al., 2011; Albanese et al., 2013; Charlesworth et al., 2013).

Physical rehabilitation for dystonia

A variety of rehabilitation interventions have been proposed for focal dystonia. These include motor training, which has been applied mostly to task-specific dystonia, including writer's cramp and musician's dystonia. Although benefit has been shown in several studies, these are small studies with a low level of evidence (Prudente, Zetterberg et al., 2018). Other approaches have included constraint therapy, sensory reorganization, and biofeedback. The limitations of

Table 12.1 Medical therapy of dystonia

- Levodopa
- Anticholinergics
- Baclofen: oral, intrathecal
- Tetrabenazine
- Anticonvulsants (carbamazepine, pregabalin, levetiracetam)
- Muscle relaxants:
- Benzodiazepines (clonazepam, lorazepam, diazepam, alprazolam)
- Other relaxants (tizanidine, cyclobenzaprine, metaxalone, carisoprodol, methocarbamol, orphenadrine)
- Sodium oxybate (salt of gamma-hydroxybutyrate)
- Clozapine
- Botulinum toxin

studies of these various techniques included small sample sizes, lack of validated outcome measures, and lack of appropriate control conditions. A recent randomized study compared specialized versus standard neck physiotherapy in 110 cervical dystonia patients using a blinded rater assessment of the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) as the primary outcome. This study demonstrated that both interventions were effective after 4 weeks, but there was no difference between the two approaches. Further, given that all patients received an intervention, the outcome could have been secondary to placebo effects (Counsell, Sinclair et al., 2016). Although rehabilitation techniques have not been demonstrated to directly affect the severity of dystonia, this intervention may be a useful adjunct to other treatments, including BTX injections, to prevent contractures and improve range of motion (Boyce, et al., 2020).

Fitted braces designed primarily to improve posture and prevent contractures have been used. Although braces are often poorly tolerated, particularly by children, they may be used in some cases as a substitute for a sensory trick. For example, some patients with cervical dystonia are able to construct neck-head braces that seem to provide sensory input by touching certain portions of the neck or head in a fashion similar to the patient's own sensory trick, thus enabling the patient to maintain a desirable head position. However, many patients with cervical dystonia who have used rigid braces in an attempt to control neck movements find that these are painful and rarely lead to symptom relief.

Various hand devices have been developed in an attempt to help patients with writer's cramp use their hands more effectively and comfortably (Ranawaya and Lang, 1991; Tas et al., 2001). In one small study of five professional musicians with focal dystonia, Candia and colleagues (1999) reported success with immobilization by splints of one or more of the digits other than the dystonic finger followed by intensive repetitive exercises of the dystonia finger. It is not clear, however, whether this "constrained-induced" therapy provides lasting benefits. In one study of eight patients with idiopathic occupational focal dystonia of the upper limb, immobilization with a splint for 4 to 5 weeks resulted in a significant improvement at a 24-week follow-up visit, based on the Arm Dystonia Disability Scale (0 = normal; 3 = marked difficulty in playing) and the Tübiana and Champagne Score (0 = unable to play; 5 = returns to concert performances) and was considered marked in four and moderate in three, and the initial improvement disappeared in one (Priori et al., 2001). The splint was applied for 24 hours every

day except for 10 minutes once a week when it was removed for brief local hygiene. Immediately on full removal of the splint, all patients reported marked clumsiness and weakness, which resolved in 4 weeks. There was also some local subcutaneous and joint edema and pain in the immobilized joint, and nail growth stopped; none of the patients developed contractures. Although the mechanisms of action of immobilization is unknown, the authors have postulated that removing all motor and sensory input to a limb might allow the cortical map to "reset" to the previous normal topography. One major concern about immobilization of a limb, particularly a dystonic limb, is that such immobilization can actually increase the risk for exacerbating or even precipitating dystonia, as has been well demonstrated in dystonia after casting or other peripheral causes of dystonia (Jankovic, 2001a). In one study of 21 patients with writer's cramp, after 4 weeks of immobilization, "retraining" for 8 weeks using drawing and writing exercises was associated with significant improvement related to baseline as assessed by the Writer's Cramp Rating Scale (Zeuner et al., 2008). A variation of the immobilization therapy, constraint-induced movement therapy, has been used successfully in rehabilitation of patients after stroke and other brain insults, and the observed benefit has been attributed to cortical reorganization (Taub et al., 1999; Levy et al., 2001; Taub and Morris, 2001; Taub et al., 2002; Wolf et al., 2002; Berque et al., 2013).

Another technique, using a repetitive task during regional anesthesia of a weak arm in patients after a stroke, was also associated with improved hand function (Muellbacher et al., 2002). Some patients find various muscle relaxation techniques and sensory feedback therapy useful adjuncts to medical or surgical treatments. Some patients with dystonia have impaired sensory perception; therefore, it has been postulated that sensory training may relieve dystonia. In a study of 10 patients with focal hand dystonia, Zeuner and colleagues (2002) showed that reading Braille for 30 to 60 minutes daily for 8 weeks improved spatial acuity and dystonia that was sustained for up to 1 year in some patients (Zeuner and Hallett, 2003). Sensory training to restore sensory representation of the hand along with mirror imagery and mental practice techniques also has been reported to be useful in the treatment of focal hand dystonia (Byl and McKenzie, 2000; Byl et al., 2003). In one study of 54 pianists with musician's dystonia the following multiple therapies have been tried: retraining (87%), hand therapy (42%), relaxation techniques (38%), physiotherapy (30%), psychotherapy (23%), acupuncture (21%), and body techniques (21%); 81.5% reported improvement, 5.6% reported complete recovery, but only 43% had objective evidence of improvement in task-specific motor performance (Van Vugt et al., 2014).

Siebner and colleagues (1999) showed that using repetitive transcranial magnetic stimulation (rTMS) delivered at low frequencies (1 Hz or less) for 20 minutes can temporarily (8/16 patients reported improvement that lasted longer than 3 hours) improve handwriting impaired by dystonic writer's cramp, presumably by increasing inhibition (and thus reducing excitability) of the underlying cortex. Despite some encouraging results from open-label pilot studies, it remains to be seen whether rTMS or transcranial direct current stimulation (tDCS) will enter the mainstream of therapeutics of dystonia (Wu et al., 2008). Recent controlled studies have had variable findings likely resulting from differences in methodology (Erro et al., 2017).

Other modalities, including acupuncture as an adjuvant therapy combined with BTX, are currently being assessed in open-label studies. (Bega, Park et al., 2018)

Oral pharmacologic therapy

No oral medications for the treatment of dystonia have been approved by the U.S. Food and Drug Administration (FDA). Before the availability of BTX and globus pallidus internus (GPi) deep brain stimulation (DBS), many oral agents were given to patients because no other effective approach was available. Currently, medications are used most frequently in combination with other interventions (Termasarasab, Tham-mongkolchai et al., 2016). In a cross-sectional study of 2026 patients enrolled in the Dystonia Coalition Biorepository and Natural History project (Yan, Hicks et al., 2015) over a 4.5-year period (2011–2015), 17% were taking oral medications alone and 35% used both oral medications and BTX treatment. The benzodiazepines were the most frequently used and the dopaminergic antagonist the least. Patients with spasmodic dysphonia and limb dystonia were least likely to take oral medications. For generalized dystonia, anticholinergic agents were taken by 22% of patients; in contrast, 5% of patients with cervical dystonia and 3% of patients with blepharospasm were currently on this class of medication (Pirio Richardson, Wegele et al., 2017). Controlled assessments of efficacy for any oral agent is lacking, although in retrospective studies, clonazepam was found to be more effective (40%) than anticholinergics (20%) or baclofen (20%), (Woo et al., 2020). In fact, the response to any oral pharmacologic agent may depend on the subtype of dystonia. In one study, escitalopram tended to be of more benefit in those patients in whom binding was increased (Zoons et al., 2020)

Dopaminergic therapies

Dopamine agonists

Although there is some evidence of reduced striatal dopamine release in dystonia, such as writer's cramp (Berman et al., 2013), pharmacologic treatment of dystonia, including the use of levodopa and other dopamine agonists, is based largely on an empirical rationale rather than a scientific one. Although case reports of efficacy are published (Mangiardi and Alfano, 2020), no controlled trials in isolated dystonia are available. Unlike Parkinson disease (PD), in which therapy with levodopa replacement is based on the finding of depletion of dopamine in the brains of parkinsonian animals and humans, our knowledge of biochemical alterations in idiopathic dystonia is very limited. One exception is dopa-responsive dystonia (DRD), in which the biochemical and genetic mechanisms have been elucidated by molecular DNA and biochemical studies in patients (Ichinose et al., 1994) and by studies of postmortem brains (Furukawa et al., 1999). Decreased neuromelanin in the substantia nigra with otherwise normal nigral cell count and morphology and normal tyrosine hydroxylase immunoreactivity were found in one brain of a patient with classic DRD (Rajput et al., 1994). There was a marked reduction in dopamine in the substantia nigra and the striatum. These findings suggested that in DRD, the primary abnormality was a defect in dopamine synthesis. This proposal is supported by the finding of a mutation

in the GTP cyclohydrolase I gene on chromosome 14q that indirectly regulates the production of tetrahydrobiopterin, a cofactor for tyrosine hydroxylase, the rate-limiting enzyme in the synthesis of dopamine (Ichinose et al., 1994; Tanaka et al., 1995; Steinberger et al., 2000). Another form of DRD has been described in four cases belonging to two unrelated families of dopa-responsive cervical dystonia, presenting between 9 and 15 years of age and similar to classic DRD manifesting diurnal variation but no levodopa-induced dyskinesia (Schneider et al., 2006).

DRD usually manifests in childhood with dystonia, mild parkinsonian features, and pseudopyramidal signs (hyper-tonicity and hyperreflexia) predominantly involving the legs. Many patients have a family history of dystonia or PD. At least half of the patients have diurnal fluctuations, with marked progression of their symptoms toward the end of the day and a relief after sleep. Many patients with this form of dystonia are initially misdiagnosed as having cerebral palsy. Some patients with DRD are not diagnosed until adulthood, and family members of patients with typical DRD may present with adult-onset levodopa-responsive parkinsonism (Harwood et al., 1994). The take-home message from these reports is that a therapeutic trial of levodopa should be considered in all patients with childhood-onset dystonia, whether they have classic features of DRD or not. A trial of levodopa in adult-onset dystonia also has been recommended given the expanding phenotype of DRD, but the levodopa trial in dystonia remains controversial (Maas, Was-senberg et al., 2017; Fan, Donsante et al., 2018)

Most patients with DRD improve dramatically even with small doses of levodopa (100 mg of levodopa with 25 mg of decarboxylase inhibitor), but some might require doses of levodopa as high as 1000 mg per day. In contrast to patients with juvenile PD (Ishikawa and Miyatake, 1995), DRD patients usually do not develop levodopa-induced fluctuations or dyskinesias. If no clinically evident improvement is noted after 3 months of therapy, the diagnosis of DRD is probably in error, and levodopa can be discontinued. In addition to levodopa, patients with DRD also improve with dopamine agonists, anticholinergic drugs, and carbamazepine (Nygaard et al., 1991). In contrast to patients with DRD, patients with idiopathic or other types of dystonia rarely improve with dopaminergic therapy (Lang, 1988). Apomorphine, however, may ameliorate dystonia, perhaps by decreasing dopamine and serotonin release (Zuddas and Cianchetti, 1996).

Sepiapterin reductase deficiency (SRD) is a frequently underrecognized levodopa-responsive disorder, often misdiagnosed as cerebral palsy. In a study of 43 patients with SRD identified from 23 international medical centers, the average age at onset is 7 months, with delay to diagnosis of 9.1 years (Friedman et al., 2012). Clinical features included motor and language delays, oculogyric crises, diurnal fluctuation, axial hypotonia and limb hypertonia, dystonia, weakness, parkinsonism, hyperreflexia, mental retardation, psychiatric and/or behavioral abnormalities, autonomic dysfunction, sleep benefit, and sleep disturbances. Most patients benefit dramatically from levodopa/carbidopa, often with further improvement with the addition of 5-hydroxytryptophan. Typical cerebrospinal fluid findings: low 5-hydroxyindoleacetic acid (5-HIAA) and homovanillic acid (HVA) and elevated total biopterin, dihydrobiopterin (BH2), and sepiapterin. Diagnosis can be confirmed by mutation analysis and/or enzyme

activity measurement in cultured fibroblasts. Whole-genome sequencing of a 14-year-old fraternal twin pair diagnosed with DRD (Mendelian Inheritance in Man #128230) identified compound heterozygous mutations in the sepiapterin reductase (SPR) gene (Bainbridge et al., 2011). Disruption of SPR causes a decrease in tetrahydrobiopterin, a cofactor required for the hydroxylase enzymes that synthesize the neurotransmitters dopamine and serotonin. Supplementation of L-dopa therapy with 5-hydroxytryptophan, a serotonin precursor, resulted in clinical improvements in both twins. Also, sapropterin (Kuvan), a pharmaceutical formulation of the natural cofactor for PAH (6R-tetrahydrobiopterin; BH4), approved for the treatment of phenylketonuria, may be tried (Blau, 2013).

Dopamine antagonists

Although dopamine receptor-blocking drugs were used extensively in the past, most clinical trials have produced mixed results with these drugs. Because of the poor response and the possibility of undesirable side effects, particularly sedation, parkinsonism, and tardive dyskinesia, the use of these drugs in the treatment of dystonia should be discouraged (Jankovic, 1995; Waln and Jankovic, 2013). Clozapine, an atypical neuroleptic, has been reported in a small open trial to be moderately effective in the treatment of segmental and generalized dystonia, but its usefulness was limited by potential side effects (Karp et al., 1999). Although antidopaminergic drugs have been reported to be beneficial in the treatment of dystonia, the potential clinical benefit is usually limited by the development of side effects. Dopamine depleting drugs, such as tetrabenazine, however, have been found useful in some patients with dystonia, particularly those with tardive dystonia (Jankovic and Orman, 1988; Jankovic and Beach, 1997). Tetrabenazine, a vesicular monoamine transporter 2 (VMAT2) inhibitor, has the advantage over other antidopaminergic drugs in that it does not cause tardive dyskinesia, although it may cause transient acute dystonic reaction (Burke et al., 1985b; Jankovic and Beach, 1997; Kenney and Jankovic, 2006). Tetrabenazine is available in the United States, but it is dispensed by prescription under the trade name Nitoman or Xenazine 25 in other countries, including the United Kingdom. The more recently developed VMAT-2 inhibitors, such as velbenazine or deutetabenazine have not been evaluated. It is possible that some of the new atypical neuroleptic drugs will be useful not only as antipsychotics, but also in the treatment of hyperkinetic movement disorders.

Risperidone, a D2 dopamine receptor-blocking drug with a high affinity for 5HT₂ receptors, has been reported to be useful in a 4-week trial of five patients with various forms of dystonia (Zuddas and Cianchetti, 1996). Clozapine, a D4 dopamine receptor blocker with relatively low affinity for the D2 receptors and high affinity for the 5-HT_{2A} receptors, has been reported to ameliorate the symptoms of tardive dystonia (Trugman et al., 1994). The treatment of tardive dystonia and other tardive syndromes is discussed in another chapter and in other reviews (Jankovic, 1995b; Waln and Jankovic, 2013).

Anticholinergic therapy

High-dosage anticholinergic medications, such as trihexyphenidyl, for dystonia were introduced by Fahn (1983) and confirmed by several groups (Marsden et al., 1984;

Greene et al., 1988; Jabbari et al., 1989; Hoon et al., 2001), including a small double-blind study (Burke et al., 1986). Although helpful in all types of dystonias, the supremacy of BTX therapy for focal dystonias has relegated anticholinergic therapy to be most useful in the treatment of generalized and segmental dystonia. In the experience of Greene and colleagues (1988), patients with blepharospasm, generalized dystonia, tonic (in contrast to clonic) dystonia, and onset of dystonia at age younger than 19 years seemed to respond better to anticholinergic drugs than did other subgroups, but this difference did not reach statistical significance. Except for short duration of symptoms before onset of therapy, there was no other variable, such as gender or severity, that reliably predicted a favorable response. Treating patients within the first 5 years of disease onset was statistically significantly more successful than delaying treatment in both children and adults regardless of severity (Greene et al., 1988). Thus, starting treatment early is important. Children usually tolerate the very high dosages of anticholinergic drugs, whereas adults do not. In one study of 20 cognitively intact patients with dystonia, 12 could tolerate 15 to 74 mg/day of trihexyphenidyl. Side effects included drug-induced impairments of recall and slowing of mentation, particularly in older patients (Taylor et al., 1991). Other anticholinergic side effects include dry mouth, sedation, cognitive slowing, confusion, mydriasis, urinary retention, and constipation. Anticholinergics are contraindicated if patients have a history of narrow-angle glaucoma (Termsarasab, Thammongkolchai et al., 2016).

Diphenhydramine, a histamine-1 (H₁) antagonist with anticholinergic properties, has been reported to have an antidystonic effect in three of five patients (Truong et al., 1995). However, the drug was not effective in 10 other patients with cervical dystonia, and it was associated with sedation and other anticholinergic side effects in most patients. Pyridostigmine, a peripherally acting anticholinesterase, and pilocarpine (a muscarinic agonist) eye drops often ameliorate many of the peripheral side effects, such as urinary retention and blurred vision. Pilocarpine (Salagen) 5 mg four times per day, cevimeline (Evoxac) 30 mg three times per day and synthetic saliva (Biotene, Glandosane, Salix) have been found effective in the treatment of dry mouth.

Other pharmacologic therapies

Many patients with dystonia require a combination of several medications and treatments (Jankovic, 2004b, 2006). High-dosage oral baclofen appears to be the next most effective agent for dystonia, particularly in combination with high-dosage anticholinergic treatment. Baclofen, a GABA_B autoreceptor agonist, has been used to treat spasticity, but it also has been found to be beneficial in the treatment of dystonia. Substantial and sustained improvement with baclofen was reported in 29% of children at a mean dose of 92 mg/day (range: 40–180 mg/day) (Greene, 1992; Greene and Fahn, 1992a). Although baclofen was initially effective in 28 of 60 (47%) adults with cranial dystonia, 18% continued baclofen at a mean dose of 105 mg/day after a mean of 30.6 months (Fahn et al., 1985a). In a more recent study of cervical dystonia, of those on medications up to 20% reported some benefit (Woo et al., 2020). The observed improvement

in dystonia with baclofen provides evidence that GABA and GABA_B receptors play a role in pathophysiologic processes of dystonia, parkinsonism, and other disorders (Benarroch, 2012).

Benzodiazepines (diazepam, lorazepam, or clonazepam) may provide additional benefit for patients whose response to anticholinergic drugs is unsatisfactory. Clonazepam might be particularly useful in patients with myoclonic dystonia. Muscle relaxants that are useful in the treatment of dystonia include cyclobenzaprine (Flexeril, 30–40 mg/day), metaxalone (Skelaxin, 800 mg two to three times per day), carisoprodol (Soma), methocarbamol (Robaxin oral and patch), orphenadrine (Norflex), and chlorzoxazone (Parafon Forte). Structurally and pharmacologically similar to amitriptyline, cyclobenzaprine has been found at doses of 30 to 40 mg/day to be superior to placebo but equal to diazepam. Sodium oxybate, a salt of gamma-hydroxybutyrate (GHB), also has been reported to be effective in myoclonus–dystonia syndrome, similar to alcohol (Frucht et al., 2005). Zolpidem, an imidazopyridine agonist with a high affinity on benzodiazepine subtype receptor BZ1 (ω 1), was found to improve blepharospasm and other forms of dystonia at doses of 5 to 20 mg/day (Miyazaki et al., 2012).

Narayan and colleagues (1991) first suggested that intrathecal baclofen (ITB) might be effective in the treatment of dystonia in 1991 in a report of an 18-year-old man with severe cervical and truncal dystonic spasms who was refractory to all forms of oral therapy and to large doses of paraspinal BTX injections. Muscle-paralyzing agents were necessary to relieve these spasms, which compromised his respiration. Within a few hours after the institution of ITB infusion, the patient's dystonia markedly improved and he was able to be discharged from the intensive care unit within 1 to 2 days. Although there was a suggestion that ITB could benefit those with dystonia (Penn et al., 1995; Dressler et al., 1997; van Hilten, 1999), controlled studies have not been conducted. Ford and colleagues (1996) reviewed the experience with ITB in 25 patients and concluded that this form of therapy may be "more effective when dystonia is associated with spasticity or pain." ITB could have a role in selected patients with dystonic storm (Dalvi et al., 1998) and in secondary dystonias associated with pain and spasticity (Ford et al., 1998a). Albright and colleagues (1998) found improvement in dystonia scores in 10 of 12 patients with cerebral palsy using an average daily dose of ITB of 575 mcg; the improvement was sustained in 6 patients. In a subsequent study involving 86 patients ages 3 to 42 years (mean: 13 years) with generalized dystonia (secondary to cerebral palsy in 71% of patients), external infusion or bolus-dose screening was positive in approximately 90% of patients (Albright et al., 2001). Programmable pumps were implanted in 77 patients. Infusion began at 200 mcg/day and increased by 10% to 20% per day until the best dose was achieved. The median duration of ITB therapy was 26 months. The mean dose increased over time, from 395 mcg at 3 months to 610 mcg at 24 months to 960 mcg at 36 months. Patients and caregivers rated quality of life and ease of care as having improved in approximately 85% of patients. Seven patients, including four with cerebral palsy, lost their response to ITB during the study, usually during the first year. The most common side effects were increased constipation (19%), decreased neck and trunk control, and drowsiness. Surgical and device complications occurred in 38% of patients, including infections and catheter breakage and disconnection. Complication rates decreased over time. The authors conclude,

"In our opinion, ITB is the treatment of choice for severe, generalized secondary dystonia after oral medications have been shown to be ineffective." One potentially serious complication of ITB is life-threatening intermittent catheter leakage, which might not be detectable by standard noninvasive methods (Bar-dutzky et al., 2003).

ITB appears effective for the treatment of spasticity and secondary dystonia, in particular dystonic cerebral palsy (Ertzgaard, Campo et al., 2017). However, side effects are frequent. A retrospective study found that of 136 patients with ITB pumps for spasticity, 25% experienced complications. Most of these were procedure or device related and typically occurred with the first year after the procedure (Pucks-Faes, Hitzemberger et al., 2018). Sudden withdrawal may be life threatening (Coffey, Edgar et al., 2002).

Other medications are used in the treatment of dystonia. For example, slow-release morphine sulfate has been shown to improve not only pain, but also dystonic movement in some patients with primary and tardive dystonia (Berg et al., 2001). Besides clonazepam, GHB, used in the treatment of alcohol abuse, has been found to be beneficial in the treatment of myoclonus–dystonia syndrome (Priori et al., 2000). It is not known whether acamprosate, another drug that is used in the treatment of alcohol abuse, is useful in the treatment of myoclonus–dystonia. Anticonvulsants, such as levetiracetam (Keppra) and zonisamide (Zonegran), have been reported to be effective in the treatment of cortical myoclonus (Hainque et al., 2016), but it is not clear whether these drugs play a role in the treatment of dystonia. An open label trial in 10 patients with segmental and generalized dystonia showed no evidence of efficacy (Hering et al., 2008).

Mexiletine, an oral derivative of lidocaine, has been found to be effective in the treatment of cervical dystonia at doses ranging from 450 to 1200 mg/day (Ohara et al., 1998). Two-thirds of the patients, however, experienced adverse effects, including heartburn, drowsiness, ataxia, and tremor. On the basis of a review and a rating of videotapes by a "blind" rater, Lucetti and colleagues (2000) reported a significant improvement in six patients with cervical dystonia who had been treated with mexiletine.

Local electromyograph (EMG)-guided injection of phenol was investigated as a potential treatment of cervical dystonia but the results have not been very encouraging because of pain associated with the procedure and unpredictable response (Ruiz and Bernardos, 2000; Massey, 2002). This treatment has largely been abandoned. Chemomyectomy with muscle-necrotizing drugs, such as doxorubicin, has been tried in some patients with blepharospasm and hemifacial spasm (Wirtschafter, 1991), but because of severe local irritation, this approach will be adopted into clinical practice.

In addition to conventional forms of therapy described previously, many patients with dystonia seek complementary or alternative forms of therapy. In one survey of 180 members of the German Dystonia Group, 131 (73%) patients used some form of alternative treatments, such as acupuncture (56%), relaxation techniques (44%), homeopathy (27%), and massages (26%) (Junker et al., 2004).

The involuntary muscle contraction can lead to "status dystonicus" or "dystonic storm" resulting a breakdown of the muscle and a life-threatening myoglobinuria (Opal et al., 2002; Mariotti et al., 2007). In a review of 37 cases of status dystonicus or dystonic storm, the following treatment

approach has been used with some success: early admission to the intensive care unit, monitor for evidence of myoglobinuria, avoid respiratory and renal compromise, sedation with intravenous midazolam (initially up to 10 mcg/kg/min and subsequently at 30–100 mcg/kg/h), possible barbiturate anesthesia combined with endotracheal intubation and mechanical ventilation, continuous intrathecal baclofen, bilateral pallidotomy or GPi DBS (Mariotti et al., 2007; Jech et al., 2009). Although administration of propofol has been suggested, we would caution against it because this drug has been demonstrated to cause or exacerbate levodopa-related dyskinesia (Krauss et al., 1996). In one study of 89 episodes of status dystonicus occurring in 68 patients, 64.7% were males, 58.8% were younger than 15 years of age, and 37.8% had secondary dystonia; tonic phenotype, present in 68.5% cases predicted poor outcome (Fasano et al., 2012).

Botulinum toxin

The introduction of BTX into clinical practice in the late 1980s revolutionized treatment of dystonia. The most potent biologic toxin, BTX has become a powerful therapeutic tool in the treatment of a variety of neurologic, ophthalmic, and other disorders that are manifested by abnormal, excessive, or inappropriate muscle contractions (Jankovic and Brin, 1991; Jankovic and Hallett, 1994; Brin et al., 2002; Thant and Tan, 2003; Jankovic, 2004a). A review focuses on the advancements in BTX therapy (Jankovic, 2017). An evidence-based review of the use of BTX for movement disorders was published in 2008 (Simpson, Blitzer et al., 2008) and updated in 2016 (Simpson, Hallett et al., 2016). The review of evidence needs to be revised as new brands of BoNT, and new uses have been evaluated.

There are four commercially available brands of BTX: onabotulinumtoxinA (Botox, Allergan, Irvine, CA, United States), abobotulinumtoxinA (Dysport, Ipsen Ltd, Slough, United Kingdom), incobotulinumtoxinA (Xeomin), and rimabotulinumtoxinB (Myobloc, NeuroBloc). Each of these has demonstrated efficacy in cervical dystonia (Oral, 2020; Rodrigues et al., 2020).

In December 1989, after extensive laboratory and clinical testing, the FDA first approved onabotulinumtoxinA as a therapeutic agent in patients with strabismus, blepharospasm, and other facial nerve disorders, including hemifacial spasm. In December 2000 the FDA approved onabotulinumtoxinA and rimabotulinumtoxinB as treatments for cervical dystonia. Subsequently, the applications of BTX expanded greatly to include a variety of ophthalmologic, gastrointestinal, urologic, orthopedic, dermatologic, secretory, painful, and cosmetic disorders (Tintner and Jankovic, 2001b; Jankovic and Brin, 2002; Thant and Tan, 2003; Jankovic, 2004a) (Tables 12.2, 12.3, and 12.4).

Few therapeutic agents are better understood in terms of their mechanism of action or have had greater impact on patients' functioning than BTX. One of the major therapeutic values of BTX is its ability to cause chemodenervation and produce local paralysis when injected into a muscle.

There are seven immunologically distinct toxins that share structurally homologous subunits. Synthesized as single-chain polypeptides (molecular weight of 150 kDa), these toxin molecules have relatively little potency until they are cleaved by trypsin or bacterial enzymes into a heavy chain (100 kDa)

Table 12.2 Clinical applications of botulinum toxin

Focal dystonia

Blepharospasm
Lid apraxia
Oromandibular-facial-lingual dystonia
Cervical dystonia (torticollis)
Laryngeal dystonia (spasmodic dysphonia)
Task-specific dystonia (occupational cramps)
Other focal dystonias (idiopathic, secondary)
Other involuntary movements
Voice, head, and limb tremor
Palatal myoclonus
Hemifacial spasm tics

Inappropriate contractions

Strabismus
Nystagmus
Myokymia
Bruxism
Stuttering
Painful rigidity
Muscle contraction headaches
Lumbosacral strain and back spasms
Radiculopathy with secondary muscle spasm
Spasticity
Spastic bladder
Achalasia (esophageal, pelvicorectal)
Other spasmic disorders
Other potential applications
Protective ptosis
Cosmetic (wrinkles, facial asymmetry)
Debarking dogs
Other

and a light chain (50 kDa). The 150-kDa protein, the active portion of the molecule, complexes with one or more non-toxin proteins that support its structure and protect it from degradation. Type A is the only serotype that forms the 900-kDa complex. Types A, B, C1, and hemagglutinin-positive D form the 500-kDa complex and 300-kDa complex; types E, F, and hemagglutinin-negative D form only the 300-kDa complex (Melling et al., 1998). The three-dimensional structure of the BTX complex is known (Hanson and Stevens, 2002). When linked by a disulfide bond, these dichains exert their paralytic action by preventing the release of acetylcholine. This is a three-step process that involves binding to the acceptors on presynaptic membrane (C-terminus heavy chain), internalization (endocytosis) into a vesicle, transport of the light chain across the vesicle membrane into the neuron cytosol (N terminal-heavy chain) and subsequent cleavage of the SNARE (soluble N-ethylmaleimide-sensitive-factor attachment protein receptors) proteins by a zinc-dependent endopeptidase (light chain) (Pirazzini, Rossetto et al., 2017). The C terminal of the heavy chain of each BTX serotypes binds to different acceptors consisting of polysialoganglioside and vesicle protein, with more than one neuraminic acid residue. BTX-A has been found to enter neurons by binding to the synaptic vesicle protein SV2 (isoform C), which acts as the BTX-A receptor (Dong et al., 2006; Mahrhold et al., 2006). The neural membrane proteins synaptotagmin-I and -II act as receptors for BTX-B and for BTX-G (Mahrhold et al., 2006).

Table 12.3 Clinical applications for botulinum toxin

Dystonia	Pain	Gastrointestinal disorders
Blepharospasm*	Chronic migraine*	Gastroparesis
Hemifacial spasm*	Osteoarthritis	Delayed gastric emptying
Cervical dystonia*	Plantar fasciitis	Achalasia
Spasmodic dysphonia	Temporomandibular joint disorders	Anal fissures
Limb dystonia	Neuropathic pain	
Oromandibular	Lower back pain	Cosmetic
Strabismus*		Glabellar rhytides*
	Secretory disorders	Horizontal lines on the forehead*
Spasticity	Sialorrhea*	Lateral control lines (crow's feet)*
Upper limb	Rhinorrhea	Depressed brow Hypertrophic orbicularis oculi muscle
Lower limb	Frye syndrome	Rhytides from upper nasalis muscle contraction
	Axillary hyperhidrosis*	Nostril flare
Other neurologic disorders	Palmar hyperhidrosis	Drooping nasal tip
Tic disorders		Nasolabial folds
Tremor	Genital-vaginal disorders	Vertical period rtytides
Camptocormia	Detrusor over activity with/without neurologic	Mouth frown
Pisa syndrome	Pelvic pain	Gummy smile
Stuttering	Erectile dysfunction	Melomental folds (marionette lines)
Restless leg syndrome	Vulvodynia	Mental crease
Synkinesias	Vaginismus	Peau d'orange chin
Nystagmus		Masseteric hypertrophy
Bruxism		Horizontal neck line platysmal bands on the neck
Depression	Cardiac disorders	
	Atrial tachycardia/fibrillation	

Webb, 2018; Choudhury et al., 2021; Dressler, 2021).

Whereas the heavy chain of the toxin binds to the pre-synaptic cholinergic terminal, the light chain acts as a zinc-dependent protease that selectively cleaves proteins that are critical for fusion of the presynaptic vesicle with acetylcholine with the presynaptic membrane and release of acetylcholine. Thus, the light chains of BTX-A and BTX-E cleave synaptosome-associated protein (SNAP-25), a protein that is needed for synaptic vesicle targeting and fusion with the presynaptic membrane. The light chains of BTX, BTX-D, and BTX-F prevent the quantal release of acetylcholine by proteolytically cleaving synaptobrevin-2, also known as vesicle-associated membrane protein (VAMP), an integral protein of the synaptic vesicle membrane. BTX-C cleaves syntaxin, another plasma membrane-associated protein. A three-dimensional study showed that syntaxin 1a forms a complex with neuronal-Sec1, forming a recognition site for the arriving vesicle through a Rab protein and the subsequent formation of the syntaxin-VAMP-SNAP-25 complex promotes membrane fusion (Misura et al., 2000) (Fig. 12.1).

The BTX-A has been studied most intensely and used most widely, but the clinical applications of other types of toxins, including BTX-B, -E and -F, are also expanding (Greene and Fahn, 1992b; Mezaki et al., 1995; Sheean and Lees, 1995; Figgitt and Noble, 2002; Jankovic, 2004a). BTX-A is harvested from a culture medium after fermentation of a high-toxin-producing strain of *Clostridium botulinum* that lyses and liberates the toxin into the culture (Schantz and Johnson, 1992). The toxin is then extracted, precipitated, purified, and finally crystallized with ammonium sulfate. The crystalline toxin is diluted from milligram to nanogram concentrations, freeze-dried, and dispensed as a white powder in small vials containing 100 mouse units (U) of the toxin. When isolated from bacterial cultures, BTX is noncovalently associated with nontoxic macromolecules, such as hemagglutinin. These nontoxic proteins enhance toxicity by protecting the neurotoxin from proteolytic enzymes in the gut, but they apparently have no effect on the potency of the toxin if injected parenterally. There have been several clinical comparisons between toxin serotypes and brands.

Table 12.4 Properties of different types of botulinum toxin tested in clinical trials

	Botox (botulinum toxin type A)	Dysport (abobotulinumtoxin A)	Xeomin (botulinum toxin type A)	Prosigne (botulinum toxin type A)	Neuronox (botulinum toxin type A)	Myobloc/ NeuroBloc (botulinum toxin type B)
Manufacturer	Allergan, Inc., Irvine, CA, USA	Ipsen Ltd, Slough, Berks, UK	Merz Pharmaceuticals, Frankfurt am Main, Germany	Lanzhou Institute of Biological Products, Lanzhou, China	CJ Corp/Medytox, Inc., Seoul, South Korea	Elan Plc, Dublin, Ireland
BTX serotype	A	A	A	A	A	B
Strain	Hall A	Ipsen strain	Hall A	?	?	Bean B
Site of SNARE hydrolysis	SNAP-25	SNAP-25	SNAP-25	SNAP-25	SNAP-25	VAMP
Reconstituted pH	7.4	7.4	7.4	6.0	6.8	5.6
Other constituents (per vial)	HSA 500 mcg NaCl 900 mcg	HSA 125 mcg Lactose 2500 mcg	HSA 1 mg Sucrose 5 mg	Gelatin 5 mg Dextran 25 mg Sucrose 25 mg	HS 500 mcg NaCl 900 mcg	?
Product- specific units/ vial	100	500	100	100	100	$2.5/5.0/10.0 \times 10^9$
Protein weight/vial (mg)	4.5	4.3	0.6			50 (5000 units vial)

Noninferiority was demonstrated in a large study comparing onabotulinumtoxinA to incobotulinumtoxinA (Benecke, Jost et al., 2005). Comparisons of onabotulinumtoxinA to abobotulinumtoxinA have demonstrated variable results, mostly arising from the lack of a clear dose equivalency between these toxins (Rystedt, Nyholm et al., 2012; Rystedt, Zetterberg et al., 2015; Yun, Kim et al., 2015).

An in vivo study using injections into the extensor digitorum brevis in healthy volunteers suggested that the muscle paralysis from BTX-B was not as complete or long-lasting as that from BTX-A (Sloop et al., 1997). Whether M-wave amplitude is a reliable measure of clinical response and whether the doses of BTX-A (7.5–10 U) and BTX-B (320–480 U), with a B/A ratio of about 45:1, are comparable are debatable. However, direct comparisons of onabotulinumtoxinA to rimabotulinumtoxinB in cervical dystonia did not show significant differences in maximal benefit and only a potential mild difference in duration of effect (Comella, Jankovic et al., 2005) (Pappert, Germanson et al., 2008). More recently, studies have suggested that abobotulinumtoxinA may have a more prolonged effect (Esquenazi et al., 2020, Fasano et al., 2020).

In addition to the brand of BTX currently available, a new formulation of BTX-A is currently undergoing clinical trials. DaxibotulinumtoxinA (Revance Therapeutics Inc., Newark, CA, United States), is a purified BTX without accessory proteins. It is formulated with a stabilizing excipient peptide that is noncovalently associated with BTX-A. This peptide prevents the adsorption of daxibotulinumtoxinA to the surface of the vial and stabilizes the activity of the toxin for a prolonged period within the neuron. In an open label dose escalation study in 33 subjects with cervical dystonia, the efficacy

was similar to that of other toxins, but the mean duration of effect was 25 weeks (Jankovic, Truong et al., 2018). A controlled trial of daxibotulinumtoxinA is currently being done.

IncobotulinumtoxinA (Merz) is free of complexing proteins, has been reported to be equivalent, in terms of efficacy and safety, to Botox in healthy volunteers and in patients with blepharospasm (Roggenkamper et al., 2006; Jankovic, 2009b) and cervical dystonia (Benecke et al., 2005). Although low antigenicity has been predicted with this new formulation of BTX, no long-term data exist, and in view of the low frequency of blocking antibodies reported with the new formulation of Botox (see later) (Jankovic et al., 2003; Brin et al., 2008; Naumann et al., 2010; Ramirez-Castaneda et al., 2013a). It may be that botulinum toxins without complexing proteins are associated with less antibody formation, but the clinical implications of this are not clear (Heftner et al., 2020; Walter et al., 2020).

Patients resistant to BTX-A often initially respond to BTX-B, but a 2006 study showed that continued treatment with MYOBLOC is associated with a high incidence of blocking antibodies (Jankovic et al., 2006).

The primary effect of BTX-B is to induce paralysis of injected skeletal muscles, especially the most actively contracting muscles. BTX paralyzes not only the extrafusal fibers, but also the intrafusal fibers, thus decreasing the activity of Ib muscle afferents (Filippi et al., 1993). This might explain the effect of BTX on reciprocal inhibition. In untreated patients with dystonia, the second phase of reciprocal inhibition is usually decreased. BTX “corrects” the abnormal reciprocal inhibition by increasing the second phase, possibly through its effect on the muscle afferents (Priori et al., 1995). Although the effect on intrafusal fibers might contribute in part to the beneficial

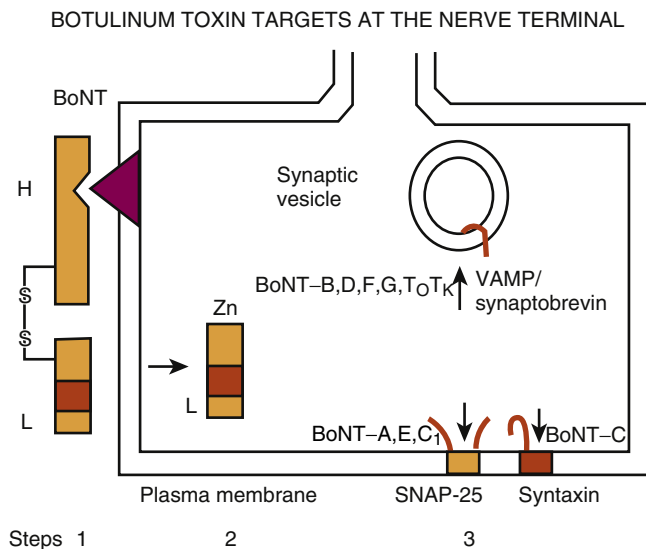


Fig. 12.1 Mechanism of action of botulinum toxin (BoNT). (Redrawn from Jankovic J. Botulinum toxin in clinical practice. *J Neurol Neurosurg Psychiatry*. 2004;75:951–957.)

Table 12.5 Risk factors for development of blocking antibodies (immuno-resistance)

- The dose (protein load) per treatment session
- The total cumulative dose
- Antigenicity of the botulinum toxin drug
- Frequency of exposure (interdose interval)
 - Booster injections
- History of immuno-resistance
- Cross-reactivity
- Individual (genetic) characteristics
 - Possible: Female gender, younger age

Table 12.6 Long-term effects of repeat botulinum toxin injections in cervical dystonia

- 326 were enrolled (mean age 50.1 years; 69.9% female) and 77% (251/326) completed the study
- Mean dose per session: 148.4 to 213.0 units
- Median 9 treatments over a mean of 2.5 years (3.2 months to 4.2 years)
- Adverse events: Weakness, dysphagia, neck pain, and injection pain
- Only 4 of 326 subjects (1.2%) had at least one positive antibody assay result
- Conclusions: BTX-A treatment is safe and effective for the chronic treatment of cervical dystonia. The current formulation of BTX-A rarely causes neutralizing antibodies in cervical dystonia subjects treated for up to 4 years

From Brin MF, Comella CL, Jankovic J, Lai F, Naumann M; CD-017 BoNTA Study Group. Long-term treatment with botulinum toxin type A in cervical dystonia has low immunogenicity by mouse protection assay. *Mov Disord*. 2008;23:1353–1360.

action of BTX in patients with dystonia, this is not its main action. BTX is effective in facial dystonia, even though the facial muscles do not have spindles.

Measuring variations in fiber diameter and using acetylcholine-esterase staining as indexes of denervation, Borodic and colleagues (1994) showed that BTX diffuses up to 4.5 cm from the site of a single injection (10 units injected

in the rabbit longissimus dorsi). Although BTX activity is focused at the neuromuscular junction, injection near motor endplates would be the most effective. Because the size of the denervation field is determined largely by the dose (and volume), multiple injections along the affected muscle rather than a single injection should therefore contain the biologic effects of the toxin in the targeted muscle (Borodic et al., 1992). Blackie and Lees (1990) also showed that frequency of dysphagia could be reduced by 50% when multiple rather than single injections are used.

With repeated injections being necessary for maintained benefit, there is a concern that patients can develop antibodies to BTX. With the early use of BTX as Botox, immuno-resistance was reported in up to 10% of patients receiving repeated injections (Greene et al., 1994) (see Tables 12.5 and 12.6). In this retrospective analysis, the investigators identified factors associated with the development of resistance, including higher doses of BTX, more frequent injections, with more “booster” injections at 2 to 3 weeks after initial injection. Based on these findings, the recommendations were to inject as infrequently as possible using the lowest doses and to avoid booster injections. However, this and other studies included a preparation of BTX-A that was initially prepared in 1977 and contained 25 ng of neurotoxin complex. Using new manufacturing practices, subsequently immuno-resistance was found to be much reduced. With repeated injections in 221 CD patients over periods of 2 to 21 years, neutralizing antibodies occurred in 14.6% of patients. However, despite the presence of these antibodies, the patients continued to respond. (Hefter, Rosenthal et al., 2016). In one study, botulinum toxin neutralizing antibodies were demonstrated in 13.9% of patients on long term treatment (Albrecht, et al., 2019). However, whether the presence of the antibody has implications on clinical benefit is controversial (Hefter et al., 2019).

The original preparation of Botox contained 25 ng of neurotoxin complex protein per 100 units, but in 1997, the FDA approved a new preparation that contains 5 ng per 100 units, which should have lower antigenicity (Aoki et al., 1999). In fact, in a 3-year follow-up of patients treated with the current Botox, no evidence of blocking antibodies was found, compared with a 9.4% frequency of blocking antibodies in patients treated with the original Botox for the same period (Jankovic et al., 2003). The low antigenicity of the current Botox is also supported by the findings from a longitudinal, multicenter study in which de novo subjects were treated with Botox and 4 in 326 (1.2%) subjects tested positive for antibodies by the mouse protective assay during the course of up to 15 cycles of treatment (Brin et al., 2008) (see Table 12.6). In the CD 140 study, which used onabotulinumtoxinA (original Botox), after a 10-week open-label study involving 214 subjects, 170 were randomized to onabotulinumtoxinA (N = 88) or placebo (N = 82) in a 10-week double-blind study (Charles et al., 2012). The primary outcome measures were the Cervical Dystonia Severity Scale (CDSS) and the physician Global Assessment Scale (GAS) at week 6. OnabotulinumtoxinA produced significantly greater improvements than CDSS (−1.81 versus −0.31 points; $P = 0.012$) and GAS (61.7% versus 41.6% improved; $P = 0.022$). Two subjects seroconverted from neutralizing antibody (nAb) negative at baseline to nAb positive at study exit but apparently remained responsive to onabotulinumtoxinA during

both the open and blinded treatment periods, suggesting the possibility of a placebo effect or low Ab titer. Rhinitis and treatment-related dysphagia were reported significantly more frequently with onabotulinumtoxinA than placebo.

The preliminary data suggest that rimabotulinumtoxinB provides clinical effects similar to those of onabotulinumtoxin, but the duration of benefits is shorter (Comella et al., 2005), although a second study comparing effects in denovo CD did not find this difference in duration (Pappert, Germanson et al., 2008). Rimabotulinumtoxin appears to have greater antigenicity than onabotulinumtoxinA, particularly in patients with prior resistance to BTX-A (Jankovic et al., 2007). To compare autonomic effects of BTX, Tintner and colleagues (2005) randomized patients with cervical dystonia to receive either BTX-A or BTX-B in a double-blind manner. Efficacy and physiologic questionnaire measures of autonomic function were assessed at baseline and 2 weeks after injection. Patients who were treated with BTX-B had significantly less saliva production ($P < 0.01$) and greater severity of constipation ($P = 0.037$) than did those treated with BTX-A but did not differ with respect to other tests of autonomic function, including changes in blood pressure, heart rate, and ocular function. The autonomic effects of BTX-B were reviewed in several additional reports (Wan et al., 2005).

The duration of effect of BTX may be influenced by a variety of factors. Increased effect is demonstrated with proximity of the injection near the motor endplate. The uptake of BTX is affected by temperature and activity. Lower temperatures reduce the uptake, and increased activity of the injected muscles promotes uptake. Hence, ice packs before injection may impede effects, and in those with occupational dystonias, having them perform the task after the injection may increase the effect (Hallett, 2015). Although the light chain is a zinc-dependent endopeptidase, supplementing with zinc before injection may improve outcomes, although this has not been firmly established (Koshy, Sharabi et al., 2012).

Many clinical studies have provided evidence not only that BTX is safe and effective, but also that this therapy leads to meaningful improvements in quality of life (Jankovic et al., 2004; Naumann and Jankovic, 2004), and the benefits are long-lasting (Mejia et al., 2005) (Video 12.1). Several studies have evaluated the effects of repeated injections of BTX. Despite its proven therapeutic value, there are still many unresolved issues and concerns about BTX. These include lack of standardization of biologic activity of the different preparations of BTX, poor understanding of toxin antigenicity, variations in the methods of injection, and inadequate assays for BTX antibodies (Brin et al., 2008). Training guidelines for the use of BTX have been established (American Academy of Neurology, 1994). Clinicians who are interested in using BTX chemodenervation in their practice must be aware of these concerns and must exercise proper precautions to minimize the potential risks associated with BTX. Most importantly, they should become thoroughly familiar with the movement disorders that they intend to treat and with the anatomy at the injection site. Possible contraindications to the use of BTX include the presence of myasthenia gravis (Emerson, 1994), Eaton-Lambert syndrome, motor neuron disease, aminoglycoside antibiotics, and pregnancy. ▶

Although BTX has been clearly demonstrated to be safe and effective, 20% to 40% of patients stop the treatment for a variety of reasons, including unsatisfactory outcomes,

which are most likely the result of suboptimal BTX doses, wrong muscles selected for injection, intolerable side effects, complex movement patterns, discordant perceptions, and incorrect diagnosis (Jankovic et al., 2015; Jinnah et al., 2016; Jinnah et al., 2018). Further, the waxing and waning of treatment benefit during the treatment interval (yo-yo effect) may also be an issue (Comella et al., 2021). The treatment of many of the focal dystonias requires expertise in the movement disorder and the ability to target the appropriate muscles (Nijmeijer, Koelman et al., 2012, 2013). Besides occasional complications, usually related to local weakness, a major limitation of BTX therapy is its high cost. Several studies analyzing the cost-effectiveness of BTX treatment, however, have demonstrated that the loss of productivity as a result of untreated dystonia and the cost of medications or surgery more than justify the financial expense of BTX treatments. It is likely that future research will result in the development of new, more effective neuromuscular blocking agents that provide therapeutic chemodenervation with long-term benefits and at lower cost.

Blepharospasm

The effectiveness of BTX in blepharospasm was first demonstrated in double-blind, placebo-controlled trials (Fahn et al., 1985b; Jankovic and Orman, 1987). In a subsequent report of experience with BTX in 477 patients with various dystonias and hemifacial spasm, Jankovic and colleagues (1990) reviewed the results in 90 patients who had been injected with BTX for blepharospasm. Moderate or marked improvement was noted in 94% of the patients. The average latency from the time of the injection to the onset of improvement was 4.2 days; the average duration of maximum benefit was 12.4 weeks, but the total benefit lasted considerably longer—an average of 15.7 weeks. Although 41% of all treatment sessions were followed by some side effects (ptosis, blurring of vision or diplopia, tearing, and local hematoma), only 2% of these affected patient's functioning. Complications usually improved spontaneously in less than 2 weeks. These results are consistent with those of other studies (Elston, 1994). There is no apparent decline in benefit, and the frequency of complications actually decreases after repeat BTX treatments (Jankovic and Schwartz, 1993a).

The efficacy and safety of another type of BTX-A, incobotulinumtoxinA (or Xeomin), in the treatment of blepharospasm was also confirmed by a prospective, double-blind, placebo-controlled, randomized, multicenter study involving 109 patients (mean total dose of Xeomin per treatment visit was 64.8 units), the Jankovic Rating Scale (JRS) severity subscore was significantly reduced compared with placebo ($P < 0.001$). The most commonly reported adverse effects related to Xeomin versus placebo were eyelid ptosis (18.9 versus 8.8%), dry eye (16.2 versus 11.8%), and dry mouth (16.2 versus 2.9%) (Jankovic, 2009b; Jankovic et al., 2011). In a multicenter, clinical, fixed-dose trial, Dysport (40, 80, and 120 units/eye) or placebo (in a 3:1 randomization ratio) were administered to 119 patients with blepharospasm, 85 of whom completed the 16-week follow-up, several parameters showed robust improvement in Dysport arms compared with placebo (Truong et al., 2008). A comparative study assessed incobotulinumtoxinA against onabotulinumtoxinA in a randomized study of 65 patients with blepharospasm.

Video 12.1 Botulinum toxin in cranial dystonia.

Both toxins reduced the BSDI and the JRS without a significant difference between drugs (Wabbels, Reichel et al., 2011).

In addition to the four different BTX-A preparations available on the market in one or more countries, Botox, Dysport, Xeomin (Merz Pharmaceuticals, Frankfurt am Main, Germany), and Prosigne (Lanzhou Biological Products, Lanzhou, China), Meditoxin (Medytox, Seoul, South Korea [also known as Neuronox]) was introduced for the treatment of BTX-A and is currently available in South Korea (Yoon et al., 2009). All of these types were evaluated in blepharospasm and were found to be comparable with respect to clinical efficacy and adverse effects (Bilyk, Yen et al., 2018).

Reasons for the gradual enhancement in efficacy and reduction in the frequency of complications with repeat treatments include greater experience and improvements in the injection technique. For example, one controlled study showed that an injection into the pretarsal rather than preseptal portion of the orbicularis oculi is associated with significantly lower frequency of ptosis (Jankovic, 1996). Ptosis can be prevented also by injecting initially only the lateral and medial portions of the upper lid, thus avoiding the midline levator muscle. We usually initially inject 5 units in each site in the upper lid and 5 units in the lower lid laterally only. This finding has been confirmed by others (Cakmur et al., 2002).

The functional improvement experienced by the vast majority of patients after BTX injection is difficult to express numerically. Many patients could not work, drive, watch television, or read before the injections. As a result of reduced eyelid and eyebrow spasms, most can now function normally. In addition to the observed functional improvement, there is usually a meaningful amelioration of discomfort, and because of less embarrassment, the patients' self-esteem also frequently improves. BTX injections are now considered by many to be the treatment of choice for blepharospasm (American Academy of Ophthalmology, 1989; American Academy of Neurology, 1990). In addition to idiopathic blepharospasm, BTX injections have been used effectively in the treatment of blepharospasm induced by drugs (e.g., levodopa in parkinsonian patients or neuroleptics in patients with tardive dystonia), dystonic eyelid and facial tics in patients with Tourette syndrome, and blepharospasm associated with apraxia of eyelid opening (Jankovic, 1994, 1996; Aramideh et al., 1995; Lepore et al., 1995; Forget et al., 2002).

In a pilot double-blind, placebo-controlled, randomized trial, daily topical application of acetyl hexapeptide-8 (AH8), a competitive SNAP-25 inhibitor AH8, in 24 patients with blepharospasm, there was a trend for longer time until return to baseline as assessed by the Jankovic Blepharospasm Rating Scale (JBRS) after injection in the active group compared with placebo (3.7 versus 3.0 months) and for better scores in the active group (Lungu et al., 2013). Although only an exploratory study, topical AH8 was considered "safe and promising for extending the duration of action of BoNT."

Oromandibular dystonia

Oromandibular dystonia is among the most challenging forms of focal dystonia to treat with BTX (Blitzer et al., 1989; Charous et al., 2011); it rarely improves with medications, there are no surgical treatments, and BTX therapy can be

complicated by swallowing problems. A systematic review of the use of BTX for treatment of oromandibular dystonia noted that higher level evidence is still needed for this disorder (Comella, 2018). The masseter muscles are usually injected in patients with jaw-closure dystonia; in patients with jaw-opening dystonia, either the submental muscle complex or the lateral pterygoid muscles are injected. In a total of 91 patients treated in 271 visits, the overall improvement was rated as 2.6 (0 = no response to 4 = marked improvement in spasms and function) (Jankovic and Schwartz, 1991b). A meaningful reduction in the oromandibular-lingual spasms and an improvement in chewing and speech were achieved in more than 70% of patients. The improvement was noted within an average of 5.5 days after injection and lasted an average of 11.5 weeks. Patients with dystonic jaw closure responded better than those with jaw-opening dystonia. Temporary swallowing problem, noted in fewer than one-third of patients and in 17% of all treatment sessions, was the most frequent complication. Early treatment with BTX may prevent dental and other complications, including temporomandibular joint syndrome and other oral and dental problems (Blitzer and Brin, 1991; Charous et al., 2011). BTX can provide lasting improvement not only in patients with primary (idiopathic) dystonia but also in orolingual-mandibular tardive dystonia (Waln and Jankovic, 2013). Clenching and bruxism are frequent manifestations of oromandibular dystonia, although nocturnal and diurnal bruxism can occur even without evident dystonia (Tan and Jankovic, 1999, 2000). Oromandibular involuntary movements caused by hemimasticatory spasms and other disorders such as Satoyoshi syndrome also have been successfully treated with BTX (Merello et al., 1994; Yaltho and Jankovic, 2011).

Laryngeal dystonia (spasmodic dysphonia)

Until the introduction of BTX, the therapy of spasmodic dysphonia was disappointing. The anticholinergic and benzodiazepine drugs only rarely provide meaningful improvement in voice quality. Unilateral transection of the recurrent laryngeal nerve, although effective in most patients, frequently causes unacceptable complications, and the voice symptoms often recur (Dedo and Izdebski, 1983). A surgical procedure that involves denervation of the adductor branch of the recurrent laryngeal nerve with reinnervation of the distal stumps with branches of the ansa cervicalis nerve was reported to produce marked improvement in patients with adductor spasmodic dysphonia (Berke et al., 1999), but further studies are needed to confirm this initial observation.

Several studies have established the efficacy and safety of BTX in the treatment of laryngeal dystonia, and this approach is considered by most to be the treatment of choice for spasmodic dysphonia (Brin et al., 1987; Blitzer et al., 1987; Jankovic et al., 1990; Brin et al., 1992; Ludlow, 1992; Brin et al., 1998; Blitzer et al., 2002). Before a patient can be considered a potential candidate for BTX injections, the diagnosis of spasmodic dysphonia must be confirmed by detailed neurologic, otolaryngologic, and voice assessment and documented by video and voice recordings.

Three approaches are currently used in the BTX treatment of spasmodic dysphonia: (1) unilateral EMG-guided injection of 5 to 30 units (Jankovic et al., 1990); (2) bilateral

approach, injecting with EMG-guidance 1.25 to 4 units in each vocal fold (Brin et al., 1992); and (3) an injection via indirect laryngoscopy without EMG (Ford et al., 1990). Irrespective of the technique, most investigators report about 75% to 95% improvement in voice symptoms. One controlled study, however, concluded that unilateral injections “may provide both superior and longer lasting benefits” than bilateral injections (Adams et al., 1993). The dosage can be adjusted depending on the severity of glottal spasms and the response to previous injections. Adverse experiences include transient breathy hypophonia, hoarseness, and rare dysphagia with aspiration.

Although more complicated and less effective, BTX injections into the posterior cricoarytenoid muscle with the EMG needle placed posterior to the thyroid lamina may be used in the treatment of the abductor form of spasmodic dysphonia (Brin et al., 1989, 1992). Using a multidisciplinary team approach, consisting of an otolaryngologist who is experienced in laryngeal injections and a neurologist who is knowledgeable about motor disorders of speech and voice, BTX injections can provide effective relief for most patients with spasmodic dysphonia (American Academy of Neurology, 1990; American Academy of Otolaryngology, 1990). Outcome assessments clearly show that BTX injections for spasmodic dysphonia produce measurable improvements in the quality of life of patients with this disorder (Courey et al., 2000). BTX may be useful in the treatment of voice tremor and stuttering, but the results are less predictable (Ludlow, 1990; Brin et al., 1994; Warrick et al., 2000).

Cervical dystonia

The goal of therapy of cervical dystonia is to improve abnormal posture of the head, alleviate pain related to cervical dystonia, improve range of motion and to prevent the development of secondary complications such as contractures, cervical radiculopathy, and cervical myelopathy (Treves and Korczyn, 1986; Waterston et al., 1989).

With the use of the TWSTRS and other scales, the efficacy and safety of BTX in the treatment of cervical dystonia have been demonstrated in several controlled and open trials (Greene et al., 1990; Jankovic and Schwartz, 1990; Poewe et al., 1992; Jankovic et al., 1994; Tintner and Jankovic, 2001b; Jankovic, 2002, 2004c; Truong et al., 2005; Brin et al., 2008) (Video 12.2, 12.3). In one double-blind, placebo-controlled study of 55 patients with cervical dystonia, 61% improved after BTX-A injection (Greene et al., 1990). BXT has been found to be superior not only to placebo, but also to trihexyphenidyl (Brans et al., 1996). In a study of 66 consecutive patients with idiopathic cervical dystonia, Brans and colleagues (1996) compared the effectiveness of abobotulinumtoxinA with that of trihexyphenidyl in a prospective, randomized, double-blind design. AbobotulinumtoxinA or saline were injected under EMG guidance at study entry and again after 8 weeks. Patients were assessed for efficacy at baseline and after 12 weeks by different clinical rating scales. A total of 64 patients completed the study, 32 in each group. The mean dose of BTX-A was 292 units (first session) and 262 units (second session). The mean dose of trihexyphenidyl was 16.25 mg. TWSTRS (primary outcome) and other scales showed a significant improvement in favor of BXT-A, and adverse effects were significantly less frequent than in the

group of patients randomized to trihexyphenidyl. In a multicenter, double-blind, randomized, controlled trial assessing the safety and efficacy of abobotulinumtoxinA in cervical dystonia patients, 80 patients were randomly assigned to receive one treatment with abobotulinumtoxinA (500 units) or placebo (Truong et al., 2005). abobotulinumtoxinA was significantly more efficacious than placebo at weeks 4, 8, and 12 as assessed by TWSTRS (10 point versus 3.8 point reduction in total score, respectively, at week 4; $P \leq 0.013$). Of participants in the abobotulinumtoxinA group, 38% showed positive treatment response, compared with 16% in the placebo group (95% confidence interval [CI], 0.02–0.41). The median duration of response to abobotulinumtoxinA was 18.5 weeks. Side effects were generally similar in the two treatment groups; only blurred vision and weakness occurred significantly more often with abobotulinumtoxinA. No participants in the abobotulinumtoxinA group converted from negative to positive antibodies after treatment. These results confirm previous reports that abobotulinumtoxinA (500 units) is safe, effective, and well tolerated in patients with cervical dystonia. ▶

IncobotulinumtoxinA has been evaluated in a double-blind, placebo-controlled study using placebo and incobotulinumtoxinA at 120 and 240 units. There were 233 cervical dystonia patients included. The primary outcome at week 4 after injection demonstrated improvement in CD with a decrease in total TWSTRS score for the active drug groups. Likewise, subscales including motor severity, disability, and pain were improved. Patient and investigator global assessments likewise showed significant improvement. Side effects included mild dysphagia, neck pain, and weakness (Comella, Jankovic et al., 2011).

Open-label studies generally report a more dramatic improvement, partly because of a placebo effect and, more important, because of greater flexibility in selecting the proper dosage and site of injection. Most trials report that about 90% of patients experience improvement in function and control of the head and neck and in pain. The average latency between injection and the onset of improvement (and muscle atrophy) is 1 week, and the average duration of maximum improvement is 3 to 4 months. The Cervical Dystonia Patient Registry for Observation of OnabotulinumtoxinA Efficacy (CD PROBE), a prospective, observational, multicenter, trial was designed to study a real-world experience in the BTX treatment of cervical dystonia (Jankovic et al., 2015). Subjects were naive to BTX, new to practice, or had not received toxin in 16 weeks or longer if in a clinical trial. Of the 1046 subjects enrolled, 74.4% were female and the mean age was 58.0 ± 14.7 years. The mean dose over 2481 treatment sessions was 189.8 ± 87.1 units, with average treatment intervals of 14.6 and 15.1 weeks. The mean TWSTRS total score in subjects who completed all assessments ($n = 479$) decreased from 39.2 at baseline to 27.1 at final visit ($P < 0.0001$). A high percentage of physicians reported improvement in Clinician Global Impression of Change: 95.0% at final visit and a high percentage of subjects reported improvement in Patient Global Impression of Change: 91.7% at final visit. Significant reductions in all Cervical Dystonia Impact Profile-58 scores were observed ($n = 407$). Overall, 26.2% of subjects reported adverse events, including muscular weakness (7.0%) and dysphagia (6.4%). Although only 61% of the subjects completed all treatment

Video 12.2 Botulinum toxin in cervical dystonia.

Video 12.3 Botulinum toxin in anterocollis.

visits, the results indicate robust improvement in clinical ratings and excellent tolerability after onabotulinumtoxinA treatment of cervical dystonia.

A similar clinical observational study assessed abobotulinumtoxinA (ANCHOR-CD study) in 350 cervical dystonia patients injected over four injection cycles. The median dose of abobotulinumtoxinA used in the study was 500 units. This study demonstrated a significant improvement in the TWSTRS total score and its subscales. Likewise, 43.6% of patients indicated that they were much or very much improved. Only 5% experienced side effects, although the method of side effects collection was only by report of the center to the safety department of the study sponsor and differed from standard assessments of adverse effects (Trosch, Espay et al., 2017).

Although on the average, BTX injections are repeated every 4 to 6 months, many patients prefer shorter interinjection intervals (Sethi et al., 2012; Comella and Bhatia, 2015). Patients with long-duration dystonia have been found to respond less well than those who were treated relatively early, possibly because prolonged dystonia produced contractures (Jankovic and Schwartz, 1991b). In one study, 28% of patients experienced some complication, such as swallowing difficulties, neck weakness, and nausea, sometime during the course of their treatment (some patients had up to 12 visits in 5 years). Dysphagia, the most common complication, was encountered in 14% of all 659 visits, but in only five instances was this problem severe enough to require changing to a soft or liquid diet. Complications are usually related to focal weakness, although distant and systemic subclinical and clinical effects, such as generalized weakness and malaise, rarely occur, possibly as a result of blood distribution or retrograde axonal transport to the spinal motor neurons (Garner et al., 1993). Most complications resolve spontaneously, usually within 2 weeks. An injection into one or both sternocleidomastoid muscles was most frequently associated with dysphagia (Jankovic and Schwartz, 1991b; Comella et al., 1992). One study showed that dosages as small as 20 units administered as a single injection into the sternocleidomastoid muscle completely eliminated muscle activity and could produce neck weakness and dysphagia (Buchman et al., 1994). In an analysis of patients who received five or more injections, the beneficial response was maintained and the frequency of complications with repeat injections actually declined, presumably as a result of improving skills (Jankovic and Schwartz, 1993a). Lindeboom and colleagues (1998), found that neurologic impairment and pain usually improve after BTX injections, but only functional status measures differentiate among patients who improve and those who have an insufficient response. Brashear and colleagues (2000) showed that two-thirds of patients who received BTX reported the injections always helped. Another long-term study showed that 75% of patients continued to benefit for at least 5 years and only 7.5% developed secondary unresponsiveness; only 1.3% discontinued BTX therapy because of intolerable side effects (Hsiung et al., 2002).

There have been only a few long-term studies of BTX treatment in cervical dystonia (Ramirez-Castaneda et al., 2013a; Ramirez-Castaneda and Jankovic, 2014). In a retrospective, longitudinal study that analyzes data on 89 patients with predominantly cranial-cervical dystonia treated with BTX or

up to 26 years (mean follow-up period of 18.5 years), the total number of onabotulinumtoxinA units received during the first injection were 140.3 compared with 224.5 at the last injection ($P < 0.0001$). Furthermore, the global response effect was 3.18 after the first injection session and 3.57 after the last injection ($P < 0.0001$). The duration of response after the initial injection session and at the last injection was 16.33 weeks versus 19.42 weeks ($P = 0.0037$), respectively. Adverse events, typically related to injection site, were reported in 19% of the visits.

Results similar to those obtained with BTX-A have been obtained in patients treated for cervical dystonia with BTX-B (Tsui et al., 1995; Lew et al., 1997; Figgitt and Noble, 2002). In a double-blind, controlled trial of 122 patients with cervical dystonia treated with BTX-B, there was a dose-response effect, particularly at doses of 10,000 units (Lew et al., 1997). Using TWSTRS, 77% of the patients were found to respond at week 4. Other studies have subsequently confirmed the efficacy of BTX-B (Brashear et al., 1999), even in patients who are resistant to BTX-A (Brin et al., 1999). In a 16-week, randomized, multicenter, double-blind, placebo-controlled trial of BTX-B, 109 patients, who previously responded well to BTX-A, were randomized into one of the treatment groups: placebo, 5000 units, and 10,000 units administered into two to four cervical muscles (Brashear et al., 1999). At week 4, the total TWSTRS score improved by 4.3, 9.3 ($P = 0.01$), and 11.7 ($P = 0.0004$), respectively, compared with baseline, and this was accompanied by significant improvements in pain, disability, and severity. The estimated median time until the total TWSTRS score returned to baseline was 63, 114, and 111 days, respectively. The most frequent side effects associated with BTX-B included dysphagia and dry mouth. An identical design was used in another study of BTX-B in cervical dystonia, with one exception: the patients were resistant to BTX-A as determined by the Frontalis type A antibody test (F-TAT) (Brin et al., 1999). A total of 77 patients were randomized to receive placebo or 10,000 unit of BTX-B. At week 4, the total TWSTRS scores improved by 2 (placebo) and 11 (10,000 units) ($P = 0.0001$). There was also significant improvement in secondary and tertiary outcome measures, including global assessments and pain visual analog scores, as well as other measures of pain, disability, and severity. The estimated duration of effect, based on a Kaplan-Meier survival analysis, was 112 days (12–16 weeks). Subsequent studies have suggested that dosages as high as 45,000 units of BTX-B (Myobloc) per session may be effective and safe in patients with cervical dystonia.

The most important determinants of a favorable response to BTX treatments include accurate selection of the involved muscles, targeting injections into the muscle, and appropriate dosage. There has not been a conclusive study to suggest that either EMG or ultrasound provides better results than clinical examination alone. One small, randomized study suggested increased magnitude of improvement using EMG (Comella, Buchman et al., 1992), another a prolongation of benefit with EMG-guided injections (Wu, Xue et al., 2016). Similarly, ultrasound has been proposed as a method to better target dystonic muscles (Schramm, Baumer et al., 2015). EMG may be helpful in some patients with obese necks or in whom the involved muscles are difficult to identify by palpation (Dubinsky et al., 1991; Gelb et al., 1991). BTX treatment not only provides effective symptomatic relief in

patients with cervical dystonia but also has likely improved long-term outcomes through the prevention of contractures. Early introduction of BTX has been shown to prevent contractures even in patients with congenital torticollis (Collins and Jankovic, 2006).

Writer's cramp and other limb dystonias

Treatment of writer's cramp with muscle relaxation techniques, physical and occupational therapy, and medical and surgical therapies has been disappointing. Several open (Rivest et al., 1990; Jankovic and Schwartz, 1993b; Karp et al., 1994; Priori et al., 1995; Pullman et al., 1996; Quirk et al., 1996; Wissel et al., 1996) and double-blind controlled (Yoshimura et al., 1992; Tsui et al., 1993; Cole et al., 1995) trials have concluded that BTX injections into selected hand and forearm muscles probably provide the most effective relief in patients with these task-specific occupational dystonias. In some studies, fine wire electrodes were used to localize bursts of muscle activation during the task, and the toxin was injected through a hollow EMG needle into the belly of the most active muscle (Cole et al., 1995). Similar beneficial results, however, were obtained in other studies without complex EMG studies (Rivest et al., 1990). Several lines of evidence support the notion that an intramuscular injection of BTX into the forearm muscles corrects the abnormal reciprocal inhibition (Priori et al., 1995).

Jankovic and Schwartz (1993b) studied the effects of BTX in 46 patients with hand dystonia who had injections into their forearm muscles in 130 treatment sessions. The average age was 49.4 years, and the dystonic symptoms had been present for an average of 8.6 years. After careful examination and palpation of the forearm muscles during writing, the toxin was injected into either the wrist flexors (116 injections) or the wrist extensors (52 injections). The average baseline severity of dystonia was 3.5 on a rating scale of 0 to 4. The average peak effect response for all treatment sessions was 2.3 (0 = no response to 4 = maximum benefit). The latency from injection to onset of effect averaged 5.6 days, and the benefit lasted an average of 9.2 weeks. Temporary hand weakness, the chief complication of this treatment, occurred in 54% of patients and in 34% of all treatment sessions. However,

nearly all patients preferred the temporary weakness, which was usually mild, to the disabling writer's cramps. Although one study showed that 14 of 38 (37%) needle placement attempts reached the proper hand muscles in the absence of EMG guidance, this does not mean that placement with EMG guidance correlates with better results, because the selection of the muscle involved in the hand dystonia is based on clinical examination, not on EMG (Molloy et al., 2002). One study showed that voluntary activity of the hand immediately after the treatment for 30 minutes enhanced the weakness produced by the injection, which may allow reduction in dosage and optimize the benefits (Chen et al., 1999).

In addition to improving writer's cramp, BTX might provide relief in other task-specific disorders affecting typists, draftsmen, musicians, athletes, and other people who depend on skilled movements of their hands (Schuele et al., 2005). Other focal distal dystonias, besides those involving the hands, might be amenable to treatment with BTX. Patients with PD, progressive supranuclear palsy, corticobasal degeneration, and other forms of parkinsonism or stroke-related hemiplegia occasionally develop secondary to fixed dystonia of the hand (dystonic clenched fist), which might benefit in terms of pain and hygiene from local BTX injections (Cordivari et al., 2001). Patients with foot dystonia as a manifestation of primary (idiopathic) dystonia and patients with parkinsonism who experience foot dystonia as an early symptom of their disease or, more commonly, as a complication of levodopa therapy might benefit from local BTX injections (Pacchetti et al., 1995). BTX injections into the foot-toe flexors or extensors might not only alleviate the disability, pain, and discomfort that are often associated with such dystonia, but also improve gait. Whether BTX injections will play an important role in the treatment of recurrent painful physiologic foot and calf cramps has yet to be determined.

Other indications for botulinum toxin

It is beyond the scope of this chapter to review the rapidly broadening indications for BTX therapy. The reader is referred to some reviews on this topic (Brin et al., 2002; Jankovic and Brin, 2002; Jankovic 2004a; Jankovic et al., 2009) and for evidence-based recommendations (Simpson et al., 2008).

Table 12.7 Evidence-based recommendations for the therapeutic use of botulinum toxin for treatment of movement disorders

Disorder	No. Trials/Subjects	Botulinum toxin formulation	Recommendations
Cervical dystonia	7/584	Botox (1), Dysport (3), Myobloc (3)	Should be offered (A)
Blepharospasm	2/17	Botox	May be offered (B)
Focal limb dystonia (upper extremity)	3/47	Botox, Dysport, not specified	May be offered (B)
Laryngeal dystonia (adductor)	1/13	Botox	May be offered (B)
Essential tremor (UE)	2/158	Botox	May be offered (B)
Hemifacial spasm	2/19	Botox, Dysport	May be considered (C)
Tics	1/18		May be considered (C)

From Simpson DM, Blitzer A, Brashear A, et al. Report of the Therapeutics and Technology Assessment Subcommittee of the AAN. *Neurology*. 2008;70:1699–1706.

Based on a thorough review of clinical trials with BTX, the American Academy of Neurology has made the following evidence-based recommendations: "BoNT should be offered as a treatment option for the treatment of cervical dystonia (Level A), may be offered for blepharospasm, focal upper extremity dystonia, adductor laryngeal dystonia, and upper extremity essential tremor (Level B), and may be considered for hemifacial spasm, focal lower limb dystonia and motor tics (Level C)" (Simpson et al., 2008) (Table 12.7).

Surgical treatment of dystonia

Although surgery has been used in the treatment of dystonia for long time (Cooper, 1965), there has been a resurgence in this approach, largely because of improvements in surgical and imaging techniques and as a result of surgical benefits observed in patients with tremor and PD (Jankovic, 1998; Lang, 1998; Ondo et al., 2001). For more detailed discussion of surgical treatment of dystonia, refer to Chapter 7.

Central ablative procedures

Improved understanding of the functional anatomy of the basal ganglia and physiologic mechanisms underlying movement disorders, coupled with refinements in imaging and surgical techniques, has led to a resurgence of interest in thalamotomy in patients with disabling tremors, dystonia, and other hyperkinetic movement disorders (Grossman and Hamilton, 1993; Jankovic et al., 1996; Ondo et al., 2001). The observation, supported by both physiologic and positron emission tomography (PET) studies, that there is a disruption of pallidothalamic-cortical projections in dystonia provides some rationale for treating dystonia by interrupting the abnormal outflow from the thalamus to the overactive prefrontal motor cortex (Lenz et al., 1990; Mitchel et al., 1990; Ceballos-Baumann et al., 1995).

In a longitudinal study of 17 patients with severe dystonia, 8 (47%) had a moderate to marked improvement in their abnormal postures and functional disability after thalamotomy (Cardoso et al., 1995). Patients with primary and secondary dystonia had similar responses, but 43% of the patients with primary dystonia deteriorated during a mean follow-up of 32.9 months, whereas 30% of patients with secondary dystonia deteriorated during a mean follow-up of 41.0 months. Neurologic complications were observed in 6 of 17 patients (35%) immediately after surgery, but deficits (contralateral weakness, dysarthria, pseudobulbar palsy) persisted in only one subject. Mild weakness contralateral to the surgery was the most common complication, noted in 3 patients immediately after the procedure. The one patient who underwent bilateral procedures had no detectable dysarthria. These results are consistent with those of other studies that have reported improvement in 34% to 70% of patients with dystonia after thalamotomy (Cooper, 1976; Andrew et al., 1983; Tasker et al., 1988). Although most studies concluded that distal dystonia responded more favorably to thalamotomy than does axial dystonia, Andrew and colleagues (1983) thought their patients with axial dystonia, including torticollis, also improved after thalamotomy. In a study of 15 patients with musician's dystonia who were followed for an average of 2.5 years (up to about 9 years) after

ventro-oral thalamotomy, all patients except 1 (93%) experienced marked improvement in symptoms without deterioration during the follow-up period (Horisawa et al., 2013). Whether DBS or focused ultrasound targeting the same nucleus offers any advantages over traditional thalamotomy is not known (Charness, 2013).

Most investigators, however, think that the best candidates for thalamotomy are patients who have disabling, particularly unilateral, dystonia (hemidystonia) that is unresponsive to medical therapy. Patients with preexisting dysarthria are also good candidates because they have less to lose from thalamotomy-related speech disturbance. Patients with secondary (symptomatic) dystonia seem to respond better than do those with idiopathic dystonia. Thalamotomy should not be recommended for patients with facial, laryngeal, cervical, or truncal dystonia.

The role of pallidotomy in the treatment of dystonia is currently being reevaluated in view of emerging use of DBS (Jankovic et al., 1997; Eltahawy et al., 2004). In one study of eight patients with severe generalized dystonia, there was 59% and 62.5% improvement in the Fahn-Marsden Dystonia Scale and in the Unified Dystonia Rating Scale, respectively, after pallidotomy (Ondo et al., 1998). The experience with pallidotomy continues to show favorable long-term effects, particularly in patients with primary dystonia (Ondo et al., 2001; Yoshor et al., 2001). Although the surgery does not slow or halt the progression of the underlying disease, most patients continue to benefit. The procedure is usually well tolerated, and the benefits have persisted for more than 10 years in most patients with primary dystonia. Pallidotomy has been also reported to be effective in a 47-year-old woman with paroxysmal dystonia induced by exercise (Bhatia et al., 1998).

Although there are no data from normal humans, microelectrode recordings from patients with generalized dystonia indicate that the mean discharge rates (~50 Hz) in the GPi are lower than those in patients with PD (80–85 Hz) (Lozano et al., 1997) or parkinsonian primates (70–75 Hz) (Filion and Tremblay, 1991) but higher than those in hemiballism (Vitek et al., 1998, 1999) and that the proportion of GPi cells that respond to stimulation is higher in patients with dystonia than in those with hemiballism (Lenz et al., 1998). In comparison to normal or parkinsonian primates, the GPi discharges in patients with dystonia seem to be more irregular, with more bursting and pauses, and the receptive fields to passive and active movements seem to be widened (Kumar et al., 1999). The intraoperative neurophysiologic recordings in 15 patients with dystonia was compared with those of 78 patients with PD undergoing pallidotomy; the discharge rates were lower in frequency and more irregular in the GPi and GPe of patients with dystonia (Sanghera et al., 2003).

Physiologic studies in patients with dystonia, based on lower mean discharge rates in GPe and GPi (Vitek et al., 1998, 1999), suggest overactivity of both direct (striatum-GPi) and indirect (striatum-GPe-GPi) pathways, the dopamine receptor ligand PET studies (Perlmutter et al., 1997; Asanuma et al., 2005) suggest increased activity in the direct and decreased activity in the indirect pathway. This is compatible with fluorodeoxyglucose (FDG) PET studies supportive of excessive activity in the direct pathway (Eidelberg et al., 1995). In multiple reports, pallidotomy (Lozano et al., 1997; Ondo et al., 1998; Vitek et al., 1999) and GPi DBS (Coubes et al., 2000; Tronnier and Fogel, 2000; Vercueil et al., 2001; Bereznaï et al., 2002;

Video 12.4 Bilateral pallidotomy for generalized dystonia.

Video 12.5 Bilateral deep brain stimulation for generalized dystonia.

Video 12.6 Bilateral pallidotomy for generalized dystonia.

BILATERAL, PALLIDAL, DEEP BRAIN STIMULATION IN PRIMARY GENERALIZED DYSTONIA: A PROSPECTIVE 3-YEAR FOLLOW-UP STUDY

22 patients with primary generalized dystonia. Motor improvement, observed at 1 year (51%), was maintained at 3 years (58%).

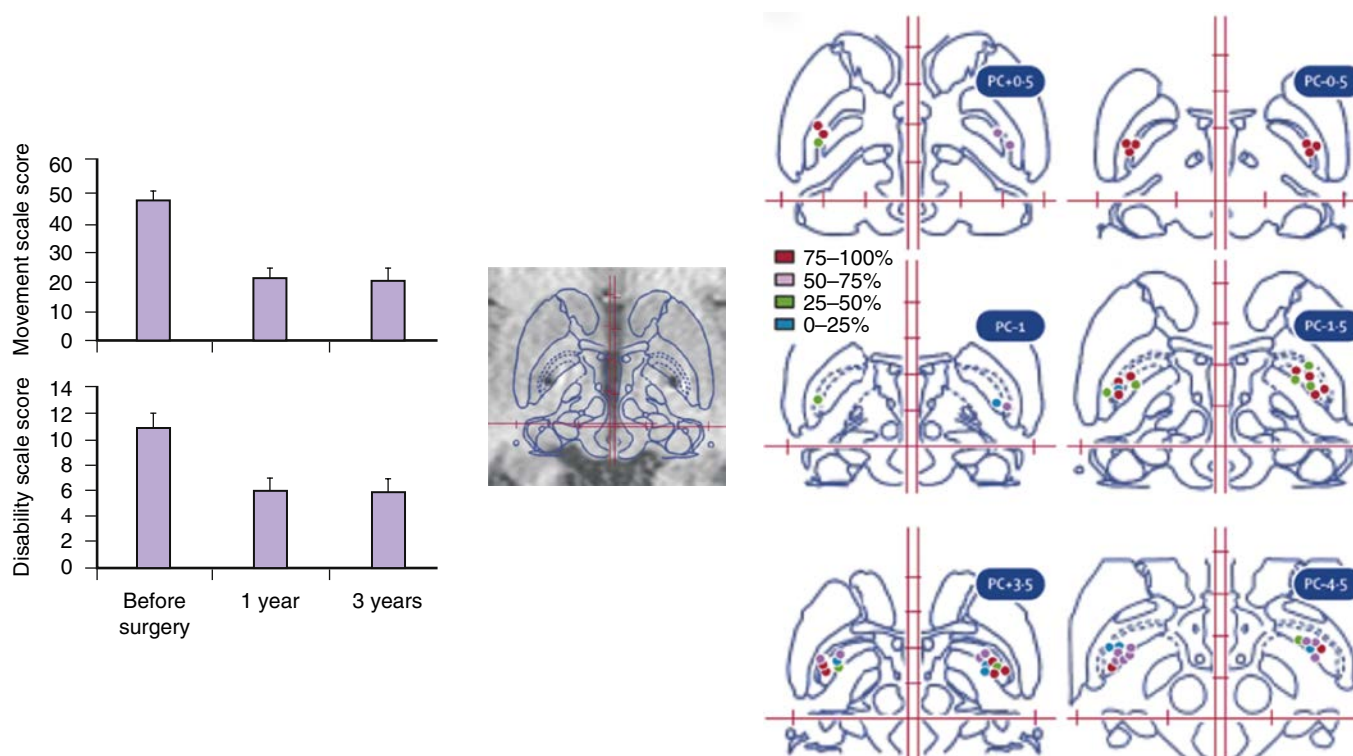


Fig. 12.2 Long-term experience with globus pallidus internus (GPI) deep brain stimulation (DBS) in dystonia. (Redrawn from Vidailhet M, Vercueil L, Houeto JL, et al., French SPIDY Study Group. Bilateral, pallidal, deep-brain stimulation in primary generalised dystonia: A prospective 3 year follow-up study. *Lancet Neurol.* 2007;6:223–229.)

Vidailhet et al., 2005; Diamond et al., 2006; Isaías et al., 2008; Isaías et al., 2009; Sensi et al., 2009) appear to be effective procedures for patients with dystonia (Fig. 12.2) (Videos 12.4, 12.5, 12.6). Both procedures may provide benefit by disrupting the abnormal GPI pattern and thus reduce cortical overactivation, characteristic of dystonia (Eidelberg et al., 1998).

Deep brain stimulation

DBS targeting GPI has generally replaced ablative surgery in patients with disabling dystonia (Ostrem and Starr, 2008; Andrews et al., 2010; Cheung et al., 2014; Fox and Alterman, 2015). DBS will be discussed in another chapter.

Peripheral surgery and other peripheral treatments

Peripheral denervation procedures were used extensively for cervical dystonia before the advent of BTX therapy. In one series of patients with cervical dystonia seen before 1990, 40 of 300 (13%) patients elected to have this type of surgery (Jankovic et al., 1991). Whereas 10% of the patients noted worsening after the surgery, 38% experienced a noticeable improvement in the ability to control their head position or in reduction of the neck pain.

Three procedures have been used in the treatment of cervical dystonia: (1) extradural selective sectioning of posterior

(dorsal) rami (posterior ramisectomy) with or without myotomy, (2) intradural sectioning of anterior cervical roots (anterior cervical rhizotomy), and (3) microvascular decompression of the spinal accessory nerve. Although the first procedure, championed by Bertrand (Bertrand and Molina-Negro, 1988), is considered by many clinicians to be the procedure of choice, no study has compared the different surgical approaches. Bertrand and Molina-Negro (1988) reported that 97 of 111 (87%) patients had “excellent” or “very good” results. In a smaller series, 5 of 9e (56%) patients had moderate benefit that was sustained during up to 21 months of follow-up (Davis et al., 1991). The procedure is performed under general anesthesia without a paralyzing agent so that intraoperative nerve root stimulation can be used to identify the innervation to the dystonic muscles. This information, coupled with preoperative EMG, is used to avulse selected nerve roots, usually the branches of the spinal accessory nerve and the posterior rami of C1 through C6. Thorough avulsion of the peripheral branches is thought to be essential in preventing recurrences. Pain seems to improve more than the abnormal posture after the cervical muscle denervation, although some patients complain of stiff neck, sometimes lasting several months after the surgery. Other complications may include local numbness, neck weakness, and rarely dysphagia. The chief disadvantage of anterior rhizotomy compared with posterior primary ramisectomy is that the former procedure causes denervation of

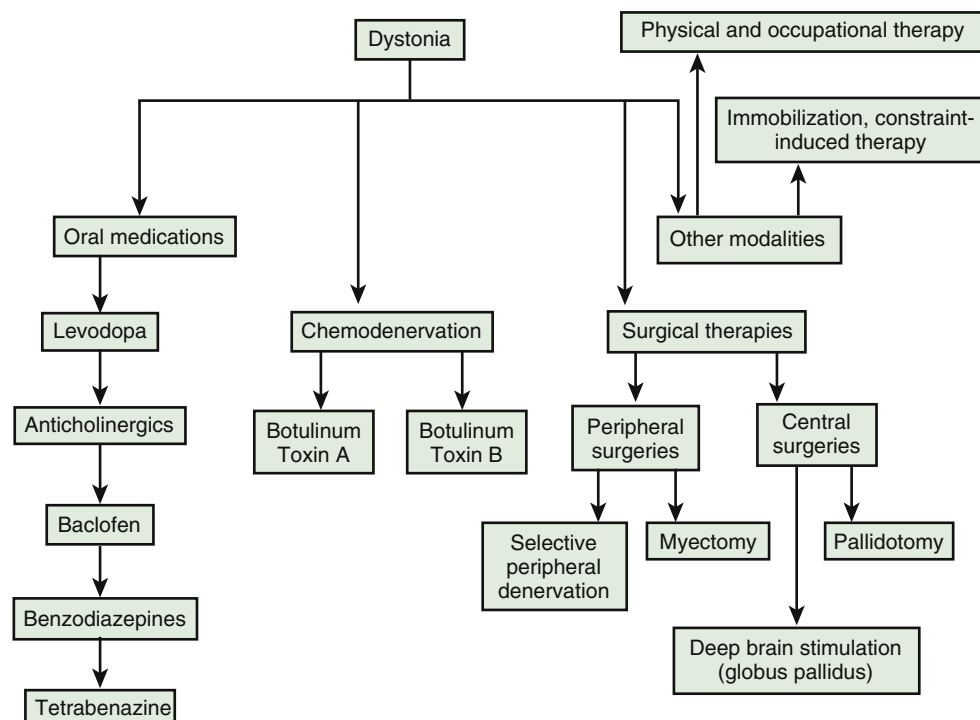


Fig. 12.3 Therapeutic algorithm in dystonia. (Redrawn from Jankovic J. *Treatment of dystonia*. *Lancet Neurol*. 2006;5:864–872.)

both involved and uninvolved muscles, and it cannot be carried out at or below the C4 level because of the potential for involvement of the roots to the phrenic nerve, leading to paralysis of the diaphragm. The posterior ramisectomy (C2–C6) allows more selective denervation of the involved muscles. Krauss and colleagues (1997) reported the effects of 70 intradural or extradural approaches in 46 patients with severe cervical dystonia. During a mean duration of follow-up of 6.5 years, 21 (46%) of the patients reported excellent or marked improvement on a global outcome scale. There was no difference in the distribution of outcome when patients who still responded to BTX were compared with the BTX nonresponders. Using a modified TWSTRS scale, there were statistically significant improvements not only in the severity of dystonia, but also in occupational and domestic work and in various activities of daily living. The results of this study are comparable with those of Ford and colleagues (1998), who reported on an open-label, retrospective study of a selective denervation for severe cervical dystonia (torticollis) in 16 patients who were refractory to injections with BTX-A. Using functional capacity scales, they concluded that 6 (37.5%) patients had “a moderate or complete return of normal neck function.” Despite some improvement in 12 of 14 (85.7%) patients on the TWSTRS dystonia rating scale applied to “blinded” ratings of videotaped examinations, the surgery failed to return patients to their occupations. On the basis of the reported experience, we conclude that surgical treatment tailored to the specific pattern of dystonic activity in the individual patient is a valuable alternative in the long-term management of cervical dystonia, particularly for patients who are anxious to avoid having the intracranial surgical procedure of DBS targeting the GPi.

Surgical treatments, such as facial nerve lysis and orbicularis oculi myectomy, once used extensively in the treatment of blepharospasm, have been essentially abolished because

BTX treatment is usually very effective and because post-operative complications, such as ectropion, exposure keratitis, facial droop, and postoperative swelling and scarring, are common (Chapman et al., 1999). Similarly, recurrent laryngeal nerve section, once used in the treatment of spasmodic dysphonia (Dedo et al., 1983), is used rarely and only when BTX fails to provide a satisfactory relief. Another once-popular procedure, spinal cord stimulation for cervical dystonia, has been shown to be ineffective by a controlled trial (Goetz et al., 1988). Radiofrequency controlled “functional electrical stimulation,” originally designed for foot drop, uses electrical stimulation of the peroneal nerve during the swing phase of gait that drives dorsiflexion and eversion of the foot and overcomes the patient’s dystonic plantarflexion (Barrett et al., 2011). Bipolar epidural motor cortex stimulation has been found ineffective in dystonia in a double-blind, crossover, multicenter study (Rieu et al., 2014).

Medical, surgical, and other therapeutic approaches to dystonia have been described in several recent reviews (Jankovic 2006, 2009a) (Fig. 12.3).

Other therapies

Inhibiting expression of mutant torsinA could be potentially a powerful therapeutic strategy in DYT1 dystonia. Using small interfering RNA (siRNA) to silence the expression of mutant torsinA, Gonzalez-Alegre and colleagues (2003) successfully suppressed expression of this abnormal protein in transfected cells that was allele-specific. Novel and experimental therapies are needed to make incremental advances in the treatment of dystonia (Jinnah and Hess, 2008).

In summary, patients with segmental or generalized dystonia beginning in childhood or adolescence should be initially tried on levodopa/carbidopa up to 1000 mg of

levodopa per day. If this therapy is successful, it should be maintained at a lowest possible dose. If it is ineffective after 3 months, high-dose anticholinergic (e.g., trihexyphenidyl) therapy should be instituted, and the dosage should be increased to the highest tolerated level. If the results are poor, then baclofen, benzodiazepines, carbamazepine, and tetrabenazine should be tried. Some patients may require triple therapy consisting of an anticholinergic agent (e.g., trihexyphenidyl), a monoamine-depleting drug (e.g., tetrabenazine), and a dopamine receptor-blocking drug (e.g., fluphenazine, pimozide, risperidol, or clozapine) (Marsden et al., 1984). Tetrabenazine alone or with anticholinergic drugs is particularly useful in the treatment of tardive dystonia (Waln and Jankovic, 2013). In some patients, BTX injections may be helpful to control the most disabling symptom of the segmental or generalized dystonia. In most patients with adult-onset dystonia, the distribution is usually focal; therefore, BTX injections are usually considered the treatment of choice. Besides the abnormal movement and posture, pain, associated depression, anxiety, and other psychological comorbidities can have an important impact on the quality of life of patients with cervical dystonia and must be appropriately treated (Ben-Shlomo et al., 2002). In some patients, this treatment might need to be supplemented by other drugs noted previously or by surgical peripheral denervation. DBS should be reserved only for patients whose symptoms continue to be disabling despite optimal medical therapy. Any form of therapy should, of course, be preceded by a thorough evaluation designed to rule out secondary causes of dystonia. Finally, it is important to emphasize that patient education and counseling are essential components of a comprehensive therapeutic approach to all patients with dystonia (see the Appendix).

Appendix

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Huntington disease

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Introduction

George Huntington published his essay “On Chorea” in 1872 (Huntington, 1872), 1 year after graduating from Columbia College of Physicians and Surgeons and while practicing general medicine with his father on Long Island, New York. In this paper, he described many of the clinical features associated with the entity later to carry his name. These features included onset in adulthood, hereditary nature, presence of abnormal movements and behavioral changes, risk for suicidality, and a relentlessly progressive course (Wexler et al., 2016). The eponym Huntington’s chorea was adapted in the literature to draw attention to chorea (derived from the Latin *choreus*, meaning “dance” and Greek *choros*, meaning “chorus”) because it is the clinical hallmark of this neurodegenerative disorder. However, the term *Huntington disease* (HD) (OMIM 143100) is more appropriate (Penney and Young, 1998; Jankovic, 2006; Fahn and Jankovic, 2009) because chorea is one of several clinical features and may not be present in some.

Although chorea (known as the “dancing mania”) has been recognized since the Middle Ages, the origin of the affected families described by Huntington was traced to the early seventeenth century in the village of Bures in southeast England. The inhabitants of this area later migrated to various parts of the world, accounting for the marked variation in the regional prevalence of HD.

HD is a model neurobehavioral and neurodegenerative disease in which the discovery of a gene mutation is being gradually translated into improved understanding of the mechanisms of cell death and pathogenesis-targeted treatments. Because of availability of predictive testing, the disease

has the potential to be amenable to disease-modifying therapies that can be initiated long before the manifestation of symptoms. According to one criterion (Ross et al., 2014) “Onset is defined as the point when a person who carries a CAG-expanded *Htt* allele develops the unequivocal presence of an otherwise unexplained extrapyramidal movement disorder (e.g., chorea, dystonia, bradykinesia, rigidity)” and cognitive impairment.

This chapter will focus on HD; other diseases, such as HDL1, HDL2, and HDL3; dentatorubral-pallidoluysian atrophy; and spinocerebellar ataxia type 17 (SCA17), which may manifest as an HD-like phenotype are discussed in the chapter on chorea and in other reviews (Toyoshima et al., 2004; Schneider et al., 2006, 2007; Wild et al., 2008; Jankovic and Fahn, 2009; Fekete and Jankovic, 2010; Mariani et al., 2016).

Epidemiology

The prevalence of HD is geographically heterogeneous, probably based on diaspora from southeast England after the founder mutation. Thus, in certain regions of the world, the prevalence is as high as 560 per 100,000 (Moray Firth, Scotland) and 700 per 100,000 (Lake Maracaibo, Venezuela) (Harper, 1992; Morrison et al., 2010). Based on a meta-analysis of 13 studies, the worldwide prevalence of HD was found to be 2.71 per 100,000 (95% confidence [CI], 1.55–4.72) and the overall incidence was 0.38 per 100,000 per year (95% CI, 0.16–0.94). (Pringsheim et al., 2012). The estimated prevalence of HD in the United States is about 6 per 100,000 population (Kokmen et al., 1994), which translates

to about 30,000 people with HD and another 200,000 at risk for developing the disease. A detailed study in Northern Ireland found the prevalence of HD to be 10.6 per 100,000, a figure that is based on the affected cases with confirmed molecular diagnosis, because older prevalence figures before 1990 were based on family history and clinical diagnosis only (Morrison et al., 2010). The figure of 10 in 100,000 is consistent with the reported world-wide estimates of prevalence of HD. Although the reason for the higher prevalence of HD in North American and European White populations compared with Asian and black populations is not known, this difference may be partly explained by differences in CAG tract size and *Htt* haplotypes (Rawlins et al., 2016). There is convincing evidence that the average CAG tract size in European populations (18.4 ± 6.3) is larger than that in Asian and African populations ($16.4\text{--}16.6 \pm 1.5$) (Squitieri et al., 2004).

Americo Negrette, a Venezuelan physician, first observed the “dancing mania” of Maracaibo in the 1950s, and his findings later led to seminal expeditions to this region, the discovery of the gene locus (1983), and identification of the gene mutation for HD (1993) (Okun and Thommi, 2004). Because many epidemiologic studies were done before the advent of genetic testing, the true prevalence of the HD gene is not known. DNA testing has largely replaced other tests, such as magnetic resonance imaging (MRI) of the brain, in the evaluation of patients with HD.

Clinical Aspects

HD is represented by a broad array of motor, psychiatric, and cognitive features (Testa and Jankovic, 2019). In a study involving 1901 patients with HD, the following were considered the most frequent presenting symptoms, in descending order: chorea, trouble walking, unsteadiness, irritability, depression, clumsiness, speech difficulty, memory loss, dropping of objects, lack of motivation, paranoia, intellectual decline, sleep disturbance, hallucination, weight loss, and sexual problems (Foroud et al., 1999). Motor features of HD can include chorea, dystonia, gait and balance impairment, falls, rigidity, and bradykinesia. In addition, motor changes can manifest as abnormal saccades and eye movements, dysarthria and speech abnormalities, and dysphagia. Cognitive features frequently affect executive function, attention, verbal fluency, memory, and judgment. Psychiatric symptoms include depression, anxiety, irritability, apathy, obsessions-compulsions, perseveration, and in some, psychosis and suicidality. Sleep, circadian, and autonomic dysfunction may also accompany HD (Arnulf et al., 2008; Bellosta Diago et al., 2017; Diago et al., 2018).

Motor features

The motor signs and symptoms of HD are highly diverse, with many different phenomenologies of movement disorders represented. Commonly associated with HD, chorea can be present in various bodily regions from face, to extremities, to trunk. Chorea may affect fine and gross motor function, activities of daily living (ADLs), and gait and balance, which can affect quality of life, lead to falls, and affect employability and independence. In addition, chorea may contribute to weight loss with increased energy expenditure, social

isolation, increased morbidity, and dependence on others, and eventually lead to institutionalization (Wheelock et al., 2003). In one study, only the change in the Unified Huntington’s Disease Rating Scale (UHDRS) chorea score correlated with the change in the complex task performance, such as peg insertion (Andrich et al., 2007). Although diagnostically helpful, chorea is not a good marker of disease severity or progression (Mahant et al., 2003). Some patients “camouflage” their chorea by incorporating the involuntary movements into semipurposeful activities, called parakinesias (Video 13.1). Interestingly, many HD patients are either unaware of their chorea, deny any symptoms, or have poor insight into their symptoms, sometimes even in the presence of pronounced motor or behavioral problems that interfere with ADLs (McCusker and Loy, 2014). In one study of 38 patients with HD, 18 (47.4%) phenoconverted from a pre-symptomatic state to demonstrating clear evidence of the disease without being aware of their own signs, thus highlighting marked inaccuracy of self-reporting, particularly in early stages of the disease (McCusker et al., 2013). Unaware patients were less likely to be depressed. Patients with HD are more likely to report functional or motor consequences of chorea such as dropping objects, clumsiness, restlessness, or “twitching.” There is little or no relationship between direct experience or awareness of chorea and actual chorea scores (Snowden et al., 1998), which may explain why the presence and degree of chorea poorly correlates with functional decline (Feigin et al., 1995). ●

HD also can manifest as hypokinetic (or akinetic)-rigid signs, in adults and more commonly its juvenile form, also termed Westphal variant (described later). Bradykinesia, usually evident in patients with the rigid form of HD, when it coexists with chorea, might not be fully appreciated on a routine examination (van Vugt et al., 1996; Sanchez-Pernaute et al., 2000). When present, hypokinesia usually coexists with cognitive and global dysfunction (Reedeker et al., 2010). Variability in isometric grip forces while grasping an object correlates well with UHDRS scores and with progressive motor deficits associated with HD (Rao et al., 2011; Reilmann et al., 2011). Although bradykinesia was most pronounced in the rigid-akinetic patients, it was also evident in patients with the typical choreic variety of HD, and when bradykinesia predominates, patients exhibit parkinsonian findings. Assessing simple repetitive movements, such as tapping, correlates with UHDRS scores and may be used to follow progression of HD (Andrich et al., 2007). Variability in speeded and metronome tapping tasks was reported in pre-manifest and manifest HD in one cross-sectional study, with associations with not only later HD stages and UHDRS total motor scores (TMSs), but also gray matter atrophy and cortical thinning on brain MRI (Bechtel et al., 2010). Such motor deficits may provide a possible outcome measure for use in future preventive clinical trials (Biglan, 2010). Micrographia also may be one manifestation of underlying parkinsonism (Phillips et al., 1994). Theories regarding bradykinesia in HD include an expression of postsynaptic parkinsonism invoking both direct and indirect pathways result from degeneration of the basal ganglia output to the supplementary motor areas concerned with the initiation and maintenance of sequential movements and failure of thalamocortical relay of sensory information (Berardelli et al., 1999). These theories may explain why a reduction in chorea with antidopaminergic drugs rarely improves overall motor functioning and indeed

Video 13.1 Huntington disease (HD).

can exacerbate motor impairment. Although bradykinesia associated with HD usually does not respond to dopaminergic therapy, late-onset levodopa-responsive HD presenting as parkinsonism has been documented (Reuter et al., 2000). Regarding the course of choreatic versus hypokinetic-rigid HD motor subtypes, a study from the European HD Network REGISTRY study investigated 4135 subjects who were classified at baseline as either predominantly choreatic ($n = 891$), hypokinetic-rigid ($n = 916$), or mixed-motor ($n = 2328$) and followed for up to 6 years (Jacobs et al., 2016). Over the follow-up period, the predominantly choreatic group showed a significant decrease in chorea, whereas the predominantly hypokinetic-rigid group had a slight increase in hypokinesia and rigidity. Those with predominantly chorea, had significantly faster rates of change over time in their total functional capacity (TFC) and cognitive scores (Stroop and verbal fluency tests). In a study analyzing 7311 manifest HD participants from the Enroll-HD study, motor deficits were worse for those HD with late onset (onset at 60 years or older) at early stages of HD and for young onset HD (onset <30 years) at more advanced stages, who also had a faster functional decline as measured by TFC scores (Kwa et al., 2020).

Fine and gross motor functions are frequently affected in HD. Gait impairment and postural instability increase with disease progression. Gait changes in HD are characterized by slowness, reduced speed, and increased variability in measures of step length, stride time, and symmetry (Vuong et al., 2018). Balance impairment reflects dysfunction in ability to anticipate changes in the base of support and perturbation and difficulty with dual-task function, particularly in the setting of cognitive changes. In one study of 24 patients with HD, 14 (58.3%) reported at least 2 falls within the previous 12 months and the fallers had worse scores on Berg Balance Scale (BBS) and the Timed Up & Go (TUG) test (Busse et al., 2009). Although loss of balance, postural instability, and falls are usually considered features of more advanced disease, computerized dynamic posturography detected impaired postural stability even in premanifest HD, suggesting that this abnormality may be a highly sensitive indicator of early motor impairment in HD (Salomonczyk et al., 2010).

Other motor symptoms that can accompany HD include dystonia, ataxia, bruxism, myoclonus, tics and tourettism, dysarthria, dysphagia, and aerophagia (Vogel et al., 1991; Carella et al., 1993; Thompson et al., 1994; Ashizawa and Jankovic, 1996; Hu and Chaudhuri, 1998; Louis et al., 1999; Tan and Jankovic, 2000; Jankovic and Ashizawa, 2003; Walker, 2007) (Videos 13.2, 13.3, 13.4, 13.5). Rarely, patients with HD present with tics and other features suggestive of adult-onset Tourette syndrome (tourettism) (Jankovic and Ashizawa, 1995) (Video 13.6). Dysphagia is one of the most troublesome and potentially life-threatening symptom of HD, particularly in advanced stages. A dysphagia scale has been developed to assess the severity of this symptom (Heemskerk et al., 2014). Another characteristic feature of HD is the inability to maintain tongue protrusion, representing motor impersistence (sometimes also referred to as “negative chorea”) (Videos 13.7, 13.8). Motor impersistence, the inability to hold constant a voluntary muscle contraction, is also described regarding hand grip, or the so-called milkmaid grip. Hung-up and pendular reflexes are also typically present in patients with HD (Video 13.8) (Brannan, 2003). ▶

Eye movements can be impaired in manifest HD and in its early stages or presymptomatic individuals. In a large

Venezuelan kindred study ($n = 593$), generation of fine motor movements and rapid eye saccades was impaired in about 50% of at-risk individuals (Penney et al., 1990). At-risk individuals with these findings were more likely than those without them to develop overt HD within several years; these abnormalities were thought to represent the earliest clinical manifestations of the disease. If the first examination was normal, there was only a 3% risk for developing symptomatic HD within 3 years. HD patients have greater defects in initiating internally than externally generated saccades (Tian et al., 1991). In 215 individuals who were at risk for or recently diagnosed with HD, a high-resolution, video-based eye tracking system demonstrated three types of abnormalities while performing memory-guided and anti-saccade tasks: increased error rate, increased saccade latency, and increased variability of saccade latency (Blekher et al., 2006). Abnormalities in saccadic latency have been demonstrated in premanifest HD patients (Antoniades et al., 2010). In another study, initiation deficits of voluntary-guided, but not reflexive, saccades occurred in individuals with preclinical HD (Golding et al., 2006). Voluntary-guided saccades in 25 presymptomatic HD individuals correlated with deficits in white matter tracts as determined by diffusion tensor brain MRI (Klöppel et al., 2008). Antisaccade performance correlated with brain volume loss in the caudate and globus pallidus (GP) and with thinning of the occipital and parietal lobes. Oculomotor defects may be seen in presymptomatic patients with a predicted time to clinical onset of up to 10 years (Hicks et al., 2010). Additional neuro-ophthalmologic abnormalities in HD include increased blink rates (Karson et al., 1984; Xing et al., 2008), irregular elevations of eyebrows as a result of frontalis muscle choreic contractions and eye closures with irregular narrowing of palpebral fissures, rarely leading to frank blepharospasm, and apraxia of eyelid opening and closure (Bonelli and Niederwieser, 2002).

Psychiatric features

A range of psychiatric features have been well documented in HD. These symptoms include personality changes, agitation, irritability, anxiety, apathy, social withdrawal, impulsiveness, depression, mania, paranoia, delusions, hostility, hallucinations, psychosis, and various sexual disorders (Fedoroff et al., 1994; Litvan et al., 1998; Paulsen et al., 2001a; Teixeira et al., 2016; Paoli et al., 2017; Ranganathan et al., 2021). In a study of 52 patients with HD, Paulsen and colleagues (2001a) found the following neuropsychiatric symptoms in descending order of frequency as represented by greater than 65%: dysphoria, agitation, irritability, apathy, anxiety; in 20% to 50%: disinhibition, euphoria, and aggression; in 5% to 12%: delusions and compulsions; and in less than 5%: hypersexuality and hallucinations (Video 13.9). In HD mutation, carriers from the European HD Network REGISTRY study, the majority exhibited some type of neuropsychiatric symptoms, and four distinct behavioral patterns were identified: depression, irritability/aggression, psychosis, and dysexecutive (which included apathy and obsessive and compulsive behaviors) (Rickards et al., 2011; van Duijn et al., 2014). In a study using the Enroll-HD database, incidence of behavioral symptoms in individuals with manifest HD was highest with those with early onset symptoms (26%), compared to those with late onset (11%) or mid-adult onset (19%) (Ranganathan et al., 2021). ▶

Video 13.2 Huntington disease (HD).

Video 13.3 Huntington disease (HD).

Video 13.4 Huntington disease (HD).

Video 13.5 Huntington disease (HD).

Video 13.6 Huntington disease (HD).

Video 13.7 Huntington disease (HD).

Video 13.8 Huntington disease (HD).

Video 13.9 Huntington disease (HD).

Depression represents the most frequent psychiatric symptom in HD patients (Paoli et al., 2017), with estimated prevalence rates of 40% to 50%, ranging from 9% to 63%. Depression may precede the onset of HD motor symptoms. In one study of presymptomatic individuals at risk for HD, gene carriers were 1.74 times (95% CI, 1–3.07) more likely to report depression than noncarriers, and the rate of depression increased when closer to clinical onset (Julien et al., 2007). However, data from the PREDICT-HD study found that depressive symptoms were more prevalent in mutation carriers but did not increase with proximity to HD diagnosis (Epping et al., 2013). In this study, increased depressive symptoms were associated with female gender, history of depression, and a slight decrease in functioning but not with time since genetic testing. Depression, poor impulse control, anxiety, and other socioeconomic factors associated with HD contribute to the markedly increased risk for suicide in patients with HD. Suicide rate in patients with HD is about 10 times greater than in the general population, that is, 138 per 100,000 person years compared with 12 to 13 per 100,000 person years in the general population (Bird, 1999; Almqvist et al., 1999) and about 4 times the expected rate for corresponding U.S. White population in which a review of records of 452 deceased patients diagnosed with HD documented that 5.7% of deaths were attributed to suicide (Farrer et al., 1986). In a study of 506 individuals with documented or suspected HD, suicide represented the third most common cause of death, accounting for 12.7% of 157 ascertained deaths, after bronchopneumonia (31.8%) and heart disease (15.3%) (Schoenfeld et al., 1984). In the REGISTRY study, 169 (8.0%) mutation carriers expressed suicidal ideation (Hubers et al., 2013), which was independently correlated with the following at baseline: disease duration, anxiety, aggression, previous suicide attempt, and a depressed mood. In a cross-sectional study of 2835 patients with “definite” diagnosis of HD with disease onset at age 20 years or later, mean age of 49.6 years, and duration of symptoms for a mean 7.6 years, 50.3% reported seeking treatment for depression and 10.3% reported at least one suicide attempt (Paulsen et al., 2005a). Patients endorsing current symptoms of depression were twice as likely to have attempted suicide in the past as those who deny symptoms of depression (15.7% versus 7.1%). In another study using UHDRS in 4171 patients with HD, the frequency of suicidal ideation doubled from 9.1% in at-risk persons with normal neurologic examination to 19.8% in at-risk individuals with soft neurologic signs and increased to 23.5% in persons with “possible” HD. In patients with diagnosed HD, the risk for suicidal ideation increased from 16.7% at stage 1 to 21.6% at stage 2 and decreased thereafter to 19.5%, 14.1%, and 9.8% in stages 3, 4, and 5, respectively (Paulsen et al., 2005b). Thus, the most critical periods of suicide risk are immediately before receiving a formal diagnosis of HD and in stage 2 of the disease, when activities, such as driving and taking care of personal finances, are beginning to be restricted and patients are becoming more dependent on others.

Other psychiatric symptoms include anxiety, which has been reported in 17% to 61% (Paoli et al., 2017). Anxiety, in contrast to depression, may be independent from the stage of illness. Irritability is commonly reported, with rates between 35% and 73% and potential increases during the disease course, associated with functional decline. Behaviors such as anxiety, irritability and agitation have been related to

degeneration of striatal and orbitofrontal-subcortical circuitry (Litvan et al., 1998). Criminal behavior, closely linked to the personality changes, depression, and alcohol abuse, has been reported to be more frequent in patients with HD than in nonaffected first-degree relatives (Jensen et al., 1998). Such behavior might be a manifestation of an impulsive disorder as part of disinhibition, seen not only in HD, but also in other frontal lobe–basal ganglia disorders, particularly Tourette syndrome (Brower et al., 2001). Obsessive and compulsive symptoms are less common than other psychiatric symptoms, with prevalence rates ranging from 7% to 50%, but can be associated with other psychiatric comorbidities (Paoli et al., 2017). Similarly, these behaviors and mental inflexibility and perseveration may result from corticostriatal dysfunction. Apathy, however, may overlap with mood dysfunction (e.g., depression) and cognitive impairment, with putative underlying anterior cingulate–subcortical circuit dysfunction. Apathy is thought to occur in about 50% to 70% of HD, with increasing rates in later disease stages (van Duijn et al., 2014). Psychosis, including paranoia and delusions, occurs in about 3% to 11%; use of antidopaminergic/antipsychotic medications for treatment of hyperkinetic motor symptoms may influence prevalence rates of psychosis in HD.

Cognitive features

The cognitive profile of HD has been characterized by subcortical deficits such as executive dysfunction, attention deficits, cognitive slowing, and visuospatial and construction impairment, which are thought to reflect underlying frontostriatal disruption (Dumas et al., 2013; Stout et al., 2016). Executive dysfunction in HD manifests as poor planning and organizing, adapting to alternatives, and mental flexibility. Later in the disease, impaired episodic memory, learning, and spatial navigation may be impaired. Early studies demonstrated dementia was found in 66% of 35 HD patients (Pillon et al., 1991). In keeping with a subcortical dementia, the profile of HD cognitive impairment differs from that of Alzheimer dementia with more prominent executive dysfunction and with a memory impairment characterized by greater retrieval deficits than encoding dysfunction.

Cognitive decline may occur as an early symptom, as described by self-report or on neuropsychologic testing. From the REGISTRY study, 8.4% of 615 patients reported having cognitive features as first disease symptoms, with an additional 13.2% reporting a mixed onset of motor and/or cognitive and/or psychiatric symptoms (Orth et al., 2010). Whereas some studies (Foroud et al., 1995) showed that cognitive deficits correlated with the number of CAG repeats in asymptomatic carriers of the HD gene, other studies found no correlation between cognitive decline and CAG repeats in symptomatic patients with HD (Zappacosta et al., 1996). Tasks requiring psychomotor or visuospatial processing, such as skills tested by the Trail Making B and Stroop Interference Test, are impaired early in the course of the disease and deteriorate at a more rapid rate than memory impairment (Bamford et al., 1995). Progressive decline in attention and executive function, consistent with frontostriatal pathologic findings, has been identified in early HD (Ho et al., 2003). In the PREDICT-HD study, mild cognitive impairment was noted in nearly 40% of 575 patients before motor diagnosis of HD (Duff et al., 2010). Furthermore, cognitive dysfunction has been linked to mobility impairments in HD. In a

retrospective study of 70 HD patients, mobility as reported on gait and balance measures correlated with executive function cognitive measures (phonemic verbal fluency, Symbol Digit Modalities Test, and Stroop Test); the latter two cognitive tests were significant predictors of the Tinetti Mobility test scores (Kloos et al., 2017). Compared with age-matched controls, HD patients ($n = 17$) had worse postural control under dual-task conditions and decreased visuospatial performance that correlated with greater total sway and jerk balance measures (Purcell et al., 2019). In addition to deficits in visual and auditory perception, patients with HD have impaired recognition of emotional facial expression (Sprenkelmeyer et al., 1996). Social cognition may be impaired in symptomatic and premanifest HD (Bora et al., 2016), with a meta-analysis demonstrating that HD patients were significantly impaired on theory of mind and emotion recognition to both facial and vocal stimuli, particularly in negative emotional contexts. Speech and language also may be affected in HD, possibly as result of striatal degeneration (De Diego-Balaguer et al., 2008). One study showed that high levels of insulin-like growth factor I (IGFI) are associated with cognitive deficits in HD (Saleh et al., 2010).

Asymptomatic at-risk individuals who are positive for the HD gene or the marker do seem to differ in their cognitive performance from asymptomatic at-risk individuals who are negative for the HD gene or marker (Foroud et al., 1995; Giordani et al., 1995; Lawrence et al., 1998). Most studies have found that neuropsychological tests do not differentiate between presymptomatic individuals who are positive for the HD gene and those who are negative (Strauss and Brandt, 1990; de Boo et al., 1997), but some studies have found that cognitive changes might be the first symptoms of HD (Hahn-Barma et al., 1998). In a longitudinal study by the Huntington Study Group of 260 individuals who were considered to be at risk for HD, Paulsen and colleagues (2001b) found that this group had worse scores on the cognitive section of the UHDRS at baseline, an average of 2 years before the development of motor manifestations of the disease.

Other features

In addition to motor, psychiatric, and cognitive changes, many HD patients lose weight during the course of their disease, despite increased appetite (Marder et al., 2009). Weight loss in HD increases with higher CAG repeats (Aziz et al., 2008). Weight loss is not unique for HD among the neurodegenerative disorders; for example, it is typically seen in patients with Parkinson disease (PD) (Jankovic et al., 1992). The pathogenesis of weight loss in HD is unknown, but one study showed that patients with HD have a 14% higher sedentary energy expenditure than that of controls and that this appears to be correlated with the severity of the movement disorder (Pratley et al., 2000). Although chorea and dystonia were not major determinants of disability, chorea was associated with weight loss. The lower body mass index in HD parallels the weight loss in transgenic mice, suggesting that it represents a clinical expression of the gene abnormality associated with HD (Djousse et al., 2002; Aziz et al., 2008). Weight loss, alterations in sexual behavior, and changes in wake-sleep cycle in HD have been attributed to involvement of the hypothalamus even in early stages of HD as demonstrated by positron emission tomography (PET) and post-mortem studies (Politis et al., 2008).

Juvenile Huntington disease

About 10% of HD cases have their onset before age 20, termed juvenile HD. Juvenile HD is usually inherited from the father (paternal versus maternal inheritance for patients with onset before age 10 years is 3:1). Juvenile HD is associated with higher CAG repeats (Andresen et al., 2007; Koutsis et al., 2013), typically greater than 50 CAG repeats. In one study, 54% of juvenile HD cases had 60 or more CAG repeats (Ribai et al., 2007). In one case of HD, associated motor neuron disease may have accounted for the progressive muscle atrophy (Sadeghian et al., 2011). Juvenile HD typically manifests with the combination of progressive parkinsonism, dementia, ataxia, myoclonus, and seizures and with less chorea than adult-onset HD. In one study of juvenile HD, 33% had seizures, generalized tonic-clonic being the most common, followed by tonic, myoclonic, and staring spells (Cloud et al., 2012). Myoclonus is particularly common in patients with juvenile HD (Video 13.10) (Rossi et al., 2012), and progressive myoclonic epilepsy has been reported as the initial presentation of juvenile HD (Gambardella et al., 2001) (Videos 13.10, 13.11, 13.12). Duration of illness is approximately 5 to 15 years. ▶

Assessments

The UHDRS was developed to assess and quantify various clinical features of HD, specifically motor function, cognitive function, behavioral abnormalities, and functional capacity (Huntington Study Group, 1996; Siesling et al., 1998). A shortened version of the UHDRS has been validated (Siesling et al., 1997). When so-called “soft signs” are identified at the initial evaluation, the cumulative relative risk for HD diagnosis at 1.5 years is 4.68 times greater than in controls (Langbehn et al., 2007). Although in contrast to other neurodegenerative diseases such as Alzheimer disease (AD) and PD, HD has an excellent “trait” biomarker, namely the genetic test for expanded CAG repeats; however, there is a need to develop a sensitive “state” biomarker that would reliably monitor the progression of the disease (Weir et al., 2011). In a systematic review and meta-analysis of clinical variables, the UHDRS Motor, UHDRS Independence, and Trail B were found to be the best determinants of separation between HD stages (Franciosi et al., 2013). In a meta-analysis of randomized controlled trials (RCTs) and cohorts to determine the most appropriate outcomes, the TFC score and the TMS of the UHDRS were considered the most appropriate outcomes (Salem et al., 2014). The lowest number of subjects required per group in an RCT was 19 (for TFC) and 30 (for TMS). The verbal fluency test was most appropriate to assess cognition. To longitudinally assess patients at advanced stages of HD, a specifically designed instrument, UHDRS-For Advanced Patients (UHDRS-FAP), was developed and found to be more sensitive to change than the original UHDRS for both motor and cognitive domains (Youssov et al., 2013). An index, referred to as CAP, consisting of $\text{age} \times (\text{CAG} - 30 - L)$, where age is the current age of the individual, CAG is the repeat length, and L is a constant near the threshold of CAG repeat expansions for disease seems to be a good predictor of clinical progression (Ross et al., 2014).

Regarding early clinical detection, Siemers and colleagues (1996) found subtle but significant abnormalities in simple

Video 13.10 Huntington disease (HD).

Video 13.11 Huntington disease (HD).

Video 13.12 Huntington disease (HD).

and choice movement time and reaction time in 103 truly presymptomatic carriers of the HD gene. These deficits correlated well with number of CAG repeats. In a follow-up longitudinal study of 43 at-risk individuals, Kirkwood and colleagues (1999) found that the following variables declined more rapidly among the presymptomatic gene carriers ($n = 12$) than among the noncarriers ($n = 31$): psychomotor speed (digit symbol subscale of the Wechsler Adult Intelligence Scale), optokinetic nystagmus, and rapid alternating movements. In contrast to the UHDRS, which is not very sensitive in detecting early clinical signs of HD, careful gait and balance analysis has detected gait bradykinesia and dynamic balance impairment in presymptomatic HD gene carriers with otherwise normal neurologic examination (Rao et al., 2008). In the PREDICT-HD study, 505 at-risk individuals, 452 of whom had more than 39 CAG repeats, but have not yet met clinical criteria for the diagnosis of HD, the striatum MRI volume decreased from 17.06 cm³ at diagnostic confidence level of 0 to 14.89 cm³ at diagnostic confidence level of 3 (probable HD, with a mean CAG repeat number of 44 and mean motor UHDRS score of 16.92) (Paulsen et al., 2006). The study found that smaller striatal volume, reduced finger tapping speed and consistency, and impaired odor identification were among the best markers of “preclinical” HD (Paulsen et al., 2008). Additional analyses found that even subtle abnormalities in finger tapping (bradykinesia), tandem gait, Luria test, saccade initiation, and chorea were associated with high probability of disease diagnosis (Biglan et al., 2009). The Luria manual sequencing task, which consists of three steps (make a fist, tap ulnar aspect of open palm, palm down fingers extended) is often abnormal in patients with frontal dysfunction. Of the 1078 individuals with a CAG expansion included in the analysis of the PREDICT-HD, followed for up to 12 years (mean: of 5.1 years), 225 (21%) received a motor diagnosis of HD during the study (Paulsen et al., 2014). The strongest predictors were in the motor, imaging, and cognitive domains: an increase of 1 SD in TMS (motor domain) increased the risk for a motor diagnosis by 3.1 times, a reduction of 1 standard deviation (SD) in putamen volume (imaging domain) increased risk by 3.3 times, and a reduction of 1 SD in Stroop word score (cognitive domain) increased risk by 2.3 times.

Several reviews from the International Parkinson’s Disease and Movement Disorder Society on rating scales used in HD have been published (Mestre et al., 2016, 2018a, 2018b, 2018c, 2018d). From six rating scales assessing motor features of HD, excluding performance testing and quantitative motor rating methods, only the UHDRS-TMS was classified as “recommended” (Mestre et al., 2018a). Regarding behavioral symptoms, three rating scales were “recommended” for screening purposes, including the Irritability Scale for Irritability, Beck Depression Inventory–II, and Hospital Anxiety and Depression Scale for depression (Mestre et al., 2016). Assessment of behavioral symptoms can be challenging because multiple behavioral symptoms occur together, patients may have limited insight, and scales may be targeted to capture severity or change with intervention or time. Regarding cognition, the Montreal Cognitive Assessment (MoCA) was “recommended with caveats” for evaluating severity of cognitive impairment but “suggested” for screening (Mestre et al., 2018b). Several other scales such as the UHDRS Cognitive Assessment, the UHDRS–For Advanced Patients cognitive section, the Alzheimer’s Disease Assessment Scale–Cognitive Subscale,

the Frontal Assessment Battery, the Mattis Dementia Rating Scale, the Mini-Mental State Examination, and the Repeatable Battery for the Assessment of Neuropsychological Status were “suggested” for evaluating severity of cognitive impairment. Smartphone-based cognitive assessments for performance-based cognitive tasks have been explored in a pilot study of manifest and premanifest HD, demonstrating feasibility and medium to strong correlations with more “traditional” cognitive tasks; further investigation of mobile technologies for cognitive and other clinical features of HD will be needed (McLaren et al., 2021). Given the effects of HD on functional ability, several performance-based measures (e.g., balance, walking, and reaching/grasping) have been examined. In the review, three performance-based measures were rated as “recommended”: the Tinetti Mobility Test for screening of fall risk and for severity assessment of mobility in patients with manifest HD (up to stage III); the BBS for severity of balance impairment; and the Six-Minute Walk Test for assessment of walking endurance (severity) in HD subjects with preserved ambulation (Mestre et al., 2018c). Quality of life, as reported by both patient- and caregiver-reported outcome measures, is recognized as an important determinant in HD. Studies have shown that the “work” and “alertness behavior” domains of the Sickness Impact Profile are affected the most (Helder et al., 2001) and that depressive mood and functional disability as measured by the 36-Item Short-Form Health Survey are key factors in health-related quality of life in HD (Ho et al., 2009). In the recent critique, the Medical Outcomes Study 36-Item Short-Form Health Survey as “recommended” for patient-outcomes but that further validation of HD-specific health-related quality of life measures was needed.

Natural course

The natural course of HD varies with an average duration of illness from onset to death of about 15 years for adult HD. The duration of illness is about 4 to 5 years shorter for the juvenile variant. Patients with juvenile onset (younger than 20 years) and with late onset (older than 50 years) of symptoms have the shortest duration of the disease (Foroud et al., 1999; Ross et al., 2014) (Fig. 13.1) (Videos 13.11, 13.12). Clinicopathologic studies reveal a strong inverse correlation between the age at onset and the severity of striatal degeneration (Myers et al., 1988). A review of clinical and pathologic data in 163 HD patients showed that patients with juvenile or adolescent onset had a more aggressive disease progression than did patients with onset in middle and late life. ►

Information regarding rates of decline comes from several longitudinal cohort studies and clinical trials. Using the TFC scale, longitudinal follow-up of patients with HD showed a 0.72 unit/year rate of decline (Marder et al., 2000). One study showed that late-onset (mean: 68.6 years) HD patients had a more rapidly progressive course than those with usual age at onset (mean: 49.7 years), reaching a severe stage of illness on average 2.8 years earlier than usual-onset HD patients ($P = 0.046$) (Koutsis et al., 2014). Furthermore, gait unsteadiness was more common at presentation in late-onset HD ($P = 0.007$), but there were no other distinguishing features compared with patients with usual age at onset. The CARE-HD study comparing coenzyme Q10 and remacemide, although ineffective therapeutically, provided natural history data, revealing that the Functional Assessment

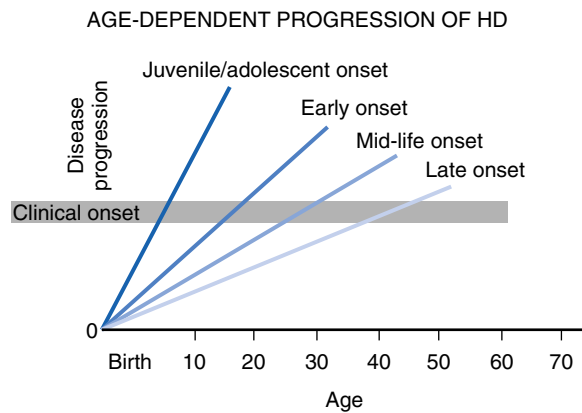


Fig. 13.1 Progression of Huntingtin disease related to age at onset.

score decreased by 2.51 points, TFC score decreased by 1.95 points, and the Independence Scale score decreased by 8.58 points after 20 months (Huntington Study Group, 2001). In another study (COHORT), 334 patients with HD and 142 caregiver and spouse controls who had no genetic risk for HD were followed for at least 3 years. There was an annual increase of 3 points on UHDRS TMS, 0.3-point increase in UHDRS chorea score, and TFC decline by 0.6 points per year (Dorsey et al., 2013). Rate of progression in a cohort of 1026 HD patients followed for a median of 2.7 years was reported to be significantly more rapid with a younger age at onset and longer CAG repeat lengths (Mahant et al., 2003). Based on a prospective study of 569 subjects followed for about 8 years, CAG repeat length alone showed a statistically significant but small effect on the progression of all clinical measures with smaller CAG expansions associated with slower decline (Rosenblatt et al., 2012). Some patients, however, have pathologic CAG expansions but more “benign” and nonprogressive courses (Dosa et al., 2013). There is emerging evidence that prodromal manifestations of HD can begin in childhood, even though the motor and behavioral symptoms do not become manifest until several decades later. This raises questions as to whether HD is a developmental (“loss-of-function”) disorder and not just a neurodegenerative (“gain-of-function”) disorder (Nopoulos et al., 2011; Marder and Mehler, 2012).

Progressive motor dysfunction, dementia, dysphagia, and incontinence can eventually lead to institutionalization and death from aspiration, infection, and poor nutrition (Leopold and Kagel, 1985). Those HD patients residing in a skilled nursing facility (7.4% in one study of 3070 diagnosed HD patients) had worse motor and psychiatric features (e.g., chorea, bradykinesia, gait and balance impairment, obsessions, compulsions, delusions, auditory hallucinations, and aggression) compared with their counterparts living at home (Wheelock et al., 2003).

Neuroimaging

A variety of neuroimaging techniques have been used in HD, ranging from structural MRI (volume and cortical thickness-based, diffusion weighted imaging tractography), resting state functional MRI, to nuclear medicine scans (single-photon PET [SPECT], PET) to define metabolic and cerebral blood flow profiles, neuroinflammation, and other receptor

binding, and in both symptomatic and premanifest HD. Caudate atrophy, as measured by the ratio of intercaudate to outer-table distances, has traditionally been used as an index of striatal atrophy in HD. In addition, volume loss of the putamen on structural MRI has been shown to be a more sensitive index of neurologic dysfunction than was caudate atrophy (Harris et al., 1992; Rosas et al., 2001). Striatal atrophy represents the most consistent MRI change in HD, with reductions of 50% to 54% in mean putamen volume and 28% to 29% mean caudate volume in mild to moderate HD (Harris et al., 1992, 1996). Putaminal involvement suggests that this structure could be underdeveloped in HD or affected early by atrophy. Interestingly, the loss of medium spiny neurons correlates well with chorea in the putamen but not in the caudate (Guo et al., 2012). Striatal volume loss on MRI correlates with length of CAG repeats, age of onset, disease duration, and motor and cognitive impairment (Rosas et al., 2001; Aylward, 2014; Niccolini and Politis, 2014). Using multimodal MRI to measure changes in macrostructural (volume) and microstructural (diffusivity) measures in 40 patients with premanifest HD, 36 patients with symptomatic HD, and 36 healthy controls over three testing sessions spanning 30 months, the investigators found greater longitudinal atrophy in participants with symptomatic HD in whole brain, gray matter, caudate, and putamen and increased caudate fractional anisotropy (FA) and caudate volume loss (Dominguez et al., 2015). Cortical thinning also appears early in HD, may exhibit a posterior to anterior direction topographic progression, and suggests that different regional patterns may be associated with different HD symptoms. For example, HD patients with greater bradykinesia had greater cortical volume loss in premotor and supplementary motor area regions compared with those with chorea (Rosas et al., 2008). Regional cortical changes also correlated with clinical measures of TFC, UHDRS, and cognitive tests.

Structural imaging of gray and white matter has been studied in premanifest HD. Prospective, longitudinal cohort studies such as TRACK-HD and PREDICT-HD demonstrate that striatal volume loss predicts disease onset in pre-HD (Tabrizi et al., 2013; Aylward 2014). In one study, intracranial volume obtained from MRI scans in 707 subjects who have undergone presymptomatic gene testing showed a significantly smaller intracranial volume in prodromal males with a 4% smaller mean volume compared with controls (Nopoulos et al., 2011), again suggesting a role of mutant huntingtin (mHtt) in neurodevelopment. Pre-HD individuals have been found to have reduced gray matter and white matter volumes, including basal ganglia–thalamocortical pathways (Stoffers et al., 2010). In another study, not only were the volumes of the caudate nucleus and putamen reduced in premanifest HD long before predicted onset (longer than 10.8 years), but atrophy of the accumbens nucleus and pallidum was also apparent in premanifest HD (van den Bogaard et al., 2011). In addition, the 12-month whole-brain atrophy rates were greater in early HD individuals and premanifest gene-positive carriers less than 10.8 years from predicted diagnosis compared with controls (Tabrizi et al., 2011); whole-brain and caudate atrophy rates correlated with UHDRS TFC scores, cognitive tests, and quantitative motor measures. Using voxel-based morphometry for gray matter atrophy in premanifest and early-HD participants in TRACK-HD, decreased composite UHDRS scores correlated with reduced gray matter volume in the basal ganglia and

parietal, occipital, and insular cortices and longitudinally with gray matter volume in occipital and parietal cortices, which may relate to impairment in visuospatial and visuomotor functions present in HD (Estevez-Fraga et al., 2021). White matter atrophy has been reported up to 12 to 15 years before HD onset and correlates with greater CAG repeats and motor and cognitive decline (Paulsen et al., 2010). Diffusion tensor imaging (DTI) studies demonstrate white matter tract abnormalities in premanifest HD gene carriers. Alterations in diffusion indices correlated with cognitive performance and with the probability of phenotypic conversion (Rosas et al., 2006; Dumas et al., 2012; Estevez-Fraga et al., 2020). A meta-analysis of 140 pre-HD, 235 symptomatic HD, and 302 controls revealed significantly increased FA in the caudate, putamen, and GP, but decreased FA in the corpus callosum of both pre-HD and symptomatic HD patients compared with controls (Liu et al., 2016). Increased mean diffusivity was found in the putamen and thalamus of pre-HD and symptomatic HD patients, but only in the caudate of those with HD with symptoms. Other imaging studies have suggested that myelin breakdown and changes in ferritin iron distribution underlie the regional toxicity and may be important in pathogenesis of HD (Bartzokis et al., 2007; Dumas et al., 2012).

PET studies such as with ^{18}F -2-fluoro-2-deoxyglucose and SPECT studies demonstrate hypometabolism and reduced regional cerebral blood flow in the basal ganglia and the cortex (Kuwert et al., 1990; Hasselbach et al., 1992; Harris et al., 1999). These measurements may reflect neuronal integrity and synaptic function. PET studies of presymptomatic HD carriers have shown initial (compensatory) thalamic hypermetabolism with subsequent decline heralding the onset of HD symptoms and signs in a setting of steady decline of striatal raclopride binding (Feigin et al., 2007). Abnormalities in striatal metabolism measured by PET scans may precede caudate atrophy (Grafton et al., 1990). Regional cerebral metabolic rate of glucose consumption has been found to be decreased by 62% in the caudate, 56% in the lenticular nucleus, and by 17% in the frontal cortex (Kuwert et al., 1990). Bilateral reduction in the uptake of technetium-99m hexamethylpropyleneamineoxime (HM-PAO) and iodine-123 isositol monophosphatase (IMP) in the caudate and putamen has been demonstrated by SPECT in patients with HD (Nagel et al., 1991). Using PET and [^{11}C]flumazenil binding to gamma-aminobutyric acid (GABA) receptors in the striatum, König and colleagues (2000) found marked reduction in the caudate (but not in the putamen) of HD patients compared with normal controls. The authors interpreted these findings as indicative of compensatory GABA receptor upregulation in the striatal (putamen) GABAergic medium spiny neurons projecting to the pallidum.

Because microglial activation has been found to be correlated with neuronal degeneration and may play a role in the pathogenesis of HD, techniques designed to image microglial activation, such as [^{11}C](R)-PK11195 PET have been examined (Niccolini and Politis 2014). PET evidence of microglia activation correlates with severity of the disease (e.g., UHDRS score) and is inversely related to D2 density as demonstrated by raclopride PET studies (Pavese et al., 2006). Similar findings were reported in presymptomatic HD gene carriers who had lower striatal raclopride binding than the controls but significantly higher striatal and cortical PK binding (Tai et al., 2007). This study provided strong evidence that widespread microglial activation occurs even

Table 13.1 Huntington's disease: neuropathology

Neuronal loss and gliosis in the cortex and striatum (caudate and putamen)
Early loss of medium-sized, spiny striatal neurons: SNpc, GPe, SNr, GPi
Loss of large (17–44 μm) striatal interneurons
Loss (<40%) of neurons in SN
Intranuclear inclusions and dystrophic neurons in cortex and striatum
GPe, Globus pallidum externus; GPi, globus pallidum internus; SN, substantia nigra; SNpc, SN compacta; SNr, SN pars reticulata.

in preclinical stages of HD and that this early pathologic change correlates with striatal neuronal dysfunction.

Neuropathology and neurochemistry

Pathologic studies provide evidence for primary involvement of the basal ganglia–thalamocortical circuitry in HD (Joel, 2001). Postmortem changes in HD brains include neuronal loss and gliosis in the cortex and the striatum, particularly the caudate nucleus (Table 13.1). Based on a detailed neuropathologic examination of a total of 523 HD brains, the investigators found that the size of the expanded CAG repeat correlates well with the degree of striatal but not cortical pathology (Hadzi et al., 2012). Morphometric analysis of the prefrontal cortex in HD patients reveals loss of cortical pyramidal cells, particularly in layers III, V, and VI (Sotrel et al., 1991). At the cortical level, motor dysfunction seems to correlate with primary motor cortex cell loss, whereas mood symptomatology is associated with cell loss in the cingulate cortex (Thu et al., 2010). Chorea seems to be related to the loss of medium spiny striatal neurons projecting to the lateral pallidum (globus pallidum externus [GPe]), whereas rigid-akinetic symptoms correlate with the additional loss of striatal neurons projecting to the substantia nigra compacta (SNpc) and medial pallidum (globus pallidum internus [GPi]) (Albin, Young et al., 1990; Albin, 1995). Pathologic studies have suggested that the earliest changes associated with HD consist of degeneration of the striato-SNpc neurons followed by striato-GPe and striato-SNr pars reticulata (SNr) neurons and finally striato-GPi neurons (Hedreen and Folstein, 1995; Albin, 1995) (Fig. 13.2). Pallidal degeneration has been found to correlate with many of the clinical symptoms of HD (Singh-Bains et al., 2016).

The number of CAG repeats correlates with severity of pathologic condition such that longer CAG repeat lengths are associated with greater neuronal loss in the caudate and putamen (Furtado et al., 1996). Significant association between pronounced mood dysfunction and loss of the GABA_A receptor marker in striosomes of the striatum has been found in an autopsy study of 35 HD brains and 13 controls (Tippett et al., 2007). Increased density of oligodendroglia and intranuclear inclusions were found in the tail of the caudate nucleus among presymptomatic HD gene carriers, suggesting that pathologic changes occur long before the onset of symptoms (Gómez-Tortosa et al., 2001). There is also evidence of increased iron in this brain area as measured by MRI, which in part might contribute to the regional neurotoxicity (Bartzokis et al., 2007; Dumas et al., 2012). Besides basal ganglia and cortical involvement, the brainstem and other regions can be implicated in HD, with one clinicopathologic study demonstrating consistent neuronal loss in the SN, pontine nuclei, reticulotegmental nucleus

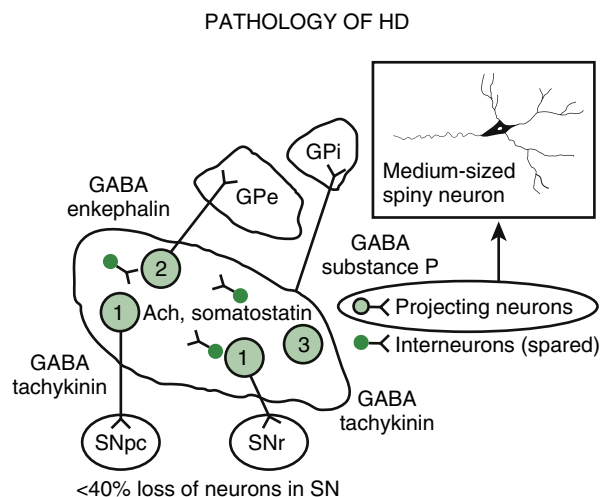


Fig. 13.2 Pathologic changes associated with Huntington disease from the earliest stages (1) to more advanced stages (3). ACh, Acetylcholine; GABA, gamma-aminobutyric acid; SN, substantia nigra; SNpc, pars compacta; SNr, substantia nigra pars reticulata (SNr).

of the pons, superior and inferior olives, in the area of the excitatory burst neurons for horizontal saccades, raphe interpositus nucleus, and vestibular nuclei, along with immunoreactive intranuclear neuronal and axonal inclusions in these areas (Rub et al., 2014). Although HD has been traditionally considered a degenerative disease of the brain, mutant *Htt* is ubiquitously expressed throughout the body, and HD is now recognized to be associated with abnormalities in peripheral tissues (van der Burg et al., 2009). Moreover, HD has been hypothesized to be a tauopathy because aggregated tau inclusions have been found in various structures of the brain; thus, the tau haplotype may influence cognitive function in HD, and the mutant *Htt* protein could alter tau splicing, phosphorylation, oligomerization, and subcellular location and potentially lead to anti-tau target strategies for HD (Gratuzze et al., 2016; Masnata et al., 2020).

Using specific monoclonal antibodies against phosphorylated and nonphosphorylated neurofilaments and neuronal cell adhesion molecules, Nihei and Kowall (1992) found marked abnormalities in these cytoskeletal components in the striatal neurons of HD brains. The earliest degenerative changes, such as the loss of medium-sized spiny neurons containing calbindin, enkephalin, and substance P immunoreactivity, occur in the dorsomedial aspect of the caudate and putamen (Ferrante et al., 1991). The enkephalin neurons appear to die before the substance P neurons. In contrast, the spiny striatal cholinergic and somatostatin-containing interneurons are spared. As a result of these degenerative changes, the matrix zone of the striatum is reduced in size and the patches (striosomes) remain unaltered. In one postmortem study, however, calbindin D28k mRNA in the striata of HD brains was normal whereas the preproenkephalin neurons were markedly reduced in the HD caudate nucleus (Richfield et al., 1995). Another class of medium-sized (8–18 μ m) striatal interneurons, characterized by intense immunostaining against calcium-binding protein calretinin, was found to be markedly increased in the striatum of brains of patients with HD compared with controls (Cicchetti and Parent, 1997). In contrast, the density of the larger, 17- to 44- μ m, interneurons was markedly decreased. Both populations of

interneurons express calretinin, the implication of the findings of the study is that calretinin, for some yet unknown reason, protects the medium-sized neurons but not the large neurons against HD-related degeneration. Curtis and colleagues (2003) observed an interesting phenomenon in the brains of patients with HD. When they were compared with non-HD control brains, there was marked increase in cell proliferation in the subependymal layer and the degree of cell proliferation increased with pathologic severity and increasing CAG repeats in the HD gene. These results suggest that progenitor cell proliferation and neurogenesis occur in the diseased adult human brain, providing further evidence for regeneration.

Huntingtin (*Htt*), the product of the HD gene, is expressed throughout the brain in both affected and unaffected regions; therefore, its contribution to neurodegeneration in HD is unclear. It has been postulated that the wild-type protein is involved in embryonic development and survival and cellular signaling and transport. Mutant *Htt* has been hypothesized to act by a toxic “gain of function” and thereby affects cellular and synaptic function. Because expression of *Htt* mRNA was not selectively increased in the neurons that were particularly susceptible to degeneration in HD, the gene mutation may not be sufficient to produce the disease and that other factors probably also contribute to its pathogenesis (Landwehrmeyer et al., 1995). An immunohistochemical study showed that neuronal staining for *Htt* is reduced in the striatal medium-sized spiny neurons, but the large striatal neurons that are spared in HD retain normal levels of *Htt* (Sapp et al., 1997). Surprisingly, however, *Htt* staining was markedly reduced in both segments of the GP. This suggests a postsynaptic response to a reduction in striatal inputs; or it might indicate that the GP is for some yet unknown reason preferentially involved in HD. N-terminal mutant *Htt* binds to synaptic vesicles and inhibits their glutamate uptake in vitro (Li et al., 2000). Using a transgenic mouse model generated by introducing mutant polyQ tract into one of the mouse genes, Li and colleagues (2000) found aggregated *Htt* only in medium striatal neurons, neurons that are most susceptible to degeneration in HD. The aggregated *Htt* was first found in neuronal nucleus and later in synaptic terminals. Scherzinger and colleagues (1999) found that the aggregation of *Htt* protein is time- and concentration-dependent, suggesting “a nucleation-dependent polymerization.” Aggregation was proportional to repeat length and no aggregation could be induced for a repeat length of 27 or fewer glutamines. This might in part explain the inverse correlation of repeat length and age at onset. Because the probability of neural death in HD with time is constant and the age at onset is inversely dependent on the length of repeats, it has been suggested that the polyglutamine aggregates are toxic when directed to the nucleus and cause the cell death in HD (Yang et al., 2002). This is supported by the physics of protein aggregation as a result of transition to a new intramolecular configuration (Perutz and Windle, 2001).

Neuronal intranuclear inclusions and dystrophic neurites are found in the cortex and striatum in HD (DiFiglia et al., 1997). These neuronal intranuclear inclusions have been found in all cortical layers and medium-sized striatal neurons, particularly in juvenile HD cases and also in the cytoplasm. Spherical and slightly ovoid dystrophic neurites have been identified in cortical layers 5 and 6. Ubiquitin

staining can be used to localize these inclusions, which are composed of granules, straight and tortuous filaments, and fibrils, but not membrane bound. Similar inclusions have been demonstrated in the HD transgenic mouse (Davies et al., 1997). Because the aggregates in the nucleus consist mostly of N-terminal fragments of the whole *Htt* protein, it has been postulated that the protein has to be cleaved before it enters the nucleus. Mutant *Htt* fragments accumulate in axon terminals and interfere with glutamate uptake (Li et al., 2000) and, as occurs in other polyglutamine disease, impair axonal transport (Szebenyi et al., 2003; Gunawardena and Goldstein, 2005). Using a yeast artificial chromosome transgenic mouse model of HD, Tang and colleagues (2005) found that repetitive application of glutamate elevates cytosolic Ca^{++} levels in medium spiny neurons from the HD mouse but not from the wild-type or control mouse. One study using yeast artificial chromosome (YAC128) mice and initiating tetrabenazine (TBZ) treatment at 2 months of age ("early" TBZ group) and at 6 months of age ("late" TBZ group) found that both "early" and "late" TBZ treatments alleviated motor deficits and reduced striatal cell loss in YAC128 mice (Wang et al., 2010). Abnormal Ca^{++} signaling seems to be directly linked with the degeneration of medium spiny neurons in the caudate nucleus in HD. Studies with YAC128 transgenic HD mouse model provide evidence for a connection between glutamate receptor activation, disturbed calcium (Ca^{++}) signaling, and apoptosis of HD striatal neurons (Tang et al., 2005, 2007). Furthermore, glutamate and dopamine signaling pathways acting via D1 receptors induce elevation of Ca^{++} signals and cause TBZ-induced striatal cell loss in these mice. Further support and mechanistic insight comes from studies using *Drosophila* that express expanded full-length human huntingtin and elevated intracellular Ca^{++} levels (Romero et al., 2008). The increased calcium leads to increased neurotransmitter release, motor dysfunction, and progressive neuronal degeneration. Partially blocking calcium channel activity or partially impairing neurotransmission restores the calcium levels and motor dysfunction and suppresses neurodegeneration.

Although some studies have shown a moderate (40%) degree of neuronal degeneration in the SN, particularly noticeable in the medial and lateral thirds (Oyanagi et al., 1989), this is probably not sufficient to cause bradykinesia either in choreic or rigid-akinetic HD patients (Albin, Reiner et al., 1990). Measurements of brain dopamine concentrations and cerebrospinal fluid (CSF) homovanillic acid (HVA) levels have yielded conflicting results (Table 13.2). In one study, CSF HVA was normal in 51 patients with early HD, and there was no correlation between HVA levels and degree of parkinsonism (Kurlan et al., 1988). Dopamine, acetylcholine, and serotonin receptors are decreased in the striatum. Using PET imaging of dihydrotetrabenazine as a marker of striatal vesicular monoamine transporter (VMAT) type-2, Bohnen (2000) found reduced binding especially in the posterior putamen, similar to PD, particularly in patients with akinetic-rigid HD. Postsynaptic loss of dopamine receptors might play a role in the parkinsonian findings in some HD patients (Sánchez-Pernaute et al., 2000). Dopamine D2 receptors, imaged with iodobenzamide-SPECT, provide evidence of D2 receptor loss in HD (Brucke et al., 1991). Using PET to measure binding of specific D1 and D2 receptor ligands in the striatum, Weeks and colleagues (1996) found

Table 13.2 Huntington's disease: neurotransmitters, peptides, and receptors

↓↓ CAT
↓↓ GABA, GAD
↓↓ Enkephalin, substance-P, cholecystokinin, angiotensin, and met-enkephalin
↑ somatostatin, TRH, neurotensin, neuropeptide-Y
↓ Glutamate (↑ CSF glutamate)
↑↑ 3-Hydroxyanthranilic acid oxidase, DA, GABA, cholinergic-muscarinic, and benzodiazepine receptors
↓↓ NMDA, ↓ phencyclidine and quisqualate receptors

CAT, choline acetyl transferase; CSF, cerebrospinal fluid; DA, dopamine; GABA, gamma-aminobutyric acid; GAD, glutamic acid decarboxylase; NMDA, N-methyl-D-aspartate receptors; TRH, thyroid releasing hormone.

that these two receptors are markedly decreased in individuals who have the HD mutation but who are still presymptomatic. In another study, Andrews and colleagues (1999) showed that loss of striatal D1 and D2 binding as determined by PET was significantly greater in the known mutation carriers than in the combined at-risk and gene-negative patients. Although some studies found that the loss of D2 receptors correlates significantly with motor and cognitive slowing (Sánchez-Pernaute et al., 2000), other studies failed to show any correlation between clinical and psychological assessments and the loss of striatal D2 receptors (Pavese et al., 2003). Turjanski and colleagues (1995) showed that HD patients with rigidity had more pronounced reduction of these receptors (also measured by PET) compared with HD patients without rigidity.

Loss of the medium-sized spiny neurons, which normally constitute 80% of all striatal neurons, is associated with a marked decrease in GABA and enkephalin levels. After examining two brains of presymptomatic individuals carrying the HD gene, Albin and colleagues (1992) concluded that striatal neurons projecting to the GPe and SN, but not those that project to the GPi, are preferentially involved in early stages of HD and even in the presymptomatic phase. Likewise, cannabinoid receptors are preferentially lost in the GPe (Richfield and Herkenham, 1994; Blazquez et al., 2011). In contrast, the cholinergic and somatostatin striatal interneurons seem to be relatively spared in HD. Other neuropeptide alterations in HD include a decrease in substance-P, cholecystokinin, and met-enkephalin and an increase in somatostatin, thyrotropin-releasing hormone, neurotensin, and neuropeptide Y. Before any clinical signs, in addition to the loss of cannabinoid receptors, there is also loss of adenosine A2a receptor binding and increased GABA_A receptor binding in the GPe. As the disease progresses, there is typically loss of D1 receptors in the striatum and cannabinoid and D1 in the SN, eventually involving the rest of the basal ganglia. Preferential loss of enkephalinergic striatal neurons correlates with the appearance of chorea (Albin et al., 1992). Loss of substance P/dynorphin neurons correlates with the increase in dystonia in the later stages of disease (see Table 13.2).

Evidence of immune activation not only of central microglia but also of the peripheral system is supported by the findings of increased levels of cytokines, such as interleukin 6 (IL-6) levels in HD gene carriers with a mean of 16 years before the predicted onset of clinical symptoms (Bjorkvist et al., 2008). The same study also found that monocytes from

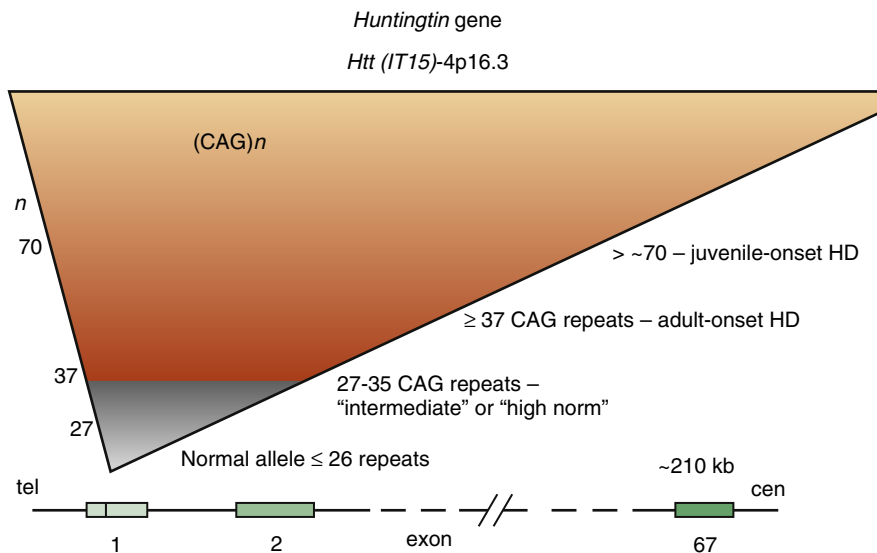


Fig. 13.3 Relationship between CAG repeats and age at onset of Huntington disease (HD). cen, centromere; BDNF, brain-derived neurotrophic factor; tel, telomere.

HD patients expressed mutant *Htt*. Autonomous immune activation was also noted in macrophages and microglia from HD mouse models and in the CSF and striatum of HD patients. There are no reliable peripheral markers of HD, but 24S-hydroxycholesterol, previously found to be associated with neurodegeneration, has been found to be significantly decreased in patients in all stages of HD, although it was not different from controls among premanifest subjects, whereas caudate volume, as measured by MRI morphometry, was significantly decreased even in pre-HD subjects (Leoni et al., 2008). Normal huntingtin protein has been found to participate in regulating cholesterol biosynthesis, but it is still not clear what role cholesterol plays in the pathogenesis of HD (Valenza and Cattaneo, 2011). When 119 blood samples for transcripts associated with HD were screened, the dynamic regulator of chromatin plasticity H2A histone family, member Y (H2AFY), was overexpressed in the blood and frontal cortex of patients with HD compared with controls (Hu et al., 2011). Because histone deacetylase inhibitors, such as sodium phenyl butyrate, reduce H2AFY levels, H2AFY may serve as a potential biomarker of HD.

There has been a growing interest in expression of phosphodiesterase 10A (PDE10A) in the brains of patients with HD, partly because of its therapeutic implications. In 12 early, premanifest HD patients, PDE10A expression was decreased in striatum and pallidum and increased in motor thalamic nuclei, compared with a group of matched healthy controls (Niccolini et al., 2015). A pilot study involving 8 patients with HD to evaluate whether striatal [(18)F]MNI-659 PET imaging of PDE10 found that this biomarker is useful to track HD disease progression (Russell et al., 2016).

Genetics

For some time, HD has been regarded as truly an autosomal-dominant disease in that homozygotes were thought to be no different from heterozygotes (Cubo et al., 2019). Linkage studies in HD families from various ethnic origins and countries have found that, despite the marked variability in phenotypic expression, genetic heterogeneity is unlikely.

Localization of a gene marker near the tip of the short arm of chromosome 4 in 1983 by Gusella and colleagues (1983) initiated an intensive search for the abnormal gene, which was finally cloned 10 years later (Bates et al., 1991; Pritchard et al., 1991; Wexler et al., 1991; Huntington's Disease Collaborative Research Group, 1993). The mutation that is responsible for the disease consists of an unstable enlargement of the CAG repeat sequence in the 5' end of a large (210 kb) gene, *huntingtin* (*Htt*), also called *IT15* (Huntington's Disease Collaborative Research Group, 1993). This gene, located at 4p16.3, contains 67 exons and encodes a previously unknown 348-kDa protein, named *Htt*, without homology to known protein sequences (Fig. 13.3). The expanded CAG repeat, located in exon 1, alters *Htt* by elongating a polyglutamine segment near the NH₂-terminus. Besides DNA CAG length, larger somatic CAG repeat length expansions (somatic instability) are associated with earlier disease onset and probably more rapid progression (Swami et al., 2009).

A CAG repeat length of greater than 39 is considered fully penetrant and causative of HD. Repeat lengths from 36 to 39 are incompletely penetrant and may be unstable in their transmission size; some people with CAG repeat lengths in this range may develop HD symptoms. CAG repeat lengths from 27 to 35 represent an intermediate range, which is not typically associated with HD symptoms but with transmission could be unstable. Fewer than 27 CAG repeats is considered unaffected. In the literature, the number of repeats has been reported to vary between 10 and 29 copies in unaffected individuals, the HD gene contains 36 to 121 of such repeats (Kremer et al., 1994). There have been case reports of HD symptoms, however, in those with intermediate-sized CAG repeats (27–35). These include a 75-year-old man with a 15-year history of clinical symptoms who had 34 CAG repeats (Andrich et al., 2008) and an autopsy-proven case of HD with 29 CAG repeats (Kenney et al., 2007; Kenney and Jankovic, 2008). In the Prospective Huntington At Risk Observational Study (PHAROS), 50 (5.1%) of the 983 participants had an intermediate allele range of 27 to 35 CAG repeats (Killoran et al., 2013). Those with intermediate alleles were similar to controls (fewer than 26 CAG repeats) on UHDRS motor, cognitive, and functional measures, but

had worse scores on some behavioral measures, particularly apathy and suicidal ideation. In the European HD registry, 657 (5.38%) of 12,190 had fewer than 36 CAG repeats, of whom 76 had intermediate alleles (Cubo et al., 2016). Compared with controls, the older intermediate allele carriers had higher chorea scores and at 1-year follow-up had greater cognitive decline. In the Cooperative Huntington's Observational Research Trial (COHORT) study, those with intermediate alleles differed in scores of some motor, cognitive, and behavioral domains of the UHDRS at baseline, and a significantly greater number of subjects with CAG repeats in the intermediate range reported at least one suicide attempt compared with the normal group (Ha et al., 2012). These findings of subtle but relevant motor, cognitive, and behavioral abnormalities in individuals with intermediate CAG repeats have important implications for the pathogenesis of the disease and genetic counseling (Ha and Jankovic, 2012; Squitieri and Jankovic, 2012; Feigin, 2013; Killoran et al., 2013; Migliore et al., 2019; Savitt and Jankovic, 2019). Hendricks and associates (2009) estimated that the probability that a male with intermediate or "high normal" (27–35) CAG repeats in one allele will have an offspring with an expanded penetrant allele ranges from 1/6241 to 1/951. In the largest clinicogenetic study of HD, involving 2318 individuals, the frequency of high normal repeat lengths (27–35) was 2.5% and repeat lengths associated with reduced penetrance (36–39) was 2.7% (Dorsey et al., 2012).

Approximately 11% of patients with clinically suspected HD exhibit no family history of HD, and some of these patients might have "new" mutations (Goldberg et al., 1993; Davis et al., 1994). In a study of 28 patients with clinically probable HD, but without a family history of HD, 25 (89%) patients were confirmed by DNA testing to have HD, and 5 of 16 (31%) patients with clinically doubtful HD had expanded triplet repeats, thereby confirming the diagnosis of HD (Davis et al., 1994). Illustrative cases of instability can be seen, such as in the example of a 50-year-old man with typical symptoms of HD since age 43 but without a family history of HD such that his asymptomatic 80-year-old father and 76-year-old paternal uncle had 30 CAG repeats each, but his maternally derived allele had 17 CAG repeats and his paternally derived allele had 45 CAG repeats (Alford et al., 1996).

Several studies demonstrate that the number of repeats inversely correlates with the age at onset (anticipation) (Duyao et al., 1993; Snell et al., 1993; Ashizawa et al., 1994; Gusella and MacDonald, 1995; Furtado et al., 1996; Brinkman et al., 1997; Nance et al., 1997; Maat-Kievit et al., 2002; Marder et al., 2002; Ravina et al., 2008). Brinkman and colleagues (1997) retrospectively examined the relationship between CAG length and age at onset and found a 50% probability of developing HD symptoms by age 65 when the CAG repeat length is 39 and by age 30 when the CAG repeat length is 50. The inverse relationship between age of onset and number of CAG repeats was confirmed in a Dutch cohort of 755 affected patients (Maat-Kievit et al., 2002). The correlation was stronger for paternal inheritance than for maternal inheritance. CAG repeat length also inversely correlates with late-stage outcomes, such as nursing home admission and placement of percutaneous endoscopic gastrostomy (Marder et al., 2002). One analysis, based on the data from the CARE-HD trial modeled progression over 30 months on

the UHDRS and concluded that 10 additional CAG repeats were associated with 7.7 (63%) increase on the UHDRS TMS and 9.2 (81%) points in progression on the Independence Scale (Ravina et al., 2008). One study showed that increasing CAG repeat size in the normal *Htt* gene diminishes the association between mutant CAG repeat size and disease severity and progression in HD (Aziz et al., 2009). However, other studies suggest no interaction between the mutant and the normal allele with respect to age at onset (Lee et al., 2012). Regarding disease progression, several studies have not found correlations between the CAG repeats and progression (Ashizawa et al., 1994; Kiebert et al., 1994; Claes et al., 1995) or between age at onset and progression of disease (Feigin et al., 1995). The rate of disease progression is generally faster in paternally transmitted HD independent of the CAG repeat length (Ashizawa et al., 1994). There is no difference in the mean number of repeats between patients presenting with psychiatric symptoms and those with chorea and other motor disorders, although, as expected, the rigid juvenile patients have the largest number of repeats (MacMillan et al., 1993; Nance and the U.S. Huntington Disease Genetic Testing Group, 1997). The trinucleotide repeat is relatively stable over time in lymphocyte DNA but may be unstable in sperm DNA, which appears to account for the marked increase in the number of trinucleotide repeats in paternal transmission, leading to a 10:1 ratio of juvenile HD when the affected parent is the father. However, after isolating X- and Y-bearing sperm of HD transgenic mice, Kovtun and colleagues (2004) found that the CAG distribution is the same as that in the founding fathers, suggesting that the "gender-dependent changes in CAG repeat length arise in the embryo."

More recent work has been to investigate the pathogenic process that precedes the onset of HD symptoms using genome-wide association (GWA) analyses (Gusella et al., 2015). In the GeM-HD consortium, GWA signals reveal loci that can modify the age of onset of HD, such that effects at the chromosome 15 locus hasten or delay onset by 6 or 1.4 years, respectively. These invoke effects of *FAN1* and *MTMR10*, respectively, which are involved in DNA repair functions. In addition, a single effect at the chromosome 8 locus hastens onset of HD symptoms by 1.6 years with the involvement of *RMR2B* and *UBR5*, which are genes involved in mitochondrial energetics, oxidative stress, and proteostasis. Another GWA analysis using TRACK-HD ($n = 218$) and REGISTRY ($n = 1773$) data found significant signals on chromosome 5 spanning 3 genes (*MSH3*, *DHFR*, and *MTRNR2L2*) associated with disease progression scores (Tome et al., 2013; Henseman Moss et al., 2017). In TRACK-HD, each copy of the minor allele at the lead single nucleotide polymorphism was associated with a 0.4 unit per year reduction in rate of change in UHDRS TMS and reduction of 0.12 unit per year in rate of change of UHDRS TFC.

Appropriate genetic counseling for presymptomatic, at-risk and symptomatic HD patients undergoing testing is essential (Jankovic et al., 1995). When appropriate genetic counseling and a multidisciplinary approach are used in presymptomatic testing, the risk for adverse events such as psychological distress and depression requiring hospitalization or leading to attempted suicide may be as low as 2% (no difference between carriers and noncarriers) (Goizet et al., 2002). Older studies report that although all the individuals

with positive results experienced transient symptoms of depression, none reported suicidal ideation and 1 year after the results of gene testing were disclosed, both increased-risk and the decreased-risk individuals had overall no increase in depression or deterioration in psychological well-being (Wiggins et al., 1992). A high rate of suicidal ideation, however, was found in a Swedish study of 13 HD carriers and 21 noncarriers (Robins Wahlin et al., 2000). An adjustment to results of testing appears to depend more on the individual's psychological makeup before the testing than on the testing itself (Meiser and Dunn, 2000). Because of potential psychological and legal implications of positive identification of an HD gene mutation in an asymptomatic, at-risk individual, predictive testing must be performed by a team of clinicians and geneticists who are not only knowledgeable about the disease and the genetic techniques, but also sensitive to the psychosocial and ethical issues associated with such testing. Although, as a result of the discovery of the HD gene, the cost of presymptomatic testing has been substantially reduced, the currently recommended extensive pretesting and post-testing counseling is still quite costly. An assessment of the cost-to-benefit ratio should be carried out. When the DNA test for HD became available, it was thought that demand for testing for HD in asymptomatic at-risk individuals would be high (Tyler et al., 1992), but recent studies have not necessarily supported this (Maat-Kievit, et al., 2000), though rates of testing may change if there are potential disease-modifying agents available in the future.

Animal models

Three types of HD transgenic mouse models have been studied: (1) mice expressing fragments, usually one or two exons of the human *huntingtin* gene that contain the polyglutamine expansion (R6/2 and N-171–82Q mice), (2) transgenic mice expressing the full-length human *huntingtin* gene with expanded polyglutamine tract (YAC128 mice); and (3) knock-in mice with pathogenic CAG repeats inserted into the existing CAG expansion (*Hdh^{Q111}*) (Hersch and Ferrante, 2004). Interestingly, the more genetically accurate the model, the more variable and subtle is the phenotype. Thus, fragment models are used more frequently for therapeutic research and these studies are then confirmed in the full-length models. Full-length *Htt*, when expressed in transgenic mice, does not produce neurologic disease, whereas the shortened or truncated form of the protein appears to be toxic to neuronal cells. Except for the mouse model that expresses the full-length *Htt* gene with 72 CAG repeats and that displays selective striatal pathologic features at 12 months of age (Hodgson et al., 1999), all transgenic-mouse cell lines develop intranuclear inclusions and neurodegeneration in widespread areas of the brain. With viral vector-mediated expression, aggregates can be found starting within 5 days after transduction and associated with striatal degeneration in rats and even in primates (Kirik and Bjorklund, 2003). Formation of inclusions correlated with longer CAG expansions and shorter protein fragments. Overexpression of a short fragment of *Htt*, carrying 82 glutamine repeats, in the putamen produced progressive dyskinesia and putamenal intranuclear aggregates and striatal degeneration (Regulier et al., 2003). Although intranuclear inclusions in HD are

traditionally thought to be neurotoxic, recent studies provide evidence that they are actually neuroprotective (Arrasate et al., 2004). Neuronal death was related to the length of polyglutamine expansions in the *Htt* protein, not to the increase in size or number of inclusion bodies. Compounds that promote the formation of inclusions have been shown to lessen the pathologic findings of HD (Bodner et al., 2000).

The R6/2 transgenic mouse line has been studied most extensively (Mangiarini et al., 1999; Ona et al., 1999). These mice develop normally until 5 to 7 weeks of age, when they start manifesting irregular gait, abrupt shuddering movements, and resting tremors, followed by epileptic seizures, muscle wasting, and premature death at 14 to 16 weeks. Striatal neurons show ubiquitinated neuronal inclusions, similar to those seen in the brains of patients with HD. Analysis of glutamate receptors in symptomatic 12-week-old R6/2 mice revealed decreases compared with age-matched littermate controls (Cha et al., 1998). Other neurotransmitter receptors that are known to be affected in HD were also decreased in R6/2 mice, including dopamine and muscarinic cholinergic, but not GABA receptors. D1-like and D2-like dopamine receptor binding was drastically reduced to one-third of controls in the brains of 8- and 12-week-old R6/2 mice. Altered expression of neurotransmitter receptors precedes clinical symptoms in R6/2 mice and may contribute to subsequent pathologic processes. Biochemical analysis at 12 weeks shows a marked reduction in striatal aconitase (Tabrizi et al., 2000), indicative of damage by superoxide (O_2^-) and peroxynitrite ($ONOO^-$), similar to human HD (Tabrizi et al., 1999). In addition, the R6/2 transgenic mouse has a marked reduction in striatal and cortical mitochondrial complex IV activity and increased immunostaining for inducible nitric oxide synthase and nitrotyrosine (Tabrizi et al., 2000). These changes occur before evidence of neuronal death; therefore, the described findings suggest that mitochondrial dysfunction and free radical damage play an important role in the pathogenesis of HD. Indeed, mutant *Htt* has been found to attach to the outer mitochondrial membrane, causing the mitochondria permeability transition pores to open, allowing an influx of calcium and releasing cytochrome c (Choo et al., 2004). N171 mice, in which the transgene is driven by the prion promoter, also have been used as models of HD, but they have not been subjected to as rigorous examination as have the R6/2 mice. In another study, mice in which the *PGC-1 α* gene had been knocked out developed brain lesions in the striatum and *PGC-1 α* levels in those particular neurons were much lower among mice with the HD mutation than in normal mice (Cui et al., 2006). Because *PGC-1 α* is involved in energy metabolism, this study shows that transcriptional repression of *PGC-1 α* leads to mitochondrial dysfunction and supports other studies suggesting that energy deficits contribute to neurodegeneration in HD (Ross and Thompson, 2006). One study of polymorphism in the *PGC-1 α* gene in over 400 individuals with HD concluded that *PGC-1 α* (which is inhibited by mutant *Htt*) has a small modifying effect on the progression of HD (Taherzadeh-Fard et al., 2009).

Important insights into the potential function of *Htt* have been gained by the study of various mouse models in which the HD homolog gene was inactivated (knockout models) (Duyao et al., 1995) or expanded CAG repeats are introduced into the mouse hypoxanthine phosphoribosyltransferase

gene (knock-in models) (Reddy et al., 1999). Homozygous inactivation resulted in embryonic death, suggesting that *Htt* is critical for early embryonic development. Because this model does not mimic adult HD and homozygote individuals apparently are indistinguishable from heterozygotes (Cubo et al., 2019), it suggests that the HD gene mutation involves “gain” rather than “loss” in function. This hypothesis, however, has been challenged because the earlier studies suggesting no phenotypic difference between heterozygous and homozygous HD were based on linkage studies and focused predominantly on the age at onset (Cattaneo et al., 2001). Furthermore, homozygous transgenic mice expressing mutant *Htt* cDNA have a shorter life span than that of heterozygous mice. This suggests that either a double-dose of mutant *Htt* or loss of the normal allele (loss of function) contributes to the disease. Either wild-type or mutant *Htt* is needed for normal brain development. Huntingtin is associated with vesicle membranes and microtubules and as such probably has a role in endocytosis, intracellular trafficking, and membrane recycling. Thus, HD appears to result from new toxic property of the mutant protein (gain of function) and loss of neuroprotective activity of the normal *Htt* (loss of function) (Cattaneo et al., 2001; Borrell-Pages et al., 2006).

In addition to the mouse models, there are other animal models. These include several *Drosophila* models (Zoghbi and Botas, 2002) that have been used to better understand the pathogenic mechanisms of HD-related neurodegeneration and for testing drugs that might have a potential for favorably modifying the disease (Agrawal et al., 2005; Imarisio et al., 2008). For example, expanded full-length *Htt* (128QHtt) mutant *Drosophila* exhibit behavioral, neurodegenerative, and electrophysiologic phenotypes, thought to be caused by a Ca^{++} -dependent increase in neurotransmitter release (Romero et al., 2008). According to this study and in contrast to previous belief, the expanded protein does not have to be cleaved to be neurotoxic. Partial loss of function in synaptic transmission (syntaxin, Snap, Rop) and voltage-gated Ca^{++} channel genes suppresses both the electrophysiologic and the neurodegenerative phenotypes, it has been postulated that increased neurotransmission plays a key role in the neuronal degeneration caused by expanded CAG repeats in human HD. Besides the mouse models, there is also an HD transgenic model in minipigs encoding huntingtin (*Htt*)1–548 under the control of the human *Htt* promoter (Baxa et al., 2013). In addition, a transgenic model of HD in a rhesus macaque monkey that expresses polyglutamine-expanded *Htt* (Wang et al., 2008; Yang et al., 2008) has been developed by injecting 130 mature rhesus oocytes with high titers of lentiviruses expressing *Htt* gene exon1 with 84 CAG repeats and green fluorescent protein (*GFP*) gene. After a transfer of 30 embryos into 6 surrogates, 5 live births were delivered at full term, including two sets of twins. Unfortunately, only one monkey survived 1 month and the others died at birth or shortly thereafter. The monkey that survived 1 month presumably demonstrated chorea and dystonia 2 days after birth, although it is difficult to characterize these movements in infants. Brain autopsy showed abundant distribution of transgenic *Htt* in the cortex and striatum and nuclear inclusions and neuropil aggregates. Similar to the HD mouse models, which demonstrate more severe phenotypes, the transgenic monkeys expressing exon1 *Htt* with a 147-glutamine repeat (147Q) died early

and showed abundant neuropil aggregates in swelling neuronal processes (Wang et al., 2008).

Pathogenesis

Multiple processes have been postulated to relate CAG expansion to neurodegeneration, including aberrant interaction between the mutant *Htt* with transcriptional factors and coactivators (Anderson et al., 2008; Ehrnhoefer et al., 2011; Ross and Tabrizi, 2011; Ross et al., 2014; Testa and Jankovic, 2019) (Fig. 13.4). Histone deacetylase complexes, enzymes that remove acetyl groups on the histone thus allowing transcription of DNA, play a role in the transcription of CAG repeats into *Htt* and promote CAG expansions in the HD gene (Debacker et al., 2012). Furthermore, aberrant interaction with histone acetyltransferase interferes with acetylation. Abnormal histone deacetylation leads to tightly packed chromatin structure and transcriptional repression, and histone deacetylase inhibitors have been suggested as potential treatment strategies in HD and in other neurodegenerative disorders (Chuang et al., 2009). Mutant *Htt* also has been shown to abnormally interact with histone acetyltransferases interfering with acetylation of histone proteins also leading to transcriptional repression. Decreasing transcriptional activation by abnormal interaction between mutant *Htt* and the transcription factor cyclic adenosine monophosphate (cAMP)-response element binding protein (CREB)-binding protein (CBP), a mediator of cell survival signals containing a short polyglutamine stretch, is another mechanism of cell death (Nucifora et al., 2001; Mantamadiotis et al., 2002). CBP is a coactivator for the transcription factor CREB linking DNA-binding proteins to RNA polymerase II transcription complex and functioning in histone acetyltransferase complex. By recruiting CREB into cellular aggregates, the mutant *Htt* prevents it from participating as a coactivator in CREB-mediated transcription, supporting the toxic gain-of-function mechanism of cell death in HD. The polyglutamine-containing domain of abnormal *Htt* protein directly binds the acetyltransferase domains of CBP and p300/CBP-associated factor (P/CAF) (Steffan et al., 2001). This reduces acetyltransferase activity and decreases acetylation of histones, proteins that package DNA, which in turn decreases gene transcription. Therefore, histone-deacetylase inhibitors could prevent HD-related neurodegeneration. Indeed, inhibition of histone deacetylase by sodium butyrate has been shown to partially protect HD R6/2 mice from neurodegeneration and against 3-nitropropionic acid neurotoxicity (3-NP) (Ferrante et al., 2003). Inhibition of κB kinase-mediated phosphorylation of the amino terminus of *Htt* targets mutant *Htt* into the nucleus, where it interferes with gene transcription (Krainc et al., 2010a, 2010b). When acetylated by CBP, mutant *Htt* is transported into autophagosomes for degradation, but mutant *Htt* that is not cleared accumulates in the nucleus and cytoplasm in the form of inclusions. Thus, neuroprotective strategies focus on increasing phosphorylation or acetylation of the mutant *Htt* to improve its clearance and reduce its neuronal toxicity. Several studies have demonstrated impaired autophagy in animal models of HD, suggesting that inefficient engulfment of cytosolic components by autophagosomes may contribute to the HD-related neurodegeneration (Martinez-Vicente et al., 2010;

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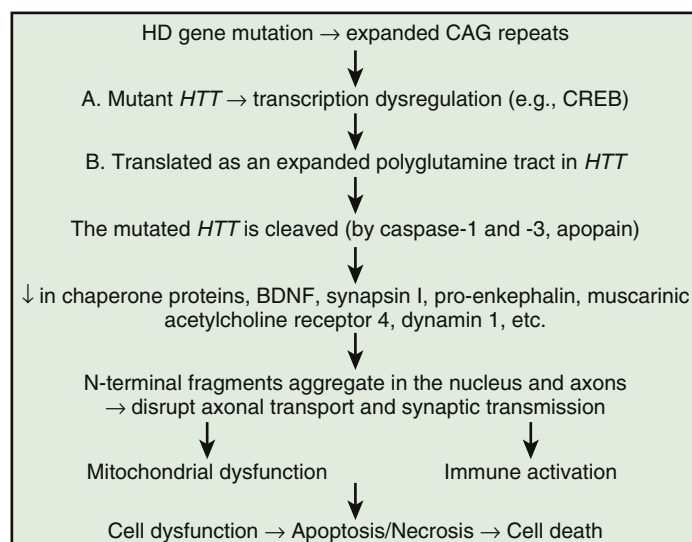


Fig. 13.4 Possible pathogenic mechanisms of Huntington disease (HD). CREB, Cyclic adenosine monophosphate (cAMP)-response element binding protein.

Martin et al., 2015). Transcriptional dysregulation as a pathogenic mechanism of neurodegeneration in HD also has been suggested by the study by Dunah and colleagues (2002), which showed that *Htt* interacts with the transcriptional activator Sp1 and coactivator TAFII130. Sp1, the first of many transcriptional activators isolated from human cells, binds to GC-box on the promoter region of DNA. It contains glutamine-rich activation domains that selectively bind to core components of the transcriptional machinery, such as TAFII13 subunit of TFIID, which contains TATA-box-binding protein and multiple TATA-box-binding protein-associated factors. Therefore, one of the earliest steps in the development of HD may involve deregulation of specific transcriptional programs as suggested by Dunah and colleagues (2002), who demonstrated that mutant *Htt* inhibited Sp1 binding to DNA in postmortem brain tissues of both presymptomatic and affected HD patients. As a result, the RNA polymerase II is not able to locate the dopamine D2 receptor promoter region, and the gene cannot be transcribed (Freiman and Tjian, 2002).

It has been postulated that the common theme linking all the diseases pathogenetically with polyglutamine-tract expansion is that the various proteins (e.g., *Htt*, atrophin, androgen receptor, and ataxins), as a result of an increase in size of their intrinsic polyglutamine sequences, accumulate in the nucleus, forming insoluble amyloid-like fibrils and then somehow interfere with normal cellular metabolism (Davies et al., 1998). Proteolytic cleavage of a glutathione-S-transferase-*Htt* fusion protein results in spontaneous formation of insoluble aggregates. Aggregate formation is directly related to *Htt* and polyglutamine length; a polyglutamine tract of 51 glutamines or longer result in these aggregates (Scherzinger et al., 1997; Martindale et al., 1998). It has been hypothesized that after the expanded CAG repeat in the HD gene is transcribed in the *Htt* mRNA and then translated as an expanded polyglutamine tract in *Htt*, the mutated protein is cleaved (e.g., by caspase, apopain). This, the earliest step in the pathogenesis of HD, is followed by the liberation of polyglutamine-containing fragments, which are linked by transglutaminase to other proteins containing lysine residues,

resulting in formation of perinuclear aggregates, eventually leading to neuronal apoptosis (Bates, 2003). The formation of inclusions, however, is not required for the initiation of cell death; in fact, neuronal intranuclear inclusions might have a protective role (Saudou et al., 1998). Kuemmerle and colleagues (1999) found that aggregate formation occurs predominantly in spared striatal interneurons rather than in the spiny neurons that are typically affected in HD. Thus, *Htt* aggregates do not predict neuronal death and might actually protect against polyglutamine-induced neurotoxicity. Several lines of evidence suggest that the expanded polyglutamine fragment of mutant *Htt* decreases protein degradation by the proteasome (Martin, 1999; Bence et al., 2001). The protein aggregates appear to be simultaneously inhibitors of the ubiquitin-proteasome system and the products that result from its inhibition. Arfaptin 2 has been shown to promote *Htt* protein aggregation, possibly by impairing proteasome function (Peters et al., 2002). Aggregating proteins besides *Htt*, including alpha-synuclein, tau, mutant SOD1, and mutant ubiquitin, inhibit proteasome function (Cookson, 2004). In addition to the brain, proteasomal dysfunction has been demonstrated in the skin fibroblasts of patients with HD (Seo et al., 2004). Abnormal clearance of mutant *Htt* because of impaired phosphorylation, which normally tags certain amino acids with phosphates for destruction by the cellular waste handling systems, proteasomes and lysosomes, is recognized as an important mechanism of cell loss in HD and in other neurodegenerative disorders. *Htt* is phosphorylated by the inflammatory kinase IKK, which regulates additional posttranslational modifications, including *Htt* ubiquitination, phosphorylation, sumoylation, acetylation, proteolytic cleavage, and palmitoylation and increases *Htt* nuclear localization, cleavage, and clearance mediated by lysosomal-associated membrane protein 2A (LAMP-2A) and Hsc70 (Thompson et al., 2009; Ehrnhoefer et al., 2012). The mutant *Htt* interferes with proteasome activity and lysosomal degradation becomes impaired, partly as a result of age-related reduction of the LAMP-2A. Furthermore, impaired phosphorylation on serines 13 and 16 of the N-terminal 17 amino acids of *Htt* has been demonstrated

to impair clearance of mutated *Htt*, but genetic engineering to either mimic phosphorylation (phosphomimetic) or resist it (phosphoresistant) in mice prevented formation *Htt* clumps (Gu et al., 2009). Mitogen-activated protein kinase (MAPK) signaling also has been found to be involved in the regulation of cellular functions in response to a variety of stimuli, and c-Jun terminal kinases (JNKs), extracellular signal-regulated kinases (ERKs), and p38, and the upstream kinase mixed lineage kinase 2 (MLK2) have been found to be overactive in HD.

Various studies show that uncleared mutant *Htt* and *Htt* fragments can accumulate and become toxic by interfering with cellular function and axonal transport. Impairment of proteasomal degradation of mutant *Htt* leads to caspase-mediated apoptosis (Jana et al., 2001). Jana and colleagues (2001), for example, found "massive accumulation" of polyubiquitinated mutant, but not normal, *Htt* after 2 days of expression in mouse neural cells, indicating lack of proteasomal processing of the mutant protein. Decline of proteasomal activity with time in the soluble fraction of the cell and an increase in the insoluble portion correlated with increased accumulation of proteasomal components in cell aggregates. Expression of mutant *Htt* (or inhibition of proteasomes with lactacystin) was associated with activation of caspases and release of mitochondrial cytochrome c, indicators of apoptosis. Wild-type *Htt* upregulates transcription of cortically derived brain-derived neurotrophic factor (BDNF) (Zuccato et al., 2001); thus, a decrease in BDNF appears to play an important role in the pathologic processes and pathogenesis of HD by causing dysfunction of striatal enkephalinergic neurons (Canals et al., 2004; Cattaneo et al., 2005). Because wild-type *Htt* has been found to transport BDNF, it is not surprising that mutated *Htt* interferes with intracellular transport of this trophic factor (Gauthier et al., 2004). This suggests that, as a result of mutated *Htt* in HD, there is insufficient neurotrophic support for striatal neurons and that treatment with BDNF might possibly restore or rescue the damaged striatal neurons. Rapamycin, an antibiotic that acts as a specific inhibitor of mammalian target of rapamycin (mTOR), a kinase that regulates important cellular processes, has been found to attenuate *Htt* accumulation and cell death in cell models of HD, possibly by enhancing the clearance of proteins that abnormally accumulate and aggregate in the cytoplasm (Ravikumar et al., 2004). Therefore, drugs such as rapamycin might play a role also in other neurodegenerative diseases that result from accumulation of unwanted protein aggregates.

Htt also interacts with chaperone proteins that unfold the expanded mutant *Htt* protein, preventing the aggregate formation in a cell culture model (Jana et al., 2001). Processing of polyglutamine-containing proteins by proteases (e.g., caspases) liberates truncated fragments with expanded polyglutamine tracts that can form aggregates through hydrogen bonding or transglutaminase activity and may be toxic to the cell. Abnormalities in proteasome function are associated with altered expression of stress-response proteins or heat shock proteins that function as chaperones. The chaperones normally maintain proteins in an appropriate conformation and denature misfolded proteins (aggregates) (Kobayashi and Sobue, 2001). Overexpression of these chaperone proteins protects cells from toxicity induced by *Htt* with expanded polyglutamines (Jana et al., 2000; Kobayashi

and Sobue, 2001). It has been postulated that the mutant *Htt* with an expanded polyglutamine tract, which is resistant to proteasome-mediated protein processing, overloads the proteasome machinery, enhancing the pathogenic effects of mutant *Htt*. Because truncated proteins that contain the expanded polyglutamine tract appear to be more toxic than the full-length protein, blocking proteolytic processing, aggregation, and nuclear uptake might be reasonable therapeutic strategies.

Caspase-1, a cysteine protease important in regulating apoptosis, has been postulated to play a role in the pathogenesis of cell death associated with HD. Ona and colleagues (1999) crossbred R6/2 with a transgenic mouse expressing dominant-negative mutant of caspase-1 in the brain. The inhibition of caspase-1 delayed the disease onset by 7.3 days and prolonged survival by 20.4 days. Furthermore, it significantly delayed the appearance of neuronal inclusions and neurotransmitter alterations. Although abnormal protein aggregation has been postulated to play an important role in the pathogenesis of HD, DiFiglia and colleagues (Kim et al., 1999) showed that aggregation was not intimately involved in cell death. General inhibitors of caspases prolonged cell life, but they did not alter aggregation, whereas specific caspase 3 inhibitors inhibited aggregation but had no effect on survival. Thus, continuous influx of the mutant protein is required to maintain inclusions. To determine whether caspase cleavage of *Htt* is a key event in the selective neurodegeneration in HD, Graham and associates (2006) found that mice expressing mutant *Htt*, resistant to cleavage by caspase-6 but not caspase-3, maintained normal neuronal function, did not develop striatal neurodegeneration, and were protected against neurotoxicity induced by multiple stressors, including NMDA, quinolinic acid, and staurosporine. These findings suggest that proteolysis of *Htt* at the caspase-6 cleavage site is critical for neurodegeneration in HD, which is enhanced by excitotoxicity. This and other studies provide strong evidence that caspases are important in the pathogenesis of cell death in HD and other neurodegenerative diseases.

The finding that N-methyl-D-aspartate (NMDA) receptors are markedly reduced in the putamen and cerebral cortex was the first clue that suggested an NMDA-mediated excitotoxicity as a mechanism of neuronal degeneration in HD (Young et al., 1988; Tabrizi et al., 1999). In addition to the 92% reduction in NMDA binding, phencyclidine binding was reduced by 67% and quisqualate by 55% in the same HD brains. NMDA receptor density was decreased by 50% in the brain of a presymptomatic HD gene carrier, suggesting that the loss of the excitatory receptors occurred early in the course of the disease (Albin, Young et al., 1990). In contrast to the study by Young and colleagues (1988), no single excitatory amino acid receptor was selectively affected. Using quantitative in-vitro autoradiography, Dure and colleagues (1991) found a 50% to 60% reduction in binding sites of all the major excitatory receptors (NMDA, MK-801, glycine, kainate, and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA]) in the caudate nucleus of HD brains. Furthermore, as was noted earlier, mutated *Htt* protein might interfere with vesicular glutamate uptake and thus contribute to excitotoxicity (Li et al., 2000). Certain excitatory neurotoxins produce useful animal models of HD. Although the activity of 3-hydroxyanthranilic acid

oxidase, the synthesizing enzyme for quinolinic acid, is markedly increased in the striatum of HD brains (Schwarcz et al., 1988), the concentration of quinolinic acid, an NMDA agonist, in the CSF and brains of patients with HD is normal (Heyes et al., 1991). Nevertheless, intrastriatal injections of quinolinic acid preferentially damage the medium-sized spiny neurons containing calbindin Dk28, enkephalin, and substance P, the very same neurons that degenerate in HD (Beal, Ferrante et al., 1991; Ferrante et al., 1993). The striatal patch-matrix pattern closely resembles that seen in HD. Pre-treatment with MK-801, a noncompetitive NMDA antagonist, protects the striatum from the quinolinic acid neurotoxicity. Despite neuronal loss and astrogliosis, the axons are spared, which might account for relatively normal dopamine, nor-epinephrine, and serotonin levels. GABA levels are markedly decreased in the GPe of these animals, similar to HD, indicating early loss of GABA afferents from the striatum to the GPe in both HD and the experimental model. In addition to pathologic and biochemical similarities between this animal model and HD, the animals also exhibit choreic movements. In addition to quinolinic acid, another excitotoxin that has been implicated in the pathogenesis of HD is glutamate. The observation that glutamate levels are decreased in the striatum of HD brains has been interpreted to be a result of chronic failure of the normal reuptake mechanism for glutamate released from the corticostriatal afferent terminals (Perry and Hansen, 1990). The resulting increase in concentration of glutamate at synapses might cause damage to the striatal neurons. The increased extracellular glutamate might also explain the finding of increased CSF glutamate in some patients with HD. Additional support for the excitotoxic theory of HD is provided by the observation that a lesion with the excitotoxin ibotenic acid, a glutamic acid agonist, in a striatum of the baboon produces behavioral and neuropathologic changes similar to those seen in patients with HD (Hantraye et al., 1990).

One hypothesis of mechanisms of cell death in HD is that a defect in mitochondrial energy metabolism makes certain neurons more vulnerable to the excitotoxic effects of endogenous glutamate (Beal, 1992; Bossy-Wetzel et al., 2008). It has been postulated that mutant *Htt* might cause mitochondrial dysfunction by either interfering with transcription of nuclear-encoded mitochondrial proteins or by causing damage directly to the mitochondria and interfering with Ca^{++} buffering or mitochondria membrane potential (Bossy-Wetzel et al., 2008). Panov and colleagues (2002) showed that lymphoblast mitochondria from patients with HD and brain mitochondria from transgenic HD mice have a lower membrane potential and depolarize at lower calcium loads than do mitochondria from controls. Because this defect preceded the onset of pathologic or behavioral abnormalities by months, the authors concluded that "mitochondrial calcium abnormalities occur early in HD pathogenesis and may be a direct effect of mutant *Htt* on the organelle." Intrastriatal injections of inhibitors of oxidative phosphorylation, such as amino-oxyacetic acid or 1-methyl-4-phenylpyridinium (MPP^{+}), or a systemic administration of 3-NP, a mitochondrial poison, into animals produce even more striking resemblance to HD than when "pure" excitotoxins are used (Beal, Swartz et al., 1991; Storey et al., 1992; Beal et al., 1993; Brouillet et al., 1993). Studies have shown that 3-NP induces striatal neurodegeneration via c-Jun N-terminal kinase/c-Jun

module (Garcia et al., 2002). Accidental ingestion of 3-NP has resulted in putaminal necrosis and delayed onset of dystonia and chorea in humans (Ludolph et al., 1991). The age-dependent neurotoxicity of 3-NP, demonstrated by increased striatal lactate levels in the older animals, appears to be related to the effect of 3-NP on energy metabolism. Severe defects have been demonstrated in the activities particularly of complexes II and III in the caudate nuclei of HD patients (Gu et al., 1996; Tabrizi et al., 1999). Using spectrophotometric techniques, Browne and colleagues (1997) found 29% and 67% reductions in the activity of the complex II to III in the caudate and putamen of HD brains, respectively. In addition, there was a 62% reduction in the complex IV activity. This finding provides further support for the potential role of oxidative damage in the pathogenesis of HD. The possibility that mitochondrial function is impaired in HD is supported by the observation of 5-fold to 11-fold increase in cortical mitochondrial DNA deletion in the brains of HD patients (Horton et al., 1995). Dichloroacetate, which stimulates pyruvate dehydrogenase complex, has been found to increase survival, improve motor function, and prevent striatal atrophy in R6/2 and N171-82Q transgenic mouse models of HD (Andreassen et al., 2001). A "toxic-oxidation cycle" has been proposed as an important mechanism in neurodegeneration associated with HD (Kovtun et al., 2007). According to this hypothesis the accumulation of DNA oxidized bases, as a result of impaired function of the repair enzyme 7,8-dihydro-8-oxoguanine-DNA glycosylase (OGG1), overwhelms the repair machinery in the genome with generation of single-strand breaks, ultimately leading to further CAG expansion and neuronal death. Defects in mitochondrial oxidative phosphorylation have been postulated to decrease cellular adenosine triphosphate (ATP) production, resulting in a concomitant decrease in sodium-potassium ATPase activity and partial membrane depolarization. Under normal circumstances, the NMDA receptor-associated channels are blocked by a voltage-dependent Mg^{++} system that pumps Mg^{++} out of the cell. As a result of decreased ATPase activity, caused by the inhibition of oxidative phosphorylation, the normal resting potential cannot be maintained, resulting in opening of the channel and influx of calcium. This triggers a cascade of events leading to a production of free radicals and associated oxidative damage to various cellular elements. Thus, as a result of inhibition of oxidative phosphorylation, even low levels of excitatory amino acids become toxic, a process that is referred to as slow excitotoxicity. More recent studies provide evidence that HD is associated with transcriptional dysregulation associated with interference in transcription mediated by Sp1 CBP coupled with mitochondrial impairment as a result of reduced activity of peroxisome proliferator-activated receptor- α coactivator 1 α (PGC-1 α), which regulates the expression of many nuclear-encoded mitochondrial proteins and of proteins that provide protection against reactive oxygen species (ROS) (Greenamyre, 2007).

It has been suggested that in HD, as a result of prolonged excitatory neurotransmission, certain neurons become "exhausted" and switch from aerobic to anaerobic glycolytic metabolism, leading to the production and accumulation of lactate. Increased lactate concentration in the cerebral cortex of patients and animal models of HD, postulated to be the result of global cerebral energy failure, has been

demonstrated by proton magnetic resonance spectroscopy (Jenkins et al., 1998). Subsequently, ^1H magnetic resonance spectroscopy was used to measure N-acetylaspartate, creatine, and choline, and a reduction in these markers correlated well with the progression of the disease and with striatal atrophy (Sánchez-Pernaute et al., 1999). Administration of agents that improve energy metabolism, such as coenzyme Q10 and nicotinamide, might protect animals against toxicity produced by malonate, a complex II inhibitor (Beal et al., 1994). Using ^{31}P magnetic resonance spectroscopy to measure lactate in the muscle and ^1H magnetic resonance spectroscopy to measure lactate in the basal ganglia and the cortex, Koroshetz and colleagues (1997) showed that treatment with coenzyme Q10 was associated with a significant decrease in cortical lactate concentrations in patients with HD. There is, however, no evidence that this biochemical change is in any way associated with clinical improvement or slowing of disease progression. Furthermore, increased lactate could not be confirmed by other studies (Hoang et al., 1998).

How the mutation in the HD gene leads to selective damage of certain neuronal populations is not fully elucidated. One explanation is that there are certain genes or proteins that are uniquely expressed in the striatum and cortex, making these structures particularly vulnerable to neurodegeneration. For example, the *CalDAG-GEFI* gene has been found to be markedly downregulated in the brains of individuals with HD and in mouse models of the disease (Crittenden et al., 2010). By following mutant mice for up to 9 months, the investigators showed that this reduction occurs gradually, in parallel with the progression of the disease, and when they blocked the expression of the gene using small interfering RNA (siRNA), the striatal neurons were protected from *Htt*-induced damage. Thus, the striking downregulation of *CalDAG-GEFI* in HD could be a protective mechanism against mHtt, but even switching off of the gene is eventually unsuccessful, resulting in the striatal neurodegeneration. Neurodegeneration in HD may be the result of abnormal interaction between mutant *Htt* and transcription factors and other proteins interfering with normal transcriptional regulation (Paulson and Fischbeck, 1996; Roses, 1996; Anderson et al., 2008). One of the most provocative clues to the selective vulnerability of neuronal damage in HD was provided initially by Li and colleagues (1995). These investigators identified a protein, called *Htt*-associated protein (HAP1), that specifically binds to *Htt*. Subsequent studies have demonstrated that HAP1 and *Htt* are anterogradely transported in axons. HAP1 normally interacts with kinesin light chain, a subunit of the kinesin motor complex that drives anterograde transport along microtubules, and it links to transport proteins such as growth factor receptor tyrosine kinase (TrkA) (Rong et al., 2006). However, when mutant *Htt* is present, HAP1 is unable to carry out its trafficking function leading to degeneration of nerve terminals. Other *Htt*-interacting proteins have been identified, such as glyceraldehyde-3-phosphate dehydrogenase (GAPDH), HAP1, HIP14, apopain, alpha-adaptin, ubiquitin, calmodulin, and PSD95 (Reddy et al., 1999; Young, 2003; Yanai et al., 2006). The *Htt* protein might also interact with clathrin and adaptor protein-2, which are involved in endocytosis and other proteins (Li and Li, 2004). The small guanine nucleotide-binding protein, Rhes (Ras homolog enriched in striatum), which is localized to the

striatum and, to a much lesser extent, in the cortex, but not in the cerebellum, binds physiologically to mutant *Htt* and leads to selective cytotoxicity (Subramaniam et al., 2009). The mechanism of the cytotoxicity is not clear, but Rhes has been shown to markedly decrease aggregation of mutant *Htt*, presumably by Rhes-mediated sumoylation, which involves binding of the small ubiquitin-like modifier (SUMO) to the mutant *Htt*. Thus, Rhes-elicited disaggregation of mutant *Htt* probably accounts for the localized neuropathology of HD in the striatum and to a lesser extent in the cortex. Subsequent study showed that cystathionine γ -lyase, the biosynthetic enzyme for cysteine, is depleted in HD brains and that supplementation with cysteine reverses abnormalities in cultures of HD tissues and in mouse models of HD (Paul et al., 2014). Therefore, drugs that block the binding of Rhes to mutant *Htt* or administration of cysteine may exert neuroprotective effects in HD.

There are many other *Htt* interacting proteins, identified with high-throughput screening, that may modify polyglutamine neurotoxicity leading to neurodegeneration (Kaltenbach et al., 2007). The long tract of glutamines in mutant HD protein weakens the interaction with *Htt*-associated protein, which is then free to bind the protein Hippi and activate apoptosis through caspase-8 and caspase-3. The latter also cleaves *Htt*, producing fragments that eventually form intra-neuronal inclusions (Gervais et al., 2002). Wild-type *Htt* has been found to partially protect cells against noxious stimuli, and removal of the caspase sites is beneficial for the cells (Young, 2003). *Htt* has been found to be normally palmitoylated at cysteine 214, which is essential for its trafficking and function, and this process is regulated by the palmitoyl transferase *Htt* interacting protein 14 (HIP14). Expansion of the polyglutamine tract of *Htt* results in reduced interaction between mutant *Htt* and HIP14 and consequently in a marked reduction in palmitoylation and increased formation of inclusions and neuronal toxicity (Yanai et al., 2006). These pathologic changes may be partly corrected by overexpression of HIP14.

The relationship of the abnormal interaction of *Htt* with other proteins and how these interactions contribute to the pathogenesis of HD is still unclear. It is possible that, as the *Htt* polyglutamine tract expands and changes its tertiary configuration, it blocks the ATP-dependent import mechanisms for succinate dehydrogenase entry into the mitochondria in the striatum. This might lead to selective, localized energy depletion and pathologic changes that are typically associated with HD. As the expansion increases, the impairment of import mechanism becomes less selective, and the pathologic changes becomes more widespread. Thus, in HD, in addition to the typical involvement of the striatum, the GPe and GPi, SNpc, and cerebellum become involved, and the patient manifests additional features, such as rigidity, bradykinesia, and ataxia (Furtado et al., 1996). Morphometric analyses of structural MRI demonstrated marked cerebellar atrophy and white matter loss in patients with HD (Fennema-Notestine et al., 2004). Although activity of glyceraldehyde-3-phosphate dehydrogenase, a *Htt*-binding protein, is normal in the brains of patients with HD, the activity of aconitase, a Fe-S-containing tricarboxylic acid cycle enzyme, is reduced to 8% in the caudate, 27% in the putamen, and 52% in the cerebral cortex of HD brains (Tabrizi et al., 1999). This enzyme is particularly sensitive

to inhibition by peroxynitrite ONOO^- and superoxide O_2^- ; it is considered to be a good marker of excitotoxic cell damage.

Htt may also contribute to the apoptotic cell death in HD; it has been found to be cleaved by apopain, an apoptosis-specific cysteine protease (Goldberg et al., 1996). It has been postulated that the aggregates of mutant *Htt* (DiFiglia et al., 1997) cannot be properly removed from the cell and therefore might interfere with the metabolic activities of the affected neurons. Because ubiquitin is important in protein degradation and this process requires energy, the cells that are most vulnerable to the accumulation of the ubiquitin-*Htt* aggregates are those whose metabolic function has been already compromised, possibly as a result of toxins that interfere with oxidative phosphorylation. This concept then might link this new finding of region-selective accumulation of *Htt* aggregates and inclusions (DiFiglia et al., 1997) with the theories of regional impairment of energy metabolism (Beal et al., 1994). It is still not clear whether the ubiquitin-proteasome system, the autophagy-lysosome pathway, or both are involved in degrading mutated *Htt* (Martin et al., 2015).

The molecular pathogenesis of HD has been considered to result from a decrease in specific chaperone proteins, such as Hdj1, HSP70, α SGT, and β SGT, as demonstrated in R6/2 mice (Hay et al., 2004). Antigliadin antibodies have been demonstrated in 44% of patients with HD, but this probably represents an epiphenomenon and a nonspecific finding, because it also has been demonstrated in ataxia and other neurodegenerative disorders (Bushara et al., 2004).

Inflammatory processes have been thought to contribute to the pathogenesis of HD. Microglia, normally present in the brain in a quiescent state, become activated as part of the neurodegenerative process and on exposure to neuronal insults such as mHtt aggregation. When activated, they release proinflammatory cytokines and cytotoxic mediators, such as interleukin-6 (IL-6). Microglial activation is an early event in the pathogenic processes of HD and is associated with subclinical progression of disease and abnormal PET scans that use ligands such as [^{11}C](R)-PK11195 (Pavese et al., 2006). Autopsy studies have also shown increased RNA levels of IL-6, IL-8, and tumor necrosis factor- α (TNF- α); IL-6 release is triggered by activation of the nuclear factor kappa-light-chain-enhancer of activated B-cells (NF- κ B) pathway.

Neurofilament light protein (NfL) may play a role in HD and could have potential to serve as a biomarker (Byrne et al., 2017; Johnson et al., 2018). NfL, the smallest of three subunits that make up neurofilaments, which make up major components of the neuronal cytoskeleton, are released from damaged neurons. There is evidence of increased NfL concentrations in CSF in various neurodegenerative diseases such as AD, frontotemporal dementia, and amyotrophic lateral sclerosis. NfL concentrations have been found to be increased in CSF in HD. In samples from TRACK-HD ($n = 366$) and an independent cohort ($n = 37$), baseline NfL concentrations correlated significantly with subsequent decline in cognition, TFC, and gray and white matter atrophy on brain MRI. Concentrations of NfL in CSF and plasma were significantly correlated in mutation carriers. This may help elucidate pathogenesis and provide a candidate biomarker of disease progression.

Treatment

Treatment of HD begins with education about the disease, its natural history, genetics, and symptom management. Topics of discussion may also include how HD affects ADLs, work, driving, and other aspects of independence. Symptom management may include medical, surgical, and rehabilitation therapies. Treating HD may involve a multidisciplinary team approach including neurologist, psychiatrist, psychologist/neuropsychologist, social worker, genetics counselor, and allied health professionals, among others. Management of HD may include a symptom-based approach for motor, psychiatric, and cognitive features (Wyant et al., 2017). Until effective neuroprotective therapy is found, the management of patients with HD will focus primarily on relief of symptoms designed to improve their quality of life (Handley et al., 2006; Jankovic, 2006; Bonelli and Hofmann, 2007; Adam and Jankovic, 2008; Frank and Jankovic, 2010; Dash and Mestre 2020). In a European survey of 2128 registered HD patients, 84% were prescribed symptomatic treatment, 50% of were treated for depression, and 28% received anti-choreic medications (Priller et al., 2008).

Motor symptoms

At present for chorea, there are several pharmacologic treatment options, including two medications approved by the U.S. Food and Drug Administration (FDA). Although many patients may not be aware of their chorea or particularly bothered by it, chorea can affect motor abilities, safety, and quality of life and, thus, may merit treatment. The two FDA-approved medications for chorea in HD include TBZ and deutetrabenazine (DTBZ).

TBZ has been used and studied for many years in the treatment of hyperkinetic movement disorders, including chorea (Jankovic and Beach, 1997; Kenney and Jankovic, 2006; Jankovic and Clarence-Smith, 2011; Jimenez-Shahed and Jankovic, 2013; Frank, 2014; Gibson and Claassen, 2021). This drug, approved under the brand name Xenazine by the FDA in 2008 for chorea associated with HD, is also marketed in other countries as Nitoman. A potent and selective depletor of dopamine and, to a lesser degree, norepinephrine and serotonin from nerve terminals, TBZ has been shown to be effective in the treatment of a variety of hyperkinetic movement disorders. The effects of TBZ are largely restricted to the central nervous system (CNS), which differentiates it from another monoamine depletor, reserpine, which was an anti-hypertensive drug that produces both central and peripheral depletion. By inhibiting the brain synaptic VMAT, TBZ impairs uptake of monoamines and serotonin into synaptic vesicles, causing them to remain in the cytoplasm, where they are rapidly degraded by monoamine oxidases (Fig. 13.5). There are two types of VMAT, type 1 (VMAT1) and type 2 (VMAT2), which are coded by two distinct genes, 8p21.3 and 10q25, respectively. In humans, VMAT2 is nearly exclusively expressed in the CNS neurons, whereas VMAT1 is present in the peripheral nerve terminals. TBZ exhibits a 10,000-fold higher affinity for human VMAT2 than for human VMAT1, reversibly binding to the intravesicular part of VMAT2. Reserpine, on the other hand, binds irreversibly to the cytoplasmic site of both VMAT1 (peripheral) and VMAT2 (central). These

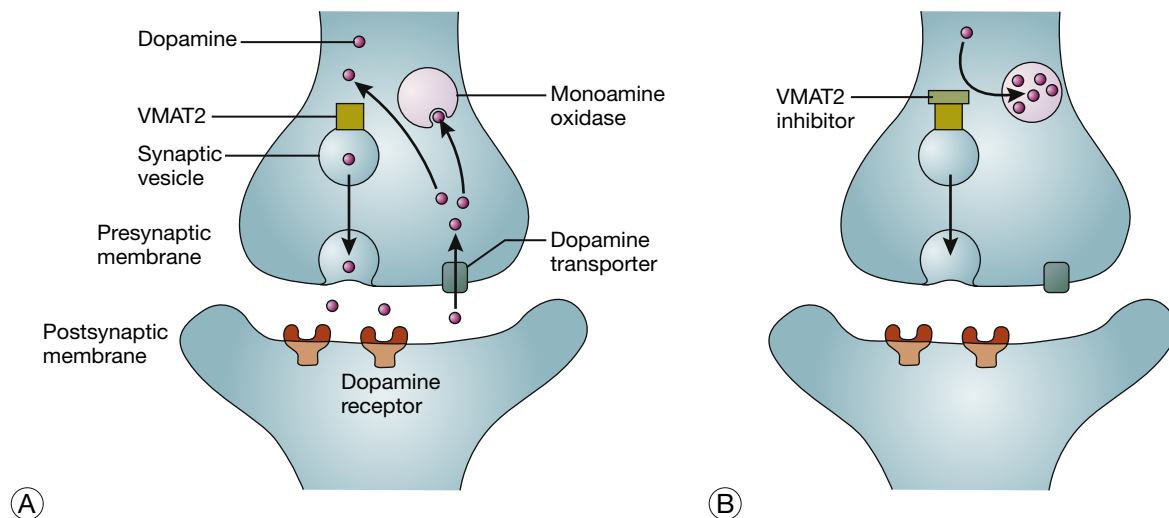


Fig. 13.5 Mechanisms of action of vesicular monoamine transporter 2 (VMAT2) inhibitors (tetrabenazine, deutetabenazine, valbenazine) (Jankovic, J. Movement disorders in 2016: Progress in Parkinson disease and other movement disorders. *Nat Rev Neurol.* 2017;13[2]:76–78.)

pharmacologic differences probably account for the absence of hypotension and gastrointestinal side effects with TBZ compared with reserpine. In addition, the duration of action is much shorter with TBZ, about 12 hours versus several days. In contrast to reserpine, which depletes all the monoamines and serotonin equally, TBZ preferentially depletes dopamine. Finally, despite early reports of dopamine receptor inhibition, more recent studies suggest that because the affinity of TBZ for the dopamine D2 receptor is 1000-fold lower than its affinity for VMAT2, it is unlikely that the weak dopamine D2 receptor antagonism is involved in the therapeutic effects of TBZ. This might be one reason why tardive dyskinesia has never been reported to occur with TBZ, one of the chief advantages of this drug over the neuroleptic, dopamine receptor-blocking drugs.

Although TBZ can cause or exacerbate depression, sedation, akathisia, and parkinsonism, it is an effective anti-chorea drug (Jankovic and Beach, 1997; Ondo et al., 2002; Kenney and Jankovic, 2006; Kenney et al., 2007a,b; Fasano and Bentivoglio, 2009; Jankovic, 2009) (Video 13.13). In one study of 15 patients who were treated for an average of 7 months at a mean dose of TBZ of 68 ± 27.1 mg/day (range: 25–150 mg/day), a “blinded” rating of videotapes showed improvement in motor scores in 12 (80%), and the mean score improved from 16 ± 3.6 to 13 ± 3.8 (Ondo et al., 2002). Adverse events included akathisia, insomnia, constipation, depression, drooling, and subjective weakness. In a multicenter, double-blind, placebo-controlled trial of TBZ involving 84 ambulatory patients with HD (TETRA-HD), TBZ treatment resulted in a reduction of 5.0 units in chorea severity compared with a reduction of 1.5 units on placebo treatment (adjusted mean effect size = $[-3.5 \pm 0.8]$ UHDRS units [mean $\pm$ standard error]; 95% confidence interval, $-5.2, -1.9$; $P < .0001$) (Huntington Study Group, 2006) (Fig. 13.6). About 50% of TBZ-treated subjects had a 6-point or greater improvement compared with 7% of placebo-treated subjects. There was also a significant benefit on ratings of clinical global improvement. There were five study withdrawals in the TBZ group and five serious adverse events in four subjects (drowning suicide, complicated fall, restlessness/suicidal ideation, and breast cancer), compared with one withdrawal and no serious adverse events in the placebo

group. This study concluded that TBZ, at adjusted dosages of up to 100 mg/day, was effective for the treatment of chorea in HD and was generally safe and well tolerated. In a retrospective study of 448 patients with hyperkinetic movement disorders (98 with chorea), treated with TBZ (mean dose at the last visit: 60.4 ± 35.7 mg) for up to 21.6 years (mean: 2.3 ± 3.4 years) at Baylor College of Medicine between 1997 and 2004, and evaluated with a clinical response scale (1 = marked reduction in abnormal movements, 5 = worsening), TBZ was found to be effective across the spectrum of the hyperactive movement disorders treated (Kenney and Jankovic, 2006). The percentage of patients with chorea who had a response of 1 or 2 at the last visit was 84.4%. The most common side effects, all dose related, were drowsiness (25%), parkinsonism (15.4%), depression (7.6%), and akathisia (7.6%), with less common side effects including nausea/vomiting, nervousness/anxiety, and insomnia. Many patients are willing to tolerate side effects such as parkinsonism (sometimes effectively treated with amantadine, levodopa, dopamine agonists) because of TBZ’s beneficial effects on their hyperkinetic movement disorder. Other longitudinal studies, albeit smaller, confirm these observations, including one study in which 68 patients with HD were followed for a mean period of 34.4 ± 25.2 months (Fasano et al., 2008). An open-label extension study after the TETRA-HD study showed that TBZ is a safe and effective drug (Frank et al., 2010). Several long-term studies, which have to be designed as open-label, observational studies, provide valuable information regarding the tolerability and safety of the treatment with TBZ of hyperkinetic movement disorders (Jimenez-Shahed, 2013; Shen et al., 2013). TBZ has been found to improve not only chorea but other motor impairments and has been found to have a favorable impact on gait and functional mobility (Ferrara et al., 2012; Kegelmeier et al., 2014). In the observational study COHORT, TBZ treatment was not associated with an increased risk for depressed mood, suicidal ideation, suicide attempts, or suicide (Dorsey et al., 2013). CYP2D6 genotyping has been recommended when doses over 50 mg doses are prescribed. Although ultra-rapid metabolizers needed a longer titration to achieve optimal benefit and required a higher average daily dose than the other patients, this finding

Video 13.13 Huntington disease (HD).

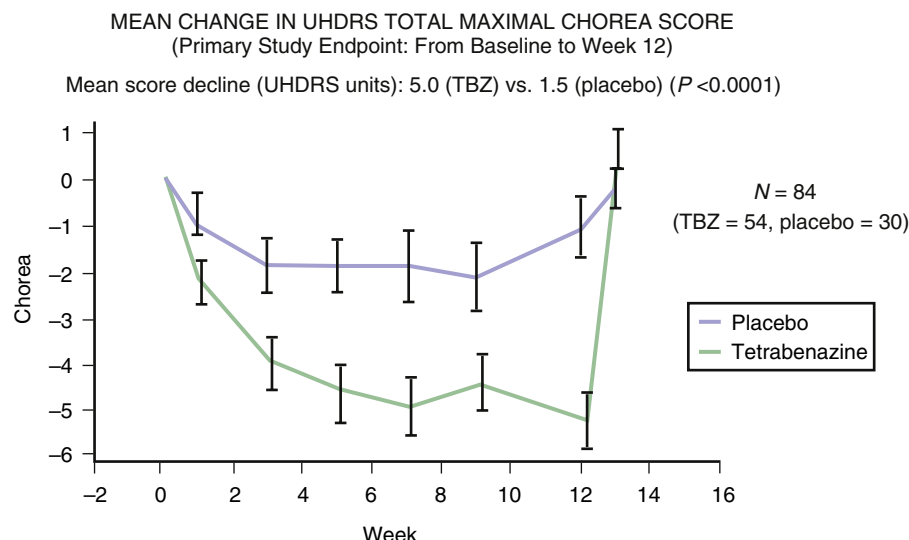


Fig. 13.6 Results of placebo-controlled trial of tetrabenazine in Huntington disease. UHDRS, Unified Huntington's Disease Rating Scale.

There was blinded washout of study drug at week 12. Change favors tetrabenazine ($P = 0.0001$; ANCOVA (ITT-LOC). Chorea scale range: 0 to 28
ANCOVA = analysis of covariance; ITT-LOC = intent-to-treat analysis

did not differentiate statistically this group of patients from those with other genotypes, and the authors concluded that "the current recommendation to systematically genotype all patients prescribed more than 50 mg/day of tetrabenazine should be reconsidered" (Mehanna et al., 2013). ●

TBZ is not only a dopamine depletor, but may also decrease the brain serotonin and norepinephrine concentrations, with a potential for causing or worsening depression. To answer the question whether TBZ is contraindicated in depression, a retrospective study examined the effects of TBZ in 518 patients treated with TBZ for hyperkinetic movement disorders, of which 52.5% had a history of depression before the treatment (Kenney et al., 2006). Of the patients without depression at the time of the treatment initiation, 11.4% were newly diagnosed with depression, and 18.4% of the patients with a previous diagnosis of depression at the time when the treatment with TBZ was started had a worsening of their depression. Overall, 15.1% of patients experienced depression for the first time or had an exacerbation of the preexisting depression. On the other hand, there are patients whose depression improves with the TBZ treatment because of the marked benefit on the underlying hyperkinesia. Although depression is a known side effect of TBZ and may be potentially exacerbated by TBZ, a diagnosis of preexisting depression should not necessarily constitute an absolute contraindication for initiating the treatment with TBZ if the patient is otherwise a good candidate, but close monitoring of such patients is clearly warranted. There are no reports to this date of tardive dyskinesia induced by TBZ, which represents a major advantage of this medication over neuroleptics.

The clinical pharmacokinetics of TBZ were studied in an open-label observational study (Kenney et al., 2007). Ten patients with HD were assessed with serial motor UHDRS and Beck Depression Inventory at baseline and after their morning dose of TBZ, after at least 12 hours off from the last dose. There was an average of 42.4% reduction in chorea, with effect lasting between 3.2 and 8.1 hours (mean:

5.4 ± 1.3 hours). Therefore, a minimum of three times daily dosing may be required in most patients to sustain the anti-chorea effects without wearing off. The best tolerated dose of TBZ necessary to provide an adequate control of symptoms varies greatly among individuals from as low as 12.5 mg/day to as high as 100–200 mg/day. Although no blood levels or other pharmacokinetic data were obtained during this study, the findings suggest that the washout period of TBZ is short. This is also supported by a double-blind study of 30 HD patients treated with TBZ, randomly assigned to one of three groups: the first group of 12 patients stopped TBZ (which was replaced with a placebo) on day 1 (withdrawal group), the second group followed the same protocol on day 3 (partial withdrawal), and the third group continued the treatment with TBZ (nonwithdrawal group) (Frank et al., 2008). The withdrawal group experienced reemergent chorea at day 3, with a difference in the UHDRS change of 5.33 units, compared with 2.94 units in the nonwithdrawal group, which was in the hypothesized direction ($P < 0.077$). Post hoc analysis of the linear trend was positive for reemergent chorea ($P = 0.0486$) and provides further support for the effectiveness of TBZ in reducing chorea. TBZ has been found to be as effective as other neuroleptics, including atypical neuroleptics such as aripiprazole (Brusa et al., 2009) in reducing chorea with a similar adverse effect profile, but it clearly has a lower risk for tardive syndrome. The Cochrane review, which examined 22 trials (1254 subjects) (Mestre et al., 2009a), concluded that based on available evidence, only TBZ showed a clear efficacy for the control of chorea.

Deutetabenazine (DTBZ) is a novel molecule that is similar to TBZ but replaces the 6 hydrogen atoms with 6 atoms of deuterium. This attenuates the CYP2D6 metabolism and increases active metabolite half-lives so that fewer and lower doses are needed. DTBZ was approved by the FDA for the treatment of chorea in HD in 2017, with the brand name of Austedo. DTBZ was studied in a clinical trial conducted by the Huntington Study Group (2016) with 90 manifest HD patients randomized to either DTBZ ($n = 45$) or placebo

($n = 45$). The dose was titrated over 8 weeks, maintained for 4 weeks, and followed by 1 week washout period. The primary endpoint was the change from baseline in the UHDRS total maximal chorea score. In the DTBZ group, the mean total maximal chorea scores improved from 12.1 (95% CI, 11.2–12.9) to 7.7 (95% CI, 6.5–8.9), whereas in the placebo group, scores improved from 13.2 (95% CI, 12.2–14.3) to 11.3 (95% CI, 10.0–12.5). The mean between-group difference was -2.5 units (95% CI, -3.7 to -1.3), which was statistically significant. In addition, there was significant improvement in the secondary outcome of patient global impression of change, but no significant difference between treatment groups in the Berg Balance test. Adverse event rates were similar for DTBZ and placebo, including depression, anxiety, and akathisia. Subsequent studies have investigated the safety of converting from TBZ to DTBZ (Frank et al., 2017). In this open-label, single-arm study, 37 patients were switched overnight from TBZ to DTBZ and then titrated on a weekly basis for optimal chorea control. DTBZ was generally well tolerated with low rates of neuropsychiatric adverse events, and overnight conversion provided a favorable safety profile. Chorea control was maintained at week 1 and significantly improved at week 8 (mean [SD] change from baseline of 2.1 [3.2]).

Several guidelines on the treatment of HD have been published (Walker, 2007; Adam and Jankovic, 2008; Phillips et al., 2008; Jankovic, 2009; Mestre et al., 2009a,b; Frank and Jankovic, 2010; Armstrong et al., 2012; Mestre and Ferreira, 2012; Frank, 2014) (Fig. 13.7). In a survey of an international group of experts, there was no consensus on first choice of antichorea drug, with antipsychotic drugs favored by the majority of clinicians in Europe, whereas antipsychotics and TBZ were used equally by experts from North America and Australia (Burgunder et al., 2011). According to the American Academy of Neurology pharmacologic treatment guidelines, if HD chorea requires treatment, the following received level B recommendation: tetrabenazine (up to 100 mg/day), amantadine (300–400 mg/day), or riluzole (200 mg/day); nabilone, a synthetic cannabinoid (Sagredo et al., 2012), received level C recommendation; and neuroleptics received Level U recommendation (Armstrong and Miyasaki, 2012). These recommendations, however, have been challenged because they are not endorsed by many experts (Reilmann, 2013; Jankovic and Roos, 2014). Given the underlying pathophysiology and effect of dopamine-blocking agents (dopamine antagonists, e.g., neuroleptics, antipsychotics) on hyperkinetic involuntary movement such as chorea, other considerations for treating chorea include these agents. When troublesome chorea is accompanied by psychosis, aggression, or impulsivity, other therapeutic choices may include aripiprazole, haloperidol, olanzapine, risperidone, or other neuroleptics (Frank et al., 2014). In addition, in the setting of weight loss with chorea and/or psychiatric symptoms, olanzapine may be considered.

Because NMDA supersensitivity might be responsible in part for chorea in patients with HD, selective NMDA antagonists might ameliorate this symptom. In a double-blind, controlled trial of 22 patients with HD, amantadine (400 mg/day) reduced extremity chorea by 36% (Verhagen Metman et al., 2002). In addition to symptomatic effect, amantadine might confer a neuroprotective effect. In another randomized placebo-controlled trial, amantadine at 300 mg/day

had no effect on HD-associated chorea (O'Suilleabhain and Dewey, 2003). A 2-hour intravenous infusion of amantadine in a double-blind, randomized crossover study showed reduction in dyskinesias scores after both intravenous and oral administration (Lucetti et al., 2003). In a pilot trial of 9 patients with HD, memantine, when titrated to the maximum dose of 20 mg/day and followed for 3.8 ± 1.0 months, showed a significant decrease in total UHDRS motor scores ($P = 0.008$), mostly because of a significant ($P = 0.008$) decrease in the maximum chorea rating at their final visit (11.5 ± 6.3 to 4.8 ± 3.8) (Ondo et al., 2007). There was no significant change in the cognitive ($P = 0.625$) or behavioral ($P = 0.258$) ratings or TFC ($P = 0.078$) and independence scale rating ($P = 1.000$). There were minimal adverse events, such as drowsiness and worsening of balance, speech, and social interaction.

Interestingly, some patients with HD benefit from dopaminergic drugs, particularly when the disease is associated with parkinsonism (Racette and Perlmuter, 1998). Apomorphine, a dopamine agonist that presumably acts by stimulating presynaptic D2 receptors and thus inhibiting dopamine release, has been found to be effective in 5 patients with HD who responded to acute apomorphine, in whom it was continuously infused subcutaneously for 5 days (Vitale et al., 2007). The “dopidines” represent a new class of dopamine stabilizers. The concept is that when dopaminergic tone is low, dopidines enhance dopamine transmission, but when tone is high, they antagonize dopamine receptors and behave more like antipsychotics. Pridopidine, a dopaminergic stabilizer that also has glutamatergic properties, has been studied in three trials in HD (Rung et al., 2008; Reilmann, 2013). The plasma half-life increases from around 8 hours after a single dosing to about 15 to 20 hours at steady state. The North American HART trial included 227 patients, not receiving antipsychotics or antidepressants, who were randomized to receive pridopidine 90, 45, or 20 mg/day or placebo for 12 weeks. Although improvements in motor scores were reported in the group of patients treated with pridopidine 90 mg/day, the differences in the modified motor score (mMS) compared with placebo did not reach statistical significance. Pridopidine treatment was well tolerated (The Huntington Study Group HART Investigators, 2013). The MermaiHD trial in Europe included 437 HD patients in 32 European centers randomized to pridopidine 90 or 45 mg/day or placebo for 26 weeks (de Yebenes et al., 2011). At the 90 mg/day dose, compared with placebo, the reduction in the mMS was -1.29 points, but the significance value for the primary study endpoint of P value of 0.042 did not meet the prespecified level of P less than 0.025. However, with inclusion of the clinically relevant CAGn adjustment, the P value less than 0.02. There were no serious adverse effects detected. In a 1-year safety and tolerability study, 353 of the original 386 patient who participated in the double-blind, placebo-controlled MermaiHD study entered the 6-month open-label extension at the 90 mg/day dosage (Squitieri et al., 2013). The study provides Class IV evidence that pridopidine (90 mg/day or less) is safe and well tolerated for up to 1 year. The Pride-HD phase II study investigated pridopidine in 400 HD patients using higher doses, longer study design, and additional outcome measures compared with prior trials. TFC scores were improved, but there was no difference in drug from placebo on TMS.

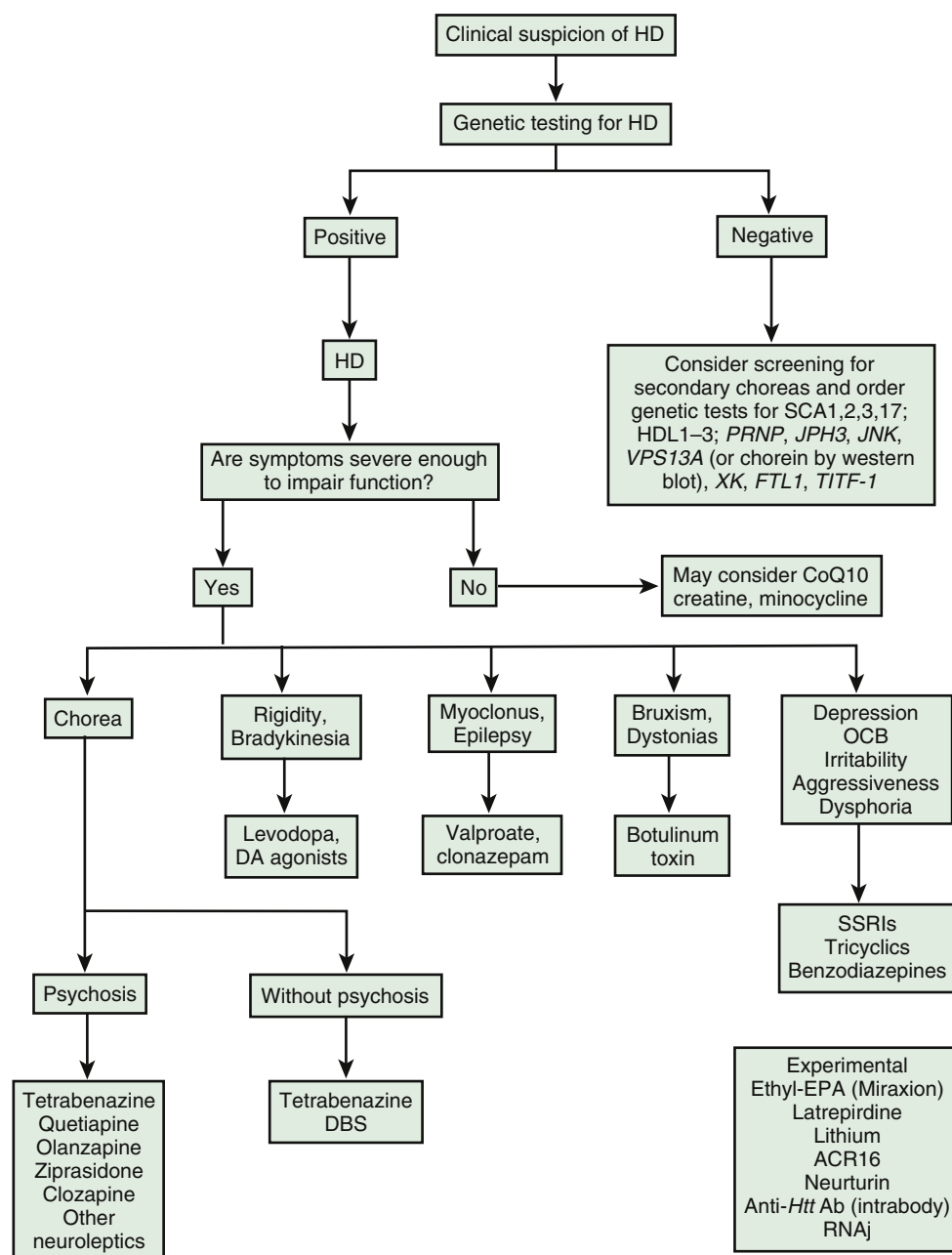


Fig. 13.7 Symptomatic treatment of Huntington disease (HD). ACR16, Pridopidine; CoQ10, coenzyme Q10; DA, dopamine; DBS, deep brain stimulation; ethyl-EPA, ethyl-eicosapentaenoate; OCB, obsessive compulsive behavior; RNAi, RNA interference; SCA, spinocerebellar ataxia; SSRIs, selective serotonin release inhibitors.

Baclofen, a putative GABA agonist, provides neither symptomatic nor protective effects in HD (Shoulson et al., 1989), though it may be considered for dystonia or spasticity. Other agents that block glutamate release from the pre-synaptic terminals by drugs such as riluzole or lamotrigine (Brodie, 1992) have not demonstrated benefit in HD. In a double-blind, placebo-controlled trial, lamotrigine failed to slow HD progression but was found to improve symptoms and lessen chorea; 54% of patients on lamotrigine reported symptomatic improvement versus 15% of those on placebo, and the chorea subscale measure showed less deterioration for lamotrigine than for placebo (Kremer et al., 1999). In a 3-year double-blind, RCT of 537 HD patients (with 379 completing the study), riluzole did not demonstrate any significant effect on the primary outcome of combined score from UHDRS motor and TFC scores; no unexpected adverse

events were reported, but the principal reason for study discontinuation was the need for antichorea medication (Landwehrmeyer et al., 2007). Nabilone, a synthetic analog of delta-9-tetrahydrocannabinol, the major psychoactive component of cannabis, has been found to exert modest symptomatic benefit in chorea associated with HD (Curtis et al., 2009). To date, clinical studies investigating effects of cannabidiol in HD have included case reports and two small and short-duration double-blind trials that did not demonstrate improvement in symptoms (Peres et al., 2018); additional studies are needed. Dystonia and bruxism, which can be present in HD, can be effectively treated with local injections of botulinum toxin (Tan et al., 2000). Myoclonus may respond to benzodiazepines or valproic acid. Physical therapy, occupational therapy, and speech-language pathology may assist in the care of HD patients regarding gait

impairment, imbalance, fall risks, ADLs, home safety, and dysarthria and dysphagia.

Palliative surgery, including pallidotomy and deep brain stimulation (DBS), has been tried in a few patients with severe chorea associated with HD, but, despite some improvement in chorea, the disease has continued to progress (Kang et al., 2011). Pallidotomy also has been found useful in the treatment of dystonia associated with HD (Cubo et al., 2000). When targeting the GPi, DBS at a frequency of 40 Hz has been able to reduce chorea without producing parkinsonian features, although the overall motor function and quality of life may not improve (Fasano et al., 2008). In one case of a patient with HD treated with bilateral GPi DBS, there was initial improvement but this was not sustained and he continued to deteriorate during the 5-year follow-up (López-Sendón Moreno et al., 2014). In a double-blind controlled trial of six patients with HD (four chorea-dominant, two Westphal variant) of DBS targeting the GPi or GPe, there was a 60.2% ($P = 0.037$) reduction in the chorea score at 6 months, irrespective of the stimulated target (Wojtecki et al., 2015). There was no improvement in the Westphal patients. Bilateral pallidal stimulation at 40 and 130 Hz improved chorea in one patient with HD and other studies regarding DBS targets in HD are emerging (Moro et al., 2004; Wojtecki et al., 2016).

Psychiatric features

Although evidence-based recommendations for psychiatric features in HD are lacking, standard treatments of depression (for non-HD) are often used (Moulton et al., 2014). The selective serotonin reuptake inhibitors (SSRIs) form the basis of depression treatment in HD. Fluoxetine, one of the SSRIs, also has been shown to stimulate CREB, increase production of BDNF, enhance glycogenolysis, block voltage-gated calcium and sodium channels, and decrease the conductance of mitochondrial voltage-dependent anion channels, and thus it may potentially exert a neuroprotective effect in HD (Mostert et al., 2008). Three studies suggest the benefit of SSRIs in HD, though, are limited in their evidence base; these include studies with venlafaxine, fluoxetine, and citalopram (Wyant, 2017). As demonstrated in small open-label series, case reports, and anecdotal evidence, antipsychotics may be helpful for refractory depression, and electroconvulsive therapy has been shown to be effective in some. Screening should be done for suicidality, as previously discussed. SSRIs and the tricyclic antidepressant clomipramine have been used to treat obsessive and compulsive behaviors. Irritability and agitation may be helped by SSRIs, or if milder and insight is present, behavioral strategies may be useful. A vasopressin 1a receptor antagonist (SRX246) has been studied for irritability in early symptomatic HD, with a Phase 2 double-blind, placebo-controlled trial demonstrating that SRX246 was safe and well-tolerated and did not affect apathy or suicidality (Brownstein et al., 2020). Apathy remains a challenging behavior to treat effectively; dopaminergic agents, antidepressants, and stimulants have been tried without evidence-based improvement. Psychosis, one of the most troublesome symptoms, usually improves with neuroleptics, such as haloperidol, pimozide, fluphenazine, and thioridazine. These drugs, however, can induce tardive dyskinesia and other adverse effects; therefore, they should be used only if absolutely needed to control symptoms. Clozapine

(Clozaril), an atypical antipsychotic drug that does not cause tardive dyskinesia, might be a useful alternative to the typical neuroleptics, but its high cost, risk for agranulocytosis, and other potential side effects might limit its use, particularly because it has antichoreic effects only in relatively high doses (Bonuccelli et al., 1994; van Vugt et al., 1997). It is likely that the other atypical antipsychotics, such as olanzapine (Zyprexa) (Paleacu et al., 2002) and quetiapine fumarate (Seroquel), will also provide a beneficial effect.

Cognitive features

Cognitive medications have been studied in several small studies in HD, but without benefit demonstrated (Cubo et al., 2006; Ondo et al., 2007; Sesok et al., 2014). The cholinesterase inhibitor donepezil (10 mg/day) was studied in a randomized, placebo-controlled study of 30 HD patients over 12 weeks (donepezil, $n = 15$; placebo, $n = 15$). Participants had mild to moderate chorea and mild cognitive impairment at baseline (Mini-Mental State Examination [MMSE] 26.8 ± 1.9 , range 24–30). However, donepezil did not improve chorea, cognition, or quality of life; adverse events did not differ between treatment groups. Donepezil was found to be ineffective in another study of the treatment of cognitive impairment or chorea associated with HD (Fernandez et al., 2000). In another small study, 18 HD patients were randomized to rivastigmine (6 mg/day) or placebo, but there was no significant change in cognitive function after 6 months. Memantine (20 mg/day), which has NMDA glutamatergic properties, was studied in a small, open-label trial ($n = 12$) with no benefit for cognition at 3 months. Given cognitive impairment and dementia, patients should be counseled about and screened for issues with home safety and driving. At least half of HD patients who are active drivers fail a driving evaluation; therefore, they need to be referred for such evaluation and, if they fail, their driving privileges suspended because they can present a danger to themselves and others (Devos et al., 2012).

Experimental therapeutics

Neuroprotective/disease-modifying treatments

Because HD is one of the few neurodegenerative diseases in which the diagnosis can be made long before the onset of clinical symptoms, this offers an opportunity to intervene in the earliest stages of the neurodegenerative cascade, perhaps even before the disease-related cell loss is initiated. Thus, HD is an excellent model for testing early neuroprotective treatments (Beal and Ferrante, 2004; Leegwater-Kim and Cha, 2004; Ryu and Ferrante, 2005; Bodner et al., 2006; Adam and Jankovic, 2008; Hersch and Rosas, 2008; Imarisio et al., 2008; Phillips et al., 2008; Roze et al., 2008; Jankovic, 2009; Frank and Jankovic, 2010; Ross and Tabrizi, 2011; Venuto et al., 2012; Chandra et al., 2014; Frank, 2014; Kil-loran and Biglan, 2014; Sampaio et al., 2014; Schapira et al., 2014; Testa and Jankovic, 2019). Unfortunately, to date, no compounds have been found to provide disease-modifying effects. A Cochrane review of the literature evaluated neuroprotective strategies of eight randomized, double-blind, placebo-controlled clinical trials (1366 subjects), but did not find disease-modifying effects, though the compounds were generally safe and well tolerated (Mestre et al., 2009b).

Subjects were treated for a mean 52 weeks (range: 30–144 weeks) with one of the following compounds: vitamin E, idebenone, baclofen, lamotrigine, creatine, coenzyme Q10 + remacemide, ethyl-eicosapentaenoic acid, and riluzole. These studies used clinical scales to measure progression of disease, but there is growing interest in the use of biomarkers for disease onset and progression.

Experimental therapeutics from animal models and other preclinical studies have suggested roles for caspase inhibitors (Ona et al., 1999; Chen et al., 2000; Yamamoto et al., 2000), creatine (Ferrante et al., 2000), paroxetine (Duan et al., 2004), coenzyme Q10 (Jankovic and Ashizawa, 2003; Ryu and Ferrante, 2005), riluzole (Schiefer et al., 2002), minocycline (Chen et al., 2000), and environmental stimulation (Carter et al., 2000; Spires et al., 2004). Based on the natural history of HD, which is critical for the design of neuroprotective trials, several of these agents have been studied in clinical trials (Paulsen et al., 2006). Although some have shown promise in early studies, larger randomized, double-blind, placebo-controlled trials have not met primary outcome measures. Coenzyme Q10 (ubiquinone) carries electrons from complexes I and II to complex II of the mitochondrial electron transport chain and, thus, can act as an antioxidant or as a pro-oxidant, depending on the cell's redox potential (Shults and Schapira, 2001). In the pilot study, coenzyme Q10 at doses of 600 and 1200 mg/day, was well tolerated, although some patients had adverse effects, such as headache, heartburn, fatigue, and increased involuntary movements (Feigin et al., 1996). In a multicenter clinical trial conducted by the Huntington Study Group (CARE-HD), 347 patients with documented HD were randomized to receive coenzyme Q10 300 mg twice daily; remacemide hydrochloride, an NMDA ion channel blocker, 200 mg three times daily; both; or placebo (Huntington Study Group, 2001) for 30 months. Although patients who were treated with coenzyme Q10 showed a trend toward slowing in total functional capacity decline (13%), this difference failed to reach statistical significance, and coenzyme Q10 was associated with higher frequency of stomach upset, and remacemide treatment was associated with higher frequency of nausea, vomiting, and dizziness. A large follow-up randomized, double-blind, placebo-controlled trial (n = 609) designed to test the hypothesis that chronic treatment with high-dosage coenzyme Q10 (2400 mg/day) in early HD would slow the progression of functional decline, as measured by the change in TFC from baseline to 60 months (McGarry et al., 2017). An interim analysis for futility prompted premature termination of the study; no statistically significant differences were evident for the primary outcome, although coenzyme Q10 was generally safe and well-tolerated. Because of these disappointing results, routine use of coenzyme Q10 in patients with HD is not warranted. Likewise, remacemide, although relatively well tolerated at 200 and 600 mg/day (Kiebert et al., 1996), cannot be recommended for the treatment of HD.

Creatine, a nutritional supplement, acts as a high-energy phosphate source for the restoration of ATP. In transgenic mice models of HD, creatine slowed progression and delayed onset of behavioral and pathologic features and extended survival. Creatine was studied in a multicenter trial for safety and tolerability of high-dose (30 g/day) creatine in premanifest HD and 50% at-risk subjects as a potential preventive intervention, called PRECREST (Rosas et al., 2014). Forty-seven HD carriers and 17 non-HD controls were randomly

allocated 15 g twice daily of creatine monohydrate or placebo for a 6-month double-blind phase followed by a 12-month open-label extension. Result revealed the gastrointestinal issues as the most common adverse events and a slowing of cortical and striatal atrophy on neuroimaging at 6 and 18 months. Subsequently, a multicenter randomized, double-blind, placebo-controlled study of up to 40 g/day of creatine in early HD (n = 553) was conducted with the primary outcome of change in TFC from baseline to 48 months, with an anticipated rate of decline of 0.82 points/year on the TFC in the drug group. However, this study was stopped for futility after the first interim analysis (Hench et al., 2017). Several agents have had promise in animal models but not significant clinical effect in human studies. The potentially useful role of riluzole regarding HD progression has been supported by R6/2 HD transgenic mice models of HD (Schiefer et al., 2002) in which riluzole-treated animals, compared with controls, had increased survival time and less ubiquitinated striatal neuronal intranuclear inclusions, but no difference in antibody staining directed against the mutated *Htt* in this component of neuronal intranuclear inclusions. In a 6-week open-label trial, another antigitamatergic drug, riluzole (100 mg/day), was found to be well tolerated and to be associated with a 35% reduction in the chorea rating score (Rosas et al., 1999). The Huntington Study Group (2003) also found that riluzole at 200 mg/day significantly improved chorea scores but without improving functional capacity, and because of abnormalities in liver transaminase, this drug could not be recommended for routine use in HD. In a large, randomized, double-blind placebo-controlled trial, conducted by the European Huntington's Disease Initiative Study Group, 537 genetically confirmed HD patients were randomized to receive riluzole 100 mg/day or placebo for 3 years, without use of other chorea medications, and were assessed periodically with the UHDRS (Landwehrmeyer et al., 2007); 379 patients completed the study with discontinuations because of the need for antichoreic treatment and consent withdrawal. Although well tolerated, riluzole had no significant effect on chorea, behavioral, cognitive, independence, and functional scores compared with the placebo group at 3 years or at any other time point during the study. Paroxetine, a commonly used serotonin reuptake inhibitor, has been found to slow the progression in *Htt* mutant mice (Duan et al., 2004). Early and sustained treatment with essential fatty acids has been demonstrated to protect against motor deficits in R6/1 transgenic mice expressing exon 1 and a portion of intron 2 of the huntingtin gene (Clifford et al., 2002).

Transglutaminase inhibitors, such as cystamine and monodansylcadaverine, reduce aggregate formation and may be potential therapeutic agents for polyglutamine expansion diseases (Igarashi et al., 1998). By inhibiting the HD mutant transgene with tetracycline, Yamamoto and colleagues (2000) showed that the neurodegeneration could be not only prevented but also reversed. Minocycline, a second-generation antibiotic with high levels of blood-brain barrier permeability, has been shown to delay disease progression in the mouse model R6/2 of HD, possibly by inhibiting caspase-1 and caspase-3 mRNA upregulation and decreasing inducible nitric oxide synthase (Chen et al., 2000). A pilot study of 30 symptomatic HD patients were treated with minocycline at the Baylor College of Medicine Huntington's Disease Center for at least 6 months, assessed by

the Abnormal Involuntary Movements Scale, the UHDRS, and the MMSE, performed at baseline and every 2 months throughout the study period, and monitored with laboratory tests (Thomas et al., 2003). Minocycline was well tolerated over the 6-month observation period with no changes on laboratory tests, but no significant improvement was observed on any clinical assessment. These findings are similar to those reported by others (Bonelli et al., 2003; Thomas et al., 2004). Minocycline was also found to be well tolerated in a larger, double-blind, placebo-controlled study of 60 HD patients (Huntington Study Group, 2004). It has been found to have a potential neuroprotective role in other neurodegenerative disorders (Zemke and Majid, 2004). Smith and colleagues (2003), however, found no effect of minocycline or doxycycline on behavioral abnormalities or *Htt* aggregates in R6/2 mice.

A growing body of evidence supports the notion that preformed polyglutamine aggregates are highly toxic when directed to the cell nucleus; therefore, more recent research has focused on pharmacologic intervention aimed at inhibiting aggregate formation (Bates et al., 2003; Sanchez et al., 2003; Bossy-Wetzel et al., 2004; Hay et al., 2004). One such strategy is to use histone deacetylase inhibitors, such as valproic acid, phenylbutyrate, SAHA, pyroxamide, vorinostat, and other molecules to arrest polyglutamine-dependent neurodegeneration (Marks et al., 2001; Steffan et al., 2001; Butler and Bates, 2006; Chuang et al., 2009). Evidence stems from models of *Drosophila* flies expressing 93Q *Htt* in which histone deacetylase inhibitors SAHA and sodium butyrate suppressed neuronal degeneration (Steffan et al., 2001; Kazantsev et al., 2002; Agrawal et al., 2005) and R6/2 mouse models in which suberoylamide hydroxamic acid also ameliorates motor deficits of HD (Hockly et al., 2003). In some in vitro cell culture models of HD, geldanamycin, a benzquinone ansamycin antibiotic that binds to HSP90 and activates the stress response, has been found to prevent polyQ aggregation, presumably by activating a heat shock response (Sittler et al., 2001), delay aggregate formation, and increase soluble exon 1 huntingtin at concentrations suggesting chaperone induction affecting the biophysical properties of the aggregates (Hay et al., 2004). These drugs do not cross the blood-brain barrier, however, and might not be clinically useful. Intraperitoneal injections of cystamine, an amino acid derivative that competitively inhibits transglutaminase, into transgenic HD mice ameliorated tremor and gait abnormalities and prolonged survival from 92 to 103 days (Karpuij et al., 2002). Other preclinical evidence comes from treatment with tauroursodeoxycholic acid, a hydrophilic bile acid, that prevented neuropathologic processes and associated behavioral deficits in the 3-NP rat model of HD and reduced striatal neuropathologic findings in the R6/2 transgenic HD mouse (Keene et al., 2002) and effects of azo dye Congo red, which inhibited polyglutamine oligomerization, interfered with the production of cytotoxic events, facilitated polyglutamine degradation by making it more accessible to proteasome (Sanchez et al., 2003), and inhibited assembly of protofibrils into fibrils, thus preventing toxicity from mature fibrils (Poirier et al., 2002). Trehalose, a disaccharide composed of two glucose molecules, has been found to alleviate polyglutamine-mediated pathologic processes in the R6/2 transgenic model of HD, including a 30% reduction in brain aggregates (Tanaka et al., 2004). Trehalose, which appears

to bind directly to proteins with expanded polyglutamines, is highly soluble and therefore can be administered orally. The drug appears to have no toxicity, and thus it is a promising therapeutic agent for various polyglutamine diseases, not just HD. Another strategy to reduce the toxic effects of pathogenic fragments of *Htt* involves SUMO-1, which at least partially prevents aggregation of *Htt* in vitro (Steffan et al., 2004). However, in a *Drosophila* model of HD, sumoylation of *Htt* fragments exacerbates neurodegeneration, whereas ubiquitination reduces HD pathologic processes. These findings suggest that SUMO-1 blockers might delay the progression of HD. Some unorthodox attempts are under way to test various putative neuroprotective agents, such as coenzyme Q10, creatine, cystamine, omega-3 fatty acids, trehalose, and blueberry extract (Couzin, 2004). A component of green tea, polyphenol (–)-epigallocatechin-3-gallate (EGCG) has been found to potently inhibit the aggregation of mutant *Htt* exon 1 protein and, when fed to transgenic HD flies overexpressing a pathogenic *Htt* exon 1 protein, photoreceptor degeneration and motor function improved (Ehrnhoefer et al., 2006). Another approach, currently investigated in HD mouse models, is the use of an engineered virus to make an intracellular antibody or “intrabody” that will clear the cytoplasm of mutated *Htt* (Wang et al., 2008). Improving clearance of the mutant protein is another strategy that is being explored in experimental models of HD. For example, increased acetylation of the mutant *Htt* at lysine residue 444 (K444) in *Caenorhabditis elegans* model of HD facilitates trafficking of mutant *Htt* into autophagosomes and improves clearance of the mutant protein by macroautophagy (Jeong et al., 2009). Intrabody gene therapy against the proline-rich domain of *Htt* (Happ1) has been found to improve motor and cognitive deficits and the neuropathologic findings in the lentiviral, R6/2, N171-82Q, YAC128, and BACHD models of HD (Southwell et al., 2009).

Ethyl-EPA, a pure, highly unsaturated fatty acid, concentrated chiefly in fish oil and caspase inhibitor, has been studied in HD. Caspase inhibitors might play a role in the treatment of HD and related neurodegenerative disorders (Friedlander, 2000; Sanchez Mejia and Friedlander, 2001). A small (n = 24) double-blind, placebo-controlled study of ethyl-EPA in HD showed possible improvement in orofacial components and total UHDRS after 6 months of treatment (Vaddadi et al., 2002). In one double-blind, placebo-controlled study, ethyl-EPA did not have benefit in the intent-to-treat cohort but an exploratory analysis revealed greater numbers of patients in the per-protocol cohort had stable or improved motor function (Puri et al., 2005). Subsequently, a multicenter, randomized, double-blind, placebo-controlled trial of ethyl-EPA (1 g twice daily) (TREND-HD) involved 316 HD patients, 190 of whom completed the 12-month trial, and showed improvement in the TMS-4 component of the UHDRS (Huntington Study Group, 2008). Although ethyl-EPA was not effective for the movement symptoms of HD when taken over 6 months, after 12 months those subjects who received ethyl-EPA for 12 continuous months had no deterioration in their UHDRS TMS, whereas those who received active treatment for 6 months worsened ($P = 0.02$) (Huntington Study Group, 2008). A European study of ethyl-EPA in mild-moderate HD (n = 290), similar to the U.S. TREND-HD study, however, did not find significant differences between ethyl-EPA and placebo groups for TMS-4

scores, UHDRS subscores, or clinical global impression scores (Ferreira et al., 2015).

Latrepirdine (Dimebon), an antihistamine drug that also inhibits butyrylcholinesterase, acetylcholinesterase, and NMDA receptor, may act as a mitochondrial enhancer by inhibiting mitochondrial permeability transition pore opening (although the latter presumably requires higher dosages than those used in clinical trials) and has been considered to exert neuroprotective effects in HD models and in a phase II trial of AD. A phase II clinical trial conducted by the Huntington Study Group showed that latrepirdine significantly improved mean MMSE scores compared with stable performance in the placebo group, but there were no significant treatment effects on the UHDRS or the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-cog) (Kieburz et al., 2010). There was no detectable mean change in MMSE score among participants randomized to latrepirdine versus placebo or in the Clinician Interview–Based Impression of Change in the HORIZON trial (Horizon Investigators et al., 2013).

Phenylbutyrate, which increases brain histone acetylation, decreases histone methylation levels, enhances the ubiquitin-proteasomal pathway, and downregulates caspases demonstrates neuroprotective effects in a transgenic mouse model of HD (Gardian et al., 2005). Lithium has been found to induce autophagy via inositol monophosphatase (IMPase) inhibition, a process independent of mTOR-induced autophagy (Pan et al., 2008), but combining it with rapamycin may be particularly useful in the treatment of neurodegenerative diseases, such as HD. However, in contrast to enhancement of autophagy via IMPase inhibition, the inhibition of glycogen synthase kinase-3 β (GSK-3 β) by lithium has the opposite effect (Sarkar et al., 2008). Various drugs have been found to induce autophagy and as such have been proposed to be potentially useful in slowing neurodegeneration associated with HD. These included L-type Ca⁺⁺ channel antagonists, the K⁺ ATP channel opener minoxidil, and the Gi signaling activator clonidine. These drugs appear to regulate autophagy through mechanisms other than the cyclical (mTOR) pathway, in which cAMP regulates inositol trisphosphate IP3 levels, influencing calpain activity, which completes the cycle by cleaving and activating Gs alpha, which regulates cAMP levels (Williams et al., 2008; Martin et al., 2015).

Posttranslational modification

Many studies aim to target posttranslational modification of mHtt to slow or prevent progression of the disease (Katsuno et al., 2014; Shannon and Frint, 2015; Zielonka et al., 2015), though some experimental approaches using various animal models of HD do not always translate to humans. The finding that phosphorylation at various serine residues, particularly serine 13 and serine 16, prevents cleavage of mHtt into more toxic fragments and prevents neurodegeneration has opened new avenues for potential neuroprotective therapies (Warby et al., 2009). Based on the observation that gangliosides, such as GM1, are decreased in HD brains (Maglione et al., 2010), ganglioside replacement has been suggested as a potential therapeutic approach in HD. In one study, normal motor function in symptomatic YAC128 HD mice was restored by intraventricular infusion of ganglioside GM1, which induces phosphorylation of mHtt at specific

serine amino acid residues (DiPardo et al., 2012). Overexpression of sirtuin 1 (Sirt1), a protein deacetylase capable of modulating mHtt acetylation and a mediator of the beneficial metabolic effects of calorie restriction, has been found to protect neurons against mutant *Htt* toxicity, but it is not known whether Sirt1 agonists will be neuroprotective in HD (Jeong et al., 2011; Jiang et al., 2011). SEN0014196 (selisistat, 6-chloro-2,3,4,9-tetrahydro-1H-carbazole-1-carboxamide), a selective Sirt1 inhibitor, has been found in in-vitro and in-vivo studies to exert neuroprotective activity against toxicity induced by mHtt. Inhibition of Sirt1 by SEN0014196 is expected to increase clearance of the mHtt without affecting levels of the normal protein. This drug was studied in an exploratory clinical trial in early HD, completed but with no results (clinicaltrials.gov, last update November 25, 2015).

Histone deacetylase inhibitors

As mentioned, histone deacetylase inhibitors also represent potential therapies in HD because they interfere with the transcription of the expanded CAG into the mutant *Htt* (Chuang et al., 2009; Debacker et al., 2012; Jia et al., 2015; Zielonka et al., 2015). Indeed, oral administration of the HDAC inhibitor 4b (licensed to Repligen), a highly specific HDAC3 inhibitor, significantly improved motor performance and other behavioral and pathologic HD-like features in the R6/2 transgenic mice that carry the human mutant HD gene (Thomas et al., 2008) and it suppressed CAG repeats by 77% in HD mice (Debacker et al., 2012). Research has demonstrated that peroxisome proliferator-activated receptor delta (PPAR- δ) interacts with *Htt* and expression of dominant-negative PPAR- δ , specifically in the striatum of medium spiny neurons in mice, yielded an HD-like model that can be largely reversed by agonist KD3010 (Dickey et al., 2016). This drug improved motor function, reduced neurodegeneration, increased survival, and reduced *Htt*-induced neurotoxicity in vitro and in medium spiny-like neurons generated from stem cells derived from individuals with HD. KD3010 crosses the blood-brain barrier and was approved for use in humans in a phase Ib trials in diabetes and metabolic disorders, including obesity. PPAR- δ also interacts with the retinoid X receptor to activate target genes, and interference with transcription of these target genes contributes to HD-related neurodegeneration. Dickey and associates (2017) evaluated bexarotene, a retinoid X receptor, in cellular and HD mouse models. Bexarotene was effective at countering neurotoxicity in mouse primary neurons, human HD patient-derived stem cell neurons, and mouse model. Inhibition of the striatal-specific cyclic nucleotide phosphodiesterase PDE10A, localized in medium spiny neurons, by TP-10 has been explored in HD (Giampa et al., 2010). In HD, the mHtt protein impairs the function of several transcription factors, in particular CREB. CREB activation can be increased by targeting phosphodiesterases such as phosphodiesterase 4 (PDE4) and phosphodiesterase 10A (PDE10A) and inhibition of both proved beneficial in the R6/2 mouse model of HD. In addition to motor improvement in the mouse model, the treatment was associated with reduced striatal and cortical cell loss and formation of striatal neuronal intranuclear inclusions, reduced microglial activation, and elevations in striatal and cortical levels of phosphorylated CREB and BDNF. PDE10A has been found to be increased in the spiny neurons

of R6/2 mice striatum, suggesting that the accumulation of PDE10A in the striatal projection neurons, by hydrolyzing greater amounts of cyclic nucleotides, is likely to contribute to cell damage in HD (Leuti et al., 2013). Preliminary PET imaging studies have found that PDE10A is decreased in the striatum of HD patients, even in early stages (Ahmad et al., 2014). It is, however, likely that PDE10A activity is highly compartmentalized, and although it may be decreased in some areas of the striatum, it appears to be increased in the striatal projection neurons (Leuti et al., 2013). PDE10A compounds have been tested in animal models of HD (AMG 579, Amgen) and in human trials (OMS824, Omeros and PF-02545920, Pfizer). The Amarylris trial of a PDE10A agent (PF-02545920, Pfizer), of 271 HD patients, however, did not meet its primary outcome (change in TMS from baseline to 26 weeks) and its open-label extension phase was stopped (clinicaltrials.gov).

Antibodies, inflammation, and metals

Another therapeutic approach focuses on the use of a monoclonal antibody (VX15, Vaccinex, Inc) to semaphorin 4D (SEMA4D), a transmembrane signaling molecule that modulates a variety of inflammatory processes identified in animal models of HD and in HD patients. Using YAC128 transgenic HD mouse model, anti-SEMA4D treatment was associated with reduction in striatal atrophy, cortical atrophy, and corpus callosum atrophy that was accompanied by improvement in anxiety-like behavior and cognitive deficits, but without effect on motor deficits (Southwell et al., 2015). A phase II, multicenter, randomized, double-blind placebo-controlled trial with VX15/2503 (SIGNAL study conducted by the Huntington Study Group and Vaccinex) is under way in late prodromal and early manifest HD. Preliminary data from the first cohort of 36 participants receiving monthly infusions of drug versus placebo for 6 months revealed that decrease in MRI brain volume and metabolic activity was less in many regions in the VX15 antibody treatment group; the trial has been completed, but results are not available to date (<http://www.vacinex.com>).

Laquinimod is an immune modulator under study in HD. Although its precise mechanism of action is unknown, laquinimod reduces nuclear factor kappa-light-chain-enhancer of activated B cells (NF κ B) activation in astrocytes, may restore BDNF levels, and may also reduce the phosphorylation of p38 and JNK. This drug, already tested in patients with multiple sclerosis though met with safety concerns at the highest dosage in clinical trial (1.5 mg/day), presumably targets the inflammatory process in HD brains. The LEGATO-HD trial was designed to assess three doses in HD patients over 12 months, though the highest dose was dropped after study start; primary outcome was change in TMS and secondary outcome measures of caudate atrophy on MRI. Results reported in the August 2018 press release stated that the primary endpoint in motor score was not met but that the reduction of brain atrophy was met in the secondary endpoint.

PBT2 is a metal protein-attenuating compound that might reduce the interaction between the mHtt protein and copper, which abnormally accumulates in the brains of patients with HD. In Reach2HD, a randomized, double-blinded, placebo-controlled trial involving 109 HD patients with early or mid-stage disease, PBT2, particularly in the group with a higher

dose, achieved a significant benefit on a composite cognitive score, primarily assessing executive function (the study's primary endpoint) (Huntington Study Group Reach2HD Investigators, 2015).

Neurotrophic factors

Based on results from animal studies, delivery of trophic factors, such as nerve growth factor and ciliary neurotrophic factor, by genetically modified cells into the striatum of patients with HD has become a reachable goal (Kordower et al., 1999; Mittoux et al., 2000; McBride et al., 2004). Implantation of nerve growth factor-producing fibroblasts into the rat striatum appeared to protect these animals against neurotoxic effects of the excitatory amino acids quinolinate and quisqualate (Schumacher et al., 1991). Another approach has been to enhance BDNF axonal transport by manipulating *Htt* and Hap1 using cysteamine (Gibrat and Cicchetti, 2011). Cysteamine, the neuroactive metabolite of cystamine that crosses the blood-brain barrier, has been found to be neuroprotective in animal models of HD, possibly by increasing BDNF, upregulating the heat shock DnaJ-containing protein 1b (HSJ1b), and acting as an antioxidant. The improved motor performance in these HD models was accompanied by reduced striatal *Htt* inclusions and improved motor performance. A phase II/III randomized, double-blind, placebo-controlled clinical trial of RP103 (DR Cysteamine, 1200 mg/day), a delayed-release cysteamine bitartrate, was conducted in 96 early-stage HD patients for 18 months but did not achieve significance in the primary endpoint of change from baseline in TMS; treatment with cysteamine was safe and well tolerated (Verny et al., 2017).

Whether intrastriatal implantations of genetically engineered cells designed to produce trophic factors, such as ciliary neurotrophic factor (Emerich et al., 1997; Kordower et al., 1999), or fetal cells will be useful in the treatment of HD awaits the results of further animal and clinical studies (Freeman et al., 2000; Bachoud-Levi et al., 2002; Greenamyre and Shoulson, 2002; Peschanski et al., 2004; Reuter et al., 2008). The observation that implanted fetal neuronal cells survive in the HD brain and reconstitute damaged neuronal connections but increasing pathology studies are challenging the idea that host HD process does not affect the grafted tissue (Cisbani et al., 2017). Prior studies have had conflicting results regarding clinical effect; some transplantation studies reveal no change in functional status or hyperkinetic movements (St. Hillaire et al., 1998; Hauser et al., 2002), whereas others demonstrate improvement in motor and cognitive function (Bachoud-Levi et al., 2000) and reduction of striatal and cortical hypometabolism on F-deoxyglucose PET in some (Gaura et al., 2004). Side effects have included subdural hemorrhages, and studies may be subject to placebo effect. In a longitudinal study of five transplanted HD patients followed for up to 6 years, improvement occurred in the first 2 years but then function again deteriorated (Bachoud-Levi et al., 2006). Autopsy studies, however, show that despite prolonged survival of the graft for up to 6 years or longer, there is poor integration with the host striatum, which probably accounts for the poor efficacy of this approach (Keene et al., 2007). The mechanisms of graft degeneration in HD are not well understood but have been attributed to allograft immunoreactivity, microglial responses targeted to grafted

cells, and, similar to grafts in PD, cell-to-cell neurotoxicity (Cicchetti et al., 2011). Mutated *Htt* aggregates have been found within intracerebral allografts of striatal tissue in three HD patients who received transplants approximately one decade earlier (Cicchetti et al., 2014). This finding provides evidence for a prion-like, cell-to-cell transmission, as also has been suggested in other nongenetic neurodegenerative disorders (Kordower and Halliday, 2014). In addition, two HD cases with fetal allografts who came to autopsy demonstrated tau pathologic findings in grafted tissue, further raising the question of acquired tau pathologic processes or accelerated aging effects (Cisbani et al., 2017). Caution is also advised based on reports of a symptomatic mass as a result of the graft overgrowth (Keene et al., 2009). Similarly, although adipose tissue stem cells implanted in the striata of R6/2 mice transgenic for HD showed some benefits, it is unclear that this will translate into a clinically useful therapeutic strategy (Lee et al., 2009). Alternative strategies have focused on neuritin, delivered via adeno-associated virus (AAV) type 2 (AAV2) vector, and implemented in rat models (Walker and Raymond, 2004; Ramaswamy et al., 2007).

Gene silencing

Gene silencing approaches conceptually include the reduction of burden of mutant *Htt* through the repression of translation with use of antisense oligonucleotides (ASOs), removal of the mutated gene in the cell such as through CRISPR-Cas gene editing, RNA interference with siRNA and micro RNA (miRNA), and repression of transcription with zinc finger proteins (Shannon and Faint, 2015; Mestre and Sampaio, 2017). One approach currently being explored as a potential treatment of HD is to use antisense technology to prevent the expression of mutant *Htt*. Researchers have identified *Htt* antisense (HTTAS), a natural antisense transcript at the HD repeat locus that contains the repeat tract (Chung et al., 2011). This HTTAS normally acts to inhibit the amount of *htt* gene that is expressed, but, in the presence of the HD mutation (e.g., in the brain), there is less HTTAS and therefore more toxic *Htt* is expressed. By experimentally altering cells so they express large amounts of HTTAS, the expression of the mutant *Htt* is suppressed. The first gene silencing clinical trial in HD using an ASO (known as IONIS-HTT Rx) was conducted as a phase I study in early manifest HD ($n = 46$) in the United Kingdom, Germany, and Canada. The results of this randomized, double-blind trial showed that intrathecal administration of four ascending doses of IONIS-HTT Rx ASO or placebo, 1 month apart, reduced the concentration of mutant *Htt* in CSF by up to 42% without any serious adverse effects (Tabrizi et al., 2019). A confirmatory phase III trial, involving 660 patients, followed for up to 2 years, is currently under way, supported by Roche/Genetech with coprimary endpoints of a 2-year change from baseline to composite UHDRS and TFC scores; other secondary clinical and biomarker measures will be followed. This larger study with a longer follow-up will hopefully address the question whether reduction in CSF *Htt* is clinically meaningful and whether application of ASO targeting mutated *Htt* translates into a disease-modifying strategy. Also under study are allele-specific ASOs with two trials in HD by Wave Life Sciences for those with single nucleotide polymorphisms (SNPs) at rs362307 (PRECISION-HD1) and those with SNPs at rs362331 (PRECISION-HD2), respectively.

Another strategy to repress mutant *HTT* involves the use of zinc finger proteins that bind longer CAG repeats more strongly than shorter repeats. Using striatal AAV delivery in R6/2 mice, up to 60% repression of mutant *HTT* was achieved (Garriga-Canuta et al., 2012). Another method, developed by scientists at Sangamo BioSciences (Richmond, CA) uses zinc finger protein transcription factors to target expanded CAG repeats (Stiles et al., 2012). Zinc finger proteins, currently in the preclinical stage of development, require delivery by viral vectors and stereotactic administration into the basal ganglia (putamen).

Finally, RNA interference (RNAi) has been suggested as a promising therapeutic strategy, but further work is needed to determine whether this method can suppress the expression of only the mutated, but not the normal, *Htt* gene, for how long the suppression is required, and what the potential negative effects of knocking down mutated and wild-type *Htt* are (Harper et al., 2009). Furthermore, silencing of the wild-type and mutant *Htt* using small hairpin RNA administered via lentiform vectors and an amelioration of HD pathologic processes was demonstrated in a rodent model of HD (Drouet et al., 2009). Studies using genetically engineered mouse models provide evidence that both cortical and striatal mutant *HTT* must be targeted for optimal effects (Wang et al., 2014). An agent by uniQure (AMT-130) is intended to inhibit production of mutant *Htt* by delivering miRNA into cells via an AAV. Mouse models demonstrated improved motor coordination, survival, and brain penetration. This compound is being pursued by Voyager Therapeutics as an approach to HD.

A listing of available and experimental therapies for HD is provided in Table 13.3. In an evidence-based review of 218 publications on pharmacologic interventions in HD since 1965, Bonelli and Wenning (2006) found 20 level I, 55 level II, 54 level III trials and 89 case reports. Chorea, the primary endpoint in nearly all studies, showed some improvement with haloperidol and fluphenazine, with less evidence for olanzapine. The analysis failed to result in any treatment recommendation of clinical relevance. In another review of potential HD treatments, among the most promising is reducing mHtt with RNA interference, ASOs, or zinc finger transcriptional repression, modulation

Table 13.3 Considerations in the treatment of Huntington's disease

Adequate nutrition
Physical, speech, and occupational therapy
Treat/prevent aspiration, fecal impaction, incontinence
Support: Life-planning, disability benefits, household help, home equipment, supervise smoking, child care, day care, institutional care, hospice
Caregiver support
Antidepressants: Selective serotonin reuptake inhibitors (SSRIs) (fluoxetine, sertraline, fluvoxamine, paroxetine, venlafaxine, citalopram), tricyclics (nortriptyline, amitriptyline, imipramine)
Anxiolytics: SSRIs, benzodiazepines, propranolol, clonidine
Dopamine (DA) depleting drugs or DA receptor–blocking drugs for chorea or chorea and psychosis: Tetrabenazine (TBZ), deutetabenazine (DTBZ); risperidone, haloperidol, olanzapine, ziprasidone, quetiapine, clozapine, fluphenazine, aripiprazole
Experimental therapeutics and research studies

of mHtt phosphorylation, chaperone upregulation, autophagy enhancement, inhibition of histone deacetylases, and monoclonal antibodies (Wild and Tabrizi, 2014). Furthermore, phosphodiesterase inhibition aimed at restoring synaptic function and restoring neurotrophic support (e.g., with BDNF) remains an important therapeutic approach, and the subject of current clinical trials.

Appendix

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References available on Expert Consult:

www.expertconsult.com.

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Chorea, Ballism, and Athetosis

Chapter contents

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Introduction

Chorea consists of involuntary, continual, abrupt, rapid, brief, unsustained, and irregular movements that flow randomly from one body part to another. Patients can partially and temporarily suppress the chorea and frequently camouflage some of the choreiform movements by incorporating them into semipurposeful activities (parakinesia). The inability to maintain voluntary contraction (motor imperistence), such as manual grip (milkmaid grip) or tongue protrusion, is a characteristic feature of chorea and results in dropping of objects and clumsiness. Chorea should be differentiated from “pseudochoreoathetosis,” a movement disorder that is phenomenologically similar to chorea or athetosis (slow chorea) but results from loss of proprioception (Sharp et al., 1994). Muscle stretch reflexes in chorea are often “hung-up” and “pendular.” Affected patients typically have a peculiar, irregular, and dancelike gait. The pathophysiology of chorea is poorly understood, but in contrast to parkinsonism, dystonia, and other movement disorders, intracortical inhibition of the motor cortex is normal in chorea (Hanajima et al., 1999). In addition, semiquantitative analysis of single-photon emission computed tomography (SPECT) in patients with hemichorea resulting from various causes suggests that there is an increase in activity in the contralateral thalamus, possibly because of disinhibition as a result of loss of normal pallidal inhibitory input (Kim et al., 2002).

Chorea may be a manifestation of a primary neurologic genetic disorder, such as Huntington disease (HD) (Testa and Jankovic, 2019), or it may occur as a neurologic complication of systemic, toxic, or other disorders (Rosenblatt et al., 1998; Cardoso, 2004; Cardoso et al., 2006; Jankovic and Fahn, 2009;

Freitas et al., 2019; Martinez-Ramirez et al., 2020) (Table 14.1; Fig. 14.1). Chorea may be seen in normal infants, but these movements usually disappear by age 8 months, and some of these movements may be purposeful (Van der Meer et al., 1995).

In this chapter we will briefly mention HD, but the focus will be on non-HD causes of chorea, because HD-like (HDL) phenotypes without the HD genotype are increasingly being described and must be recognized. Several neurodegenerative disorders, some with expanded trinucleotide repeats, have been reported as phenocopies of HD, including spinocerebellar ataxia (SCA), particularly SCA2 and SCA3 (Kawaguchi et al., 1994), pure cerebello-olivary degeneration (Fox et al., 2003), and dentatorubral-pallidoluysian atrophy (DRPLA) (see following section) (La Spada et al., 1994; Ikeuchi et al., 1995; Komure et al., 1995; Warner et al., 1995; Ross et al., 1997; Rosenblatt et al., 1998; Wild et al., 2008). In a study of 285 patients with clinical features consistent with those of HD, but who tested negative for HD by a DNA analysis, the following diagnoses were identified: five cases had HDL1 type 4 (HDL4), one had HDL1, one had HDL2, and one had Friedreich ataxia (Wild et al., 2008).

Dentatorubral-pallidoluysian atrophy and Huntington disease–like disorders

DRPLA is an autosomal dominant neurodegenerative disorder that is particularly prevalent in Japan, but it also has been identified in Europe and in African American families (Haw River syndrome) (Burke et al., 1994; Thomas and Jankovic, 2001; Wardle et al., 2009; Chaudhry et al., 2020). Usually beginning in the fourth decade, the disorder may occur as an

Table 14.1 Differential Diagnosis of Chorea**Inherited Chorea**

HD (*HTT*)
 HDL1 (*PRNP*), HDL2 (*JPH3*), HDL3
 DRPLA (*JNK*)
 Neuroacanthocytosis (*VPS13A*)
 McLeod (*XK*)
 Brain–lung–thyroid (*NKX2-1*)
 ADCY5-related movement disorder
 NBIA: PKAN, neuroferritinopathy, aceruloplasminemia, infantile neuroaxonal dystrophy (*PLA2G6*), mitochondrial membrane protein–associated neurodegeneration (MPAN; *C19orf12*)
 Wilson disease
 Ataxia–chorea: SCA 1, 2, 3, 17; Friedreich ataxia, AOA, AT
 Mitochondrial disorders
 Other genetic choreas: *GNAO1*, *FOXG1*, *PDE10A*, *PDE2A*, *OPA3*, *PCCA/PCCB*

Sporadic/Secondary Chorea

Static encephalopathy
 Sydenham chorea
 Other autoimmune choreas (SLE, APS, NMDAR encephalitis, paraneoplastic syndromes, etc.)
 Vascular chorea, polycythemia
 Sporadic C-J disease
 Hyperthyroidism
 AIDS
 Tardive dyskinesia
 Metabolic encephalopathy
 Hepatolenticular degeneration
 Nonketotic hyperglycemia
 Hypoglycemia
 Renal failure
 Ketogenic diet
 Psychogenic chorea

AOA, Ataxia with oculomotor apraxia; AIDS, acquired immunodeficiency syndrome; APS, Antiphospholipid syndrome; AT, Ataxia telangiectasia; C-J, Creutzfeldt–Jakob; DRPLA, dentatorubral–pallidoluysian atrophy; HD, Huntington disease; HDL, HD-like; NBIA, neurodegeneration with brain iron accumulation; NMDAR, N-methyl-D-aspartate receptor; PKAN, pantothenate kinase–associated neurodegeneration; SLE, systemic lupus erythematosus.

early-onset DRPLA (before 20 years of age) manifested by a variable combination of myoclonus, epilepsy, intellectual disability, or late-onset DRPLA (after 20 years of age), manifested by cerebellar ataxia, choreoathetosis, dystonia, rest and postural tremor, parkinsonism, and dementia (Video 14.1). ●

Unstable CAG expansion has been identified as the mutation in the *DRPLA* (or *ATN1*) gene on chromosome 12p13.31 (Koide et al., 1994; Komure et al., 1995; Warner et al., 1995; Becher et al., 1997; Ross et al., 1997). The *DRPLA* gene codes for protein that has been identified as a phosphoprotein, c-Jun NH(2)-terminal kinase, one of the major factors involved in its phosphorylation. In DRPLA, this protein appears to be slowly phosphorylated; thus, it may delay a process that is essential in keeping neurons alive (Okamura-Oho et al., 2003). Similar to HD, there is an inverse correlation between the age at onset and the number of CAG repeats (Ikeuchi et al., 1995). The early-onset type of DRPLA is associated with greater number of CAG repeats (62–79) compared with the late-onset type (54–67 repeats) (Ikeuchi et al., 1995). Testing for the various gene mutations will undoubtedly lead to better recognition and appreciation

of the spectrum of clinical and pathologic changes associated with these disorders. For example, a family with spastic paraplegia, truncal ataxia, and dysarthria, but without other clinical features of DRPLA, has been found to show homozygosity for an allele that carries intermediate CAG repeats in the *DRPLA* gene (Kuroharas et al., 1997). The *DRPLA* gene is expressed predominantly in neurons, but neurons that are vulnerable to degeneration in DRPLA do not selectively express the gene (Nishiyama et al., 1997).

Neuroimaging studies in patients with DRPLA often show evidence of cortical, brainstem, cerebellar atrophy, and widespread white matter changes (Koide et al., 1997; Muñoz et al., 1999; Munoz et al., 2004). Neuropathologic findings consist chiefly of degeneration of the dentatorubral system, globus pallidum externus (GPe), subthalamic nucleus, and, to a lesser extent, striatum, substantia nigra (SN), inferior olive, and thalamus (Warner et al., 1994) and demyelination and reactive astrogliosis in the cerebral white matter (Munoz et al., 2004). Involvement of oligodendrocytes in autopsied brains and an increased number of affected glia, as well as larger expansions in CAG in these glia, in transgenic mice might explain the widespread demyelination (Yamada et al., 2002). Several pathologic reports have noted widespread deposition of lipofuscin. Similar to HD and other diseases associated with CAG repeat expansions, DRPLA also has been associated with the formation of perinuclear aggregates that can be prevented by the use of transglutaminase inhibitors such as cystamine and monodansyl cadaverine (Igarashi et al., 1998). These intranuclear inclusions stain intensely with ubiquitin (Becher and Ross, 1998). Subsequent studies have demonstrated accumulation of mutant atrophin-1 in the neuronal nuclei, rather than neuronal intranuclear inclusions, as the predominant pathologic feature in this neurodegenerative disorder (Yamada et al., 2001).

Other Huntington disease–like disorders

An autosomal dominant HDL neurodegenerative disorder, now classified as HDL1 and mapped to chromosome 20p (Xiang et al., 1998), is a familial prion disease with an expanded PrP. A 192-nucleotide insertion in the region of the prion protein gene (*PRNP*) encoding an octapeptide repeat in the prion protein, was found in a single family with HD phenotype, suggesting that *PRNP* mutations can result in HD phenocopies (Moore et al., 2001).

Another disorder, termed HDL2, is characterized by onset in the fourth decade, involuntary movements such as chorea, dystonia, and other movement disorders (bradykinesia, rigidity, tremor); dysarthria; hyperreflexia; gait abnormality; psychiatric symptoms; weight loss; and dementia with progression from onset to death in about 20 years (Margolis et al., 2001, 2004; Walker, Jankovic et al., 2003). The disorder appears to be present exclusively or predominantly in individuals of African origin. The neuroimaging and neuropathologic findings are very similar to those in HD, except that there appears to be more severe involvement of the occipital cortex (Greenstein et al., 2007) and the intranuclear inclusions stain with 1C2 but not with antihuntingtin antibodies. Unlike the family linked to chromosome 20p, seizures are not present in the HDL2 family. All 10 affected family members had a CAG repeat expansion of 50 to 60

Video 14.1 Dentatorubralpallidoluyian atrophy (DRPLA).

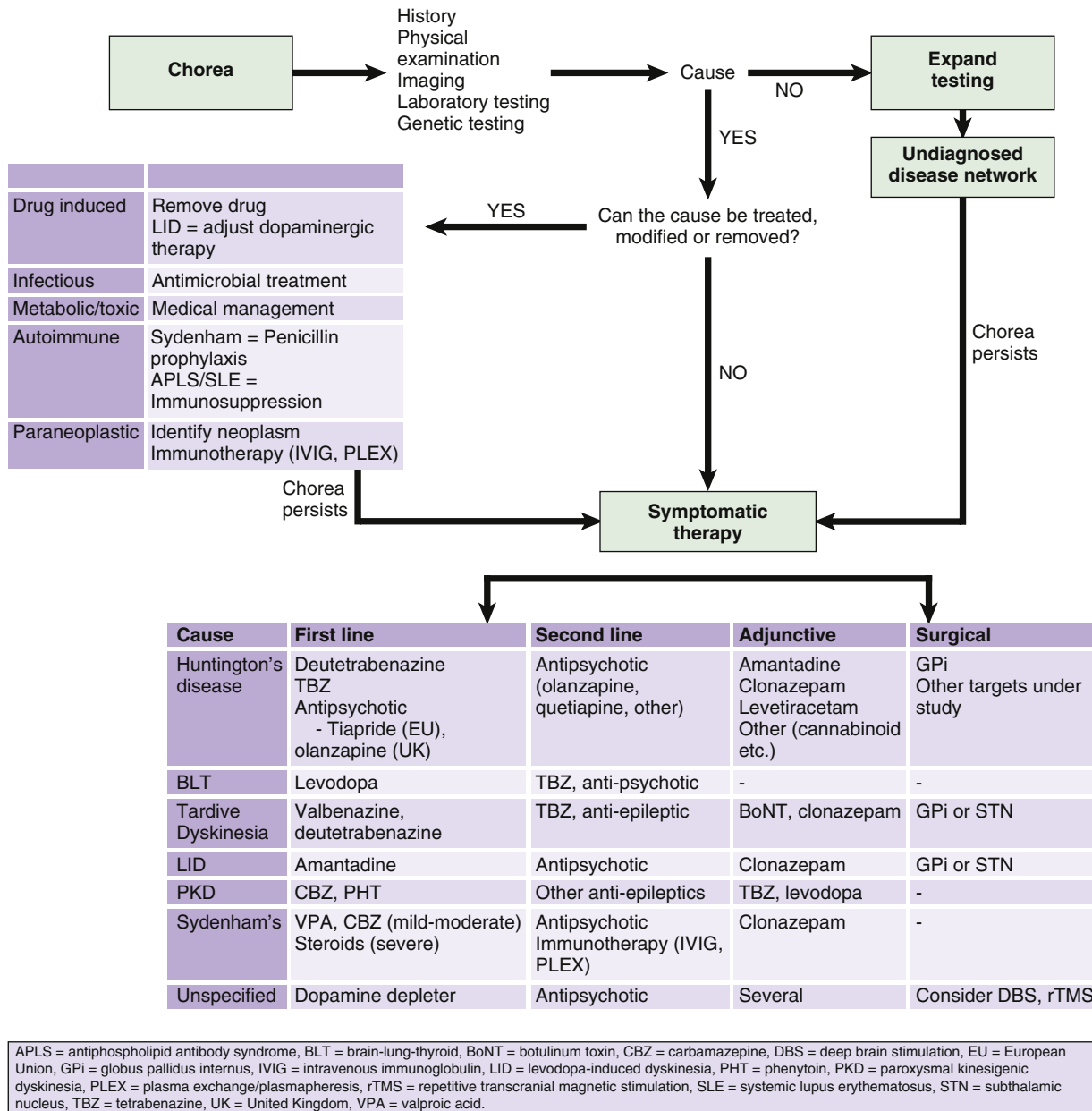


Fig. 14.1 Diagnostic and therapeutic approach to chorea. (Reproduced with permission from Bashir H, Jankovic J. Treatment options for chorea. *Expert Rev Neurother.* 2018;18[1]:51–63)

triplets. The gene was later mapped to chromosome 16q24.3 and was found to encode juncophilin-3, a protein of the junctional complex linking the plasma membrane and the endoplasmic reticulum (Holmes et al., 2001). Although acanthocytosis was emphasized by Walker and colleagues (2002; Walker, Rasmussen et al., 2003) in their initial report and in 1 of 3 patients reported subsequently (Walker, Rasmussen et al., 2003), we have not been able to confirm the presence of acanthocytes in 1 member of the original family or in the other members when we carefully examined the peripheral smear.

The mutation associated with HDL2 has been identified as a CTG/CAG trinucleotide repeat expansion within the juncophilin-3 (*JPH3*) gene and loss of its protein product, Jph3, contributes to the pathogenesis of this autosomal dominant neurodegenerative disorder (Seixas et al., 2012). In the

normal population, the repeat length ranges from 6 to 27 CTG triplets, whereas affected individuals have 41 to 58 triplets. One family, previously described as “autosomal dominant chorea-acanthocytosis with polyglutamine-containing neuronal inclusions” (see later) (Walker et al., 2002) was subsequently found to have the triple nucleotide expansion of HDL2 (Stevanin et al., 2003; Walker, Rasmussen et al., 2003). The CTG repeat expansion at the HDL2 locus has been found to be responsible for 2% of patients with typical features of HD but without expanded CAG repeats in the *IT15* gene and 0.2% of all HD families, again providing evidence that HD is clinically and genetically heterogeneous (Stevanin et al., 2002). This group later analyzed 252 patients with an HDL phenotype, including 60 with typical HD, who had tested negative for pathologic expansion in the *IT15* gene and found 2 patients who had an abnormal CTG

expansion in the *JPH3* gene and 2 other patients with abnormal CAG expansion in the gene coding for TATA-binding protein (TBP/SCA17), important in initiation of transcription (Stevanin et al., 2003; Toyoshima et al., 2004; Schneider et al., 2006). SCA17, categorized as HDL4, has many clinical features that overlap with those of HD (Schneider et al., 2007; Bech et al., 2010). Thus, the frequency of mutation in either the *JPH3* gene or *TBP* gene among patients with HDL phenotype is about 3%. Initially, the TBP expansion was found in the family with SCA17, characterized clinically by intellectual deterioration, cerebellar ataxia, epilepsy, and chorea. CUG repeat-containing RNA foci, resembling myotonic dystrophy type 1, were detected in neurons of HDL2 brains, suggesting that RNA toxicity may play a role in the pathogenesis of this neurodegenerative disorder (Rudnicki et al., 2007). HDL2 resembles HD clinically and pathologically more than any other disease (Rudnicki et al., 2008). In one study, 10 of 514 (2%) patients with HD phenocopy had C9orf72 expansion (Hensman et al., 2014). Thus, this mutation is one of the most common genetic causes of HDL disorders.

Although the majority of genetic forms of chorea are inherited in an autosomal dominant pattern, a novel autosomal recessive neurodegenerative HDL disorder has been described (Kambouris et al., 2000). Beginning at 3 to 4 years of age and manifested by chorea, dystonia, ataxia, gait disorder, spasticity, seizures, mutism, intellectual impairment, and bilateral frontal and caudate atrophy, this neurodegenerative disorder has been linked to 4p15.3, different from the 4p16.3 HD locus, but confirmation of this finding is lacking. Although classified as HDL3, because of its autosomal recessive inheritance and clinical features atypical for HD, it should not be categorized as HDL. In fact the HDL terminology should be replaced with specific disorders in which genetic mutation has been identified.

Some cases of neuronal intranuclear inclusion disease, caused by expanded CAG repeats and characterized by the combination of parkinsonism, dystonia, chorea, and cognitive, lower motor neuron signs, and cognitive and behavioral abnormalities resulting in death by the third decade, also show intranuclear aggregates, similar to the other CAG disorders (Lieberman et al., 1998).

Neuroacanthocytosis

After HD, neuroacanthocytosis is perhaps the most common form of hereditary chorea. Previously also referred to as chorea-acanthocytosis, it is now recognized that this multisystem, neurodegenerative disorder can be expressed by a wide variety of clinical and laboratory abnormalities, hence the term *neuroacanthocytosis* (Spitz et al., 1985; Danek et al., 2005; Thomas and Jankovic, 2006; Walker et al., 2006). The term *neuroacanthocytosis* was coined by Jankovic and colleagues (Jankovic et al., 1985) to replace the old term *Levine-Critchley syndrome choreoacanthocytosis* to draw attention to the heterogeneous presentation with a variety of hyperkinetic (chorea, dystonia, tics) and hypokinetic (parkinsonism) movement disorders in addition to other neurologic deficits and abnormal laboratory findings. Symptoms usually begin in the third and fourth decades of life (range: 8–62 years) with lip and tongue biting followed by

orolingual (eating) dystonia, motor and phonic tics, generalized chorea, stereotypies, and neck flexions (head drops), and trunk flexion and extension resembling a “rubber-man” (Schneider et al., 2010) (Video 14.2). Besides neuroacanthocytosis, head drops are also characteristic of other movement disorders, including tics, stereotypies, choreas, myoclonus, hypotonic disorders, bobble head syndrome, ACDY5, Sandifer syndrome, and a variety of epileptic and sleep disorders (Antelmi et al., 2015).

Other features of neuroacanthocytosis include cognitive and personality changes, seizures, dysphagia, dysarthria, vertical ophthalmoparesis, parkinsonism, amyotrophy, areflexia, evidence of axonal neuropathy, and elevated serum creatine kinase without evidence of myopathy. Hardie and colleagues (1991) reviewed the clinical, hematologic, and pathologic findings in 19 patients (10 males and 9 females) with a mean age of 32 years (range: 8–62 years) with more than 3% acanthocytes on peripheral blood smear. Of these patients, 12 with neuroacanthocytosis were familial and 7 were sporadic; 2 had the McLeod phenotype (see later). In their series, Hardie and colleagues (1991) found a variety of movement disorders, including chorea (58%), orofacial dyskinesia (53%), dystonia (47%), vocalizations (47%), tics (42%), and parkinsonism (34%). Although lip and tongue biting was observed in 16% of the patients, this is a characteristic feature of neuroacanthocytosis and, when present, strongly suggests the diagnosis. The use of a mouth guard has been reported to be effective in the treatment of oral self-mutilation associated with neuroacanthocytosis (Fontenelle and Leite, 2008). Besides movement disorders, other associated features included dysarthria (74%); absent or reduced reflexes (68%); dementia (63%); psychiatric problems such as depression, anxiety, and obsessive-compulsive disorder (OCD) (58%); dysphagia (47%); seizures (42%); muscle weakness and wasting (16%); and elevated creatine phosphokinase (CK) in 58%. Magnetic resonance volumetry and fluorodeoxyglucose positron emission tomography (PET) show striatal atrophy in patients with neuroacanthocytosis (Jung et al., 2001). Longitudinal morphometric study in 13 patients with genetically or biochemically confirmed neuroacanthocytosis versus 25 matched controls showed not only reduction in size but also abnormality of shape of the head of caudate (Walterfang et al., 2011).

Although autosomal dominant, X-linked recessive, and sporadic forms of neuroacanthocytosis have been reported, the majority of the reported families indicate autosomal recessive inheritance. A genome-wide scan for linkage in 11 families with autosomal recessive inheritance showed a linkage to a marker on chromosome 9q21, indicating a single locus for the disease (Rubio et al., 1997). Ueno and colleagues (2001) carried out a linkage-free analysis in the region of chromosome 9q21 in the Japanese population and identified a 260-base pair (bp) deletion in the expressed sequence tags (EST) region K1AA0986 in exons 60 and 61 that was homozygous in patients with neuroacanthocytosis and heterozygous in their parents. Further sequencing has identified a polyadenylation site with a protein with 3096 amino acid residues that has been named “Chorein” by the authors. This deletion is not found in normal Japanese and European populations (Ueno et al., 2001). In another study by Rampoldi and colleagues (2001) in European patients, a novel gene encoding a 3174-amino-acid protein on chromosome 9q21 with 73 exons was identified.

Video 14.2 Neuroacanthocytosis.

They identified 16 mutations in the chorea acanthocytosis (ChAc) gene, later renamed *VPS13A* gene. These mutations were identified in various exons. They suggested that chorea acanthocytosis encodes an evolutionarily conserved protein that is involved in protein sorting (Rampoldi et al., 2002). Other single heterozygous mutations have been identified in this gene (Saiki et al., 2003). Molecular analysis by screening all 73 exons of the *VPS13A* gene showed marked genotype-phenotype heterogeneity (Lossos et al., 2005). The function of the protein product chorein is not yet fully understood, but it is probably involved in intracellular protein trafficking. Using antichorein antisera, the expression of chorein in peripheral red blood cells has been found to be absent or markedly reduced in patients with neuroacanthocytosis, but not with McLeod syndrome or HD (Dobson-Stone et al., 2004; Weaver et al., 2019). Loss of chorein expression, measured by western blot analysis, has been found to be a reliable diagnostic test for neuroacanthocytosis.

Walker and colleagues (2002) described a family with chorea or parkinsonism and cognitive changes inherited in an autosomal dominant pattern. At autopsy, there was marked degeneration of the striatum and intranuclear inclusion bodies immunoreactive for ubiquitin, expanded polyglutamine CAG repeats, and torsinA. Interestingly, one of the patients had fragile X syndrome and two had expanded trinucleotide repeats at permutation range, previously associated with postural/kinetic tremor, parkinsonism, ataxia, and cognitive decline (Hagerman et al., 2001). The family reported by Walker and colleagues (2002) turned out to have the trinucleotide repeat expansion associated with HDL2, but subsequent analysis of the family shed doubt on the presence of acanthocytes as a feature of the HDL2 syndrome (Walker, Jankovic et al., 2003).

Identifications of novel mutations in the *XK* gene, responsible for McLeod syndrome are expanding its clinical phenotype (Weaver et al. 2019). Two patients from the original study by Rubio and colleagues (1997) were found to have the McLeod phenotype, an X-linked (Xp21) recessive form of acanthocytosis associated with depression, bipolar and personality disorder, and neurologic manifestations, including chorea, involuntary vocalizations, seizures, motor axonopathy, hemolysis, liver disease, and high creatine kinase levels (Witt et al., 1992; Danek et al., 2001a,b; Roulis et al., 2018). The phenotype of McLeod syndrome is similar to that of neuroacanthocytosis, but presentation is more variable, movement disorder may be minimal (chorea, dystonia, and parkinsonism), and there is no self-mutilation. Patients may also have variable psychiatric/cognitive symptoms, mild axonal neuropathy, myopathy, cardiomyopathy, and chronic granulomatous disease (Roulis et al., 2018).

Another genetic cause of a syndrome similar to neuroacanthocytosis is a rare mitochondrial disease resulting from mutations in the *ELAC2* gene (Paukar et al., 2018). Clinical manifestations include cognitive decline, olfactory hallucinations, perioral chorea and distal chorea, dystonia, apraxia, bradykinesia, waddling gait, myopathy, hearing loss, diabetes, polyneuropathy, hypertrophic cardiomyopathy, and delayed psychomotor development. Death usually occurs during childhood.

Although 20 families have been described, the family history is usually negative. Neuroimaging in patients with neuroacanthocytosis typically reveals caudate and occasionally cerebellar atrophy with a rim of increased T2-intensity in

the lateral putamen. Functional neuroimaging studies show evidence of downregulation of D2 dopamine receptors. In contrast to the autosomal recessive form of neuroacanthocytosis linked to mutations in *VPS13A* gene on chromosome 9, patients with McLeod syndrome usually do not exhibit lip-biting or dysphagia. This multisystem disorder is associated with low reactivity of Kell erythrocyte antigens (weak antigenicity of red cells) because of the absence of Kx 37-kDa, 444 AA, membrane protein that forms a complex with the Kell protein. The disorder is caused by different mutations in the *XK* gene encoding for the KX protein (Ho et al., 1996; Danek et al., 2001a; Jung et al., 2001). Mutations identified by various authors include frame shift mutations in exon 2 at codon 151, deletion at codon 90 in exon 2 and at codon 408 in exon 3, and splicing mutations in intron 2 of the *XK* gene (Dotti et al., 2000; Ueyama et al., 2000; Danek et al., 2001a; Jung et al., 2001). Rarely, neuroacanthocytosis may be associated with abetalipoproteinemia resulting from mutations in the microsomal triglyceride transfer protein (Sharp et al., 1993). In addition to acanthocytosis, the patients exhibit retinopathy; malabsorption, including that of vitamin E; low serum cholesterol levels; and abnormal serum lipoprotein electrophoresis. Abetalipoproteinemia can also cause movement disorders and acanthocytosis (Bohlega et al., 1998).

An examination of wet blood or Wright-stained, fast-dry blood smear usually reveals over 15% of red blood cells as acanthocytes. In mild forms of acanthocytosis, scanning electron microscopy might be required to demonstrate the red blood cell abnormalities (Feinberg et al., 1991). In a study of two patients with pathologically proven neuroacanthocytosis, Feinberg and colleagues (1991) noted that the yield in demonstrating acanthocytosis may be increased by using a coverslip because the contact with glass causes the fragile cells to undergo morphologic changes. Diluting the blood with normal saline, incubating the Wright-stained smear with ethylenediaminetetraacetic acid (EDTA), using a scanning electron microscope, and employing other techniques designed to increase "echinocytotic stress" are also helpful (Feinberg et al., 1991; Orrell et al., 1995). The characteristic acanthocytic appearance of red blood cells has been attributed to abnormalities in transmembrane glycoprotein band 3 that can be demonstrated on gel electrophoresis. It is not yet clear how the gene mutation leads to the abnormal morphology of the red cells.

By using high-performance liquid chromatography, fatty acids of erythrocyte membrane proteins were analyzed in six patients with neuroacanthocytosis (Sakai et al., 1991). In comparison with normal controls and patients with HD, erythrocytes of patients with neuroacanthocytosis showed a marked abnormality in the composition of covalently bound fatty acids: an increase in palmitic acid (C16:0) and a decrease in stearic acid (C18:0).

Brain MRI in patients with neuroacanthocytosis usually shows caudate and more generalized brain atrophy, but some cases also show extensive white matter abnormalities (Nicholl et al., 2004). Caudate hypometabolism and atrophy have been demonstrated by PET studies and by neuroimaging. Similar to the findings in Parkinson disease (PD), PET scans in six patients with neuroacanthocytosis showed a reduction to 42% of normal in [¹⁸F]dopa uptake in the posterior putamen; in contrast to PD, however, there was a

Table 14.2 Classification of neurodegeneration with brain iron accumulation

Classification of Neurodegeneration with Brain Iron Accumulation Condition (Acronym)	Synonym	Gene	Chromosomal position
PKAN	NBIA1	<i>PANK2</i>	20p13
PLAN	NBIA2, PARK14	<i>PLA2G6</i>	22q12
FAHN	SPG35	<i>FA2H</i>	16q23
MPAN	—	<i>C19orf12</i>	19q12
Kufor-Rakeb disease	PARK9	<i>ATP13A2</i>	1p36
Aceruloplasminemia	—	<i>CP</i>	3q23
Neuroferritinopathy	—	<i>FTL</i>	19q13
BPAN	SENDA	<i>WDR45</i>	X-chromosome
Idiopathic late-onset cases	—	Probably heterogeneous	Probably heterogeneous

marked reduction in the striatal [¹¹C]raclopride (D2) receptor binding (Brooks et al., 1991).

Neuronal loss and gliosis were particularly prominent in the striatum and pallidum but may also affect the thalamus, SN, and anterior horns of the spinal cord (Rinne et al., 1994b). The neuronal loss in the SN is most evident in the ventrolateral region, similar to that in PD, but the nigral neuronal loss is more widespread in neuroacanthocytosis (Rinne et al., 1994a). The preservation of the cerebral cortex, cerebellum, subthalamic nucleus, pons, and medulla may serve to differentiate pathologically among neuroacanthocytosis, HD, and DRPLA. However, autopsy findings in brains of two brothers with neuroacanthocytosis manifested by parkinsonism without chorea showed no significant neuronal loss within the SN pars compacta (SNpc), but there was a low count of parvalbumin-positive interneurons in the cortex and striatum (Connolly et al., 2014). Brain biochemical analyses showed low substance P in the SN and striatum and increased levels of norepinephrine in the putamen and pallidum (De Yebenes et al., 1988).

Unfortunately, there is no effective treatment for neuroacanthocytosis, although chorea, stereotypy, dystonia, seizures, and other neurologic symptoms can be treated symptomatically, similar to other disorders. The associated parkinsonism rarely improves with dopaminergic therapy, probably because there is loss of postsynaptic dopamine receptors. We have seen some patients whose condition remained static for several years, followed by further progression and an eventual demise as a result of aspiration pneumonia or other complications of chronic illness.

Neurodegeneration with brain iron accumulation

A group of neurodegenerative disorders, formerly known as Hallervorden-Spatz disease, has received increasing attention as the genetic and pathogenic mechanisms of the various subtypes have become elucidated. The disease was first described in 1922 by Julius Hallervorden and Hugo Spatz, who later actively participated in Nazi euthanasia while

working at the Kaiser Wilhelm Institute for Brain Research (Shevell, 2012; Zeidman and Pandey, 2012). Because of their terrible past and shameless involvement with Nazi activities, this group of disorders has been renamed neurodegeneration with brain iron accumulation (NBIA) (Schneider, 2016; <http://nbiacure.org>) (Table 14.2). The prototype form of NBIA consists of an autosomal recessive disorder characterized by childhood-onset progressive rigidity, generalized dystonia, often associated with dystonic opisthotonus (Stamelou et al., 2013) and oro-mandibular-lingual dystonia, choreoathetosis, spasticity, optic nerve atrophy, levodopa-responsive parkinsonism, and dementia (Malandrini et al., 1996; Racette et al., 2001; Thomas et al., 2004; Aggarwal et al., 2010; Van Craenenbroeck et al., 2010). Although chorea is not a typical feature of NBIA, “senile chorea” has been described in a patient with pathologically proven NBIA type 1 (NBIA-1) (Grimes et al., 2000).

The most classic NBIA, NBIA type 1 (NBIA-1) is the pantothenate kinase-associated neurodegeneration (PKAN). Linkage analyses initially localized the NBIA-1 gene on 20p12.3–p13; subsequently, 7-bp deletion and various missense mutations were identified in the coding sequence of the *PANK2* gene, which codes for pantothenate kinase (Zhou et al., 2001; Hayflick et al., 2003). Pantothenate kinase is an essential mitochondrial regulatory enzyme in coenzyme A biosynthesis (Nemeth, 2014). It has been postulated that as a result of phosphopantothenate deficiency, cysteine accumulates in the globus pallidus (GP) of brains of patients with NBIA-1. It undergoes rapid auto-oxidation in the presence of nonheme iron that normally accumulates in globus pallidus internus (GPi) and SN, generating free radicals that are locally neurotoxic (Benarroch et al., 2009). Interestingly, atypical subjects were found to be compound heterozygotes for certain mutations for which classic subjects were homozygous. The disorder with the clinical phenotype of NBIA associated with mutations in the *PANK2* gene is now referred to as PKAN (Thomas et al., 2004). On the basis of an analysis of 123 patients from 98 families with NBIA-1, Hayflick and colleagues (2003) found that “classic Hallervorden-Spatz syndrome” was associated with *PANK2* mutation in all cases and that one third of “atypical” cases had the mutations within

the *PANK2* gene. Those who had the *PANK2* mutation were more likely to have dysarthria and psychiatric symptoms, and all had the typical “eye of a tiger” abnormality on brain MRI with a specific pattern of hyperintensity within the hypointense GPi (McNeill et al., 2008; Lee et al., 2020).

Neuroacanthocytosis and NBIA may overlap in some clinical features. Although PKAN may be associated with acanthocytosis, another neuroacanthocytosis syndrome, linked to PKAN, is the hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration (HARP syndrome) (Orrell et al., 1995). This disorder is associated with dystonia, particularly involving the oromandibular region, rather than chorea and self-mutilation. Indeed, a homozygous nonsense mutation in exon 5 of the *PANK2* gene that creates a stop codon at amino acid 371, found in the original HARP patient, establishes that HARP is part of the PKAN disease spectrum (Ching et al., 2002; Houlden et al., 2003).

The classification of NBIA is continuously being revised as our understanding of this group of disorders is improving. In addition to PKAN, other forms of NBIA include neuroferritinopathy, infantile neuroaxonal dystrophy, and aceruloplasminemia, and PLA2G6-associated neurodegeneration (PLAN), with mutations in the *PLA2G6* gene, on chromosome 22q13.1 (Schneider et al., 2009; Aggarwal et al., 2010; Dusek et al., 2012; Schneider et al., 2012; Nemeth, 2014) (see Table 14.2). These disorders are chiefly manifested by childhood-onset axial hypotonia, spasticity, bulbar dysfunction, ataxia, dystonia, choreoathetosis, and MRI changes indicative of iron deposition in the GP and SN (Kurian et al., 2008). Previously diagnosed as infantile neuroaxonal dystrophy, now classified as NBIA-2, PLAN may also manifest as adult-onset, levodopa-responsive dystonia–parkinsonism without iron on brain imaging (McNeill et al., 2008; Paisán-Ruiz et al., 2008; Schneider et al., 2009). Another gene, *FA2H*, when mutated, has been found to cause not only leukodystrophy and hereditary spastic paraplegia, but also NBIA (Kruer et al., 2010). The *FA2H*-associated neurodegeneration (FAHN) is characterized by childhood-onset gait impairment, spastic paraparesis, ataxia, and dystonia (Kruer et al., 2010; Schneider and Bhatia, 2010). *FA2H* is involved in lipid and ceramide metabolism. Another form of NBIA was highlighted by a report of 11 children with a biochemical profile suggestive of dopamine transporter (DAT) deficiency syndrome (Kurian et al., 2011). Manifesting in infancy, this disorder is usually characterized by severe parkinsonism–dystonia syndrome, but chorea, oculomotor deviations, and spasticity may also dominate the clinical phenotype. The cerebrospinal fluid (CSF) ratio of homovanillic acid to 5-hydroxyindoleacetic acid is usually increased. This autosomal recessive disorder has been attributed to homozygous or compound heterozygous *SLC6A3* mutations and complete loss of DAT activity in the basal nuclei (indicated by abnormal DAT scan SPECT). Mutations in *C19orf12*, a gene that codes for mitochondrial membrane protein, hence the term mitochondrial membrane protein–associated neurodegeneration (MPAN), have been recently identified in patients with NBIA phenotype manifested by parkinsonism and levodopa-induced dyskinesias (Savitt and Jankovic, 2019). Although autosomal recessive inheritance has been reported, there is some evidence that an autosomal dominant mechanism also may play a role (Gregory et al., 2019).

Another NBIA associated with chorea and frequently misdiagnosed as HD is neuroferritinopathy, a progressive but potentially treatable disorder caused by mutations in the ferritin light chain gene (*FTL1*), located on 19q13.3–q13.4 (Chinnery et al., 2007; Ondo et al., 2010). Patients may be initially diagnosed as having idiopathic dystonia, PD, HD, or a variety of other disorders. In a study of a group of 41 genetically homogeneous subjects with the 460InsA mutation in *FTL1*, the mean age at onset was 39.4 ± 13.3 years (range: 13–63), beginning with chorea in 50%, focal lower limb dystonia in 42.5%, and parkinsonism in 7.5% (Chinnery et al., 2007). The disease progressed over a 5- to 10-year period, eventually leading to aphonia, dysphagia, severe and often asymmetric motor disability, and finally dementia in the advanced stages. A characteristic action-specific facial dystonia was present in 65%. Serum ferritin levels were low in the majority of males and postmenopausal females, but may be normal, particularly in premenopausal females. Magnetic resonance imaging (MRI) typically shows gradient echo T2* hypointensity in red nuclei, SN, and GP brain imaging and was abnormal in all affected individuals and one presymptomatic carrier and T1 hyperintensity in the GP and posterior putamen. Chorea associated with neuroferritinopathy responds well to tetrabenazine (TBZ), a dopamine depletor (Ondo et al., 2010).

Another form of NBIA is the clinical syndrome previously called static encephalopathy of childhood with neurodegeneration in adulthood (SENDA), but as a result of identification of mutations in the X-chromosomal *WDR45* gene encoding a beta-propeller protein, postulated to play a role in autophagy, the disorder is now referred to as BPAN (Hayflick et al., 2013; Horvath, 2013; Rathore et al., 2014). Initially manifesting as global developmental delay with intellectual disability in infancy or early childhood, the patients (girls outnumber boys) then gradually become clumsy and develop spasticity and epilepsy and are often misdiagnosed as having cerebral palsy (CP). The second phase, which usually starts in adolescence and young adulthood, is manifested by progressive dystonia, cognitive decline, speech difficulties, and parkinsonism but no tremor. Patients initially respond to levodopa but often develop disabling motor fluctuations and dyskinesias and require deep brain stimulation (DBS) (Hayflick et al., 2013). Because of sleep disturbances, hand stereotypies, and other abnormalities, many of these patients are initially diagnosed as having atypical Rett syndrome. In addition to iron accumulation in the SN, the pallidum may appear hypointense on gradient-echo or T2* sequences; T1-weighted signal hyperintensity with a central band of hypointensity in the SN seems to be a specific finding in BPAN. Although *WDR45* is located on the X chromosome (most variants are nonsense mutations), affected individuals seem to be sporadic cases with no family history of NBIA. Abnormal autophagy has been proposed as the mechanism of neurodegeneration in this disorder, although it is not clear how increased autophagy relates to iron accumulation.

One entity that should be added to the NBIA group of disorders is pallidonigroluysial atrophy (PNLA) (Ahmed et al., 2008; Wong et al., 2013). In a series of 25 cases of pathologically proven PNLA cases the mean age at onset was 54.3 ± 14.3 years and average duration of disease was 7.9 ± 5.8 years (Wong et al., 2013). In addition to gait or balance disturbance, often initially diagnosed as progressive supranuclear palsy,

chorea was encountered in 20%; 36% had coexistent motor neuron disease. Besides extensive gliosis, many brains showed iron-positive pigments in the pallidonigroluysian system, and p62-positive glial inclusions without evidence of tauopathy.

Treatment of NBIA syndrome is challenging, but regression of symptoms after 6 months of iron chelation with deferiprone has been reported in some patients with NBIA (Forni et al., 2008). Another approach, based on a mouse model of the disease (knockout exacerbated by ketogenic diet), suggests that treatment with pantethine, the dimeric form of pantothenic acid (vitamin B₅), may be beneficial even in the human condition (Brunetti et al., 2014). Potential therapeutics may involve strategies that reactivate pyruvate dehydrogenase due to its relationship with coenzyme A-dependent activation of mitochondrial acyl carrier protein (Lambrechts et al., 2019).

Essential chorea is a form of adult-onset, nonprogressive chorea without family history of chorea or other symptoms suggestive of HD and without evidence of striatal atrophy on neuroimaging studies. Sometimes referred to as senile chorea, essential chorea usually has its onset after age 60, and in contrast to HD, it is not associated with dementia or positive family history. Some cases of senile chorea, however, have been reported to have pathologic changes identical to those of HD; others have had predominant degeneration of the putamen rather than the caudate (Friedman and Ambler, 1990). The CAG repeat length should, by definition, be normal, but Ruiz and colleagues (1997) found abnormal CAG expansion in three of six clinically diagnosed cases of senile chorea. Although the authors suggest that some patients with senile chorea have a sporadic form of HD, the term essential (or senile) chorea should be reserved for those patients with late-onset chorea without family history, without dementia, without psychiatric problems, and without CAG expansion. These criteria are necessary to separate senile or essential chorea from HD.

Other familial choreas

Besides HD and neuroacanthocytosis, genetically transmitted choreas include brain–lung–thyroid syndrome, a nonprogressive chorea of childhood onset (Wheeler et al., 1993; Kleiner-Fisman and Lang, 2007; Adam and Jankovic, 2010; Inzelberg et al., 2011) (Table 14.3). Brain–lung–thyroid syndrome usually starts in early childhood and progresses until the second decade, after which time it remains static or even spontaneously improves. The patients may have a slight hypotonia and motor delay because of chorea, slight gait ataxia, dystonia, and tics, and their handwriting may be impaired, but the disorder is self-limiting after adolescence in most cases, although it may persist as a mild chorea beyond age 60 years. Inherited as an autosomal dominant disorder, Brain–lung–thyroid syndrome has been linked to a marker on chromosome 14q13.1–q21.1 (de Vries et al., 2000; Fernandez et al., 2001; Breedveld et al., 2002) and a novel single nucleotide substitution in the *NKX2-1* (previously called *TITF1*) gene (also referred to as *TTF*, and *T/ebp*) on chromosome 14q13, coding for a transcription essential for the organogenesis of the lung, thyroid, and basal ganglia, and has been identified initially in one Canadian family and later in many other families (Schrag et al., 2000; Kleiner-Fisman et al., 2003; Kleiner-Fisman and Lang, 2007; Ferrara et al., 2008; Gras et al., 2012; Peall et al., 2014; Patel and Jankovic, 2014). This syndrome

Table 14.3 Clinical features of benign hereditary chorea

- Onset in early childhood
- Progresses until second decade → static or spontaneously improves (may persist > 60)
- No dementia or other abnormalities
- MRI normal, but may show hypoplastic pallidum, lack of differentiation of medial and lateral components, and bilateral signal hyperintensities on T2-weighted images
- No pathologic changes, but may have reduced number of striatal and neocortical interneurons
- Autosomal dominant associated with mutation in *TITF1* gene on chromosome 14q13–q21.1
- *TITF1* gene mutation should be considered in patients with chorea, intellectual disability, chronic lung disease and congenital hypothyroidism, hence the term brain–lung–thyroid (BLT) syndrome
- May improve markedly with levodopa

also has been described in patients with deletion of not only the *NKX2-1* gene, but also the contiguous *PAX9* gene (Devos et al., 2006). These mutations should be considered in children and adults with chorea, intellectual disability, congenital hypothyroidism, and chronic lung disease, hence the term brain–lung–thyroid syndrome proposed for this disease (Willemssen et al., 2005; Devos et al., 2006). In one series of 18 patients from 13 families, thyroid abnormalities were found in 67% and lung problems in 46% of patients (Gras et al., 2012). MRI has been generally reported to be unremarkable, but some cases showed hypoplastic pallidum, lack of differentiation of medial and lateral components, and bilateral signal hyperintensities on T2-weighted MRI images (Kleiner-Fisman and Lang, 2007). Two autopsied brains from patients with brain–lung–thyroid syndrome resulting from *NKX2-1* gene syndrome showed no pathologic abnormalities (Asmus et al., 2005), but specific immunochemical investigations suggested a reduced number of striatal and neocortical interneurons, consistent with a defect in migration normally mediated by the *NKX2-1* gene (Kleiner-Fisman et al., 2005). Subsequently, other patients and families have been described with a variable phenotype, including hypotonia and chorea in early infancy, delayed motor milestones, learning difficulties, intellectual disability, dystonia, myoclonus, tics, and attention deficit–hyperactivity disorder, similar to Tourette syndrome (Gras et al., 2012). Although initially referred to in the literature as “benign hereditary chorea” the *NKX2-1* gene phenotype has been expanding beyond chorea and may include myoclonus, seizures, gross motor delay, gait impairment, cognitive deficits, and other neurologic, psychiatric, and medical problems (Parnes et al., 2019). Surprisingly, the chorea may improve with levodopa (Asmus et al., 2005) and with TBZ and other vesicular monoamine transporter type 2 (VMAT2) inhibitors.

Animal studies provide some insight into the pathophysiology of the complex disorder. Homozygous knockout of the *NKX2* gene in mice results in a very severe phenotype and still birth, but heterozygous mice, which would be the model for the human disease, do not have readily apparent neurologic deficits. However, conditional removal of *NKX2* suggests that *TITF-1* is involved in the differentiation of interneurons, projections of striatal medium spiny neurons, and formation of the GP (Flandin et al., 2010).

Adult-onset, autosomal dominant, benign chorea without dementia, initially reported in Japan, in which HD, HDL1, HDL2, DRPLA, SCA17, and mutations in the *NKX2-1* gene were excluded, revealed linkage to a novel locus on chromosome 8q21.3–q23.3 in two Japanese families with benign hereditary chorea type 2 (Shimohata et al., 2007), but this is yet to be confirmed.

Another form of “benign” chorea with relatively intact cognitive function is an autosomal dominant syndrome associated with *ADCY5* mutation (Mencacci et al., 2015; Dy et al., 2016; Carecchio et al., 2017). Similar to *NKX2-1* gene phenotype, which was initially describes as “benign,” *ADCY5* mutations have been increasingly recognized to cause a variety of neurologic and psychiatric symptoms, including delayed motor milestones, hypotonia, falls, “myopathic facial appearance,” heart failure, and other manifestations. One characteristic feature is fluctuating course with episodic exacerbations observed on awakening, triggered by asleep, intercurrent illnesses, excitement, or stress. Many attacks represent medial frontal lobe seizures and are often misdiagnosed as psychogenic. Because of language and motor delay, the patients are often wrongly diagnosed as having cerebral palsy. The patients are generally unresponsive to medical therapy, and DBS provided variable outcomes.

There are new hereditary choreas reported at an exponential rate as novel gene mutations are identified. One recently recognized genetic cause of chorea is the *GNAO1* syndrome, due to mutations in the *GNAO1* gene that codes for the α subunit of heterotrimeric guanine nucleotide-binding protein (Gi protein), a membrane protein widely expressed in the CNS. This autosomal dominant disorder, with typical onset in the first 2 years of life, is a heterogeneous syndrome characterized by epileptic encephalopathy, delayed development, hypotonia, and a variety of hyperkinetic movement disorders including chorea, dystonia and orofacial dyskinesia (Schirinzi et al., 2019) (Video 14.3). These often fluctuate, often be triggered or exacerbated by fever or other stressors, and may evolve into life-threatening exacerbations, such as status dystonicus. Indeed, the presence of chorea seems to be predictive of a higher risk of movement disorder emergency. The condition usually does not respond to treatment, even deep brain stimulation (de Almeida Marcelino et al., 2020).

Hereditary chorea without dementia and with a benign course has been also described (Behan and Bone, 1977). In one family of German ancestry with the phenotype of familial essential (benign) chorea (onset 2–19 years), manifested by predominantly perioral and periorbital myokymia and face, neck, and upper limb dystonic/choreic movements, also known as familial dyskinesia with facial myokymia (FDFM), mutation in the adenylyl cyclase 5 (*ADCY5*) gene on chromosome 3p21–3q21 was found by single exome sequencing (Chen et al., 2012). Other families with this mutation have been since described, but the phenotype has expanded to include dystonia, myoclonus-marked axial hypotonia, episodic and fluctuating painful spasms associated with falls, sleep disturbance, and other manifestations (Carapito et al., 2015) (Video 14.4). Several mutations have been described in the *ADCY5* gene localized to 3p21–3q21.9. *FOXP1* mutations have been associated with a wide variety of movement disorders, including a mixture of dystonia, choreoathetosis, and orolingual/facial dyskinesias and other neurologic abnormalities, including microcephaly, epilepsy, and intellectual deficit (Papandreou et al., 2016).

Choreoathetosis, along with developmental regression, intellectual disability, pendular nystagmus, optic atrophy, dysphagia, dystonia, spasticity, and severe bilateral striatal atrophy with response to biotin, is a feature of familial infantile bilateral striatal necrosis (IBSN) (Straussberg et al., 2002; Basel-Vanagaite et al., 2006). IBSN, an autosomal recessive neurodegenerative disorder, was found to be associated with mutation of *nup62* on chromosome 19q13.32–13.41 (Basel-Vanagaite et al., 2006). Biotin may slow disease progression.

Ataxia-telangiectasia, an autosomal recessive multisystem disease, is another disorder often associated with chorea. In a retrospective analysis of the clinical characteristics in 18 adult patients with ataxia-telangiectasia from 9 families and 6 unrelated adults documented with elevated alpha-fetoprotein, chromosomal instability, and mutations in the A-T mutated (*ATM*) gene and measurements of ATM protein expression and kinase activity, chorea-athetosis was present in 14 of 18 (78%) cases (Verhagen et al., 2009). Other common abnormalities included dysarthria, oculomotor apraxia, dystonia, rest tremor, neuropathy, immunodeficiency, restricted respiratory function, and malignancies. Not all affected individuals have telangiectasia.

Another disorder, rarely considered in the differential diagnosis of chorea, is the familial dyskinesia and facial myokymia (FDFM), characterized by childhood-onset adventitious movements and perioral or periorbital myokymia. These movements may be paroxysmal in early stages, increase in frequency and severity, and become constant in the third decade, without intellectual impairment or shortening of life span. Frontotemporal dementia, particularly associated with TDP-43 abnormalities resulting from *TARDBP* mutations may be associated not only with amyotrophic lateral sclerosis, but also supranuclear gaze palsy and chorea (Kovacs et al., 2009). The combination of chorea, dystonia, ataxia, and pyramidal tract signs caused by mutations in *OPA3* was reported in two affected cousins from a consanguineous Pakistani family (Arif et al., 2013).

Infectious chorea

A variety of infections that affect the central nervous system have been associated with chorea. Acute manifestations of bacterial meningitis, encephalitis, tuberculous meningitis, and aseptic meningitis include movement disorders such as chorea, athetosis, dystonia, and hemiballismus (Alarcon et al., 2000). Human immunodeficiency virus (HIV) also has been reported to cause chorea and other features similar to HD, either as the result of HIV encephalitis (Sevigny et al., 2005) or as the result of focal opportunistic infections such as toxoplasmosis (Nath et al., 1987; Gallo et al., 1996; Pardo et al., 1998; Piccolo et al., 1999).

Postinfectious and autoimmune choreas

Sydenham chorea

Occasionally still referred to as St. Vitus chorea or St. Vitus dance (Krack, 1999), Sydenham chorea was described originally by Thomas Sydenham, an English physician, in 1686. Considered an autoimmune disorder, a consequence of infection with group A beta-hemolytic streptococcus (GABHS), the

Video 14.3 Sydenham disease.
Video 14.4 Sydenham disease.

phenomenology has broadened to include not only chorea but also a variety of other neurologic, psychiatric, cardiac, rheumatologic, and other disorders (Swedo, 1994; Cardoso et al., 1997; Cardoso, 2004; Oosterveer et al., 2010) (Videos 14.5, 14.6). Because chorea is only one of many neurologic and nonneurologic manifestations, the term *Sydenham disease* is preferred, rather than *Sydenham chorea*, but the latter is used so frequently in the literature that its usage may be difficult to change. Osler, in his seminal paper “On Chorea and Choreiform Affections,” published in 1894, drew attention to the distinction between Sydenham chorea and HD (Goetz, 2000). Although the majority of Sydenham patients have bilateral involvement, the distribution of chorea is usually asymmetrical, and pure hemichorea can be seen in 20% of all Sydenham chorea patients. The individual contractions are slightly longer in Sydenham disease (greater than 100 ms) compared with those in HD (50–100 ms) (Hallett and Kaufman, 1981). Using transcranial magnetic stimulation to evaluate motor cortex hyperexcitability, some investigators found decreased excitability of the axons synapsing onto cortical motor neurons, possibly because of compensation from the involuntary movements (Hallett and Obeso, 2015; Khedr et al., 2015). ▶

Other features of Sydenham chorea include dysarthria and decreased verbal output, hypometric saccades, oculogyric crisis, papilledema, central retinal artery occlusion, and seizures. Similar to Tourette syndrome (Kwak et al., 2003b), migraine is more common in children with Sydenham chorea than in controls (Teixeira et al., 2004). Unlike arthritis and carditis, which occur soon after streptococcal infection, chorea and various neurobehavioral symptoms may be delayed for 6 months or longer and may be the sole manifestation of rheumatic fever (Stollerman, 1997). In 50 consecutive patients with rheumatic fever, 26% developed chorea, but arthritis was more frequent in patients without chorea (84%) than in those with chorea (31%) (Cardoso et al., 1997). In patients with well-documented GABHS infections, a rise in antistreptolysin-O (ASO) titer can often be demonstrated after 1 week, but titers may not reach maximal levels until 5 weeks after the infection and tend to decline gradually to preinfection levels by 6 to 12 months. Titers over 500 are indicative of recent GABHS infection, but about 20% of patients fail to show an antibody response to GABHS and in those patients antidesoxyribonuclease B (anti-DNAse B) titers may be elevated.

Some features of Sydenham chorea overlap with those of Tourette syndrome. Although tics are often differentiated from chorea by the presence of premonitory sensation, as reported by more than 90% of patients with Tourette syndrome (Kwak et al., 2003a), some patients with Sydenham chorea and chorea also report sensory symptoms (Rodopman-Arman et al., 2004). There is controversy as to whether pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), which may be associated with motor and phonic tics, is a variant of Sydenham chorea or a separate entity (Kurlan, 2004; Kurlan et al., 2008; Singer et al., 2008). This entity is discussed in more detail in the chapter on Tourette syndrome.

Behavioral problems associated with Sydenham chorea include irritability, emotional lability, OCD, hyperactivity, learning disorders, and other behavioral problems that are typically observed in patients with Tourette syndrome. One study compared 56 patients with Sydenham chorea with 50 rheumatic fever patients and 50 healthy subjects and found

that obsessive-compulsive behavior was present in 19%, OCD in 23.2%, and attention deficit–hyperactivity disorder in 30.4%, all significantly more frequently than in the diseased or healthy controls (Maia et al., 2005). The neurobehavioral symptoms usually begin within 2 to 4 weeks after the onset of the choreic movements. The disorder tends to resolve spontaneously in 3 to 4 months but may persist in half of the patients during a 3-year follow-up (Cardoso et al., 1999). Female gender and the presence of carditis might be risk factors for persistent disease. In some cases of Sydenham chorea the chorea recurs during pregnancy (chorea gravidarum) or when the patient is exposed to estrogen. In 20 patients with prior history of Sydenham chorea, 15 (75%) developed chorea gravidarum and all patients with chorea gravidarum who were later treated with oral contraceptives developed recurrence of chorea (Maia et al., 2012). Sydenham chorea, once relatively common, is now encountered relatively rarely in developed countries (Eshel et al., 1993). Recurrences of Sydenham chorea are not associated with anti–basal ganglia antibodies (Harrison et al., 2004).

In addition to occasionally elevated titers of ASO, which is not specific for GABHS infection because it can also reflect group G, the majority of patients with Sydenham chorea have immunoglobulin G (IgG) antibody reactivity with neurons in the caudate and subthalamic nuclei (Kiessling et al., 1993; Swedo et al., 1993). These antineuronal antibodies are found in nearly all patients with Sydenham chorea (Swedo, 1994; Abraham et al., 1997; Mittleman, 1997). The rheumatic B-cell alloantigen D8/17 is also frequently found in patients with rheumatic chorea, but it is not clear whether this could be used as a diagnostic test (Feldman et al., 1993). Anti–basal ganglia antibodies have been identified in patients with acute and persistent Sydenham chorea, providing further evidence that the disease is an antibody-mediated disorder (Church et al., 2002). Rats exposed to the GABHS antigen exhibited motor symptoms (impaired food manipulation and beam walking) and compulsive behavior (increased induced grooming) that improved by the administration of the D2 blocker haloperidol (Brimberg et al., 2012). Furthermore, streptococcal exposure resulted in antibody deposition in the striatum, thalamus, and frontal cortex, and concomitant alterations in dopamine and glutamate levels in cortex and basal ganglia. Autoantibodies (IgG) of GABHS rats reacted with tubulin and caused elevated calcium/calmodulin-dependent protein kinase II signaling in SK-N-SH neuronal cells. These studies suggest that autoantibodies targeted against dopamine D1 and D2 receptors may be involved in the mechanism of motor and behavioral symptoms associated with Sydenham chorea.

Brain MRI is usually normal in patients with Sydenham chorea except for selective enlargement of the caudate, putamen, and GP (Giedd et al., 1995). In contrast to other choreic disorders, PET scans in patients with Sydenham chorea indicate increased rather than decreased striatal glucose consumption (Weindl et al., 1993).

The standard of care for all children diagnosed with Sydenham chorea, even in cases of isolated chorea, is secondary prevention with penicillin to reduce the risk for recurrence of chorea but especially to reduce the likelihood that future GABHS infections could cause carditis and permanent valvular damage (Panamonta et al., 2007; Cardoso, 2008). Current recommendations in the United States are for treatment until age 21 years with either monthly intramuscular or daily oral

penicillin. Evidence suggests that an injection of benzathine penicillin G every 2 or 3 weeks seems preferable to an injection every 4 weeks, because rheumatic fever recurs less frequently in those who received the injection every 2 or 3 weeks compared with every 4 weeks (Oosterveer et al., 2010). Although cephalosporins are equally effective, penicillin 500 to 1000 mg of penicillin G four times per day or one intramuscular injection of 600,000 to 1.2 million units of benzathine penicillin is considered the drug of choice for pharyngitis caused by GABHS infection (Garvey and Swedo, 1997). Despite an adequate (10-day) course, the bacteriologic failure rate is as high as 15% and some patients develop rheumatic fever. Therefore, oral rifampin 20 mg/kg every 24 hours for four doses is recommended during the last 4 days of the 10-day course of penicillin therapy. Alternatively, oral rifampin 10 mg/kg can be given every 12 hours for eight doses with one dose of intramuscular benzathine penicillin G. Another alternative is oral clindamycin 20 mg/kg/day in three doses for 10 days. The best prevention of rheumatic fever is accurate diagnosis and adequate treatment of the initial acute pharyngitis. Penicillin prophylaxis is advisable in all patients for at least 10 years after rheumatic fever. Symptomatic treatment for movement disorder symptoms usually consists of antidopaminergic drugs such as TBZ, valproic acid, and carbamazepine until the condition resolves spontaneously. A double-blind, placebo-controlled study of prednisone showed beneficial effects on chorea associated with Sydenham chorea (Paz et al., 2006).

One case of poststreptococcal disorder, which may include chorea, but more commonly is characterized by parkinsonism and dystonia, is poststreptococcal acute disseminated encephalomyelitis (PSADEM). This syndrome is also associated with the anti-basal ganglia antibodies (Dale et al., 2001). Although both Sydenham disease and PSADEM are associated with brain MRI T2 hyperintensities, the lesions described in PSADEM had normal T1 sequences and the white matter and brainstem are additionally involved.

Other autoimmune choreas

Chorea also has been recognized in a variety of other autoimmune processes, such as Sydenham disease systemic lupus erythematosus (SLE) (Baizabal-Carvallo and Jankovic, 2012, 2018; Baizabal-Carvallo, Bonnet et al., 2013; O'Toole et al., 2013). These and other autoimmune choreas are discussed in more detail in the chapter on autoimmune movement disorders. Chorea occurs in 2% of patients with SLE, and choreic movements precede the diagnosis of SLE in 22% of these cases. Choreic movements associated with pregnancy (chorea gravidarum) and with birth control pills probably result from common pathogenesis, and chorea gravidarum may be the first manifestation of SLE or may represent a variant of Sydenham chorea. Chorea in SLE has been associated with the presence of antiphospholipid antibodies, a heterogeneous group of antibodies that produce platelet endothelial dysfunction and promote thrombogenesis. The primary antiphospholipid syndrome is characterized by the presence of antiphospholipid antibodies in patients who have autoimmune phenomena but insufficient clinical or serologic features to be classified as having SLE. Antiphospholipid antibody syndrome is defined by a clinical event of thrombosis or miscarriage in the setting of persistently present and sufficiently high titers of antibodies,

either anticardiolipin IgG or IgM, lupus anticoagulant, or anti- β 2-glycoprotein 1 (Sapporo criteria) (Orzechowski et al., 2008). In a cohort of 1000 patients who met the Sapporo criteria for definite antiphospholipid syndrome, chorea occurred in 13 (1.3%) patients. In addition to a hypercoagulable state, a variety of neurologic and movement disorders, such as chorea, ballism, dystonia, parkinsonism, and paroxysmal dyskinesias, have been associated with the antiphospholipid syndrome (Gutrecht et al., 1991; Lang et al., 1991; Cervera et al., 1997; Martino et al., 2006; Wu et al., 2007; Huang et al., 2008; Orzechowski et al., 2008). Other clinical features include spontaneous abortions, arthralgias, Raynaud phenomenon, digital infarctions, transient ischemic attacks, and stroke (Sanna et al., 2006). Antiphospholipid antibodies present in patients with this syndrome include lupus anticoagulant, anticardiolipin antibody, and anti- β 2-glycoprotein-I antibodies. Anticardiolipin antibodies, frequently found in SLE, are absent in patients with Sydenham chorea. Contralateral striatal hypermetabolism was documented by a ^{18} F-fluorodeoxyglucose PET scan in a 23-year-old woman with alternating hemichorea and antiphospholipid syndrome (Furie et al., 1994). The striatal D1 and D2 receptor binding, measured by PET scans, was normal in one patient with SLE (Turjanski et al., 1995). Two cases of subacute chorea as the initial feature of autoimmune encephalitis associated with antibodies against leucine-rich glioma inactivated 1 (LGI1), a component of the voltage-gated potassium channel (VGKC) complex, have been described (Tofaris et al., 2012). In addition to chorea, LGI1 antibody also produces a syndrome of limbic encephalitis, faciobrachial dystonia, parkinsonism, and tremor (Ramdhani and Frucht, 2014). In a series of 36 adults with autoimmune chorea identified at Mayo Clinic between 1997 and 2012, women accounted for 21 patients (58%); median age at symptom onset was 67 years (range: 18–87 years) (O'Toole et al., 2013). The estimated incidence for Olmsted County was 1.5 per million person years. The following characteristics defined this cohort: all had subacute onset; 2 patients had synaptic IgG antibodies novel to the context of chorea (GAD65, 1; CASPR2, 1); of the 13 patients with a histopathologically confirmed neoplasm, small cell carcinoma and adenocarcinoma were most common; 6 had paraneoplastic autoantibody, including CRMP-5-IgG, ANNA-1, and VGKC complex of CASPR2 specificity. The most frequent coexisting autoimmune disorders were SLE and antiphospholipid syndrome, with autoantibodies detected in 21. In addition to rapid onset, male gender, older age, severe chorea, coexisting peripheral neuropathy, and weight loss increased the likelihood of underlying cancer. Essentially all patients with idiopathic chorea responded to corticosteroids or other forms of immunotherapy.

Another form of autoimmune chorea that is receiving growing attention is anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis (Irani et al., 2010; Baizabal-Carvallo and Jankovic, 2012; Titulaer et al., 2013; Baizabal-Carvallo, Stocco et al., 2013; Hacohen et al., 2014). This neuropsychiatric disorder is characterized by a multistage course, often starting with behavioral and psychiatric manifestations and followed by an acute or subacute emergence of a movement disorder. Often associated with ovarian teratoma, other benign tumors also have been identified in some cases. Although well characterized in adults, the syndrome is more variable and atypical in children. In one series involving 9 children with documented anti-NMDAR encephalitis, all patients presented with at least

one movement disorder, including chorea ($n = 4$); stereotypic movements ($n = 4$); ataxia ($n = 3$); limb dystonia ($n = 2$); limb myorhythmia ($n = 2$); oromandibular dystonia ($n = 2$); or facial myorhythmia, blepharospasm, opisthotonus, athetosis, and tremor ($n = 1$, each) (Baizabal-Carvallo, Stocco et al., 2013). Of 571 patients with IgG antibodies against the NR1 subunit of the NMDAR, 23 (4%) had isolated psychiatric episodes as the only manifestation of anti-NMDAR encephalitis (Kayser et al., 2013). Predominant symptoms included delusional thinking (74%), mood disturbances (70%, usually manic), and aggression (57%). Indeed, the spectrum of neurologic and movement disorders associated with anti-NMDAR encephalitis is expanding and not all patients have encephalopathy (Hacohen et al., 2014). Brain magnetic resonance imaging findings were abnormal in 10 of 22 patients (45%) and CSF showed pleocytosis in 17 of 22 patients (77%). Of the patients, 83% had full or substantial recovery after immunotherapy and tumor resection when appropriate. Another condition, termed Morvan fibrillary chorea (MFC), has been classified as a form of autoimmune disorder associated with autoantibodies directed at the voltage-gated potassium channel (VGKC-Abs) (Lee et al., 2013). Although termed “chorea,” the motor disorder is actually myokymia and neuromyotonia. Typically associated with insomnia disturbances and dysautonomia (particularly hyperhidrosis, cardiovascular and gastrointestinal problems), MFC mainly manifests in men as a subacute-onset autoimmune or paraneoplastic disorder. Majority of the patients recover with appropriate treatment consisting of corticosteroids, intravenous immunoglobulins and plasma exchange, or surgical removal of the underlying neoplasm.

Other choreas

One of the most common forms of chorea encountered in a movement disorder clinic is drug-induced chorea associated with the use of dopaminergic or antidopaminergic drugs, anticonvulsants, and other drugs (Hyde et al., 1991; Jankovic, 1995). Levodopa-induced dyskinesia in patients with PD is often manifested by stereotypies, dystonia, myoclonus, and chorea (Jankovic, 2005) (Video 14.7). Although the dominant hyperkinetic movement disorder seen in patients with tardive dyskinesia is stereotypy, some patients have associated chorea, and chorea is the chief manifestation in children with withdrawal emergent syndrome (Mejia and Jankovic, 2010). Chorea, often accompanied by ataxia and deafness, has also been associated with mitochondrial DNA mutations (Nelson et al., 1995) and other evidence of mitochondrial cytopathies, including mutations in the *POLG* gene (Caer et al., 2005; Wong et al., 2008). The disorder of early-onset ataxia with oculomotor apraxia and hypoalbuminemia resulting from mutations in the *aprataxin* gene on chromosome 19p13 has also been associated with chorea (Shimazaki et al., 2002). ▶

Besides vasculitis, chorea has been associated with a variety of other vascular causes, but few have been documented pathologically. The topic of vascular chorea has been reviewed in a report of an 85-year-old woman who developed progressive dementia and chorea at age 70 (Bhatia et al., 1994). At autopsy, her brain showed neostriatal neuronal loss and gliosis associated with congophilic angiopathy and atherosclerosis. Hemichorea also has been reported after endarterectomy for carotid stenosis (Galea et al., 2008).

During the 1980s, there was an increase in the number of children with chorea as sequelae to cardiac surgery, but with modification of treatment strategies during the perioperative period, the incidence of this complication has subsequently decreased (Robinson et al., 1988). This postpump chorea appears to be associated with prolonged time on pump, deep hypothermia, and circulatory arrest (Medlock et al., 1993; Newburger et al., 1993; du Plessis et al., 2002) (Videos 14.8, 14.9). Others have suggested that hypoxia rather than hypothermia is critical in the development of choreoathetosis and orofacial dyskinesia, hypotonia, and pseudobulbar signs (CHAP) syndrome after surgery for congenital heart disease. In most patients, the chorea persists, and fewer than 25% improve with antidopaminergic therapy such as haloperidol. Corticosteroid-responsive chorea was described in a patient after heart transplant (Blunt et al., 1994). Although the chorea may improve, long-term studies have shown that these children have persistent deficits in memory, attention, and language (du Plessis et al., 2002). ▶

A variety of systemic (Janavs and Aminoff, 1998), metabolic and neurodegenerative disorders can be associated with chorea, such as hypocalcemia or hypercalcemia, hyperglycemia (Ahlskog et al., 2001; Chu et al., 2002; Oh et al., 2002; Pisani et al., 2005; Sitburana and Ondo, 2006), hyperthyroidism (Pozzan et al., 1992), B₁₂ deficiency (Pacchetti et al., 2002), Lesch-Nyhan syndrome (Jankovic et al., 1988; Jinnah et al., 1994; Ernst et al., 1996), propionic acidemia (Nyhan et al., 1999), and other metabolic disorders such as GM1 gangliosidosis (Shulman et al., 1995; Stacy and Jankovic, 1995), mitochondrial acetoacetyl-coenzyme A thiolase (beta-ketothiolase) deficiency (Buhás et al., 2013), glutaric aciduria, glucose transporter type 1 (Glut1) deficiency (Pérez-Dueñas et al., 2009; Yang et al., 2011). The latter is characterized by infantile-onset seizures, delayed development, microcephaly, paroxysmal chorea, dystonia or ataxia, alternating hemiplegia, hypoglycorrhachia, and decreased erythrocyte glucose uptake.

Chorea (with or without associated ballism) has been reported as the presenting feature of renal failure (Kujawa et al., 2001) and paraneoplastic striatal encephalitis (Tani et al., 2000; Vernino et al., 2002; Kinirons et al., 2003; Kleining et al., 2009; Grant and Graus, 2009). In a series of 16 patients with paraneoplastic chorea, 11 had small cell carcinoma, all had CRMP-5 IgG, and 6 had ANNA-1 (anti-Hu) antibodies (Vernino et al., 2002). Another metabolic cause of chorea is liver disease, particularly chronic acquired hepatocerebral degeneration (Thobois et al., 2002) (Video 14.10).

Many of the metabolic choreas are associated with abnormalities on brain MRI scans. For example, hepatocerebral degeneration and hyperglycemic chorea are often associated with high signal intensity on T1-weighted MRI, involving the striatum and pallidum (Ahlskog et al., 2001; Thobois et al., 2002; Sitburana and Ondo, 2006). In a report of two patients with hyperglycemic hemichorea-hemiballism, Chu and colleagues (2002) found high signal intensities on T1- and T2-weighted images and on diffusion-weighted MRI accompanied by a reduction in diffusion coefficient, suggestive of hyperviscosity, rather than petechial hemorrhages, as the mechanism of edema in the striatum. This is also supported by another study of 7 patients with hyperglycemic choreoathetosis using MRI and MR spectroscopy (Kandiah et al., 2009). Interestingly, the presence of high acanthocyte count may predispose patients with diabetes to develop hyperglycemic chorea (Pisani et al., 2006). A spectrum of focal striatal pathologic processes may be responsible,

Video 14.5 Levodopa-induced dyskinesia.

Video 14.6 Postpump chorea.

Video 14.7 Postpump chorea.

Video 14.8 Hepatic chorea.

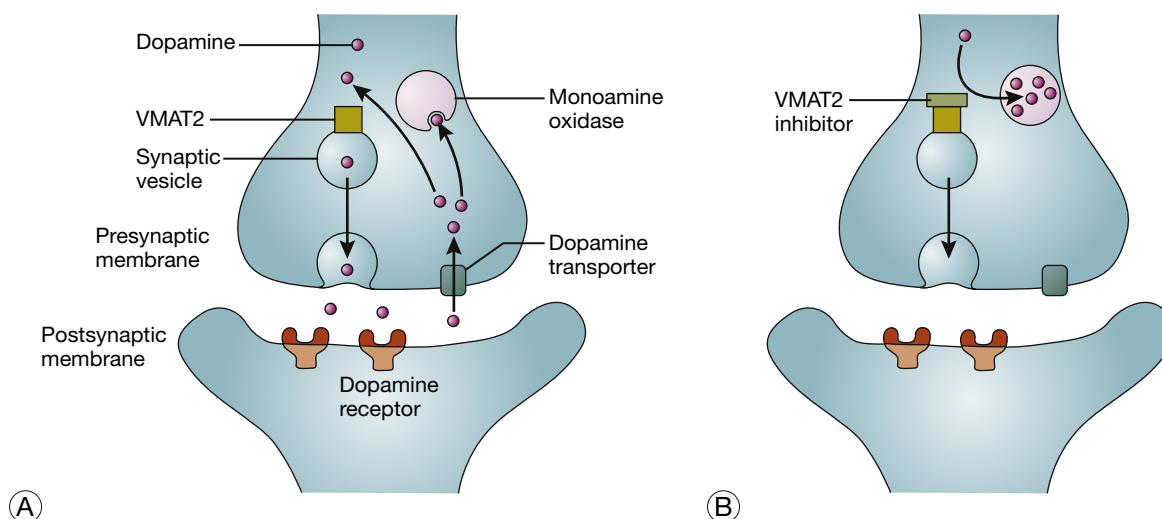


Fig. 14.2 Mechanism of action of vesicular membrane transport type 2 (VMAT2) inhibitors. (A) VMAT2 mediates loading of dopamine into synaptic vesicles for release. Breakdown of dopamine is mediated by monoamine oxidase. (B) VMAT2 inhibitors block transport of dopamine into synaptic vesicles, reducing dopamine release and depleting dopamine levels through its breakdown by monoamine oxidase. (Reproduced with permission from Jankovic J. *Progress in Parkinson disease and other movement disorders. Nat Rev Neurol.* 2017;13:76–78.)

because there are reports of focal microhemorrhage and of striatal gliosis (Alves et al., 2012). The hyperglycemic hemichorea-hemiballism syndrome is one manifestation of a movement disorder associated with cerebrovascular disease (Mehanna and Jankovic, 2013).

Other disorders frequently associated with this MRI abnormality include manganese toxicity, Wilson disease, abnormal calcium metabolism (Nicolas et al., 2013), neurofibromatosis, hypoxia, and hemorrhage. Chorea has been associated with a variety of other causes, including CSF leak (Mokri et al., 2006). Idiopathic basal ganglia calcification, one potential cause of chorea, has been associated with mutations in *SLC20A2* and *PDGFRB* (Nicolas et al., 2013). Among the symptomatic cases, the most frequent signs were cognitive impairment (58.8%), psychiatric symptoms (56.9%), and movement disorders (54.9%); akinetic-hypertonic chorea was the second most common movement disorder. Based on retrospective analysis of 150 cases, chorea was reported to be the most common hyperkinetic movement disorder associated with variant Creutzfeldt-Jakob disease, even more common than myoclonus (Heath et al., 2011). Any type of movement disorder, however, can herald the onset or occur in this disorder.

Treatment of chorea

The first step in the treatment of chorea is the identification of a specific cause. Chorea has been treated successfully with drugs that interfere with central dopaminergic function, such as the dopamine receptor-blocking drugs (neuroleptics) reserpine, TBZ, and other VMAT 2 inhibitors, such as deutetrabenazine (DTBZ) and valbenazine (Jankovic and Beach, 1997; Chatterjee and Frucht, 2003; Kenney and Jankovic, 2006; Sitburana and Ondo, 2006; Fasano and Bentivoglio, 2009; Jankovic, 2009; Jankovic and Clarence-Smith, 2011; Jankovic, 2016; Bashir and Jankovic, 2018a; Feinstein and Walker, 2020) (Fig. 14.2). Indeed, TBZ provides the most effective relief of chorea with only minimal, dose-related side effects, such as drowsiness, insomnia, depression, and parkinsonism. TBZ and DTBZ are

effective not only for the treatment of chorea associated with HD (Ondo et al., 2002; Huntington Study Group, 2006; Bashir and Jankovic, 2018b) but also choreatic disorders associated with tardive dyskinesia (Ondo et al., 1999), CP (Aisen et al., 2011), and postpump encephalopathy (Chatterjee and Frucht, 2003) (Video 14.8). Whereas some studies have suggested that sodium valproate may be effective in the treatment of chorea (Daoud, 1990; Hoffman and Feinberg, 1990), other reports have been less conclusive (Sethi and Patel, 1990). Levetiracetam has been reported to markedly improve a patient with CP and postinfectious chorea (Recio et al., 2005). DBS, particularly targeting the GPi, may be considered a last-resort alternative as a treatment in patients with disabling chorea unresponsive to pharmacologic therapy (Edwards et al., 2012).

There is no consensus on the optimal management of autoimmune chorea (Baizabal-Carvallo and Jankovic, 2012). Patients with Sydenham chorea should be treated with penicillin prophylactically to prevent rheumatic fever. Symptomatic suppression of chorea with dopamine antagonists may lessen disability. Anticoagulation, immunosuppressants, and plasmapheresis have been used with variable success, and the frequent occurrence of spontaneous remissions makes the results of treatment difficult to interpret. Until prospective therapeutic trials can be designed, careful selection of treatment that best seems to suit the severity of the patient's illness might be indicated. The presence of true vasculitis might require more aggressive management. Corticosteroids are sometimes recommended for the treatment of autoimmune chorea, and this treatment was found effective also in chorea associated with heart transplant (Blunt et al., 1994). Stereotactic surgery is occasionally needed in very severe and disabling cases of hemichorea and hemiballism (Krauss and Mundinger, 2000).

Ballism

Chorea, athetosis, and ballism represent a continuum of involuntary, hyperkinetic movement disorders. Ballism is a form of forceful, flinging, high-amplitude, coarse, chorea

Video 14.9 Ballism.
Video 14.10 Ballism.

(Videos 14.11, 14.12). Ballism and chorea are often interrelated and may occur in the same patient (Harbord and Kobayashi, 1991; Hawley and Weiner, 2012). The involuntary movement usually affects only one side of the body; the term *hemiballism* is used to describe unilateral ballism. Although various structural lesions have been associated with ballism (Rossetti et al., 2003), damage to the subthalamic nucleus and the pallidum-subthalamic pathways appears to play a critical role in the expression of this hyperkinetic movement disorder (Guridi and Obeso, 2001). Subthalamotomy has been found to ameliorate the motor disturbances in human and experimental parkinsonism, but the procedure can produce transient or permanent hemiballism (Bergman et al., 1990; Aziz et al., 1991; Guridi and Obeso, 2001; Chen et al., 2002).

When caused by a hemorrhagic or ischemic stroke, the movement disorder is often preceded by hemiparesis. Anterior parietal artery stroke, without any evidence of involvement of the basal ganglia, thalamus, or subthalamic nucleus, has been associated with contralateral hemiballism and neurogenic pain (Rossetti et al., 2003). This and other similar cases suggest that the lesion associated with hemiballism may extend beyond the contralateral subthalamic nucleus and connecting structures into the adjacent internal capsule. Less common causes of hemiballism include abscess, arteriovenous malformation, cerebral trauma, hyperosmotic hyperglycemia (Ahlskog et al., 2001), multiple sclerosis, and tumor (Glass et al., 1984). Rarely, ballism occurs bilaterally (paraballism), usually because of bilateral basal ganglia strokes or calcification (Inbody and Jankovic, 1986; Vidakovic et al., 1994). In a series of 21 patients with hemiballism, hemichorea, or both, an identifiable cause was found in all (Dewey and Jankovic, 1989). Stroke was the most common cause, followed by tumors, abscesses, encephalitis, vasculitis, and other causes. In a series of 23 patients with hemiballism and 2 with biballism, Vidakovic and colleagues (1994) found ischemic and hemorrhagic strokes to be the most common causes of hemiballism. Only two patients had “pure” hemiballism, and only six showed a lesion in the subthalamic nucleus on neuroimaging studies. The prognosis for spontaneous remission was good; 9 patients completely recovered, and in 7 additional patients, there was complete recovery of the ballism, but mild chorea persisted. Whereas hemichorea–hemiballism is usually contralateral to a basal ganglia lesion, ipsilateral hemichorea–hemiballism has been described in patients with contralateral hemiparesis (Krauss et al., 1999). The mechanism of this peculiar phenomenon is unknown. Survival rates after vascular hemiballismus are similar to those of vascular disease, with 32% survival and 27% stroke-free survival 150 months after the onset of the movement disorder (Ristic et al., 2002).

Other causes of ballism include encephalitis, Sydenham chorea, SLE, basal ganglia calcifications (Nicolas et al., 2013), tuberous sclerosis, and overlap between Fisher syndrome and Guillain-Barré syndrome (Odaka et al., 1999; Postuma and Lang, 2003). In addition to structural lesions, metabolic disorders, such as hyperglycemia (Sitburana and Ondo, 2006), nutritional vitamin D deficiency (Fernandez et al., 2007), and certain drugs, such as phenytoin and lamotrigine (Yetimalar et al., 2007), have been associated with ballism.

Treatment of ballism

The frequent occurrence of spontaneous remission makes the assessment of therapy for ballism difficult. Dopamine

receptor-blocking drugs such as haloperidol, chlorpromazine, pimozide, and atypical neuroleptics have been used most frequently (Dewey and Jankovic, 1989; Bashir and Manyan, 1994; Shannon, 2005). Dopamine-depleting drugs, such as reserpine and TBZ, have also been used successfully (Jankovic and Beach, 1997). TBZ is our preferred drug because of its rapid onset of action and its effectiveness, without the danger of inducing tardive dyskinesia if chronic antidopaminergic treatment is needed (Sitburana and Ondo, 2006). Other drugs that are sometimes beneficial in the treatment of ballism include sodium valproate and clonazepam. Finally, ventrolateral thalamotomy and other stereotactic surgeries may be needed to control violent and disabling contralateral hemiballism (Cardoso et al., 1995; Krauss and Munding, 2000). Although effective and relatively safe, this procedure should be used only as a last resort in patients with disabling and medically intractable movement disorder.

Athetosis

Athetosis is a slow form of chorea that consists of writhing movements resembling dystonia, but in contrast to dystonia, these movements are not sustained, patterned, repetitive, or painful. Originally described by Hammond in acquired hemidystonia and by Shaw in CP, athetosis should be viewed as a movement disorder separate from dystonia (Morris et al., 2002a). The relationship of athetosis to chorea is highlighted not only by the continuously changing direction of movement, but also by the observation that chorea often evolves into athetosis or vice versa. In some patients, particularly children, chorea and athetosis often coexist, hence the term *choreoathetosis*. Dystonia, particularly involving the trunk causing opisthotonic posturing, also frequently accompanies athetosis, particularly in children with CP (Video 14.11). In contrast to idiopathic dystonia, athetosis associated with perinatal brain injury often causes facial grimacing and spasms, particularly during speaking and eating, and the bulbar function is usually impaired. ▶

Athetosis is typically present in children with CP, but may have many various causes (Kyllerman, 1982; Foley, 1983; Murphy et al., 1995; Goddard-Finegold, 1998; Morris et al., 2002b; Cowan et al., 2003; Ashwal et al., 2004; Koman et al., 2004; Bax et al., 2006; Keogh and Badawi, 2006; Monbaliu et al., 2017) (Table 14.6). In a study of 431 children diagnosed with CP, 26.2% had hemiplegia, 34.4% had diplegia, 18.6% had quadriplegia, 14.4% had dyskinesia, and 3.9% had ataxia (Bax et al., 2006). In a study of 1817 of the 2357 (77%) children born preterm (22–32 weeks of gestation) who survived at least 5 years, CP was diagnosed in 9% and 5% had severe, 9% moderate, and 25% minor disability; cognitive and motor disability was most common in children born at 24 to 28 weeks of gestation (49%) (Larroque et al., 2008). In addition to motor disorders manifested chiefly by weakness and hypertonia (i.e., spasticity, rigidity, athetosis, dystonia), patients with CP may also have cognitive impairment, intellectual disability, epilepsy, visual and hearing problems, and other neurologic deficits. Although many patients with dyskinetic CP have well-preserved intellectual function, most of them have a variety of comorbidities. In one study the following comorbidities were documented: nonverbal 22.2%

Video 14.11 Cerebral palsy.

Table 14.4 Clinical, epidemiologic, and pathophysiologic features of cerebral palsy

- CP is a developmental, nonprogressive disorder manifested by abnormal movements (chorea, athetosis, dystonia), spasticity, and/or ataxia accompanied by disturbances of cognition, behavior, communication, and other neurologic and musculoskeletal problems.
- CP is attributed to damage in the developing fetal or infant brain, such as perinatal hypoxia–ischemia, intracranial hemorrhage or cerebral infarction, neonatal hyperbilirubinemia (kernicterus), and brain maldevelopment.
- Prevalence: 1.7 to 3.1 in 1000 live births, higher in developing countries; the most common cause of disability in early childhood.
- Dyskinetic CP is the third most common form of CP (15%), after spastic (hemiplegic > quadriplegic > diplegic) and ataxic CP.
- Dystonia, choreoathetosis: exacerbated by action
- 70% have lesions in the basal ganglia or thalamus
- Exclude CP mimickers (e.g., dopa responsive dystonia (DRD), sepiapterin reductase deficiency (SRD), beta-propeller protein–associated neurodegeneration (BPAN), congenital disorders of glycosylation (CDG), *ADCY5*-related movement disorders

(54/243), active afebrile seizure disorder 16.9% (41/243), severe auditory impairment 11.5% (28/243), cortical blindness 9.5% (23/243), and gavage feeding requirement 7.8% (19/243) (Shevell et al., 2009). Children with ataxic-hypotonic, spastic quadriplegic, and dyskinetic CP subtypes experienced about five times the numerical burden (i.e., frequency) of comorbidities compared with children with the spastic diplegic or hemiplegic variants; dyskinetic children had a particularly high frequency of nonverbal (8/16 [50%]) and auditory impairment (6/16 [38%]).

In contrast to the other forms of CP (e.g., diplegic or spastic and hemiplegic), the athetoid variety, which constitutes only about a quarter of all cases, is usually not associated with significant cognitive impairment or epilepsy. Although here we emphasize athetosis, the most common movement disorder in patients with CP is spasticity (Albright, 1995). As a result of hypertonia, many patients with untreated CP develop fixed contractures. With the advent of botulinum toxin treatment, intrathecal baclofen infusion, and selective dorsal rhizotomy, coupled with aggressive physical therapy and antispastic drugs, these sequelae can be largely prevented.

CP affects about 0.3% of individuals, and the rate of 2 to 3.5 cases per 1000 live births has remained unchanged over the past 40 years despite a steady decline in infant mortality (Aisen et al., 2011; Colver et al., 2014). Because of the higher frequency of premature births, the frequency of certain types of CP, such as spastic diplegia, has been increasing. In one study of children born at 25 or fewer completed weeks of gestation, half of the patients at 30 months of age were considered disabled, 18% were diagnosed with CP, and 24% had gait difficulties (Wood et al., 2000).

Often referred to as static encephalopathy, the neurologic deficit associated with CP, however, may progress with time. Motor development curves derived by assessing patients with the Gross Motor Function Measure, used to prognosticate gross motor function in patients with CP, indicate that, depending their level of impairment (levels I–V) 3 to 10 years after birth, the natural course becomes static (Rosenbaum et al., 2002). We and others, however, found that some

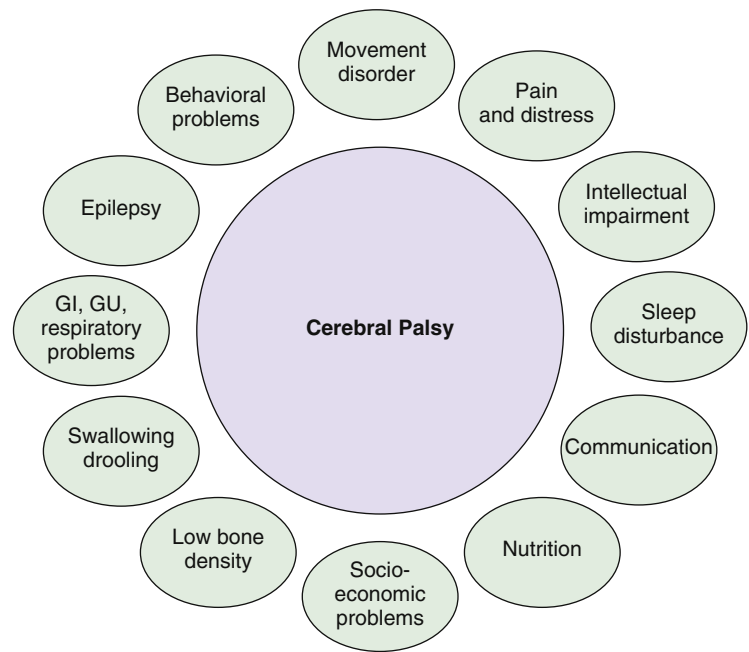
patients continue to progress and others may progress after a period of static course. In about half of the patients with CP, the abnormal movements become apparent within the first year of life, but in some cases, they might not appear until the fifth decade or even later. The mechanism by which such “delayed-onset” movement disorder becomes progressive after decades of a static course is unknown, but aberrant regeneration and sprouting of nerve fibers have been considered (Scott and Jankovic, 1996). In addition to dystonia and myoclonus, chorea also may be a manifestation of delayed-onset movement disorder after anoxic brain injury (Virmani et al., 2013). CP is clearly a multifactorial disorder requiring a multidisciplinary approach (Fig. 14.3).

Kernicterus, once a common cause of CP because of bilirubin encephalopathy associated with neonatal jaundice, is now quite rare, although still an important cause of childhood disabilities in developing countries (Maisels et al., 2009; Watchko and Tiribelli, 2013). Besides delayed developmental milestones and athetotic or dystonic movements, patients with kernicterus often exhibit vertical ophthalmoparesis, deafness, and dysplasia of the dental enamel (Video 14.14). Hearing abnormalities, very common in chronic bilirubin encephalopathy, can be present as the only finding of kernicterus. The high-frequency sensorineural hearing loss has been attributed to damage to the cochlear nuclei and auditory nerves, possibly as a result of bilirubin’s interference with intracellular calcium homeostasis (Shapiro and Nakamura, 2001). Unconjugated bilirubin can also cause damage to endoplasmic reticulum membranes lead to neuronal excitotoxicity and mitochondrial energy failure.

Although improved perinatal care has reduced the frequency of birth-related injuries, birth asphyxia with anoxia is still a relatively common cause of CP (Kuban and Leviton, 1994; Cowan et al., 2003). Expression of tyrosine hydroxylase was reduced in the putamen in cases of acute kernicterus and in the GP of acute and chronic postkernicterus (Hachiya and Hayashi, 2007).

The cause of CP is multifactorial, and the pathogenesis of neurologic sequelae are not well understood (Aisen et al., 2011; Volpe, 2012; Colver et al., 2014). It is likely that the prenatal and functional architecture of the brain, largely determined by prenatal transcriptional processes (Miller et al., 2014), is altered as a result of various prenatal insults. Although the term *neonatal encephalopathy* has been used in the past to describe perinatal insult presumably resulting from hypoxia–ischemia, the term hypoxic–ischemic encephalopathy (HIE), or presumed HIE has been proposed to better describe the clinical–imaging–pathologic disorder (Volpe, 2012; Wu et al., 2012). Although there is some overlap, four general patterns can be delineated based on imaging studies: (1) cerebral cortex/white matter, including subcortical and central white matter and overlying cortex, usually in a parasagittal distribution; (2) deep nuclear structures, especially putamen and thalamus; (3) brainstem tegmentum; and (4) cerebral white matter (periventricular and central). The border zones between the major cerebral arteries (“watershed”) are most vulnerable to asphyxia (Folkerth, 2005). In the striatum, the excitatory glutamate receptors and GABA-ergic neurons are particularly sensitive to asphyxia. Striatal neurons also die by glutamate-mediated excitotoxicity in which apoptosis may be delayed over days to weeks. Leukomalacia was the most common MRI abnormality, found in 42.5%,

Fig. 14.3 Multifactorial aspects of cerebral palsy. GI, Gastrointestinal; GU, genitourinary.



followed by basal ganglia lesions in 12.8%, cortical/subcortical lesions in 9.4%, malformations in 9.1%, and infarcts in 7.4%. Although athetosis is usually associated with perinatal brain injury, the neuroimaging studies often fail to show basal ganglia pathology.

Intrauterine insults, particularly chorioamnionitis and prolonged rupture of membranes (Murphy et al., 1995), might be also responsible for many of the cases of CP. In one study of 351 full-term infants with neonatal encephalopathy, early seizures, or both, excluding infants with congenital malformations and obvious chromosomal disorders, MRI showed evidence of an acute insult in 69% to 80% (Cowan et al., 2003). The higher figure correlated with evidence of perinatal asphyxia. The vast majority of children with neurologic deficits associated with perinatal asphyxia show abnormalities within the basal ganglia with shrinkage of the striatum. In addition, defects in myelination are often associated with a marbled gross appearance (hypermyelination-status marmoratus) or dysmyelination.

Both above-normal and below-normal weight at birth are also significant risk factors for CP (Jarvis et al., 2003). These data strongly suggest that events in the immediate perinatal period are most important in the neonatal brain injury. An analysis of 58 brains of patients with clinical diagnosis of CP showed wide morphologic variation, but the authors were able to classify the brains into three major categories: thinned cerebral mantle ($n = 10$), hydrocephalus ($n = 3$), and microgyria-pachygyria ($n = 45$) (Tsusi et al., 1999). Of the 19 brains that were examined microscopically, four showed heterotopic gray matter, three showed cortical folding (cortical dysplasia), and three showed neuronal cytomegaly. The majority of the examined brains showed a variable degree of laminar disorganization in the cortex and disorientation of neurons, suggesting impaired neuronal migration during cortical development.

A growing number of studies also draw attention to inflammation and coagulation abnormalities in children

with CP (Hagberg et al., 2012; Fleiss and Gressens, 2012). The increased concentrations of interleukins, tumor necrosis factor, reactive antibodies to lupus anticoagulant, anti-cardiolipin, antiphospholipid, antithrombin III, epidermal growth factor, and other abnormal cytokine patterns may play an important role in the cause of CP (Nelson et al., 1998; Kaukola et al., 2004). Kadhim and colleagues (2001) suggest that an early macrophage reaction and associated cytokine production and coagulation necrosis, coupled with intrinsic vulnerability of the immature oligodendrocyte, lead to periventricular leukomalacia, the most common neuropathologic changes found in premature infants who develop CP. Although infection and inflammation, along with free radicals, can activate the process that leads to periventricular leukomalacia and even to delayed progression (Scott and Jankovic, 1996), the cause or pathogenesis of CP is still not well understood. There is, however, a growing body of evidence that inflammation has long-term consequences and may increase the risk for a variety of neurologic disorders, including CP, autism, multiple sclerosis, dementia, and PD (Le et al., 2009; Hagberg et al., 2012). Furthermore, it is not known why some children have a static or progressive course, whereas others seem to recover from early injury. Although “neuroplasticity” and variable “vulnerability” often have been invoked to explain different outcomes after early brain insult, some investigators have suggested that the two represent extremes along a “recovery continuum” (Anderson et al., 2011). Hyperbaric oxygen is not effective in improving motor function in children with CP (Lacey et al., 2012).

Because 5% to 10% of patients with athetoid CP have a family history, genetic factors are considered important in the pathogenesis of this disorder (Fletcher and Foley, 1993; Pearson et al., 2019). In a study based on the Swedish registry, 40% of cases of CP were thought to have a genetic basis (Costeff, 2004). Other investigators have suggested that about 20% of CP cases are inherited (Kruer

et al., 2013). The genetic causes of CP include guanosine triphosphate (GTP) cyclohydrolase deficiency, hereditary spastic paraplegias mutations in *GAD1*, *KANK1*, *ADD3* (Kruer et al., 2013), and many other genes and the adaptor protein complex-4 deficiency syndromes (Moreno-De-Luca et al., 2021). As a result of advances in sequencing technologies, multiple genetic factors, similar to other neurodevelopmental disorders, are now considered to play a role in its pathogenesis. Indeed, using these advanced techniques, pathogenic variants were found in 32.7% of children and 10.5% of adults diagnosed with CP (Moreno-De-Luca et al., 2021).

Unless a curable or treatable pathogenesis target is found, the treatment of patients diagnoses with CP will be challenging and will continue to rely on symptomatic therapy of chorea, dystonia, and spasticity, coupled with intense physical, occupational, speech and other supportive therapies (Chin and Gwynn, 2020).

Many other disorders associated with developmental delay and intellectual disability can cause chorea and athetosis, some of which are due to errors in metabolism and include acidurias, lipidoses, and Lesch–Nyhan syndrome (Jankovic et al., 1988; Stacy and Jankovic, 1995) (see Table 14.1). Chromosomal microarray, karyotype, fluorescent in situ hybridization (FISH), X-linked and metabolic studies have been recommended for individuals with unexplained developmental delay/intellectual disability, autism spectrum disorders, or multiple congenital anomalies (Miller et al., 2010; Michelson et al., 2011).

Finally, athetotic movements, or pseudoathetosis, can be seen in patients with severe proprioceptive deficit (Sharp et al., 1994).

Treatment of athetosis

Athetosis usually does not respond well to pharmacologic therapy. Because dopa-responsive dystonia is sometimes confused with athetoid CP, it is prudent to treat all of these patients with a trial of levodopa. If levodopa fails to provide any meaningful benefit, anticholinergic drugs should be tried in the same manner as is done in treating dystonia. Although generally recommended, physical therapy might or might not prevent contractures, and its role in altering the eventual outcome is uncertain (Palmer et al., 1988). Other complications of CP, such as carpal tunnel syndrome, cervical spondylosis with radiculopathy, and myelopathy, require independent assessment and treatment (Hirose and Kadoya, 1984; Treves and Korczyn, 1986). Bilateral GPi DBS has been reported to produce about 24.4% improvement in the Burke-Fahn-Marsden Dystonia Rating Scale in adult patients with dystonia–choreoathetosis associated with CP (Vidailhet et al., 2009). Meta-analysis of other studies found similar improvement in the Burke-Fahn-Marsden Dystonia Rating Scale in 68 patients with CP treated with DBS (Koy et al., 2013).

Appendix

Testing for various causes of chorea available at the following sites:

<http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim>
<http://www.naadvocacy.org/>
<https://www.athenadiagnostics.com/view-full-catalog>;
<https://www.invitae.com/en>; <https://www.genedx.com/>
<http://www.genome.gov>
<http://www.mayomedicallaboratories.com/testcatalog/index.html>
<http://www.genetests.org>
www.kumc.edu/gec/
<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM>
<https://www.familytreedna.com/faq2.html>
<http://ccr.coriell.org/>
dnalab@bcm.edu
<https://www.23andme.com>

HDL-1 Laboratory of Pierluigi Gambetti, MD
 National Prion Disease Pathology Surveillance Center
 Institute of Pathology
 Case Western Reserve University
 2085 Adelbert Road, Room 418
 Cleveland, Ohio 44106
 Tel: (216) 368-0587

HDL-2 Laboratory of Russell Margolis, MD
 Neurogenetic Testing Laboratory
 Johns Hopkins University
 600 North Wolfe Street
 Meyer 2-181
 Baltimore, Maryland 21287
 Tel: (410) 955-1349

References available on Expert Consult:
www.expertconsult.com.

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Tics and Tourette syndrome

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Introduction

Tourette syndrome (TS), which should be more appropriately called Gilles de la Tourette syndrome, is a neurologic disorder manifested by motor and vocal or phonic tics starting during childhood and often accompanied by obsessive-compulsive disorder (OCD), attention deficit-hyperactivity disorder (ADHD), poor impulse control, and other comorbid behavioral problems (Kurlan, 2010; Bloch et al., 2011; Jankovic and Kurlan, 2011; Thenganatt and Jankovic, 2016; Robertson et al., 2017). Once considered a rare psychiatric curiosity, TS is now recognized as a relatively common and complex neurobehavioral disorder. There have been speculations that many notable historical figures, including Dr. Samuel Johnson, Wolfgang Amadeus Mozart, and Leonardo Da Vinci (Ashoori and Jankovic, 2007; Bhattacharyya and Rai, 2015) were afflicted with TS.

One of the earliest reports of TS dates to 1825, when Itard (1825) described a French noblewoman with body tics, barking sounds, and uncontrollable utterances of obscenities. Sixty years later, the French neurologist and a student of Charcot, Georges Gilles de la Tourette (1885) reviewed Itard's original case and added eight more patients. He noted that all nine patients shared one feature: they all exhibited brief involuntary movements or tics. Additionally, six made noises, five shouted obscenities (coprolalia), five repeated the words of others (echolalia), and two mimicked others' gestures (echopraxia) (Ganos et al., 2012a). Although Tourette considered the disorder he described to be hereditary, it was ascribed to psychogenic causes for nearly a century after the original report. The perception of TS began to change in the 1960s, when the beneficial effects of neuroleptic drugs on the symptoms of TS began to be recognized (Shapiro and Shapiro, 1968). This observation helped refocus attention

from a psychogenic cause to a central nervous system (CNS) cause. Despite these advances, TS is still often misunderstood and wrongly labeled as a mental or psychiatric disorder. Insurance compensation for patients with TS used to be frequently denied because the condition was considered "mental" or "psychiatric," but this has been improving since the implementation of International Classification of Diseases, 10th revision (ICD-10) codes: Tourette's disorder—F95.2, also includes: TS and Gilles de la Tourette's disease or syndrome (motor-verbal tic); Persistent (Chronic) Motor or Vocal Tic Disorder—F95.1; Single or multiple motor or vocal tics; Provisional tic disorder—F95.0; Tics present for less than 1 year (replaced transient tics of childhood); Tic disorder, unspecified—F95.9).

The cause of TS is yet unknown, but the disorder appears to be inherited in the majority of patients (Jankovic and Kurlan, 2011; Black et al., 2014; Hallett, 2015; Yael et al., 2015). The clinical expression of this genetic defect varies from one individual to another, fluctuations in symptoms are seen within the same individual, and different manifestations occur in various family members. This variable expression from one individual to another, even within members of the same family, contributes to diagnostic uncertainty is a partial explanation why no TS-specific gene has been identified (see later discussion of genetics of TS). Without a specific biologic marker, the diagnosis depends on a careful evaluation of the patient's symptoms and signs by an experienced clinician. Educational efforts directed to physicians, educators, and the general public have increased awareness about TS, and there has been an exponential increase in the number of scientific publications related to TS (Black et al., 2014). As a result of this improved awareness, the self-referral rate of patients has increased, and the correct diagnosis is made earlier than was the case in the past. Many patients, however, still remain

undiagnosed, or their symptoms are wrongly attributed to habits, allergies, asthma, dermatitis, hyperactivity, nervousness, and many other conditions (Jankovic et al., 1998; Hogan and Wilson, 1999). Despite increased awareness about TS, there are still many misconceptions about this disorder. These include, but are not limited to, the following: TS is a rare psychiatric condition; all TS patients shout obscenities; it is seen only in children who eventually outgrow it; tics are suggestible and suppressible, and therefore they must be psychogenic; tics are motor (not sensory) symptoms; tics disappear during sleep; phonic (vocal) tics are not motor tics; tics may be embarrassing but are not disabling; behavioral comorbidities are rare; and there is no effective treatment. This chapter is intended to provide a comprehensive and balanced review of TS and to correct the various misconceptions about this neurodevelopmental disorder.

Phenomenology of tics

Tics, the clinical hallmark of TS, are relatively brief and intermittent movements (motor tics) or sounds (vocal or phonic tics). Recognition of the full spectrum of phenomenology of tics is critical to the diagnosis of TS (Jankovic, 2008). Motor tics typically consist of sudden, abrupt, transient, often repetitive and coordinated (stereotypical) movements that may resemble gestures and mimic fragments of normal behavior, vary in intensity, and are repeated at irregular intervals (Videos 15.1–15.8). Currently accepted criteria for the diagnosis of TS, based on the *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition (DSM-5) (American Psychiatric Association, 2013), code 307.23, require both types of tics to be present. This division into motor and vocal/phonic tics, however, is artificial, because vocal/phonic tics are actually motor tics that involve respiratory, laryngeal, pharyngeal, oral, and nasal musculature. Contractions of these muscles may produce sounds by moving air through the nose, mouth, or throat. The term *phonic tic* is preferable, because not all sounds produced by TS patients involve the vocal cords. ▶

To better understand the categorization of tics and how they fit in the general schema of movement disorders, it might be helpful to provide a simple classification of movements (Jankovic, 1992). All movements can be categorized into one of the following four classes:

1. Voluntary
 - a. Intentional (planned, self-initiated, internally generated)
 - b. Externally triggered in response to some stimulus (e.g., turning the head toward a loud noise or withdrawing the hand from a hot plate)
2. Semivoluntary (unvoluntary)
 - a. Induced by an inner sensory stimulus (e.g., the need to “stretch” a body part)
 - b. Induced by an unwanted feeling or compulsion (e.g., compulsive touching or smelling)
3. Involuntary
 - a. Nonsuppressible (e.g., reflexes, seizures, myoclonus)
 - b. Suppressible (e.g., tics, tremor, dystonia, chorea, stereotypy)
4. Automatic
 - a. Learned motor behaviors performed without conscious effort (e.g., the act of walking or speaking)

Studies have shown that automatic, learned behaviors appear to be encoded in the sensorimotor portion of the striatum (Jog et al., 1999). Some support for the proposed classification is provided by the findings of Papa and colleagues (1991). They recorded normal premovement (readiness) electroencephalographic, slow, negative potential (the Bereitschaftspotential) 1 to 1.5 seconds before self-induced, internally generated (voluntary) movement in normal individuals but not before externally triggered movement induced by electrical stimulation (Colebatch, 2007). Most tics can be categorized as either semivoluntary (unvoluntary) or involuntary (suppressible). In some cases, learned voluntary motor skills are incorporated into the tic repertoire. This is exemplified by a case of a woman with TS who incorporated sign language into her tic behavior, suggesting that semantics is more important than phonology in the generation of tics (Lang et al., 1993).

Tics may be simple or complex. Simple motor tics involve only one group of muscles, causing a brief, jerk-like movement. They are usually abrupt in onset and rapid (clonic tics), but they may be slower, causing a briefly sustained abnormal posture (dystonic tics) or an isometric contraction (tonic or isometric tics) (Jankovic and Fahn, 1986; Jankovic, 1992). Examples of simple clonic motor tics include blinking, nose twitching, and head jerking. Rhythmical clonic tics may rarely resemble tremor or rhythmical myoclonus, such as palatal myoclonus (Schwingschuh et al., 2007; Adam et al., 2009). Simple dystonic tics include blepharospasm, oculogyric movements, bruxism, sustained mouth opening, torticollis, and shoulder rotation (Videos 15.3, 15.9). Tensing of abdominal or limb muscles is an example of a tonic tic (Video 15.10). To characterize clonic and dystonic tics further, 156 patients with TS were studied; 89 (57%) exhibited dystonic tics, including oculogyric deviations (28%), blepharospasm (15%), and dystonic neck movements (7%) (Jankovic and Stone, 1991). Because patients with dystonic tics did not differ significantly on any clinical variables from those with only clonic tics, we concluded that despite previous reports (Feinberg et al., 1986), the presence of dystonic tics should not be considered atypical or unusual. In fact, subsequent observation of the patient in the case report by Feinberg and colleagues was actually a case of TS with typical dystonic tics (Fahn, 1987). Dystonic tics should be distinguished from persistent dystonia, which is typically seen in patients with primary dystonia (Jankovic and Fahn, 2002). Dystonic (and tonic) muscle contraction might be responsible for so-called blocking tics (Video 15.11). These blocking tics are due to either prolonged tonic or dystonic tics that interrupt ongoing motor activity such as speech (intrusions) or a sudden inhibition of ongoing motor activity (negative tic). Clonic and dystonic tics may occasionally occur in patients with primary dystonia more frequently than in the general population. In nine patients with coexistent TS and persistent primary dystonia, the onset of tics was at a mean age of 9 years, and dystonia followed the onset of tics by a mean of 22 (10–38) years (Stone and Jankovic, 1991). In one study, 20 of 224 (8.9%) patients with tics had coexistent dystonia (Damasio et al., 2011). The patients with tics–dystonia combination had a later age at onset, less severe tics, and lower frequency of associated features. Other reports have drawn attention to the possible association of tics and dystonia, although the two disorders may coexist by chance alone

Video 15.1 Facial tics.

Video 15.2 Cervical tics.

Video 15.3 Shoulder tics.

Video 15.4 Limb tics.

Video 15.5 Truncal-abdominal tics.

Video 15.6 Complex tics.

Video 15.7 Simple phonic tics.

Video 15.8 Complex phonic tics.

(Pringsheim et al., 2007). The occasional co-occurrence of tics and dystonia in the same family, however, provides additional evidence for a possible etiologic relationship between the two disorders (Németh et al., 1999; Yaltho et al., 2010). Dopa-responsive dystonia with mutations in the *GCH1* gene and TS was found in various members of a large Danish family (Romstad et al., 2003). Some complex tics consist of repetitive, ritualistic, patterned movements that can be characterized as stereotypic tics. Finally, there are some movements or sounds that are primarily driven by underlying urge to perform the movement or noise behavior, and hence, the term “compulsive tics” is sometimes applied to these behaviors. This has therapeutic implications because anti-OCD medications or behavioral strategies may be used to control these types of tics. ►

Motor (particularly dystonic) and phonic tics are preceded by premonitory sensations in over 80% of patients (Banaschewski et al., 2003; Kwak et al., 2003a; Woods et al., 2005; Prado et al., 2008; Ganos et al., 2012b; Kano et al., 2020; Matsuda et al., 2020). This premonitory phenomena consist of localizable sensations or discomforts, such as a burning feeling in the eye before an eye blink, tension or a crick in the neck that is relieved by stretching of the neck or jerking of the head, a feeling of tightness or constriction that is relieved by arm or leg extension, nasal stuffiness before a sniff, a dry or sore throat before throat clearing or grunting, and itching before a rotatory movement of the scapula. Some liken this phenomenon to a sneeze. Rarely, these premonitory sensations, termed in one report extracorporeal phantom tics, involve sensations in other people and objects and are temporarily relieved by touching or scratching them (Karp and Hallett, 1996). In one study, premonitory sensations were experienced by 92% of 135 patients with TS, and these were localized chiefly to the shoulder girdle, palms, midline abdominal region, posterior thighs, feet, and eyes (Cohen and Leckman, 1992). We administered a questionnaire regarding various aspects of premonitory sensations associated with their motor tics to 50 TS patients with a mean age of 23.6 ± 16.7 years (Kwak et al., 2003a). Of 50 subjects, 46 (92%) reported some premonitory sensations, the most common of which was an urge to move and an impulse to tic (“had to do it”). Other premonitory sensations included an itch, tingling/burning, numbness, and coldness. Thirty-seven (74%) also reported intensification of premonitory sensations if the patient was prevented from performing a motor tic, 36 (72%) reported relief of premonitory sensations after performing the tic, and 24 (48%) stated that their motor tic would not have occurred if they had not experienced a premonitory sensation. Of 40 patients (68%), 27 described a motor tic as a voluntary motor response to an involuntary sensation rather than as a completely involuntary movement. Besides the local or regional premonitory sensations, this premonitory phenomenon may be a nonlocalizable, less specific, and poorly described feeling, such as an urge, anxiety, anger, and other psychic sensations. The observed movement or sound sometimes occurs in response to these premonitory phenomena, and these movements or sounds have been previously referred to as sensory tics (Kurlan et al., 1989; Chee and Sachdev, 1997; Kano et al., 2020; Matsuda et al., 2020). In a study of 60 patients with tic disorders, 41 (68%) thought that all their tics were intentionally produced and 15 (25%) additional patients had both voluntary and involuntary movements; thus, 93% of the tics were perceived to be “irresistibly

but purposefully executed” (Lang, 1991). This “intentional” component of the movement may be a useful feature in differentiating tics from other hyperkinetic movement disorders, such as myoclonus and chorea. The sensations or feelings that often precede motor tics usually occur out of a background of relative normalcy and are clearly involuntary, even though the movements (motor tics) or noises (phonic tics) that occur in response to these premonitory symptoms may be regarded as semivoluntary or involuntary. Chee and Sachdev (1997) suggest that sensory tics, which we and others refer to as premonitory sensations, “represent the subjectively experienced component of neural dysfunction below the threshold for motor and phonic tic production.” Many patients report that they have to repeat a particular movement to relieve the uncomfortable urge until “it feels good.” The “just right” feeling has been associated with compulsive behavior, and thus the “involuntary” movement may be regarded as a compulsive tic (Leckman et al., 1994). Although many patients describe a gradually increasing inner tension as tic suppression is maintained and a rebound effect of a flurry of tics when the tics are finally expressed, formal objective studies of tic frequency during and after voluntary suppression have failed to detect a rebound increase (Himle and Woods 2005; Meidinger et al., 2005), and, when reinforced, tic suppression may last at least 40 consecutive minutes (Woods et al., 2008). The premonitory urges and tic inhibition do not seem to be directly linked and the two phenomena may be mediated by distinct neural systems (Ganos et al., 2012b). One study found that tic suppression (inhibition) was most effective in the body parts that exhibited the fewest tics (Ganos, Bongert et al., 2015). The same investigators have found lower interoceptive awareness in TS but greater interoceptive awareness (possibly reflecting a self-attentive capacity) was associated with more urges (Ganos, Garrido et al., 2015).

The pathophysiology of premonitory sensations is not well understood, but the phenomenon seems to represent an example of increasingly recognized sensory aspects of movement disorders (Patel et al., 2014; Ruhrman et al., 2017; Isaacs and Riordan, 2020; Kano et al., 2020). Some investigators have suggested that premonitory urges result from a “sensorimotor gating” dysfunction (Rajagopal et al., 2013). The supplementary motor area (SMA) and the anterior cingulate cortex, which receive dense dopaminergic projections from midbrain structures and substantia nigra, may be involved in these premonitory sensations. This is supported by the observation that electrical stimulation of the SMA produced an urge to move or unusual sensations (Fried et al., 1991). It is possible that in TS, as a result of the abnormal sensorimotor gating, the basal ganglia are not able to select or suppress the various convergent and competing programs and allow the abnormal expression of the sensory rather than motor pattern (Bohlhalter et al., 2006; Kano et al., 2020). When resting-state functional magnetic resonance imaging (MRI) was performed in 13 adults with TS and 13 matched controls, the right dorsal anterior insula demonstrated higher connectivity, especially with the frontostriatal nodes of the urge-tic network and bilateral SMA, even though the patients did not exhibit any overt tics (Tinaz et al., 2015). These findings suggest that the right dorsal anterior insula is part of the urge-tic network and could influence the urge- and tic-related cortico-striato-thalamic regions in TS (Jackson et al., 2020). The dorsal anterior part of the insula has been found

Video 15.9 Shoulder tics.

Video 15.10 Tonic (isometric) tics.

Video 15.11 Blocking tics.

to integrate sensory and emotional information with cognitive valuation. The right dorsal anterior insula also participates in urge suppression in healthy subjects.

Complex motor tics consist of coordinated, sequenced movements resembling normal motor acts or gestures that are inappropriately intense and timed (Videos 15.6, 15.12, 15.13). They may be seemingly nonpurposeful, such as head shaking or trunk bending, or they may seem purposeful, such as touching, throwing, hitting, jumping, and kicking. Additional examples of complex motor tics include gesturing “the finger” and grabbing or exposing one’s genitalia (copropraxia) or imitating gestures (echopraxia). Burping, vomiting, and retching have been described as part of the clinical picture of TS, but it is not clear whether this phenomenon represents a complex tic or some other behavioral manifestation of TS (Rickards and Robertson, 1997). Air swallowing (Weil et al., 2008) and pathologic laughter (Cavanna et al., 2010) are examples of other unusual tics described in TS. Another unusual tic is ear dyskinesia, which consists of anterior-posterior displacement of the external ear (Cardoso and Faleiro, 1999). Complex motor tics may be difficult to differentiate from compulsions, which frequently accompany tics, particularly in TS. A complex, repetitive movement may be considered a compulsion when it is preceded by, or associated with, a feeling of anxiety or panic and an irresistible urge to perform the movement or sound because of fear that if it is not promptly or properly executed, “something bad” will happen. However, this distinction is not always possible, particularly when the patient is unable to verbalize such feelings. Some coordinated movements resemble complex motor tics but may actually represent pseudovoluntary movements (parakinesias) that are designed to camouflage the tics by incorporating them into seemingly purposeful acts, such as adjusting one’s hair during a head jerk. Some head jerks may occur in a form of intermittent head drops, such as seen in Sandifer syndrome associated with gastroesophageal reflux, sleep disorders, seizures, and other non-tic disorders (Antelmi et al., 2015). ●

Simple phonic tics typically consist of sniffing, throat clearing, grunting, squeaking, screaming, coughing, blowing, and sucking sounds. Complex phonic tics include linguistically meaningful utterances and verbalizations, such as shouting of obscenities or profanities (coprolalia), repetition of someone else’s words or phrases (echolalia), and repetition of one’s own utterances, particularly the last syllable, word or phrase in a sentence (palilalia). Some TS patients also manifest sudden and transient cessation of all motor activity (blocking tics) without alteration of consciousness.

In contrast to other hyperkinetic movement disorders, tics are usually intermittent and may be repetitive and stereotypic (Table 15.1). Many patients with TS also have leg stereotypy syndrome, described in chapter on stereotypies (Lotia et al., 2018) (Chapter 17). Tics may occur as short-term bouts or bursts or long-term waxing and waning (Peterson and Leckman, 1998). They vary in frequency and intensity and often change distribution. Typically, tics can be volitionally suppressed, although this might require intense mental effort (Banaschewski et al., 2003). Suppressibility, although characteristic and common in tics, is not unique or specific for tics, and this phenomenon has been well documented in other hyperkinetic movement disorders (Walters et al., 1990). Using functional MRI (fMRI), Peterson and colleagues (1998a) showed decreased neuronal

Table 15.1 Classification of tics

- | |
|---|
| A. Primary |
| 1. Sporadic |
| a. Transient motor or phonic tics (<1 year) |
| b. Chronic motor or phonic tics (>1 year) |
| c. Adult-onset (recurrent) tics |
| d. TS |
| 2. Inherited |
| a. TS |
| B. Secondary |
| 1. Inherited |
| a. Huntington disease |
| b. Primary dystonia |
| c. Neuroacanthocytosis |
| d. Neurodegeneration with brain iron accumulation |
| e. Tuberous sclerosis |
| f. Wilson disease |
| g. Duchenne muscular dystrophy |
| 2. Infections: Encephalitis, Creutzfeldt-Jakob disease, neurosyphilis, Sydenham disease |
| 3. Drugs: Amphetamines, methylphenidate, pemoline, levodopa, cocaine, carbamazepine, phenytoin, phenobarbital, lamotrigine, antipsychotics, and other dopamine receptor-blocking drugs (tardive tics, tardive tourettism) |
| 4. Toxins: Carbon monoxide |
| 5. Developmental: Static encephalopathy, intellectual disability syndromes, chromosomal abnormalities, autistic spectrum disorders (Asperger syndrome) |
| 6. Chromosomal disorders: Down syndrome, Klinefelter syndrome, XYY karyotype, fragile X syndrome, triple X and 9p mosaicism, partial trisomy 16, 9p monosomy, citrullinemia, Beckwith-Wiedemann syndrome |
| 7. Other: Head trauma, stroke, neurocutaneous syndromes, schizophrenia, neurodegenerative diseases |
| C. Related manifestations and disorders |
| 1. Stereotypies/habits/mannerisms/rituals |
| 2. Self-injurious behaviors |
| 3. Motor restlessness |
| 4. Akathisia |
| 5. Compulsions |
| 6. Excessive startle |
| 7. Jumping Frenchman |

activity during periods of suppression in the ventral globus pallidus (GP), putamen, and thalamus. There was increased activity in the right caudate nucleus, right frontal cortex, and other cortical areas that are normally involved in the inhibition of unwanted impulses (prefrontal, parietal, temporal, and cingulate cortices). Using event-related fMRI in 26 children with bipolar disorder deficits in the ability to engage striatal structures and the right ventral prefrontal cortex were found during unsuccessful inhibition, thus suggesting that deficits in motor inhibition contribute to impulsivity and irritability in children with bipolar disorder and possibly also with TS (Leibenluft et al., 2007). Using a behavioral paradigm to study intermanual conflict, diffusion-weighted and fMRI, individuals with TS were found to exhibit enhanced control of motor output providing “evidence for compensatory brain reorganization that may underlie the increased self-regulation mechanisms that have been hypothesized to bring about the control of tics during adolescence” (Jackson et al., 2011). This suggests that their long-standing effort to suppress tics resulted in permanent functional changes, possibly as a result of compensatory neuroplasticity.

Video 15.12 Complex motor tics.

Video 15.13 Complex motor tics.

Besides temporary suppressibility, tics are characterized by suggestibility and exacerbation with stress, excitement, boredom, fatigue, and exposure to heat (Lombroso et al., 1991). Emotional stress associated with life events or other stresses have been documented to potentially markedly exacerbate tics, but onset of TS is not necessarily related to stressful life events (Wood et al., 2003; Hoekstra et al., 2004; Horesh et al., 2008). Tics may also increase during relaxation after a period of stress.

In contrast to other hyperkinetic movement disorders that are usually completely suppressed during sleep, motor and phonic tics may persist during all stages of sleep (Cohrs et al., 2001; Jankovic et al., 1984; Silvestri et al., 1990; Fish et al., 1991; Hanna and Jankovic, 2003; Rothenberger et al., 2001; Jiménez-Jiménez, et al. 2020). In addition, patients with TS often have disturbances of sleep, such as increased sleep fragmentation, higher frequency of arousals, decreased rapid eye movement (REM) sleep, and enuresis (Hanna and Jankovic, 2003). Many patients note a reduction in their tics when they are distracted while concentrating on mental or physical tasks (such as when playing a video game or during an orgasm). Other patients experience increased frequency and intensity of their tics when distracted, especially when they no longer have the need to suppress the tics. Tics are also typically exacerbated by dopaminergic drugs and by stimulants, including methylphenidate and cocaine (Cardoso and Jankovic, 1993). Finally, it should be noted that a broad spectrum of movements may be present in patients with TS that can be confused with tics, such as akathisia, chorea, dystonia, compulsive movements, and fidgeting, as part of hyperactivity associated with ADHD (Jankovic, 1997; Kompoliti and Goetz, 1998; Wilens et al., 2004).

Clinical features of Tourette syndrome

Motor symptoms

TS, the most common cause of tics, is manifested by a broad spectrum of motor and behavioral disturbances (Fig. 15.1). This clinical heterogeneity often causes diagnostic difficulties and presents a major challenge in genetic linkage studies. To aid in the diagnosis of TS, the *Tourette Syndrome Classification Study Group* (1993) formulated the following criteria for definite TS: (1) Both multiple motor and one or more phonic tics have to be present at some time during the illness, although not necessarily concurrently. (2) Tics must occur many times a day, nearly every day, or intermittently throughout a period of more than 1 year. (3) The anatomic location, number, frequency, type, complexity, or severity of tics must change over time. (4) Onset must be before age 21. (5) Involuntary movements and noises cannot be explained by other medical conditions. (6) Motor and/or phonic tics must be directly witnessed by a reliable examiner at some point during the illness or must be recorded by videotape or cinematography. Probable TS type 1 meets all the criteria except for number 3 and/or number 4, and probable TS type 2 meets all the criteria except for number 1; it includes either a single motor tic with phonic tics or multiple motor tics with possible phonic tics. According to DSM-5 (American Psychiatric Association, 2013) the following are criteria required for the diagnosis of definite TS:

A. Both multiple motor and one or more vocal tics are present at some time during the illness, although not necessarily concurrently.

B. The tics may wax or wane in frequency but have persisted for more than 1 year since first tic onset.

C. Onset is before age 18 years.

D. The disturbance is not attributable to the physiologic effects of a substance (e.g., cocaine) or a general medical condition (e.g., Huntington disease [HD], postviral encephalitis).

According to DSM-5, if child has tics of less than 1-year duration, the most appropriate diagnosis is provisional tic disorder (PTD), which replaced the term transient tic disorder (Black et al., 2016). The point prevalence of PTD varies with age, but it has been estimated that about 20% of children aged 5 to 10 years have PTD, although the lifetime prevalence is much higher. The majority of children whose tics started within the past year will continue to have tics, and only about 32% remain completely tic-free over the next 5 to 10 years.

The TSA International Genetic Collaboration developed the Diagnostic Confidence Index, which consists of 26 confidence factors, with weightings given to each of them and a total maximum score of 100. The most highly weighted diagnostic confidence factors include history of coprolalia, complex motor or vocal tics, a waxing and waning course, echo phenomenon, premonitory sensations, an orchestrated sequence, and age at onset. The Diagnostic Confidence Index was found to be a useful instrument in assessing the lifetime likelihood of TS (Robertson et al., 1999). Several instruments, some based on ratings of videotapes and others on monitoring wearable devices (Bernabei et al., 2010), have been developed to measure and quantitate tics, but they all have some limitations (Goetz and Kompoliti, 2001; Goetz et al., 2001). The most widely used instrument to assess tics is the Yale Global Tic Severity Scale (YGTSS), which consists of two broad domains: Total Tic Severity (TTS) (with five dimensions: number, frequency, intensity, complexity, and interference, each rated on 0–5 scale), with two subdomains: Motor and Phonic Tics and Impairment. The TTS ranges from 0 to 50 (the usual range in most studies is 15–30) and the Total YGTSS is the sum of TTS and Impairment (0–50). A health-related quality of life (HRQOL) scale has been developed and validated for internal consistency, test–retest reliability, and against other clinical scales (Cavanna et al., 2008). Use of the HRQOL scale showed that comorbidities such as ADHD and OCD rather than tic severity are more predictive of the long-term outcome. The Movement Disorders Society (MDS) subcommittee commissioned to rate psychometric quality of severity and screening instruments for tics and related sensory phenomena associated with TS, issued their recommendations (Martino et al., 2016). Of the severity scales, the authors “recommended” five: (1) YGTSS, (2) Tourette Syndrome Clinical Global Impression, (3) Tourette’s Disorder Scale, (4) Shapiro TS Severity Scale, and (5) Premonitory Urges for Tics Scale, and “suggested” six scales: (1) Rush Video-Based Tic Rating Scale; (2) Motor Tic, Obsessions and Compulsions, Vocal Tic Evaluation Survey (MOVES); (3) Tourette Syndrome Global Scale; (4) Global Tic Rating Scale; (5) Parent Tic Questionnaire; and (6) Tourette Syndrome Symptom List. They also “recommended” two diagnostic screening instruments: (1) MOVES and (2) Autism-Tics, ADHD, and other comorbidities inventory. They concluded that there was no need to develop new tic severity or screening instruments.

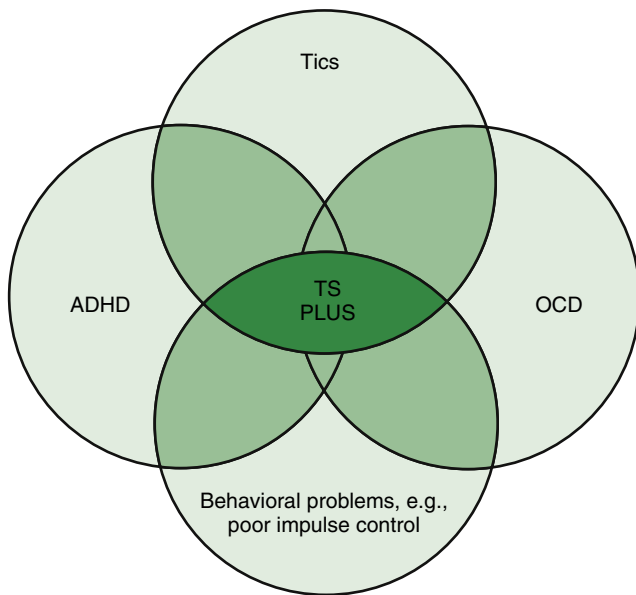


Fig. 15.1 An overlap of disorders typically coexisting in patients with Tourette syndrome (TS). ADHD, Attention deficit–hyperactivity disorder; OCD, obsessive-compulsive disorder.

The clinical criteria are designed to assist in accurate diagnosis, in genetic linkage studies, and in differentiating TS from other tic disorders (Jankovic, 1993b) (see Table 15.1). A body of evidence supports the notion that many, if not all, patients with other forms of idiopathic tic disorders represent one end of the spectrum in a continuum of TS (Kurlan et al., 1988). The most common and mildest of the idiopathic tic disorders is the transient tic disorder (TTD) of childhood. This disorder is essentially identical to TS except the symptoms last less than 1 year, and therefore the diagnosis can be made only in retrospect. TTD has been estimated to occur in up to 24% of schoolchildren (Shapiro et al., 1988). Chronic multiple tic disorder is also similar to TS, but the patients have either only motor or, less commonly, only phonic tics lasting at least 1 year. Chronic single tic disorder is the same as chronic multiple tic disorder, but the patients have only a single motor or phonic tic. This separation into transient tic disorder, chronic multiple tic disorder, and chronic single tic disorder seems artificial because all can occur in the same family and probably represent a variable expression of the same genetic defect (Kurlan et al., 1988).

Although the diagnostic criteria require that the onset is present before the age of 21, in 96% of patients the disorder is manifested by age 11 (Robertson, 1989). In 36% to 48% of patients, the initial symptom is eye blinking, followed by tics involving the face and head. Blink rate in TS is about double of that of normal, age-matched controls (Tulen et al., 1999). During the course of the disease, nearly all patients exhibit tics involving the face or head, two-thirds have tics in the arms, and half have tics involving the trunk or legs. According to one study, the average age at onset of tics is 5.6 years, and the tics usually become most severe at age 10; by 18 years of age, half of the patients are tic-free (Leckman et al., 1998). In a study of 58 adults who had been diagnosed with TS during childhood, Goetz and colleagues (1992) found that tics persisted in all patients but were moderate or severe in only 24%, although 60% had moderate or severe

tics during the course of the disease. Tic severity during childhood had no predictive value for the future course, but patients with mild tics during the preadult period had mild tics during adulthood. In a longitudinal study that involved structured interviews of 976 children, aged 1 to 10 years, 776 of whom were reassessed 8, 10, and 15 years later, tics and ADHD symptoms were associated with OCD symptoms in late adolescence and early adulthood (Peterson et al., 2001). Furthermore, ADHD was associated with lower IQ and lower social status, whereas OCD was associated with higher IQ. These findings are similar to those of another study designed to address the long-term prognosis of children with TS as they reach adulthood (Bloch et al., 2006). In this study, 46 children with TS underwent a structured interview at a mean age of 11.4 years and again at 19.0 years. The mean worst-ever tic severity score was 31.6 out of a possible 50 on the YGTSS and occurred at a mean age of 10.6 years. By the time of the second interview, mean YGTSS score decreased to 10. This first prospective longitudinal study also showed that 22% continue and nearly one-third were in complete remission of tic symptoms at follow-up. In contrast to the study by Goetz and associates (1992), the severity of childhood tics was predictive of increased tic severity at follow-up. The peak OCD severity occurred 2 years after peak tic severity. Interestingly, a 10-point increase in baseline IQ increased the risk for OCD symptoms at follow-up by 2.8 fold. The authors point out that the later average onset of OCD symptoms indicates the importance of counseling parents about the possibility of OCD development in children recently diagnosed with tics. Although the long-term prognosis for TS is generally favorable for most patients, a minority of cases may have persistent, severe tic symptoms, which may be resistant to medications (Eapen et al., 2002). In a large prospective study in which the clinical cohort was recruited at the Danish National Tourette Clinic, with data collected at baseline ($n = 314$, age range 5–19 years) and at follow-up 6 years later ($n = 227$), tic severity declined yearly (0.8 points on the YGTSS during adolescence (Groth et al., 2017). Of all the participants older than 16 years, 17.7% had no tics, 59.5% had minimal or mild tics, and 22.8% had moderate or severe tics. However, the authors found that 63.0% of participants had comorbidities or coexistent psychopathologic conditions at last follow-up. In another study, the investigators reviewed videotapes of 31 patients, with an average age of 24.2 ± 3.5 years, approximately 12 years after their initial video and found that 90% of the adults still had tics, even though they often considered themselves tic-free (Papert et al., 2003). There was, however, a significant improvement in tic disability and tic severity. When 40 children and 31 adults with TS were compared no difference in tic phenomenology or severity was found, but children were more frequently managed without medications, and sedation was more common in adults but weight gain was more common in children (Cubo et al., 2008). We reviewed 43 adults with TS referred to our Movement Disorders Clinic over the past 5 years and compared them with 100 TS patients 18 years of age or younger (Jankovic et al., 2010). We found that adult TS patients had significantly more facial and truncal tics, as well as a greater prevalence of substance abuse and mood disorders, but fewer phonic tics and lower rates of ADHD and oppositional behavior than children with TS. Furthermore, adult TS largely represented a re-emergence or exacerbation

of childhood-onset TS. During the course of TS, phonic and complex motor tics, self-injurious behaviors (SIBs), and ADHD tend to improve, but facial, neck, and trunk tics dominate the adult TS phenotype.

Although the vast majority of tics in adults represent recurrences of childhood-onset tics, rare patients may have their first tic occurrence during adulthood (Chouinard and Ford, 2000). In adults with new-onset tics, it is important to search for secondary causes, such as infection, trauma, stroke (Kwak and Jankovic, 2002; Gomis et al., 2008), multiple sclerosis (Silvers and Menkes, 2009), cocaine use, neuroleptic exposure, and peripheral injury (Video 15.14) (Chouinard and Ford, 2000; Jankovic, 2001b; Jankovic and Mejia, 2006). One study of eight patients with adult-onset tics (three of whom had childhood-onset OCD and three of whom had a family history of tics and OCD) found that in comparison to the patients with more typical childhood-onset tics, the former group had more severe symptoms, greater social morbidity, and less favorable response to medications (Eapen et al., 2002). Poor motor control, which can lead to poor penmanship and, at times, almost illegible handwriting, can contribute to the academic difficulties faced by many patients with TS. ●

Tics, although rarely disabling, can be quite troublesome for TS patients because they cause embarrassment, interfere with social interactions, and at times can be quite painful or uncomfortable. Rarely, cervical tics may be so forceful and violent, the so-called “whiplash tics,” that they may cause secondary neurologic deficits, such as cervical artery dissection and noncompressive (Isaacs et al., 2010; Lehmann et al., 2011) or compressive cervical myelopathy (Krauss and Jankovic, 1996; Huasen et al., 2014) (Video 15.2). The truncal bending tics, which resemble intermittent, repetitive camptocormia, may cause secondary degenerative changes in the thoracic spine (Azher and Jankovic, 2005) (Video 15.5). These disabling tics and other severe symptoms of TS draw attention to the subset of patients with TS so severe that they may be life-threatening, hence labeled as “malignant” TS. Of 332 TS patients evaluated at Baylor College of Medicine Movement Disorders Clinic during a 3-year period, 17 (5.1%) met criteria for malignant TS, defined as two or more emergency department (ED) visits or one or more hospitalizations for TS symptoms or its associated behavioral comorbidities (Cheung et al., 2007). The patients exhibited tic-related injuries, SIB, uncontrollable violence and temper, and suicidal ideation/attempts. Compared with patients with nonmalignant TS, those with malignant TS were significantly more likely to have a personal history of obsessive compulsive behavior/disorder (OCB/OCD), complex phonic tics, coprolalia, copropraxia, SIB, mood disorder, suicidal ideation, and poor response to medications. Severe or malignant TS, associated with SIB and other disabling features, also has been reported in families, including consanguine kindreds (Motlagh et al., 2008). In a study of 75 patients diagnosed with “tic disorder,” ages 6 to 18 years, 61% expressed at least some suicidal ideation and 8% expressed clinically significant symptoms (Johnco et al., 2016). Suicidal ideation correlated with higher anxiety, depression and externalizing symptoms, affective lability, lower distress tolerance, and overall function; tic severity was not associated with suicidal ideation. ●

Vocalizations have been reported as the initial symptom in 12% to 37% of patients, throat clearing being the most common (Robertson, 1989). Phonic tics can be quite troublesome for patients and those around them. In addition to involuntary noises, some patients have speech dysfluencies that resemble developmental stuttering and up to half of all patients with developmental stuttering have been thought to have undiagnosed TS (Abwender et al., 1998). Coprolalia, perhaps the most recognizable and certainly one of the most distressing symptoms of TS, is actually present in only half of patients (Videos 15.8, 15.15). When describing the distress caused by his severe coprolalia, one of our patients remarked that immediately after shouting an obscenity, he reaches out with his hand in an attempt to “catch the word and bring it back before others can hear it.” Coprolalia appears to be markedly influenced by cultural background. Although in one retrospective analysis of 112 children with TS, only 8% exhibited coprolalia (Goldenberg et al., 1994), the true prevalence of coprolalia in TS children and adults is about 50% in the U.S. population, when mental coprolalia (without actual utterance) is included. In a study of 597 individuals with TS from seven countries, coprolalia occurred at some point in the course of the disease in 19.3% of males and 14.6% of females, and copropraxia in 5.9% of males and 4.9% of females (Freeman et al., 2009). Coprolalia has been reported to occur in 26% of Danish patients and 4% of Japanese patients (Robertson, 1989). Copropraxia has been found in about 20% of patients, echolalia in 30%, echopraxia in 25%, and palilalia in 15%. Although coprolalia is a characteristic feature of TS and, based on fMRI studies, attributed to abnormal activation particularly in the left middle frontal gyrus and right precentral gyrus, and possibly the caudate nucleus, cingulate gyrus, cuneus, left angular gyrus, left inferior parietal gyrus, and occipital gyri (Gates et al., 2004), this language abnormality is not universally present or specific for TS.

Except tics, the neurologic examination in patients with TS is usually normal. In one case-control study, TS patients were found to have a shorter duration of saccades, but the saccades were performed with a greater mean velocity than in normal controls, and the TS patients had fewer correct antisaccade responses, suggesting a mild oculomotor disturbance in TS (Farber et al., 1999). Although the ability to inhibit reflexive saccades is normal, TS patients make more timing errors, indicating an inability to appropriately inhibit or delay planned motor programs (LeVasseur et al., 2001).

Behavioral symptoms

Patients with TS generally have normal intelligence and may even perform better and faster than age-matched controls on certain tasks that require grammar skills that depend on procedural, rather than declarative memory (Walenski et al., 2007). Although TS patients have no cognitive deficits, they often exhibit a variety of behavioral symptoms, particularly ADHD and OCD (Gaze et al., 2006). In the Tourette International Consortium (TIC) database, which includes information on 3500 patients with TS evaluated by neurologists or psychiatrists, 12% had tics only, without other comorbidities (Freeman et al., 2000). Kurlan and colleagues (2002) interviewed 1596 children, ages 9 to 17, in schools in Rochester and Monroe Counties, New York, and identified tics in 339

Video 15.14 Peripherally induced tics.

Video 15.15 Coprolalia.

children (21%) after 60 to 150 minutes of observation. They found the following behavioral problems more frequently ($P < 0.05$) in children with tics than in those without tics: OCD, ADHD, separation anxiety, overanxious disorder, simple phobia, social phobia, agoraphobia, mania, major depression, and oppositional defiant behavior. In addition, children with tics were younger (mean age: 12.5 versus 13.3 years) and were more likely to require special education services (27% versus 19.8%). In cross-sectional structured diagnostic interviews conducted in 1374 patients with TS and in 1142 TS-unaffected family members, the lifetime prevalence of any psychiatric comorbidity among individuals with TS was 85.7%; 57.7% of the population had two or more psychiatric disorders, and 72.1% of the individuals met the criteria for OCD or ADHD (Hirschtritt et al., 2015). Other disorders, including mood, anxiety, and disruptive behavior, each occurred in approximately 30% of the participants. The age of greatest risk for the onset of most comorbid psychiatric disorders was between 4 and 10 years, with the exception of eating and substance use disorders, which began in adolescence (interquartile range, 15–19 years for both).

A thorough discussion of the pathogenesis of comorbid disorders and their relationship to TS is beyond the scope of this review, and the reader is referred to some reviews on these topics (Tannock, 1998; Stein, 2002; Volkow and Swanson, 2013). The diagnosis of ADHD and OCD is based on clinical history; there are no laboratory or other tests that reliably diagnose these neurobehavioral disorders (Dulcan and AACAP Works Group on Quality Issues, 1997; Goldman et al., 1998; Swanson et al., 1998; Grant, 20014; Pauls et al., 2014) (Table 15.2). The biologic basis of frequent coexistence of ADHD and OCD is not well understood, but certain genetic variants are present in both disorders and similar deficits in executive functions are shared by the two disorders and may be responsible for the compulsive symptoms in OCD and disinhibited and impulsive symptoms in ADHD (Brem et al., 2014). These comorbid behavioral conditions often interfere with learning and with academic and work performance (Singer, Schuerholz et al., 1995). In contrast to tics, ADHD and obsessional symptom severity are significantly associated with impaired social and emotional adjustment (Carter et al., 2000). The clinician should be skilled not only in the recognition and treatment of ADHD but also in documenting the ADHD-related deficits (Richard et al., 1998). One study provided compelling evidence that patients with TS experience substantial academic underachievement across all educational levels compared with children without the diagnosis of TS (Pérez-Vigil et al., 2018). Such documentation is essential for the parents and educators to provide the optimal educational setting for the affected individual.

Because nearly all studies on the frequency of associated features have been based on a population of TS patients who have been referred to physicians, usually specialists, there is a certain selection bias; therefore, accurate figures on the prevalence of these behavioral disorders in TS patients are not available. It has been estimated, however, that 3% to 6% of the school-aged population suffers from ADHD (Goldman et al., 1998) and probably a majority of patients with TS have had symptoms of ADHD, OCD, or both at some time during the course of their illness (Coffey and Park, 1997). In a review of 1500 patients with TS, 48% were diagnosed

Table 15.2 Attention deficit–hyperactivity disorder/hyperkinetic disorder

Inattention
Fails to attend to details
Difficulty sustaining attention
Does not seem to listen
Fails to finish
Has difficulty organizing tasks
Avoids sustained effort
Loses things
Distracted by external stimuli
Forgetful
Hyperactivity
Fidgets with hands or feet
Leaves seat in classroom
Runs about or climbs
Has difficulty playing quietly
Motor excess (“on the go”)
Talks excessively
Impulsivity
Talks excessively
Blurts out answers
Has difficulty waiting turn
Interrupts or intrudes on others

as having ADHD, a figure that is consistent with the results of other studies (Comings and Comings, 1988b). The symptoms of ADHD may be the initial manifestations of TS and may precede the onset of motor and phonic tics by about 3 years. During this time, therapy with stimulant drugs may trigger the onset of tics and may precipitate the emergence of other TS symptoms (Price et al., 1986).

There are three types of ADHD: predominantly inattentive, predominantly hyperactive-impulsive, and combined (Dulcan et al., 1997) (see Table 15.2). ADHD is one of the most common neurobehavioral disorders, affecting 3% to 10% of children and 4% of adults (Wilens et al., 2004; Rappley, 2005). Adults with ADHD often have childhood histories of educational and discipline problems; and during adulthood they usually have lower socioeconomic status, lower rates of professional employment, and higher rates of marital problems, driving violations, and other life failures. In a genome scan of 106 families, including 128 affected sib-pairs with estimated heritability of 60% to 80%, multipoint multilevel selection values greater than 1 were evidence of a gene locus on chromosomes 4, 9, 10, 11, 12, 16, and 17 (Smalley et al., 2001). Further research is needed to improve our understanding of the genetics and neurobiology of ADHD (Efron et al., 2015; Thapar and Cooper, 2015).

Although attention deficit is certainly one of the most common and disabling symptoms of TS, in many patients the inability to pay attention is due to not only a coexistent ADHD but also uncontrollable intrusions of thoughts. Some patients are unable to pay attention because of a compulsive fixation of gaze. For example, while they are sitting in a classroom or a theater or during a conversation, their gaze becomes fixated on a particular object, and despite concentrated effort, they are unable to break the fixation. As a result, they miss the teacher’s lesson or a particular action in a play. Another reason for impaired attention in some TS patients is mental concentration exerted in an effort to suppress tics. Yet

another cause for inattention is the sedative effect of anti-TS medications. It is therefore important to determine which mechanism or mechanisms are most likely to be responsible for the patient's attention deficit. This is particularly important in selecting the best therapeutic approach. Despite growing publicity about ADHD, there is little evidence of widespread overdiagnosis or overtreatment of ADHD (Goldman et al., 1998). One study showed that children and adolescents with ADHD compared with those without ADHD are more likely to have major injuries and asthma, and their 9-year medical costs are double (Leibson et al., 2001). The mechanism of ADHD with or without TS is not well understood, and there are no specific pathologic abnormalities identified. However, by using high-resolution MRI, abnormal morphology was observed in the frontal cortices, reduction in the anterior temporal cortices, and increased gray matter in the posterior and inferior parietal cortices in children and adolescents with ADHD (Sowell et al., 2003). Children with ADHD have been found to have great theta/beta power on electroencephalogram (EEG). The U.S. Food and Drug Administration (FDA) approved the Neuropsychiatric EEG-Based ADHD Assessment Aid to be used by a clinician as confirmatory support or to pursue further testing after an evaluation for ADHD, in a child aged 6 to 17, but subsequent reviews suggested more research was needed before it could be recommended as a routine test for ADHD (Loo and Makig, 2012).

OCD as a part of the spectrum of neurobehavioral manifestations in TS is well accepted (Rapoport, 1988; Towbin, 1988; Black, 1992; Stein, 2002; Grant, 2014; Pauls et al., 2014). OCD, with an estimated lifetime prevalence of 2% to 3% (Sasson et al., 1997; Snider and Swedo, 2000) and an incidence of 0.55 per 1000 person years (Nestadt et al., 1998) is one of the most frequent causes of disability (Jenike et al., 2004). It may occur alone without other features of TS (Micallef and Blin, 2001). The instrument used most frequently to measure the severity of OCD is the Yale-Brown Obsessive Compulsive Scale (Scahill et al., 1997). A distinction should be made between obsessive-compulsive symptoms or traits, obsessive-compulsive personality disorder, and OCD. Obsessions are characterized by intense, intrusive thoughts, such as concerns about bodily wastes and secretions; unfounded fears; need for exactness, symmetry, evenness, and neatness; excessive religious concerns; perverse sexual thoughts; and intrusions of words, phrases, or music. Compulsions consist of subjective urges to perform meaningless and irrational rituals, such as checking, counting, cleaning, washing, touching, smelling, hoarding, and rearranging. Leckman and colleagues (1994) have drawn attention to the frequent occurrence of the "just right" perception in patients with OCD and TS. Although obsessional slowness accounts for some of the school problems experienced by TS patients, cognitive slowing (bradyphrenia) is also a contributing factor (Singer, Schuerholz et al., 1995). Patients with OCD can usually be divided into those with a predominantly cognitive form (in which an idea is followed by a ritual) and those with a sensorimotor type (in which a physical sensation is followed by a movement). In contrast to primary OCD, in which the symptoms relate chiefly to hygiene and cleanliness, the obsessive symptoms associated with TS usually involve concerns with symmetry, violent aggressive thoughts, forced touching, fear of harming self or others, and need for

saying or doing things "just right" (Eapen et al., 1997b). A principal-components factor analysis of 13 categories that are used to group types of obsessions and compulsions in the Yale-Brown Obsessive Compulsive Scale symptom checklist identified the obsessions and checking and the symmetry and ordering factors as particularly common in patients with tic disorders (Leckman, Grice et al., 1997). Miguel and colleagues (2000) showed that patients who have OCD associated with TS tend to have more bodily sensations occurring either before or during the patient's performance of the repetitive behaviors and mental sensations, including urge only, energy release (mental energy that builds up and needs to be discharged), and "just right" perceptions. Cognitive inflexibility manifested by impaired task-switch ability in patients with OCD has been suggested to be due to "imbalance in brain activation between dorsal and ventral striatal circuits" (Gu et al., 2008). Studies have found that OCD patients exhibited excessive habits that were associated with hyperactivation of the caudate nucleus (Gillan et al., 2014).

In addition to an idiopathic sporadic or familial disorder and TS, OCD has been reported to occur as a result of a variety of lesions in the frontal-limbic-subcortical circuits (Berthier et al., 1996; Kwak and Jankovic, 2002; Voon, 2004). Although both ADHD and OCD are regarded as integral findings of the syndrome, only OCD has been shown to be genetically linked to TS (Alsobrook and Pauls, 1997). A pathogenic link between TS and OCD is also suggested by the finding in one study that 59% of 54 patients with OCD had a lifetime history of tics, and 14% fulfilled the criteria for TS during the 2- to 7-year follow-up (Leonard, 1992). Alsobrook and Pauls (2002) identified four significant factors: (1) aggressive phenomena (e.g., kicking, temper fits, argumentativeness), (2) purely motor and phonic tic symptoms, (3) compulsive phenomena (e.g., touching of others or objects, repetitive speech, throat clearing), and (4) tapping and absence of grunting, which accounted for 61% of the phenotypic symptom variance in TS probands and their first-degree relatives.

An important link between motor and behavioral manifestations of TS is the loss of impulse control. Many TS patients suffer from poor impulse control, disinhibition of aggression and emotions, and obsessive thoughts that may dictate their actions. Indeed, many behavioral symptoms of TS, including some complex tics, coprolalia, copropraxia, and many behavioral problems, can be explained by loss of normal inhibitory mechanisms (disinhibition) manifested by poor impulse control. It is as though the TS patients have lost their ability to suppress vestiges of primitive behavior. Poor impulse control might also explain the inability to control anger, as a result of which many patients have frequent and sometimes violent temper outbursts and rages. Rarely, TS patients exhibit inappropriate sexual aggressiveness and antisocial, oppositional, and even violent, unlawful, or criminal behavior. TS, indeed, serves as a model medical disorder that can predispose one to engage in uncontrollable and offensive behaviors that are misunderstood by the law-abiding community and the legal justice system (Jankovic et al., 2006). The social and legal aspects of TS patients have yet to be investigated, but there is growing concern regarding media misrepresentation that attributes violent criminal behavior in certain individuals to TS. Although TS should not be used as an excuse to justify unlawful or criminal

behaviors, studies are needed to determine whether TS-related symptoms and neurobehavioral comorbidities predispose TS patients to engage in such behaviors. Often, the avolitional nature of behaviors in response to involuntary internal thought and emotional patterns is supported by the subsequent remorse and lack of secondary gain. This suggests that the preponderance of unlawful acts committed by TS patients are not premeditated but may result from a variety of TS-related mechanisms such as poor impulse control, OCD associated with addictive behavior (e.g., drugs, alcohol, gambling), attention deficit disorder (ADD), distractibility (e.g., motor vehicle accidents), and coprolalia. Furthermore, there is no evidence that anti-TS medications increase risk for criminal behavior and, in fact, anti-ADHD medications have been found to reduce the risk for criminality (Lichtenstein et al., 2012). A previous study (Comings and Comings, 1987) compared conduct in 246 TS patients to that of controls for behaviors such as lying, stealing, fighting or inability to stop fighting, violence against animals, physically attacking peers or parents, vandalism, running away from home, starting fires, poor temper control, alcohol and drug abuse, and other misdemeanors. A group of 35% of TS patients had a conduct score higher than 13, significantly greater than the 2.1% of controls with high scores ($P < 0.0005$). All behaviors with the exception of running away from home and trouble with the law occurred at a significantly greater rate in TS patients. Although no difference was found for the law variable, TS patients were significantly more likely to vandalize ($P < 0.0005$), fight ($P < 0.0005$), abuse drugs or alcohol ($P < 0.003$), and steal ($P < 0.015$). An interesting finding in this study was that certain behaviors, such as starting fires, shouting, and physically attacking, were significantly greater only in TS patients with comorbid ADD, supporting the well-established association of ADD in conduct disorder (Blair et al., 2014). It was estimated from this study that 10% to 30% of conduct disorder cases in non-economically disadvantaged children may be attributed to a possible TS gene. In a more recent study, however, TS accounted for 2% of all cases that were referred for forensic psychiatric investigation in Stockholm, Sweden, between 1990 and 1995; 15% of the subjects had ADHD, 15% had PDD, and 3% had Asperger syndrome (Siponmaa et al., 2001). Scandinavian investigators also failed to find increased criminal behavior among schizophrenics or patients with bipolar disorder and general population (Fazel et al., 2010). There is no evidence that TS patients carry mutations in genes that have been implicated in violent behavior, such as monoamine oxidase A low-activity genotype or the *CDH13* gene (coding for neuronal membrane adhesion protein) (Tiihonen et al., 2014).

Focal frontal lobe dysfunction, demonstrated in TS by various functional and imaging studies, has been associated with impulsive subtype of aggressive behavior (Brower and Price, 2001). It has been postulated that impulse disorders stem from exaggerated reward-, pleasure-, or arousal-seeking brain centers, resulting in failure of inhibition. Animal studies of rats with lesions of the nucleus accumbens core, the brain region that is noted for reward and reinforcement, showed that the lesioned rats preferred small, immediate rewards over larger, delayed rewards (Cardinal et al., 2001). In addition to the ventromedial prefrontal cortices, lesions in the amygdala have also been known to result in altered

decision-making processes and a disregard for future consequences (Bechara et al., 2000).

One of the most distressing symptoms of TS is an SIB, which has been reported in up to 53% of all patients (Robertson, 1989; Robertson et al., 1990). A common form of SIB is damage of skin by biting, scratching, cutting, engraving, or hitting, particularly in the eye and throat (compulsions), often accompanied by an irresistible urge (obsession) (Jankovic et al., 1998) (Videos 15.16, 15.17). In some patients, SIB can be life-threatening, hence the term “malignant” TS (Cheung et al., 2007). The mechanism of SIB is not well understood, but animal model may shed some light on this very important behavioral disorder that may accompany TS. A mouse with genetic deletion of *Sapap3*, a gene that codes for postsynaptic scaffolding protein at excitatory striatal synapses, has been proposed as a possible model of OCD because its phenotype is characterized by excessive compulsive grooming resulting in SIB, such as facial hair loss and skin lesions (Welch et al., 2007). The similarity of this behavior to OCD is further supported by the observation that the mice markedly improved after treatment with a selective serotonin reuptake inhibitor (SSRI). Thus, SIB appears to be related to OCD, which has treatment implications. Besides OCD, SIB also correlates with impulsivity (Mathews et al., 2004). Conduct disorders and problems with discipline at home and in school are recurrent themes during discussions of behavioral problems with TS families. The inability to suppress or “edit” intentions because of a “dysfunctional intention editor” has been proposed as one of the chief reasons for poor impulse control in patients with TS (Baron-Cohen et al., 1994). ●

The TS gene(s) may, in addition to tics, ADHD, and OCD, express itself in a variety of behavioral manifestations, including learning and conduct disorders, schizoid and affective disorders, antisocial behaviors, oppositional defiant disorder, anxiety, depression, conduct disorder, severe temper outbursts, rage attacks, impulse control problems, inappropriate sexual behavior, and other psychiatric problems (Comings, 1987; Robertson, 2000). Personality disorder and depression have been reported in 64% of patients with TS (Robertson et al., 1997). Whether these behavioral problems indeed occur with higher frequency in TS patients and whether they are pathogenically linked to TS are debatable (Comings and Comings, 1988a; Pauls et al., 1988).

Besides comorbid behavioral conditions, TS has been reported to be frequently associated with migraine headaches. In one study, 26.6% of TS patients, with a mean age of 11.9 years, exhibited migraine headaches (Barabas et al., 1984). We found migraine headaches in 25 carefully screened TS patients at a significantly greater rate than the estimated 11% to 13% in the general adult population ($P < 0.0001$) and the general pediatric population ($P < 0.04$) (Kwak et al., 2003). This compares to 4.0% to 7.4% in the general population of school-aged children. In a study of 109 TS patients, Ghosh and associates (2012) found either migraine headaches or tension-type headaches in 55% of the patients; the rate of migraine headache within the TS group was found to be four times greater than that of the general pediatric population. Unfortunately, the interpretation of the data is difficult because the investigators did not administer the same questionnaire to a control, age-matched population without TS. This limitation, coupled with the selected

Video 15.16 Self-injurious behavior.

Video 15.17 Self-injurious behavior.

population of patients from a tertiary referral center, may not make the findings generalizable.

The Tourette International Consortium Database (Free-man et al., 2000), which included information on 3500 patients with TS collected from 64 centers from around the world, showed that 12% of patients with TS had no other disorders; ADHD was seen in 60%, symptoms of OCD in 59%, anger control problems in 37%, sleep disorder in 25%, learning disability in 23%, mood disorders in 20%, anxiety disorders in 18%, and SIB in 14%.

Pathogenesis

Neurophysiology

Although the pathogenic mechanisms of TS are still unknown, the weight of evidence supports an organic rather than psychogenic origin, probably involving the basal ganglia circuitry (Leckman, Peterson et al., 1997; Palumbo et al., 1997; Jankovic, 2001a; Leckman, 2002; Berardelli et al., 2003; Albin and Mink, 2006; Worbe et al., 2012; Gunduz and Okun, 2016) (Fig. 15.2). Despite the observation that some tics may be voluntary, at least in part, physiologic studies suggest that tics are not mediated through normal motor pathways used for willed movements (Obeso et al., 1982). Using back-averaging techniques, Obeso and colleagues (1982) observed normal Bereitschaftspotential in six subjects who voluntarily simulated tic-like movements, but no such premovement potential was noted in association with an actual tic. The common absence of premotor potentials in simple motor tics suggests that tics are truly involuntary or that they occur in response to some external cue (Papa et al., 1991). Karp and colleagues (1996), however, documented premotor negativity in 2 of 5 patients with simple motor tics. In another study Bereitschaftspotential was identified before tics in 6 in 14 (43%) of TS patients (Van der Salm et al., 2012). Although the investigators could not correlate the presence of Bereitschaftspotential with the premonitory sensation, the physiology of the premovement phenomenon requires further studies. Human physiologic

recordings have revealed low frequency (1–10 Hz), the centro-median parafascicular (CM-PF) activity during tics, and modulations in beta rhythms over the motor cortex (Shute et al., 2016).

Transmagnetic stimulation used to study cortical excitability in 11 TS patients found evidence of motorcortical disinhibition at rest (Heise et al., 2010). Using optogenetics in mice repeated stimulation of orbitofrontal cortex (OFC)-ventromedial striatum (VMS) (5 minutes per day for 5 days) generated a progressive increase in grooming, a behavior considered analogous to human OCD (Ahmari et al., 2013). This behavior was reversed by chronic treatment with fluoxetine. Thus, increased activity at OFC-VMS may lead to dysregulation of cortico-striato-thalamo-cortical circuit and “multiple downstream events including (i) plasticity in downstream structures such as thalamus and prefrontal cortex and increased motivational saliency mediated by the ventral tegmental area.” This is consistent with the findings from clinical studies showing “efficacy of ventral capsule-ventral striatum deep brain stimulation (DBS) in OCD, which is thought to act via inhibition of OFC hyperactivity.” Further studies are needed to elucidate the pathophysiologic mechanisms of OCD and OCD subtypes (Rauch and Carlezon, 2013).

Conventional neurophysiologic investigations have found that TS patients have defective inhibitory mechanisms, as is suggested by the increased duration of the late response of the blink reflex and reduced inhibition at paired pulse testing (Smith and Lees, 1989; Berardelli et al., 2003). TS patients also have exaggerated audiogenic startle response (Gironell et al., 2000). About 20% of patients with TS have exaggerated startle responses, which may fail to habituate with repetition (Stell et al., 1995).

As was noted before, fMRI showed decreased neuronal activity during periods of suppression in the ventral globus pallidus, putamen, and thalamus and increased activity in the right caudate nucleus, right frontal cortex, and other cortical areas that are normally involved in the inhibition of unwanted impulses (prefrontal, parietal, temporal, and cingulate cortices) (Peterson et al., 1998a). In another

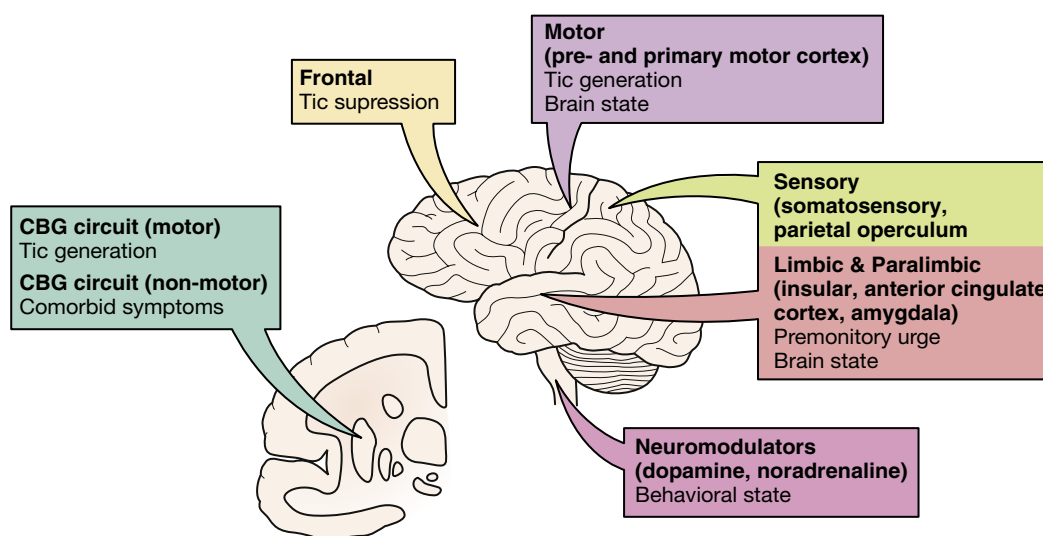


Fig. 15.2 Brain pathways involved in tic disorders. CBG, Cortico–basal ganglia circuit. (Yael D, Vinner E, Bar-Gad I. Pathophysiology of tic disorders. *Mov Dis.* 2015;30[9]:1171–1178.)

study of three patients with TS, fMRI showed marked reduction or absence of activity in secondary motor areas while the patient attempted to maintain a stable grip-load force control (Serrien et al., 2002). The authors interpreted the findings as an ongoing activation of the secondary motor reflecting patients' involuntary urges to move. In a study of children with ADHD, fMRI showed increased frontal activation and reduced striatal activation on various tasks and an enhancement of striatal function after treatment with methylphenidate (Vaidya et al., 1998). fMRI studies show decreased neuronal activity during periods of suppression in the ventral GP, putamen, and thalamus and increased activity in the caudate, frontal cortex, and other cortical areas that are normally involved in the inhibition of unwanted impulses (prefrontal, parietal, temporal, and cingulate cortical areas) (Peterson, 2001). By using event-related fMRI in 10 patients with TS, a brain network of paralimbic areas such as anterior cingulate and insular cortex, SMA, and parietal operculum was identified that predominantly activated before tic onset, whereas at the beginning of tic action, significant fMRI activities were found in sensorimotor areas, including superior parietal lobule bilaterally and cerebellum (Bohlhalter et al., 2006). Resting-state functional connectivity MRI (rs-fcMRI) in 33 adolescents with TS, Church and colleagues (2009) found anomalous connections primarily in the frontoparietal network, suggesting widespread immature functional connectivity, particularly in regions related to adaptive online control. Functional immaturity and global functional disorganization of cortico-basal ganglia networks was found in another study using fMRI (Worbe et al., 2012). Using microinjections of bicuculline into the sensorimotor putamen as model of tics (predominantly in the orofacial region) in primates, the investigators found that 64% of the recorded cerebellar cortex neurons exhibited increases in activity in relationship to the tics (McCairn et al., 2013). Furthermore, the occurrence of tic movement was most closely associated with local field potential spikes in the cerebellum and primary motor cortex, indicating cerebellar involvement in the pathophysiology of tics. It is, however, doubtful that the orofacial movements produced by the bicuculline injections represent a true example of motor tic.

Transcranial magnetic stimulation studies have demonstrated a shortened cortical silent period and defective intracortical inhibition (determined in a conditioning test paired-stimulus paradigm) in patients with TS (Orth et al., 2005, 2008) and OCD (Greenberg et al., 1998), thus providing a possible explanation for intrusive phenomena. Subsequent studies using the same technique have demonstrated that patients with tic-related OCD have more abnormal motor cortex excitability than do OCD patients without tics (Greenberg et al., 2000). Transcranial magnetic stimulation studies have also demonstrated that TS children have a shorter cortical silent period but that their intracortical inhibition was not different from that of controls, although intracortical inhibition is reduced in children with ADHD (Moll et al., 2001). There is evidence of additive inhibitory deficits, as demonstrated by reduced intracortical inhibition and a shortened cortical silent period in children with TS and comorbid ADHD. In another study, ADHD more than tics were associated with short-interval intracortical inhibition (Gilbert et al., 2004). Both short-interval intracortical inhibition and short-interval afferent inhibition, modulated by nicotinic receptors, were

reduced in 8 patients with TS (aged 24–38 years) compared with 10 matched healthy controls (Orth et al., 2005). Comprehensive discussion of the neuroscience of ADHD is beyond the scope of this chapter, but the reader is referred to some reviews of this topic (Castellanos and Tannock, 2002). In addition to repetitive transcranial magnetic stimulation, transcranial electric stimulation targeting supplementary motor area or the temporo-parietal junction is being investigated as a treatment option in TS (Kleimaker et al., 2020).

Sleep studies have provided additional evidence that some tics are truly involuntary (Jiménez-Jiménez et al., 2020). Polysomnographic studies in 34 TS patients recorded motor tics in various stages of sleep in 23 patients and phonic tics in 4 patients (Glaze and Frost, 1983; Jankovic and Rohaidy, 1987). Additional sleep studies have suggested that some patients with TS have alterations of arousal, decreased percentage (up to 30%) of stage 3/4 (slow wave) sleep, decreased percentage of REM sleep, paroxysmal events in stage 4 sleep with sudden intense arousal, disorientation and agitation, restless legs syndrome (RLS), and periodic leg movement in sleep (Voderholzer et al., 1997; Chokroverty and Jankovic, 1999; Picchetti et al., 1999). RLS has been reported to be present in about 10% of patients with TS and in 23% of parents (Lesperance et al., 2004). In this regard, it is of interest that in a study in which 14 single-nucleotide polymorphisms were typed spanning the 3 genomic loci associated with RLS in 298 TS trios, 322 TS cases (including 298 probands from the cohort of TS trios), and 290 control subjects, the same variant of the gene BTBD9 that increases the risk for RLS also increases the risk for TS without OCD or ADD ("pure" TS) (Rivière et al., 2009). Other sleep-related disorders that are associated with TS include sleep apnea, enuresis, sleepwalking and sleep talking, nightmares, myoclonus, bruxism, and other disturbances (Rothenberger et al., 2000; Hanna and Jankovic, 2003).

Neuroimaging

Although standard anatomic neuroimaging studies in TS are unremarkable, by using special volumetric, metabolic, blood flow, ligand, and functional imaging techniques, several interesting findings have been reported that have strong implications for the pathophysiology of TS (Peterson, 2001; Albin and Mink, 2006; Frey and Albin, 2006). Careful volumetric MRI studies have suggested that the normal asymmetry of the basal ganglia is lost in TS (Peterson et al., 1993; Singer et al., 1993; Peterson, 2001). In one study, the normal left > right asymmetry (Singer et al., 1993) in the volume in the right anterior brain, right caudate, and right pallidum was reversed in TS subjects (Castellanos et al., 1996). Caudate volumes have been reported to correlate significantly and inversely with the severity of tic and OCD in early adulthood (Bloch et al., 2005). The volumetric studies, however, have not always produced consistent results (Moriarty et al., 1997). In another volumetric MRI study, Frederickson and colleagues (2002) found evidence of smaller gray matter volumes in the left frontal lobes of patients with TS, further supporting the findings of loss of normal left > right asymmetry. Quantitative MRI studies have found a subtle, but possibly important, reduction in the volume of caudate nuclei in patients with TS. In 10 pairs of monozygotic twins, the right caudate was smaller in the more severely affected individuals, providing evidence for the role of environmental events in the

pathogenesis of TS (Hyde et al., 1995). In contrast, the corpus callosum has been found to be larger in children with TS than in normal controls (Baumgardner et al., 1996). Subsequent study showed that this finding was gender-related and was present only in boys with TS (Mostofsky et al., 1999). An MRI–diffusion tensor imaging (DTI) study of monozygotic twins showed that the mean fractional anisotropy values were significantly lower, particularly in the posterior portion of the corpus callosum in the twin affected with TS (Cavanna et al., 2010). Using voxel-based morphometry and high-resolution MRI in 31 TS patients, increased gray matter was found in the left mesencephalon compared with 31 controls (Garraux et al., 2006). This finding, however, could not be replicated in a smaller study of 14 boys with TS using the same technique (Ludolph et al., 2006). This latter study found increased gray matter volumes in bilateral ventral putamen and regional decreases in gray matter volumes in the left hippocampus gyrus. The difference was attributed to younger mean age in the latter study compared with the previous study (12.5 versus 32 years). MRI-DTI used to investigate the structural integrity of the basal ganglia and thalamus in 23 children with TS found increased mean water diffusivity bilaterally in the putamen and decreased anisotropy in the right thalamus, indicating impairment of white matter integrity in the fronto-striatal-thalamic circuit at a microstructural level (Makki et al., 2008). Using tractography of the fronto-striato-thalamic circuit, the same group showed that TS patients had significantly lower probability of connection between caudate nucleus and anterior-dorsolateral-frontal cortex on the left and that OCB was negatively associated with connectivity score of the left caudate and anterior dorsolateral frontal cortex, and was positively associated with connectivity score for the subcallosal gyrus and for the lentiform nucleus (Makki et al., 2009). Additional imaging studies have identified frontal and parietal cortical thinning, most prominent in ventral portions of the sensory and motor homunculi in patients with TS (Sowell et al., 2008). Using cortical thickness estimation and voxel-based analysis of T1- and diffusion-weighted structural MRI in a study of 60 adult patients with TS and 30 age- and gender-matched control subjects, Worbe and colleagues (2010) found that in patients with simple tics, cortical thinning was mostly found in primary motor regions whereas in patients with simple and complex tics, thinning extended into larger premotor, prefrontal, and parietal regions. In patients with associated OCDs, there was a trend for reduced cortical thickness in the anterior cingulate cortex with additional alteration in hippocampal morphology. Draganski and colleagues (2010) examined 40 adults with TS and 40 age- and gender-matched healthy controls. There was a relative gray matter volume reduction in patients with TS, particularly in the orbitofrontal, anterior cingulate, and ventrolateral prefrontal cortices bilaterally. In addition, the investigators found cortical thinning that extended into the limbic mesial temporal lobe. Prefrontal cortical thickness reduction correlated negatively with tic severity, whereas volume increase in primary somatosensory cortex depended on the intensity of premonitory sensations. These results suggest that TS represents a developmental disorder with the symptom severity–related gray matter volume increase as evidence of ongoing structural plasticity. Despite reports of some abnormalities on imaging studies, these findings could not be confirmed in a cohort of children with medication-free

TS (Jeppesen et al., 2014). Nevertheless, abnormal development in TS is supported by other imaging studies that have found abnormal structural pattern of cortical sulci that correlated with severity of clinical symptoms. Using 3-tesla structural neuroimaging, the investigators compared sulcal depth, opening, and length and thickness of sulcal gray matter in 52 adult patients with TS and 52 matched controls (Muellner et al., 2015). Patients with TS had lower depth and reduced thickness of gray matter in the precentral and postcentral and superior, inferior, and internal frontal sulci. A whole-brain analysis of cortical (gray matter) thickness in 29 children and young adults with TS investigated the association between gray matter thickness and “premonitory sensory phenomena” (Draper et al., 2016). They found this phenomenon is inversely associated with gray matter thickness measurements within the insula and sensorimotor cortex. Gray matter thickness was significantly reduced in these areas in individuals with TS relative to a closely age- and gender-matched group of typically developing individuals.

Dopaminergic hyperfunction (Albin et al., 2003), possibly as a result of overproduction of synapses in mid-childhood (Giedd et al., 1999), might be associated with increased striatal volume in childhood that may be lost in adulthood. Positron emission tomography (PET) has shown variable rates of glucose usage in the basal ganglia compared with controls. In one study, [¹⁸F]fluorodeoxyglucose PET has shown evidence of increased metabolic activity in the lateral premotor and supplementary motor association cortices and in the midbrain (pattern 1), and decreased metabolic activity in the caudate and thalamic areas (limbic basal ganglia–thalamocortical projection system) (pattern 2) (Eidelberg et al., 1997). Pattern 1 is reportedly associated with tics, and pattern 2 correlates with the overall severity of TS. In a follow-up study, involving 12 TS adult patients (untreated for longer than 2 years) and 12 controls, the investigators found a TS-related metabolic pattern that was characterized by increased premotor cortex and cerebellum activity and reduced resting activity of the striatum and orbitofrontal cortex (Pourfar et al., 2011). They also provided evidence for an OCD-related pattern that was characterized by reduced activity of the anterior cingulate and dorsolateral prefrontal cortical regions associated with relative increases in primary motor cortex and precuneus. This pattern significantly correlated with the severity of the OCD symptoms.

In contrast to dystonia, which is characterized by lentiform nucleus–thalamic metabolic dissociation, attributed to overactivity of the direct striatopallidal inhibitory pathway, the pattern of TS is characterized by concomitant metabolic reduction in striatal and thalamic function. The authors suggested that this pattern can be explained by a reduction in the indirect pathway resulting in reduction in subthalamic nucleus (STN) activity. This is in part consistent with another study that found evidence of increased activation in the direct pathway, but the activity in the prefrontal cortex and STN has been found to be increased presumably as a result of compensatory activation (Baym et al., 2008). Using event-related [¹⁵O]H₂O PET combined with time-synchronized audiotaping and videotaping of six patients with TS, Stern and colleagues (2000) found increased activity in the sensorimotor, language, executive, paralimbic, and frontal-subcortical areas that were temporarily related to the motor and phonic tics and the irresistible urge that precedes these behaviors. Using similar technique Lerner and associates (2007) found

robust activation of cerebellum, insula, thalamus, and putamen during tic release. Rauch and colleagues (1997) showed bilateral medial temporal (hippocampal/parahippocampal) activation on PET in patients with OCD compared with normal controls and absence of activation of inferior striatum, seen in normal controls. Various neuroimaging studies have also demonstrated moderate reduction in the size of the corpus callosum, basal ganglia (particularly caudate and GP), and frontal lobes (Filipek et al., 1997) and striatal hypoperfusion (Vaidya et al., 1998) in patients with ADHD.

An autopsy study of three TS brains found consistent increases in dopamine transporter (DAT), dopamine D2 receptor, D1 and α -2A density, suggesting that dopaminergic hyperfunction in the frontal lobe may play a role in the pathophysiology of TS (Yoon et al., 2007). Another pathologic study showed a marked increase in total number of neurons in the globus pallidus internus (GPi) and decreased number in the globus pallidus externus (GPe) and in the caudate nucleus of brains of patients with TS (Kalanithi et al., 2005). Furthermore, an increased number and proportion of the GPi neurons were positive for the calcium-binding protein parvalbumin in tissue from TS subjects, whereas lower densities of parvalbumin-positive interneurons were observed in both the caudate and putamen of TS subjects. These abnormalities have been interpreted as indicating a developmental defect in the migration of some GABAergic neurons. In a follow-up study of five brains from TS patients there was a 50% to 60% decrease of both parvalbumin (PV)+ and choline acetyltransferase (ChAT)+ cholinergic interneurons in the striatum that was thought to contribute to an impaired cortico-thalamic control of striatal neuron firing in TS (Kataoka et al., 2010).

An abnormality in the GABAergic system in TS has gained more support based on functional imaging studies. For example, in a study of 11 patients with TS and 11 healthy controls, PET scan using [^{11} C]flumazenil, and structural MRI provided evidence of decreased binding of GABAA receptors in TS patients bilaterally in the ventral striatum, GP, thalamus, amygdala, and right insula and increased binding in the bilateral substantia nigra, left periaqueductal gray, right posterior cingulate cortex, and bilateral cerebellum (Lerner et al., 2012).

Neurochemistry

An alteration in the central neurotransmitters has been suggested chiefly because of relatively consistent responses to modulation of the dopaminergic system (Harris and Singer, 2006). Dopamine antagonists and depleters generally have an ameliorating effect on tics, whereas drugs that enhance central dopaminergic activity exacerbate tics (Jankovic and Rohaidy, 1987; Jankovic and Orman, 1988). Low cerebrospinal fluid homovanillic acid, coupled with a favorable response to dopamine receptor-blocking drugs, has been interpreted as evidence in support of the notion that tics and TS are due to supersensitive dopamine receptors (Singer, 2000). Postmortem binding studies of dopamine receptors, however, have failed to provide support for this hypothesis (Singer, 2000).

Neurochemical studies of TS have been hampered by the lack of available postmortem brain tissue. Biochemical abnormalities in the few postmortem brains that have been

studied include low serotonin, low glutamate in the medial GP, and low cyclic adenosine monophosphate (AMP) in the cortex (Singer, 2000). Haber and Wolfer (1992) reported that in a blind rating of five TS brains, three had low dynorphin immunoreactivity in the ventral portion of the medial GP. A defect in tryptophan oxygenase in TS has been proposed by Comings (1990), who analyzed 1400 blood samples from patients with TS or ADHD and their relatives and controls; he found decreased platelet serotonin and low blood tryptophan levels in TS patients and their parents. In support of the "tryptophan hypothesis" is a study that used alpha-[(^{11} C)methyl-L-tryptophan (AMT) PET to assess global and focal brain abnormalities of tryptophan metabolism in 26 children with TS and nine controls. The findings indicate that tryptophan uptake is significantly decreased in the dorsolateral prefrontal cortex and increased in the thalamus of TS patients (Behen et al., 2007). There is growing support for the association of genetic variation in the serotonin transporter gene, particularly the polymorphic region known as 5-HTTLPR, in patients with OCD (Walitza et al., 2014).

One intriguing hypothesis, supported partly by the increased 3H-mazindol binding to the presynaptic dopamine uptake carrier sites, suggests that TS represents a developmental disorder resulting in dopaminergic hyperinnervation of the ventral striatum and the associated limbic system (nucleus accumbens) (Singer et al., 1991). Using [^{11} C]raclopride PET and amphetamine stimulation, Singer and colleagues (2002) found evidence for increased dopamine release in the putamen of patients with TS. They postulate that in TS, there is increased activity of the DAT leading to increased dopamine concentration in the dopamine terminals and stimulus-dependent increase in dopaminergic transmission. Support for this hypothesis has been provided by the imaging studies of Albin and colleagues (2003). The authors used PET with the vesicular monoamine transporter type 2 ligand [^{11} C]dihydro-tetrabenazine that binds to type 2 vesicular monoamine transporter (VMAT2) to quantify striatal monoaminergic innervation in patients with TS ($n = 19$) and control subjects ($n = 27$). With voxel-by-voxel analysis, the investigators found increased [^{11} C]dihydro-tetrabenazine binding in the ventral striatum (right > left) in patients with TS compared with age-matched controls. However, a subsequent PET study involving 33 adults with TS and using not only [^{11} C]dihydro-tetrabenazine but also [^{11} C]methylphenidate, a ligand for DAT, they found no differences between subjects with TS and controls (Albin et al., 2009). In a study of 8 patients with TS and 8 controls [^{11} C]FLB 457 PET in conjunction with an amphetamine challenge used to evaluate extrastriatal D2/D3 receptor binding and DA release, TS patients showed decreased [^{11} C]FLB 457 binding potentials bilaterally in cortical and subcortical regions outside the striatum, including the cingulate gyrus, middle and superior temporal gyrus, occipital cortex, insula, and thalamus (Steeves et al., 2010). Furthermore, amphetamine challenge induced widespread increased DA release in TS patients, which extended more anteriorly to involve anterior cingulate and medial frontal gyri. The authors suggested that "reductions in D2/D3 receptor binding in both frontal cortex and thalamus are consistent with data demonstrating similar abnormalities of D2/D3 binding in TS patients using a different PET ligand." A postmortem examination

of two brains of patients with typical childhood-onset TS and one with adult-onset tics showed that the prefrontal cortex rather than the striatum showed most abnormalities, including increased D2 receptor protein, and increases in DAT, VAMP2, and α -2A (Minzer et al., 2004).

Although this idea is highly speculative, it is possible that the genetic defect in TS somehow interferes with the normal regulation of the neuronal progenitor cells during development, thus resulting in the increased innervation of the ventral striatum (Ikonomidou et al., 1999; Itoh et al., 2001; Hanashima et al., 2004). This implies that the genetic defect somehow interferes with the programmed cell suicide that is needed to control cell proliferation in normal development and growth. The ventral striatum is the portion of the basal ganglia that is anatomically and functionally linked to the limbic system. The link between the basal ganglia and the limbic system might explain the frequent association of tics and complex behavioral problems, and a dysfunction in the basal ganglia and the limbic system seems to provide the best explanation for the most fundamental behavioral disturbance in TS, namely, loss of impulse control and a state of apparent "disinhibition." The notion that deficits in inhibitory functions are at the core of the clinical phenotype associated with TS is supported by studies by Baron-Cohen and colleagues (1994) showing that patients with TS are not able to appropriately edit their intentions and by Swerdlow and colleagues (1996) showing that TS patients demonstrate deficits on the visuospatial priming tasks.

Functional neuroimaging studies have been used to aid in the understanding of neurotransmitter and receptor alterations in TS. Using [^{123} I] β -carboxymethoxy-3 β -(4-iodophenyl) tropane (CIT) single-photon emission computed tomography (SPECT) scans, Malison and colleagues (1995) demonstrated a mean of 37% increase in binding of this DAT ligand in the striatum in five adult patients with TS compared with age-matched controls. In contrast, Heinz and colleagues (1998) found no difference in [^{123} I] β -CIT binding in the midbrain, thalamus, or basal ganglia between 10 TS patients and normal control subjects. There was, however, a significant negative correlation between the severity of phonic tics and β -CIT binding in the midbrain and thalamus. In another study involving 12 TS adult patients, β -CIT scans showed evidence of increased DAT binding (Müller-Vahl et al., 2000). Combining SPECT and MRI, Wolf and colleagues (1996) found 17% greater binding of IBZM, a D2 receptor ligand, in the caudate (but not putamen) nucleus in five of the more affected monozygotic twins who were discordant for TS. It is important to note, however, that two of the five subjects were taking neuroleptics for up to 6 weeks before the SPECT studies. These findings, if confirmed by other studies of neuroleptic-naïve patients, support the notion that the presynaptic dopamine function is enhanced in TS. This might, in turn, lead to a reduced inhibitory pallidal output to the mediodorsal thalamus. The observation that in patients with Parkinson's disease (PD) the severity of childhood-onset tics was not influenced by the development of parkinsonism or by its treatment with levodopa, however, argues against the role of dopamine in the pathogenesis of TS symptoms (Kumar and Lang, 1997a). This is supported by the results of PET ligand studies showing normal D2 receptor density (Turjanski et al., 1994). Furthermore, Meyer and colleagues (1999) used PET imaging

of (+)- α -[^{11} C]dihydrotetrabenazine to determine the density of VMAT2, a cytoplasm-to-vesicle transporter that is linearly related to monoaminergic nerve terminal density unaffected by medications, in 8 TS patients and 22 controls. This study showed no significant difference in terminal density between patients and controls, thus failing to provide support for the concept of increased striatal innervation. However, these studies do not exclude the possibility of abnormal regulation of dopamine release and uptake. Subsequent study involving 19 adult patients with TS showed that the [^{11} C] dihydrotetrabenazine-binding potential is significantly increased, thus supporting the notion that striatal monoaminergic innervation is increased in the ventral striatum (right > left) of TS patients (Albin et al., 2003). The results of this study contrasted with previous findings of 30% to 40% increase in DAT (Müller-Vahl et al., 2000; Singer et al., 2001). Furthermore, in a small sample of TS patients, PET studies have demonstrated a 25% increase in accumulation of fluoro-dopa in the left caudate ($P = 0.03$) and a 53% increase in the right midbrain ($P = 0.08$) (Ernst et al., 1999). These findings indicate possible dopaminergic dysfunction in the cells of origin and in the dopaminergic terminals, suggesting increased activity of dopa decarboxylase.

Functional imaging has provided insights not only into the mechanisms of TS, but also ADHD. In 53 adults with ADHD (without tics) compared with 44 healthy controls, a reduction in dopamine markers was demonstrated, using ^{11} C-cocaine as a marker for DAT and ^{11} C-raclopride, a ligand for D2/D3 receptors (Vokow et al., 2009).

Despite some limitations and inconsistencies, the imaging ligand and biochemical studies provide support for the hypothesis that the corticostriatal-thalamic-cortical circuit plays an important role in the pathogenesis of TS and related disorders (Witelson, 1993; Peterson, 2001). The dorsolateral prefrontal circuit, which links Brodmann areas 9 and 10 with the dorsolateral head of the caudate, appears to be involved with executive functions (manipulation of previously learned knowledge, abstract reasoning, organization, verbal fluency, and problem solving; it is closely related to intelligence, education, and social exposure) and motor planning. An abnormality in this circuit has been implicated in ADHD. The lateral orbitofrontal circuit originates in the inferior lateral prefrontal cortex (area 10) and projects to the ventral medial caudate. An abnormality to this circuit is associated with personality changes, mania, disinhibition, and irritability. Last, the anterior cingulate circuit arises in the cingulate gyrus (area 24) and projects to the ventral striatum, which also receives input from the amygdala, hippocampus, medial orbitofrontal cortex, and entorhinal and perirhinal cortex. A variety of behavioral problems, including OCD, may be linked to an abnormality in this circuit.

Reduced metabolism or blood flow to the basal ganglia, particularly in the ventral striatum, most often in the left hemisphere, has been demonstrated in the majority of the studies involving TS subjects. These limbic areas are thought to be involved in impulse control, reward contingencies, and executive functions, and these behavioral functions appear to be abnormal in most patients with TS. The radioligand studies have been less consistent, but they provide some support for increased D2 receptor density in the caudate nucleus. Imaging studies of presynaptic markers such as dopa decarboxylase, dopamine, and DAT have produced results that

are even less consistent. Future imaging and ligand studies should include children, because this population has been largely excluded because of ethical considerations. The studies should also rigorously characterize comorbid disorders and should take into consideration potential confounding variables, such as the secondary effects of chronic illness and medications.

Immunology

The potential role of immunologic mechanisms and specifically antineuronal antibodies is currently being explored in a variety of neurologic disorders, including TS (Allen, 1997; Hallett and Kiessling, 1997; Hallett et al., 2000; Morshed et al., 2001; Church et al., 2003; Harris and Singer, 2006; Singer et al., 2008; Martino et al., 2009; Hsu et al., 2021). Several studies have suggested that exacerbations of TS symptoms correlated with an antecedent GABHS infection (demonstrated by elevated antistreptococcal titers) and the presence of serum antineuronal antibodies (Kiessling et al., 1993). Epitopes of streptococcal M proteins have been found to cross-react with the human brain, particularly the basal ganglia, and may be pathogenetically important in various neurologic disorders, such as Sydenham disease, TS-like syndrome, dystonia, and parkinsonism (Bronze and Dale, 1993; Dale et al., 2001). In 10 patients with poststreptococcal acute disseminated encephalomyelitis (PSADEM) after exposure to GABHS, Dale and colleagues (2001) showed anti-basal ganglia antibodies in all with three (60, 67, and 80 kDa) dominant bands. Furthermore, MRI showed hyperintense basal ganglia in 80% of the patients. The B lymphocyte antigen D8/17 is considered to be a marker for rheumatic fever but is also frequently overexpressed in patients with tics, OCD, and autism (Murphy et al., 1997; Swedo et al., 1997; Hoekstra et al., 2001). In one study, children and adults with TS had significantly higher serum levels of antineuronal antibodies against the putamen, but not the caudate or GP, compared with controls (Singer et al., 1998). The potential relevance of this finding has been questioned, however, because there is no relationship between the presence of the antineuronal antibodies and age at onset, severity of tics, or the presence of comorbid disorders. Trifiletti and Packard (1999) confirmed the presence of a specific brain protein at an apparent molecular weight of 83 kDa that is recognized by antibodies in the serum of 80% to 90% of patients with TS or OCD. They concluded that there may be a subset of patients with TS and OCD, perhaps up to 10% of all cases, in whom a streptococcal infection triggers the onset of symptoms (Trifiletti and Packard, 1999). In a large case-control study of 150 patients with tics compared with 150 controls, Cardona and Orefici (2001) found a correlation between the occurrence of tics and prior exposure to streptococcal antigens and that the severity of tic disorder correlates with the magnitude of the serologic response to streptococcal antigens measured by antistreptolysin O (ASO) titers (38% of the children with tics compared with 2% of the control subjects had ASO titers of 500 international units or greater [$P < 0.001$]). In another study involving 25 adult patients with TS and 25 healthy controls, increased antibody titers against streptococcal M12 and M19 proteins were found in the TS group compared with the healthy controls (Müller et al., 2001). In yet another study involving 81 patients with TS, 27 with Sydenham disease, 52 with autoimmune

disorders, and 67 normal controls, Morshed and colleagues (2001) found elevated titers of IgG antineuronal antibodies in diseased individuals compared with controls, but there was no relationship between the antibody titers and the age, severity of TS, or comorbid disorders. Church and colleagues (2003) studied 100 patients with TS, 50 children with neurologic disease, 40 with recent uncomplicated streptococcal infection, and 50 healthy adults. They found elevated ASO titers in 64% of TS children compared with 15% of pediatric controls ($P < 0.0001$) and in 68% of adults with TS compared with 12% of adult neurologic controls and 8% of adult healthy controls ($P < 0.05$). Evidence of basal ganglia antibodies were found in 20% to 27% of TS patients, compared with 2% to 4% of controls. Similar to the proposed antigen in Sydenham disease, the most common antigen in TS was 60-kDa protein. Furthermore, 91% of patients with positive basal ganglia antibodies were found to have elevated ASO titers, whereas 57% of those without such antibodies had high ASO titers. The authors concluded that these findings “suggest a pathogenic similarity between Sydenham disease and some patients with TS. In another study, 65% of 65 patients with atypical movement disorders, including dystonia and tics, had anti-basal ganglia antibodies (Edwards et al., 2004b). Edwards and colleagues (2004a) also reported four adult cases of tic disorder and stereotypies associated with the presence of anti-basal ganglia antibodies. There was no difference when clinical features of TS patients (53 children and 75 adults) with and without antinuclear antibodies, determined by western immunoblot showing bands for at least one of three reported striatal antigens (40, 45, and 60 kDa), were compared (Martino et al., 2009). When brain MRI T1 and DTI were compared in 9 adults with TS who had anti-basal ganglia antibodies with 13 without detectable antibodies, the voxel-based morphometry analysis failed to detect any significant difference in gray matter density between the two groups, again suggesting lack of relevance of the anti-basal ganglia antibodies to the pathogenesis of TS. Although there are many inconsistencies in the reported results related to autoantibodies in TS, and increased activation of immune responses in TS has been suggested by some investigators, further studies are needed before it can be concluded that TS is an autoimmune disorder (Martino et al., 2009).

Development of dyskinesias (paw and floor licking, head and paw shaking) and phonic utterances has been reported in rodents after the microinfusion of dilute IgG from TS subjects into their striatum (Hallett et al., 2000). They extended their initial observations by demonstrating that intrastriatal microinfusion of TS sera or gamma immunoglobulins (IgG) in rats produced stereotypies and episodic utterances, analogous to involuntary movements seen in TS, and confirmed the presence of IgG selectively bound to striatal neurons (Hallett et al., 2000). Peterson and colleagues (2000) found that ADHD was associated significantly with titers of two distinct antistreptococcal antibodies, ASO, and antideoxyribonuclease B, but no significant association was seen between antibody titers and a diagnosis of either chronic tic disorder or OCD. When basal ganglia volumes were included in these analyses, the relationships between antibody titers and basal ganglia volumes were significantly different in OCD and ADHD subjects compared with other diagnostic groups. Higher antibody titers in these subjects were associated with larger volumes of the putamen and GP nuclei.

Variably referred to as pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) or pediatric infection-triggered autoimmune neuropsychiatric disorders (PITANDS), this area has become one of the most controversial topics in pediatric neurologic and psychiatric literature (Kurlan, 1998b; Trifiletti and Packard, 1999; Hoekstra et al., 2002; Murphy and Pichichero, 2002; Church et al., 2003; Snider and Swedo, 2003; Kurlan, 2004; Gabbay et al., 2008; Gilbert and Kurlan, 2009; Schrag et al., 2009). The following are the diagnostic criteria for PITANDS, which are similar to those for PANDAS except that they define an episode of illness more specifically:

1. The patient must have met diagnostic criteria for a tic disorder or OCD at some point in life.
2. Symptom onset must have occurred between 3 years of age and puberty.
3. Symptom onset must be clinically sudden or demonstrate a pattern of sudden, recurrent, clinically significant symptom exacerbations and remissions.
4. Increased symptoms must be pervasive and severe enough to warrant consideration of a treatment intervention or, if untreated, last for at least 4 weeks. Symptom exacerbations should not occur exclusively during a period of stress or illness.
5. There must be evidence of an antecedent or concomitant infection. This evidence might include a positive throat culture; positive GABHS serologic findings (ASO antibodies with a peak at 3–6 weeks or anti-DNAase B antibodies with highest titers at 6–8 weeks); or a history of illness such as pharyngitis, sinusitis, or flulike symptoms (Allen et al., 1997). Because GABHS infections are quite common (an average of three episodes during childhood), it is difficult to make the association between such infections and the subsequent development or exacerbation of tics or OCD.

The PANDAS concept has some other shortcomings: (1) The streptococcal infection may cause stress, which can exacerbate tics; (2) some patients with PANDAS may simply have a variant of Sydenham disease; and (3) there is no established temporal link between antecedent streptococcal infection and the exacerbation of tics. One piece of evidence supporting the notion that PANDAS simply represents one spectrum of Sydenham disease is the frequent occurrence of TS comorbidities in patients with Sydenham disease. One study compared 56 patients with Sydenham disease with 50 rheumatic fever patients and 50 healthy subjects; it found that OCB was present in 19%, OCD in 23.2%, and ADHD in 30.4% of Sydenham disease patients, all significantly more frequent than in the diseased or healthy controls (Maia et al., 2005). Nevertheless, the concept of postinfectious OCD is gradually seeping into the literature, even though definite proof is still lacking (Leonard et al., 1999). One observation, yet to be confirmed, that has been used in support of the autoimmune hypothesis of TS is that infusion of sera from patients with TS who have high titers of antibodies against nuclear or neural protein into ventrolateral striata of rats was associated with a higher rate of oral stereotypies as recorded by “blinded” raters (Taylor et al., 2002). This observation, however, could not be reproduced by other investigators who infused sera from patients with TS who had antiputamin antibodies ($n = 9$) and from patients with PANDAS ($n = 8$) into the striatum of rats (Loiselle et al., 2004).

No stereotypic behavior or abnormal movements were observed. Furthermore, there was no difference in anti-basal ganglia antibodies between patients with PANDAS and patients with TS as measured by enzyme-linked immunosorbent assay (Singer et al., 2004). In a study of 40 subjects prospectively evaluated with intensive laboratory testing for GABHS for an average of 2 years with additional testing at the time of any clinical exacerbations, Kurlan and colleagues (2008) found that 5 of 64 exacerbations were temporally associated (within 4 weeks) with a GABHS infection, which is significantly higher than the number that would be expected by chance alone (1.6). In another study, no correlation between a variety of immune markers and clinical exacerbations in children with PANDAS was found, arguing against autoimmunity as a pathophysiologic mechanism in this disorder (Singer et al., 2008). In a study that involved consecutive ratings of tics and behavioral symptoms in 45 cases and 41 matched control subjects over a 2-year period, only a small minority of children with TS and early-onset OCD were found to be sensitive to antecedent GABHS infections (Lin et al., 2009). In a case-control study of a large primary care database of 678,862 patients with an average follow-up of 5.08 years, no support was found for a strong relationship between streptococcal infections, neuropsychiatric syndromes such as OCD or TS or PANDAS (Schrag et al., 2009). Although, in contrast to the findings of Schrag and associates (2009), similar health services database studies in the United States found modest statistical associations between streptococcal infections and tic or OCD diagnoses, “current evidence indicates that for the ordinary TS/OCD phenotype of waxing and waning symptoms, GABHS infection does not seem to be an important etiologic factor and therefore not an appropriate target for assessment or therapy” (Gilbert and Kurlan, 2009). In an attempt to address the controversy surrounding PANDAS, a new entity, termed pediatric acute-onset neuropsychiatric syndrome (PANS) has been proposed to acknowledge that there is a subgroup of children presenting with an abrupt onset of OCD and acute neuropsychiatric symptoms, accompanied by a variety of comparably severe and acute neuropsychiatric symptoms (Swedo et al., 2012). In contrast to PANDAS, the diagnostic criteria for PANS no longer include tics.

Untreated GABHS infection is often complicated by rheumatic fever within 10 to 14 weeks and by Sydenham disease within several months. Several studies have provided evidence for an overlap between TS and Sydenham disease, tics and OCD being manifested in both disorders (Church et al., 2003). It is therefore not clear whether TS and OCD are independent sequelae of GABHS or whether the observed symptoms of TS and OCD are manifestations of Sydenham disease. In one study, serum autoantibodies that bind to neuronal cell surface antigens were found to be present in Sydenham disease, but not in PANDAS or TS, thus supporting the notion that Sydenham disease, but not PANDAS or TS, is due to a pathogenic autoantibody (Brilot et al., 2011). In a 3-year prospective study of 12 children, 5 to 11 years old, with documented acute GABHS tonsillopharyngitis, Murphy and Pichichero (2002) noted a sudden onset of OCD symptoms in all patients and tics in 3 patients concurrently with the acute infection or within 4 weeks. These symptoms resolved in all patients within 2 weeks of initiation of antibiotic therapy. Although this intriguing hypothesis requires further studies,

plasmapheresis, intravenous IgG, and immunosuppressant therapies are currently being investigated in the treatment of TS (Allen, 1997). In a study of 30 children in whom OCD or tics were presumably triggered or exacerbated by GABHS, there were striking improvements in various measures of OCD after intravenous immunoglobulin (IVIG) and in tics after plasma exchange (Perlmutter et al., 1999). Twenty-nine children with PANDAS were randomized in a partially double-blind fashion (no sham plasmapheresis) to an IVIG, IVIG placebo (saline), and plasmapheresis (PEX) group. One month after treatment, the severity of obsessive compulsive symptoms (OCS) were improved by 58% and 45% in the PEX and IVIG groups, respectively, compared with 3% in the IVIG control group. In contrast, tic scores were improved only after PEX treatment (i.e., reductions of 49% [PEX], 19% [IVIG], and 12% [IVIG placebo]). Improvements in both tics and OCS were sustained for 1 year. However, there was no control PEX group and the control comparisons were limited to the 1-month visit. Furthermore, there was no relationship between rate of antibody removal and therapeutic response. Until the results of this study are confirmed, these treatment modalities are not justified in patients with TS. Furthermore, because of uncertainties about the possible cause-and-effect relationship between GABHS and tics and OCD, an antibiotic treatment for acute exacerbations of these symptoms is currently considered unwarranted (Kurlan, 1998b). Some studies have suggested that encephalitis lethargica is also part of the spectrum of poststreptococcal autoimmune diseases (Dale et al., 2004; Vincent, 2004).

Other hypotheses

Although direct evidence is still lacking, TS is currently viewed as a disorder of synaptic transmission involving disinhibition of the corticostriatal-thalamic-cortical circuitry. Several studies have provided evidence in support of the notion that the basal ganglia, particularly the caudate nucleus, and the inferior prefrontal cortex play an important role in the pathogenesis of not only TS but also comorbid disorders, particularly OCD (Baxter et al., 1992; McGuire, 1995; Swoboda and Jenike, 1995). For example, Laplane and colleagues (1989) described eight patients with bilateral basal ganglia lesions (anoxic or toxic encephalopathy) who showed stereotyped activities and OCB. Several imaging studies (reviewed earlier in the chapter) have implicated the ventral striatum–limbic system complex as playing an important role in the primitive reproductive behavior. A disturbance in sex hormones and certain excitatory neurotransmitters that normally influence the development of these structures may be ultimately expressed as TS (Kurlan, 1992). This hypothesis may explain the remarkable gender difference in TS, with males outnumbering females by 3:1; the exacerbation of symptoms at puberty and during the estrogenic phase of the menstrual cycle (Schwabe and Konkol, 1992); the characteristic occurrence of sexually related complex motor and phonic tics; and a variety of behavioral manifestations with sexual content. According to this hypothesis, the gene defect in TS results in an abnormal production of gonadal steroid hormones and increased trophic influence exerted by the excitatory amino acids, causing disordered development and increased innervation of the striatum and the limbic system. This is consistent with the finding of increased presynaptic dopamine uptake sites in brains of patients with TS (Singer et al., 1991).

Several animal models of tics have been developed (Bronfeld et al., 2013). These include microinjections of bicuculline into the sensorimotor putamen and primary motor cortex of a monkey (McCairn et al., 2013), injections of axonal tracers into the primate striatum (Worbe et al., 2012), and numerous other primate and rodent models (Bronfeld et al., 2013). Although there are no animal models that express all the typical features of TS, studies of stereotypies in animals may provide insight into the pathogenesis of habits, rituals, tic-like and impulsive behaviors in humans (Cools, 2008; Graybiel, 2008). These studies have shown that a broad spectrum of repetitive behaviors and rituals can become habitual and stereotyped through learning, partly as a result of experience-dependent neuroplasticity. Several families of horses with equine self-mutilation syndrome have been described with features that resemble human TS (Dodman et al., 1994). These horses exhibit a variety of stereotypic behaviors, such as glancing, biting at the flank or pectoral areas, bucking, kicking, rubbing, spinning, rolling, and vocalizing (squealing). Similar to TS, this condition is much more common in young males, is typically exacerbated by stress and during restful nonvigilance or boredom, and may be triggered by head trauma and relieved by castration. Genetic factors, however, seem to be most important.

Genetics

The heritability of tic disorders has been estimated to be 0.77 (Mataix-Cols et al., 2015) but no gene or genes responsible for TS have been identified. Finding a genetic marker and, ultimately, the gene has been the highest priority in TS research during the past decade (Keen-Kim and Freimer, 2006; Deng et al., 2012; Pauls et al., 2014; Forde et al., 2016; Huang et al., 2017; Fernandez et al., 2018). Unfortunately, despite concentrated effort by many investigators, the TS gene has thus far eluded this intensive search. A systematic genome scan using 76 affected sib-pair families with a total of 110 sib-pairs showed two regions, 4q and 8p, with a logarithm of the odds (LOD) score of 2.38 and 2.09, respectively; four additional regions, on chromosomes 1, 10, 13, and 19, had a LOD score over 1.0 (Tourette Syndrome Association International Consortium on Genetics, 1999). An analysis of 91 Afrikaner nuclear families with one or more affected children on chromosomes provided evidence of linkage to loci on chromosomes 2p11, 8q22, and 11q23–24, respectively (Simonic et al., 2001). This provides support for the finding in a previous study of a large French Canadian family of a LOD score of 3.24 for association with chromosome 11q23 (Merette et al., 2000). Other gene loci that are of interest in TS include 17q25 (Paschou et al., 2004) and 18q22 (Cuker et al., 2004). Assuming that genetic heterogeneity is not an important factor in TS, over 95% of the genome has been already excluded (Pakstis et al., 1991; Heutink et al., 1992). A linkage of TS with a known gene defect may help in the search for the TS gene. In this regard, a 16-year-old boy was found to have with typical TS who had a deletion of the terminal portion of the short arm of chromosome 9 (Taylor et al., 1991). A 7;18 translocation was identified in a patient with sporadic form of TS, and the relevant regions in chromosome 18q22.3 and 7q22–q31 will be searched for possible markers (Boghossian-Sell et al., 1996; Patel,

1996). The identification of balanced reciprocal translocation near 18q22.1 in families with TS and a deletion in the same locus in one patient with tics and OCD (and dysmorphic facial features) led to the tentative assignment of the TS gene in this region (Alsobrook and Pauls, 1997). Two families with translocations involving the 8q13 have been identified (Crawford et al., 2003). Linkage disequilibrium has been demonstrated between a D4 receptor locus (on chromosome 11) and TS (Grice et al., 1996). It is possible that the clue to the TS gene(s) will come from genetic studies of ADHD. In this regard, it is of interest that a genome-wide scan in patients with ADHD identified five “hot spots”: 17p11 (MLS = 2.98) and four nominal regions with MLS values greater than 1.0, including 5p13, 6q14, 11q25, and 20q13 (Ogdie et al., 2003). On the basis of analysis of several genomic regions, 17q25 appears to be of special interest, having the highest LOD score of 2.61 ($P = 0.002$) (Paschou et al., 2004). Intronic variants in *BTBD9*, which has been associated with RLS and periodic limb movements, also have been associated with TS (Rivière et al., 2009). In a genome-wide screening of single nucleotide polymorphism (SNP) genotyping microarray identified 5 exon-affecting rare variants on 1q21.1, 2p16.3, and 10q21.3 loci, not found in 73 ethnically matched controls (Sundaram et al., 2010). Some of these copy number variants have been implicated previously by other studies in schizophrenia, autism, and ADHD. Although potentially important, this study has many limitations and the data have to be interpreted cautiously (Scharf and Mathews, 2010). Using a genome-wide linkage scan, linkage to chromosome 14q31.1 (multipoint LOD = 2.4) was detected in one Italian kindred with TS (Breedveld et al., 2010). The relevance of this locus to TS is supported by the finding of a linkage to an overlapping region of chromosome 14q in a pair of TS siblings (Tourette Syndrome Association, 2007).

A major advance in the search for the elusive TS gene or genes has been made by the discovery of a frameshift mutation in the *Slit* and *Trk*-like 1 (*SLITRK1*) gene on chromosome 13q31.1 (Abelson et al., 2005). These variants were absent in 172 other TS and in 3600 control chromosomes. *SLITRK1* gene mutation, however, is a rare cause of TS (Deng et al., 2006; Fabbri et al., 2007; Scharf et al., 2008, 2012; Deng et al., 2012). One parent of a TS patient carried the *SLITRK1* mutation but displayed only symptoms of trichotillomania. In a study of 44 families with one or more members who had trichotillomania, two mutations in the *SLITRK1* gene were found among some individuals with trichotillomania but not in their unaffected family members (Zuchner et al., 2006). *SLITRK1* mutations have been estimated to account for 5% of trichotillomania cases. The *SLITRK1* gene has been found to be expressed in brain regions previously implicated in TS, such as the cortex, hippocampus, thalamic, subthalamic, and GP nuclei, striatum, and cerebellum, and it appears to play a role in dendritic growth. Analysis of 988 parents of children with TS estimated the prevalence of *SLITRK1* variants to be 0.1% (Scharf, 2008). Another genetic abnormality implicated in TS is the L-histidine decarboxylase gene (*HDC*) mutation W317X, located on 15q21.1–15q21.3, inherited in an autosomal dominant fashion in a two-generation family (Ercan-Sencicek et al., 2010). L-histidine decarboxylase is the rate-limiting enzyme that catalyzes the biosynthesis of histamine from histidine. Histaminergic neurons are located

chiefly in the posterior hypothalamus but have widespread axonal connections. Although these findings suggest the possibility of using pharmacologic manipulation of histaminergic neurotransmission to treat TS, it is unknown how histamine abnormalities might cause or contribute to TS symptoms. Potentially an important finding, it is unlikely that the W317X mutation is relevant to the pathogenesis of TS in most cases because the mutation was not found in 720 other patients with TS. Intriguingly, however, chromosomal inv(15) (q13;q22.3), which includes the 15q21.1–15q21.3 region, was identified in one of our patients, a 10-year-old boy with tics (Jankovic and Deng, 2007). Consistent with the findings of increased motor activity in response to CNS stimulants and to dopamine and increased dopamine turnover, the *HDC* knockout mice (*HDC* KO) have decreased brain histamine levels (Dere et al., 2004). Conversely, in mice lacking the H3 histamine receptor (*H3R*-KO), locomotor activity and stimulant-induced stereotypic behaviors are decreased (Okuda et al., 2009). These findings suggest that *H3R* antagonist such as PF-0365476 may have a beneficial effect in the treatment of tics (Brioni et al., 2011; Wager et al., 2011). Although mutations in *HDC* and *SLITRK1* are only rarely associated with TS, careful studies of monogenic cases may provide insights into the pathogenesis of this complex neurobehavioral disorder. Another potential candidate gene mutation is Gln20X mutation in the 5-hydroxytryptamine receptor 2B gene (*HTR2B*, MIM 601122), located on chromosome 2q36.3–q37.1, reported to be associated with impulsivity in a Finish population of violent criminals (Bevilacqua et al., 2010). None of the 252 samples of patients with TS, including 132 Chinese people and 120 White people, showed the Gln20X mutation (Guo et al., 2012). One gene that has been identified by GWAS is the lymphocytic gene *FLT3*, raising a possibility for the involvement of a neuroinflammatory and neuroimmunologic involved in TS pathogenesis (Tsetsos et al., 2021).

In summary, chromosome abnormalities on 3q, 7q31, 7q35–36.2, 8q22.1, 9p, 9q, 13q31, 15q13–q22.3, 16p13.11; 16q, 17q25, and 18q22 and other loci based on linkage analysis, including 1p, 2p11, 2p32.2, 3p, 3q, 4q34–q35, 5p, 5q35.2–q35.3, 6p, 8p, 8q22, 11q23–q24, 14q31.1, 15q21.1–q21.3, 17q25, 20q, 21q have been associated with TS or TS-like disorders (Deng et al., 2012). In the first genome-wide association study (GWAS) of TS involving 1285 cases and 4964 ancestry-matched controls, no markers achieved a genome-wide threshold of significance, but a signal was found in rs7868992 on chromosome 9q32 in the *COL27A1* gene, which codes for a fibrillar collagen primarily expressed in cartilage and in the cerebellum during development (Scharf et al., 2012). In an attempt to examine the contribution of large, rare CNVs to TS and OCD susceptibility using a genome-wide, cross-disorder design in 2699 cases (1086 TS, 1613 OCD) and 1789 controls, deletions were located in the locus 16p13.11, suggesting that mutations in this region may be associated with increased susceptibility of TS, OCD, and possibly other neurodevelopmental disorders (McGrath et al., 2014). Another gene that has been implicated both in TS and OCD is the serotonin transporter (*SERT*) gene (solute carrier family 6, member 4, *SLC6A4*) (Moya et al., 2013). In another study, 42 SNPs were genotyped based on a GWAS study (Scharf et al., 2013) in 609 independent cases and 610 ancestry-matched controls; only rs2060546 on chromosome

12q22 remained significant (Paschou et al., 2014). This is closely associated with a gene coding for NTN4, an axon guidance molecule expressed in developing striatum. Based on a GWAS in 2723 cases (1310 with OCD, 834 with TS, 579 with OCD plus TS), 5667 ancestry-matched controls, and 290 OCD parent-child trios, no individual SNPs achieved genome-wide significance (Yu et al., 2014). However, polygenic score analyses identified a significant polygenic component for OCD but not for TS. The study concluded that “OCD with co-occurring TS may have different underlying genetic susceptibility compared with OCD alone.”

Current concepts of the genetics of TS support a sex-influenced autosomal dominant mode of inheritance with a nearly complete penetrance for males and 56% penetrance for females when only tics are considered and 70% when OCD is included (Robertson, 1989; Pauls et al., 1991). Comings and Comings (1992), however, have proposed that TS is a semidominant, semirecessive disorder. This model takes into account the common observation that both parents of a TS child often exhibit TS or a forme fruste of TS and that the full and more severe motor-behavioral syndrome in the offspring represents a homozygous state (Fig. 15.3). Indeed, bilineal transmission was noted in 33% (considering tics) and 41% (considering tics or OCB) of TS families (Kurlan et al., 1994). In another study, McMahon and colleagues (1996) examined 175 members of a large, four-generation, TS family and 16 spouses who married into this family. Interestingly, they found evidence of TS in 36% of the family members and in 31% of the married-in spouses (some form of a tic was found in 67% and 44%, respectively). Multivariate analysis showed that tics were more severe in the offspring of both parents with tics. This study raises the possibility of assortative mating (like marrying like) in TS, as also proposed for autism and other disorders (Baron-Cohen, 1996; Zietsch et al., 2011), in contrast to random, nonassortative mating, which is presumed in the general population. However, even in the general population there is genetic and, more likely, educational assortative mating (Domingue et al., 2014). Thus bilineal transmission may lead to frequent homozygosity and high density of TS in some families. Walkup and colleagues (1996) failed to find TS in both parents, but when the broader definition was allowed, 19% of families had both parents affected. Using rigorous diagnostic criteria, we found that 25% of our TS cases had both parents with some features of TS: tics, 8%; OCB, 4%; and ADD, 12% (Hanna et al., 1999) (see Fig. 15.3). The TS patients were compared with a control population of 1142 students who were observed in second-, fifth-, and eighth-grade classrooms. In contrast to the 5% frequency of ADD in one parent of controls, the occurrence of tics was 31% in at least one parent of TS cases, 45% in at least one parent of ADD cases, and 41% in at least one parent of OCB cases. Among all the parents of TS cases, tics were present in 24%, OCB in 25%, and ADD in 34%, whereas 3% of parents of controls exhibited ADD. Bilineal transmission violates the standard principle of one-trait-one-locus, and it might explain why a gene marker has not yet been identified in TS despite intense collaborative research effort. These results are similar to those of Lichter and colleagues (1999), who found bilineal transmission in 6% of patients; tics or OCB were represented bilineally in 22% of patients. In a large family study and segregation analysis, Walkup and colleagues (1996) provided

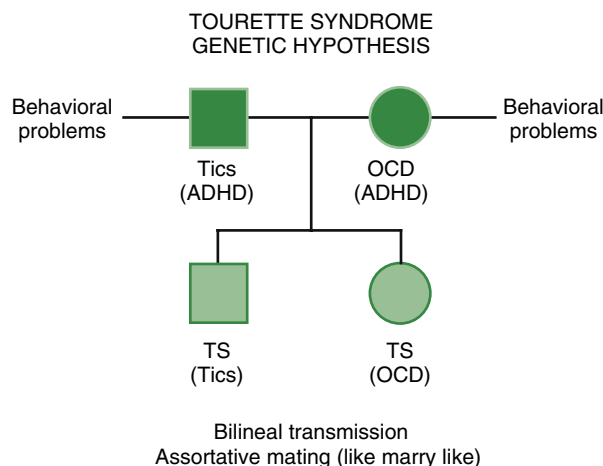


Fig. 15.3 Bimodal distribution typically present in Tourette syndrome (TS) nuclear families. *ADHD*, Attention deficit–hyperactivity disorder; *OCD*, obsessive-compulsive disorder.

evidence for a mixed model of inheritance rather than a simple autosomal mode of inheritance. This complex model of inheritance suggests that the majority of TS patients have two copies of the gene, one from each parent. This is consistent with the observation that many TS patients have both parents affected.

Based on various epidemiologic-genetic studies, the rate of TS in the parents of a proband ranges from 6.5% to 16%, with fathers demonstrating a much higher risk (11.9%–23.1%) compared with mothers (1%–9.6%) (Pauls et al., 1991; Walkup et al., 1996). A Japanese population study, however, found the rate of TS for both parents was 1.9% and the rate of tics for both parents was approximately 11.5% (Kano et al., 2001). Sibs have approximately an 8% risk of TS and a 9.7% to 22% risk for OCD. The empirical risk to offspring of a proband with TS was reported as 22% for TS and greater than 50% for a tic disorder (McMahon et al., 2003). In bilineal families the risk for TS for offspring increased to 42.8% compared with 15% for unilineal families. Additionally, rates of any tic diagnosis, OCD, and ADHD were increased (McMahon et al., 2003).

Twin studies, showing 89% concordance for TS and 100% concordance for either TS or chronic multiple tic disorder, provide strong support for the genetic etiology of TS (Also-brook and Pauls, 1997; Singer, 2000). How much influence environmental factors have on the phenotypic expression of this disorder is not known. In searching for nongenetic factors in the pathogenesis of TS, Leckman and colleagues (1990) found that maternal life stress, nausea, and vomiting during first trimester of pregnancy were some of the perinatal factors that influenced the expression of the TS gene. In a study of 16 pairs of monozygotic twins, 94% of whom were concordant for tics, low birth weight was a strong predictor of tic severity, supporting a relationship between birth weight and phenotypic expression of TS (Hyde et al., 1992). Subsequent study involving 586 participants with a chronic tic disorder and 527 unaffected family controls found that premature birth (odds ratio [OR], 1.72), morning sickness requiring medical attention (OR, 2.57), and prenatal and perinatal complications (OR, 1.07) was higher in those with a tic disorder than in controls (Abdulkadir et al., 2016). Kurlan (1994) hypothesized that the clinical features associated

with TS may occur to a variable degree in the course of normal childhood development and that genetic influences determine the severity of clinical symptoms in a given individual with TS. Eapen and colleagues (1997a) found evidence for earlier age at onset in maternally transmitted cases, suggesting genomic imprinting. The evidence for genomic imprinting in TS is, however, quite weak, and the genetic mechanism of TS remains elusive (Sadovnick and Kurlan, 1997). Because of phenotypic overlap between TS and Rett syndrome and myoclonus–dystonia, we have examined the genes for the latter disorders and found no mutations in our TS population (De Carvalho et al., 2004). TS has been reported to be associated with recurrent exonic CNVs (Sundaram et al., 2010), an abnormality that has been linked to the general group of neurodevelopmental disorders (Scharf et al., 2010).

One of the major concerns with the genetic linkage studies has been the lack of specificity of the current clinical criteria for diagnosis of TS. The boundaries of neurologic and behavioral manifestations of TS have not been clearly defined. Whereas some investigators think that the spectrum of behavioral expression of TS gene is quite broad, encompassing, in addition to ADHD and OCD, such diverse symptoms as conduct disorders, stuttering, dyslexia, panic attacks, phobias, depression, mania, and severe anxiety (Comings, 1987; Comings and Comings 1988a), others argue that more restrictive criteria for TS are needed, particularly for genetic linkage studies (Pauls et al., 1991). Pauls and colleagues (1991) studied 338 biologic relatives of 86 TS probands and compared them to 21 biologically unrelated relatives of adopted TS probands. They confirmed their earlier observations and concluded that TS and OCD are etiologically

related. The debate as to whether TS, OCD, and ADHD are genetically related or whether they merely represent comorbid neurobehavioral disorders will not be resolved until a TS-specific genetic marker is found.

Discovering the gene or genes for OCD would have important implications for TS and would help clarify the relationship between the two disorders. One study showed that men with OCD are significantly more likely to have both alleles of the gene for catechol-O-methyltransferase in a low activity form (L/L) than in the L/H form (Karayiorgou et al., 1997). As was noted earlier, the B lymphocyte antigen D8/17 has been suggested to be a possible peripheral marker for childhood-onset OCD and TS (Murphy et al., 1997). It is also likely that discoveries of gene mutations or variations responsible for ADHD may have implications for the study of genetics of TS (Lionel et al., 2011). Genome-wide complex trait analysis (GCTA) indicated that there is genetic overlap between TS and OCD, but that the two disorders have distinct genetic architectures (Davis et al., 2013). A GWAS study involving 1065 families (containing 1406 patients with OCD) and population-based samples from 5061 individuals, found a significant marker on chromosome 9, near the *PTPRD* gene, which encodes the presynaptic PTPRD protein that promotes the differentiation of glutamatergic synapses and interacts with *SLITRK3* to regulate the development of inhibitory GABAergic synapses (Mattheisen et al., 2015).

The identification of gene mutations or genetic variants that confer risk for TS has been challenging, and candidate gene associations have not replicated. It is likely that TS is a multi-genetic disorder involving a combination of small- and large-effect genetic variants that confer a variable risk (Fig. 15.4).

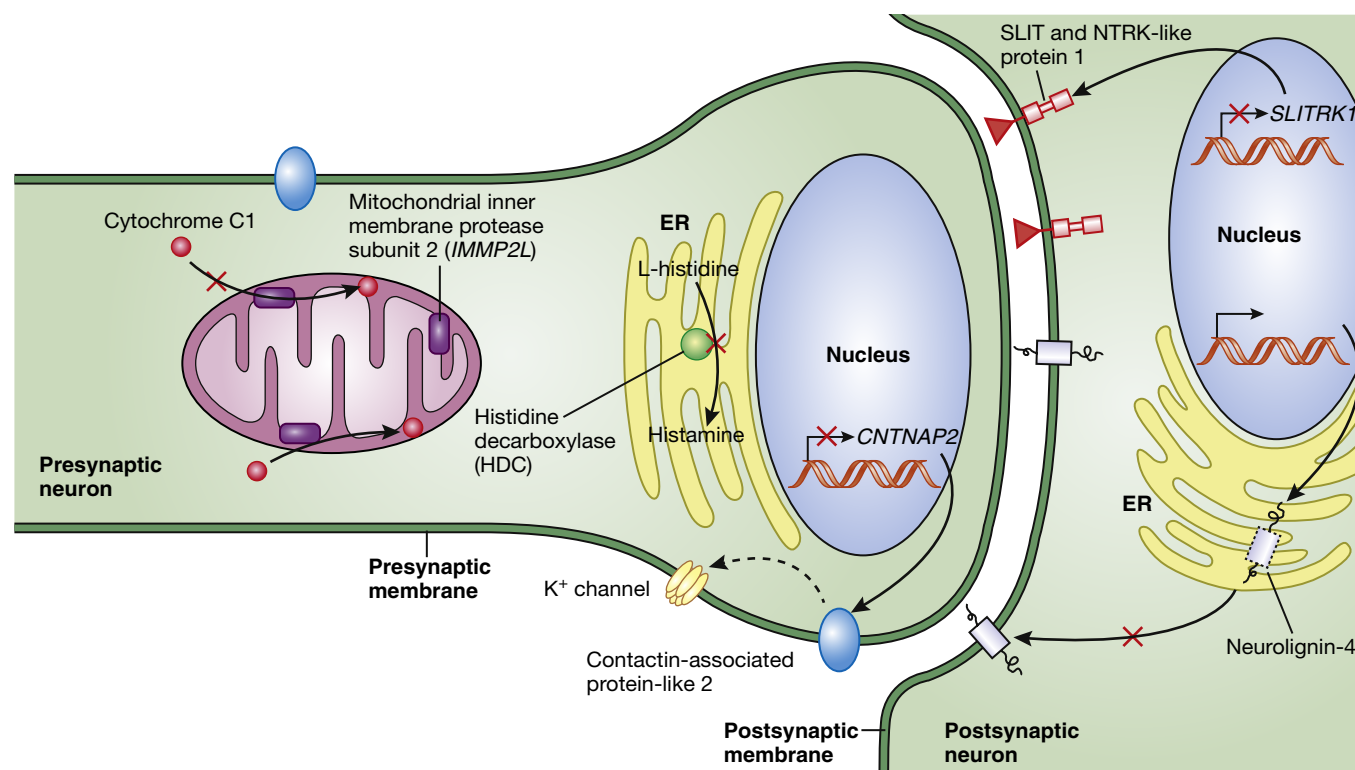


Fig. 15.4 Neuronal location and possible function of the gene products associated with Tourette syndrome (TS). Other genes implicated in TS include: *SLITRK1*, *HDC*, *COL27A1*, *NRXN1*, *CNTN6*, *TBC1D7*, *WWC1*, *CELSR3*, *NIPBL*, *FN1*, *FLT3*. ER, Endoplasmic reticulum. (Reproduced with permission from Deng H, Gao K, Jankovic J. The genetics of Tourette syndrome. *Nat Rev Neurol*. 2012;8[4]:203–213.)

Cause of tics (secondary tourettism)

Although TS is probably the most common cause of tics, there are many other neurologic disorders that are manifested by tics and other symptoms of TS, supporting the notion of a multifactorial genesis of TS (see Table 15.1) (Jankovic, 2001a; Jankovic and Mejia, 2006). Of these, tics associated with static encephalopathy, autistic spectrum disorders, neuroacanthocytosis (Spitz et al., 1985; Saiki et al., 2004), HD (Jankovic and Ashizawa, 1995), pantothenate kinase-associated neurodegeneration (Pellecchia et al., 2005), fragile X syndrome (Schneider et al., 2008), beta-mannosidase deficiency (Sedel et al., 2006), and certain drugs such as dopamine receptor-blocking drugs, cocaine, and antiepileptics (Cardoso and Jankovic, 1993; Bharucha and Sethi, 1995; Kumar and Lang, 1997b; Lombroso, 1999) are particularly important to consider, especially in patients who do not fulfill the clinical criteria of TS. In one report, lamotrigine, a phenyltriazine drug that is structurally unrelated to other antiepileptic medications, was associated with dose-related motor and phonic tics in three children and features of OCD in one (Lombroso, 1999). The author speculated that in these rare cases, lamotrigine in high doses inhibited the presynaptic release of excitatory amino acids and resulted in an abnormal regulation of dopamine uptake in the striatum, leading to the production of tics and related TS symptoms. Rarely, "tourettism" can follow head trauma (Krauss and Jankovic, 1997; Kumar and Lang, 1997b); nonspecific cerebral insults, such as ischemia, hypoxia, and hypothermia (Singer et al., 1997); or striatal encephalitis caused by varicella zoster (Dale et al., 2003). The study of the mechanisms of the secondary tourettism could provide insights into the pathogenesis of TS. For example, although TS symptoms have been reported to be exacerbated by various structural lesions involving the basal ganglia and the limbic system (Jankovic, 2001a), one patient with TS had complete resolution of tics after an MRI-proven midbrain lesion as a result of Wernicke encephalopathy (Pantoni et al., 1997). This report would suggest that an intact midbrain tegmentum is required for the expression of motor tics.

Autistic spectrum disorders (or pervasive developmental disorders) represent one of the largest groups of pediatric disorders in which features of TS, such as tics, ADHD, and OCD, may be present. In a study of 7288 participants enrolled in the Tourette Syndrome International Database Consortium Registry, 334 (4.6%; 1 of every 22 participants) had a comorbid pervasive developmental disorder, 13 times the expected rate (Burd et al., 2009). Autism is a behaviorally defined syndrome manifested by poor social interaction; disordered language; and atypical responses to people, objects, and events (Volkmar and Pauls, 2003). The syndrome is typically associated with severe disturbances in cognition, language, and behavior that appear before the age of 30 months. Stereotypic movements include body rocking, repeated touching and sniffing of objects, ritualistic ordering, and insistence on precisely following routines. Similar to TS, there is about a 3:1 male-to-female preponderance. A study of children 3 to 10 years old found a 0.34% prevalence of autism with cognitive impairment in 68% (Yeargin-Allsopp et al., 2003). A review of home videos during early development in 17 autistic children found evidence of abnormal movement at the age of 4 to 6 months and sometimes even at birth, long

before the diagnosis of autism (Teitelbaum et al., 1998). The authors suggest that their findings support the view that movement disturbances play an intrinsic part in the phenomenon of autism, that movement disturbances in autistic children are present at birth, and that such movement disturbances can be used to diagnose the presence of autism in the first few months of life. Other studies have suggested that TS symptoms are more common than expected in patients with autism, with an estimated frequency of 6.5% (Baron-Cohen et al., 1999). Asperger syndrome is a form of pervasive developmental disorder in which language and self-help skills are relatively intact. It is often considered a mild form of autism, but its relationship to other autistic disorders has not been well defined. Asperger syndrome patients frequently exhibit repetitive movements (stereotypies) and may have motor and phonic tics in addition to other behavioral abnormalities (Ringman and Jankovic, 2000). Other childhood behavioral disorders that may overlap in symptomatology with autism and TS include Williams syndrome, characterized by remarkable conversational skills and excessive empathy; Prader-Willi syndrome, associated with temper tantrums and obsessive-compulsive behavior; Angelman syndrome, characterized by hyperactivity and a constantly happy disposition (Cassidy and Morris, 2002); and Rett syndrome, an X-linked autistic disorder associated with stereotypies and other movement disorders. However, we excluded mutations in *MECP2* gene on chromosome X28, responsible for Rett syndrome (Rosa et al., 2003). We also excluded mutations in the *SGCE* gene, responsible for the dystonia-myoclonus syndrome, which shares some clinical features with TS, in a population of well-defined TS (De Carvalho Aguiar et al., 2004). Another genetic disorder, but with yet unidentified molecular cause, is Primrose syndrome, which consists of cognitive and motor delay, facial dysmorphism, cataracts, hearing impairment, spastic paraparesis, joint contractures, distal muscle wasting, and a variety of movement disorders, including parkinsonism, ataxia, tics, stereotypies, and self-flagellation (Dalal et al., 2010).

Other related conditions that may have resemblance to tics and TS are the jumping Frenchmen of Maine, "ragin' Cajuns" of Louisiana, latah of the Malays, and myriachit of Siberia (Lees, 2001; Bakker et al., 2013). First described in 1878, these culture-bound conditions are characterized by an excessive startle response, sometimes with echolalia, echopraxia, or forced obedience. It is considered by some as an operant conditioned behavior rather than a neurologic or even hysteric disorder (Saint-Hilaire et al., 1986). The rare late-onset startle-induced tics may resemble these culture-bound syndromes and other startle responses (Tijssen et al., 1999). Rarely, psychogenic tics are present in patients with TS, but this very rare occurrence is difficult to confirm clinically (Kurlan et al., 1992; Baizabal-Carvallo and Jankovic, 2014; Demartini et al., 2014). In a series of nine patients (five females; mean age at onset: 34.1 years) with psychogenic tics the following features helped differentiate these patients from those with organic tics: lack of premonitory sensations, absence childhood and family history of tics, inability to suppress the movements and coexistence with other psychogenic movement disorders and pseudoseizures (Baizabal-Carvallo and Jankovic, 2014). Furthermore, compared with patients with TS, those with psychogenic tics were more likely females and were older.

The discussion of the numerous causes of tics and other manifestation of TS is beyond the scope of this review, and the reader is referred to other reviews of secondary causes of tics (Kumar and Lang, 1997; Jankovic 2001b; Jankovic and Mejia, 2006).

Epidemiology

Discovery of a disease-specific marker would be helpful not only in improving our understanding of this complex neurobehavioral disorder but also in clarifying the epidemiology of TS (Kadesjo and Gillberg, 2000; Scahill et al., 2001; Kurlan et al., 2002). Validated screening instruments are needed to assist in epidemiologic studies. One proxy report questionnaire was found to 92% sensitivity, 38% positive predictive value, and 97% negative predictive value when completed by observers, teachers, and parents (Cubo et al., 2011). Using different methods, up to 24% of children may have tics sometime during their childhood (Robertson, 2008a,b). The prevalence rates have varied markedly and have been estimated to be as high as 4.2% when all types of tic disorders are included (Costello et al., 1996) and 1 in 83 (1.2%) (Comings and Comings, 1988b) or as low as 28.7 in 100,000 (0.03%) (Caine et al., 1988) and 1 in 10,000 (0.01%) (Singer, 2000). There are many reasons for this wide variation, the most important of which are different ascertainment methods, different study populations, and different clinical criteria. About one-third of patients with tics do not even recognize their presence; thus, it is difficult to derive more accurate prevalence figures for TS without a well-designed door-to-door survey (Kurlan et al., 1987). In one study, 3034 students in three schools in Los Angeles were monitored over a 2-year period by a school psychologist; the frequency of definite TS was 1 in 95 males and 1 in 759 females (Comings et al., 1990). Because the observed population included special education children, the authors adjusted the final prevalence figure to 0.63%. This figure is similar to that derived from our own observational study of 1142 children in second, fifth, and eighth grades of a general school population, among whom 8 children (0.7%) had some evidence of TS (Hanna et al., 1999). In another school-based study involving 167 randomly selected 13- and 14-year-olds in English high schools, the prevalence of TS based on DSM III-R was estimated at 3%, but 18% screened positive for tics (Mason et al., 1998). A follow-up study with improved methods found a TS prevalence of 0.76% to 1.85% (Hornsey et al., 2001). Snider and colleagues (2002) observed 553 schoolchildren (kindergarten to sixth grade) monthly over an 8-month period and found tics in 135 (24%); 34 children had persistent tics (6.1%). Those with persistent tics were more likely to be males and had more behavioral problems than those without persistent tics. Kurlan and colleagues (2001) found that 27% of 341 special education students had tics compared with 19.7% of 1255 students in regular classroom programs; the frequency of TS was 7% and 3.8%, respectively. In another study, based on an interview of 1596 children, Kurlan and colleagues (2002) found that 339 (21%) had tics. Children with tics were younger, were more likely to be male and attend special education classes, and had a lower mean IQ. The prevalence of tics was studied in 867 children attending two schools in

the Basque country and was estimated to be 6.5% (Linazaro et al., 2006). Thus, epidemiologic studies have shown that 20% to 30% of children exhibit tics sometime during childhood and 2% to 3% of children develop some features of TS, although the world-wide prevalence of TS in children has been reported to range from 0.3% to 0.8% (Scahill et al., 2009). Meta-analysis of 13 studies of children yielded a prevalence of TS of 0.77% (95% confidence interval [CI], 0.39%–1.51%); the ratio of boys to girls was 1.06%:0.25% and meta-analysis of two studies assessing adults with TS revealed a prevalence of 0.05% (95% CI, 0.03%–0.08%) (Knight et al., 2012). The prevalence of tic disorders was higher in all studies performed in special education populations. Similar findings were reported based on a prospective cohort study following 6768 children in Avon, United Kingdom, in which 0.3% of 13-year-old children met criteria for clinically definite TS and 0.7% with clinically probably TS (Scharf et al., 2012). It is not known why tics disappear in the majority of children, and further studies are needed to understand mechanisms of conversion from pre-TS state to TS. Among the 21 population-based prevalence studies, the pooled TS population prevalence estimate was 0.52% (95% CI, 0.32–0.85), 0.3% to 0.9% in children, but the true prevalence was thought to be much higher (Scharf et al., 2015).

In terms of potential risk factors, prenatal maternal smoking was associated with slightly increased risk for TS, suggesting a link between prenatal tobacco exposure and altered brain development in TS (Browne et al., 2016).

Treatment

The first step in the management of patients with TS is proper education of the patient, relatives, teachers, and other individuals who frequently interact with the patient about the nature of the disorder (Scahill et al., 2006; Jankovic, 2009; Shprecher and Kurlan, 2009). School principals, teachers, and students can be helpful in implementing the therapeutic strategies. In addition, the parents and the physicians should work as partners in advocating the best possible school environment for the child. This might include extra break periods and a refuge area to allow release of tics, waiving time limitations on tests or adjusting timing of tests to the morning, and other measures designed to relieve stress. National and local support groups can provide additional information and can serve as a valuable resource for the patient and his or her family (see the Appendix).

Before deciding *how* to treat TS-related symptoms, it is important to decide *whether* to treat them. Even in our tertiary referral center about 20% do not need pharmacologic therapy. Counseling and behavioral modification might be sufficient for those with mild symptoms. Medications, however, may be considered when symptoms begin to interfere with peer relationships, social interactions, academic or job performance, or activities of daily living. Because of the broad range of neurologic and behavioral manifestation and varying severity, therapy of TS must be tailored specifically to the needs of the individual patient (Jimenez-Jimenez and Garcia-Ruiz, 2001; Lang, 2001; Silay and Jankovic, 2005; Gilbert, 2006; Jankovic and Kurlan, 2011; Gilbert and Jankovic, 2014; Quezada and Coffman, 2018) (Table 15.3). The most troublesome symptoms should be targeted first. Medications

Table 15.3 Treatments used in Tourette syndrome

Tics
Tetrabenazine
Deutetrabenazine
Valbenazine
Clonazepam
Fluphenazine
Pimozide
Haloperidol
Thiothixene
Trifluoperazine
Molindone
Sulpiride
Tiapride
Flunarizine
Olanzapine
Risperidone
Quetiapine
Clozapine
Pergolide
Nicotine
Naltrexone
Flutamide
Cannabinoids
Botulinum toxin
Obsessive-compulsive disorder
Imipramine
Clomipramine
Fluoxetine
Sertraline
Nefazodone
Fluvoxamine
Paroxetine
Venlafaxine
Citalopram
Lithium
Buspirone
Clonazepam
Trazodone
Clonazepam
Attention deficit disorder/Attention deficit-hyperactivity disorder
Clonidine
Imipramine
Nortriptyline
Desipramine
Deprenyl
Bupropion
Guanfacine
Carbamazepine
Dextroamphetamine
Methylphenidate
Adderal
Pemoline
Modafinil
Atomoxetine
Mecamylamine
Neurosurgery

should be instituted at low doses, titrated gradually to the lowest effective dosage, and tapered during nonstressful periods (e.g., summer vacations). Another important principle of therapy in TS is to give each medication and dosage regimen an adequate trial. This approach will avoid needless changes made in response to variations in symptoms during the natural course of the disease. Although an evidence-based

approach, based on double-blind, placebo-controlled studies, is desirable to objectively evaluate the efficacy of a drug, long-term observational studies provide useful information about not only the efficacy of the drug, but also its safety (Mesulam and Peterson, 1987).

Before discussing pharmacologic therapy of TS symptoms, it is appropriate to make a few remarks about behavioral therapy (Piacentini and Chang, 2001; Piacentini et al., 2010). Different forms of behavioral modification have been recommended since the disorder was first described, but, until recently, very few studies of behavioral treatments have been subjected to rigorous scientific scrutiny. Most of the reported studies suffer from poor or unreliable assessments, small sample size, short follow-up, lack of controls, no validation of compliance, and other methodologic flaws. Given these limitations, the following behavioral techniques have been reported to provide at least some benefit: (1) massed (negative) practice (voluntary and effortful repetition of the tic leads to a buildup of a state termed reactive inhibition, at which point the subject is forced to rest and not perform the tic because of a build-up of a negative habit); (2) operant techniques/contingency management (tic-free intervals are positively reinforced, and tic behaviors are punished); (3) anxiety management techniques (relaxation training); (4) exposure-based treatment (desensitization to address tic-triggering phenomena such as premonitory sensory urges); (5) awareness training (direct visual feedback, self-monitoring, and awareness-enhancing techniques, such as saying the letter "T" after each tic); and (6) habit-reversal training (HRT), consisting of competing response training with reenactment of tic movements while looking in a mirror, training to detect and increase awareness of one's tics, identification of high-risk situations, training to isometrically contract the tic-opposing muscles, and training to recognize and resist tic urges (Piacentini and Chang, 2001; Deckersbach et al., 2006; Himle et al., 2006; Piacentini et al., 2010). Wilhelm and colleagues (2003) studied 32 patients with TS who were randomly assigned to 14 sessions of either HRT (awareness training, self-monitoring, relaxation training, competing response training, and contingency management) or supportive psychotherapy. The 16 patients who were assigned to the HRT group "improved significantly" and "remained significantly improved over pretreatment at 10-month follow-up." This approach also has been found useful in the management of phonic tics (Woods et al., 2003). Another behavioral therapeutic approach is the so-called exposure plus response prevention, already found useful in the treatment of OCD. The behavioral intervention, called Comprehensive Behavioral Intervention for Tic Disorders (CBIT) is primarily based on HRT, which employs competing-response training, which is different from deliberate tic suppression in that it teaches the patient to initiate a voluntary behavior to manage the premonitory urge. CBIT also includes relaxation training and a functional intervention. In a multicenter study designed to test the efficacy of CBIT, 126 children ages 9 to 17 with moderate to severe TS were randomly assigned to receive either CBIT or supportive counseling and education about TS (Piacentini et al., 2010). About one-third of the children in the study were on a stable dose of anti-tic medication. Behavioral intervention led to a significantly greater decrease on the Yale Global Tic Severity Scale (24.7

versus 17.1) from baseline to endpoint compared with very minimal change in the control treatment group (24.6 versus 21.1) with the overall effect size of 0.68. Furthermore, 52.5% of children receiving CBIT were rated as significantly improved, compared with 18.5% of those in the control group. The decrease of 7.6 points (31% from baseline) on the TTS score of the YGTSS in the CBIT group is less than the decrease reported in clinical trials of antipsychotic medications or topiramate (see later discussion) (Jankovic et al., 2010). Although the attrition rate was only 9.5% and 87% of available responders apparently exhibited continued benefit for 6 months after treatment, there are some limitations to the CBIT that were not fully acknowledged in the study. However, CBIT is safe and, if available, is a viable first-line therapy before the use of pharmacologic approaches. Another anticonvulsant that may be helpful in some cases of severe complex tics is valproic acid (Ye and Lippman, 2014). A systematic review and meta-analysis of eight randomized controlled trials involving 438 subjects with TS concluded that CBIT produced moderate treatment effects and participants receiving CBIT were more likely to exhibit a treatment response compared with control interventions (McGuire et al., 2014).

The success of this behavioral management is critically dependent on active involvement by the parents and the therapist, both of whom must be well trained and skilled in the various CBIT techniques (Woods et al., 2008). Although “half the subjects in the CBIT trials did not show a positive response,” some have suggested that “CBIT can be considered a first-line treatment for persons with tic disorders” (Scahill et al., 2013). Although there has been a great deal of effort exerted over the last several decades making the scientific, clinical, and lay community understand the biologic basis of TS, the reported response to behavioral therapy may be misinterpreted by some as evidence that tics and TS are of psychological cause. This is one reason why behavioral therapies are often not covered by insurance or other third-party payors. Thus, only a limited number of patients will be able to access this behavioral therapy compared with pharmacologic treatment, which actually may be more effective. Nevertheless, behavioral therapies are useful not only as ancillary techniques but as first-line therapeutic strategies (Jankovic, 2020; Pringsheim et al., 2019 a,b). In the Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology, 46 recommendations were made regarding the assessment and management of tics (Pringsheim et al., 2019 a,b). The report found high confidence that CBIT was more likely than psychoeducation and supportive therapy to reduce tics. The conclusions from this report, which focused on controlled trials and evidence-based data, however, should be interpreted cautiously. Although controlled randomized trials provide evidence-based data, these trials have limitations because they tend to be relatively small and short. Furthermore, because of rigid inclusion/exclusion criteria they do not allow observations on long-term efficacy and safety, possible interactions with other drugs, or the effects of and on comorbidities. Therefore, in addition to evidence-based data, the following discussion also includes a more pragmatic approach, based on long-term experience and expert opinion.

Management of tics

The goal of treatment should not be to completely eliminate all the tics but rather to achieve a tolerable suppression of the tics and improve quality of life of patients with TS (Jankovic, 2015, 2019). Because of the variability of tics in terms of severity, frequency, and distribution, the assessment of efficacy of a therapeutic intervention on tics is often quite problematic. A number of tic-rating scales have been developed, but none of them are ideal. Although at-home videotapes can be used to capture tics that are not appreciated by patients or when patients are examined in the clinic, video-based tic-rating scales have many shortcomings (Goetz et al., 1999, 2001). The Rush Video-Based Rating Scale (Goetz et al., 1999) has been used in some clinical trials as an outcome measure, but this instrument has some limitations because TS patients tend to suppress their tics when they are in front of a camera (even when left alone) and the 5-minute video epoch is too short to capture the full spectrum of motor and phonic tics. Despite some drawbacks, the YGTSS and YGTSS TTS (discussed earlier) have been used most frequently as outcome measures in therapeutic clinical trials.

Controlled and open-label trials have found that of the pharmacologic agents that are used for tic suppression, the antidopaminergic drugs, such as dopamine receptor-blocking drugs (neuroleptics) (Robertson, 2000; Jimenez-Jimenez and Garcia-Ruiz, 2001; Mogwitz et al., 2013) and dopamine-depleting drugs (Jankovic, 2016, 2019) are clearly most effective (see Tables 15.2 and 15.3). Haloperidol, pimozide, and aripiprazole, all dopamine receptor-blocking drugs, are the medications approved by the FDA for the treatment of TS. In one randomized, double-blind, controlled study, pimozide was found to be superior to haloperidol with respect to efficacy and side effects (Sallee et al., 1997). Routine monitoring of the electrocardiogram (ECG) is recommended when using pimozide because the drug can prolong the Q-T interval. In a retrospective review of 268 patients with TS evaluated at the Baylor College of Medicine Movement Disorders Clinic and treated with fluphenazine for up to 16.8 years, fluphenazine was initiated at a mean age of 15.8 ± 10.7 years (range, 4.1–70.2) and titrated to an optimal dose of 3.24 ± 2.3 mg/day (range, 0.5–12.0), which was continued for an average of 2.6 ± 3.2 years (range, 0.01–16.8) (Wijemanne et al., 2014). Marked to moderate improvement was noted in 211 (80.5%). The most common side effects included drowsiness, fatigue, or both, observed in 70 (26.1%) patients; there were no cases of tardive dyskinesia. Risperidone, a neuroleptic with both dopamine- and serotonin-blocking properties, has been shown to be effective in reducing tic frequency and intensity in most (Bruggeman et al., 2001) but not in all studies (Robertson et al., 1996). A double-blind, placebo-controlled, 8-week trial in which 24 patients were randomly assigned to receive risperidone at doses of 0.5 to 6 mg/day (median dose of 2.5 mg/day) and 24 were assigned to placebo, risperidone was found to be significantly ($P < 0.05$) superior to placebo on the Global Severity Rating of the Tourette Syndrome Severity Scale (Dion et al., 2002). The proportion of patients who improved by at least 1 point on this 7-point scale was 60.8% in the risperidone group and 26.1% in the placebo group. Hypokinesia and tremor increased in the risperidone group, but there were no other “extrapyramidal” side effects. Fatigue and somnolence were the most common adverse events

associated with risperidone. In another placebo-controlled study, 12 patients who were randomized to risperidone had a 36% reduction in tic symptoms compared with 11% reduction in the 14 patients receiving placebo (Scahill et al., 2003). One randomized, double-blind study found risperidone to be more effective than clonidine in the treatment of TS-associated OCD (Gaffney et al., 2002). Risperidone has been also found to be effective in the treatment of tantrums, aggression, and SIB in children with autism (Research Units on Pediatric Psychopharmacology Autism Network, 2002). Some atypical, second-generation neuroleptics have been found to increase the risk for obesity and type 2 diabetes, but risperidone and ziprasidone appear to be associated with a lower risk for these complications (Gianfrancesco et al., 2002; Stahl and Shayegan, 2003).

It is not clear whether the atypical neuroleptics, such as clozapine, olanzapine, or quetiapine, will be effective in the treatment of tics and other manifestations of TS. Quetiapine, a dibenzothiazepine that blocks not only D1 and D2 receptors but also 5HT_{1A} and 5HT₂ receptors, has been reported to provide beneficial effects in some patients with TS, but the clinical improvement might not be sustained. Ziprasidone, a potent blocker of 5HT_{2A}, 5HT_{2C}, 5HT_{1A}, 5HT_{1D}, and α_1 receptors more than D2 or D3 receptors, was found to decrease tic severity by 35% compared with a 7% change in the placebo group (Sallee et al., 2000). Because of its relatively high D2 receptor occupancy, ziprasidone is pharmacologically more similar to risperidone and olanzapine than to clozapine and quetiapine (Mamo et al., 2004). Because TS patients may have increased cortical 5HT₂ density, it is possible that the beneficial effects of some of the atypical drugs are mediated by their 5HT₂ and 5HT₃ blocking effects (Haugbol et al., 2007). A few small studies have indeed shown some benefit in patients with TS treated with serotonin antagonists such as ketanserin and ondansetron (Bonnier et al., 1999; Toren et al., 2005). Similar to pimozide, ziprasidone may prolong the QT interval (Blair et al., 2005) but has the advantage over other atypical neuroleptics in that it is less likely to cause weight gain and sexual side effects. It also appears to have strong antiapathy, promotivational, and antidepressant effect. The clinical significance of a prolonged QT interval is controversial, but it may be associated with *torsades de pointes*, which can potentially degenerate into ventricular fibrillation and sudden death. Besides pimozide and ziprasidone, other drugs that can prolong the QT interval include haloperidol, risperidone, thioridazine, and desipramine. However, according to experts, the low rate of QTc prolongation in *torsades de pointes* is not likely to be a serious problem (Glassman and Bigger, 2001). Aripiprazole, another atypical antipsychotic medication (Goodnick and Jerry, 2002; Seo et al., 2008), acts as an antagonist of D2 receptors in the mesolimbic pathway, but also as a partial D2 agonist. It displays strong 5HT_{2A} receptor antagonism and is similar to ziprasidone in also having agonistic activity at the 5HT_{1A} receptor. As a partial dopamine agonist it reduces dopamine synthesis and release through an agonist action at the dopamine autoreceptor.

Among the atypical antipsychotics, aripiprazole displays the lowest affinity for alpha-1 adrenergic (α_1), histamine (H1), and muscarinic (M1) receptors and thus has a relatively low incidence of side effects, including orthostatic hypotension, weight gain, sedation, dry mouth, and constipation. In

one study, 10 of 11 patients with TS were reported to improve with 10 to 20 mg/day dose of aripiprazole (Davies et al., 2006). In a 10-week, multicenter study, of 61 TS patients, 89% of whom completed the study, aripiprazole was associated with a significant reduction from baseline to end of study with the mean total tic score of the YGTSS of 15.0 compared with 9.6 reduction in the placebo group ($P = 0.0196$) (Yoo et al., 2014). Furthermore, there was also significant improvement in some of the secondary measures. The drug was apparently well tolerated, but there was a significant increase in mean body weight, body mass index, and waist circumference. These findings were confirmed by a phase III, randomized, double-blind, placebo-controlled trial, which enrolled 133 patients (Sallee et al., 2017). At week 8, the treatment difference in YGTSS TTS versus placebo was -6.3 ($P = 0.0020$) and -9.9 ($P < 0.0001$), respectively. Furthermore, 69% (29/42) of patients in the low-dose (5–10 mg/day) and 74% (26/35) of patients in the high-dose aripiprazole (10–20 mg/day) groups indicated that they were much or very much improved. Similar to other atypical and typical neuroleptics, however, aripiprazole can also cause tardive dyskinesia, despite the claims by the pharmaceutical companies to the contrary (Peña et al., 2011; Carbon et al., 2018).

The role of other antipsychotic drugs, such as paliperidone, bifeprunox, and lurasidone, atypical neuroleptics that also act as mood stabilizers in the treatment of tics and TS is unknown (Nasrallah, 2008). Other drugs that are used in the treatment of tics include sulpiride, tiapride, metoclopramide, and piquindone (Jimenez-Jimenez and Garcia-Ruiz, 2001; Scahill et al., 2006). Pimavanserin, a serotonin receptor inverse agonist, currently FDA approved for treatment of psychosis in PD, is also currently studied in the treatment of TS.

The side effects associated with neuroleptics, such as sedation, depression, weight gain, and school phobia, seem to be somewhat less frequent with fluphenazine than with haloperidol and the other neuroleptics (Bruun and Budman, 1996). The most feared side effects of chronic neuroleptic therapy include tardive dyskinesia and hepatotoxicity. In addition, pimozide may prolong the QT interval; therefore, patients who are treated with the drug should have an ECG before starting therapy and it should be repeated about 3 months later and once a year thereafter. It is important to note that certain antibiotics, such as clarithromycin, can raise the blood levels of pimozide and indirectly contribute to the drug's cardiotoxicity. Tardive dyskinesia, usually manifested by stereotypic involuntary movements, is only rarely persistent in children. However, tardive dystonia, a variant of tardive dyskinesias that is most frequently encountered in young adults, may persist and occasionally progresses to a generalized and disabling dystonic disorder (Singh and Jankovic, 1988; Silva et al., 1993) (Video 15.18). Other movement disorders that are associated with neuroleptics include bradykinesia, akathisia, and acute dystonic reactions (Jankovic, 1995). Although tardive dyskinesia appears to be relatively rare in patients with TS, and some have even suggested that TS might be protective against this iatrogenic disorder (Müller-Vahl and Krueger, 2011), careful monitoring of the patients treated with neuroleptics is essential, and whenever possible, the dosage should be reduced or even discontinued during periods of remission or during vacations. ●

A novel antidopaminergic drug, a selective D1 dopamine receptor antagonist, ecopipam (Chipkin et al., 1988), has

Video 15.18 Tics and tardive dystonia.

been recently reported to be effective in an open label, phase II trial. In this trial, 18 adults (mean age: 36.2 years; range: 18–63 years) were enrolled and 15 completed the study. The mean YGTSS TTS score decreased from 30.6 ± 8.8 at baseline to 25.3 ± 9.2 at 8 weeks ($P = 0.0004$) (Gilbert et al., 2014). The most commonly reported adverse events were sedation (39%), fatigue (33%), insomnia (33%), somnolence (28%), anxiety (22%), and headache (22%). These encouraging findings were confirmed in a subsequent larger study. This was a 4-week double-blind, placebo-controlled crossover study of 40 TS patients, aged 7 to 17 years, who were randomized to either ecopipam (50 mg/day for weight of less than 34 kg, 100 mg/day for weight of greater than 34 kg) or placebo for 30 days and followed by a 2-week washout and then crossed to the alternative treatment for 30 days (Gilbert et al., 2018). The YGTSS TTS decreased more robustly in patients randomized to ecopipam relative to those exposed to placebo: from 32.8 to 27.2 (–5.6) with ecopipam versus from 33.7 to 30.3 (–3.4) with placebo ($P = 0.043$). Further studies are needed before the drug will be approved by the FDA for the treatment of TS.

Dopamine-depleting drugs have been increasingly used in the treatment of a variety of hyperkinetic movement disorders, including tics. Tetrabenazine (TBZ), a monoamine-depleting drug that acts by inhibiting VMAT2, approved in 2008 for the treatment of chorea associated with HD, has been used in the treatment of tics for several decades (Kenney et al., 2007; Jankovic and Clarence-Smith, 2011; Jankovic 2016). This drug has been found to be very effective in the treatment of TS in several open-label trials but no double-blind, placebo-controlled trial of TBZ in the treatment of TS has been published. In 92 patients with TS treated with TBZ at Baylor College of Medicine, for a mean of 1.6 years (up to 20.4 years) at a maintenance dose of 53.3 mg/day (range: 6.25–150), 77.8% reported complete or nearly complete abolishment of tics (Silay and Jankovic, 2005). TBZ was generally well tolerated, although some patients experienced drowsiness (32.6%), nausea/vomiting (8.7%), depression (7.6%), insomnia (6.5%), akathisia (5.4%), and other less frequent, dose-related side effects. The drug has the advantage over the conventional neuroleptics in that it does not cause tardive dyskinesias. Furthermore, it appears to be associated with less weight gain than the typical neuroleptics (Ondo et al., 2008). In the United States TBZ (now available as a generic drug) carries a black-box warning regarding the risk for depression and suicidality. Some studies, however, have suggested that TBZ may not have an increased risk for depression or suicidality, even in individuals with a history of depression (Schultz et al., 2018).

Besides the potential side effects noted earlier, there are other limitations of TBZ, including its relatively short half-life that necessitates administration at least 3 times daily. This is one reason why other dopamine depleters with longer duration of action are currently being investigated. These include deutetabenazine (DTBZ) and valbenazine, which are administered twice or once per day, respectively (Jankovic, 2016). In a pilot study involving 23 children with TS the mean (standard deviation [SD]) baseline YGTSS TTS score of 31.6 (7.9) decreased by 11.6 (8.2) points at week 8, a 37.6% reduction in tic severity ($P < 0.0001$) (Jankovic et al., 2016). Other measures of TS also improved in this open-label 8-week study suggesting that DTBZ may be a safe and effective treatment of tics

associated with TS. Based on studies in HD and tardive dyskinesia, DTBZ seems to be better tolerated than TBZ, including less sedation (Bashir and Jankovic, 2018; Niemann and Jankovic, 2018; Billnitzer and Jankovic, 2020; Jankovic, 2020).

The initial phase II trial of valbenazine, already approved by the FDA for the treatment of tardive dyskinesia, did not reach the primary endpoint in adults and children with TS, but this was thought to be due to underdosing and other methodologic problems. Similar explanation has been suggested for the failed T-Force GOLD study of valbenazine in children with TS. Further and better designed double-blind, placebo-controlled trials are currently under way with valbenazine and DTBZ for the treatment of tics. Although no randomized, double-blind, placebo-controlled trials have been published with the VMAT2 inhibitors in the treatment of tics, many experts used them as a first-line treatment in patients with TS who experience troublesome tics.

Several nonneuroleptic treatments have been reported to be effective in the treatment of tics. The dopamine agonist pergolide has been found to be useful in an open-label trial in 32 patients with TS, particularly if the TS is associated with RLS (Lipinski et al., 1997). In another study, 24 patients with TS (ages 7–17 years) who were medication-free for 4 weeks before treatment were randomized to receive either placebo or pergolide (150–300 mcg/day) for 6 weeks, followed by a 2-week washout, and then crossed over to other treatment arm (Gilbert et al., 2000). Nineteen patients completed the study. Tic severity, as determined by the main outcome measure, the YGTSS, fell by 50% on pergolide versus 42% on placebo ($P < 0.0011$). There was no significant difference between the two treatments on the Clinical Global Impression-Severity scale or on the parent-rated Tic Severity Self Report. In a follow-up randomized, placebo-controlled trial, the researchers concluded that “pergolide appeared to be an efficacious and safe medication for tic reduction in children, and may also improve attention deficit hyperactivity disorder symptoms” (Gilbert et al., 2003). Ropinirole, another dopamine agonist, also has been found to be effective in the treatment of TS (Anca et al., 2004). These findings seem paradoxical in view of the well-known beneficial effects of dopamine receptor blockers. It is possible, however, that the observed effects of dopamine agonists could be mediated by their action on dopamine D2 autoreceptors, thus reducing endogenous dopamine turnover. A single-blind levodopa challenge in six adult patients with TS resulted in a decrease in self-rated tic severity (Black and Mink, 2000), but this preliminary study needs to be confirmed by a larger and well-designed clinical trial. Pramipexole, a D3 and D2 receptor agonist, has not been found to be effective in a double-blind, placebo-controlled trial (Kurlan et al., 2012). Despite these studies suggesting modest benefit with dopamine agonists, these drugs are almost never used in the treatment of TS.

Various antiepileptics have been tried in patients with TS but, except for topiramate, have not been commonly used. In a randomized, double-blind, placebo-controlled, parallel group study of topiramate versus placebo involving 29 patients (26 males) with TS, mean age 16.5 (SD 9.89) years, there was a 14.29 (± 10.47) point reduction in the YGTSS TTS from baseline to visit five (day 70) with topiramate (mean dose: 118 mg) compared with a 5.00 (± 9.88) point reduction in the placebo group ($P = 0.0259$) (Jankovic et al., 2010). There were also statistically significant improvements in the

other components of the YGTSS and improvements in various secondary measures. No differences were observed in the frequency of adverse events between the two treatment groups. Although levetiracetam has been found to be effective in the treatment of tics in an open-label trial involving 60 patients with TS (Awaad et al., 2005), it is not clear whether this will be useful in the treatment of TS.

Clonazepam is sometimes useful in treating patients with TS, particularly in clonic tics such as blinking. Because some of the premonitory sensations resemble obsessions and the tics may be viewed as “compulsive” movements, anti-OCD medications also can be helpful. Treatment of the premonitory sensations may lead to improvement of these tics. Because sex steroids affect the expression of the TS gene and also modulate multiple neurotransmitter systems, antiandrogens have been tried in the treatment of TS. Flutamide, an acetanilide nonsteroidal androgen antagonist, has been found in one double-blind, placebo-controlled study to modestly and transiently reduce motor, but not phonic, tics, with a mild improvement in associated symptoms of OCD (Peterson et al., 1998b). Because of potentially serious side effects, such as diarrhea and fulminant hepatic necrosis, this drug should be reserved only for those patients in whom tics remain a disabling problem despite optimal anti-tic therapy. Baclofen, a GABA_B autoreceptor agonist, has been found to markedly decrease the severity of motor and phonic tics in 95% of 264 patients with TS (Awaad, 1999), but a double-blind, placebo-controlled, crossover trial of 9 patients with TS showed that the beneficial response to baclofen was due to improvement in the overall impairment score rather than a reduction of tic activity (Singer et al., 2001). Donepezil, a noncompetitive inhibitor of acetylcholinesterase, has been reported anecdotally to suppress tics (Hoopes, 1999). This observation, coupled with the finding that there is a marked reduction in cholinergic neurons in brains of patients with TS, should stimulate further research into the potential role of cholinergic system in TS (Benarroch, 2012).

Since the discovery that cannabinoids markedly potentiate neuroleptic-induced hypokinesia in rats, that cannabinoid receptors are densely located in the output nuclei of the basal ganglia, and that activation of these receptors increases GABAergic transmission and inhibition of glutamate release (Müller-Vahl et al., 1999; Müller-Vahl, 2013), coupled with some clinical observations, there has been growing interest in cannabinoids as a treatment of various movement disorders, including TS (Kluger et al., 2015; Lim et al., 2017). Many patients with TS reported that marijuana and cannabinoid helped them control their tics more than prescribed medications. Delta9-tetrahydrocannabinol (THC) was reported to reduce tics in a single-dose, crossover study in 12 patients and in a 6-week, randomized trial in 24 patients with TS (Müller-Vahl, 2003). Based on the available evidence the Cochrane review concluded that there is “Not enough evidence to support the use of cannabinoids in treating tics and obsessive compulsive behavior in people with Tourette’s syndrome” (Curtis et al., 2009). Well-designed controlled studies with a large number of patients are needed to determine the efficacy and safety of cannabinoids for treatment of TS.

Nicotine gum (e.g., Nicorette, 2 mg) and transdermal nicotine patch (e.g., NicoDerm, 7 mg) have been reported to potentiate the anti-tic effects of neuroleptics, but this observation needs to be confirmed by a placebo-controlled study

(Hughes et al., 1999). Open trials indicate that nicotine may suppress tics even in patients who have not been treated with D2 receptor-blocking drugs. The onset of anti-tic effect is quite rapid (0.5–3 hours) and the effects appear to persist for about 10 days after a 24-hour application of the patch (to the deltoid area). Side effects of the nicotine patch include local irritation and itching, nausea (in up to 70% lasting 4–6 hours), and transient headache with or without dizziness. There was apparently no evidence of nicotine dependence in these open trials. Although nicotine is a potent agonist of nicotinic acetylcholine receptors, when used chronically it causes desensitization of these receptors, thus exerting an antagonist effect. This is consistent with the observation that mecamylamine (Inversine, approved by the FDA as an antihypertensive and antismoking drug at 2.5 mg twice daily), an antihypertensive agent that acts as a peripheral ganglionic blocker with central antinicotinic, anticholinergic properties, improved tics and behavioral problems in 11 of 13 patients with TS at doses up to 5 mg/day (Sanberg et al., 1998). A subsequent double-blind, placebo-controlled study, however, failed to demonstrate a significant benefit in symptoms associated with TS (Silver et al., 2001). Nicotine also causes the presynaptic release of acetylcholine, GABA, norepinephrine, dopamine, serotonin, vasopressin, and beta-endorphins (Toth et al., 1992). Although the mechanism of action of nicotine in TS is unknown, it is interesting that nicotine initially activates midbrain dopamine neurons, but after longer exposure to nicotine, these neurons become desensitized, thus possibly accounting for the antidopaminergic (and anti-tic) effect of the drug (Pidoplichko et al., 1997). Studies suggest that nicotine inhibits some (e.g., $\alpha 4\beta 2$), but not other (e.g., $\alpha 3\beta 4$), striatal nicotinic receptors and that this inhibition could persist for several days (Lindstrom, 1997).

Both motor and phonic tics may be successfully treated with botulinum toxin (BTX) injections in the affected muscles (Videos 15.15, 15.19) (Kwak et al., 2000; Aguirregomozcorta et al., 2008; Vincent, 2008; Lotia and Jankovic, 2016; Billnitzer and Jankovic, 2020; Jankovic, 2020). Such focal chemodenervation has been shown not only to ameliorate the involuntary movements but also the premonitory sensory component. In the first patient treated for severe coprolalia with BTX injections into the vocalis muscles, the patient noted nearly complete resolution of the premonitory urge in his throat that was associated with marked improvement in his coprolalia (Scott et al., 1996). The benefits of BTX typically last 3 to 4 months, on average, and there are usually no serious complications except for transient focal weakness. In a follow-up study of 35 patients treated for troublesome or disabling tics in 115 sessions, the mean peak effect response was 2.8 (range: 0–4, 0 = no improvement, 4 = nearly complete resolution of tics) (Kwak et al., 2000). The mean duration of benefit was 14.4 weeks (up to 45 weeks). The latency to onset of benefit was 3.8 days (up to 10 days). The mean duration of tics before initial injections was 15.3 years (range: 1–62 years), and the mean duration of follow-up was 21.2 months (range: 1.5–84 months). Of 25 (84%) patients with notable premonitory sensory symptoms, 21 derived marked relief of these symptoms from BTX (mean benefit: 70.6%). Patients reported an overall global response of 62.7%. In a placebo-controlled study of 18 patients with simple motor tics, Marras and colleagues (2001) found a 39% reduction in the number of tics per minute within 2 weeks after injection

with BTX compared with an 6% increase in the placebo group ($P = 0.004$). In addition, there was a 0.46 reduction in urge scores with BTX compared with a 0.49 increase in the placebo group ($P = 0.02$). This preliminary study, however, lacked the power to show significant differences in other measured variables, such as severity score, tic suppression, pain, and patient global impression. There were many limitations of this study: the full effect of BTX might not have been appreciated at only 2 weeks; a single treatment protocol does not reflect the clinical practice of evaluating patients after several adjustments in doses and sites of injections; and the patients' symptoms were relatively mild, because the patients "did not rate themselves as significantly compromised by their treated tics" at baseline (Kurlan, 2001). In another study, involving 30 TS patients treated with BTX, improvement in phonic tics was reported by 93% of patients and 50% were reportedly free of phonic tics after the BTX; premonitory sensation and quality of life also improved (Porta et al., 2004). The most common side effect was hypophonia, noted in 80% of patients. BTX is clearly an effective treatment, particularly in patients with bothersome tics that are refractory to oral medications, such as repetitive cervical extension (so called "whiplash tics") seen in some cases with "malignant" TS (Cheung et al., 2007). BTX injections into the extensor muscles of the neck have been reported to reverse compressive cervical myelopathy as a complication of the "whiplash" tics (Krauss and Jankovic, 1996). Although focal weakness can occur after BTX injection, this is rarely troublesome or disabling and it is always transient. Although botulinum toxin injections have been found useful in many case series, rigorously conducted controlled studies are lacking (Pandey et al., 2018). ▶

A single-blind, placebo-controlled trial of two 20-minute applications of repetitive transcranial magnetic stimulation on two consecutive days provided no evidence that repetitive transcranial magnetic stimulation is of any benefit for patients with TS (Munchau et al., 2002). Improvement lasting up to 3 months with 1-Hz repetitive transcranial magnetic stimulation to bilateral SMA has been reported in patients with adult TS (Mantovani et al., 2007; Orth and Münchau, 2013).

Management of behavioral symptoms

Attention deficit–hyperactivity disorder

Behavioral modification, school and classroom adjustments, and other techniques described previously may be useful in the management of behavioral problems associated with TS for some selected patients, but in our experience, these approaches are rarely effective and at best play an ancillary role. Such behavioral strategies, however, may provide important emotional support for the patient and the family members and may be helpful in raising self-esteem and improve motivation (Peterson and Cohen, 1998).

Pharmacologic therapy is usually required when behavioral measures do not allow for a satisfactory adaptation and the symptoms of ADHD impair interpersonal relationships and interfere with academic or occupational performance (Elia et al., 1999; Zametkin and Ernst, 1999; Riddle and Carlson, 2001; Silay and Jankovic, 2005). It is estimated that there are more than 4 million children in the United States diagnosed with ADHD and compared with their non-ADHD

peers, children with ADHD suffer lower grades and achievement scores, and higher dropout rates. Although only half of the patients used anti-ADHD medications, several studies have found that such medications improve math and reading grades and overall have a favorable impact on academic performance (Scheffler et al., 2009).

It is beyond the scope of this review to discuss pharmacologic therapy of ADHD, but some current concepts will be reviewed briefly. CNS stimulants, such as methylphenidate, dextmethylphenidate, methamphetamine, dextroamphetamine, and pemoline are frequently used in the treatment of ADHD. CNS stimulants may exacerbate or precipitate tics in some patients, but it is still reasonable to use CNS stimulants and titrate the dosage to the lowest effective level (Wilens et al., 1995) (see Tables 15.2 and 15.3). In a 16-week, multicenter, randomized, double-blind clinical trial in which 136 children with ADHD and a chronic tic disorder were randomly administered clonidine alone, methylphenidate alone, combination of the two drugs, or placebo, the greatest benefit in improving attention occurred with the combination of the two active drugs (Tourette's Syndrome Study Group, 2002). Although 28% of the patients reported moderate or severe sedation with clonidine, the drugs were generally well tolerated. The results of this study argue against prior recommendations to avoid CNS stimulants in patients with the combination of TS and ADHD. Nevertheless, it is generally considered a prudent practice to attempt to control tics first (usually with antidopaminergic drugs) before introducing CNS stimulants.

Although methylphenidate was initially thought to work by raising brain levels of dopamine, more recent studies have suggested that its beneficial effects on ADHD are mediated via the serotonin system (Gainetdinov et al., 1999). A strain of mice with an inactivated gene for DAT has been described to have behavioral symptoms similar to those in children with ADHD. The hyperactivity of the mice was markedly ameliorated by methylphenidate, and this improvement correlated with an increase in brain serotonin. Other investigators have provided evidence that ADHD is a noradrenergic disorder (Biederman and Spencer, 1999). Although it has been suggested that long-term use of CNS stimulants might lead to substance abuse, some studies have demonstrated that untreated ADHD is a significant risk factor for substance abuse and that treatment of ADHD with CNS stimulants significantly reduces the risk for substance use disorder (Biederman et al., 1999).

Alpha-2 adrenergic agonists and tricyclic antidepressants are also useful in the treatment of ADHD, particularly if CNS stimulants are not well tolerated or are contraindicated. Clonidine, a presynaptic alpha-2 adrenergic agonist that is used as an antihypertensive because it decreases plasma norepinephrine, improves symptoms of ADHD and of impulse control problems. Despite "strong recommendation" made by some investigators for the use of clonidine and guanfacine in children with TS (Steeves et al., 2012), we find the drug less effective than the antidopaminergic drugs in the treatment of tics in children and adults.

Another drug that is increasingly used in the treatment of ADHD and impulse control problems is guanfacine. Guanfacine may have some advantages over clonidine in that it has a longer half-life, it appears to be less sedating, and it produces less hypotension. It also seems to be a more selective alpha-2

Video 15.19 Treatment with botulinum toxin.

noradrenergic receptor agonist and binds more selectively to the postsynaptic alpha-2A adrenergic receptors located in the prefrontal cortex. Although both clonidine and guanfacine appear to be effective in the treatment of attention deficit with and without hyperactivity, they appear to be particularly useful in the management of oppositional, argumentative, impulsive, and aggressive behavior. Although less effective than methylphenidate, the drugs have an advantage over methylphenidate in that they do not increase tics (Horrigan and Barnhill, 1995). The efficacy of this drug is supported by a pilot study of 13 patients with ADHD (but without TS) (Hunt et al., 1995). Another study, a 4-week, double-blind, placebo-controlled study of mild TS patients, however, failed to show significant neuropsychiatric or tic benefits (Cumings et al., 2002). The most frequently encountered side effects of the two drugs include sedation, dry mouth, itchy eyes, dizziness, headaches, fatigability, and postural hypotension. The beneficial effects might not be appreciated for several weeks after initiation of therapy, and the symptoms might markedly intensify if the medications are withdrawn abruptly.

We have also found deprenyl or selegiline, a monoamine oxidase-B (MAO-B) inhibitor, to be effective in controlling the symptoms of ADHD without exacerbating tics. Using the DuPaul Attention Deficit Hyperactivity Scale, the efficacy of this drug in ADHD has been confirmed by a double-blind placebo-controlled study (Feigin et al., 1996). It is not clear how deprenyl improves symptoms of ADHD, but the drug is known to metabolize into amphetamines. Other drugs that are frequently used in relatively mild cases of ADHD include imipramine, nortriptyline, and desipramine. Because of potential cardiotoxicity, an ECG or cardiologic evaluation might be needed before initiation of desipramine therapy, and follow-up ECGs should be performed every 3 to 6 months. Bupropion, an atypical antidepressant with stimulant properties, may be also useful in the management of ADHD, although like the other CNS stimulants, it may possibly exacerbate tics. Some nonstimulant drugs such as modafinil and atomoxetine (inhibitor of presynaptic nor-epinephrine transporter) (Michelson et al., 2001; Kratochvil et al., 2002) have been reported to be useful in the treatment of ADHD associated with TS. Modafinil, a nonschedule stimulant, alpha-1 receptor agonist that also acts on GABA and glutamate, has been found to be ineffective in a double-blind, placebo-controlled study of ADHD (Pliszka, 2003). Desmopressin, either as a nasal spray or in tablet form, with or without imipramine, can be used in the treatment of enuresis, which is frequently associated with ADHD.

Obsessive compulsive disorder

The role of cognitive-behavioral therapy in the treatment of OCD has not been well defined, although some investigators argue that when used alone or in combination of pharmacotherapy, it is the psychotherapeutic treatment of choice (Grant, 2014; Pauls et al., 2014). Although imipramine and desipramine have been reported to be useful in the treatment of OCD, the most effective drugs are the SSRIs (Silay and Jankovic, 2005). In addition to its antidepressant and anti-OCD effects, fluvoxamine has been found to be an effective treatment for children and adolescents with social phobia and anxiety (Research Unit on Pediatric Psychopharmacology

Anxiety Study Group, 2001). Up to 25% of patients with OCD show no meaningful improvement with the SSRIs and may therefore require polypharmacy (Laird, 1996). In some treatment-refractory cases, SSRIs might need to be combined with buspirone, clonazepam, lithium, and even neuroleptics (Goodman et al., 1998). When a combination or polypharmacy is used, it is prudent practice to discuss with the patients potential adverse reactions, including the serotonin syndrome (confusion, hypomania, agitation, myoclonus, hyperreflexia, sweating, tremor, diarrhea, and fever), and withdrawal phenomenon.

Systematic review of published and unpublished data on SSRIs in the treatment of childhood depression raised some questions about the safety and efficacy of these drugs in this population of depressed patients (Whittington et al., 2004). In addition to the SSRIs, anxiolytics, such as alprazolam and clonazepam, have been used with modest success. Similarly, MAO inhibitors, trazodone, and buspirone have limited efficacy in the treatment of OCD. Finally, surgical treatment such as DBS of the STN and other subcortical areas, may be used as a last resort in patients with disabling, medically intractable OCD (Greenberg et al., 2008; Mallet et al., 2008).

Surgical treatments

Surgical treatment of TS is covered in Chapter 7 and only briefly reviewed here. Although the overall experience of stereotactic ablative surgery in the treatment of tics has been rather disappointing, an increasing number of reports have provided evidence that DBS involving the thalamus, GP, and other targets may be a very effective strategy to treat uncontrollable tics (Viswanathan et al., 2012; Frait et al., 2015; Schrock et al., 2015; Martinez-Ramirez et al., 2018; Johnson et al., 2019) (Fig. 15.5). Experience with 17 patients, median age 23 years (range: 11–40), who have been treated with ablative procedures between 1970 and 1998 was reviewed by Babel and associates (2001). Unilateral zona incerta and nucleus ventrolateralis thalamus/lamina medullaris thalamus (VL/LM) lesioning was used, and occasional second surgery on the contralateral side was performed. The authors concluded that the procedure(s) “sufficiently” reduced both motor and phonic tics. Transient complications were reported in 68% of patients, and only one patient suffered permanent complication. Medial thalamus, particularly centromedian/parafascicular complex (CM-PF), has long been considered a target not only in ablative procedures but also in DBS treatment of tics and OCD (Nuttin et al., 1999; Vandewalle et al., 1999; Diederich et al., 2005; Savica et al., 2012). Nuttin and colleagues (2003) noted beneficial effects in OCD with bilateral anterior capsular stimulation after 1 year of stimulation, but all six patients remained defective in several domains of HRQOL. The GPi has been increasingly used as the target in patients with disabling tics and because of its extensive connections to the prefrontal cortex, an area that influences cognition and mood (Diederich et al., 2005; Shahed et al., 2007; Dehning et al., 2008, 2011; Zhang et al., 2014; Kefalopoulou et al., 2015). This selection is supported by previous reports of successful treatment with bilateral GPi DBS in two TS patients. In one study, a comparison of bilateral GPi to bilateral medial thalamic stimulation in the same patient found greater tic reduction (95% versus 80%) at lower settings with GPi stimulation (Diederich et al., 2005),

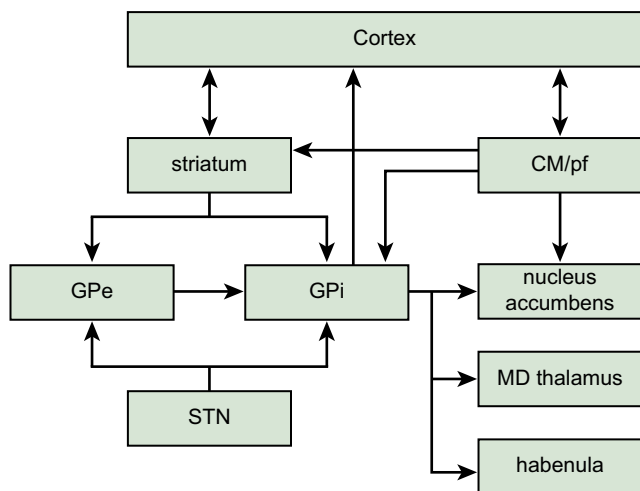


Fig. 15.5 Deep brain stimulation for Tourette syndrome: target selection. CM-PF, Centro-medial parafascicular; GPe, globus pallidus externus; GPi, globus pallidus internus; MD, mediodorsal; STN, subthalamic nucleus.

(Reproduced with permission from Viswanathan A, Jimenez-Shahed J, Baizabal Carvallo JF, Jankovic J. Deep brain stimulation for Tourette syndrome: Target selection. *Stereotact Funct Neurosurg.* 2012;90[4]:213–224.)

but another report described similar degrees of improvement using either site (Ackermans et al., 2006). In a follow-up of 13 patients with medically intractable TS treated with GPi DBS, there was a mean 52.1% reduction in the YGTSS score, with gradual improvement during the follow-up period (Zhang et al., 2014). In a randomized, double-blind, crossover trial of GPi DBS, 15 patients with severe medically refractory TS (11 men, mean age: 34.7 years; range: 25–55), 13 of whom completed all the blinded assessments, the mean YGTSS total score decreased from 87.9 (± 9.2) at baseline to 68.3 (± 18.6) during the on-stimulation assessment ($P = 0.048$) (Kefalopoulou et al., 2015). The electrodes were placed under general anesthesia with MRI guidance (rather than via microelectrode recording) into the anteromedial GPi, which is more directly connected to the limbic pathways (2 patients had posteroventral GPi placement). Despite only modest improvement in mean YGTSS (6 patients had less than 10% improvement) and in video-based tic count, no significant improvement in OCD measures, and 13% infection rate, the authors concluded that “GPi stimulation led to a significant improvement in tic severity, with an overall acceptable safety profile.” This conclusion was largely based on 40.1% improvement in tics and improvements in the Beck Depression Inventory and in quality of life measurement during the open-label phase of the study compared with baseline.

Although DBS may be associated with behavioral and cognitive complications, neuropsychological and psychiatric comorbidities in TS should not necessarily be a contraindication to DBS, because these conditions may in fact improve after GPi stimulation. Martinez-Fernandez and colleagues (2011) reported their experience with five patients implanted in the GPi for TS. Three patients were implanted in the posteroventral GPi, and two patients underwent implantation in the anteromedial GPi. One patient who initially had implantation in the posteroventral GPi underwent revision to the anteromedial target because of capsular side effects limiting the level of stimulation. They report the follow-up for the six implantations performed in these five patients

over a mean follow-up of 1 year. The mean YGTSS decreased by 29% from 77.8 to 54.2, and the mean Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) decreased from 16.3 preoperatively to 10.8 postoperatively, an improvement that was maintained at last follow-up. In a patient with cervical myelopathy secondary to cervical tics, anteromedial pallidal DBS resulted in marked and sustained improvement in her tics, limb strength, and bladder symptoms (Huasen et al., 2014).

Martinez-Fernandez (2018) published 1-year outcomes on a worldwide experience using TS DBS. The International Deep Brain Stimulation Database and Registry enrolled 185 patients. “The mean (SD) total Yale Global Tic Severity Scale score improved from 75.01 (18.36) at baseline to 41.19 (20.00) at 1 year after DBS implantation ($P < .001$). The mean (SD) motor tic subscore improved from 21.00 (3.72) at baseline to 12.91 (5.78) after 1 year ($P < .001$), and the mean (SD) phonic tic subscore improved from 16.82 (6.56) at baseline to 9.63 (6.99) at 1 year ($P < .001$). The overall adverse event rate was 35.4% (56 of 158 patients), with intracranial hemorrhage occurring in 2 patients (1.3%), infection in 4 patients with 5 events (3.2%), and lead explantation in 1 patient (0.6%). The most common stimulation-induced adverse effects were dysarthria (10 [6.3%]) and paresthesia (13 [8.2%]).” (Martinez-Ramirez et al., 2018).

Careful selection of patients, experience with DBS procedure, and comprehensive assessments at baseline and at follow-up visits are essential for successful outcome of DBS in TS (Mink et al., 2006; Schrock et al., 2015). Although these observations must be confirmed by a controlled trial before DBS can be recommended even to severely affected patients, it suggests that stimulation of certain targets involved in the limbic striatopallidal-thalamocortical system could be beneficial in the treatment of various aspects of TS. DBS of the median part of the thalamus also resulted in a marked improvement in tics (Bajwa et al., 2007). DBS of the ventral capsule and ventral striatum also has been reported to be effective in patients with severe OCD (Greenberg et al., 2006). Based on a double-blind assessment of 5 patients with TS undergoing bilateral thalamic DBS, there was a significant ($P < 0.03$) reduction in the modified Rush Video-Based Rating Scale score (primary outcome measure) (Goetz et al., 1999) and improvement was also noted in motor and phonic tic counts and on the YGTSS and TTS Symptom List scores (secondary outcome measures) (Maciunas et al., 2007). In addition, there was evidence of improvement in the quality of life indices and 3 of 5 patients had marked improvement according to all primary and secondary outcome measures. In another double-blind clinical trial, involving 6 TS patients with DBS targeting the centromedian nucleus-substantia periventricularis-nucleus ventro-oralis internus cross point, the tic severity during “on” stimulation was significantly lower than during “off” stimulation, with substantial improvement (37%) on the YGTSS (mean: 41.1 ± 5.4 versus 25.6 ± 12.8 ; $P = 0.046$) (Ackermans et al., 2011). The benefits were sustained 1 year after surgery, with significant improvement (49%) on the YGTSS (mean: 42.2 ± 3.1 versus 21.5 ± 11.1 ; $P = 0.028$) compared with preoperative assessments. There were no improvements in secondary outcome measures, and there was some deterioration in attention. Serious adverse events included one small hemorrhage ventral to the tip of the electrode, one infection of

the pulse generator, subjective gaze disturbances, and reduction of energy levels in all patients. In the largest reported series of DBS in TS, 18 TS patients underwent bilateral DBS of the centro-median parafascicular (CM-PF) and ventralis oralis complex of the thalamus (Servello et al., 2008). Followed up to 18 months, most patients apparently showed improvement in tics and OCD, SIB, and other comorbidities. In a prospective 24-month follow-up of 15 of the original 18 patients, there continued to be marked improvement in tics, OCD, anxiety, and depression with subjective perception of improved social functioning and quality of life (Porta et al., 2009). It would be helpful to know what happened to the 3 patients not included in this open label, observational study. In addition, a blinded review of videos before and after

treatment would provide more objective measure of efficacy (Black et al., 2009). OCD without TS also has been reported to improve with STN DBS (Polosan et al., 2016). Selection guidelines for DBS in patients with TS have been updated (Schrock et al., 2015).

Finally, the observation that vagal nerve stimulation also favorably modifies the frequency and intensity of facial tics suggests that the brainstem plays a role in generation of modulation of tics (Diamond et al., 2006).

The management of TS is evolving as new medications and interventions are being developed. In addition to conventional medical and surgical treatment, there is growing interest in experimental therapeutics of TS (Fig. 15.6).

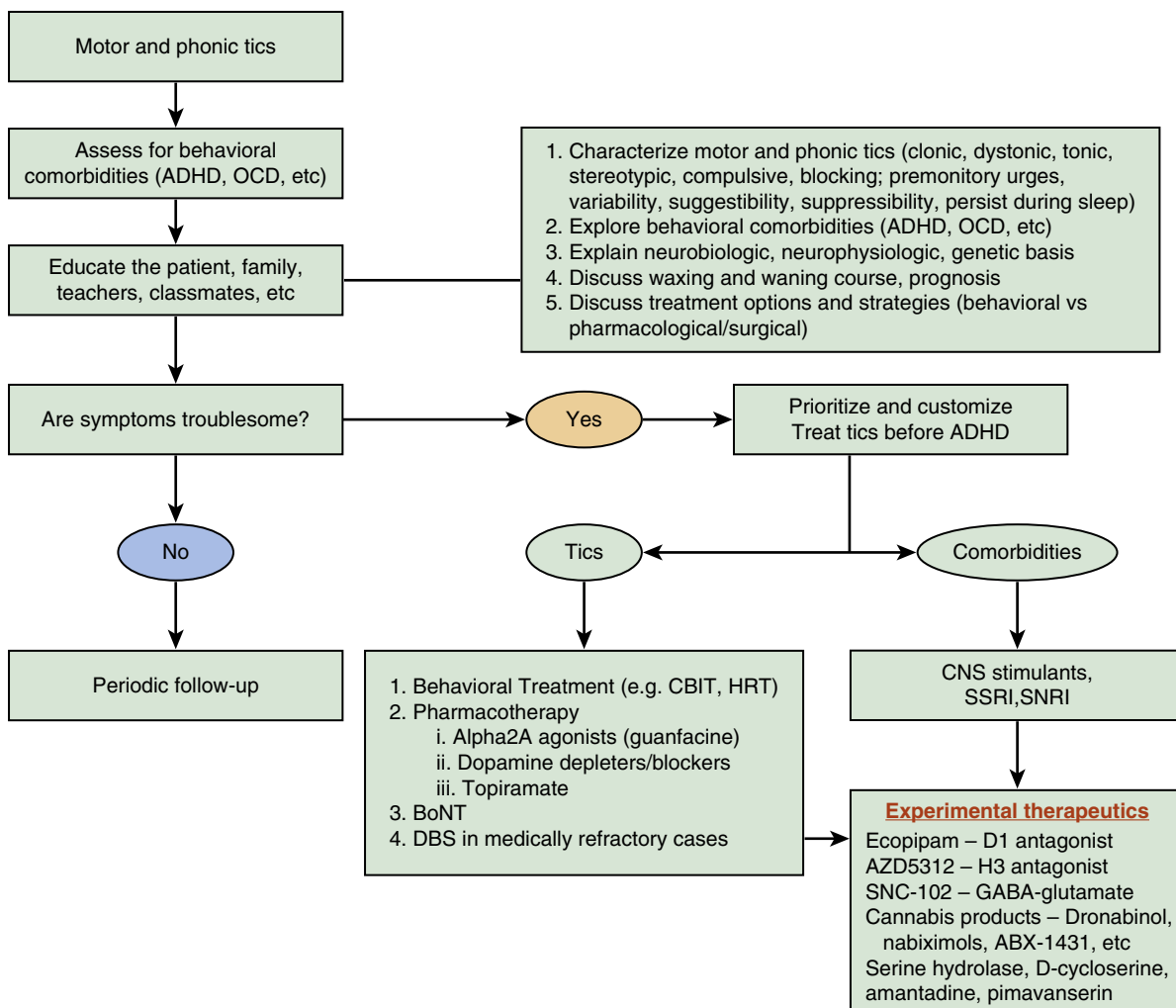


Fig. 15.6 Treatment algorithm for Tourette syndrome. ADHD, Attention deficit–hyperactivity disorder; BTX, botulinum toxin; CBIT, Comprehensive Behavioral Intervention for Tic Disorders; CNS, central nervous system; DBS, deep brain stimulation; GABA, gamma-aminobutyric acid; HRT, habit-reversal training; OCD, obsessive-compulsive disorder; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Appendix

Tourette Association of America

<https://tourette.org/>

Obsessive Compulsive Foundation

<http://www.ocfoundation.org/>

Children and Adults with Attention-Deficit Disorder

<http://www.chadd.org/>

References available on Expert Consult:

www.expertconsult.com.

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Stereotypies

Chapter contents

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Introduction

Stereotypies may be defined as involuntary or involuntary (in response to or induced by inner sensory stimulus or unwanted feeling), coordinated, patterned, repetitive, rhythmic, seemingly purposeless movements or utterances (Jankovic, 1994; Jankovic, 2005; Singer, 2009; Edwards et al., 2012; Oakley et al., 2015). Although each child tends to have his or her own repertoire of movements, typical motor stereotypies include body rocking, head nodding, head banging, hand waving, covering ears, fluttering of fingers in front of the face, repetitive and sequential finger movements, eye deviations, lip smacking, and chewing movements, pacing, object fixation, skin picking; phonic stereotypies include grunting, moaning, and humming. Stereotypies are usually either continuous (uninterrupted), such as those seen in patients with tardive dyskinesia, intellectual disability or autism, or continual (with interruption), such as the stereotypic tics seen in patients with Tourette syndrome (TS). They can be either continual or intermittent in patients with intellectual disability or autism. Mannerisms, which are gestures that are peculiar or unique to the individual, may at times seem stereotypic (patterned), but they are usually not continual.

Automatisms in patients with seizures can be viewed as paroxysmal stereotypies (Sadleir et al., 2009). These are usually manifested by repetitive, rhythmic behaviors that occur during frontal lobe seizures and in a reproducible pattern for a given patient. In 17 patients with frontal lobe epilepsy who manifested motor and/or verbal stereotypies during recordings with depth electrodes (stereoelectroencephalography) as part of pre-surgical evaluation, the progression of stereotypies correlated with a rostrocaudal gradient within the frontal lobes (McGonigal and Chauvel, 2014).

One unusual form of stereotypic seizures is the “sunflower syndrome”, a form of photosensitive epilepsy characterized by

paroxysmal episodes of hand waving stereotypies, induced by the patients when they look toward a light source, often the sun, and wave one hand with abducted fingers in front of their face (Barnett et al., 2020; Greenen et al. 2021). This may be associated with eye fluttering or blinking, and this may evolve into generalized tonic-clonic and other seizures. EEG usually shows a normal background with 3–4 Hz spike waves $\pm$ polyspike waves as well as a photoparoxysmal response (Baumer and Porter, 2018). It usually responds to valproate or lamotrigine, but not to levetiracetam.

There is often an overlap between stereotypies and self-injurious behavior (SIB), such as biting, scratching, and hitting (Jankovic and Sekula, 1998; Schroeder et al., 2001; Lutz et al., 2003; Fischer et al., 2020). SIB, defined as “deliberate, repetitive and persistent behaviors that are directed towards the body and lead to physical injury”, may be seen in a variety neurological, developmental, metabolic and genetic disorders (Fischer et al., 2020).

In addition to motor and phonic types, stereotypies can be classified as either simple (e.g., foot tapping, body rocking) or complex (e.g., complicated rituals, sitting down in and rising from a chair). Stereotypies also can be described according to the distribution of the predominant site of involvement (orolingual, hand, leg, truncal). The term *stereotypy* should be used to describe a phenomenologic, not an etiologic, category of hyperkinetic movement disorders. However, recognition of stereotypy as a distinct movement disorder can logically lead from a phenomenologic to an etiologic diagnosis (Table 16.1). Thus, stereotypy is a motor-behavioral disorder that is found most frequently in patients who are in the borderland between neurology and psychiatry.

There are no validated stereotypy scales designed to measure severity and response to treatment. In one study of behavioral intervention, the Stereotypy Severity Scale was used, which was modified from the Yale Global Tic Severity Scale (Miller et al., 2006).

Table 16.1 Classification of stereotypies**Physiologic**

- Mannerisms or habits
- Normal developmental stereotypies
- Spasmus nutans
- Shuddering attacks
- Gratification (masturbatory) behavior

Pathologic

- Intellectual disability
- Pervasive developmental disorders (autism)
- Schizophrenia
- Catatonia
- Obsessive-compulsive disorder
- Frontotemporal degeneration
- Tourette syndrome
- Neuroacanthocytosis
- Restless leg syndrome
- Epileptic automatism
- Structural lesions (medial-frontoparietal cortex, cerebellum)
- Tardive (dopamine receptor–blocking drugs) and other dyskinesias (levodopa)
- Akathisia
- Psychogenic

Pathophysiology of stereotypies

There is no clear anatomic-clinical correlation for stereotypies, although it is thought that both cortical and subcortical structures are involved. Although dysfunction in the basal ganglia has been implicated in the pathogenesis of certain stereotypies, some studies have also provided evidence for the role of the mesolimbic system, particularly the nucleus accumbens–amygdala pathway, in the pathogenesis of stereotypic movements. Stereotypies with or without associated obsessive-compulsive behavior (OCB) have been observed in patients with structural lesions in different anatomic areas, including bilateral lesions of the medial frontoparietal cortices (Sato et al., 2001; Kwak and Jankovic, 2002) and cerebellum (Hottinger-Blanc et al., 2002). Some have suggested motor stereotypy is a manifestation of poor sensorimotor integration, but further studies are needed to elucidate the pathophysiologic processes of this hyperkinetic disorder (Shafer et al., 2017).

Studies of stereotypies in animals may provide insight into the pathogenesis of habits, rituals, and other repetitive behaviors in humans (Graybiel, 2008). Stereotypic behavior is common in animals in lower species up to and including the primates and are particularly common in farm and zoo animals that are housed in restraining environments with low stimulation (Garner et al., 2003; Lutz et al., 2003; Fischer et al., 2020) (Video 16.1). SIB, observed in 14% of housed monkeys, may be viewed as a form of stereotypy (Novak, 2003). Therefore, stereotypy has been viewed as either a self-generating sensory stimulus or a motor expression of underlying tension and anxiety. The repetitive and ritualistic behavior that some animals display has been used as an experimental model of obsessive-compulsive disorder (OCD). Indeed, studies of animal and human stereotypies have provided important insights into relationships between motor function and behavior. Some veterinarian scientists have even suggested changing the nomenclature of stereotypies to OCB, but there is little evidence to

indicate that the stereotypic behavior that is observed in animals is driven by underlying obsessions and represents compulsive behavior (Garner et al., 2003; Low, 2003). ●

The pathophysiology of stereotypies is not well understood. In one study of children with “primary motor stereotypies” movement-related cortical potentials (MRCPs), which precede and are associated with activation of cortical areas involved in the generation of self-initiated voluntary movements, no such potentials were found before the occurrence of a complex stereotypy (Houdayer et al., 2014). Because the premotor cortical areas are apparently not involved in the preparation of these complex movements, stereotypies may be viewed as truly involuntary movements. It is not clear whether the underlying pathophysiologic mechanisms are different in other forms of stereotypies.

Most studies of stereotypic behavior in experimental animals have focused on the role of dopaminergic systems in the basal ganglia and limbic structures. Intrastriatal injection of dopamine and systemic administration of both presynaptically active dopaminergic drugs, such as amphetamine, and postsynaptically active dopamine agonists, such as apomorphine, in rats produce dose-related repetitive sniffing, gnawing, licking, biting, rearing, head bobbing, grooming, and other stereotyped learned activities.

The observation that self-biting behavior induced by dopaminergic drugs in 6-hydroxydopamine rats and monkeys with a unilateral lesion in the ventral medial tegmentum can be blocked by a selective D1 antagonist (SCH 23390) suggests that SIB is mediated primarily by the D1 receptors (Schroeder et al., 2001). Selective dopamine receptor agonists and antagonists have been used in experimental models to study different effects of D1 and D2 receptors on stereotypic behavior. SKF 38393, a D1 agonist, produced no stereotypic behavior in normal rats, but it did enhance stereotypy induced by apomorphine, a mixed D1 and D2 agonist (Koller and Herber, 1988). This suggests that the D2 dopamine receptors mediate stereotypic behavior and that activation of the D1 receptors potentiates these D2-mediated effects. Additional evidence for the role of D2 dopamine receptors in the pathogenesis of stereotypies is the observation that upregulation of D2 receptors (e.g., with haloperidol, a selective D2 antagonist) but not of D1 receptors (e.g., with SCH 23390, a selective D1 antagonist), enhanced apomorphine-induced stereotypies (Chipkin et al., 1987). Drug-induced models of stereotypy, however, might not accurately reflect spontaneous or disease-related repetitive behaviors. Using several selective dopaminergic agonists (apomorphine, SKF81297, and quinpirole) and intrastriatal administration of the D2 receptor antagonist raclopride to study stereotypic behaviors in the deer mouse model of spontaneous and persistent stereotypy showed that spontaneously emitted and drug-induced stereotypies may have different mechanisms (Presti et al., 2004). Nevertheless, these studies suggest that the striatal dopaminergic system is significantly involved in stereotypic behaviors. Oral and forelimb stereotypies can be induced in the rat with injections of amphetamine into the ventrolateral striatum (Canales et al., 2000), and certain genes can be activated in the striasomes with these drugs when they are administered orally (Canales and Graybiel, 2000). These studies provide further support for a basal ganglia involvement in stereotypies. Although there is experimental evidence from rodent and primate studies to support the notion that differential activation of striosomes

Video 16.1 Animal stereotypes.

in the basal ganglia plays an important role in pathophysiology of stereotypes (Saka and Graybiel, 2003), some studies found that motor stereotypes do not require enhanced activation of striosomes (Glickstein and Schmauss, 2004).

In addition to the basal ganglia, the pontine tegmentum has been implicated in certain stereotypes, particularly repetitive involuntary leg movements that are somewhat similar to the leg movement in patients with restless legs syndrome (RLS) (Lee et al., 2005).

Besides the classic neurotransmitters, evidence is accumulating in support of involvement of neuropeptides as modulators of stereotypic behavior. For example, microinjection of cholecystokinin and neurotensin into the medial nucleus accumbens markedly potentiated apomorphine-induced stereotypy (Blumstein et al., 1987). Because injection of these peptides into the striatum had no effect on the apomorphine-induced stereotypy, these studies provide additional evidence for the involvement of the limbic system in the pathogenesis of this movement disorder. Improvement in SIB observed in autistic children after administration of the opiate blockers naloxone and naltrexone has been interpreted as evidence for the role of endogenous opiates (e.g., beta-endorphins) in this abnormal behavior (Sandman, 1988; Fischer et al., 2020). Additional support for the role of endorphins in self-injurious and stereotypic behavior is the finding of elevated plasma and cerebrospinal fluid levels of beta-endorphins in autistic patients with these behavioral abnormalities (Sandman, 1988). The emphasis has shifted to the serotonin system, supported by the observation that certain animal behaviors improve with serotonin uptake inhibitors (Hugo et al., 2003).

Physiologic stereotypes

Physiologic stereotypes are stereotypic movements that are not due to any identifiable cause or associated with abnormal pathologic features. They are reported in about 2% to 4% of otherwise normally developing children (Foster, 1998). Certain stereotypes, such as hair twisting, drumming with fingers, tapping of the feet, adduction-abduction, and crossing-uncrossing and other repetitive movements of the legs, may be part of a repertoire of movements, also referred to as mannerisms or habits, seen in otherwise normal individuals (Bonnet et al., 2010). Developmental and benign movement disorders in childhood include benign jitteriness or myoclonus of newborn, sleep-related rhythmic movements, spasmus nutans, paroxysmal tonic gaze, benign paroxysmal torticollis, shuddering attacks, transient dystonia of infancy, gratification behavior, mirror movements, Sandifer syndrome, and a variety of normal stereotypes (Bonnet et al., 2010). In infants and children, there seems to be a progression of normal stereotypes (Castellanos et al., 1996). For example, thumb sucking and hand sucking in infancy are later replaced by body rocking, head rolling, and head banging. Some infants demonstrate head stereotypes that resemble bobble-head doll syndrome, sometimes associated with ataxia but without any other neurologic deficit and normal subsequent development (Hottinger-Blanc et al., 2002). A review of 40 “normal” children, aged 9 months to 17 years, with complex hand and arm stereotypes, such as flapping, shaking, clenching, posturing, and other “ritual” movements, showed that the movements can be temporarily suppressed in nearly all when cued

(Mahone et al., 2004). Although the children were classified as “normal,” 25% had comorbid attention deficit-hyperactivity disorder (ADHD), and 20% had learning disability, probably the result of referral bias, because this group is also known for their work in TS. This was supported by a relatively high family history of stereotypes (25%) and tics (33%). A variety of stereotypes can be observed in children (Castellanos et al., 1996; Tan et al., 1997) and young adults (Niehaus et al., 2000) without any other neurologic deficits. We have observed otherwise normal children with persistent head stereotypes similar to the bobble-head syndrome but without abnormal neuroimaging studies. Stereotypes may also occur during development of otherwise normal children who are congenitally blind (Troster et al., 1991) or deaf (Bachara and Phelan, 1980).

Head banging is seen in up to 15% of normal children (Sallustro and Atwell, 1978). Some girls exhibit stereotypic crossing and extending of legs, which actually represents a self-gratifying or masturbatory behavior (Mink and Neil, 1995; Yang et al., 2005; Bonnet et al., 2010) (Video 16.2). Otherwise normal children can also develop bruxism, nail biting, trichotillomania, and other stereotypic behaviors. These behaviors often have been attributed to underlying generalized anxiety disorder or OCD. However, when stereotypy is accompanied by other behavioral and neurologic findings, it usually indicates the presence of a serious underlying neurologic and/or psychiatric disorder. Although motor stereotypes most frequently occur in a setting of intellectual disability or autism, in a clinical cohort of 100 normally developing children with motor stereotypes, some involuntary or unvoluntary movements continued in 62% of the children followed for over 5 years (Harris et al., 2008). Nearly half the children exhibit other comorbidities, including ADHD (30%), tics (18%), and OCB or OCD (10%). It is possible, however, that many of these children had TS, as suggested by the comorbidities typically associated with TS and positive family histories of involuntary movements in 25%. The study also suggested that the clinical course of children who exhibit head nodding may be more favorable than those whose motor stereotypy predominantly involves the hands and arms. In another study designed to better characterize stereotypic movements and differentiate them from tics, Freeman and colleagues (2010) evaluated 40 children (31 males), with mean age at onset of stereotypes at 17 months, without SIB, intellectual disability, sensory impairment, or an autistic spectrum disorder, and found neuropsychiatric comorbidity in 30 (ADHD in 16, tics in 18, developmental coordination disorder in 16, and OCD in 2). In contrast to their parents, children liked their movements, which were usually associated with excitement or imaginative play. Of the 39 children followed for longer than 6 months, the behavior stopped or was occurred primarily privately in 25. In one study, based on a telephone survey of parents of 49 patients with primary stereotypes (mean age at time of follow-up 13.1 ± 3.2 years, range 9.0 to 20.8 years) the involuntary movements began in nearly all children before the age of 3 years and persisted for 10 to 15 years in half of the subjects (Oakley et al., 2015). Furthermore, over a third had a family history of stereotypes. In this series, 21% of had stereotypes less than once a day (continual). Because patients with comorbid tics and ADHD, noted in 22% and 63% of subjects, respectively, were included in the study, it is not clear whether the findings are generalizable to a population without these comorbidities. ►

Video 16.2 Self-gratifying behavior.

Pathologic stereotypies

Leg stereotypy syndrome

One of the most common primary stereotypies that can have onset in childhood but persisting through adulthood is leg stereotypy syndrome (Jankovic, 2015; Lotia et al., 2018). Although most people with this condition do not seek medical attention and may not be even fully aware of the leg movement, the disorder can be quite troublesome to many affected individuals and very disruptive to others. This condition is often manifested by repetitive, continuous movement present almost exclusively in the legs while the patient is seated but may also occur while standing, during which time it involves not only the legs but also may manifest by swaying of the trunk. Although some individuals describe these movements as soothing, there is no evidence that they are associated with or driven by anxiety or an irresistible urge to move, as is typically seen with akathisia or RLS. Frequently leg stereotypy syndrome is familial; however, the epidemiologic factors, pathophysiologic processors, and treatment have not been studied. There have been other descriptions in the literature of motor leg restlessness, especially in patients with Parkinson disease (PD), the features of which may overlap with but are clearly distinct from leg stereotypy syndrome (Suzuki et al., 2017; Matsubara et al., 2018).

Intellectual impairment

It is beyond the scope of this chapter to review the current notions about the clinical features and pathogenesis of intellectual impairment, but the reader is referred to a review of this topic (Nokelainen and Flint, 2002). In one study of 102 institutionalized mentally retarded people, with a mean age of 35 years (range: 21–68 years), 34% exhibited at least one type of stereotypy (rhythmic movement, 26%; bizarre posturing, 13%; object manipulation, 7%; and others) (Dura et al., 1987). In another study, 100 individuals with severe or profound intellectual disability were randomly selected and followed for 26 years (Thompson and Reid, 2002). Their behavior was recorded through carer and psychiatrist ratings using the Modified Manifest Abnormality Scale of the Clinical Interview Schedule. The follow-up evaluations found that stereotypies, emotional abnormalities, eye avoidance, and other behavioral symptoms persist. Although there seems to be an inverse correlation between stereotypies and IQ, stereotypic behavior may be seen even in the mildly retarded. In some intellectual disability disorders, typically Lesch–Nyhan syndrome, stereotypies are associated with SIB (Fischer et al., 2020) (Videos 16.3 and 16.4). Supersensitivity of D1 receptors, possibly in response to abnormal arborization of dopamine neurons in the striatum, has been postulated as a possible mechanism of SIB in Lesch–Nyhan syndrome (Jankovic et al., 1988). More recently, it has been shown that mice missing *HPRT1*, the gene mutated in Lesch–Nyhan syndrome, and the first gene ever “knocked out,” and engineered with a copy of the related human gene, called *PRTFDC1*, are more aggressive and, under the influence of amphetamines, display repetitive behavior resembling nail-biting and other SIBs (Keebaugh et al., 2011; Fischer et al., 2020). 🎧

Autistic spectrum disorders

Autism is a type of pervasive developmental disorder, sometimes referred to as autistic spectrum disorders, with onset

during infancy or childhood, characterized by impairment in reciprocal social and interpersonal interactions, impairment in verbal and nonverbal communication, markedly restricted repertoire of activities and interests, and stereotyped movements (Bodfish et al., 2001; Gritti et al., 2003; Lam et al., 2008; Goldman and Greene, 2013; Baumer and Spence, 2018) (Tables 16.2 and 16.3). Many autistic patients also exhibit other abnormal behaviors, such as preoccupations, circumscribed interest patterns, abnormal

Table 16.2 Clinical features associated with autism

- Insistence on sameness; resistance to change
- Difficulty in expressing needs; uses gestures or pointing instead of words
- Aggressive and self-injurious behavior
- Repeating words or phrases in place of normal, responsive language
- Laughing, crying, showing distress for reasons not apparent to others
- Prefers to be alone; aloof manner
- Tantrums
- Difficulty in mixing with others
- May not want to cuddle or be cuddled
- Little or no eye contact
- Unresponsive to normal teaching methods
- Sustained odd play
- Spins objects
- Inappropriate attachments to objects
- Apparent oversensitivity or undersensitivity to pain
- No real fears of danger
- Noticeable physical overactivity or extreme underactivity
- Uneven gross/fine motor skills
- Not responsive to verbal cues; acts as if deaf although hearing tests in normal range

Table 16.3 Stereotypies associated with autism

Body parts	Types of movements
Face	Grimacing, lips, tongue movements, opening the mouth
Head, trunk, shoulders	Head tilting, shaking, nodding; body rocking, bending, scrunching; arching the back; shrugging the shoulders
Arm / leg	Flapping, crossing the arms on the chest, stamping the feet
Hand / finger	Shaking, tapping, waving, clapping, opening–closing, twirling the hand or fingers
Hand / finger	Shaking, tapping, twirling an object with object
Gait	Pacing, jumping, running, skipping, spinning
Self-directed	Covering the ears; mouthing; smelling; rubbing the eyes; tapping the chin; banging the arms against the body; slapping self or an object or surface; touching genitals
Visual	Staring at an object or the fingers “out of the corner of the eyes”

From Goldman S, Wang C, Salgado MW, Greene PE, Kim M, Rapin I. Motor stereotypies in children with autism and other developmental disorders. *Dev Med Child Neurol*. 2009;51:30–38.

Video 16.3 Lesch–Nyhan syndrome.

Video 16.4 Lesch–Nyhan syndrome.

object attachments, cognitive rigidity, exaggerated sensory responses. Earlier studies have suggested that about 0.1% of all children are autistic (Sugiyama and Abe, 1989), but more recent epidemiologic studies have estimated that the prevalence of autistic disorders and related pervasive developmental disorders to range between 0.3% (Yeargin-Allsopp et al., 2003) and 0.6% (Chakrabarti and Fombonne, 2001). In children and adults with autism of any cause, stereotypes and other self-stimulatory activities constitute the most recognizable symptoms. Typical stereotypes that are seen in autistic individuals include facial grimacing, staring at flickering light, waving objects in front of the eyes, producing repetitive sounds, arm flapping, rhythmic body rocking, repetitive touching, feeling and smelling of objects, jumping, walking on toes, and unusual hand and body postures. In a study of motor stereotypes recorded during 15 minutes of videos of standardized play sessions in 277 children (209 males, 68 females), 129 with autistic disorder and 148 cognitively matched nonautistic developmentally disordered children, hand/finger repetitive movements, and pacing, jumping, and spinning movements during gait were two types of stereotypes that were especially suggestive of autism (Goldman et al., 2009). In one study, primary stereotypes in developing children (N = 28) were compared with secondary stereotypes, those occurring in autistic or mentally retarded children (N = 28) (Ghosh et al., 2012). The investigators found that primary stereotypes were predominantly motor, simple, of shorter duration, and of less frequency, whereas secondary stereotypes had more vocalization, complexity, longer durations, and higher frequencies. In one study of 615 children with autistic spectrum disorder designed to examine gender differences in restricted and repetitive behaviors and interests found boys were more likely to have heightened stereotyped behaviors and restricted interests whereas compulsivity, sameness, restricted, and SIB were more prominent in girls (Antezana et al., 2018). In another study involving 1024 children with autism spectrum disorder, the difference, if any, between males and female were quite subtle (Knutsen et al., 2018).

The motor manifestations are often associated with insensitivity or excessive sensitivity to sensory stimuli, including pain and extremes of temperature, preoccupations with perceptual sensations such as lights or odors, insistence on preservation of sameness, and absence of fear or other emotional reactions. Self-stimulatory and SIBs, such as self-biting and head banging, are also common. In addition to these and other behavioral and developmental abnormalities, some autistic individuals have isolated areas of remarkable and sometimes spectacular mental skills, the so-called savant syndrome (Miller, 1999; Treffert, 1999). The mechanism of the savant phenotype in the setting of autism is not well understood, but studies of one genetic model of autism, the Shank1 knockout mice, may provide some insight (Hung et al., 2008). The Shank family of postsynaptic scaffold proteins have been found to be abundantly present in the postsynaptic density of central excitatory synapses. When these postsynaptic proteins are altered, Shank1 knockout mice as is expressed in cultured hippocampal neurons, Shank promotes the maturation and enlargement, surprisingly the mice displayed enhanced performance in a spatial learning task, although their long-term memory retention in this task was impaired (Hung et al., 2008). The authors suggested that the superior learning ability of these mutant mice was similar to what has been observed in human autistic savants. *Shank3*

gene mutations have been found to be associated with the 22q13 deletion syndrome (Phelan-McDermid syndrome), an autistic spectrum disorder, presumably caused by striatal dysfunction related to SHANK3, a postsynaptic protein critical in the normal development of neuronal connectivity (Peca et al., 2011). Mice with *Shank3* gene deletions exhibit self-injurious repetitive grooming and deficits in social interaction.

Autism has been diagnosed in many neurodevelopmental disorders including Rett syndrome, fragile X syndrome, Down syndrome, Angelman syndrome, Prader-Willi syndrome, Smith-Magenis syndrome, Williams syndrome, neurofibromatosis type 1, tuberous sclerosis, Sanfilippo syndrome, phenylketonuria, adenylosuccinate lyase deficiency, and Smith-Lemli-Opitz syndrome. Asperger syndrome is one of the most common forms of autism, found in 1 to 3 children in 1000 (Gillberg, 1989). Characterized by social isolation in combination with odd and eccentric behavior, Asperger syndrome shares many features with infantile autism. Several studies have indeed noted an overlap in various clinical and demographic characteristics between Asperger syndrome and infantile autism (Szatmari et al., 1989). In one study of 23 patients, the children with Asperger syndrome seemed to have relatively poor motor skills and had a stiff and awkward gait (without arm swing), and their speech development was delayed, although they acquired better expressive speech than did the children with infantile autism. In contrast to infantile autism, Asperger syndrome usually does not become fully manifest until 30 to 36 months of age, but some children may have their first symptoms in infancy. A study of seven patients with the combination of Asperger syndrome and TS showed magnetic resonance imaging (MRI) evidence of cortical and subcortical abnormalities in five of these patients (Berther et al., 1993). Because children with Asperger syndrome are generally brighter than those with TS, it has been suggested that Asperger syndrome merely represents a mild variant of autism. We studied eight patients with Asperger syndrome and an additional four with other forms of pervasive developmental disorder who were referred to our movement disorders clinic for evaluation of tics (Ringman and Jankovic, 2000). All patients exhibited stereotypic movements; in addition, seven had tics, and six of these met inclusion diagnostic criteria for TS. Of the six patients with clinical features of both Asperger syndrome and TS, three had severe congenital sensory deficits, suggesting that sensory deprivation contributes to the development of adventitious movements in this population. Autistic children often show tics and other features of TS, including stereotypic tics (Rapin, 2001; Termine et al., 2020).

In patients with intellectual disability and autism, irrespective of cause, stereotypes are often associated with SIB (Fischer et al., 2020). This is particularly true for patients with body-rocking movements, a stereotype that is most often associated with self-hitting (Rojahn, 1986). Although head banging and other SIBs may occur in normal children, this type of behavior is usually abnormal and is particularly common in patients who also exhibit stereotypic behavior.

Some studies in autistic children reported that stereotypy interfered with learning, suggesting that treatment of stereotypes in patients with autism facilitates learning (Koegel and Covert, 1972) and implying that controlling stereotypic behavior was a necessary precondition for learning. Drugs that block postsynaptic dopamine and serotonin receptors, such as risperidone, have been found to be effective in the treatment of tantrums, aggression, and SIBs in patients with autistic

disorders (Research Units on Pediatric Psychopharmacology Autism Network, 2002; Gagliano et al., 2004). These benefits, however, must be weighed against potential side effects, such as sedation, weight gain, and parkinsonism. Other agents that are used in the treatment of autistic disorders include central nervous system stimulants, anticonvulsants, naltrexone, lithium, anxiolytics, and other treatments, but well-controlled, double-blind studies are lacking (Owley, 2002).

The pathogenesis of autism is still unknown; one hypothesis suggests that in autistic children, the normal high brain serotonin synthesis capacity is somehow disrupted during early development (Chugani and Chugani, 2000), which might explain the beneficial effects of selective serotonin uptake inhibitors in some patients with autism (DeLong, 1999). Based on the observation that gamma-aminobutyric acid (GABA)-acting benzodiazepines exert paradoxical excitatory effects in autism, the diuretic NKCC1 chloride importer antagonist bumetanide, which decreases Cl^- and reinforces GABAergic inhibition, has been studied in autism and was found to improve emotion recognition that was associated with enhanced activation of brain regions involved in social and emotional perception (Hadjikhani et al., 2013). In one autopsy study, increased dendritic spine density with reduced developmental spine pruning in layer V pyramidal neurons of the temporal lobe was found in brains of patients with autistic spectrum disorder compared with normal controls (Tang et al., 2014). Typical 19-year-olds had 41% fewer synapses than toddlers, but those in their late teenage years with autism had 16% fewer than young children with autism. These spine deficits correlate with hyperactivated mTOR and impaired autophagy. Thus, this study provides support for the notion that impaired pruning of dendritic synapses leading to overconnectivity plays an important role in the pathogenesis of autism.

Although the cause of autism is not yet clear, genetic studies, including high concordance in monozygotic twins strongly argue for the role of genetic abnormalities in the pathogenesis of this developmental disorder. One potential candidate gene involved in autism is the *CNTNAP2* gene on chromosome 7q35 that codes for contactin associated protein-like 2, a neurexin family member involved in myelination of axons (Alarcon et al., 2008; Arking et al., 2008; Bakkaloglu et al., 2008). In one study, instead of the normal adenine or thymine, children with autism tended to have inherited the thymine variant (inherited more likely from mothers than fathers) (Arking et al., 2008). Another chromosome implicated in the genetics of autism is chromosome 16p13.1 (Ullmann et al., 2007). The use of DNA microarrays and exome sequencing to detect pathologic copy number variants and point mutations, respectively, and next-generation sequencing have revolutionized the identification of new genetic causes of autism. Some of the newly discovered forms of autism may be caused by inborn errors of metabolism, such as carnitine deficiency, can be treated or even prevented (Beaudet, 2012).

Dysfunction of the frontoparietal cortex, neostriatum, thalamus, and cerebellum in autistic patients has been suggested by various metabolic and imaging studies. MRI studies have found left frontal and brainstem atrophy in some autistic patients (Hashimoto et al., 1989), but other studies have failed to find any characteristic abnormalities on MRI scans of autistic children (Kleiman et al., 1992). More recent MRI studies have found white matter enlargement in patients with

autism (Herbert et al., 2004). Other imaging studies have shown that autistic children have a reversal of asymmetry in frontal language-related cortex (De Fosse et al., 2004).

Neuropathologic studies have not found consistent abnormalities, but most have found increased cell density and smaller neuronal size in the limbic system, decreased number of Purkinje cells in the cerebellum, and cerebellar cortical dysgenesis, but additional studies using new techniques are needed before a consistent picture will emerge (Palmen et al., 2004). In one study “focal patches of abnormal laminar cytoarchitecture and cortical disorganization of neurons, but not glia, in prefrontal and temporal cortical tissue” was found in 10 of 11 children with autism but only 1 of 11 unaffected children (Stoner et al., 2014).

Rett syndrome

Although the genes for most autistic disorders have yet to be identified, Rett syndrome is one of the first autistic spectrum disorders in which genetic abnormality was identified (Muhle et al., 2004; Chahrour and Zoghbi, 2007; Percy, 2011; Sandweiss et al., 2020). Rett syndrome is an autistic disorder that occurs almost exclusively in girls and is manifested clinically by stereotypic movements and other movement disorders (Fitzgerald et al., 1990a; Percy, 2002; Roze et al., 2007; Temundo et al., 2007) (Videos 16.5, 16.6). The prevalence of Rett syndrome has been reported to range between 1 in 10,000 and 1 in 28,000 (Kozinetz et al., 1993). In contrast to infantile autism and intellectual disability, patients with Rett syndrome tend to have normal development until 6 to 18 months of age; this is then followed by gradual regression of both motor and language skills. Usually between the ages of 9 months and 3 years, there is a gradual social withdrawal and psychomotor regression with loss of acquired communication skills. Acquired finger and hand skills are gradually replaced by stereotypic hand movements, including hand clapping, wringing, clenching, washing, patting, rubbing, picking, and mouthing (Fitzgerald et al., 1990a; Temundo et al., 2007) (Table 16.4, Figs. 16.1 and 16.2). In contrast to hand and arm stereotypies in other autistic disorders, which are usually simple, bilateral, intermittent, and often involving objects, hand stereotypies in Rett patients are predominantly complex, continuous, localized to the body midline, and involving mouthing (Goldman and Temudo, 2012). In an analysis of 83 patients with Rett syndrome, 53 with *MECP2* gene mutation, 62% had hand stereotypies, and in combination with bruxism, these features seemed to differentiate between Rett patients with and without mutation (Temudo et al., 2008). Among 12 girls with confirmed Rett syndrome 14 years old or older, the mean age at onset of stereotypies was 19.4 months consisting chiefly of hand repetitive movements, pill rolling, mouthing, and twisting and these can persist into middle age (Vignoli et al., 2009) but may evolve into parkinsonism in older age (Roze et al., 2007). Boys with *MECP2* duplication, in addition to autism, also manifested stereotypies and choreiform movements and recurrent respiratory infections (Ramocki et al., 2009; Percy, 2011). ▶

Besides hand stereotypies, girls with Rett syndrome often exhibit body-rocking movements and shifting of weight from one leg to the other. Although most girls with Rett syndrome are able to walk, they tend to walk on their toes;

Table 16.4 Diagnostic features associated with Rett syndrome

1. Female sex
2. Normal prenatal and postnatal period
3. Normal development through first 6 months
4. Normal head circumference at birth; deceleration of head growth: 5 months to 4 years
5. Loss of hand skills: 6–30 months
6. Loss of communications skills 6–30
7. Psychomotor retardation and social withdrawal
8. Stereotypic hand movements
9. Gait and truncal “apraxia/ataxia”
10. Diagnosis tentative until age 2–5 years

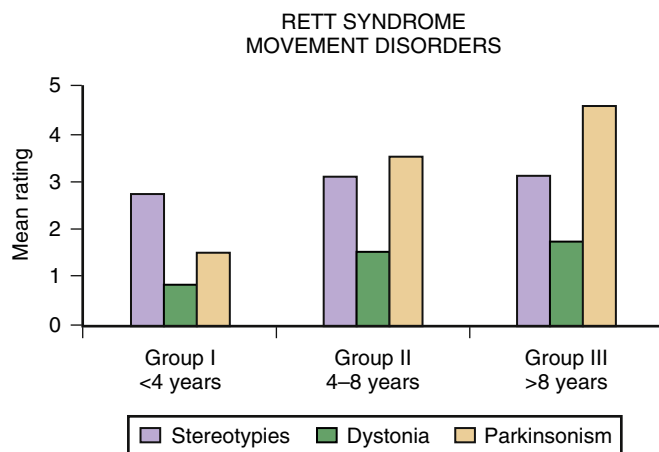


Fig. 16.1 Diagnostic features associated with Rett syndrome. (From Fitzgerald PM, Jankovic J, Glaze DG, et al. Extraparamidal involvement in Rett's syndrome. *Neurology*. 1990;40:293–295.)

their gait is usually broad-based and apraxic and associated with retropulsion and loss of balance. Other motor disturbances include respiratory dysregulation with episodic hyperventilation and breath holding, bruxism, ocular deviations, dystonia, myoclonus, athetosis, tremor, jerky truncal and gait ataxia, and parkinsonian findings. In a study of 32 patients with Rett syndrome, ages 30 months to 28 years, we suggested that the occurrence of the different motor disorders seemed to be age-related (Fitzgerald et al., 1990b). The hyperkinetic disorders were more common in younger girls, whereas bradykinetic disorders seemed more prominent in the older patients. Although typically diagnosed in young girls, the diagnosis of Rett syndrome should be also considered in adult women with stereotypes and psychomotor retardation (Roze et al., 2007).

The pathophysiologic basis of the motor disturbances in Rett syndrome has not been fully elucidated (Akbarian et al., 2003). MRI studies have shown generalized brain and bilateral caudate atrophy (Reiss et al., 1993). Electroencephalographic recordings show age-related progressive deterioration characterized by slowing, loss of normal sleep characteristics, and the appearance of epileptiform activity. In a few postmortem examinations of brains of people with Rett syndrome, besides marked reduction in both gray and white matter volume, particularly involving the caudate nucleus (Subramaniam et al., 1997), some studies also found spongy degeneration of cerebral and cerebellar white matter, deposition of lipofuscin, and depigmentation of the substantia nigra and locus coeruleus (Hagberg, 1989). The various neuropathologic findings have been interpreted as a failure in the proper development or maintenance of synaptic connections. Because there is no evidence of a neurodegenerative process, there is a possibility of a therapeutic intervention that might not only alter the symptoms but also favorably modify the natural course of the disease.



Fig. 16.2 Collage of hand and mouthing stereotypes exhibited by girls with Rett syndrome.

Video 16.5 Rett syndrome.

Video 16.6 Rett syndrome.

The major advance in understanding the biology of Rett syndrome has come with the discovery of a gene that is responsible for most, but not all, cases of Rett phenotype. Since the initial discovery of the gene in 1999 (Amir et al., 1999), loss-of-function mutations of the X-linked gene encoding methyl-CpG binding protein 2 (MECP2) have been found to be responsible for more than 80% of Rett cases (Akbarian, 2003). The phenotypic spectrum of MECP2 mutations is broadening, and it includes not only the classic Rett syndrome but also Rett variants, mentally retarded males, and autistic children (Neul and Zoghbi, 2004). The function of the MECP2 protein is still unknown, but it is expressed ubiquitously in neurons and binds primarily, but not exclusively, to methylated DNA; it is thought to regulate gene expression, chromatin composition, and chromosomal architecture and might be important for maintenance of neuronal chromatin during late development and in adulthood. The MECP2 protein is expressed exclusively in neurons at the time when they are starting to form synapses. In the cerebellum, the Purkinje cells, which are born early, strongly express MECP2 soon after birth, but granule cells, which mature later, do not express the protein until several weeks after birth. Thus, the protein is not turned on until it is needed for the formation of synapses. Furthermore, selective knockout of the gene in mice results in a Rett-like phenotype, including a reduction in brain atrophy and neuronal dystrophy. Rett syndrome appears to be a disorder of synapse formation and proliferation.

A broad range of mutations associated with MECP2 have been described involving not only girls and women but also males; they include a variety of autistic spectrum disorders, such as Angelman syndrome, learning disability, intellectual disability, and fatal encephalopathy (Percy, 2002, 2011). Although stereotypies are sometimes present in patients with TS, we excluded mutations in the MECP2 gene in our population of patients with TS (Rosa et al., 2003).

Using a mouse heterozygous for a conditionally silenced MECP2 gene, containing a stop cassette flanked by *loxP* sites, researchers are exploring potential therapeutic strategies in Rett syndrome. The animal model shares some clinical characteristics of Rett syndrome, including inertia, breathing abnormalities, gait abnormalities, hindlimb claspings, and weight gain between 4 and 12 months, which then stabilizes. Mice also expressed a Cre-recombinase enzyme linked to a tamoxifen receptor. When MECP2 gene is activated in mice, symptoms such as breathing and mobility difficulties ceased. Over a 4-week period, the mice often became undistinguishable from healthy counterparts. When exposed to tamoxifen, Cre targeted the *loxP* sequences and removed the stop cassette, restoring expression of MECP2 (Guy et al., 2007). Tamoxifen appeared to reverse or prevent these symptoms. These findings suggest that gene therapy is a reachable goal in the treatment of Rett syndrome.

Furthermore, antisense nucleotide approaches will likely be investigated in Rett syndrome, as they have been already successfully employed in other genetic disorders such as spinal muscular atrophy (Sandweiss, et al. 2020).

Besides Rett syndrome, there are many other genetic forms and other causes of autism but it is beyond the scope of this review to comprehensively review this topic. Instead, the reader is referred to relevant publications (Ziats and Rennert, 2016; Constantino and Charman, 2016).

Table 16.5 Clinical features associated with Williams syndrome

- Greet and interact with strangers (hypersociability)
- Cardiac defect—supravalvular aortic stenosis and arch hypoplasia
- Multiple peripheral pulmonary arterial stenoses
- Elfin face, dental malformation
- Mental and statural deficiency
- Infantile hypercalcemia
- Ophthalmologic features
 - Strabismus 54%
 - Blue irides 77%
 - Esotropia 97%
 - Stellate iris pattern of the anterior stroma 74%
- Uneven cognitive strengths and weaknesses
- Hemizygous deletion in chromosome band 7q11.23, including the gene for elastin (*ELN*), also in LIM kinase-1, *RFC2*, *LIMK1*, *CYLN2* genes postulated as factors

Data from Doyle TF, Bellugi U, Korenberg JR, Graham J. "Everybody in the world is my friend": Hypersociability in young children with Williams syndrome. *Am J Med Genet.* 2004;124A:263–273.

Other developmental genetic disorders

Patients with Williams syndrome, a hypersociable behavior associated with hemizygous 1.5 MB deletion in chromosome band 7q11.23, that includes about 24 to 28 genes, such as elastin (*ELN*), *LIM kinase-1*, *RFC2*, *LIMK1*, and *CYLN2* genes, also can present with slow, complex, persistent head stereotypies (Doyle et al., 2004; Meyer-Lindenberg et al., 2006; Chailangkarn et al., 2016) (Video 16.7) (Table 16.5). Williams syndrome is a genetic neurodevelopmental disorder characterized clinically by an uncommon hypersociability and pathologically by abnormalities in layer V/VI cortical neurons with unusually long dendrites, increased numbers of spines and synapses, aberrant calcium oscillation, and altered network connectivity. Associated with breakpoints in chromosome band 7q11.23 mutations in gene frizzled 9 (*FZD9*) have been identified in this syndrome (Chailangkarn et al., 2016). Although the pathogenesis of the syndrome is still not well understood, the *FZD9* gene has been shown to regulate cell division and programmed cell death. Some have suggested that some of the stereotypic behavior in patients with Williams syndrome may be due to associated RLS because many patients with Williams syndrome seem to have a frequent coexistence of periodic limb movement in sleep (Arens et al., 1998). Other developmental disorders frequently associated with repetitive, stereotypic behaviors include Angelman, Cornelia de Lange, fragile X, Lowe, Prader-Willi, Cri-du-Chat, and Smith-Magenis syndromes (Moss et al., 2009). ▶

Schizophrenia and catatonia

Various stereotypies were described in schizophrenic patients long before neuroleptics were first introduced for the treatment of psychotic disorders. Stereotypies in untreated childhood schizophrenia have not been well studied; thus, the discussion of this topic is beyond the scope of this review (Ihara et al., 2002). In a study of 200 antipsychotic-naïve patients with schizophrenia spectrum disorders a variety of abnormal involuntary movements, such as grimacing, stereotypies, and abnormal blinking, were observed along

with catatonia, echo-phenomena, catalepsy, and parkinsonism (Peralta et al., 2010; Compton et al., 2015). Catatonia is a complex neuropsychiatric syndrome characterized by a broad range of motor, speech, and behavioral abnormalities, including stereotypes, waxy flexibility, posturing, and catalepsy (Wijemanne and Jankovic, 2015). Although controlled trials are lacking, benzodiazepines are considered first-line therapy, but in some cases electroconvulsive therapy may be necessary to control this neuropsychiatric disorder.

Obsessive-compulsive disorder and tic disorders

Stereotypes can be encountered in various tic disorders, including TS and neuroacanthocytosis, both of which also can be associated with OCD. TS is discussed elsewhere in this volume (see Chapter 17); therefore, only a brief discussion of other tic disorders and OCD follows. In addition, the reader is referred to recent reviews on this topic (Jankovic, 2001a,b; Jenike, 2004).

Progression from a hyperkinetic to a bradykinetic movement disorder, as seen in Rett syndrome, may be also encountered in neuroacanthocytosis, another disorder that is manifested by stereotypic and self-injurious (e.g., lip and tongue biting) behavior. Symptoms usually first begin in the third and fourth decades but may start during childhood, with lip and tongue biting followed by orolingual (“eating”) dystonia, motor and phonic tics, generalized chorea, distal and body stereotypes, parkinsonism, vertical ophthalmoparesis, and seizures. Other features include cognitive and personality changes, dysphagia, dysarthria, amyotrophy, areflexia, evidence of axonal neuropathy, and elevated serum creatine kinase without evidence of myopathy. Besides movement disorders, other associated features included dysarthria; absent or reduced reflexes; dementia; psychiatric problems, such as depression, anxiety, and OCD; dysphagia; seizures; muscle weakness and wasting; and elevated creatine phosphokinase. Magnetic resonance volumetry and fluorodeoxyglucose positron emission tomography (PET) show striatal atrophy in patients with neuroacanthocytosis (Jung et al., 2001).

Although autosomal dominant, X-linked-recessive, and sporadic forms of neuroacanthocytosis have been reported, the majority of the reported families indicate autosomal recessive inheritance. Genome-wide scan for linkage in 11 families with autosomal recessive inheritance showed a linkage to a marker on chromosome 9q21, indicating a single locus for the disease. Sequencing has identified a polyadenylation site with a protein with 3096 amino acid residues, which has been named Chorein, and subsequent studies have identified multiple mutations in the *CHAC* gene (Rampoldi et al., 2001).

Another psychiatric disorder that is frequently accompanied by stereotypic movements is OCD (Jenike, 2004). Foot tapping, crossing and uncrossing the legs, tapping fingers on a chair arm, and similar stereotypic behaviors may be associated with obsessive-compulsive symptoms (Niehaus et al., 2000). OCD was once considered a rare psychiatric disorder, but epidemiologic studies indicate that the lifetime prevalence of OCD is approximately 2.5% (Snider and Swedo, 2000). Compulsions might be difficult to differentiate from stereotypes. In contrast to stereotypes, compulsions are usually preceded

by or associated with feelings of inner tension or anxiety and a need to perform the same act repeatedly in the same manner. Examples of compulsions are ritualistic hand washing; repetitively touching the same place; evening up; and arranging and checking doors, locks, and appliances. Reports of focal striatal lesions giving rise to severe OCD and the frequent association of OCD with basal ganglia disorders such as TS, PD, and Sydenham disease (Church et al., 2002; Kwak and Jankovic, 2002) provide additional support for the link between abnormal behavior, such as OCD, and motor dysfunction (Cummins, 1993; Rosario-Campos et al., 2001).

Other stereotypes

It is well known that stereotypes often accompany a variety of behavioral disorders, such as anxiety, OCD, TS, schizophrenia, autism, intellectual disability, akathisia, RLS, and a variety of neurodegenerative disorders, including frontotemporal dementia (Nyatsanza et al., 2003; Mateen and Josephs, 2009; Singer, 2009; Baizabal-Carvallo and Jankovic, 2016), and postinfectious disorders such as subacute sclerosing panencephalitis (SSPE) (Jankovic et al., 1998) (Video 16.8) (Table 16.6). Stereotypes may accompany dementias, particularly frontotemporal dementias, in which motor and vocal stereotypes occur in over 75% of patients whose diagnosis was confirmed by autopsy (Baizabal-Carvallo and Jankovic, 2016). Head nodding has been described in otherwise normal children, but also in disorders or lesions of brainstem and cerebellum, bobble-head doll syndrome associated with abnormalities in the third ventricle or diencephalon, and Sandifer syndrome associated with gastroesophageal reflux. ▶

Akathisia—a combination of complex stereotypes, such as hair and face rubbing, picking at clothes, crossing and uncrossing legs, adduction–abduction and up-and-down leg pumping, sitting down and standing up, marching in place, pacing and shifting weight, and feelings of restlessness—is typically a manifestation of tardive dyskinesia but also may be seen in patients with PD, in patients with various forms of intellectual disability, and in autism (Bodfish et al., 1997), and as part of tardive dyskinesia (see later) (Video 16.9). ▶

In some individuals, particularly those who abuse amphetamines or cocaine and in patients with PD taking levodopa and particularly dopamine agonists, certain stereotypic behaviors, called punding, are seen (Fernandez and

Table 16.6 Stereotypes associated with frontotemporal degeneration

- 19 of 32 (60%) patients with FTLD had stereotypes
- Median age of symptom onset suggestive of FTLD was 58 years (range: 37–74), with a mean time to stereotypy onset of 2.1 years
- Stereotypes were simple in all
- Compulsive behavior more frequent in those with stereotypes (58% versus 15%, $P = 0.02$)
- 9 of 16 (56%) had motor stereotypes; 9 were appendicular and 7 were craniocervical
- 3 had vocal stereotypes, and 3 had both vocal and motor stereotypes

FTLD, Frontotemporal degeneration.

Data from Mateen FJ, Josephs KA. The clinical spectrum of stereotypes in frontotemporal lobar degeneration. *Mov Disord* 2009;24:1237–1240.

Video 16.7 Williams syndrome.

Video 16.8 Subacute sclerosing panencephalitis.

Video 16.9 Tardive akathisia.

Table 16.7 Classification of movement disorders associated with dopamine receptor blockers (neuroleptics)**Acute Disorders**

- Dystonic reaction
- Parkinsonism
- Akathisia
- Neuroleptic malignant syndrome

Chronic Disorders

- Tardive dyskinesia
 - Stereotypic
 - Oral-facial-lingual-masticatory
 - Trunk-pelvic
 - Respiratory
 - Choreic: limbs
- Tardive dystonia
- Tardive tics
- Tardive myoclonus
- Tardive tremor
- Tardive akathisia
- Tardive gait
- Tardive parkinson

Data from Jankovic J. Tardive syndromes and other drug-induced movement disorders. *Clin Neuropharmacol*. 1995;18:197–217.

Friedman, 1999; Evans et al., 2004; Stamey and Jankovic, 2008; Voon et al., 2009). These include compulsive sorting of objects, nail polishing, shoe shining, hair dressing, and intense fascination with repetitive handling and examining of mechanical objects, such as picking at oneself or taking apart watches and radios, or sorting and arranging of common objects, such as lining up pebbles, rocks, or other small objects. This stereotypic behavior has not been previously described in children, even in those taking central nervous system stimulants for ADHD, although no studies specifically designed to study punding in children have been reported.

Tardive dyskinesia

Repetitive and patterned movements, phenomenologically identical to stereotypy, are characteristically seen in patients with tardive dyskinesia (Jankovic, 1995; Mejia and Jankovic, 2010) (Table 16.7). All types of movement disorders, including parkinsonism, tremor, chorea, dystonia, tics, myoclonus, and stereotypy, can result from the use of dopamine receptor-blocking drugs (neuroleptics) both acutely and chronically (tardive). See Chapter 20 in this volume for a detailed review. The most typical form of tardive dyskinesia, the orofacial-lingual-masticatory movement, is one of the best examples of a stereotypic movement disorder (Miller and Jankovic, 1990). Tardive dystonia tends to occur more frequently in younger patients, although it is quite rare in children. Tardive stereotypy is more typically observed in middle-aged or elderly patients, particularly women, and this is a very rare complication in children. However, there is a report of a 1-year-old girl who developed orofacial-lingual stereotypy at age 2 months after a 17-day treatment

with metoclopramide for gastroesophageal reflux (Mejia and Jankovic, 2005; Pasricha et al., 2006; Kenney et al., 2008). The stereotypy, documented by sequential videos, persisted for at least 9 months after the drug was discontinued. This patient, perhaps the first documented case of tardive dyskinesia in an infant, draws attention to the possibility that this disorder is frequently unrecognized in young children.

Although with the advent of atypical neuroleptics the incidence of tardive dyskinesia was thought to markedly decrease, there is a growing number of reports of tardive dyskinesia in patients, including children, treated with atypical (second and third generation) neuroleptics (Mejia and Jankovic, 2010; Pena et al., 2010). Campbell and colleagues (1997), in their 15-year-long prospective double-blind, placebo-controlled study of autistic children exposed to haloperidol, reported that tardive dyskinesia developed in 9 of 118 children (7.6%) (Campbell et al., 1997).

A comprehensive review of 702 patients reported in 17 studies of children exposed to dopamine receptor-blocking drugs, 69 (9.8%), 60% females, had tardive dyskinesia (Mejia and Jankovic, 2010). The children were treated with the neuroleptics for various psychiatric conditions (N = 463, 65.9%), autism (N = 118, 16.8%), intellectual disability (N = 116, 16.5%), TS (N = 5, 0.7%), and gastroesophageal reflux disease (GERD; N = 2, 0.3%). The phenomenology of tardive dyskinesia consisted chiefly of orofacial stereotypies with or without dystonic or choreic movements of the trunk and limbs.

The most important step in the management of tardive dyskinesia is prevention; dopamine receptor-blocking drugs, particularly the typical neuroleptics, should be used only if other drugs do not adequately control the behavior or neurologic disorder, such as TS. Atypical antipsychotics might be better alternative medications with less risk for causing tardive dyskinesia and should be considered whenever possible. Drugs that have been found to be useful in the treatment of tardive dyskinesia include clonazepam and other benzodiazepines and dopamine depleters such as tetrabenazine (TBZ) (Jankovic and Beach, 1997; Vuong et al., 2004; Kenney and Jankovic, 2006) (Table 16.8). Beta-blockers and opioids also have been found effective in some patients with akathisia. Antidepressant citalopram was not found to be effective in children with repetitive behaviors associated with autism (King et al., 2009) (Table 16.9).

Treatment

Treatment of stereotypies is quite challenging. In addition to behavioral therapy (Miller et al., 2006), some patients benefit from pharmacologic therapy targeted to relieve associated comorbidities, such as anxiety, OCD, and impulse control problems. In addition, TBZ has been found to be very effective in the treatment of the involuntary repetitive movements (Kenney and Jankovic, 2006). In severe cases that cannot be controlled with medications, deep brain stimulation may be an effective treatment for disabling stereotypies (Sato et al., 2009; Stocco and Baizabal-Carvallo, 2014).

Table 16.8 Mechanism of action of tetrabenazine

- Tetrabenazine selectively and reversibly inhibits striatal VMAT2
- Dopamine rapidly degraded by cytoplasmic monoamine oxidase inhibitors (MAOIs) → presynaptic depletion
- Selective for dopamine >> norepinephrine and/or 5HT
- Tetrabenazine reduces dopamine transmission selectively in the central nervous system

5HT, 5-Hydroxytryptamine; VMAT2, vesicular monoamine transporter 2.

Table 16.9 Therapeutic approaches in tardive dyskinesia

- Slowly taper and discontinue the offending drug
- DA-depleting drugs: tetrabenazine, reserpine, alpha-methylparatyrosine
- Treat adverse events (AEs) (parkinsonism, depression, etc.)
- Atypical neuroleptics: antipsychotic agents: clozapine and quetiapine
- DA receptor agonist (low doses to activate only the presynaptic dopamine receptor and inhibit synthesis of DA)
- For tardive dystonia, try anticholinergics, botulinum toxin
- For tardive akathisia, try propranolol, electroconvulsive therapy
- Typical antipsychotic (coupled with tetrabenazine) when all other approaches fail
- Globus pallidus internus deep brain stimulation

DA, Dopamine.

References available on Expert Consult:
www.expertconsult.com.

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The tardive syndromes

Phenomenology, concepts on pathophysiology and treatment, and other neuroleptic-induced syndromes

Chapter contents

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Introduction

The topic of tardive dyskinesia (TD) syndromes is very broad, covering different phenomenologies. There have been several recent reviews written on this topic, but most research has focused on new treatments (Cornett, Novitch et al., 2017; Correll, 2017; Rakesh, Muzyk et al., 2017; Caroff, Ungvari et al., 2018; D'Abreu, Akbar et al., 2018; Jain and Correll, 2018). This chapter will cover tardive and nontardive neuroleptic-induced movement disorders, further extending the scope of material to review. Because of the volume of material to cover, the essential features of the TD syndromes are highlighted in this summary section to allow the reader to understand the most pertinent material in a simple fashion.

1. The term "neuroleptic" was coined by Delay and Deniker (1956, 1968) and Denker (1956) to describe the calming effect of reserpine and chlorpromazine with their liability of causing drug-induced parkinsonism. Reserpine was subsequently discovered to deplete monoamines, including dopamine, and the drug-induced parkinsonian state was reversed by levodopa (Carlsson et al., 1957). When newer antipsychotic drugs were later found to induce parkinsonism, they too were labeled as neuroleptics. These antipsychotic drugs were shown to block dopamine receptors, especially the D2 receptors (dopamine receptor-blocking agents [DRBAs]), and this action was recognized as the pathogenic mechanism to induce parkinsonism. Drug-induced parkinsonism correlates with the dosage of the neuroleptic and disappears when the drug is withdrawn, although it may take up to 1 year for symptoms to subside.
2. The TD syndromes are the result of treatment with DRBAs. These disorders tend to appear late in the course of treatment, hence the term *tardive*. Syndromes with similar clinical phenomenology in the absence of a reliable history of having received such medications exclude this diagnosis. Tardive syndromes have not been caused by dopamine depleters and only rarely by the "true atypical" antipsychotics, such as clozapine. Some DRBAs are marketed for gastrointestinal problems (e.g., metoclopramide [Reglan]), for depression (e.g., amoxapine [Asendin]; perphenazine/amitriptyline [Triavil]), and for cough (e.g., promethazine [Phenergan]).
3. In addition to TD syndromes, the DRBAs can cause acute and subacute movement disorders, including parkinsonism (mentioned previously), dystonia, and akathisia. These acute/subacute disorders resolve with the discontinuation of the DRBA. Neuroleptic malignant syndrome is a neurologic emergency that is also associated with DRBAs. These will be discussed in another section.
4. The TD syndromes tend to persist and can remain permanently. It is generally thought that the sooner the offending drugs are withdrawn, the more likely it is that the syndrome will improve with time. But evidence is lacking that prolonging the use of the drugs will increase the severity of the dyskinesia.
5. The TD syndromes can occur when the patient is taking these drugs or within a period of time after stopping the drugs. The criterion should be set for the longest acceptable time after stopping the drugs that the disorder can still be considered to be due to the drugs.
6. Withdrawing the offending drugs often exacerbates the severity of the movements because of removal of dopamine receptor blockade. Increasing the dosage of these drugs often ameliorates the movements because of increasing the blockade.
7. The TD syndromes present in a variety of phenomenologies. The most common is the pattern of repetitive, almost rhythmic, movements that can be labeled as

stereotypic. This pattern often occurs in the oral-buccal-lingual (O-B-L) region, usually presenting as complex chewing movements with occasional popping out of the tongue and with writhing movements of the tongue when it should be at rest in the mouth. Other parts of the body may also express rhythmic movements, such as the hands, feet, and trunk. Respirations may also be affected with an altered rhythmical pattern. This pattern of dyskinesia goes by the name *classic tardive dyskinesia*, or *tardive dyskinesia*. Because the individual movements may have the speed and brevity of choreoathetosis, the name chorea has been attached by some clinicians, but this only serves to confuse because the movements of classic chorea and athetosis are random or flowing and not rhythmic. Other names that have been used are *tardive stereotypy* and *rhythmical chorea*. In this chapter the strikingly characteristic movement pattern is simply called *classic tardive dyskinesia* or *tardive dyskinesia*. It is exceedingly rare for such a pattern to be caused by any condition besides DRBA. These movements can be seen with levodopa usually in the context of underlying neurodegeneration, such as Parkinson disease (PD), with brain-stem strokes, and as an idiopathic disorder. These latter disorders are not called TD. There are other patterns of oral dyskinesias; they should not be confused with the pattern seen in TD. The most common idiopathic and spontaneous oral dyskinesia is oromandibular dystonia.

8. TD is often accompanied by a feeling of inner restlessness (akathisia), which can be whole-body restlessness or uncomfortable sensations in a specific part of the body. Generalized akathisia is often accompanied by a pattern of movement that appears to be executed in an attempt to relieve the abnormal uncomfortable sensations ("unvoluntary" movement). These movements are often rhythmical, repetitive, and stereotypical, such as body rocking, crossing and uncrossing of the legs, and caressing of the scalp. Sometimes these characteristic movement patterns are present without the patient's being able to express a feeling of restlessness. The discomfort of generalized akathisia can lead to constant moaning by the patient.
9. The third most common phenomenology in the TD syndromes is dystonia, which can mimic idiopathic torsion dystonia, usually focal or segmental. Some differences include an increased tendency for tardive dystonia to cause retrocollis and opisthotonic posturing, accompanied by internal rotation of the shoulders, extension of the elbows, and flexion of the wrists. Focal tardive dystonias are usually cranial in location, particularly affecting the jaw, tongue, and facial muscles. Tardive dystonia also may be accompanied by tardive akathisia and classic TD. The presence of classic TD or akathisia in a patient with dystonia who has had exposure to DRBA makes the diagnosis of tardive dystonia extremely likely. Tardive dystonia can occur at all ages, whereas classic TD is more common in the elderly.
10. In addition to tardive dystonia, which is usually persistent, children tend to get classic chorea, called withdrawal emergent syndrome when the DRBA dose is reduced or discontinued. This is self-limiting, eventually disappearing over several weeks if the offending drugs are withdrawn.

11. Other clinical phenomenology has been described in the spectrum of the TD syndromes. These include myoclonus, tremor, oculogyric crisis, and tics. Some cases that have been reported as tardive tics might have actually been the movements of tardive akathisia that were mistaken for tic-like movements.
12. The "atypical" antipsychotic agents, ranked in order of clozapine, quetiapine, and olanzapine, are less tightly bound to the D2 receptor than the typical antipsychotic agents. This pharmacologic characteristic probably accounts for these "atypicals" being much less likely to cause drug-induced parkinsonism, acute dystonic reactions, acute akathisia, neuroleptic malignant syndrome (NMS), or the tardive syndromes, but there are some case reports of these complications from these drugs.
13. At the present time, clozapine is the gold standard for the atypical antipsychotics, with quetiapine being a close second in terms of not inducing parkinsonism or worsening existing PD. The third-ranking drug is olanzapine. Newer atypical antipsychotics need to be in use clinically before their full side effect profile can be known, and, except for clozapine and quetiapine, they all worsen PD and can cause TD. For example, although risperidone had been labeled an atypical antipsychotic, it readily induces and worsens parkinsonism and can induce TD; it should be removed from this classification. It therefore resembles classic antipsychotic agents. Today, the designation of first-generation (FGA) and second-generation (SGA) antipsychotics is being used, rather than typical and atypical.

Clozapine and quetiapine in high doses have been reported to be successful in some patients in reducing the severity of TD and tardive dystonia, but there remains uncertainty whether symptoms are reduced (1) because of D2-blocking activity with high doses; (2) because there is no such activity, and tincture of time has resolved the tardive symptoms; or (3) because these drugs have some other action that can reduce TD. By and large, these two drugs are ineffective in reducing tardive symptoms at low doses, and it is likely the D2-blocking activity of their high doses that reduces symptoms. Drugs that deplete dopamine or block D2 receptors have been the most effective medications in reducing tardive disorders. The U.S. Food and Drug Administration (FDA) in the United States approved two drugs, valbenazine and deutetrabenazine (DTBZ), for TD. These are vesicular monoamine transporter 2 (VMAT2) inhibitors similar to tetrabenazine (TBZ), but with different pharmacologic profiles.

Fundamentals and definitions

A variety of neurologic adverse effects are seen with drugs that block dopamine D2 receptors. Because these complications are mainly movement disorders and likely relate to the D2 receptors in the striatum and limbic system, they have been referred to as extrapyramidal reactions, although more appropriately called drug-induced movement disorders. These are listed in [Table 17.1](#) and are covered in the clinical sections that follow.

The term *tardive syndromes* refers to a group of disorders that fit the following criteria. (1) Phenomenologically, the clinical features are those of a movement disorder (i.e.,

Table 17.1 Neurologic adverse effects of dopamine receptor antagonists

1. Acute reactions
 - a. Acute dystonia
 - b. Acute (subacute) akathisia
2. Toxicity state (overdosage)
 - a. Drug-induced parkinsonism
3. Neuroleptic malignant syndrome (NMS)
4. Tardive syndromes
 - a. Withdrawal emergent syndrome
 - b. Classic tardive dyskinesia (TD)
 - c. Tardive dystonia
 - d. Tardive akathisia
 - e. Tardive myoclonus
 - f. Tardive tremor
 - g. Tardive tics
 - h. Tardive chorea
 - i. Tardive parkinsonism?

Modified from Fahn S. The tardive dyskinesias. In: Matthews WB, Glaser GH, eds. Recent Advances in Clinical Neurology, vol. 4. Edinburgh: Churchill Livingstone, 1984; pp. 229–260.

abnormal involuntary movements or a sensation of restlessness that often causes “unvoluntary” movements; (2) the disorder is caused by exposure to at least one DRBA for at least 1 month within 6 months of the onset of symptoms and lasting for at least 1 month after the discontinuation of a DRBA, and in exceptional cases, exposure could be up to 12 months; and (3) the disorder persists for at least 1 month after stopping the offending drug (Fahn, 1984a; Stacy and Jankovic, 1991). The question arises as to what to call persistent dyskinesias that are induced by drugs other than DRBAs. For example, Miller and Jankovic (1992) described such a patient who had been exposed to flecainide, a drug not known to be a DRBA. Another drug, buspirone, an azospirone compound, is an anxiolytic that is not known to have any dopamine receptor–blocking activity. Yet there is a report of two patients who had persistent movement disorders after prolonged treatment with this drug (LeWitt et al., 1993). One patient had cervicocranial dystonia, and the other had an exacerbation of preexisting spasmodic torticollis and TD. It is possible, however, that future laboratory investigation will reveal flecainide and buspirone or one of their metabolites to be a DRBA.

Although there are several phenomenologically distinct types of tardive disorders, the collective group is referred to as *tardive dyskinesia* for historical reasons. Unfortunately, the term tardive dyskinesia also is often used to refer to a phenomenologically specific type of tardive syndrome, so the literature is often confusing; this note of caution is particularly important in trying to understand whether the author of a paper is referring to the tardive syndromes collectively or to a specific tardive syndrome. Because there could be different pathophysiologic mechanisms and treatments for the different forms of tardive syndromes, it is best that they be divided phenomenologically (Table 17.2). In this review, the tardive syndromes as a whole are referred to as tardive dyskinesia, and the specific type that was historically and initially labeled as tardive dyskinesia is referred to as classic TD. Other names have been used for classic TD (see Table 17.2). The phenomenologically essential component of classic TD

Table 17.2 Terminology of the tardive syndromes

Descriptions	Equivalent common names
Tardive syndromes as a group	Tardive syndrome
	Tardive dyskinesia
Repetitive, rhythmic movements, usually in the oral-buccal-lingual region	Classic tardive dyskinesia (TD)
	Oral-buccal-lingual (O-B-L) dyskinesias
	Tardive stereotypy
	Rhythmic chorea
Dystonic movements and postures	Tardive dystonia
Restlessness and the movements that occur as a result	Tardive akathisia
Myoclonus	Tardive myoclonus
Tremor	Tardive tremor
Tics	Tardive tics
	Tardive tourettism
Chorea	Withdrawal emergent syndrome
	Tardive chorea
Oculogyria	Tardive oculogyric crisis
Parkinsonism	Tardive parkinsonism (if it exists)

is the presence of repetitive, almost rhythmical, movements. These are almost always present in the mouth region, and therefore are also called O-B-L dyskinesias. The terminology (nosology) of the various tardive phenomenologies has been clarified by Frei and colleagues (2018) in their description of the historical clinical introductions of the different tardive phenomenologies.

Thus, TD is an iatrogenic syndrome of persistent abnormal involuntary movements that occur as a complication of drugs that competitively block dopamine receptors, particularly the D2 receptor, but possibly also the D3 receptor, which is in the D2 family of receptors.

Tardive dyskinesia was first described in a single-page report in January 1957 by Schöneck (1957a) in three patients who were treated for schizophrenic psychosis with antipsychotics for a prolonged time. The patients had O-B-L movements, which persisted after the medication had been discontinued. Adding to the confusion in citations, in December that same year and same journal, Schöneck (1957b) reported five teenagers with acute dystonic reactions. Schöneck's O-B-L paper (1957a) went unrecognized, and it was the report of Sigwald and colleagues in 1959 that brought attention to this disorder. Because these abnormal O-B-L movements appeared late in the course of treatment, in contrast to acute dystonic reactions and drug-induced parkinsonism, the term tardive dyskinesia was subsequently coined (Faurbye et al., 1964). The offending antipsychotics are DRBAs. Because of the first descriptions, TD also has been noted in patients without psychiatric disorders who had other indications for using dopamine receptor antagonists, such as those

with gastrointestinal complaints (Casey, 1983), Gilles de la Tourette syndrome (TS) (Riddle et al., 1987), or dystonia (Greene and Fahn, 1988).

Dopamine receptor antagonists produce many undesirable side effects, most of which occur relatively early in the course of treatment and are reversible on discontinuation of the medication. However, disfiguring and disabling abnormal involuntary movements were also noted to often occur late in the course of treatment and these were often noted to persist, even after discontinuation of the medication. The term tardive dyskinesia served to distinguish this latter group. Initially the term tardive dyskinesia was equated with stereotypic repetitive movements of O-B-L distribution (Schöneck, 1957a), but subsequently other types of movements have been recognized (Burke et al., 1982; Fahn, 1984a). Thus, the concept of TD has evolved and has been modified considerably since the initial recognition of the syndrome.

The prevalence of drug-induced parkinsonism and the various tardive syndromes have been compared by van Harten and colleagues (1996b) on the island of Curaçao, which has only one psychiatric facility. In 194 inpatients, the prevalence for classic TD was 39.7%, that for drug-induced parkinsonism was 36.1%, that for tardive dystonia was 13.4%, and that for akathisia was 9.3%. Combinations of two or more of these phenomenologies occurred in 30% of patients (van Harten et al., 1997). van Harten and colleagues (2006) continued to follow their patients over 9 years (mean duration of 18 years exposure to first-generation antipsychotic [FGA] drugs); they found the annual incidence rate for classic TD to be 10.2% and for tardive dystonia to be 0.7%. Severity was associated with age and akathisia but not with drug-induced parkinsonism.

Dopamine receptors and their antagonists

TD is an iatrogenic disorder, and the most constant feature of the syndrome is the pharmacologic class of the responsible etiologic agent; therefore, it is important to understand the nature of the drugs that produce TD (Table 17.3). Although models of abnormal basal ganglia circuitry have been proposed to explain the mechanism of TD (Marchand and Dilda, 2006), the pathophysiology is still poorly understood. Dopamine receptors are classified into five subtypes, based on the genetics of the receptors; they are labeled D1, D2, D3, D4, and D5 (Kebabian and Calne, 1979; Sokoloff et al., 1990). Table 17.4 characterizes the five dopamine receptors. It is the dopamine D2 receptor–blocking action of drugs that has been linked to the tardive syndromes and other neuroleptic drug–induced movement disorders (described later and listed in Table 17.5).

The drugs listed in Table 17.3, that is, iloperidone (Jain, 2000), ziprasidone (Hirsch et al., 2002), amisulpride (Curran and Perry, 2002), aripiprazole (Tamminga and Carlsson, 2002), paliperidone ER (Chwieduk and Keating, 2010), levosulpiride (Shin et al., 2009), asenapine (Kane et al., 2010), and lurasidone (Zheng, Cai et al., 2018) need to be in clinical use for several years before their full potential in causing TD syndromes can be known. The ones listed earlier have already been found to induce the acute and delayed movement disorders described in this chapter. In Table 10.3 the calcium channel blockers deserve comment. Cinnarizine (1-

Table 17.3 Drugs that can produce tardive syndromes

Class of drug	Examples of drugs in each class
1. Phenothiazines	
a. Aliphatic	Chlorpromazine (Thorazine) Triflupromazine (Vesprin)
b. Piperidine	Thioridazine (Mellaril) Mesoridazine (Serentil)
c. Piperazine	Trifluoperazine (Stelazine) Prochlorperazine (Compazine) Perphenazine (Trilafon) Fluphenazine (Prolixin) Perazine
2. Thioxanthenes	
a. Aliphatic	Chlorprothixene (Tarctan)
b. Piperazine	Thiothixene (Navane)
3. Butyrophenones	Haloperidol (Haldol) Droperidol (Inapsine)
4. Diphenylbutylpiperidine	Pimozide (Orap)
5. Dibenzazepine	Loxapine (Loxitane) Asenapine (Saphris)
6. Dibenzodiazepine	Clozapine (Clozaril) Quetiapine (Seroquel)
7. Thienobenzodiazepine	Olanzapine (Zyprexa)
8. Pyrimidinone	Risperidone (Risperdal) Paliperidone ER (9-hydroxyrisperidone)
9. Benzisothiazole	Ziprasidone (Geodon)
10. Benzisoxazole	Iloperidone (Zomaril)
11. Substituted benzamides	Metoclopramide (Reglan) Tiapride (Tiapridex) Sulpiride (Meresal) Clebopride Remoxipride Veralipride (Agregal, Agradil) Amisulpride (Solian) Levosulpiride
12. Indolones	Molindone (Moban)
13. Quinolinone	Aripiprazole (Abilify)
14. Tricyclic	Amoxapine (Asendin)
15. Calcium channel blockers	Flunarizine (Sibelium) Cinnarizine (Stugeron)
16. N-acetyl-4-methoxytryptamine	Melatonin
17. Interferon-alpha	Pegylated interferon alpha 2b (IFN- α) (Pegylated = polyethylene glycol (PEG) attached to proteins)
18. Atypical antipsychotic	Lurasidone

diphenylmethyl-4-(3-phenyl-2-propenyl) piperazine) and its difluorinated derivative flunarizine can induce parkinsonism (Teive et al., 2004). They are antagonists at the D2 receptors (Belforte et al., 2001), and they also inhibit the magnesium

Table 17.4 Characteristics of dopamine receptors

Feature	D1	D2	D3	D4	D5
Chromosome	5q31–34	11q22–23	3q13.3	11p	4p16.3
Region	Striatum	Striatum	Accumbens	Frontal cortex	Hippocampus
DA affinity	μmolar	μmolar	nmolar	Subμmolar	Subμmolar
Agonist	SKF-82526	Bromocriptine	7-OH-DPAT	?	SKF-82526
Antagonist	SCH-23390	Haloperidol	UH 232	Clozapine	SCH-23390
Adenyl cyclase	Stimulates	Inhibits	?	Inhibits	Stimulates

Table 17.5 A brief listing of receptor binding profiles of second-generation antipsychotic agents

Drug	D1	D2	5HT _{2A}	M ₂	α ₁	H ₁
Clozapine	85	125	2	1.9	7	6
Quetiapine	455	160	220	120	7	11
Olanzapine	31	11	4	1.9	19	7
Risperidone	75	3	0.6	>10 000	2	155

Data are Ki (nM). The lower the number, the greater the affinity of the drug for the receptor.
 α₁, Alpha NE type 1; D1, dopamine D1; D2, dopamine D2; H₁, histamine type 1 receptors; 5HT_{2A}, serotonin 2A; M₂, muscarinic type 2.
 Data from Worrel JA, Marken PA, Beckman SE, Ruehler VL. Atypical antipsychotic agents: A critical review. *Am J Health Syst Pharm*. 2000;57:238–255; and Schmidt AW, Lebel LA, Howard HR Jr, Zorn SH. Ziprasidone: A novel antipsychotic agent with a unique human receptor binding profile. *Eur J Pharmacol*. 2001;425:197–201.

adenosine triphosphate (Mg ATP)-dependent generation of a transmembrane proton electrochemical gradient and dopamine vesicular uptake (Terland and Flatmark, 1999). Whether either of these latter mechanisms, rather than a proposed DRBA action, is responsible for the neuroleptic activity is uncertain. In regard to melatonin, there is a case report of withdrawal-emergent O-B-L dyskinesias associated with akathisia that occurred with sudden discontinuation of chronic melatonin use (Giladi and Shabtai, 1999). Such withdrawal syndromes are typical of drugs that block dopamine receptors. On resumption of melatonin, the patient's O-B-L dyskinesia and akathisia cleared. Sudden cessation of the drug again brought on the symptoms; slow taper over 2 months was effective without incident. This case suggests that either the melatonin product the patient was taking was impure and was contaminated with a DRBA or melatonin itself has dopamine receptor antagonist properties. In support of the latter is the result of a blinded crossover study showing some suppression of the TD with melatonin (Shamir et al., 2001). Pegylated interferon alpha-2b (IFN-α), used in the treatment of hepatitis C virus infection, has been reported to cause parkinsonism, akathisia, and acute dystonic reaction (Quarantini et al., 2007). IFN-α has been shown to decrease dopaminergic activity in mice (Shuto et al., 1997).

Some drugs that block dopamine D2 receptors are promoted for medical problems other than psychosis, but these drugs can cause drug-induced parkinsonism, acute dystonic reactions, tardive syndromes, and NMS, just like the drugs that are promoted for the treatment of psychosis. Metoclopramide (Ganzini et al., 1993) and clobopride (Sempere et al., 1994) are used mainly for dyspepsia and as antiemetic agents. Amoxapine has a tricyclic structure and is marketed as an antidepressant drug, but a metabolite has dopamine receptor-blocking activity and has been implicated in producing TD (Kang et al., 1986; Sa et al., 2001). Veralipride

is a substituted benzamide that is used for the treatment of menopausal hot flushes (Masmoudi et al., 1995). Pimozide is marketed for the treatment of TS. Some commercial preparations contain dopamine receptor antagonists in combination with other drugs, and this can lead to inadvertent use of these drugs. A popular combination is that of perphenazine and amitriptyline, marketed as Triavil and Etrafon. Risperidone is commercially promoted with the suggestion that it might have less risk for drug-induced complications, but this appears not to be the case. Parkinsonism and TD have been noted in association with the calcium channel antagonists flunarizine and cinnarizine (Micheli et al., 1987). Both of these medications have mild dopamine receptor antagonist activity, which is thought to be the mechanism for their complications (Micheli et al., 1989). Recognition of these drugs is essential not only in making the diagnosis of TD but also in preventing the occurrence of TD by being able to avoid using them.

Clozapine is a special drug that is discussed more thoroughly later in the chapter; it has greater affinity for blocking the D4 receptor than the D2 receptor and deserves the classification as an atypical antipsychotic because it rarely causes parkinsonism or worsens PD. The newer antipsychotic quetiapine also qualifies as an atypical antipsychotic with just slightly more propensity to induce parkinsonism than clozapine. Olanzapine has more propensity to induce parkinsonism and worsen PD. Many agents that are promoted as atypical antipsychotics should not be classified as such.

The D1 and D5 receptors were both previously known as D1 receptors; both are distinct in activating adenyl cyclase. The D2, D3, and D4 receptors were all previously lumped together as the D2 receptor and are still considered in the D2 family of receptors.

The D1 and D2 receptors are found mainly in the striatum and nucleus accumbens and in the substantia nigra (SN), amygdala, cingulate cortex, and entorhinal area. The anterior

lobe of the pituitary gland has only D2 receptors, and the thalamus and cerebral cortex outside of the cingulate and entorhinal area contain D1 receptors only (De Keyser et al., 1988). D2 receptor affinities of dopamine receptor antagonists correlate closely with antipsychotic and antiemetic properties of the drugs (Creese et al., 1976). Dopamine receptor antagonists are often referred to as neuroleptics or antipsychotics; the former term indicates the effect of drugs in producing parkinsonism, and the latter indicates the effect of controlling psychosis.

The D3 receptor, another target of neuroleptics, is found chiefly in the mesolimbic areas. Because it is involved in emotional behaviors, it may be involved in tardive akathisia. Clozapine, an atypical antipsychotic that has a low potential to induce parkinsonism or tardive syndromes is primarily a D4 receptor antagonist. However, it has some D2-blocking action, which increases with higher doses.

Atypical antipsychotics

The label “atypical” refers to a lower propensity of the antipsychotic agent to induce parkinsonism or a variety of other movement disorders described later (and listed in Table 17.5), that is, these agents have a lower propensity to be neuroleptics. A number of epidemiologic studies have found that the atypicals are less likely to induce TD and other movement disorder problems (Tarsy and Baldessarini, 2006). Dolder and Jeste (2003) found that the atypicals reduced the incidence of TD by half. A 2018 meta-analysis of the randomized controlled studies included in the Cochrane Database of Systematic Reviews assessed the frequency of different movement disorders associated with both FGA and SGA when used for treatment of schizophrenia. The study found a high prevalence of acute movement disorders, with the FGAs (21%–29%) for drug-induced parkinsonism and 11% to 16% for acute dystonia. The SGAs had a reduced prevalence of parkinsonism, with clozapine and asenapine having the lowest prevalence (2%–4%) and ziprasidone and risperidone the higher prevalence (10%–12%). Likewise, the prevalence of akathisia was higher with the FGAs (16%–25%) than the SGA (3%–14%). However, there was considerable overlap (Martino, Karnik et al., 2018).

A second meta-analysis evaluated outcomes of studies that directly compared one of the SGAs or an SGA with an FGA used for the treatment of any psychiatric or medical diagnosis. This analysis included 57 studies with a trial duration of at least 3 months. The analysis showed that the TD risk ratio was significantly lower with the SGAs compared with the FGA. However, the relative incidence of TD with the SGAs was 2.6%, with clozapine and olanzapine having the lowest TD risk (Carbon, Kane et al., 2018).

Although the risk for TD is less with the SGA, the increasingly widespread use of these drugs for a variety of conditions, including mood disorders, fibromyalgia, and gastrointestinal disorders, is likely to lead to an increase in the prevalence of TD.

Dopamine and serotonin (5HT) receptor antagonism

Although drugs that are labeled as atypical antipsychotic agents block dopamine D2 receptors, they also block

serotonin 5HT_{2A} receptors, and some investigators attribute their antipsychotic effect to this mechanism and recommend research and drug development of newer agents that block other 5HT receptors (Meltzer, 1999).

How tightly drugs to bind to the D2 receptor (their occupancy rate) is currently considered to be important in the propensity of the drug to cause drug-induced side effects such as parkinsonism and TD. Seeman and Tallerico (1998) found that the atypical antipsychotic drugs bind more loosely than classic antipsychotic drugs (neuroleptics) to the D2 receptors. Kapur and colleagues (1999) measured D2 and 5HT₂ receptor occupancies by positron emission tomography (PET) scan for patients receiving clozapine, risperidone, or olanzapine. Clozapine showed a much lower D2 occupancy (16%–68%) than risperidone (63%–89%) and olanzapine (43%–89%); all three showed greater 5HT₂ occupancy than D2 occupancy at all doses, although the difference was greatest for clozapine. In their PET study, Moresco and colleagues (2004) found that striatal D2 receptor occupancy was significantly higher with olanzapine than with clozapine. All of these studies support the relationship between receptor occupancy and the clinical observations that clozapine and quetiapine are the most “atypical,” with the least propensity to cause parkinsonism, tardive syndromes, or other neuroleptic drug reactions.

Despite interest in the 5HT_{2A} receptor, it is the D2 receptor that is associated with the antipsychotic effect (Seeman, 2010). Antipsychotic clinical doses correlate with their affinities for this receptor. The receptor has high- and low-affinity states. Clozapine and quetiapine do not elicit parkinsonism and rarely result in TD because they are released from D2 within 12 to 24 hours. Traditional antipsychotics remain attached to D2 receptors for days, preventing relapse, but allowing accumulation that can lead to TD. Glutamate agonists that treat schizophrenia have affinity for the dopamine D2(High) receptor and the D3 receptor (Seeman and Guan, 2009).

A comparison of the receptor-binding profiles of quetiapine, clozapine, olanzapine, and risperidone is presented in Table 17.5. Both quetiapine and clozapine have poor affinity for the dopamine D2 receptor, which probably accounts for the low incidence of inducing parkinsonism and tardive syndromes. Risperidone has the highest affinity for the D2 receptor, resembling haloperidol (Table 17.6), and is therefore more of a typical than an atypical antipsychotic.

In one PET study, striatal D1 and D2 receptor occupancies were evaluated (Tauscher et al., 2004). D1 occupancy ranged from 55% with clozapine to 12% with quetiapine (rank order: clozapine > olanzapine > risperidone > quetiapine). The striatal D2 occupancy ranged from 81% with risperidone to 30% with quetiapine (rank order: risperidone > olanzapine > clozapine > quetiapine). The ratio of striatal D1/D2 occupancy was significantly higher for clozapine (0.88) relative to olanzapine (0.54), quetiapine (0.41), or risperidone (0.31). In a [¹²³I]epidepride single-photon emission computed tomography (SPECT) study involving clozapine-, olanzapine-, and haloperidol-treated schizophrenia patients, drug-naïve patients, and healthy controls, midbrain D(2/3) receptor occupancy was studied. Of those on medication, occupancy was least for those on clozapine (5%), next for those on olanzapine (28%), and greatest for those on haloperidol (40%); no significant differences were observed

Table 17.6 Listing of affinities for human receptors and rat transporters by antipsychotic drugs

Receptor	Haloperidol	Clozapine	Quetiapine	Olanzapine	Risperidone	Ziprasidone
Dopamine D1	15	53	390	10	21	9.5
Dopamine D2	0.82	36	39	2.1	0.44	2.8
Dopamine D3	2.5	22	>500	17	13	28
5HT _{1A}	2600	710	>830	7100	21	37
5HT _{1B/1D}						
5HT _{2A}	28	4.0	82	1.9	0.39	0.25
5HT _{2C}	1500	5.0	1500	2.8	6.4	0.55
5HT _{2D}						
5HT ₆	6600	9.5	33	10	2400	n.t.
5HT ₇	80	21	290	120	1.6	4.9
α ₁ -Adrenoceptor	7.3	3.7	4.5	7.3	0.69	1.9
α ₂ -Adrenoceptor	1600	51	1100	140	1.8	390
Histamine H ₁	>730	17	21	5.6	88	510
Muscarinic M ₁	570	0.98	56	2.1	>5000	>10 000

Receptor bindings are presented as Ki values (nmol/L).

Data from Horacek J. Novel antipsychotics and extrapyramidal side effects: Theory and reality. *Pharmacopsychiatry*. 2000;33:34–42; and Schmidt AW, Lebel LA, Howard HR Jr, Zorn SH. Ziprasidone: A novel antipsychotic agent with a unique human receptor binding profile. *Eur J Pharmacol*. 2001;425:197–201.

in the temporal poles (Tuppurainen et al., 2009). All imaging studies are compatible with the clinical results in that clozapine and quetiapine, with the least neuroleptic features, have the lowest D2 receptor occupancy rate.

Clozapine

Clozapine was the first agent to be labeled as an atypical antipsychotic and deservedly so, although rare case reports do exist of drug-induced parkinsonism (Kurz et al., 1995), but it has been reported not to induce rigidity and it rarely induces parkinsonian tremor (Gerlach and Peacock, 1994). It has also caused rare cases of acute akathisia (Friedman, 1993; Safferman et al., 1993), acute dystonic reaction (Kastrup et al., 1994; Thomas et al., 1994), tardive syndromes (Dave, 1994), tardive dystonia (Bruneau and Stip, 1998; Molho and Factor, 1999a, van Harten et al., 2008b), tardive akathisia (Kyriakos et al., 2005), tardive oculogyria (Uzun and Doruk, 2007), and NMS (Sachdev et al., 1995; Benazzi, 1999; Lara et al., 1999; Gambassi et al., 2006). Parkinsonian features are also seen with clozapine. In a prospective study, 7 of 25 patients on clozapine developed TD (Bunker et al., 1996). In a retrospective study, comparison of clozapine and typical antipsychotics showed no lower prevalence of TD in the clozapine group (Modestin et al., 2000). But it is not clear that the patients in the clozapine group had not been previously exposed to typical antipsychotics and had not developed TD while receiving them. What is clear from this study is that the conversion to using clozapine has not markedly reduced the prevalence of extrapyramidal syndromes; this finding supports the realization that clozapine does not effectively treat TD once it has developed. How effective its use would be in preventing TD in the first place still needs to

be verified. For patients with PD, the low propensity to augment existing parkinsonism makes clozapine very useful in treating patients who have dopaminergic drug-induced psychosis (Factor and Friedman, 1997; Friedman et al., 1999).

A SPECT study measuring dopamine D2 receptor binding reveals lower binding with clozapine than with typical neuroleptics (Broich et al., 1998). In animal studies, rats that have been pretreated with haloperidol for 4 weeks develop vacuous chewing movements (VCMs) after treatment with a dopaminergic, whereas rats that have been pretreated with clozapine do not (Ikeda et al., 1999).

A problem with clozapine is the side effect profile. Common side effects associated with clozapine include sedation, weight gain, seizures, sialorrhea, orthostatic hypotension, and blood dyscrasias. Up to 2% of treated patients can develop at least transient neutropenia that can progress to agranulocytosis (De Berardis, Rapini et al., 2018). Currently, complete blood counts are required weekly until 6 months, every 2 weeks for 6 to 12 months, and monthly thereafter. If neutropenia occurs (less than 1000/μL), discontinuation of the drug with more frequent monitoring is required until recovery. Uncommon adverse effects include metabolic syndrome, delirium, and NMS. Myocarditis associated with clozapine has been reported (Hill and Harrison-Woolrych, 2008).

Quetiapine

After clozapine, quetiapine is the most favorable in being least likely to induce parkinsonism, NMS (Stanley and Hunter, 2000), or tardive syndromes. In a prospective, head-to-head comparison with risperidone treatment in schizophrenia, quetiapine had far fewer extrapyramidal adverse

effects, but more orthostasis (Perez et al., 2008). D2 receptor antagonism is relatively selective for limbic rather than striatal receptors for clozapine and sertindole, followed by quetiapine, ziprasidone, olanzapine, and remoxipride, whereas risperidone in many respects has a profile that resembles that of haloperidol (Arnt and Skarsfeldt, 1998). In primates, quetiapine and clozapine were equally less likely to induce oral dyskinesias compared with standard antipsychotics (Peacock and Gerlach, 1999). Like clozapine, quetiapine easily induces drowsiness, so when it is used to treat dopa-induced psychosis, it should be taken at bedtime. The major advantage over clozapine is that it does not require blood tests because it does not induce agranulocytosis. However, there may be a rare risk that quetiapine can cause agranulocytosis (Ruhe et al., 2001). Since its introduction, there have been reports of acute dystonic reactions (Jonnalagada and Norton, 2000; Desarker and Sinha, 2006), acute akathisia (Prueter et al., 2003), NMS (El-Gaaly et al., 2009; Gortney et al., 2009), and TD (Ghaemi and Ko, 2001). In 367 patients treated for 12 months with quetiapine (mean dose 720 mg/day), parkinsonism was seen in 10%, akathisia in 3%, dystonia in 1.4%, and "hyperkinesia" in 1.7% (Perez et al., 2008).

In a SPECT study using the D2/D3 ligand [^{123} I]-epidepride the percent occupancy of receptors in the limbic system (temporal lobe) and striatal receptors while patients were receiving quetiapine was 60% and 32%, respectively, which is similar to that for clozapine (Stephenson et al., 2000). In another SPECT study, quetiapine was shown to occupy 5HT_{2A} receptors in the frontal and temporal cortex (Jones et al., 2001). A PET study using [^{18} F]fallypride showed similar results (Vernaleken et al., 2010).

A patient with oculogyric crisis, who failed to improve after withdrawal of antipsychotic medication, was successfully treated with quetiapine (Gourzis et al., 2007). Drug-induced parkinsonism and acute akathisia caused by other neuroleptics can be reduced by switching patients to quetiapine (Cortese et al., 2008). Drowsiness and weight gain are common; postural hypotension is not infrequent. A rare complication of quetiapine is hepatotoxicity (Shpaner et al., 2008).

Olanzapine

In contrast to clozapine and quetiapine, olanzapine more readily increases parkinsonian symptoms in patients with PD (Jimenez-Jimenez et al., 1998; Granger and Hanger, 1999; Molho and Factor, 1999b), but does so less readily than risperidone and conventional antipsychotics. Drug-induced parkinsonism, including the rabbit syndrome, is seen with olanzapine (Durst et al., 2000), but less than with haloperidol (Peuskens et al., 2009). It can induce acute akathisia (Kurzthaler et al., 1997; Jauss et al., 1998) and TD but less so than haloperidol (Tollefson et al., 1997; Wood 1998). It can also induce NMS (Filice et al., 1998; Moltz and Coeytaux, 1998; Burkhard et al., 1999; Levenson, 1999; Margolese and Chouinard, 1999; Sierra-Biddle et al., 2000; Abu-Kishk et al., 2004; Zaragoza Fernandez et al., 2006), TD (Herran and Vazquez-Barquero, 1999), and tardive dystonia (Dunayevich and Strakowski, 1999). Acute dystonic reactions also occur (Beasley et al., 1997; Landry and Cournoyer, 1998; Vena et al., 2006).

A direct comparison with chlorpromazine showed similar parkinsonism and acute akathisia for the two drugs (Conley

et al., 1998). A double-blind comparison with haloperidol by Beasley and colleagues (1999) showed a much lower risk for developing TD with olanzapine. After 1 year of exposure, 0.52% of patients developed TD with olanzapine and 7.45% developed TD with haloperidol. An open-label comparison with conventional antipsychotics after a 9-month follow-up after discharge from the hospital favored olanzapine, with TD being present in 2.3% for olanzapine (2/87), and 16.7% (12/72) for the conventional treatment (Mari et al., 2004). There are case reports of agranulocytosis induced by olanzapine (Meissner et al., 1999; Naumann et al., 1999; Tolosa-Vilella et al., 2002), including in a patient who had previously had agranulocytosis with clozapine (Benedetti et al., 1999). This has been attributed to some similar structural and pharmacologic properties of clozapine. A case of restless legs syndrome with periodic movements in sleep has been attributed to olanzapine (Kraus et al., 1999).

Olanzapine has relative regional mesolimbic dopaminergic selectivity and a broad-based binding affinity for serotonin (all 5HT₂ receptor subtypes and the 5HT₆ receptor), dopamine (D2, D3, and D4 receptors), muscarinic, and alpha-1 adrenergic receptors (Bymaster et al., 1999). A PET study in schizophrenic patients being treated with olanzapine revealed that this drug is a potent 5HT₂ blocker, but also a blocker of D2 dopamine receptors similar to risperidone and less so than clozapine (Kapur et al., 1998). Patients on olanzapine were also studied with [^{123} I]iodobenzamide (IBZM) SPECT; the D2 receptor was occupied 60% and 83% of the time at doses of 5 mg/day and 10 mg/day, respectively (Raedler et al., 1999). Such high rates of occupancy probably account for olanzapine's tendency to worsen parkinsonism and induce DRBA complications, because, as was noted earlier, D2 receptor occupancy rates are directly related to neuroleptic potential.

Risperidone

With the success of clozapine, there is a commercial advantage for pharmaceutical companies to tout other antipsychotics as atypical. Such has been claimed for risperidone, but this drug can readily induce parkinsonism, including the rabbit syndrome (Levin and Heresco-Levy, 1999), tardive syndromes (Haberfellner 1997; Silberbauer 1998; Hong et al., 1999; Ananth et al., 2000), and NMS (Newman et al., 1997; Norris et al., 2006). The prevalence of parkinsonism from risperidone is usually considered to be less than that with conventional neuroleptics, but it was observed in 42% compared with 29% in those on haloperidol (Knable et al., 1997). TD and tardive dystonia occurred in a patient who was exposed only to risperidone (Bassitt and Garcia, 2000). The annual incidence of TD in patients taking risperidone has been estimated to be 0.3%, compared with an annual incidence in patients taking conventional neuroleptics of 5% to 10% (Gutierrez-Esteinou and Grebb, 1997). However, in an open-label prospective study of 255 institutionalized patients with dementia who were treated with risperidone, the 1-year cumulative incidence of TD was 2.6% (Jeste et al., 2000).

Like conventional neuroleptics, risperidone induces acute dystonic reactions in marmosets, in contrast to clozapine, which does not (Fukuoka et al., 1997). In a report of an open-label comparison with haloperidol, Rosebush and Mazurek

(1999) found the two drugs to have a similar side effect profile. In a prospective follow-up of first-episode schizophrenic patients treated with risperidone, movement disorders developed in more than one-third of these patients, who had previously never been exposed to antipsychotic drugs (Lang et al., 2001). When risperidone is compared with low-potency antipsychotics, such as thioridazine, no difference was discerned in the rates of developing movement disorders (Schillevoort et al., 2001).

In a SPECT study, dopamine receptor binding with IBZM showed risperidone to have effects between those of haloperidol and clozapine, with a dose-response curve for risperidone showing greater similarity to that of haloperidol (Dresel et al., 1998). A PET study showed dopamine D2 receptor occupancies of about 70% and 60% in the striatum and extrastriatum, respectively (Ito et al., 2009). Clearly, risperidone is not an atypical antipsychotic agent. Risperidone's occupancy of the 5HT₂ receptors is about 90%, and its occupancy of the D2 receptors is between 50% and 80%, but the latter correlates with the extrapyramidal side effects (Yamada et al., 2002).

Ziprasidone

This benzisothiazole was approved by the FDA in 2001. There are already case reports of acute dystonic reactions (Weinstein et al., 2006; Yumru et al., 2006; Rosenfield et al., 2007), NMS, rhabdomyolysis, and pancreatitis (Murty et al., 2002; Yang and McNeely, 2002; Gray 2004). It has been reported to cause TD (Mendhekar, 2005) and tardive dystonia (Papapetropoulos et al., 2005; Tsai et al., 2008). Although it is a potent 5HT_{2A} antagonist (like risperidone, olanzapine, and clozapine), it is also a D2 antagonist in humans as detected by PET scan (Bench et al., 1993, 1996). But in-vitro studies reveal much lower affinity for the D2 receptor than for the 5HT_{2A} receptor (Seeger et al., 1995), and ziprasidone also binds less tightly to the D2 receptor than dopamine (Seeman, 2002). Ziprasidone has two other unique features compared with other antipsychotic agents: (1) it is a potent 5HT_{1A} agonist and thus inhibits dorsal raphe serotonergic cell firing (Sprouse et al., 1999) and increases cortical dopamine release (Rollema et al., 2000), and (2) it inhibits neuronal uptake of 5HT and norepinephrine in a manner comparable to that of the antidepressant imipramine (Schmidt et al., 2001). What these unique actions might contribute to antipsychotic activity or to propensity for or against extrapyramidal reactions is unclear. Ziprasidone has been reported to induce a case of oculogyric crisis in an adult (Viana Bde et al., 2009).

Aripiprazole

This quinolinone has a novel mechanism of action. Like a number of other atypical antipsychotics, it is an antagonist at the 5HT_{2A} receptors. It is also a 5HT_{1A} partial agonist (Jordan et al., 2002). What is novel is that it is a partial agonist at the dopamine D2 receptor. It has a higher affinity for the presynaptic autoreceptor than for the postsynaptic receptor. Hence, it reduces dopamine synthesis and release through an agonist action at the dopamine autoreceptor (Tamminga and Carlsson, 2002). Because of its novel action as a partial D2 agonist, it was anticipated that it might cause fewer extrapyramidal adverse effects, and clinical trials reported favorable

results (Kane et al., 2002). However, D2 ligand-binding PET revealed a dose-related high occupancy state of 71.6% at 2 mg/day to 96.8% at 40 mg/day (Kegeles et al., 2008). With wider use, it has been shown to worsen PD (Friedman et al., 2006; Wickremaratchi et al., 2006), and there are already reports of it causing parkinsonism (López-Torres et al., 2008), NMS (Chakraborty and Johnston, 2004; Hammerman et al., 2006; Palakurthi et al., 2007), acute dystonic reactions (Desarkar et al., 2006; Fountoulakis et al., 2006), and TD (Zaidi and Faruqi, 2008; Abbasian and Power, 2009; Friedman, 2010).

Amisulpride

Amisulpride, a substituted benzamide, is a highly selective antagonist for dopamine D2 and D3 receptors in the limbic region, which would predict potent antipsychotic activity with a low potential to cause extrapyramidal symptoms (Lecrubier, 2000). It binds less tightly to the D2 receptor than do the typical antipsychotics (Seeman, 2002). Using the full range of recommended amisulpride dosage, striatal occupancies up to 90% can be measured (Vernaleken et al., 2004). It is not yet commercially available in the United States. It has already been reported to induce tardive oculogyric crisis (Mendhekar et al., 2010).

Adverse effects from second-generation antipsychotics

Aside from the D2-blocking effects described previously, the five drugs in Table 17.7 have a number of other adverse effects. Sedation is a particular problem seen with each of them, but particularly clozapine and quetiapine. Metabolic side effects are now widely recognized with the SGAs, with weight gain, glucose intolerance, and diabetes being common problems (Leucht et al., 2009; Patel et al., 2009; Jeon and Kim 2017). Table 17.7 lists the common adverse effects of these drugs, along with haloperidol, for comparison.

It is not likely that drug-induced tardive syndromes will disappear because use of both typical and atypical agents continues. In a survey in Lombardy, Italy, 35,363 individuals over the age of 65 were prescribed an antipsychotic prescription (2.18 subjects per 100 inhabitants, with two-thirds receiving FGAs) (Percudani et al., 2004). Although there may be a lower risk for developing these disorders with atypicals, these drugs can induce them (Table 17.8). It is even possible that if physicians consider atypicals safe to use, their use will increase, even in situations in which the risk from typicals might have precluded their use. In the United States the prevalence of atypical antipsychotic use was found to be 267.1 per 100,000 subjects aged 19 years and younger and was more than twice as high for male patients as for female patients (Curtis et al., 2005).

In a large U.S. randomized controlled trial (RCT) (the CATIE study) comparing second-generation antipsychotics (SGAs) (olanzapine, quetiapine, risperidone, perphenazine, or ziprasidone) with the first-generation perphenazine, only olanzapine had a slightly more favorable outcome of both the patients' ability to stay on this drug for a longer duration and with slightly less drug-induced parkinsonism, akathisia, and TD than all other drugs, including perphenazine (Table 17.9); perphenazine fared as well as the other so-called

Table 17.7 Adverse effect profile of “atypical” neuroleptics

Adverse effect	Haloperidol	Clozapine	Quetiapine	Olanzapine	Risperidone
Sedation	+	+++	++	+	+
Seizures	+	+++	+	+	+
Hypotension	+	+++	++	++	++
Increased prolactin	+++	0	0	++	+
Weight gain	+	+++	++	+++	++

0, none; +, mild; ++, moderate; +++, severe.

Data from Worrel JA, Marken PA, Beckman SE, Ruehter VL. Atypical antipsychotic agents: A critical review. *Am J Health Syst Pharm*. 2000;57:238–255.

Table 17.8 Extrapyramidal adverse effects reported with “atypical” neuroleptics

Adverse effect	Haloperidol	Clozapine	Quetiapine	Olanzapine	Risperidone
Parkinsonism	Yes	Yes	Not yet	Yes	Yes
Acute akathisia	Yes	Yes	Yes	Yes	Yes
Acute dystonia	Yes	Yes	Yes	Yes	Yes
Neuroleptic malignant syndrome	Yes	Yes	Yes	Yes	Yes
Tardive syndrome	Yes	Yes	Yes	Yes	Yes

Table 17.9 Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) study

Drug	Dose/capsule (mg)	Mean dose (mg)	No.	Duration* (hazard ratio versus others; <i>P</i> =)	AIMs (%)	Akathisia (%)	DIP (%)
Olanzapine	7.5	20.1	336	Longest duration and used as comparator	14	5	8
Quetiapine	200	543.4	337	0.63; 0.0001	13	5	4
Risperidone	1.5	3.8	341	0.75; 0.002	16	7	8
Perphenazine	8	20.8	261	0.78; 0.021	17	7	6
Ziprasidone	40	112.8	185	0.78; 0.028	14	9	4

AIMs, Abnormal involuntary movements; DIP, drug-induced parkinsonism.

*Duration is the amount of time on a drug before it was discontinued for any reason. Olanzapine had the longest duration, and the hazard ratios for the other drugs are based on their comparison to olanzapine.

From Lieberman JA, Stroup TS, McEvoy JP, et al.; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353(12):1209–1223. © 2005 Massachusetts Medical Society. All rights reserved.

atypicals (Lieberman et al., 2005). A similar outcome was seen in a smaller British study (CUTLASS) (Jones et al., 2006). This was a clinical RCT involving 57 centers, with flexible dosing up to 4 capsules/day in 1460 schizophrenic subjects (after excluding 33 from one center for integrity concern). The primary outcome was time to discontinuation, with a maximum observation of 18 months. TD was present in 231 subjects at baseline, and these subjects were excluded from the perphenazine arm. The outcome had multiple comparisons, requiring a *P* value of 0.017 or less to be significant.

In a more detailed assessment of extrapyramidal side effects in the CATIE study, there were no significant differences in incidence or change in rating scales for parkinsonism, dystonia, akathisia, or TD when comparing the SGAs with perphenazine or comparing between SGAs (Miller et al., 2008). Secondary analyses revealed greater rates of concomitant antiparkinsonism medication among

individuals on risperidone and lower rates among individuals on quetiapine.

Metoclopramide

After the introduction of metoclopramide for gastrointestinal disorders, reports of acute dystonic reactions in children and TD in adults began to appear (Cochlin, 1974; Kataria et al., 1978; Lavy et al., 1978). Today, metoclopramide has become a common cause of TD, and the legal profession has found such cases ripe for lawsuits. The annual incidence of TD from metoclopramide has been reported to be between 4.5% and 23% per year (Grimes, 1981; Ganzini et al., 1993), about the same as that for haloperidol of approximately 5.7% per year (Tollefson et al., 1997; Beasley et al., 1999; Csernansky et al., 2002), but higher than those for risperidone at about 1.8% per year (Lemmens et al., 1999; Davidson et al., 2000;

Jeste et al., 2000; Csernansky et al., 2002) and olanzapine at approximately 1.2% per year (Tollefson et al., 1997; Beasley et al., 1999). Because antipsychotic drugs have an affinity for brain neuromelanin (Seeman, 1988), Chen and colleagues (2010) examined the amount of metoclopramide and antipsychotic drugs binding to postmortem human SN. They found that in clinical conditions the amount of metoclopramide that would bind to nigra is much higher than the amount of raclopride, haloperidol, or olanzapine that would be expected to be bound and suggest that this binding might explain the higher annual incidence of TD induced by metoclopramide.

Neurologic side effects of dopamine D2 receptor antagonists

To better understand the tardive syndromes, it is important to recognize the variety of other movement disorders that are induced by the dopamine receptor antagonists at different points in the course of treatment. These movement disorders are often lumped together as extrapyramidal syndromes, but the lumping often hinders the effort to sort out the clinical characteristics and pathophysiology of separate syndromes. It is better to subdivide them into their phenomenologic types (see [Table 17.1](#)). Movements that may be seen include acute dystonia, acute akathisia, parkinsonism, tardive syndromes, and NMS. Both dystonia and akathisia also occur as subtypes of tardive syndromes and both subtypes are discussed in more detail in the section on tardive syndromes.

Acute dystonia

The earliest abnormal involuntary movement to appear after initiation of dopamine receptor antagonist therapy is an acute dystonic reaction. In about half of the cases, this reaction occurs within 48 hours, and in 90% of cases, it occurs by 5 days after starting the therapy (Ayd, 1961; Garver et al., 1976). The reaction may occur after the first dose (Marsden et al., 1975).

Dystonic movements are sustained muscle contractions, frequently causing twisting and repetitive movements, or abnormal postures (Fahn, 1988). In a series of 3775 patients, Ayd (1961) found that acute dystonia is the least frequent side effect, affecting about 2% to 3% of patients, with young males being most susceptible. The incidence rate increases to beyond 50% with highly potent dopamine receptor blockers such as haloperidol (Boyer et al., 1987). In one prospective study, Aguilar and colleagues (1994) reported that 23 of 62 patients developed acute dystonia after haloperidol was introduced, that anticholinergic pretreatment significantly prevented this, and that younger age and severity of psychosis were risk factors. In the prospective study by Kondo and colleagues (1999), 20 (51.3%) of 39 patients placed on nemonapride had dystonic reactions, onset occurring within 3 days after the initiation of treatment in 90%. As in other series, the incidence of acute dystonia was significantly higher in males than in females (77.8% versus 28.6%, $P < 0.05$), and younger males (30 years or younger) had an extremely high incidence (91.7%). The incidence is much lower with the atypical antipsychotics; Raja and Azzoni (2001) observed only 41 cases in 1337 newly admitted patients treated with

antipsychotics, which included 8 treated with risperidone, 1 with olanzapine, and 1 with quetiapine. A meta-analysis compared intramuscular injections of SGAs to haloperidol injections (Satterthwaite et al., 2008). SGAs were associated with a significantly lower risk for acute dystonia (relative risk [RR], 0.19) and acute akathisia (RR, 0.25) compared with haloperidol alone.

All agents that block D2 receptors can induce acute dystonic reactions, including risperidone (Brody, 1996; Simpson and Lindenmayer, 1997) and clozapine (Kastrup et al., 1994). One child developed an acute dystonic reaction after ingestion of a dextromethorphan-containing cough syrup (Graudins and Fern, 1996). Dextromethorphan has several different known pharmacologic actions, but D2 receptor blockade is not one of them. A case of acute dystonia after abrupt withdrawal of bupropion (DA reuptake blocker) was reported (Wang et al., 2007). A case of acute dystonia after abrupt withdrawal of dexamphetamine in a patient taking risperidone was also reported (Keshen and Carandang, 2007). Serotonergic agents also have been reported to induce acute dystonic reactions (Lopez-Aleman et al., 1997; Madhusoodanan and Brenner, 1997; Olivera, 1997). The mechanism could relate to inadequate release of dopamine from the nerve terminals in the striatum owing to the inhibitory effect of serotonin on dopamine neurons in the SN pars compacta (SNc). The opioid σ_1 and σ_2 receptors also have been implicated (Matsumoto and Pouw, 2000).

Acute dystonic reactions most often affect the ocular muscles (oculogyric crisis), face, jaw, tongue, neck, trunk, and less often the limbs. Oculogyric crisis has previously been noted to occur as a common feature of postencephalitic parkinsonism (Duvoisin and Yahr, 1965). A typical acute dystonic reaction may consist of head tilt backward or sideways with tongue protrusion and forced opening of the mouth, often with arching of trunk and ocular deviation upward or laterally (Rupniak et al., 1986). The forcefulness of the muscle contractions can be extremely severe and led to auto-amputation of the tongue in one patient (Pantanowitz and Berk, 1999).

Mazurek and Rosebush (1996) studied the timing in the development of an acute dystonic reaction in 200 patients who were taking a neuroleptic medication for the first time. The neuroleptic was given twice daily, and over 80% of the episodes of acute dystonia occurred between 12 noon and 11 PM.

Reserpine and alpha-methylparatyrosine, which deplete presynaptic monoamines, have not been associated with acute dystonic reactions (Duvoisin, 1972; Marsden et al., 1975; Walinder et al., 1976). However, another dopamine depleter, TBZ, has been reported to induce acute dystonic reactions (Burke et al., 1985). One possible explanation for this difference is that in addition to depleting dopamine, TBZ blocks dopamine receptors (Reches et al., 1983).

It is important to mention the case described by Wolf (1973) of a patient who developed an oral dyskinesia while taking reserpine. [Fig. 17.1](#) in his paper clearly shows a dystonic phenomenon and not the complex, rapid, stereotypic movements of classic TD. This development appeared too late after initiation of reserpine to be considered an acute dystonic reaction, however. Whether this could be an example of tardive dystonia is not clear, because the phenomenology of tardive dystonia is identical to that of naturally

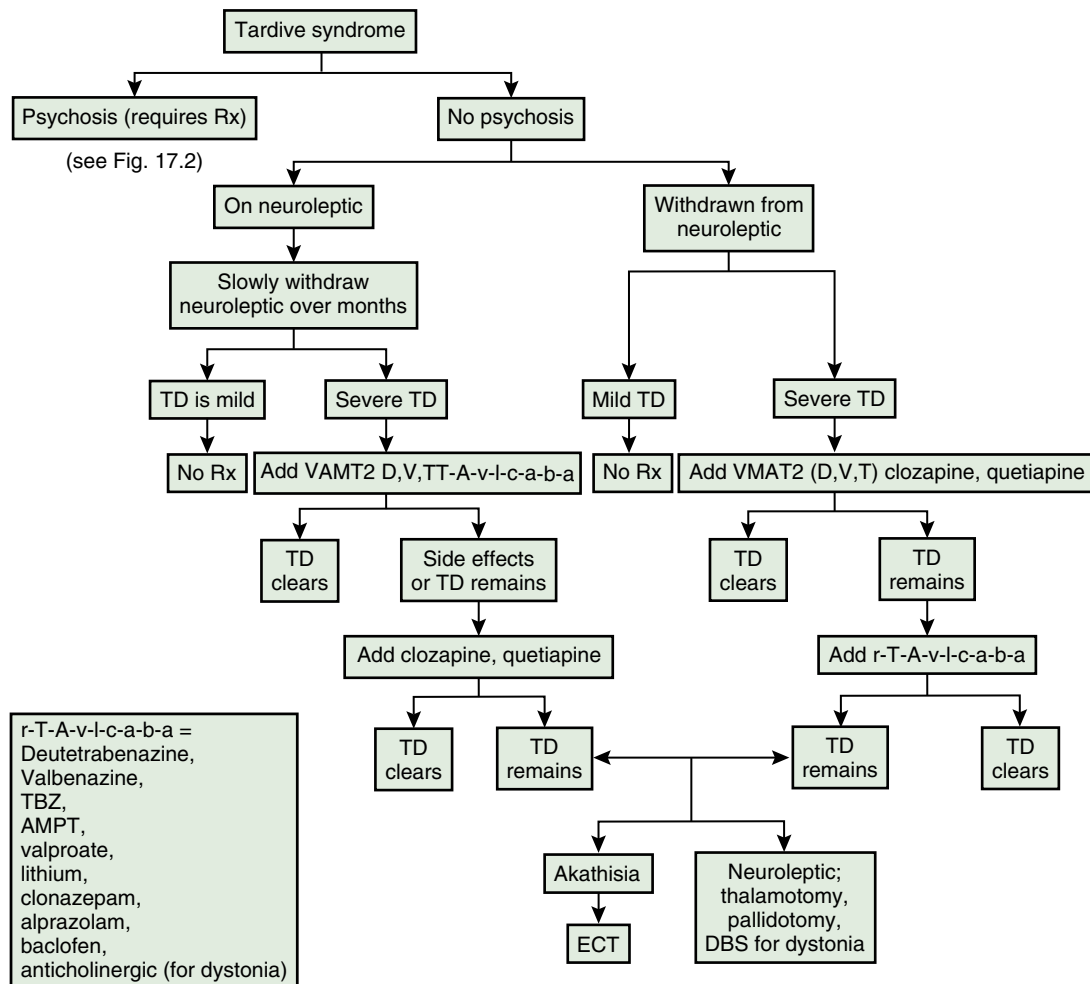


Fig. 17.1 Flowchart for treating tardive dyskinesia in the absence of psychosis. AMPT, Alpha-Methylparatyrosine; DBS, deep brain stimulation; ECT, electroconvulsive therapy; TBZ, tetrabenazine; TD, tardive dyskinesia.

occurring primary dystonia; therefore, the patient could have had a coincidental case of spontaneous, idiopathic oromandibular dystonia (Fahn, 1984b). Thus, there is no absolute evidence that reserpine induces acute dystonic reactions, classic TD, or tardive dystonia. In fact, symptoms of these three tardive syndromes can be suppressed by reserpine, and eventually reserpine can be withdrawn successfully in many patients without exacerbation of the symptoms (Fahn, 1983). Furthermore, the long time that reserpine has been available without a clear-cut case of tardive syndromes can be compared with the much shorter duration of use of metoclopramide, in which there are already cases of acute dystonic reactions, classic TD, and tardive dystonia as a consequence of its use (Casteels-Van Daele et al., 1970; Gatrad, 1976; Pinder et al., 1976; Reasbeck and Hossenbocus, 1979; Miller and Jankovic, 1989; Lang, 1990).

Of 452 patients given high-dosage oral metoclopramide to control emesis, Kris and colleagues (1983) observed 14 who developed acute dystonic reactions. However, there was a distinct preponderance of the reactions occurring in children (6/22) compared with adults (8/430). Intravenous metoclopramide is more likely to induce it than oral administration (Pinder et al., 1976). In a study at a Veterans Administration hospital, comparing patients treated with metoclopramide and controls, the relative risk for TD was 1.67, and the

relative risk for drug-induced parkinsonism was 4.0 (Ganzini et al., 1993).

The available biochemical explanations for the acute dystonic reaction are unsatisfactory, but several observations contribute to the understanding of the phenomena, relating it to dopamine, muscarinic, and sigma receptors. Acute neuroleptic administration produces sudden increase of dopamine release and increased turnover lasting for 24 to 48 hours after a single dose (O'Keefe et al., 1970; Marsden and Jenner, 1980). This effect is blocked by anticholinergics consistent with their efficacy in treatment of acute dystonic reactions (O'Keefe et al., 1970). Moreover, in baboons that were pretreated with reserpine and alpha-methylparatyrosine, which markedly reduces presynaptic dopamine concentration, haloperidol-induced acute dystonic reaction is abolished or greatly reduced (Meldrum et al., 1977). On the other hand, blockade of the postsynaptic receptor fades in about 12 hours after a single dose of antipsychotics, and supersensitivity of receptors begins to develop. Therefore, presynaptic dopaminergic excess in combination with the emerging supersensitive postsynaptic dopamine receptors could result in markedly increased striatal dopaminergic activity at about 20 to 40 hours after a neuroleptic dose. This period corresponds to the critical time for acute dystonic reactions in human subjects who were given a single dose of

butaperazine (Garver et al., 1976). However, extrapolating the data from experimental animals to the clinical situation has limitations, including the fact that rats do not develop acute dystonic reactions. Further data on human cerebrospinal fluid (CSF) dopamine metabolites as an indicator of pre-synaptic function might prove to be of value in pursuing the hypothesis. Jeanjean and colleagues (1997) suggested that the σ_2 receptors could be involved in the acute dystonic reaction. They found a correlation between the clinical incidence of neuroleptic-induced acute dystonia and binding affinity of drugs for the sigma receptor.

Another animal model of acute dystonia is the common marmoset that is treated with haloperidol (Fukuoka et al., 1997). But it takes at least 6 weeks of such treatment to develop this reaction. The dystonia subsides only to reappear when haloperidol treatment is restarted; other neuroleptics, including risperidone, can also make the dystonia reappear, but clozapine was without such an effect. In this animal model, the anticholinergic agent trihexyphenidyl inhibited the induction of acute dystonia.

In patients with acute dystonic reactions, symptoms can be relieved within minutes after parenteral anticholinergics or antihistaminics (Paulson, 1960; Waugh and Metts, 1960; Smith and Miller, 1961). Diphenhydramine 50 mg, benztropine mesylate, or biperiden 1 to 2 mg is given intravenously and can be repeated if the effect is not seen in 30 minutes. Intravenous diazepam also has been shown to be effective and can be used as an alternative therapy (Korczyński and Goldberg, 1972; Gagrut et al., 1978; Rainer-Pope, 1979). If untreated, the majority of cases still resolve spontaneously in 12 to 48 hours after the last dose of the dopamine receptor antagonists. Dopamine receptor antagonists with high anticholinergic activities have low incidence rates of acute dystonic reactions (Swett, 1975). Therefore, prophylactic use of anticholinergics (Arana et al., 1988) and benztropine (Goff et al., 1991) has been studied and reported to be helpful in reducing the risk for acute dystonic reactions, especially in young patients on high-potency drugs. Three cases of recurrent episodes of acute dystonia and oculogyric crises despite withdrawal of the offending DRBAs (haloperidol in two cases, metoclopramide in one) have been reported, responding to anticholinergics each time (Schneider et al., 2009). The response of acute dystonic reactions to anticholinergics is so characteristic that it is difficult to explain the report of a few cases apparently caused by amitriptyline, which has considerable anticholinergic activity and no known DRBA activity (Ornadel et al., 1992).

A case of an acute dystonic reaction occurring in an elderly person with bipolar disorder taking the serotonin uptake inhibitor paroxetine has been reported (Arnone et al., 2002). Speculation about the risk because of previous exposure to neuroleptics was raised. This class of drug can reduce firing rate of nigral dopaminergic neurons owing to their inhibition by serotonin.

Acute akathisia

The term akathisia, from the Greek, meaning unable to sit down, was coined by Haskovec in 1901 (cited by Mohr and Volavka, 2002), long before antipsychotic drugs were introduced. Akathisia was seen in some patients with advanced parkinsonism, and in others it was frequently thought to be

functional. Akathisia refers to an abnormal state of excessive restlessness, a feeling of the need to move about, with relief of this symptom on actually moving. Today, it is most frequently encountered as a side effect of neuroleptic drugs.

Two major issues of akathisia remain in confusion. First, there is no consensus about diagnostic criteria. Some authors consider akathisia to be an abnormal subjective state and regard the movements as an expression of the subjective state but not a necessary feature for the diagnosis (Van Putten, 1975). Others recognize the characteristic patterns of restless movements and consider presence of movements to be sufficient for the diagnosis (Munetz and Cornes, 1982; Barnes et al., 1983; Gibb and Lees, 1986). A second point of confusion is that akathisia occurs not only in an early-onset, self-limited form (acute akathisia), but also as a late-onset, persistent form (tardive akathisia). Much of the literature on akathisia does not distinguish between acute and tardive akathisia, which makes the interpretation of the literature difficult. The recognition of tardive akathisia as a distinct subsyndrome of tardive syndromes has been more recent (Fahn, 1978, 1983; Braude and Barnes, 1983; Weiner and Luby, 1983). For the discussion of the clinical features of akathisia, acute and tardive akathisia are lumped together because they are similar but their treatments and most likely their pathophysiologies are distinct.

The subjective aspect of akathisia is characterized by inner tension and aversion to remaining still. Patients complain of vague inner tension, emotional unease, or anxiety with vivid phrases such as "jumping out of my skin" or "about to explode." Subjective descriptions, however, can be non-specific. Inner restlessness and inability to remain still can be present in a significant number of psychiatric patients without akathisia and in control subjects without psychiatric problems (Braude et al., 1983). In an attempt to clarify the issue, Braude and colleagues (1983) systematically surveyed the frequency of various complaints and found that inability to keep the legs still was the most characteristic complaint and was present in over 90% of patients with akathisia in contrast to about 20% of those with other psychiatric disturbances. Others noted more conservative estimation of the frequency of complaints related to the legs from 27% (Gibb and Lees, 1986) to 57% (Burke et al., 1989). Various authors also described atypical features such as "acting out," suicidal ideation, disruptive behaviors, homicidal violence, sexual torment, terror, and exacerbation of psychosis as akathitic phenomena (Van Putten and Marder, 1987). Evaluation of the subjective aspect also depends on patients' ability to describe their feelings. Those with psychosis, dementia, or learning disability are often unable to provide useful descriptions for diagnosis. Although akathisia may manifest as subjective feeling alone, lack of specific subjective feeling and variable expression by patients pose a diagnostic dilemma. Therefore, the presence of the motor phenomenon is very helpful for the diagnosis.

Akathisia can manifest as focal pain or burning, usually in the oral or genital region (Ford et al., 1994). The symptom of moaning may be a verbal expression of the subjective feeling of akathisia. Some patients may moan as part of a generalized akathitic state and have other motor evidence of akathisia, such as marching in place, inability to sit still accompanied by associated walking about, inability to lie quietly with writhing and rolling movements, and making

stereotypic caressing or rocking movements. The differential diagnosis of moaning includes parkinsonism, akathisia, levodopa usage (Fahn et al., 1996), dementia, pain, and other syndromes of phonations, such as tics, oromandibular dystonia, and Huntington disease (HD), as discussed by Fahn (1991).

The motor aspect of akathisia (akathitic movements) is generally described as excessive movements that are complex, semipurposeful, stereotypic, and repetitive. Braude and colleagues (1983) found that rocking from foot to foot, walking on the spot, and coarse tremor and myoclonic jerks of the feet were characteristic of akathitic movements. Others agree that various leg and feet movements are more common in patients with akathisia than in those with TD (Gibb and Lees, 1986; Burke et al., 1989). However, they also noted that these did not distinguish akathisia from the group that did not meet criteria for akathisia (Gibb and Lees, 1986), and movements involving other parts of the body such as trunk rocking, respiratory grunting, face rubbing, and shifting weight while sitting were also frequent (Burke et al., 1989). Although there are not enough data and no consensus on the diagnostic movements of akathisia, these movements seem to be characteristic enough to be recognized by different authors who have independently documented similar phenomena.

Akathisia is seen in patients with PD (Lang and Johnson, 1987), in patients abusing cocaine (Daras et al., 1994), and as an adverse effect of selective serotonin uptake inhibitors (Poyurovsky et al., 1995). Acute akathisia occurs not only as an adverse effect of DRBAs but also fairly commonly as an acute adverse effect of the dopamine depleters reserpine, TBZ, and alpha-methyltyrosine (Marsden and Jenner, 1980).

In Ayd's review (1961), half of the cases of acute akathisia occurred within 25 days of drug treatment and 90% occurred within 73 days. Acute akathisia was the most common side effect of DRBAs, occurring in 21.2% of patients in that study (Ayd, 1961). In a more recent study by Sachdev and Kruk (1994) of 100 consecutive patients placed on neuroleptics, mild akathisia developed in 41% and moderate to severe akathisia in 21%. In a literature review, Sachdev (1995b) reported that incidence rates for acute akathisia with conventional neuroleptics vary from 8% to 76%, with 20% to 30% being a conservative estimate. Sachdev stated that preliminary evidence suggests that the newer atypical antipsychotic drugs are less likely to produce acute akathisia. Using the criterion that both subjective and objective phenomena are required for the diagnosis of acute akathisia, Miller and colleagues (1997) found an incidence rate of 22.4%, 75% of which occurred within the first 3 days of exposure to a neuroleptic. Muscettola and colleagues (1999) found a prevalence rate of 9.4%.

The potency of neuroleptics has been associated with incidence of akathisia, ranging from 0.5% for reserpine (Marsden and Jenner, 1980) to 75% for haloperidol (Van Putten et al., 1984). Other risk factors are neuroleptic dose, the rate of dosage increase, and the development of drug-induced parkinsonism (Sachdev and Kruk, 1994). Akathisia has occurred with FGAs and SGAs (Kane et al., 2009).

As with acute dystonic reactions, akathisia also has been induced by serotonergic agents (Chong, 1996; Lopez-Aleman et al., 1997). The mechanism was discussed in the earlier section on acute dystonia.

As was noted previously, akathisia needs to be distinguished from other conditions such as agitated depression; restless legs syndrome, in which similar subjective sensations may be described by patients but are mainly localized to legs and are present particularly at night (Blom and Ekblom, 1961); complex motor tics with preceding aura, which show more variety of abnormal movements; and complex vocal tics (Jankovic and Fahn, 1986). Akathisia also can be obscured by other psychiatric disorders, or it could be mistaken for a psychiatric disease. For example, when patients with psychosis develop akathisia after withdrawal from antipsychotic drugs, it may be mistaken for recurrence of psychosis. Paradoxical dystonia (see Chapter 11) in which dystonic movements are relieved by movement can be mistaken for akathisia.

The pathophysiology of acute akathisia remains poorly understood. On the basis of the observation in rats that show increased locomotor activity after blockade of the mesocortical dopamine system (Carter and Pycock, 1978), reduction of this dopaminergic projection was suggested to be responsible for akathisia (Marsden and Jenner, 1980). However, tardive akathisia cannot be explained by this hypothesis because dopamine depleters can ameliorate those symptoms. The observation that acute akathisia can occur with a serotonin uptake inhibitor (Altshuler et al., 1994) indicates that inhibiting dopamine neurons in the SN by such drugs could link the dopamine system with akathisia. These types of drugs have been reported to increase parkinsonism in patients with PD (Meco et al., 1994). One attractive possibility is that akathisia might reflect an alteration of the dopaminergic mesolimbic system.

Because propranolol has been reported to be beneficial in treating acute akathisia, another suggestion is that acute akathisia results from alterations in the cingulate cortex, the piriform cortex, or area 1 of the parietal cortex based on effects of propranolol in these regions in haloperidol-treated rats (Ohashi et al., 1998).

Ayd (1961) noted that acute akathisia is self-limited, disappearing on discontinuation of neuroleptics, and is well controlled by anticholinergics despite continuation of neuroleptics. Others have noted that only patients with concomitant parkinsonism improve significantly with anticholinergics (Kruse, 1960; Braude et al., 1983). Amantadine may also help, but patients can develop a tolerance (Zubenko et al., 1984a). Beta-blockers at relatively low doses, below 80 mg of propranolol per day, have been noted to be effective in many studies, including one with a double-blind design (Lipinski et al., 1984; Zubenko et al., 1984b; Adler et al., 1986; Dupuis et al., 1987). Nonlipophilic beta-blockers that have poor penetration to the central nervous system (CNS) are not as effective (Lipinski et al., 1984; Dupuis et al., 1987). Selective beta-blockers might not be as effective as nonselective ones (Zubenko et al., 1984b); however, when two equally lipophilic beta-blockers, propranolol and betaxolol, were compared, they were equally effective in treating acute akathisia (Dumon et al., 1992), although the former is a beta-2-blocker and the latter is a beta-1-blocker. In a rat model of acute akathisia (neuroleptic-induced defecation), a lipophilic beta-1-blocker was found to be effective in reducing the phenomenon (Sachdev and Saharov, 1997).

Clonidine also reduces central noradrenergic activity by stimulating central alpha-2 receptors and has been noted

to be effective in a small number of studies. The sedating effect is pronounced, however (Adler et al., 1987). Nicotine patches have been reported to reduce akathisia (Anfang and Pope, 1997). Weiss and colleagues (1995) found cyproheptadine, an antiserotonergic agent, to be effective in ameliorating akathisia. In a small placebo-controlled trial, mianserin, a 5HT₂ antagonist, was found to reduce the severity of acute akathisia (Poyurovsky et al., 1999). Trazadone also has been reported to be beneficial (Stryjer et al., 2003). Poyurovsky and Weizman (2001) discuss the potential of serotonin agents in akathisia. A literature search revealed mirtazapine to be effective and superior to propranolol (43.3% versus 30.0%) (Hieber et al., 2008).

Parkinsonism

Neuroleptic-induced parkinsonism (usually referred to as extrapyramidal syndrome (EPS) by psychiatrists and as drug-induced parkinsonism by neurologists) is a dose-related side effect and is indistinguishable phenomenologically from idiopathic PD, including high frequency of tremor and asymmetrical signs (Hardie and Lees, 1988). SPECT imaging of the dopamine transporter (DAT), however, may be helpful in determining whether the neuroleptic-induced parkinsonism is entirely drug-induced or an exacerbation of subclinical PD (Lorberboym et al., 2006). It develops with use of both DRBAs and dopamine-depleting drugs such as reserpine and TBZ. Some authors have noted perioral tremor and termed this rabbit syndrome, which is a localized form of parkinsonian tremor (Decina et al., 1990). The incidence of parkinsonism varies. Korczyn and Goldberg (1976) found 61%, and Muscettola and colleagues (1999) found 19.4%. Women are affected almost twice as frequently as men, which is the reverse of the ratio in idiopathic PD. Neuroleptic-induced parkinsonism also occurs increasingly with advanced age (Ayd, 1961; Hardie and Lees, 1988) in parallel with the incidence of idiopathic PD.

Blockade of dopamine receptors by antagonists or depletion of presynaptic monoamines by drugs such as reserpine mimics the deficient dopamine state in PD. All DRBAs can induce parkinsonism, except clozapine (there are only rare reports with clozapine) (Factor and Friedman, 1997). Risperidone can do so (Gwinn and Caviness, 1997; Simpson and Lindenmayer, 1997), as can olanzapine and only rarely quetiapine. Parkinsonism from neuroleptics is typically reversible when the medication is reduced or discontinued. Sometimes, the reversal can take many months; an interval of up to 18 months has been noted in the literature (Fleming et al., 1970).

Some patients show persisting parkinsonism despite prolonged discontinuation of neuroleptics (Stephen and Williamson, 1984; Hardie and Lees, 1988), giving rise to consideration of a proposed condition of tardive parkinsonism. A study of 8-week exposure of rats to haloperidol found a highly significant 32% to 46% loss of tyrosine hydroxylase (TH)-immunoreactive neurons in the SN, and 20% contraction of the TH-stained dendritic arbor (Mazurek et al., 1998). Perhaps such pathologic changes account for some cases of prolonged drug-induced parkinsonism in humans. Several cases in the literature had initial resolution of parkinsonism and later reappearance of the symptoms without reexposure to neuroleptics (Hardie and Lees, 1988). Two

cases that had complete resolution of drug-induced parkinsonism after withdrawal of neuroleptics showed evidence of mild PD at autopsy (Rajput et al., 1982). Although one assumes that these patients had subclinical PD, the effect of neuroleptics on the disease progression is unknown. The use of the term "tardive parkinsonism" to refer to cases of persistent parkinsonism remains an enigma. Some cases are due to concurrent development of progressive PD, and there are no autopsied proven examples of non-PD in any example. Therefore, this suggests that there is as yet no evidence of tardive parkinsonism.

With the introduction of selective serotonin reuptake inhibitors (SSRIs) to treat depression, it has been noticed that these drugs can sometimes worsen parkinsonism in patients with PD (Meco et al., 1994) and occasionally can induce parkinsonism in patients who never had symptoms of PD (Coulter and Pillans, 1995; DiRocco et al., 1998). In an intensive monitoring program in New Zealand of the SSRI drug fluoxetine over a 4-year period, there were 15 reports of parkinsonism in 5555 patients who were exposed to the drug (Coulter and Pillans, 1995). Of these 15 patients, 4 were also on a neuroleptic and 1 was on metoclopramide. In a literature search, parkinsonism was found with different classes of antidepressants, is not dose related, and can develop with short-term or long-term use (Madhusoodanan et al., 2010). The explanation for inducing or enhancing parkinsonism is that increased serotonergic activity in the SN will inhibit dopamine-containing neurons, thus causing functional dopamine deficiency in the nigrostriatal pathway (Baldessarini and Marsh, 1992).

The possibility of the existence of tardive parkinsonism comes up from time to time because some patients have continued parkinsonism despite long-term discontinuation of the DRBA (Melamed et al., 1991). However, there is always the possibility that the patient had preclinical PD before developing drug-induced parkinsonism. Then, when the DRBA is withdrawn, the parkinsonism persists because of progressively worsening PD. One would need to show that there are no Lewy bodies or that the PET scan shows no loss of fluorodopa uptake in patients thought to have tardive parkinsonism.

Anticholinergics can be effective in reducing the severity of the parkinsonism induced by DRBAs, whereas dopaminergic drugs (that activate the dopamine receptors) are ineffective, probably because they are not able to displace the DRBA from its binding to the receptor. Levodopa up to 1000 mg in combination with a peripheral dopa decarboxylase inhibitor had no significant effect (Hardie and Lees, 1988), nor did apomorphine, a dopamine receptor agonist (Merello et al., 1996). On the other hand, levodopa can effectively reverse parkinsonism induced by dopamine depleters, such as reserpine. In fact, the discovery of the dopamine hypothesis for parkinsonism was based on this observation (Carlsson et al., 1957; Carlsson 1959). Treatment is usually initiated with anticholinergics or amantadine (Mindham et al., 1972; Johnson, 1978; Konig et al., 1996).

Neuroleptic malignant syndrome

NMS is an idiosyncratic reaction that can sometimes be life-threatening. The clinical triad consists of (1) *hyperthermia*, usually with other autonomic dysfunctions such as

tachycardia, diaphoresis, and labile blood pressure; (2) *extrapyramidal signs*, usually increased muscle tone of rigidity or dystonia, often with accompanying elevation of muscle enzymes; and (3) *alteration of mental status*, such as agitation, inattention, and confusion. Fever is not an essential symptom (Peiris et al., 2000), and it can be delayed (Norris et al., 2006). The syndrome begins abruptly while the patient is on therapeutic, not toxic, dosages of medication. In a review of 340 clinical reports of NMS in the literature (Velamoor et al., 1994), changes in either mental status or rigidity were the initial manifestations of NMS in 82.3% of cases with a single presenting sign. All the symptoms are fully manifest within 24 hours and reach a maximum within 72 hours. There does not seem to be any relationship with the duration of therapy. NMS can develop soon after the first dose or at any time after prolonged treatment. Recovery usually occurs within 1 to several weeks, but can be fatal in 20% to 30% of cases (Henderson and Wooten, 1981; Gute and Baxter, 1985). Even with awareness of the potential of fatality in modern medicine, death still occurs (van Maidegem et al., 2002). Muscle biopsies have shown swelling and edema, with 10% to 50% of fibers involved with vacuoles but scanty mononuclear infiltration (Behan et al., 2000).

All agents that block D2 receptors can induce NMS, including risperidone (Raitasuo et al., 1994; Webster and Wijeratne, 1994; Dave, 1995; Singer et al., 1995; Levin et al., 1996), clozapine (Miller et al., 1991; Amore et al., 1997; Dalkilic and Grosch, 1997), amisulpride (Bottlender et al., 2002), olanzapine (Kontaxakis et al., 2002; Kogoj and Velikonja, 2003), and phenothiazines with antihistaminic activity, such as alimemazine (van Maidegem et al., 2002). A case of NMS associated with bupropion has been reported (Kasantikul and Kanchanatawan, 2006). TBZ has been reported to cause NMS; this seems likely to be due to its D2-blocking activity (Reches et al., 1983) rather than to its dopamine-depleting action (by blocking the vesicular DAT). Reserpine has no known dopamine receptor antagonism, only dopamine-depleting activity (also by blocking the vesicular DAT) and has not been reported to cause NMS.

In a Japanese study, 10 of 564 (1.8%) patients who received antipsychotics developed NMS (Naganuma and Fujii, 1994), many more than the 12 of 9792 patients (0.1%) reported previously (Deng et al., 1990). Risk factors that were found were psychomotor excitement, refusal of food, weight loss, and oral administration of haloperidol at 15 mg/day or above (Naganuma and Fujii, 1994). Young males appear to be more predisposed to NMS (Gratz and Simpson, 1994), but the reason for this is uncertain. In a case-control study searching for risk factors, Sachdev and associates (1997) found that patients with NMS were more likely to be agitated or dehydrated, often needed restraint or seclusion, had received larger doses of neuroleptics, and more often had previous treatment with electroconvulsive therapy (ECT) before the development of the syndrome.

The pathophysiologic mechanism of NMS is not well understood. Autopsies failed to show any consistent findings (Itoh et al., 1977). A similar syndrome has been reported after abrupt withdrawal of levodopa (Friedman et al., 1985; Hirschorn and Greenberg, 1988; Keyser and Rodnitzky, 1991), suggesting a common mechanism of acute dopamine deficiency (Henderson and Wooten, 1981). IBZM SPECT in one patient showed the dopamine receptor to be blocked

in the acute phase of NMS, but the patient had been receiving a D2 blocker, which would be expected to result in this finding (Jauss et al., 1996). There is a report of a patient who developed NMS after abrupt withdrawal of the combination of a long-acting neuroleptic and an anticholinergic agent (Spivak et al., 1996). Because it responded to procyclidine administration, it implicates a muscarinic overactivity. There are also reports of an NMS-like syndrome after the sudden withdrawal of amantadine (has dopaminergic and anti-muscarinic activity) (Ito et al., 2001), and after withdrawal of baclofen, with recovery after reintroduction of baclofen (Turner and Gainsborough, 2001).

The idiosyncratic nature and rarity of the syndrome remain unexplained. Ram and colleagues (1995) evaluated the structure of the D2 receptor gene in 12 patients who had a history of NMS. One patient was found to have a nucleotide substitution of an exon of the D2 gene. The A1 allele of the TaqI A polymorphism of the dopamine D2 receptor gene appears to occur more commonly in patients who developed NMS (Suzuki et al., 2001). Kishida and associates (2004) found that patients with NMS had a higher association with a polymorphism in the D2 receptor gene.

Treatment of NMS consists of discontinuing the antipsychotic drugs and providing supportive measures. Rapid relief of symptoms has been reported with the use of dantrolene, bromocriptine, or levodopa (Granato et al., 1982; Gute and Baxter, 1985). Nisijima and colleagues (1997) found levodopa to be more effective than dantrolene, but Tsujimoto and colleagues (1998) found intravenous dantrolene plus hemodialysis to be effective. Subcutaneous apomorphine has been found to be effective as a solo treatment (Wang and Hsieh, 2001). Gratz and Simpson (1994) recommended using anticholinergics in an attempt to reverse rigidity before using bromocriptine. Carbamazepine was dramatically effective in two patients (with recurrence on withdrawal of the drug) (Thomas et al., 1998). Corticosteroids added to standard therapy have been reported to speed recovery time (Sato et al., 2003). Reexposure to dopamine receptor antagonists does not necessarily lead to recurrence of NMS (Singh and Albaranzanchi, 1995; Singh and Hambidge, 1998). Residual catatonia that can last weeks to months has been reported, with some patients responding to ECT (Caroff et al., 2000). Hyponatremia can sometimes occur; it has been attributed to inappropriate secretion of antidiuretic hormone and also to cerebral salt-wasting syndrome associated with the NMS (Lenhard et al., 2007). When present, salt replacement is necessary.

Tardive syndromes

The first use of dopamine receptor antagonists for psychiatric disorders was in the early 1950s, and credit for the first report of TD is given to [Schönecker \(1957a\)](#). The condition became recognized with the subsequent report by Sigwald and colleagues (1959). Uhrbrand and Faurbye (1960) published the first systematic review of this complication among 500 psychiatric patients and noted 29 patients with the disorder. Faurbye and colleagues (1964) later coined the term TD and emphasized the increased incidence of the syndrome with chronic exposure. Despite numerous reports of the classic O-B-L repetitive stereotypic movements, establishment

of this disorder as a distinct clinical entity took decades of epidemiologic studies (American Psychiatric Association, 1980; Jeste and Wyatt, 1982a; Kane and Smith, 1982). Confusion arose in part from the difficulty of characterizing and communicating the exact type of movements these patients develop and distinguishing these from the ones that occur spontaneously. It should be noted that these drug-induced movements can be variable in duration; they may be short-lasting and fade slowly after discontinuation of the medication, suppressed by the medication itself, or persistent.

Rigorous epidemiologic data are available only for classic TD (Jeste and Wyatt, 1982a; Kane and Smith, 1982), but tardive dystonia and tardive akathisia warrant separate recognition beyond their differences in clinical phenomenology because prognosis, at-risk population, and treatment are different. Some authors have noted chronic vocal and motor tics resembling TS (Klawans et al., 1978; Bharucha and Sethi, 1995), and others noted myoclonic movements (Little and Jankovic, 1987; Tominaga et al., 1987) as a chronic persistent problem of neuroleptic therapy, but further studies are necessary to establish them as distinct entities. A combination of resting, postural, and action tremor has been reported in five patients that persisted despite withdrawal of the offending DRBAs and that improved with treatment with the antidopaminergic TBZ (Stacy and Jankovic, 1992). The tremor was accompanied by other tardive phenomenology, and the authors suggested that this is another tardive syndrome, calling it tardive tremor. Tardive tremor has been reported with metoclopramide (Tarsy and Indorf, 2002).

Withdrawal emergent syndrome

Withdrawal emergent syndrome was first described in children who had been on antipsychotic drugs for a long period and then were withdrawn abruptly from their medication (Polizos et al., 1973). The movements are choreic and resemble those of Sydenham disease (Videos 17.1, 17.2). The abnormal movements are brief and flow from one muscle to another in a seemingly random way. They differ from the movements of classic TD, which are brief but stereotypical and repetitive. The movements in withdrawal emergent syndrome involve mainly the limbs, trunk, neck, and rarely the oral region, which is the most prevalent site in classic TD. The dyskinetic movements disappear spontaneously within several weeks after withdrawal of the DRBA. For immediate suppression of movements, dopamine receptor antagonists can be reinstituted and withdrawn gradually without recurrence of the withdrawal emergent syndrome (Fahn, 1984a). A withdrawal reaction from melatonin with O-B-L dyskinesia and akathisia was reported by Giladi and Shabtai (1999) and was described earlier in the chapter. ●

Withdrawal emergent syndrome is analogous to the classic TD seen in adults, except that the course is more benign and movements are more generalized, resembling the choreic movements of Sydenham disease. In fact, most cases of TD that have been reported in children have a benign course and the phenomenology has been reported to be more generalized choreic movements rather than stereotypic repetitive movements of O-B-L distribution. Acute withdrawal of chronic antipsychotic drugs in adults can also lead to transient TD, which disappears within 3 months. These types of

movements have been labeled withdrawal dyskinesia (Gardos et al., 1978; Schooler and Kane, 1982).

On the other hand, acute withdrawal of DRBA can precipitate a persistent akathisia (Poyurovsky et al., 1996; Rosebush et al., 1997) or dyskinesia, that is, tardive akathisia and other tardive syndromes. Acute withdrawal should be avoided because of the propensity to induce TD, and a slow taper and withdrawal should be substituted. Abrupt withdrawal of risperidone therapy in one elderly person resulted in a near-fatal development of respiratory dyskinesia (Komatsu et al., 2005).

Classic tardive dyskinesia

Dyskinesia is a general term referring to abnormal involuntary movements. The term tardive dyskinesia has been used to refer to abnormal movements that are seen as a complication of long-term dopamine receptor antagonist therapy, mainly the type that manifests with rapid, repetitive, stereotypic movements involving the O-B-L areas. However, over the years, other types of movements have been noted as complications of dopamine receptor antagonist therapy. These movements have more specific terminologies, such as dystonia and akathisia. Therefore, some authors refer to the type of movements that were originally described as “classic tardive dyskinesia” for lack of a more specific and distinct name for the movements (Fahn, 1989). Some have called them tardive stereotypy (Stacy and Jankovic, 1991; Jankovic, 1994) because of their repetitive, rather than random, nature. However, the stereotypical movements in classic TD are so characteristic and resemble those seen in almost all patients with this disorder, in contrast to other types of stereotypies that are seen in patients with learning disability, autism, and psychosis, that the term tardive stereotypy does not convey this uniqueness and therefore seems unsatisfactory. Stereotyped hand claspings appears to be a rare form for the presentation of classic TD (Kaneko et al., 1993).

On the other hand, some have used the term tardive dyskinesia as equivalent to any oral dyskinesia. It therefore needs to be emphasized that the term “tardive” has become synonymous with chronic neuroleptic complications and should be reserved for these disorders. Sustained dystonic movements of the lower face must be distinguished from classic TD. Frequently, patients on anticholinergics or other medications develop oral dyskinesia with dryness of mouth. Other movements such as myokymia, myoclonus, and tics must be distinguished. The differential diagnosis of oral dyskinesia is summarized in Table 17.10, and Table 17.11 compares clinical features of TD, HD, and oromandibular dystonia, the three most common forms of oral dyskinesias.

Clinical features of classic tardive dyskinesia

The clinical features of classic TD are quite distinct from the features of other movement disorders (Fahn, 1984a). The principal site is the face, particularly around the mouth, typically called oral-buccal-facial (O-B-L) dyskinesias. The limbs and trunk are affected less often than the mouth. Even when they are involved, it is usually in addition to involvement of the mouth. The forehead and eyebrows are seldom involved unless tardive dystonia is also present; this is in contrast to HD, in which chorea of the forehead and eyebrows is more

Video 17.1 Withdrawal emergent syndrome.

Video 17.2 Withdrawal emergent syndrome.

Table 17.10 Differential diagnosis of oral dyskinesias

1. **Chorea, rhythmic, stereotypic** (see also Kurlan and Shoulson, 1988)
 - a. Encephalitis lethargica: postencephalitic
 - b. Drug-induced
 - i. Dopamine receptor antagonists (classic tardive dyskinesia)
 - ii. Levodopa
 - iii. Anticholinergic drugs
 - iv. Phenytoin intoxication
 - v. Antihistamines
 - vi. Tricyclic antidepressants
 - vii. Lithium
 - c. Huntington disease
 - d. Hepatocerebral degeneration
 - e. Cerebellar infarction
 - f. Edentulous malocclusion
 - g. Brainstem infarcts
 - h. Idiopathic
2. **Dystonia**
 - a. Idiopathic cranial facial dystonia
 - b. Symptomatic dystonias
 - i. Dopamine receptor antagonists (acute dystonia, tardive dystonia)
 - ii. Other secondary dystonias (see Calne and Lang, 1988)
3. **Tics**
4. **Tremor**
 - a. Parkinsonian tremor of jaw, tongue, and lips
 - b. Essential tremor of neck and jaw
 - c. Cerebellar tremor of neck and jaw
 - d. Idiopathic tremor of neck, jaw, tongue, or lips
5. **Myoclonus**
 - a. Facial myoclonus of central origin
6. **Others**
 - a. Hemifacial spasm
 - b. Myokymia
 - c. Facial nerve synkinesis
 - d. Bruxism
 - e. Epilepsia partialis continua

Modified from Fahn S. The tardive dyskinesias. In: Matthews WB, Glaser GH, eds. Recent Advances in Clinical Neurology, vol. 4. Edinburgh: Churchill Livingstone, 1984; pp. 229–260.

common than choreic movements of the oral musculature. In TD, the mouth tends to show a pattern of repetitive, complex chewing motions (Video 17.3, Video 1.73), occasionally with smacking and opening of the mouth, tongue protrusion (flycatcher tongue) (Video 17.4), lip pursing, sucking movements, and fishlike lip puckering movements. The rhythmicity and coordinated pattern of movement are striking. This stereotypic pattern is in contrast to the dyskinesias that are seen in HD, in which the movements are without a predictable pattern. Usually, the limb involvement is limited to the distal part. Like the mouth region, the movements of the distal limbs show a repetitive pattern, earning the label of piano-playing fingers and toes. When the patient is sitting, the legs often move repeatedly, with flexion and extension movements of the toes and foot tapping. When the patient is lying down, flexion and extension of thighs may be seen. Rhythmic truncal rocking can be seen when the patient is lying, sitting, or standing (Video 17.5). The respiratory pattern can be involved with dyskinesia, causing hyperventilation at times and hypoventilation at other times (Yassa and Lai, 1986). In a study of the breathing pattern in patients

Table 17.11 Clinical features of classic tardive dyskinesia (TD), oromandibular dystonia (OMD) and Huntington disease (HD)

Clinical signs	TD	OMD	HD
Type of involuntary movements	Stereotypic	Dystonic	Choreic
Flowing movements	0	0	+++
Repetitive movements	+++	+	±
Sustained contractions	+	+++	±
Movements of mouth	+++	+++	+
Blepharospasm	+	+++	±
Forehead chorea	±	±	++
Masticatory muscles	+++	+++	±
Nuchal muscles	+	++	±
Trunk, legs	++	0	+++
Akathisia	++	0	0
Marching in place	++	0	0
Truncal rocking	++	0	+
Motor imperistence (tongue, grip)	0	0	+++
Stuttering-ataxic gait	±	0	+++
Postural instability	0	0	+++
Effect of:			
Antidopaminergics	Decrease	Decrease	Decrease
Anticholinergics	Increase	Decrease	±
Effect on:			
Talking, chewing	±	+++	+
Swallowing	0	++	+++

0, not seen; ±, may be seen; +, occasionally seen; ++, usually seen; +++, almost always seen.

From Fahn S, Burke RE. Tardive dyskinesia and other neuroleptic-induced syndromes. In: Rowland LP, Pedley TA, eds. Merritt's Textbook of Neurology, 12th ed. Philadelphia: Lippincott Williams & Wilkins, 2010; pp. 778–781.

with TD, patients had an irregular tidal breathing pattern, with a greater variability in both tidal volume and time of the total respiratory cycle (Wilcox et al., 1994). The presence of respiratory dyskinesia never causes a medical problem, although it might look alarming. Esophageal (associated with lingual) dyskinesias have been reported, resulting in increased intraesophageal pressure and death from asphyxiation in one patient (Horiguchi et al., 1999). ▶

The involuntary movements of the mouth in classic TD are readily suppressed by patients when asked to do so. Furthermore, the movements cease as the patient is putting food in the mouth, when talking, or when a finger is placed on the lips. Because the movements do not interfere with basic functions, patients are often unaware of their movements. When the patient is asked to keep the tongue at rest inside the mouth, the tongue tends to assume a continual writhing motion of athetoid side-to-side and coiling movements. The constant lingual movements might lead to tongue

Video 17.3 Oral-buccal-lingual dyskinesia.

Video 17.4 Oral-buccal-lingual dyskinesia with tongue popping.

Video 17.5 Rhythmic rocking movements of the trunk and marching in place.

hypertrophy, and macroglossia is a common clinical sign. On command, however, most patients with TD can keep the tongue protruded out without darting back into the mouth for more than half a minute; patients with the chorea of HD typically cannot maintain a protruded tongue. This inability to sustain a voluntary contraction is called motor impersistence, which is not seen in TD.

Abnormal movements in schizophrenia in the absence of exposure to DRBAs

TD as an entity induced by dopamine receptor blockers has been challenged by reports claiming that spontaneous movements are sometimes encountered in patients with schizophrenia who have never been exposed to neuroleptic agents (see the review by Boeti et al., 2003). McCreadie and colleagues (2002) evaluated 37 schizophrenic patients never treated with antipsychotics and followed for 18 months. A total of 9 (24%) had dyskinesia on both occasions, 12 (33%) on one occasion, and 16 (43%) on neither occasion; 21 (57%) had dyskinesia on at least one occasion; and 13 patients (35%) had parkinsonism on at least one occasion. It is critical that the quality of the dyskinesia be reported because the classic O-B-L dyskinesias are very distinct and almost specific for TD, whereas many other types of movements could represent a different disorder. The presence of parkinsonism, though, suggests that the patients had been exposed to neuroleptics, but that the investigators were clueless as to the exposure.

Many authors noted the existence of spontaneous oral dyskinesia occurring in untreated populations and in untreated schizophrenics. McCreadie and colleagues (1996) examined 308 elderly individuals in Madras, India, looking for abnormal movements and found them in 15%. The prevalence of spontaneous dyskinesia has been reported to be as high as 20% in psychiatric or nursing home patients (Brandon et al., 1971), but the average rate is about 5% (Jeste and Wyatt, 1982a; Kane and Smith, 1982). Others noted increasing prevalence of spontaneous dyskinesia with age (Klawans and Barr, 1982). Some studies looking at healthy elderly populations estimate the prevalence rate to be about 1% (Lieberman et al., 1984; D'Alessandro et al., 1986). Blanchet and colleagues (2004) evaluated 1018 (69.3% women) noninstitutionalized, frail elderly subjects attending day care centers to document the prevalence and phenomenology of spontaneous oral dyskinesia. The prevalence rate for spontaneous oral dyskinesia was 3.7% (4.1% for women and 2.9% for men). They reported more frequent ill-fitting dental devices, oral pain, and a lower rate of perception of good oral health compared with nondyskinetic subjects.

The true prevalence rate of spontaneous oral dyskinesia that can mimic TD may be even lower, considering the fact that many other identifiable oral dyskinesias listed in [Table 17.10](#), such as oromandibular dystonia, can be difficult to distinguish from classic TD and may be counted as spontaneous dyskinesia in epidemiologic studies. On the other hand, spontaneous oral dyskinesia resembling the stereotypical O-B-L dyskinesia of classic TD has been reported in an aged cynomolgus monkey (Rupniak et al., 1990). Some patients with oral dyskinesias resembling those of TD and unexposed to DRBAs would seemingly be idiopathic in origin, but careful workup might reveal other causes

(see [Table 17.10](#)), including treatment with lithium (Meyer-Lindenberg and Krausnick, 1997) and brainstem infarcts (Fahn et al., 1986).

Reports of oral dyskinesias occurring in schizophrenic patients who have never been exposed to neuroleptics raise the question as to how specifically the O-B-L movements should be attributed to DRBAs and whether they could be due to the schizophrenia. Fenn and colleagues (1996) examined 22 never-medicated persons with schizophrenia in Casablanca, Morocco. Three had abnormal movements that are said to be characteristic of TD. Fenton and colleagues (1997) compared the prevalence of spontaneous oral dyskinesias among drug-naïve patients with schizophrenia and patients with other psychiatric disorders. They found that dyskinetic movements were more common in the former group. Gervin and colleagues (1998) reported 6 (7.6%) of 79 first-episode patients with schizophrenia to have spontaneous dyskinesias. Until movement disorder experts can evaluate the movement phenomenology, it is possible that these individuals have some disorder other than TD. Moreover, it is possible that the history of non-drug exposure is faulty. The overwhelming evidence is that the abnormal movements that are seen with DRBAs are due to these drugs.

As was mentioned earlier, a major concern in diagnosing spontaneous oral dyskinesias is the distinction between the stereotypic movements of TD and the movements of oromandibular dystonia. Authors should publish the videotape demonstrations of the abnormal movements so that the medical community can judge whether the movements do indeed fit the phenomenologic criteria of movements seen in TD.

Epidemiology, risk factors, and natural history

Epidemiologic studies looking into the prevalence of TD have been confounded by the factors that affect the detection of the abnormal involuntary movements and the variables that affect the prognosis of the movements. Therefore, it is not surprising to find a wide range of prevalence estimations from 0.5% to 65% in the literature (Jeste and Wyatt, 1982a; Kane and Smith, 1982). The prevalence of TD has been noted to have increased from 5% before 1965 to 25% in the late 1970s (Jeste and Wyatt, 1982a; Kane and Smith, 1982). Mean prevalence rates calculated by two different reviewers, however, agree well at around 20% (Jeste and Wyatt, 1982a; Kane and Smith, 1982).

The prevalence rates of spontaneous dyskinesias and dyskinesias in people who have been exposed to neuroleptics have been compared. In the study by Woerner and colleagues (1991) the overall prevalence of spontaneous dyskinesias was 1.3% in 400 healthy elderly people and 4.8% in elderly inpatients, with a range of 0% to 2% among psychiatric patients who had never been exposed to neuroleptics. These investigators reported prevalence of TD of 13.3% and 36.1% in voluntary and state psychiatric hospitals, respectively. There was an interplay between age and gender. Among younger patients, men had higher rates; among subjects over age 40 years, rates were higher in women. Van Os and colleagues (1999) also found an increased risk for men in the younger population.

In one prospective study examining development of TD with low-dose haloperidol, the 12-month incidence of

probable or persistent TD was 12.3% (Oosthuizen et al., 2003). In a much larger study, the annual incidence rates range from 5% in a younger population (mean age 28) (Kane et al., 1986) to 12% in an older group (mean age 56) (Barnes et al., 1983). Kane and colleagues' data (1986) also show that the cumulative incidence of TD increases linearly with increasing duration of neuroleptic exposure at least for the first 4 to 5 years of such exposure. In a subsequent study by these authors, Chakos and colleagues (1996) studied prospectively 118 patients in their first episode of psychosis who were treatment-naïve and were then followed for up to 8.5 years while they were on neuroleptics. The cumulative incidence of presumptive TD was 6.3% after 1 year of follow-up, 11.5% after 2 years, 13.7% after 3 years, and 17.5% after 4 years. Persistent TD had a cumulative incidence of 4.8% after 1 year, 7.2% after 2 years, and 15.6% after 4 years. Thus, the earlier findings of Kane and colleagues (1986) of about 5% a year cumulative incidence seem to have been confirmed.

Jeste and associates (1999) looked at the cumulative incidence of TD after exposure to neuroleptics in patients over the age of 45 years. The mean cumulative incidence was 3.4%, 5.9%, and 22.3% at 1, 3, and 12 months, respectively. Woerner and his colleagues (1998) studied patients over the age of 54 when first exposed to neuroleptics. The cumulative rates of TD were 25%, 34%, and 53% after 1, 2, and 3 years of cumulative antipsychotic treatment. A greater risk for TD was associated with a history of ECT treatment, higher mean daily and cumulative antipsychotic doses, and the presence of extrapyramidal signs early in treatment. From both of these studies, the incidence rates for patients beginning treatment with conventional antipsychotics in their fifth decade or later are three to five times what has been found for younger patients, despite treatment with lower doses.

Studies have been carried out in other countries. A prospective study of 11 psychiatric facilities in Japan found the prevalence of TD to be 7.6%, the annual incidence rate to be 3.7%, and an annual remission rate to be 28.7% (Inada et al., 1991). On the other hand, Hayashi and colleagues (1996) reported a prevalence of 22.1% in 258 patients receiving neuroleptics. A study in Austria reported the follow-up of the 270 patients still in a psychiatric hospital after 10 years out of an original population of 861 patients; the prevalence rate of TD was 3.7% in 1982 and 12.7% in 1992; and the major risk factor for TD was advanced age (Miller et al., 1995). Jeste and colleagues (1995) followed 266 patients over the age of 45 years to determine incidence and prevalence rates of TD after exposure to neuroleptics, using electromechanical sensors to detect the presence of movements. Cumulative incidence of TD was 26%, 52%, and 60% after 1, 2, and 3 years, respectively. These rates, which are higher than those found by Kane and his colleagues, might reflect the sensitive sensors used, and these could possibly give false-positive findings. The same group compared the development of abnormal movements in the orofacial and limb-truncal areas in these 266 middle-aged and elderly patients treated with neuroleptics and found that the cumulative incidence of orofacial TD was 38.5% and 65.7% after 1 and 2 years, respectively, whereas that of limb-truncal TD was 18.6% and 32.6% after 1 and 2 years, respectively (Paulsen et al., 1996).

Host and treatment factors affect the development, severity, and persistence of TD, thereby resulting in different prevalence rates. Age of the patient has been the most

consistent factor that adversely affects the incidence, prognosis, and severity of TD (Smith and Baldessarini, 1980; Jeste and Wyatt, 1982a; Kane and Smith, 1982; Kane et al., 1986). Possibly the youngest individual who developed O-B-L TD was a 2-month-old girl after a 17-day treatment with metoclopramide for gastroesophageal reflux (Mejia and Jankovic, 2005). The movements persisted for at least 9 months after the drug was discontinued. This patient is the first documented case of TD in an infant.

Female sex has been associated with increased prevalence of TD, especially in the older population (Jeste and Wyatt, 1982a; Kane and Smith, 1982; Kane et al., 1988). Several authors noted increased incidence and prevalence among patients with affective disorders compared with schizophrenia or schizoaffective disorders (Gardos and Casey, 1983). Other host factors such as presence of previous brain damage as noted by increased ventricular size remain controversial (Jeste and Wyatt, 1982a; Kane and Smith, 1982). Some noted poor treatment response of schizophrenia to drug treatment as a risk factor for development of TD (Chouinard et al., 1986). The parameters of drug exposures such as dose, duration, type of neuroleptics, and drug-free intervals have been very difficult to correlate with risk for TD partly because accurate history concerning the drug treatment is usually not available and the drug itself can affect the detection of TD by masking or uncovering it.

Ethnicity has been found to be an important risk factor in both the development and prognosis of TD, with African Americans being more susceptible than European Americans (Wonodi et al., 2004a). In a meta-analysis of the literature, the only statistically significant risk factors for TD were non-white ethnicity and having developed drug-induced parkinsonism; the association with older age was suggestive but inconclusive (Tenback et al., 2009).

Prospective studies have noted that the total cumulative drug exposure correlates with incidence of withdrawal TD (Kane et al., 1985), and development of TD 5 years later in patients who did not have TD initially (Chouinard et al., 1986). Continued use of DRBAs after the appearance of TD also adversely affects subsequent prognosis (Kane et al., 1986). Drug holidays were once advocated to decrease the risk for TD, but an increased number of drug-free intervals were found to worsen the prognosis after withdrawal (Jeste et al., 1979). The risk for developing TD is three times as great for patients with more than two neuroleptic interruptions as for patients with two or fewer interruptions (van Harten et al., 1998). Other than reduced risk with clozapine, olanzapine, and quetiapine, no other particular type of neuroleptic, including depot preparations, has been clearly identified as a risk factor (Yassa et al., 1988). The effect of other drugs such as anticholinergics on the incidence and prevalence of TD is controversial, although anticholinergics may increase its severity (Yassa, 1988). Lithium may decrease the chance of TD development (Kane et al., 1986; van Harten et al., 2008a). Development of parkinsonism tends to predispose patients to TD (Chouinard et al., 1986; Kane et al., 1986). Substance abuse also has been reported to be a risk factor (Bailey et al., 1997). Lacking the cytochrome P450 enzyme required for metabolism of exogenous toxins because of nonfunctional alleles of the *CYP2D6* gene appears to be a risk factor for developing both TD and drug-induced parkinsonism (Andreassen et al., 1997). Another genetic risk factor

Table 17.12 Annual incidence of tardive dyskinesia comparing the second-generation antipsychotics with haloperidol

Population	Second-generation antipsychotics (%)	Haloperidol (%)
Children	0	
Adults	0.8	5.4
Mixture of adults and elderly	6.8	
Older than 53 y	5.3	

Data from Correll CU, Leucht S, Kane JM. Lower risk for tardive dyskinesia associated with second-generation antipsychotics: A systematic review of 1-year studies. *Am J Psychiatry* 2004;161(3):414–425.

is polymorphism in the *ATP13A* gene, especially for drug-induced parkinsonism (Kasten et al., 2011).

A review of the literature by Correll and colleagues (2004) found a lower incidence with the newer generation of antipsychotics (Table 17.12). A European consortium of investigators looking at 6-month results came to a similar conclusion (Tenback et al., 2005). In their review of the literature, Tarsy and Baldessarini (2006) also suggest that there may be a declining incidence of TD as the SGAs are being more regularly used. On the other hand, in a survey on elderly patients with dementia treated with older or newer generation antipsychotics, no statistical difference was found in the development of nonparkinsonian movement disorders in relation to treatment class (Lee et al., 2005). Children appear to be increasingly treated with atypical antipsychotics and in one study, 9% developed TD (Wonodi et al., 2007).

Although the majority of TD occurs while patients are on chronic treatment with DRBAs or shortly after discontinuing them, many cases have been reported in which the TD occurred after only a short interval of treatment and persisted. Some authors define TD arbitrarily as dyskinesias that occur after a minimum of 3 months of dopamine receptor antagonist therapy (Schooler and Kane, 1982), but it appears that there is no safe low-incidence period right after the initiation of treatment with DRBAs nor is there any particularly high-risk period. The overall risk appears to accumulate as time goes on, although whether it continues to increase linearly even after the first several years of exposure is not clear from available data. Kang and colleagues' (1986) retrospective data also show that the cumulative number of patients who developed tardive dystonia increased almost linearly from the first few months.

Probably most patients with TD have mild cases that could improve and disappear over time if the offending DRBAs were withdrawn. In an attempt to look at risk factors for the severe forms of TD, Caligiuri and colleagues (1997) conducted a longitudinal prospective study to determine the incidence of severe TD in middle-aged and elderly psychiatric patients. The cumulative incidence of severe TD was 2.5% after 1 year, 12.1% after 2 years, and 22.9% after 3 years. Risk factors for severe TD were higher daily doses of neuroleptics at study entry, greater cumulative amounts of prescribed neuroleptic, and greater severity of worsening negative psychiatric symptoms.

Once established, TD does not frequently become more severe even though the DRBA is continued (Labbate et al., 1997). Fernandez and colleagues (2001) evaluated the

dyskinesia of TD and the clinical features of parkinsonism in 53 patients residing in a state psychiatric hospital over a 14-year period. TD improved and parkinsonism worsened in patients who continued to receive neuroleptic drugs. But the natural history of TD is not easy to determine because the DRBAs that cause the movement disorders also tend to suppress the movements, although they can cause drug-induced parkinsonism.

Movements that disappear with increasing dose or resumption of DRBAs have been called masked TD (Schooler and Kane, 1982). Conversely, movements of TD typically increase after discontinuation of the DRBAs. Transient dyskinesias that appear after withdrawal of DRBAs have been called withdrawal dyskinesias (Gardos et al., 1978). The term covert dyskinesia has also been used for dyskinesia that is not detectable during drug administration and is first noted during drug reduction or withdrawal and becomes permanent (Gardos et al., 1978). Therefore, the difference between withdrawal and covert dyskinesia is in duration. In fact, the spectrum of TD ranges from mild transient withdrawal dyskinesia to severe irreversible TD, which can occur during or after discontinuation of the antipsychotic drugs. These examples illustrate the complexity in the detection of TD in the presence of DRBAs. In an attempt to estimate the false-negative rate of detection for TD in patients taking DRBAs, Kane and colleagues (1988) withdrew the drug from patients who showed no evidence of TD while taking DRBAs. Withdrawal TD was seen in 34% of 70 subjects, with persistence beyond 3 months in 7 of them.

Pathophysiology

Although TD is an iatrogenic condition with an established etiologic connection to dopamine receptor antagonism, the pathophysiology is not well understood. Any proposed mechanism for TD will have to explain (1) the cumulative increase of risk with increasing duration of treatment, (2) frequent persistence of the condition despite discontinuation of the treatment, (3) increasing risk with age and other individual dispositions that leave only a portion of the population affected, (4) increased risk with intermittent exposure to DRBAs, and (5) clinical pharmacology of TD (i.e., improvement of the condition by drugs that depress dopaminergic activity and worsening by increasing dopaminergic activity with levodopa or amphetamine).

Anatomic pathology—human and animal models

Postmortem pathologic studies are few and show nonspecific findings in the striatonigral system, which might be due to aging or other uncontrolled factors (Christensen et al., 1970). Jellinger (1977) found swollen large (i.e., cholinergic) neurons in the rostral caudate nucleus in 46% of neuroleptic-treated patients. In a review of the literature Harrison (1999) notes other studies in which cholinergic neurons are affected by these drugs. In a magnetic resonance imaging (MRI) study, 2-year exposure to neuroleptics in schizophrenic patients resulted in an increase in caudate and lenticular nucleus volume, while in those who were similarly exposed to atypical antipsychotics, there was a decrease in volume (Corson et al., 1999).

Because TD is etiologically related to DRBAs and the clinical pharmacology is most consistent with dopaminergic

hyperactivity, many studies have been directed to the dopamine system (Klawans, 1973). Chronic dopamine receptor antagonist treatment in rats shows evidence of cell loss in ventrolateral striatum (Nielson and Lyon, 1978), changes in synaptic patterns in the striatum at the electron microscopic level (Benes et al., 1985), and increases in glutamatergic synapses in the striatum (Meshul et al., 1994). In the accumbens in rats who developed VCMs, the dendritic surface area is reduced and dynorphin-positive terminals contact more spines and form more asymmetrical specializations than those in animals without the syndrome (Meredith et al., 2000). Andreassen and colleagues (2001) found electron microscopic changes in rats who developed haloperidol-induced VCMs. The nerve terminal area in the striatum was increased but with a lower density of glutamate immunoreactivity. These results suggest that striatal glutamatergic transmission is affected in association with haloperidol-induced VCMs.

Anatomic pathology—in-vitro models

Galili-Mosberg and colleagues (2000) exposed neuronal and PC-12 cultures to haloperidol and its three metabolites. These induced cell death by apoptosis, which was protected by the antioxidants vitamin E and N-acetylcysteine. Marchese and colleagues (2002) found a shrinkage of TH-immunostaining (TH-IM) cell bodies in the SNc and reticulata and a reduction of TH-immunostaining in the striatum of haloperidol-treated rats with the arising of VCMs. No differences were observed in TH-IM neurons of the ventral tegmental area and nucleus accumbens versus control rats.

Rodent models—dopamine and other neurotransmitter biochemistry

In experimental animals, a short-term treatment of dopamine receptor antagonist can increase striatal dopamine synthesis and turnover that revert to normal levels within a few days despite continuing treatment (Asper et al., 1973). Receptor binding increases in 2 days and persists for up to a week (Asper et al., 1973; Klawans, 1973; Muller and Seeman, 1977). The change in receptor state correlates well with stereotypic gnawing movements by rats that are induced by a dopamine agonist such as apomorphine (Clow et al., 1980). Chronic treatment for a year in rats produces an increase in receptor binding sites by the sixth month of treatment, overcoming the initial effects of receptor blockade. The increase of receptor binding and functional hypersensitivity takes about 6 months to return to baseline after withdrawal of drug treatment. Increased response of striatal adenylate cyclase to dopamine still persists at 6 months (Clow et al., 1980). The significance of this finding is not clear. Extrapolating from this rodent model of dopaminergic supersensitivity to patients with TD has limitations. Rats do not usually develop spontaneous movements such as TD, but they do demonstrate increased sensitivity to exogenously administered dopamine agonists and can develop VCMs.

The receptor supersensitivity in rodents develops in all the animals treated relatively early in the course of dopamine antagonist treatment and is completely reversible in 100% of animals shortly after withdrawal. This is clearly at odds with human TD, in which large individual variations and susceptibility factors are important and the disorder often starts late in the course of treatment and becomes persistent.

Nonetheless, this model has been most useful for quick screening of potential neuroleptics that are likely to cause TD from those that are not. Calabresi and colleagues (1992) suggested that hypersensitivity of the D2 presynaptic receptors located on terminals of glutamatergic corticostriatal fibers in animals with chronic treatment with haloperidol would inhibit glutamate release in the striatum, thereby reducing the gamma-aminobutyric acid (GABA) output from postsynaptic striatal neurons. Dopamine D2 receptor occupancy appears to be a contributing factor in the development of the rodent model (Turrone et al., 2002). Andreassen and Jorgensen (2000) review the possible role of increased striatal glutamatergic activity in the rat model as an etiologic factor and suggest that excitotoxicity is a possible cause of TD. Anatomical changes found by these authors were presented in the previous section.

Rodent models—behavioral changes

A common rodent model is that based on the increased rate of VCMs in rats, which develop after several months of dopamine receptor antagonist treatment (Gunne et al., 1982). The movements persist for several months after neuroleptic withdrawal. The behavioral syndrome is spontaneous in contrast to the stereotypic gnawing movement that requires apomorphine to induce. The pharmacologic response is similar to that seen with TD in that acute haloperidol alleviates the behavioral syndrome. In these aspects, this model is closer to the characteristics of human TD than models that are based on dopamine receptor supersensitivity.

The VCMs that persist after withdrawal of dopamine receptor antagonist do so at the time when the receptor-binding studies show no supersensitivity (Waddington et al., 1983). Blocking N-methyl-D-aspartate (NMDA) receptors with memantine while the rats are receiving treatment with haloperidol allowed these rats to lose the VCMs sooner than those animals who did not receive memantine (Andreassen et al., 1996). This result supports the concept that excessive NMDA receptor stimulation might be a mechanism underlying the development of persistent dyskinesias in humans. Opioid receptor antagonists were also shown to block VCMs in rats, suggesting that increases in dynorphin in the direct striatonigral pathway and enkephalin in the indirect striatopallidal pathway after chronic neuroleptic administration are both likely to contribute to TD (McCormick and Stoessl, 2002).

In one study of chronic haloperidol treatment in the rat, the animals that developed VCMs were compared with those that did not develop the movements (Shirakawa and Tamminga, 1994). Whereas all animals showed an increase in the dopamine D2 family receptor binding in the striatum and in the nucleus accumbens, and an increase in GABA-A receptors in the SN pars reticulata (SNr), only those with VCMs had a significant decrease in dopamine D1 receptor density in the SNr. One explanation is that increased dopamine release from dendrites in the SNr downregulates the D1 receptor. But how this would produce dyskinesias is not clear. In dorsal striatal neurons, however, there was no change in D1 receptor mRNA nor was there a change in cell counts in rats with neuroleptic-induced VCMs (Petersen et al., 2000).

Stereotyped behavior was evaluated in rats treated chronically with haloperidol, followed by D1 and D2 agonists. Somatostatin levels were then measured. The

results suggested that somatostatin—but not enkephalin-containing striatal neurons—contribute to the expression of haloperidol-induced stereotypies (Marin et al., 1996).

Other neurotransmitters in the striatum also may be involved. Chronic haloperidol treatment in rats increases preproenkephalin messenger RNA in striatal neurons, but fail to do so in rats that develop VCMs (Andreassen et al., 1999a). Some authors noted that decreases of glutamic acid decarboxylase (GAD) and GABA in the SN correlate with increased VCM rates (Gunne and Haggstrom, 1983). Others noted no consistent change in GAD and choline acetyltransferase levels (Mithani et al., 1987). However, Delfs and colleagues (1995) reported that rats treated with haloperidol for up to 12 months showed a decrease of GAD mRNA in the external globus pallidus (GP). This result suggests that there is reduced GABAergic transmission in the projection neurons of the external pallidum. Blocking NMDA receptors with memantine while the rats are receiving treatment with haloperidol allowed these rats to lose the VCMs sooner than animals that did not receive memantine (Andreassen et al., 1996). This result supports the concept that excessive NMDA receptor stimulation could be a mechanism underlying the development of persistent dyskinesias in humans. Lesioning the subthalamic nuclei (and thus its glutamatergic efferents) eliminates VCMs after 1 to 3 weeks (Stoessl and Rajakumar, 1996). The 5HT₃ receptor antagonist ondansetron reverses haloperidol-induced VCMs in rats (Naidu and Kulkarni, 2001).

As a test for the oxidative stress hypothesis in causing TD, rats were cotreated with coenzyme Q10 along with haloperidol. Cotreatment with coenzyme Q10 did not attenuate the development of the VCMs (Andreassen et al., 1999b). Coenzyme Q10 was absorbed, as detected in the serum, but there was no increase of coenzyme Q10 in the brain.

Primate models with behavioral changes

The model that best resembles human TD is that induced in nonhuman primates by DRBAs (Klitenberg et al., 2002). Primates show delayed onset of dyskinesia during the course of treatment and only a fraction of the population that is treated is affected by dyskinesia. The behavioral effect is spontaneous and bears resemblance to human TD. The dyskinesia also persists after withdrawal of the DRBAs. Unfortunately, neuropathologic and biochemical data from this model are limited. One group suggested that the best neurochemical correlate of dyskinesia induced by DRBAs has been a decrease in GABA and GAD activity in the SN, subthalamic nucleus, and medial GP compared with control animals without drug treatment or animals with drug treatment but without dyskinesia (Gunne et al., 1984). This finding correlates with postmortem biochemical studies on humans with TD (see the next section) and with a 2-deoxyglucose study in primates with TD. In the latter study, Mitchell and colleagues (1992) reported that primates with TD had a reduced glucose metabolism in the medial GP and in the ventral anterior and ventral lateral nuclei of the thalamus. These findings correlate with other similar studies of chorea and ballism and suggest a reduced subthalamopallidal output, so that the medial pallidum is not activated. Such a finding would be seen in the hemiballistic animal.

In a 5-year study of fluphenazine treatment of *Cebus apella* monkeys, reexposure after 91 weeks of withdrawal increased dyskinesias and dystonias by 300% (Linn et al., 2001). This

observation correlates with earlier clinical studies that found that intermittent treatment with neuroleptics can dramatically increase the incidence of dystonias and dyskinesias.

In a study looking for a proposed mitochondrial dysfunction in TD, baboons were treated for 41 weeks with haloperidol, producing TD; the animals were followed for another 17 weeks after withdrawal of haloperidol, during which the TD persisted (Eyles et al., 2000). Striatal mitochondria were examined by electron microscopy and showed no difference in either size or number between treated and control animals.

Human markers

Postmortem analysis

In a study that was well controlled for the premortem state of patients, a significant decrease in GAD activity was found in the subthalamic nucleus of five TD patients compared with age-matched controls (Andersson et al., 1989). Dopamine receptor binding is not increased in postmortem brains of TD patients (Crow et al., 1982; Cross et al., 1985; Kornhuber et al., 1989). One study noted increased homovanillic acid (HVA) levels in the putamen and nucleus accumbens of the postmortem brain (Cross et al., 1985).

Cerebrospinal fluid

CSF GABA concentration was found to be significantly lower in five patients with chronic schizophrenia and TD than in five patients with chronic schizophrenia without TD who were matched for age, duration of schizophrenia, and duration of neuroleptic therapy (Thaker et al., 1987). CSF cyclic adenosine monophosphate (cAMP) is thought to reflect the dopamine receptor function, and is not significantly elevated in patients with TD. CSF dopamine metabolite studies do not show significant elevation of HVA (Bowers et al., 1979; Nagao et al., 1979). CSF studies also showed a higher concentration of excitatory amino acid neurotransmitters and markers of oxidative stress in patients with TD, supporting the hypothesis of oxidative stress caused by enhanced striatal glutamatergic neurotransmission by blocking presynaptic dopamine receptors (Tsai et al., 1998).

PET and SPECT

PET data on the postsynaptic receptor status have failed to show an elevation of striatal receptor density compared with normal controls, but there was a positive correlation with severity of TD (Blin et al., 1989). No increase in DAT binding in the striatum was found in a SPECT study, indicating no loss on dopaminergic nerve terminals (Lavalaye et al., 2001). A prospective study was carried out by using FDG PET in patients receiving antipsychotic drugs. Those who later developed TD had a relative hypermetabolism in temporolimbic, brainstem, and cerebellar regions and hypometabolism in parietal and cingulate gyrus (Szymanski et al., 1996).

Dopamine release studies using amphetamine after raclopride binding of the D₂ receptor showed no differences between subjects with and without TD, indicating that dopamine release does not seem to be a factor (Adler et al., 2002).

Genetics

Steen and colleagues (1997) reported that a specific allelic variation of the dopamine D₃ receptor (*DRD3*) gene is

found at a higher frequency (22%–24%) of homozygosity among patients with TD compared with the relative underrepresentation (4%–6%) of this genotype in patients with no TD. Subsequent studies (Segman et al., 1999; Liao et al., 2001) supported and extended an association between D3 receptor gene and TD in schizophrenia patients. A serine to glycine polymorphism in the first exon of the *DRD3* gene appears to be a risk factor for developing TD (Liao et al., 2001; Ozdemir et al., 2001). Lerer and colleagues (2002) also found the presence of the glycine allele carries a higher risk for developing TD. On the other hand, Chong et al. (2003) found the serine allele to have a higher risk. A meta-analysis of genetic studies supports the view that a serine to glycine polymorphism in the D3 receptor gene has a higher risk (odds ratio = 1.17) for developing TD (Bakker et al., 2006). Other polymorphisms in *DRD3* have also been associated with TD (Zai et al., 2009).

Beta-arrestin 2 (*ARRB2*) is an important mediator between *DRD2* and serine-threonine protein kinase (AKT) signal cascade. A case-control study to evaluate the association between a polymorphism (Ser280Ser) and antipsychotic-induced TD was performed among 381 patients (TD/non-TD = 228/153) in a Chinese population. This polymorphism was significantly more common in those with TD ($P = 0.025$) (Liou et al., 2008).

A meta-analysis of genetic studies reported that there appears to be a protective effect against developing TD by being (1) a Val-Met heterozygote or a Met carrier for *COMT* and (2) Ala-Val and Val carriers for *MnSOD*. There is a greater risk for TD by having an A2 variant or being an A2-A2 homozygote for *DRD2* (Bakker et al., 2008).

Polymorphisms of the *CYP2D6* gene, which encodes the cytochrome P450 enzyme debrisoquine/spartein hydroxylase, has been reported to be possibly associated with an increased susceptibility to developing TD (Kapitany et al., 1998; Ohmori et al., 1998; Vandel et al., 1999).

Searches for polymorphisms in the *HTR_{2A}* receptor gene did not find any significant difference among patients with or without TD (Basile et al., 2001; Segman et al., 2001), but this has been inconsistent (Tan et al., 2001). An association of the *HSPG2* gene and TD has been reported (Zai, Lee et al. 2018).

Neuroendocrine

Assessment of tuberoinfundibular dopaminergic sensitivity as a general indicator of dopamine supersensitivity shows lack of hyperresponsiveness of growth hormone and prolactin to dopamine agonist (Tamminga et al., 1977). Although these data on human TD are preliminary and indirect, the evidence for dopaminergic hypersensitivity has not been confirmed in human studies (Jeste and Wyatt, 1981; Fibiger and Lloyd, 1984).

Phenylalanine loading

In a double-blind study, 100 mg/kg of phenylalanine or placebo was given orally to 10 patients with TD (Mosnik et al., 1997); the dyskinesia was exacerbated after ingestion of phenylalanine, confirming earlier reports. Impaired phenylalanine metabolism was found in men but not in women (Richardson et al., 1999).

Human imaging

Results of imaging studies are inconsistent. In one MRI study Buchanan and colleagues (1994) found no difference

between schizophrenic patients who had TD and those who did not when measuring volumes of the caudate, putamen, and pallidum. In contrast, Brown and colleagues (1996) reported larger caudate nuclei, particularly the right, in schizophrenic patients with TD compared with those without TD. To confuse this subject more, a computed tomography (CT) study using special statistical methods found that the left caudate nucleus was smaller and the temporal sulci were enlarged (Dalgarrondo and Gattaz, 1994). Brain iron was found to be normal in the basal ganglia in an MRI study (Elkashef et al., 1994).

Hoffman and Casey (1991) reviewed the literature on reports on CT evaluation of patients with TD. They found that there is a trend toward larger cerebral ventricles in TD patients but that the overall difference with controls is small. Mion and colleagues (1991) compared MRI scans in young TD patients versus controls and found that the volumes of the caudate nuclei were significantly smaller in the TD patients than in normal controls and in patients on neuroleptics without TD. But covariate analysis failed to show a significant difference.

Oxidative stress and excitotoxicity

Maurer and Moller (1997) studied the effect on mitochondria of neuroleptics added to normal human brain cortex in vitro. Complex I activity was inhibited by all neuroleptics in the following order: haloperidol > chlorpromazine > risperidone >> clozapine. Haloperidol increases reactive oxygen species (generated from mitochondria) in rat cortical cell lines (Sagara, 1998). Erythrocyte Cu,Zn-superoxide dismutase activity was found to be reduced in patients on neuroleptics with TD compared with those without TD (Yamada et al., 1997). There were no differences in plasma vitamin E levels between TD and non-TD schizophrenic patients treated with neuroleptics (Brown et al., 1998). The CSF results mentioned earlier support the notion that by blocking presynaptic dopamine receptors, antipsychotics increase striatal glutamatergic transmission and subsequently excitotoxic stress (Tsai et al., 1998). Finding striatal changes in glutamate terminals in a rodent model lends support to the concept of excitotoxicity as a possible mechanism for developing TD (Andreassen et al., 2001) (see section entitled "Anatomic pathology—human and animal models").

Developing TD in the presence of dopamine deficiency states

If dopamine receptor supersensitivity plus active dopamine release from nerve terminals with activation of these supersensitive receptors plays any role in the pathogenesis of TD, then one might anticipate that a state of deficiency of dopamine storage would be incompatible with the development of TD. There appears to be some merit to this concept. Fahn and Mayeux (1980) presented the first report of a patient with PD who developed TD. Their patient had unilateral PD, was treated with a dopamine receptor blocker, and subsequently developed classic TD on the contralateral side of the body. There was no TD on the side with the parkinsonism. In essence, this case supports the notion that a marked deficiency of dopamine release renders the development of TD unlikely, as is seen in the parkinsonian half of the body. The other side probably had partial reduction of dopamine stores and reduced release of dopamine but was still capable

of developing TD. So perhaps this suggests a quantitative requirement (i.e., a threshold of dopamine availability before an individual could develop TD). This concept is compatible with observations that patients with TD who are treated with dopamine-depleting agents, such as reserpine, can substitute the excessive movements with a parkinsonian state.

The second case was a patient with dopa-responsive dystonia (DRD) who developed TD on long-term haloperidol therapy (de la Fuente-Fernandez, 1998). In DRD, there is a reduction of dopamine stores, but not a complete depletion. So again, if the quantity of dopamine available is the critical factor, a state of DRD seems to be quantitatively sufficient with dopamine.

Pathophysiology—summary

The biochemical basis of TD is still unclear, and the explanation involving dopamine receptor supersensitivity alone does not seem to be sufficient. There is little dispute that the primary and early effect of dopamine receptor antagonist is on the dopaminergic system with presynaptic and postsynaptic hypersensitivity. However, the changes do not seem to distinguish patients who develop TD from those who do not. Gerlach (1991) suggested that TD might be due to an increased ratio of D1/D2 receptor activity. The typical neuroleptics block presynaptic and postsynaptic D2 receptors, leaving D1 receptors spared. Thus, it is proposed that an increased D1 receptor activation would lead to the dyskinesias.

The effect of DRBAs is not restricted to the dopaminergic system, and the influence on other interconnected systems such as cholinergic, GABAergic, and peptidergic system needs to be studied. Clinical response to antidopaminergic drugs does not necessarily indicate a central pathophysiologic process in that system either. A good example is treatment of PD with anticholinergics, which does not directly reflect the dopaminergic deficiency of the disease. Moreover, changes may occur at the ultrastructural level such as altered synaptic patterns between subsets of dopaminergic neurons and other interconnected neurons. Findings similar in humans and primate models of TD of decreased GABA activity in the subthalamic nucleus lend support to involvement of this nucleus in TD.

Oxyradicals have been implicated in the pathogenetic mechanism for the tardive syndromes (Lohr, 1991). This is based on the concept that DRBAs cause an increase in dopamine turnover, resulting in an increased synthesis of hydrogen peroxide, a metabolite of oxidative deamination of dopamine. Hydrogen peroxide, if not rapidly metabolized, will form oxyradicals, which can damage cell membranes and other cellular components. This hypothesis has received support from a study in which simultaneous administration of tocopherol to chronic haloperidol treatment in rats prevented the development of behavioral supersensitivity to apomorphine (Gattaz et al., 1993).

Additional studies and new approaches are needed to understand the pathophysiology of classic TD.

Tardive dystonia

Dystonia is most often an idiopathic disorder and can occur at all ages. Persistent dystonic movement as a complication of DRBA therapy has long been noted (Druckman et al., 1962). However, it had not been studied systematically to show that

this represents a distinct syndrome until reported by Burke and colleagues (1982). Tardive dystonia has a different epidemiology and pharmacologic response from those of classic TD. Although secondary dystonia can be caused by many neurologic disorders (Calne and Lang, 1988), tardive dystonia is one of the most common causes (Kang et al., 1986). A rigorous epidemiologic study is not available for tardive dystonia, but the prevalence of tardive dystonia in chronic psychiatric inpatients has been estimated to be 1.5% to 2% (Friedman et al., 1986; Yassa et al., 1986). When mild forms of dystonia were evaluated, 27 of 125 patients on chronic antipsychotic medications had some form of dystonia (Sethi et al., 1990), indicating that the prevalence could be higher than was initially realized. Idiopathic torsion dystonia is a much less common condition, with one of the most generous estimations of prevalence at around 1 per 3000 population (Nutt et al., 1988). Therefore, dystonic movements seem to be much more frequent in patients who have been exposed to DRBAs.

In primary dystonia, patients at younger age of onset tend to develop generalized dystonia and those with onset in adulthood are more likely to have craniocervical focal or segmental dystonia. Kang and colleagues (1986) and Kiriakakis and colleagues (1998) reviewed large series of cases of tardive dystonia and found a similar correlation between distribution of dystonia and age at onset. They found a correlation between the site and age of onset; the site of onset ascended from the lower limbs to the face as the mean age of onset increased. But tardive dystonia rarely affects legs alone even in youngsters (Kang et al., 1986). Regardless of age at onset, tardive dystonia usually progresses over months or years from a focal onset to become more widespread; only 17% remain focal at the time of maximum severity (Kiriakakis et al., 1998). As in primary dystonia, tardive dystonia in adults tends to remain focal or segmental and tends to involve the craniocervical region.

The onset of tardive dystonia can be from days to years after exposure to a DRBA (Kang et al., 1986). Kiriakakis and colleagues (1998) found the range to extend from 4 days to 23 years of exposure (median 5, mean 6.2 ± 5.1 years) in their series of 107 patients, with a mean ($\pm$ standard deviation [SD]) age at onset of 38.3 ± 13.7 years (range 13–68 years). There is no period that is safe from development of tardive dystonia; one patient in the series by Burke et al. (1982) developed it after a 1-day exposure. Men are significantly younger than women at onset of dystonia, and it develops after shorter exposure in men (Kiriakakis et al., 1998). Yassa and colleagues (1989) found that severe tardive dystonia was more common in young men and severe classic TD was more common in older women.

The phenomenology of tardive dystonia can be indistinguishable from that of idiopathic dystonia, including the improvement with sensory tricks (*geste antagoniste*), which can be used to advantage in creating mechanical devices to reduce the severity of the dystonia (Krack et al., 1998). Focal dystonias, such as tardive cervical dystonia (Molho et al., 1998) and tardive blepharospasm (Sachdev, 1998), can resemble primary focal dystonias (Video 17.6). Retrocollis is more likely to be due to tardive dystonia (Video 17.7), and less likely head or neck trauma, while primary dystonia is uncommon (Papapetropoulos et al., 2007).

A comparison of tardive and primary oromandibular dystonia (OMD) showed similar demographics, both occurring predominantly in women, with jaw-closing dystonia being the most common form (Tan and Jankovic, 2000). Patients with primary OMD were more likely to have coexistent cervical dystonia, and the two types of dystonia responded equally well to botulinum toxin (BTX) injections. Limb stereotypies, akathisia, and respiratory dyskinesia were seen only in the tardive OMD. ▶

One clinical presentation of tardive dystonia is particularly more characteristic of tardive dystonia, the combination of retrocollis, trunk arching backward, internal rotation of the arms, extension of the elbows, and flexion of the wrists (Video 17.8) (Kang et al., 1986), whereas patients with idiopathic dystonia more often have lateral torticollis and twisting of the trunk laterally. The presence of lightning-like (myoclonic) movements in association with dystonia may be more common in tardive dystonia than in primary dystonia (Video 17.9). Reduction of dystonic movements with voluntary action such as walking is often seen in tardive dystonia. This is distinctly unusual in idiopathic dystonia, in which the dystonic movements are usually exacerbated by voluntary action. It can be severe enough to jeopardize patients by causing life-threatening dysphagia (Hayashi et al., 1997; Samie et al., 1987). ▶

Tardive dystonia tends to occur in all ages without predilection for any particular age range. The mean age of onset in the literature is about 40 years. This is in contrast to idiopathic dystonia, which shows a bimodal distribution with one early peak in childhood and another later peak in adulthood (Fahn, 1988). Tardive dystonia affects both sexes equally, and men have a younger age of onset than women. Duration of exposure to dopamine receptor antagonists at the onset of tardive dystonia can range from as short as 3 weeks to close to 40 years. The mean duration is 7 years, and as many as 20% of cases develop within a year of the therapy. If the cumulative percentage of patients is plotted against the duration of exposure, the data show a linear line extrapolated to the origin of the graph at zero. This suggests that the risk for developing tardive dystonia starts at the initiation of therapy without any safe minimum period of exposure (Kang et al., 1986).

Wojcik and colleagues (1991) reviewed 32 patients with tardive dystonia and found that most were men but that women had a shorter exposure time to DRBAs. None of their patients had a complete remission, and the condition causes notable disability. On the other hand, van Harten and colleagues (2008b) reported a remission rate of 80% in mild cases of tardive dystonia; the patients remained on antipsychotic medications, so one cannot be certain that the underlying symptoms would not reappear after withdrawal of the DRBAs.

Many patients with tardive dystonia also have classic TD at some point in their course (Kang et al., 1986; van Harten et al., 1997). It is not clear why some develop dystonia whereas others develop classic TD or why some develop both. When patients have both types, dystonic symptoms are usually much more pronounced and disabling (Kang et al., 1986; Gardos et al., 1987).

The dystonia can be so severe that complications can occur. One patient with powerful retrocollis fractured the odontoid process (Konrad et al., 2004).

Tardive akathisia

Originally, akathisia was mainly thought of as an acute to subacute side effect of dopamine receptor antagonists. Various authors, however, noted different variants of akathisia that occurred late in the course of the neuroleptic therapy and/or persisted despite discontinuation of neuroleptic therapy (Braude and Barnes, 1983; Fahn, 1983; Weiner and Luby, 1983). Concomitant or subsequent development of TD was also noted (Munetz and Cornes, 1982; Burke et al., 1989). Barnes and Braude (1985) made a systematic attempt to classify the complex variety of akathisia syndromes. They defined the disorder by the presence of both the subjective and objective features and confirmed that there are acute and chronic variants of akathisia. They also distinguished two types of chronic akathisia; one that occurred early in the course at the time of increasing neuroleptic dose and persisted (acute persistent akathisia) and one that occurred during long-term therapy, sometimes during reduction of their neuroleptic dose (tardive akathisia). Burke and colleagues (1989) reviewed experience with 30 patients with persistent akathisia who met both subjective and objective criteria. They found it difficult to distinguish between acute persistent and tardive akathisia in many cases owing to imprecise information about the onset of the disorder relative to initiation of therapy. It is not clear whether these are distinct syndromes or simply two ends of a continuum. Therefore, some researchers prefer to lump them together as tardive akathisia in line with other persistent movement disorders from dopamine receptor antagonists (Burke et al., 1989). Some attempts to classify akathisia syndromes are complex (Lang, 1994; Sachdev, 1995a); a simple method is to consider persistent neuroleptic-induced akathisia to be the tardive akathisia, and withdrawal, transient akathisia to be acute akathisia, as is done here.

The clinical phenomenology of tardive akathisia is thought to be the same as that of acute akathisia. Moaning (Videos 17.10, 1.36) and focal pain are more common in tardive akathisia than in acute akathisia. In Burke and colleagues' study (1989), the mean age at onset of tardive akathisia was 58 years with a range from 21 to 82 years, similar to the age range of classic TD. The mean duration of dopamine receptor antagonist exposure before the onset was 4.5 years, with a range from 2 weeks to 22 years. Over half of the patients had onset within 2 years. In tardive akathisia, there is a strong likelihood that there will be accompanying TD (Video 17.11) or tardive dystonia (Video 17.12) movements. All of the patients with tardive akathisia in the study by Burke and colleagues (1989) also had either TD (93%), tardive dystonia (33%), or both (27%) at the same time. But isolated tardive akathisia can exist as well. The pathophysiology of akathisia is not understood. ▶

Treatment of tardive syndromes

The most important point to remember in the management of tardive syndromes is that they are iatrogenic disorders. One should avoid using a DRBA if possible. Patients should be forewarned of the risk for a TD syndrome before being placed on the drug. In a survey of 520 psychiatrists, only 54% of them disclose this risk (Kennedy and Sanborn,

Video 17.6 Segmental jaw, neck, and arm dystonia, along with classic oral-buccal-lingual dyskinesia.

Video 17.7 Retrocollis as the feature of tardive dystonia.

Video 17.8 Retrocollis, opisthotonus, internal rotation of the arms, extension of the elbows, and flexion of the wrists.

Video 17.9 A combination of dystonia with myoclonic or ballistic movements.

Video 17.10 Moaning as a manifestation of tardive akathisia.

Video 17.11 A combination of tardive dyskinesia and tardive akathisia.

Video 17.12 A combination of tardive dyskinesia, tardive dystonia, and tardive akathisia.

1992). A study of the impact of informed consent based on questionnaires showed that patients did retain the information both at 4 weeks and at 2 years (Kleinman et al., 1996). Another study comparing patients' knowledge of TD by a questionnaire revealed that those who were educated about the disorder had more knowledge about it 6 months later (Chaplin and Kent, 1998).

Once a tardive syndrome has been encountered, removal of the etiologic agent must be seriously considered as the first consideration. If it is to be discontinued, a slow taper appears to be safer than sudden withdrawal; the latter might exacerbate the severity of the syndrome. In classic TD, prospective data show 33% remission in 2 years after elimination of the DRBA (Kane et al., 1986). In retrospective studies, the remission rates were 12% for tardive dystonia and 8% for tardive akathisia (Kang et al., 1986; Burke et al., 1989). Some of these patients remitted only after at least 5 years of abstinence from DRBAs (Klawans et al., 1984; Kang et al., 1986). Younger age is associated with better chance of remission (Smith and Baldessarini, 1980) and earlier detection and discontinuation of dopamine receptor antagonists were more favorable for remission (Quitkin et al., 1977). In a study involving patients with chronic schizophrenia, only 1 of 49 patients who discontinued the antipsychotic drugs had a lasting recovery, but 10 others had some improvement 1 year later (Glazer et al., 1990).

There are necessary indications for long-term use of DRBAs, such as chronic psychotic disorders (American Psychiatric Association, 1980). When patients are not able to discontinue antipsychotic medications, the concern is whether their TD will inexorably get worse and require increasingly higher doses of antipsychotics to suppress the symptoms, but there are no data to indicate a worsening in most patients (Labbate et al., 1997), and the majority of patients show improvement over time (Gardos et al., 1988). Casey and colleagues (1986) noted that those with decreased neuroleptic doses showed no change in their dyskinesia score, and those with stable doses and increased doses showed a mean decrease in their dyskinesia scores at 3- to 11-year follow-up. Although these data do not answer whether the symptoms were simply masked or whether the disease itself has improved in its natural course, at least it appears that continuing antipsychotics does not necessarily aggravate the symptoms.

Therefore, a prudent approach is to keep the patients at the minimum dose of the drug necessary for their control of psychosis and add other forms of therapy for TD. Many patients who are withdrawn from DRBAs still require symptomatic suppression of their movements when remission is not achieved or while waiting for remission. The clinical pharmacology is different in each subsyndrome, and thus they are discussed separately.

Treatment of classic tardive dyskinesia

VMAT2 inhibitors

Vesicular monoamine transporter 2 (VMAT2) is a protein that is responsible for the transporting of dopamine, norepinephrine, and serotonin from the cytoplasm into "packages" (synaptic vesicles) located at the nerve terminal. This mechanism is part of the recycling of these monoamines. For example, dopamine that has been taken up from the synaptic cleft into the cytoplasm is packaged by VMAT2 into the synaptic

Table 17.13 Pharmacologic profiles of VMAT 2 inhibitors

	Tetrabenazine	Valbenazine	Deutetrabenazine
Half Life	Short ($T_{1/2}$ = 4.8 hours)	Long ($T_{1/2}$ = 20 hours)	Medium ($T_{1/2}$ = 8.6 hours)
Efficacy	++	+++	+++
Dosing	Three times daily	Nightly	Twice daily
Side effects	++++	+	+
	Sedation Depression Suicidal ideation Akathisia Parkinsonism Prolonged QTc Orthostatic hypotension	Sedation	Headache Sedation

vesicles, which provides storage and reutilization of dopamine (Nickell, Siripurapu et al., 2014). This is safe storage; otherwise the monoamines in the cytoplasm would be oxidized and deaminated by monoamine oxidase (MAO). The VMAT2 inhibitors prevent the vesicular storage of dopamine, resulting in the subsequent degradation of the neurotransmitter by MAO, and producing a depletion of dopamine.

TBZ was the first drug characterized as a VMAT2 inhibitor. TBZ was initially used in the 1950s as an antipsychotic and antihypertensive agent. It is rapidly metabolized into four stereoisomers of dihydrotetrabenazine (DHTBZ): (+)- α -DHTBZ; (-)- α -DHTBZ; (+)- β -DHTBZ and (-)- β -DHTBZ. The (+)- α -DHTBZ is a potent VMAT2 inhibitor, whereas the other metabolites have much lower affinities for VMAT2, and were found to affect other receptor subtypes, including serotonergic, dopaminergic, and adrenergic receptors (Grigoriadis, Smith et al., 2017). TBZ has a short half-life of approximately 5 hours, requiring three daily doses. It undergoes hepatic metabolism primarily by CYP2D6 and CYP3A4 to inactive compounds.

In the late 1990s, TBZ was reported in small, controlled studies, open-label studies, and retrospective studies to reduce the hyperkinetic movements associated with TD. However, the side effects, including sedation, depression, and parkinsonism, limited the usefulness of this agent (Scott and Factor, 2018) (Solmi, Pigato et al., 2018). In addition, the short half-life and interpatient variability of hepatic metabolism lead to wide variations in plasma levels.

TBZ was FDA approved for the treatment of the chorea of HD in 2008. The pivotal clinical trial included 84 HD patients randomized to TBZ or placebo in a 2:1 ratio. The study demonstrated the efficacy of TBZ for chorea but also the dose-limiting adverse symptoms that included sedation (27%), akathisia (8%), parkinsonism (4%), and depression (2%) (Huntington Study Group, 2006). TBZ has not undergone sufficient clinical trials for the treatment of TD.

Valbenazine is a prodrug of DHTBZ linked to a valine molecule, which prolongs the half-life of the drug. Valbenazine is a highly selective inhibitor of VMAT2 primarily through its main metabolite (+)- α -DHTBZ. In contrast to TBZ, valbenazine does not have metabolites that affect other targets and has a prolonged half-life of 20 hours. The development of valbenazine from the first phase I trials in late 2009 to FDA

approval in April of 2017 is seen as a model of rapid drug development for debilitating conditions such as TD, which had no safe and effective treatment at the time (Davis, Miller et al., 2017). In early 2012 the FDA granted a "Fast Track" designation to the drug and a "Breakthrough Therapy" designation in late 2014 (Kim, 2017). This allowed for increased discussions between the FDA and the sponsor (Neurocrine Biosciences), with a high priority for review. The phase II studies (Kinect and Kinect 2) were completed in late 2013.

The Kinect 2 study was the first efficacy, safety, and tolerability study (O'Brien, Jimenez et al., 2015). The study was a 6-week, randomized, placebo-controlled, double-blind study that included 100 subjects with TD who received escalating doses of valbenazine (NBI-98854) up to 75 mg once daily. The primary outcome of the study was the change in the Abnormal Involuntary Movement Scale (AIMS) as rated by a central panel of movement disorders specialists from randomized videotape segments. Adverse effects were determined at each study site. Dopamine receptor-blocking agents were continued at stable doses throughout the study. The results showed a median reduction in the AIMS of 3 points compared with 0.5 points in the placebo group. The most frequent side effects occurred in less than 10% of the treated subjects and included fatigue, headache, decreased appetite, and sedation/somnolence.

The Kinect 3 study was a 6-week, randomized, placebo-controlled, double-blind study that included 225 patients with TD. This study was a fixed-dose study that included three arms: placebo, 40 mg, and 80 mg of valbenazine. Similar to Kinect 2, the primary outcome was the change from baseline in the AIMS dyskinesia score at week 6. The AIMS scores were obtained from randomized patient videos using a central rating panel of movement disorder specialists in which two raters reached consensus on the scores for each subject. The site investigator assessed the secondary outcome (Clinical Global Impression of Change in TD [CGIC-TD]) and adverse effects. The results showed a dose-dependent improvement in both active treatments groups for the change in the AIMS score (−3.7 in the 80-mg group; −1.9 in the 40-mg group versus −0.1 in placebo). However, there were no significant differences in the CGI-TD in any dose group. Side effects included somnolence (5.3%), akathisia (3.3%), and dry mouth 3.3%) (Hauser, Factor et al., 2017). The patients in Kinect 3 were invited to enter a 42-week extension period, followed by a 4-week treatment washout period. In this study, patients on active valbenazine continued in the dose group randomized in the double-blind study, and placebo patients were randomized to either 40 or 80 mg/day. The outcome measures, AIMS and CGI-TD, were assessed using the same methodology as in the double-blind study. Of the 205 patients in the double-blind study, 62% completed the extension study. This study demonstrated a continued reduction in the AIMS score over the 42-week treatment period, with a return to baseline scores after the 2-week washout. The CGI-TD scores showed improvement with a worsening washout. Treatment-related adverse events occurred in 69%, with discontinuation in 15.7%. The most frequent treatment-related side effects were headache (7.1%) and urinary tract infection (6.6%). Approximately 5% had suicidal ideation, and 4% reported depression (Factor, Remington et al., 2017).

The Kinect 4 study is a 48-week open-label study that included two doses of valbenazine, 40 and 80 mg. The

study was designed to assess long-term effects of valbenazine. There were 163 TD patients included who received 40 mg of valbenazine for the first 4 weeks, with a dose increase to 80 mg if tolerated. Of the 163 participants enrolled, 149 completed at 8 weeks, and 103 completed the full 48 weeks. The most frequent reason for discontinuation was side effects, occurring in 15.6%. The most frequent adverse event included headache and urinary tract infection. One death, which occurred in the 80-mg group, was due to breast cancer and not related to valbenazine treatment. Of the total patient group, 6.7% had suicidal ideation or behavior during the treatment period. There were no significant changes in laboratory or electrocardiograms, suggesting that valbenazine is well tolerated with no unexpected side effects (Singer, Comella et al., 2018).

DTBZ is a VMAT2 inhibitor that has incorporated the substitution of an atom of deuterium (a nonradioactive isotope of hydrogen) for an atom of hydrogen into the TBZ molecule. In contrast to TBZ, the addition of this isotope results in a slower clearance and lower peak concentrations compared with TBZ. The lower peak concentration and reduced fluctuations in plasma levels likely underlies the increased tolerability to the drug with reduced side effects. The half-life of DTBZ is approximately 9 to 10 hours, allowing for twice-daily dosing (Solmi, Pigato et al., 2018). DTBZ is metabolized into four isomers, DEU(+)- α -DHTBZ; DEU(−)- α -DHTBZ; DEU(+)- β -DHTBZ and DEU(−)- β -DHTBZ. The DEU(+)- α -DHTBZ is the selective VMAT2 inhibitor. The remaining three metabolites have a low affinity for VMAT2. The metabolism of DTBZ to inactive compounds is primarily hepatic through CYP2D6.

DTBZ was initially FDA approved for the treatment of chorea associated with HD. This clinical trial was a double-blind, randomized, placebo-controlled study. In this study, 90 HD patients were randomized to active drug or placebo. During the first 8 weeks, the dose of DTBZ was optimized up to 48 mg and followed by a 4-week maintenance period and a subsequent 1 week washout period. The patients treated with DTBZ received a mean dose of 39.7 mg. There was a reduction of 4.4 points in chorea scores versus placebo difference of −1.9. Both chorea and dystonia improved. After washout, the chorea scores returned to baseline levels. Global scales likewise demonstrated successful treatment in 51% of the treated group versus 20% of the placebo group. Adverse events did not differ between the treatment groups (Huntington Study Group, Frank et al., 2016). A subsequent open-label study in 37 HD patients receiving stable TBZ doses demonstrated the safety of switching overnight from TBZ to DTBZ (Frank, Stamler et al., 2017).

There were two large randomized, placebo-controlled studies of DTBZ for the treatment of TD. The ARM-TD study included 117 patients randomized to placebo or twice-daily DTBZ (Fernandez, Factor et al., 2017). After a titration period of 6 weeks, there was a 6-week maintenance phase with a mean total daily dose of 38.8 (7.92) mg/day. The primary outcome was the AIMS severity score from baseline to week 12. A central panel of blinded raters rated patient videos randomized for visit. Two raters rated each patient, and the final score was a consensus of the two raters. The Clinical Global Impression of Change (CGIC) was the key secondary endpoint. At week 12, patients in the treatment arm had significantly greater reduction in AIMS than those in the

placebo group. There was no significant difference in the CGIC between groups. Adverse events were similar in each group. There was a greater frequency of psychiatric adverse events in the treatment group who were also treated with concomitant antipsychotics (19.6%) versus those in the placebo group (9.8%).

In the AIM-TD study, 298 TD patients randomized to placebo or DTBZ at 12 mg, 24, or 36 mg/day were titrated upward for 4 weeks and maintained treatment for an 8 week period, with a 1 week washout subsequently (Anderson, Stamler et al. 2017). At week 12 there was a significant improvement of the AIMS with significant improvement over placebo from baseline in the 24 mg/day and 36 mg/day groups. Similarly for the CGIC. Adverse events overall were similar among the four groups. Although somnolence and depression were more frequent in the treatment groups, the frequency was low at less than 4%. There was no difference in adverse events in those patients receiving concomitant treatment with stable doses of dopamine receptor antagonists.

Currently, the VMAT2 inhibitors valbenazine and DTBZ have Level A evidence for efficacy in the treatment of TD (Bhidayasiri, Jitkritsadakul et al., 2018). Valbenazine has a longer half-life providing for once-daily dosing. DTBZ has a shorter half-life and is dosed twice daily (Stahl, 2018). There have been no direct comparisons of these drugs in humans.

Atypical antipsychotics

By definition the atypical antipsychotics have a reduced propensity to induce extrapyramidal adverse effects, TD included. However, a range of adverse effects are encountered from the variety of drugs that have at one time or another been labeled as atypical neuroleptics. Today, the dibenzodiazepines (clozapine and quetiapine) are strong candidates for this labeling, and the thienobenzodiazepine olanzapine is less so. Originally the “atypical” label was applied to the benzamine derivatives, such as sulpiride, metoclopramide, and tiapride. However, all three compounds have been reported to induce TD or NMS (Casey, 1983; Achiron et al., 1990; Miller and Jankovic, 1990; Duarte et al., 1996). Similarly, risperidone has been touted as “atypical,” but it more resembles a typical antipsychotic, causing parkinsonism and inducing TD (Buzan, 1996). The typical antipsychotics, including sulpiride, tiapride, and risperidone, by blocking and occupying dopamine D2 receptors, are effective in reducing the severity of TD (Chouinard, 1995). But so do even stronger DRBAs, such as phenothiazines and haloperidol. The problem with using typical antipsychotics to treat TD is that they are in the class of the offending drugs and thus will prolong the exposure of the patient to the drugs that cause TD.

The question is whether the true “atypical” antipsychotics, such as clozapine and quetiapine, can reduce the symptoms of TD and still allow the healing process in the brain to proceed to eventually eliminate the pathophysiologic causation of the symptoms. There are reports of clozapine successfully reducing the abnormal movements of TD and tardive akathisia (Huang et al., 1980; Wirshing et al., 1990; Bassitt and Neto, 1998) and in some patients with tardive dystonia (Lieberman et al., 1989, 1991; Van Putten et al., 1990; Friedman, 1994; Trugman et al., 1994; Wolf and Mosnaim, 1994; Raja et al., 1996; van Harten et al., 1996a; Bassitt and Neto, 1998). But the response rate is lower than

that with typical antipsychotics, such as haloperidol. Clozapine permits the dyskinesia to disappear in about half the cases in one report (Gerlach and Peacock, 1994). In another, 8 of the 20 patients with TD improved after an average time of 261 ± 188 days of treatment (Bunker et al., 1996). With an average dose of approximately 400 mg/day, Bassitt and Neto (1998) obtained a 50% lessening of dyskinesia. It is still not clear whether the reduction of dyskinesia is due to the small amount of D2-blocking effect or whether actual healing of the TD can take place in the presence of clozapine. The proof of the latter and preferred category would be the lack of reappearance when clozapine is withdrawn. There has not been a report of such a case. Without that evidence, it is likely that the reductions of TD and tardive dystonia are due to the small amount of D2-blocking activity by clozapine.

There is a case report of TD improving on quetiapine 600 mg/day (Vesely et al., 2000). The patient was not withdrawn from the drug. A large, randomized study on high-dose quetiapine also found quetiapine to be effective (Emsley et al., 2004), but high dosages of the atypical antipsychotics become typical by blocking D2 receptors, so the reduction of TD can be due solely to further D2 receptor blockade.

The questions that were raised from clozapine apply here as well. Is the reduction of dyskinesias due to its D2-blocking effect that would occur at high doses? If so, then withdrawal of the drug would be associated with a return of the dyskinesias. Is the reduction of dyskinesias the result of a natural healing process, as has been demonstrated mainly with reserpine and somewhat with TBZ? If so, then withdrawal of the drug would not be associated with a return of the dyskinesias. The advantage of dopamine depleters, such as reserpine and TBZ, is that they allow symptomatic benefit and still allow the brain to heal spontaneously so withdrawal of medication might be possible someday.

However, clozapine and quetiapine could substitute for a typical antipsychotic in a patient with a tardive syndrome who also has psychosis, thereby controlling the psychosis and possibly still allowing a chance for a complete remission to occur. Such a remission would not take place in the presence of the typical antipsychotic. Like clozapine, quetiapine needs to be tested. Olanzapine has successfully reduced the symptoms of TD (Littrell et al., 1998). However, olanzapine is not a true atypical antipsychotic, and the reduction of the symptoms and signs is probably obtained by blocking D2 receptors. This would convey no advantage over using the more classic and conventional typical antipsychotics.

Dopamine agonists

Some investigators have tried to activate the presynaptic dopamine receptors by using low doses of a dopamine agonist, which in turn would reduce the biosynthesis and release of dopamine. Another approach by Alpert and Friedhoff (1980) was the use of levodopa in an attempt to desensitize the postsynaptic dopamine receptors. This can cause initial worsening of symptoms before eventual improvement is expected after discontinuation of levodopa. Unfortunately, dopaminergic drugs can also lead to overt recurrence of underlying psychosis (Fahn, 1983). This approach has theoretical merit but is very difficult to carry out in many patients and has not been widely used since the initial reports.

Amantadine has been reported to have some benefit (Angus et al., 1997), but it may be due to its glutamate receptor blocking effect rather than its dopaminergic effect.

Nondopaminergic medications

Although neuroleptics are most effective in controlling the abnormal movements, some patients do not respond to the treatment. Numerous investigators (Jeste and Wyatt, 1982b; Jeste et al., 1988) have attempted nondopaminergic treatments. Agents that enhance GABA transmission have been tried because of GABA's inhibitory effect on the dopaminergic system and experimental data, indicating changes in the GABA system in patients and animals that have been treated with chronic neuroleptics. Use of benzodiazepines, baclofen, valproate, and gamma-vinyl GABA has met with limited success, partly owing to tolerance and side effects such as worsening of psychosis. Some improvement was found with clonazepam (Thaker et al., 1990). Propranolol, fusaric acid, and clonidine decrease the noradrenergic activity and have been reported to be useful but require further study to clarify their role in treating TD. Use of cholinergic drugs was based on the reciprocal dopamine–acetylcholine balance in the basal ganglia. Despite a flurry of reports in the 1970s, this modality has been quite limited and should be reconsidered now that some adequate cholinergic drugs are available. Anticholinergics, pyridoxine, tryptophan, cyproheptadine, vasopressin, naloxone, morphine, and estrogen were reported to be of no benefit. But in a controlled clinical trial involving 15 patients, pyridoxine was found to reduce the severity of TD (Lerner et al., 2001). Buspirone has been reported to be beneficial (Moss et al., 1993), but it is not clear that this drug does not have dopamine receptor–blocking activity. Calcium channel blockers have been reported to reduce the severity of TD (Kushnir and Ratner, 1989; Duncan et al., 1990; Suddath et al., 1991), but not in all studies (Loonen et al., 1992). A combination of acetazolamide and thiamine was found to reduce both TD and drug-induced parkinsonism (Cowen et al., 1997). Lithium not only may decrease the chance of TD development (Kane et al., 1986; van Harten et al., 2008a) but also may reduce its severity if applied as a treatment (van Harten et al., 2008a).

A review of randomized clinical trials (RCTs) was presented by Soares and McGrath (1999) with a meta-analysis when more than one RCT had been carried out. Meta-analysis showed that baclofen, deanol, and diazepam were no more effective than a placebo. Single RCTs demonstrated a lack of evidence of any effect for bromocriptine, ceruletide, clonidine, estrogen, gamma-linolenic acid, hydergine, lecithin, lithium, progabide, selegiline, and tetrahydroisoxazopyridinol. Meta-analysis found that five interventions were effective: levodopa, oxypertine, sodium valproate, tiapride, and vitamin E; neuroleptic reduction was marginally significant. Vitamin E is more thoroughly discussed in the next paragraph. Data from single RCTs revealed that insulin, alpha-methyl dopa, and reserpine were more effective than a placebo. Meta-analysis found that 37.3% of placebo-treated subjects improved.

A role for antioxidants has been raised (Cadet and Lohr, 1989; Behl et al., 1995). Treatment with vitamin E has been found to reduce the severity of TD (Elkashef et al., 1990; Dabiri et al., 1994; Adler et al., 1998; Sajjad, 1998) or have no

effect (Lam et al., 1994). The meta-analysis mentioned earlier showed effectiveness. A small clinical trial of 41 subjects comparing 1200 international units/day of vitamin E and placebo found the former to better reduce severity of abnormal involuntary movements (45.9% versus 4.3%) (Zhang et al., 2004). However, the largest double-blind study, carried out by the Veterans Administration multicenter, a placebo-controlled clinical trial (Adler et al., 1999), found vitamin E not to be effective. As a potential prophylactic agent, vitamin E (3200 international units/day) was found not to protect against development of drug-induced parkinsonism (Eranti et al., 1998). Nor was vitamin E treatment able to prevent neuroleptic-induced VCMs in rats (Sachdev et al., 1999). In a small open-label trial combining vitamins E and C, improvement in TD was seen (Michael et al., 2003).

There continue to be reports of TD responding to open-label trials. Gabapentin (Hardoy et al., 1999, 2003), pyridoxine (Lerner et al., 1999), and branched-chain amino acids (Richardson et al., 2003) are such compounds. Levetiracetam was helpful in a small trial (Konitsiotis et al., 2006).

Injections of BTX into the muscles causing oral dyskinesia have been reported to be effective in reducing the movements (Rapaport et al., 2000). This includes tongue protrusion, which has been successfully treated with injections into the genioglossal portion of the tongue (van Harten and Hovestadt, 2006).

Sporadic reports noted efficacy of ECT in refractory cases of TD (Price and Levin, 1978), but Yassa and colleagues (1990) reported success in only one of nine patients.

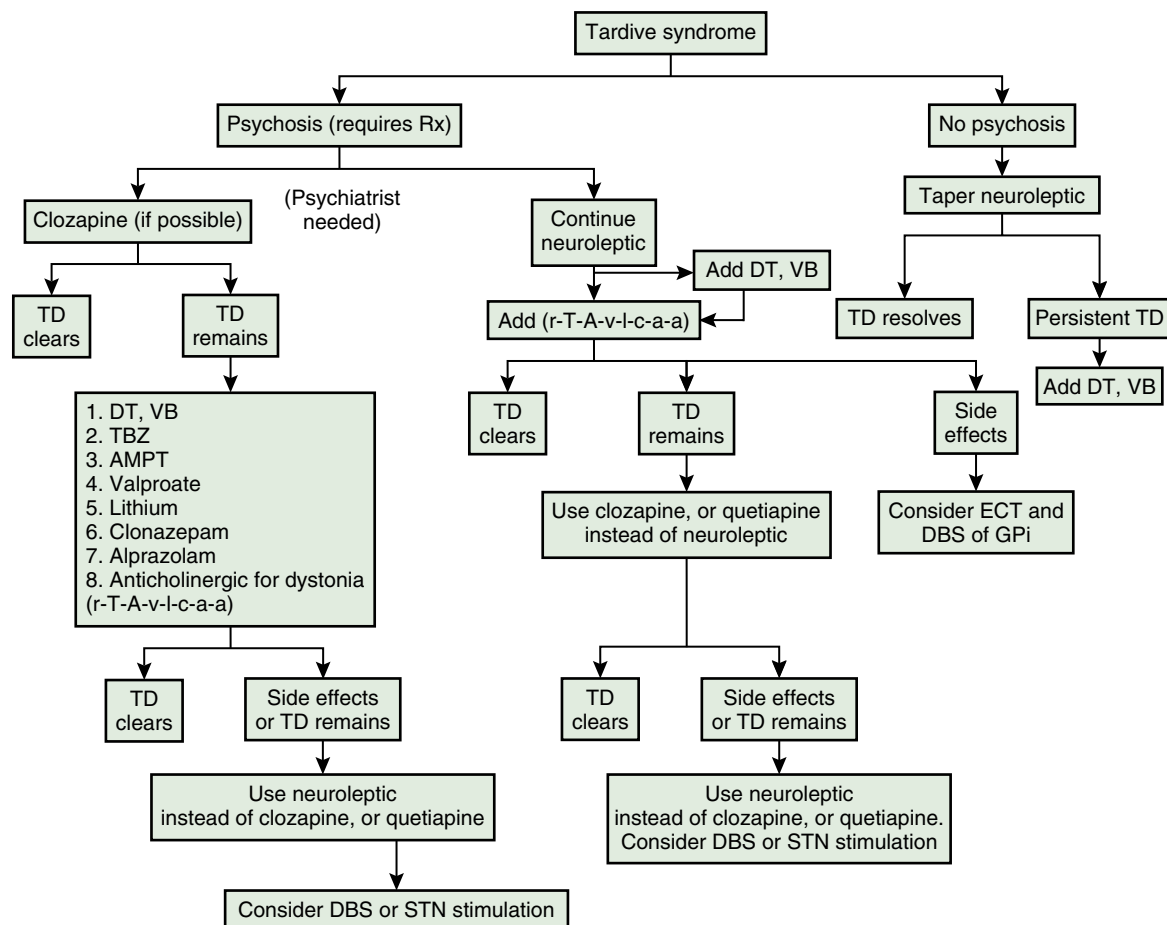
Conclusions on classic tardive dyskinesia

By blocking D2 receptors, neuroleptics are effective in reducing the abnormal involuntary movements of TD. Depleting dopamine from synaptic terminals using VMAT2 inhibitors does not cause TD and is therefore preferred. Avoiding side effects, particularly drug-induced parkinsonism, is a major limiting factor. DRBAs, while controlling symptoms, are the agents causing TD; thus, the underlying pathophysiologic processes of TD may continue to be an issue. If one needs to use an antipsychotic, it seems safer to use one that is suspected of having less ability to induce TD, such as clozapine and quetiapine. Olanzapine comes closer to being a typical, rather than an atypical, antipsychotic. When clozapine and quetiapine occasionally reduce dyskinesias, the doses that are used suggest the response is from their D2-blocking activity.

Figs. 17.1 and 17.2 are flowcharts that provide a useful algorithm for treating TD.

Tardive dystonia

As with classic TD, the most effective medications for tardive dystonia are also antidopaminergic drugs (Kang et al., 1986), but the percentage of patients who improve is smaller. Reserpine and TBZ each produce improvement in about 50% of patients. Reserpine is no longer available in the United States. Some patients who do not respond or have intolerable side effects to one might respond to the other. DRBAs are more effective in suppressing the movements (77%). Symptomatically, those who remained on DRBAs after the onset of tardive dystonia and those who were withdrawn from them do not have a significant difference in their improvement rate. This again is in agreement with the data in classic TD, in which continued use of DRBAs does not necessarily lead to



Abbreviations, see Figure 17.1

Fig. 17.2 Flowchart for treating tardive syndromes in the presence of psychosis. AMPT, Alpha-Methylparatyrosine; DBS, deep brain stimulation; ECT, electroconvulsive therapy; GPi, globus pallidus internus; TBZ, tetrabenazine; TD, tardive dyskinesia. *PT*, deutetabenazine; VB, valbenazine. (Factor et al., 2019; Factor 2020; Scorr, 2018).

aggravation of their movements (Casey et al., 1986; Gardos et al., 1988). The atypical antipsychotic clozapine has been helpful in some patients with tardive dystonia (Lieberman et al., 1989, 1991; Van Putten et al., 1990; Friedman, 1994; Trugman et al., 1994; Wolf and Mosnaim, 1994; Raja et al., 1996; van Harten et al., 1996a). There are reports of quetiapine's effectiveness as well (Gourzis et al., 2005). It is likely that its treatment of tardive dystonia in some situations is due to its D2 receptor-blocking activity resulting in a masking of the symptoms, because withdrawal would exacerbate the dystonia (Krack et al., 1994) when either drug alone was much less satisfactory (Shapleske et al., 1996).

In tardive dystonia, antimuscarinics are almost as effective as antidopaminergic drugs. This is different from classic TD, which may get worse with antimuscarinics (Yassa, 1988). Kang and colleagues (1986) reported a 46% improvement rate on antimuscarinics such as trihexyphenidyl and ethopropazine. CNS side effects of the antimuscarinics include forgetfulness, lethargy, psychosis, dysphoria, and personality changes; elderly patients are more susceptible to these. Peripheral side effects include blurred vision, dry mouth, constipation, urinary retention, and orthostatic dizziness. Those who develop side effects to one anticholinergic drug may tolerate another anticholinergic better. Although there is no evidence that one anticholinergic is more efficacious than the others, ethopropazine may produce fewer CNS side effects in elderly patients. Although peripheral pharmacokinetics show

relatively short half-lives, their central effects have a very slow onset of action and several weeks are often required before benefit is noticed. Therefore, the medications are started at a low dose, 2.5 mg of trihexyphenidyl or 25 mg of ethopropazine, and increased slowly by 2.5 mg of trihexyphenidyl or 25 mg of ethopropazine weekly until sufficient control of dystonia or intolerable side effects are achieved. As in idiopathic dystonia, many patients respond only to a high dose of anticholinergics. Therefore, every attempt must be made to control side effects so that high-dose anticholinergics may be tried. Kang and colleagues (1986) reported use of a maximum of 450 mg ethopropazine or 32 mg of trihexyphenidyl, and higher doses may be tolerated in young patients if judiciously used. Peripheral side effects are often controlled by peripheral cholinergic drugs, such as oral pyridostigmine and pilocarpine eye drops.

The clinical pharmacology of tardive dystonia indicates two subtypes: one group that responds to antidopaminergic drugs like the other tardive syndromes and one that responds to anticholinergics like idiopathic dystonia. Analysis of clinical characteristics of patients who respond to antidopaminergic drugs and those who respond to anticholinergic drugs has not shown any significant difference (Kang et al., 1986). However, the data from Kang and colleagues (1986) are retrospective and the treatment choice between the two classes of drugs was rather arbitrary, partly based on anticipated side effects. For example, patients who were elderly or who had

dementia were treated with dopamine-depleting drugs first, because these patients have greater risk for anticholinergic side effects such as memory loss and confusion. Patients with depression might have relapse of their symptoms on dopamine-depleting drugs and were treated preferentially with anticholinergics. This is a reasonable clinical approach, but characterization of subtypes will require a controlled study with random assignment of the treatment. If either a dopamine depleter or antimuscarinic is ineffective by itself, the combination should be tried.

Benzodiazepines are mainly helpful as adjunctive therapy with dopamine-depleting or anticholinergic drugs, and occasionally can be quite beneficial (Yamamoto et al., 2007). Minimal success with propranolol, levodopa, carbamazepine, and baclofen has been noted. Bromocriptine, deanol, clonidine, lisuride, amantadine, and valproate were reported with mixed results. The calcium channel blocker verapamil was reported to be effective in one patient (Abad and Ovsiew, 1993). Opioids do not have lasting value in suppressing tardive dystonia (Berg et al., 2001). But one study found the combination of naltrexone and clonazepam to offer some benefit (Wonodi et al., 2004b).

If any residual dystonia remains that is localized to one or a few parts of the body, injections of BTX into the affected parts, such as the orbicularis oculi, masseters, or cervical muscles, might be useful (Chatterjee et al., 1997; Tarsy et al., 1997; Kanovsky et al., 1999).

ECT might be effective in intractable cases (Yoshida et al., 1996), and deep brain stimulation in the GP internus (GPi) is often effective (Franzini et al., 2005; Sako et al., 2008; Gruber et al., 2009), as is intrathecal baclofen (Dressler et al., 1997). Surgery is not always effective and does pose risks for complications (Trottenberg et al., 2001). However, deep brain stimulation in the pallidum can be safe and effective (Capelle et al., 2010; Chang et al., 2010); it is worth considering when medications fail.

A centrally acting muscle relaxant, eperisone, was successful in treating one patient with tardive dystonia (Nisijima et al., 1998). Eperisone is a beta-aminopropiophenone derivative.

Figs. 17.1 and 17.2 depict flowcharts for therapy that can be applied to tardive dystonia, as well as to classic TD.

Tardive akathisia

As was noted earlier, variants of akathisia have been the source of confusion in the literature. Most of the papers do not distinguish between acute and tardive akathisia or usually refer to acute akathisia and not tardive akathisia. Very few studies have focused on the treatment of tardive akathisia.

Tardive akathisia is difficult to treat and does not respond to anticholinergics, which have been reported to help acute akathisia. It and tardive dystonia are the most distressing and disabling features of the tardive symptoms, and their treatment is important. In the study of tardive akathisia by Burke and colleagues (1989), all of the patients noted that the subjective sensations were distressing. The same study reported that 87% of patients improved on reserpine up to 5 mg/day and 58% on TBZ up to 175 mg/day. In one-third of these patients, the movements were completely suppressed. In this respect the clinical pharmacology is more like that of classic TD than that of acute akathisia. Opioids were reported to be

Table 17.14 Practical clinical approach to treatment for tardive dyskinesia syndromes

1. Taper and slowly eliminate causative agents if clinically possible. Avoid sudden cessation of these drugs, which could exacerbate the tardive syndrome.
2. Avoid drugs, if possible (i.e., wait for spontaneous recovery). This is possible only if the dyskinesia is not severe or there is no accompanying tardive akathisia or tardive dystonia. Akathisia and dystonia are more distressing and disabling than classic tardive dyskinesia (TD).
3. If necessary to treat the symptoms, VMAT2 inhibitors are typically the first line. Two VMAT inhibitor drugs are FDA approved for use: deutetrabenazine and valbenazine. Another VMAT2 inhibitor, tetrabenazine, is also used, although it appears to have more side effects than the more recently approved VMAT2 inhibitors.
4. Consider melatonin on the basis of one report (Shamir et al., 2001).
5. Consider the atypical antipsychotic agents clozapine and quetiapine.
6. If these fail, consider very small doses of a dopamine receptor agonist to activate only the presynaptic dopamine receptor and reduce the biosynthesis of dopamine.
7. For tardive dystonia, consider antimuscarinics or botulinum toxin for focal areas of dystonia.
8. For intractable tardive akathisia, consider electroconvulsive therapy.
9. Typical antipsychotic agents can be used to control the dyskinesias when all previously mentioned approaches fail. Combining this with a dopamine depleter may increase the potency of the antidyskinetic effect, and may theoretically protect against a worsening of the underlying tardive pathology.
10. Deep brain stimulation of the thalamus and pallidum have been performed for tardive dystonia with success. Deep brain stimulation of the pallidum appears to be the preferred surgical procedure if the symptoms remain severe and all medication trials fail.

beneficial (Walters et al., 1986), but the effect has not been persistent (Burke et al., 1989). ECT can be effective in those patients whose akathisia has proved to be intractable (Hermesh et al., 1992).

Figs. 17.1 and 17.2 depict flowcharts on therapy that can also be applied to tardive akathisia.

Treatment summary

Table 17.14 summarizes a useful approach to treat tardive syndromes in general. The approach to treatment should be earmarked according to whether the patient is psychotic and requires antipsychotic medication or is not psychotic. For detailed, step-by-step decisions in the treatment of the tardive syndromes, the flowcharts of Figs. 17.1 and 17.2 should be helpful.

In summary, because of the initial description of TD as an iatrogenic complication of dopamine receptor antagonists, considerable progress has been made in understanding the risks, epidemiology, and clinical subtypes of the condition. However, pathogenesis and characteristics of distinct subtypes are still poorly understood. Management of tardive syndromes must be based on proper understanding of these aspects of the disorder. The only effective and safe antipsychotic agents that do not produce, or rarely produce, TD

appear to be clozapine and quetiapine. Meanwhile, prevention is possible by avoiding indiscriminate use of DRBAs and limiting their use to disorders for which no other type of medication is available or effective. When prevention and withdrawal of the offending drugs for eventual remission fail, symptomatic suppression can be achieved in many patients with pharmacologic treatments. New approaches

are needed, and prospective controlled clinical trials with particular attention to clinical subtypes are necessary for better management of these conditions.

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Myoclonus

Phenomenology, etiology, physiology, and treatment

Chapter contents

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Introduction

Literally, myoclonus means “a quick movement of muscle.” Sudden, brief jerks may be caused not only by active muscle contractions, positive myoclonus, but also by sudden, brief lapses of muscle contraction in active postural muscles, negative myoclonus or asterixis ([Shibasaki, 1995](#)).

The history of myoclonus has been described by [Marsden and colleagues \(1982\)](#), [Hallett \(1986\)](#), and [Fahn \(2002\)](#). Friedrich first defined myoclonus as a discrete entity in a case report published in 1881 of a patient with what might be called “essential myoclonus.” He wanted to separate the involuntary movement that he saw from epileptic clonus, a single jerk in patients with epilepsy, and chorea, which was the only previously described type of involuntary movement. For the next 10 to 20 years, many other types of involuntary movements, such as tic and myokymia, were also called myoclonus, but in 1903 Lundborg proposed a classification of myoclonus that cleared up much of the confusion. Lundborg classified myoclonus into three groups: symptomatic myoclonus, essential myoclonus, and familial myoclonic epilepsy.

Myoclonus is distinguished from tics because the latter can be controlled by an effort of will, at least temporarily, whereas myoclonus cannot. In addition, many tics are complex movements that are accompanied by a conscious urge to move and by relief of tension after the tic has occurred. Many of the individual movements of chorea may be myoclonic jerks, but in chorea, the movements continue in a constant flow, randomly distributed over the body and randomly distributed in time. Many patients with dystonia have brief muscle spasms, sometimes repetitively (myoclonic

dystonia), but these drive the body part into distinctive dystonic postures. Sometimes, myoclonic jerks may be rhythmic, giving a superficial impression of tremor.

Myoclonus is a common movement disorder. [Caviness and colleagues \(1999\)](#) reviewed the record linkage system for Olmsted County at the Mayo Clinic, Rochester, Minnesota for the years 1976 to 1990 and found an average annual incidence of myoclonus of 1.3 cases per 100,000, and a prevalence in 1990 of 8.6 cases per 100,000.

Classification of myoclonus

Myoclonus can be classified on the basis of its clinical characteristics, its pathophysiologic features, or its cause ([Table 18.1](#)) ([Marsden et al., 1982, 1987](#); [Fahn, 2002](#)). In this chapter, after introductory material, most of the entities will be discussed under a clinical classification.

Clinical features

The whole body or most of it may be affected in a single jerk (generalized myoclonus) and with prominent involvement of the trunk could be called “axial” myoclonus. Many different parts of the body may be affected, not necessarily at the same time (multifocal myoclonus); or myoclonus may be confined to one particular region of the body (focal or segmental myoclonus) ([Video 18.1](#)). Myoclonic jerks may occur repetitively and rhythmically or irregularly. They may be evident at rest, on maintaining a posture, or on movement (action myoclonus). Jerks may be triggered by external stimuli (reflex myoclonus), which can be visual, auditory, or somesthetic (touch, pin-prick, muscle stretch) ([Video 18.2](#)). ▶

Video 18.1 Examples of different types of myoclonus. (A) This patient presented with just some focal twitching of the left hand; present at rest, it was increased with movement. Subsequently, dementia developed, and a brain biopsy proved Alzheimer disease. (B) The second segment from this same patient taken 2 years later shows worsening of the myoclonus and difficulty in moving the arm. (C) The next patient has a multifocal myoclonus from an unknown encephalopathy. She has myoclonus at rest, but it is brought out with kinetic movement. She also has sensory evoked myoclonus that is triggered by quick stretches to the finger flexors.

Video 18.2 Examples of negative myoclonus. (A) This patient has Lafora body disease and demonstrates negative myoclonus, also called asterixis. (B) The second patient has negative myoclonus triggered by sensory stimuli. (A, Courtesy Hiroshi Shibasaki, MD.)

Table 18.1 Classification schemes for myoclonus

Clinical	Pathophysiology	Etiology
Spontaneous	Cortical	Physiologic
Action	Focal	Essential
Reflex	Multifocal	Myoclonus of epilepsy
Focal	Generalized	Symptomatic
Axial	Epilepsia partialis continua	Storage diseases
Multifocal		Cerebellar degenerations
Generalized	Thalamic	Basal ganglia degenerations
Irregular	Brainstem	Dementias
Repetitive	Reticular	Viral encephalopathies
Rhythmical	Startle	Metabolic encephalopathies
	Palatal	Toxic encephalopathies
	Spinal	Hypoxia
	Segmental	Focal damage
	Propriospinal	
	Peripheral	
	Essential	

Pathophysiology

The clinical features of myoclonus and the results of electrophysiologic investigation allow a relatively precise prediction as to its site of origin in the nervous system (Shibasaki and Hallett, 2005; Hallett and Shibasaki, 2008; Toro and Hallett, 2012). On this basis, myoclonus may be shown to arise in the cerebral cortex (cortical myoclonus), in the brainstem (brainstem myoclonus), or in the spinal cord (spinal myoclonus). Rarely, lesions of spinal roots, nerve plexi, or peripheral nerves can cause myoclonus (peripheral myoclonus) (Hudson et al., 2013), although purists might say that true myoclonus arises only from the central nervous system. Hemifacial spasm, the result most often of neurovascular compression of the seventh cranial nerve, might be considered a form of peripheral myoclonus. Disorders arising from peripheral injury are discussed in more detail in Chapter 26.

Cortical myoclonus, in which the abnormal activity originates in the sensorimotor cortex and is transmitted down the spinal cord in pyramidal pathways, may manifest as focal jerks, sometimes repetitive (epilepsia partialis continua), that can propagate into focal motor seizures, with or without secondary generalization (Hallett et al., 1979). Rapid rhythmic myoclonus can present as “cortical tremor” (Latorre et al., 2020).

Myoclonus arising in the *brainstem* may take different forms (Hallett, 2002). One employs the pathways responsible for the startle reflex, causing exaggerated startle syndromes and the hyperekplexias. Another is independent of startle mechanisms, but causes generalized muscle jerks (brainstem reticular myoclonus). A third is the palatal myoclonus (tremor) syndrome.

In the *spinal cord*, two forms of myoclonus are recognized; spinal segmental myoclonus affects a restricted body part, involving a few spinal segments, and propriospinal myoclonus produces generalized axial jerks, usually beginning in the abdominal muscles.

Neurophysiologic assessment

Polymyography (recording the duration, distribution, and stimulus sensitivity of electromyographic [EMG] activity in affected muscles) is the first step in assessing a patient with

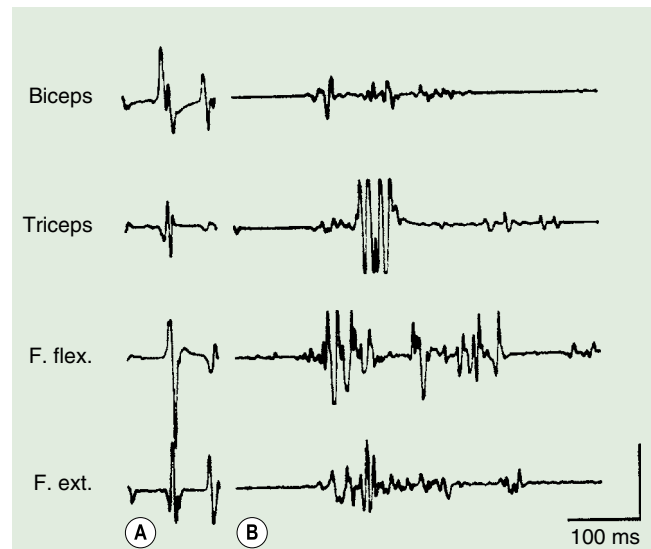


Fig. 18.1 Electromyogram (EMG) patterns underlying two types of myoclonus. (A) From a patient with posthypoxic myoclonus. (B) From a patient with a type of essential myoclonus (ballistic movement overflow myoclonus). The time scale is the same for both; vertical calibration is 1 mV for A and 0.5 mV for B. In A, the EMG burst is very short and synchronous in antagonist muscles, and in B, the EMG bursts are longer and asynchronous. (From Chadwick D, Hallett M, Harris R, et al. Clinical, biochemical, and physiological features distinguishing myoclonus responsive to 5-hydroxytryptophan, tryptophan with a monoamine oxidase inhibitor, and clonazepam. *Brain*. 1977;100[3]:455–487, with permission.)

myoclonus (Shibasaki and Hallett, 2005; Hallett and Shibasaki, 2008; Toro and Hallett, 2012; Merchant et al., 2020). Most myoclonic jerks are due to brief EMG bursts of 10 to 50 ms. In this circumstance, the origin must be a brief discharge of a cluster of neurons controlling the motor system, such as in primary motor cortex. The underlying physiology is likely to be a paroxysmal depolarizing shift (PDS), and, thus, is a “fragment of epilepsy.” Therefore, this type of myoclonus can be called *epileptic myoclonus*. EMG bursts in the 100-ms range are observed in select situations such as spinal myoclonus. Longer jerks of more than 100 ms are likely to be dystonic or functional (psychogenic), though occasionally these have been shown to be organic. In myoclonus, agonists and antagonists usually fire synchronously (Fig. 18.1).

The distribution of muscles involved may suggest that it arises as a result of a lesion of a peripheral nerve, part of a plexus, a spinal root, or a restricted number of segments of the spinal cord (*segmental myoclonus*). Myoclonic muscle jerks affecting axial muscles (neck, shoulders, trunk, and hips) may arise in the brainstem as an exaggerated startle response or brainstem reticular myoclonus, or in the spinal cord. In *brainstem myoclonus*, there is no preceding cortical discharge. Cranial nerve muscles are usually activated from the XI nucleus up the brainstem; limb and axial muscles are activated in descending order. In *propriospinal myoclonus*, the first muscles activated are usually in the thoracic cord, with slow upward and downward spread. *Cortical myoclonus* is indicated when somatosensory evoked potentials produced by peripheral nerve stimulation are pathologically enlarged, and a cortical correlate can be back-averaged in the ongoing electroencephalogram (EEG) by triggering from the EMG of the muscle jerk (Hallett and Shibasaki, 2008; Toro and Hallett, 2012). Stimuli generating giant somatosensory evoked potentials often

provoke a subsequent EMG burst of myoclonic activity (the C reflex) at a latency compatible with conduction through fast corticomotoneuron pathways from the motor cortex to muscle. The giant somatosensory evoked potentials usually consist of an enlarged P₂₅/N₃₃ component; the first major cortical negative peak (N₂₀), reflecting arrival of the sensory volley in the cortex, usually is of normal size. The motor volleys in cortical myoclonus activate the cranial and limb musculature in descending order via fast-conducting corticospinal pathways. Abnormal corticomuscular and intermuscular coupling also can be a sensitive physiologic feature in cortical myoclonus (Grosse et al., 2003). The increased cortical excitability in cortical myoclonus may well be due to loss of inhibitory interneurons (Hanajima et al., 2008). Cortical reflex myoclonus usually consists of positive EMG discharges, but negative cortical reflex myoclonus also occurs (Shibasaki, 1995; Toro et al., 1995; Tassinari et al., 1998), where a giant somatosensory cortical potential is time-locked to EMG silence. *Subcortical myoclonus* is suggested when reflex myoclonus triggered by peripheral stimuli occurs after a latency that is too short to involve cortical pathways (Thompson et al., 1994; Cantello et al., 1997).

Functional (psychogenic) myoclonus is suggested if stimulus-evoked jerks are of very variable latency and longer than a voluntary reaction time (Thompson et al., 1992; Brown, 2006; Hallett, 2010), and when the Bereitschaftspotential is evident before EMG bursts on jerk-locked back-averaging of the EEG, as in voluntary movement (Terada et al., 1995; Hallett, 2010). Event-related desynchronization study, in addition to the Bereitschaftspotential, may increase the sensitivity (Beudel et al., 2018). Psychogenic myoclonus can affect any part of the body (Monday and Jankovic, 1993). Findings that helped to establish the functional nature of the myoclonus are improvement with distraction or placebo, complexity of the movement rather than a simple jerk, prolonged latency to sensory induced jerks, and the presence of other psychogenic features such as incongruous sensory loss or false weakness. The general approach to functional disorders is reviewed in Chapter 27.

Zutt and colleagues (2018) carried out a large study to evaluate the utility of electrophysiologic testing in myoclonus. There were 72 patients with a variety of types of myoclonus and the physiologic assessment aided in establishing the diagnosis in about half the patients. Elsewhere the authors point out that, in their experience with referrals to the clinical neurophysiology laboratory, functional myoclonus is the most frequent followed next by cortical myoclonus (Zutt et al., 2017).

Cause

With regard to cause, many neurologic conditions may produce myoclonus and a classification has been published in a textbook of neurology (Table 18.2) (Marsden et al., 1982; Hallett et al., 1987; Fahn, 2002; Hallett and Shibasaki, 2008). It is, however, useful to consider several broad categories.

Physiologic myoclonus refers to muscle jerks occurring in specific circumstances in normal subjects. These include sleep jerks (hypnic jerks) and hiccup. Essential myoclonus consists of multifocal myoclonus in which there is no other neurologic deficit or abnormality on investigation. Although this has traditionally been a category, even from the time of Lundborg, most cases of essential myoclonus are now recognized

as dystonic myoclonus. Myoclonus of epilepsy refers to conditions in which the major clinical problem is one of epilepsy, but one of the manifestations of the epileptic attacks is myoclonic jerks. Symptomatic myoclonus refers to the many conditions in which generalized or multifocal muscle jerking is a manifestation of an underlying identifiable neurologic disease. Psychogenic (functional) myoclonus refers to myoclonus produced as a conversion symptom (Thompson et al., 1992; Monday and Jankovic, 1993; Czarnecki and Hallett, 2012).

In the survey by Caviness and colleagues (1999), symptomatic myoclonus was most common, followed by myoclonus of epilepsy and essential myoclonus. Dementing illnesses were the most common cause of symptomatic myoclonus. More modern epidemiology may offer different results because a retrospective study might miss myoclonus in patients with prominent epilepsy and because essential myoclonus is now only rarely considered. Finally, psychogenic myoclonus was not well recognized at the time of that study.

Making the diagnosis

It is convenient to consider myoclonus according to its clinical distribution, for this is how neurologists first assess the patient. Thus, we will first describe focal myoclonus restricted to one body part, for example, a limb or brainstem-innervated muscles. Then we will describe axial (neck, trunk, and proximal limb muscles) myoclonus, followed by generalized multifocal myoclonus. It is crucial to consider both the cause and pathophysiology in any patient. Treatment would be best if it could be directed to the cause. If this cannot be done, symptomatic treatment depends on the pathophysiology.

Algorithms for diagnosing myoclonus have been proposed from clinical to laboratory testing (Zutt et al., 2015).

Focal myoclonus

Jerking of one body part may arise anywhere from the peripheral nerve to the motor cortex (Table 18.3). With peripheral nerve lesions, the myoclonus may well arise because of secondary central nervous system changes (Shin et al., 2007). Another possibility is that there is a peripheral ectopic generator that triggers the myoclonus (Tyvaert et al., 2009), as has been strongly suggested for hemifacial spasm. Spontaneous rhythmic focal myoclonus is likely to be *epilepsia partialis continua* or *spinal segmental myoclonus*. Stimulus-sensitive myoclonus, particularly affecting the distal limbs, is most likely to arise in the cerebral cortex although it could also arise from the brainstem. Polymyography, somatosensory evoked potentials, and back-averaging from spontaneous jerks, as described earlier, are often valuable in trying to define the site of origin.

A variety of lesions of the peripheral nerve and spinal cord have been described as causing focal myoclonus (Jankovic and Pardo, 1986; Massimi et al., 2009; Lagueny et al., 2014). These include peripheral nerve tumors, trauma or radiation, and spinal cord trauma, tumor, vascular lesions, multiple sclerosis, and other inflammatory myelitis. Spinal segmental myoclonus characteristically is rhythmical (0.5–3 Hz), is confined to muscles innervated by a few spinal segments, and persists

Table 18.2 Etiologic classification of myoclonus

I. Physiologic myoclonus (normal subjects)	
A. Sleep jerks (hypnic jerks)	
B. Anxiety-induced	
C. Exercise-induced	
D. Hiccup (singultus)	
E. Benign infantile myoclonus with feeding	
II. Essential myoclonus (no known cause other than genetic and no other gross neurologic deficit)	
A. Hereditary (autosomal dominant and most are likely myoclonus dystonia)	
B. Sporadic	
III. Epileptic myoclonus (seizures dominate and no encephalopathy, at least initially)	
A. Fragments of epilepsy	
Isolated epileptic myoclonic jerks	
Photosensitive myoclonus	
Myoclonic absences in petit mal	
Epilepsia partialis continua	
B. Childhood myoclonic epilepsies	
Infantile spasms	
Myoclonic astatic epilepsy (Lennox–Gastaut)	
Cryptogenic myoclonus epilepsy (Aicardi)	
Juvenile myoclonus epilepsy of Janz	
C. Benign familial myoclonic epilepsy (Rabot)	
D. Progressive myoclonus epilepsy (Unverricht–Lundborg)	
IV. Symptomatic myoclonus (progressive or static encephalopathy dominates)	
A. Storage disease	
Lafora body disease	
Lipidoses (e.g., GM1 and GM2 gangliosidosis, Krabbe)	
Ceroid-lipofuscinosis (Batten)	
Sialidosis (“cherry-red spot”)	
B. Spinocerebellar degeneration	
Unverricht–Lundborg disease	
Ataxia telangiectasia	
Adult-onset cerebellar ataxias	
Some spinocerebellar ataxias (SCAs)	
Multiple system atrophy type C	
C. Basal ganglia degenerations	
Wilson disease	
Dystonia	
Pantothenate kinase–associated neurodegeneration	
Progressive supranuclear palsy	
Multiple system atrophy type P	
Huntington disease	
Corticobasal ganglionic degeneration	
Dentatorubro-pallidolusian atrophy	
Parkinson disease	
D. Dementias	
Creutzfeldt–Jakob disease	
Alzheimer disease	
E. Viral encephalopathies	
Subacute sclerosing panencephalitis (SSPE)	
Encephalitis lethargica	
Arbor virus encephalitis	
Herpes simplex encephalitis	
Postinfectious encephalitis	
Whipple disease	
AIDS	
SARS-CoV-2	
F. Autoimmune	
Opsoclonus–myoclonus syndrome	
Celiac disease	
G. Metabolic	
Hepatic failure	
Renal failure	
Dialysis syndrome	
Hyponatremia	
Hypoglycemia	
Infantile myoclonic encephalopathy	
Nonketotic hyperglycemia	
Mitochondrial encephalomyopathy	
Multiple carboxylase deficiency	
Biotin deficiency	
H. Toxic encephalopathies	
Bismuth	
Heavy-metal poisons	
Methyl bromide, DDT	
Drugs, including levodopa	
Serotonin syndrome (e.g., SSRIs)	
I. Physical encephalopathies	
Posthypoxic (Lance–Adams)	
Posttraumatic	
Heat stroke	
Electric shock	
Decompression injury	
J. Focal central nervous system damage	
Poststroke	
Postthalamotomy	
Tumor	
Trauma	
Dentato-olivary lesions (palatal myoclonus/tremor)	
K. Functional	

during sleep (Fig. 18.2) (Video 18.3). Spinal segmental myoclonus appears to be due to loss of inhibitory interneurons in the posterior horns, which may be demonstrated physiologically (Di Lazzaro et al., 1996). As a result, there is spontaneous bursting of groups of anterior horn cells. Usually it is not stimulus-sensitive, but it can be (Davis et al., 1981). Clonazepam is most likely to help. One case was responsive to topiramate (Siniscalchi et al., 2004), and intrathecal baclofen also has been used (Chiodo and Saval, 2012). In one case resulting from a discogenic cervical myelopathy, surgery was curative (Christodoulides et al., 2018). ▶

Palatal myoclonus (alternatively referred to as palatal tremor) describes the syndrome of rhythmical palatal movements at about 1.5 to 3 Hz, sometimes synchronously affecting the eyes, face, tongue, and larynx, and even the head,

trunk, intercostal muscles, and diaphragm (Deuschl et al., 1990; Deuschl, Toro, and Hallett, 1994; Deuschl, Toro, Valls-Sole et al., 1994; Bhattacharjee, 2020). The movements usually are bilateral and symmetrical, and, in some circumstances, persist during sleep. There are two forms, essential palatal myoclonus and symptomatic palatal myoclonus (Table 18.4) and (Video 18.4). The main symptom caused by these movements, seen only in the essential form, is clicking in the ear resulting from rhythmic contractions of tensor veli palatini which opens the eustachian tube. The tensor veli palatini is innervated by the trigeminal nerve. ▶

In many cases, a focal brainstem lesion can be identified (symptomatic palatal myoclonus/tremor), usually a stroke, encephalitis, multiple sclerosis, tumor, trauma, or degenerative disease (Table 18.5). Often the palatal myoclonus

Video 18.3 Spinal myoclonus. The spinal myoclonus in this patient is of unknown cause. Note the rhythmical jerking of the right shoulder area that is continuous, day and night. (Courtesy Hiroshi Shibasaki, MD.)

Video 18.4 Different types of palatal myoclonus (palatal tremor).

(A) This first example is of symptomatic palatal myoclonus resulting from contractions of the levator palatini muscle. Note that the back edge of the palate moves but the roof does not. (B) This second example is from another patient with symptomatic palatal myoclonus. In these patients, there is virtually always involvement of the seventh cranial nerve, here seen with a twitch at the corner of the mouth. (C) The third patient has essential palatal myoclonus as a result of contractions of the tensor veli palatini muscle. Note the involvement of the roof of the palate. (A and C, From Deuschl G, Toro C, Hallett M. Symptomatic and essential palatal tremor. Part II. Differences of palatal movements. *Mov Disord.* 1994;9:676–678, with permission.)

appears some months after the acute lesion. Such patients will have symptoms appropriate to the brainstem damage and to the underlying cause, in addition to the palatal myoclonus. They also may have pendular vertical nystagmus (ocular myoclonus) and facial, intercostal, and diaphragmatic jerks in synchrony with the palatal myoclonus. There can be a myorhythmia of the limbs associated as well (Panades-de Oliveira et al., 2018). The pathologic processes

in symptomatic palatal myoclonus damages the dentato-olivary pathway, often in the brainstem central tegmental tract (Fig. 18.3); the resulting denervation of the inferior olive leads to hypertrophy (Fig. 18.4), which can be seen on brain magnetic resonance imaging (MRI) (Deuschl, Toro, and Hallett, 1994). In this situation, the palatal movement is due to contractions of the levator veli palatini (innervated by the nucleus ambiguus). Only rarely can the ear clicking be caused by spontaneous contractions of the levator veli palatini (Jamieson et al., 1996).

In other cases, no cause is evident (essential palatal myoclonus/tremor) (Zadikoff, 2006). The complaint of these patients is the clicking, the eye and other structures are not involved, and there are no other symptoms or signs. These patients tend to be younger and do not appear to develop other diseases. Clonazepam, anticholinergics, carbamazepine, or sumatriptan may help some patients with palatal myoclonus (Sakai and Murakami, 1981; Jabbari et al., 1987; Scott et al., 1996), but not in patients with symptomatic palatal myoclonus. Ear clicking can be relieved by injection of botulinum toxin into the appropriate muscles (Deuschl et al., 1991; Jamieson et al., 1996; Sinclair et al., 2014; Ozdogan et al., 2015). Ear clicking occasionally may be due to simple partial seizures (Ebner and Noachtar, 1995). Some, or even most, of these patients may have a functional cause (Pirio Richardson et al., 2006; Stamelou et al., 2012; Vial et al., 2020).

Middle ear myoclonus is a disorder, perhaps similar to palatal myoclonus, where crackling noises in the ear are ascribed to periodic movement of the stapedius or tensor tympani muscle (Ellenstein et al., 2013; Park et al., 2013). Some of these patients also are likely to have a psychogenic cause (Ellenstein et al., 2013).

Cortical myoclonus produces spontaneous muscle jerks (spontaneous cortical myoclonus), jerks triggered by external stimuli (cortical reflex myoclonus), or jerks on movement (cortical action myoclonus) (Hallett et al., 1979; Obeso et al., 1985). Such patients have neurophysiologic evidence of an

Table 18.3 Causes of focal myoclonus

Category	Source	Cause
Peripheral lesions	Peripheral nerve Plexus Nerve roots	Trauma Tumor Electrical injury Surgery Hemifacial spasm
Spinal lesions	(1) Spinal segmental myoclonus (2) Propriospinal myoclonus	Trauma Inflammation Infection Demyelination Tumor Arteriovenous malformation Ischemic myelopathy Spondylitic myelopathy Spinal anesthesia Idiopathic Trauma Tumor Idiopathic
Brainstem lesions	Palatal myoclonus	See Table 18.5
Cortical lesions	Sensorimotor cortex	See Table 18.6
Idiopathic		

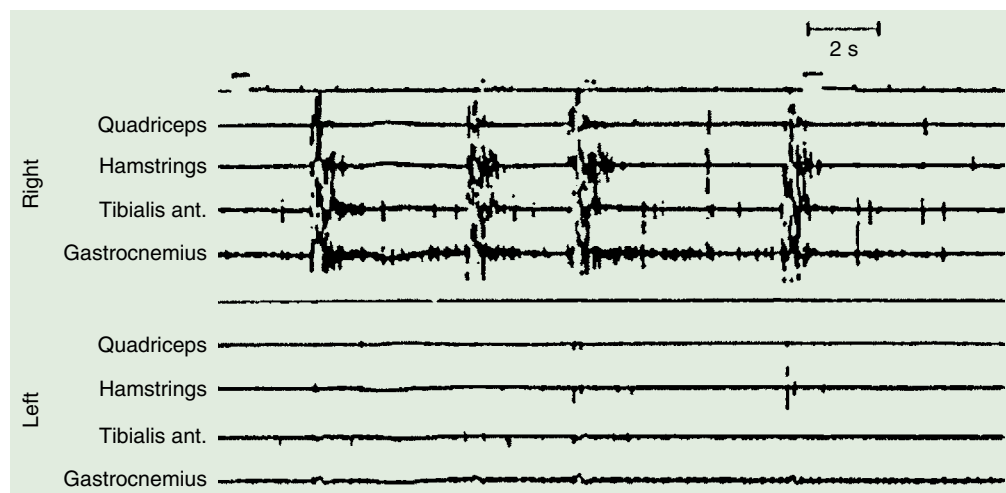


Fig. 18.2 Spinal segmental myoclonus. Myoclonic jerking of right leg: surface recording of electromyographic activity in both legs. This 75-year-old man developed involuntary jerking of the right leg 8 days before investigation. He had an abdominal aortic aneurysm and died 3 months later. Autopsy showed ischemic loss of interneurons in the thoracolumbar cord. (From Davis SM, Murray NM, Diengdoh JV, et al. Stimulus-sensitive spinal myoclonus. *J Neurol Neurosurg Psychiatry*. 1981;44[10]:884–888, with permission.)

Table 18.4 Differences between essential and symptomatic palatal myoclonus**Essential palatal myoclonus**

Ear click

Tensor veli palatini muscle (CN5): Elevates the roof of the soft palate and opens eustachian tube

Stops during sleep

Hypertrophy of the inferior olive is *not* found**Symptomatic palatal myoclonus**

Levator veli palatini muscle (CN7 or CN9): Lifts and pulls back the soft palate

May be accompanied by synchronous activity of adjacent muscles

Continues during sleep

Exerts remote effect on limb muscles

Associated with ipsilateral cerebellar dysfunction

Contralateral hypertrophy of inferior olive

Table 18.5 Causes of palatal myoclonus in 287 patients

Condition	Number
(A) Primary (essential) palatal myoclonus	77
(B) Secondary (symptomatic) palatal myoclonus	210
1. Vascular disease	115
2. Trauma	23
3. Tumor (brainstem)	19
4. Multiple sclerosis	9
5. Degenerations	7
6. Encephalitis	5
7. Other (e.g., arteriovenous malformation, herpes zoster)	32

From Deuschl G, Mischke G, Schenck E, Schulte-Monting J, Lücking CH. Symptomatic and essential rhythmic palatal myoclonus. *Brain*. 1990;113(Pt 6):1645–1672.

abnormal discharge in the sensorimotor cortex generating the myoclonic jerks via fast conducting corticomotoneuron pathways (Figs. 18.5 and 18.6). Myoclonus arising in the cerebral cortex can be focal, affecting one body part such as a hand or foot, but multiple cortical discharges can cause multifocal jerks, each jerk being due to a discrete discharge in one part of the motor cortex. In addition, cortical discharges can cause generalized muscle jerks, either by intracortical and transcallosal spread to activate both motor cortices (Brown, Day et al., 1991; Brown and Marsden, 1996; Brown et al., 1996), or by corticoreticular pathways activating brainstem myoclonic generators. Such multifocal and generalized cortical myoclonus is discussed later. Patients with focal cortical myoclonus also exhibit *epilepsia partialis continua* (Juul-Jensen and Denny-Brown, 1966), partial motor seizures, and secondary generalization with tonic-clonic grand mal seizures (Cowan et al., 1986) (Fig. 18.7). Focal slow-frequency repetitive transcranial magnetic stimulation has suppressed focal cortical myoclonus in a patient with cortical dysplasia (Rossi et al., 2004).

Epilepsia partialis continua is defined clinically as a syndrome of continuous focal jerking of a body part, usually localized to a distal limb, occurring over hours, days, or even years, as a result of a cerebral cortical abnormality

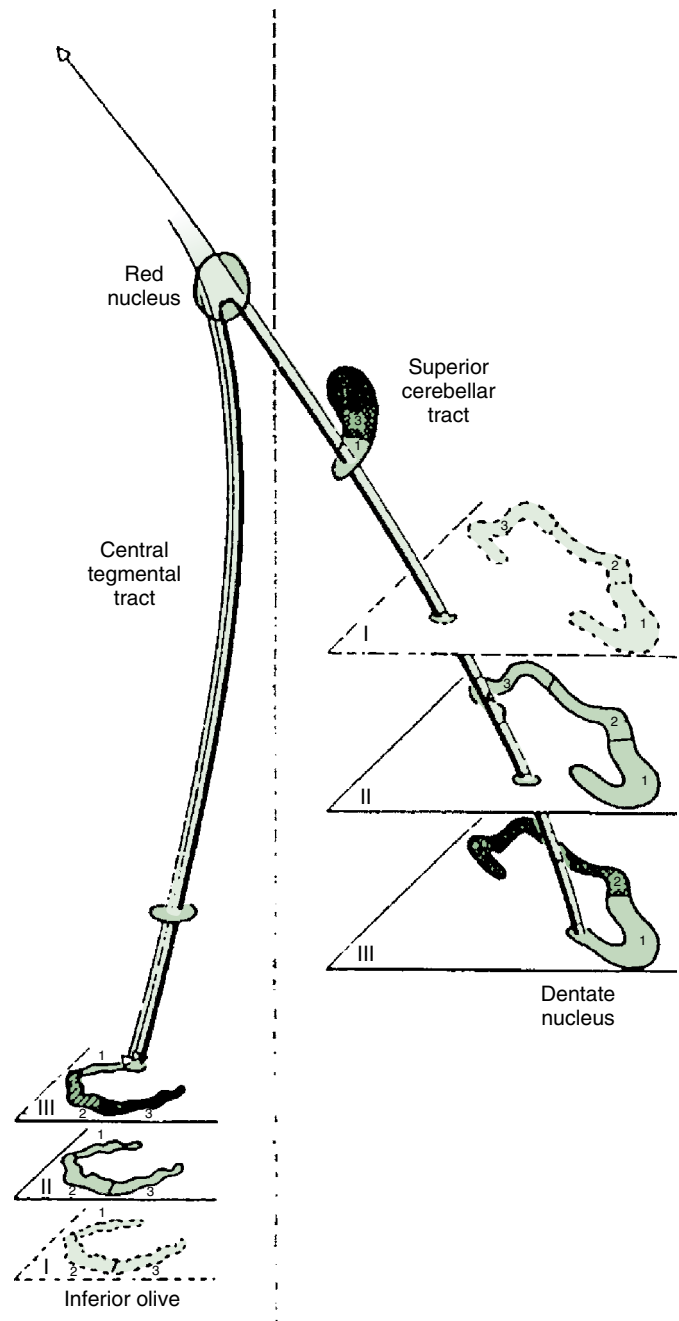


Fig. 18.3 Palatal myoclonus. Dentato-olivary somatotopic relationships in humans are crossed in both horizontal and vertical planes; somatotopic relationships between the dentate nucleus and homolateral superior cerebellar peduncle are direct. The dentato-olivary pathway (continuous dark line) passes from the dentate nucleus through the superior cerebellar peduncle and joins the contralateral central tegmental tract on its way to the inferior olive; in the red nucleus region, this pathway (broken line) passes by the internal and dorsal surfaces of this structure. (Modified from Lapresle J. Palatal myoclonus. *Adv Neurol*. 1986;43:265–273, with permission.)

(Cockerell et al., 1996) (Fig. 18.8). The most common causes are Rasmussen encephalitis and cerebrovascular disease. Most, but not all, patients have epileptic or other EEG abnormalities, and over half have identifiable cortical lesions on brain MRI. A similar clinical picture can occur with subcortical lesions, in which case it was suggested that the term “myoclonia continua” be employed (Cockerell

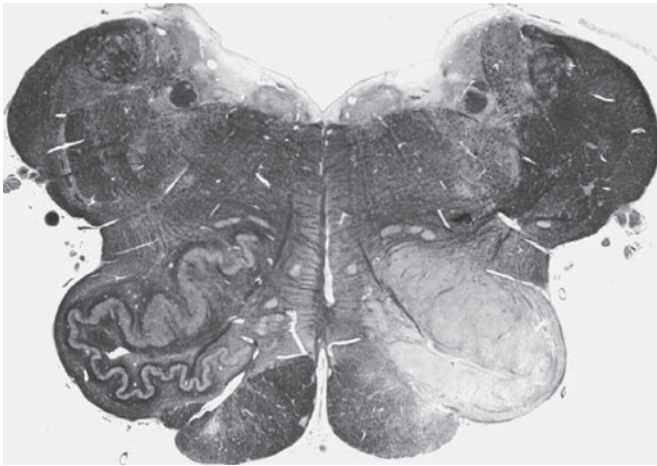


Fig. 18.4 Unilateral hypertrophy of the inferior olive in a patient with unilateral symptomatic palatal myoclonus. (From Deuschl G, Toro C, Valls-Solé J, et al. Symptomatic and essential palatal tremor. Part I. Clinical, physiological, and MRI analysis. *Brain*. 1994;117:775–788, with permission.)

et al., 1996), but this is not commonly used. Cortical myoclonus sometimes is so rhythmical as to produce a tremor (Ikeda et al., 1990; Toro and Hallett, 2004) (Video 18.5). Cortical tremor can be a genetic disorder (Regragui et al., 2006; Coppola et al., 2011). A focal cortical lesion produces focal myoclonus in the contralateral appropriate body part. Such lesions include those caused by vascular disease, tumor, granulomas, and focal encephalitis (Table 18.6) (Thomas et al., 1977; Cockerell et al., 1996). ▶

Chronic, prolonged focal myoclonic jerking in children suggests the possibility of Rasmussen encephalitis. Rasmussen encephalitis is a disorder of childhood and adolescence in which a unilateral focal seizure disorder is accompanied by a progressive hemiplegia resulting from focal cortical inflammation and destruction (Hart, 2004; Bien et al., 2005; Freeman, 2005). The seizures are severe, often with epilepsy partialis continua, partial motor seizures, and secondary generalization. The EEG may show focal epileptiform activity, or periodic lateralized discharges (PLEDs), or both. In addition to the progressive hemiplegia, there often is cognitive decline. The cause appears to be due to an autoimmune process, but the exact mechanism is not clear (Armangué et al., 2012). Immunotherapy (corticosteroids, plasmapheresis, or intravenous human immunoglobulin [IVIG]) may help some, but hemispherectomy may be necessary.

Axial myoclonus

Typically, axial myoclonus consists of neck and trunk flexion with abduction of the arms and flexion of the hips.

Axial myoclonic jerks may arise in the spinal cord or brainstem. Propriospinal myoclonus was named because of presumed involvement of long propriospinal fibers in the spinal cord distributed to axial muscles (Brown, Thompson, Rothwell et al., 1991) (Fig. 18.9). The most prominent movement of propriospinal myoclonus is truncal flexion, and it can be either spontaneous or stimulus induced (Video 18.6). A review of 60 patients noted a middle-aged male predominance (Roze et al., 2009). The myoclonus

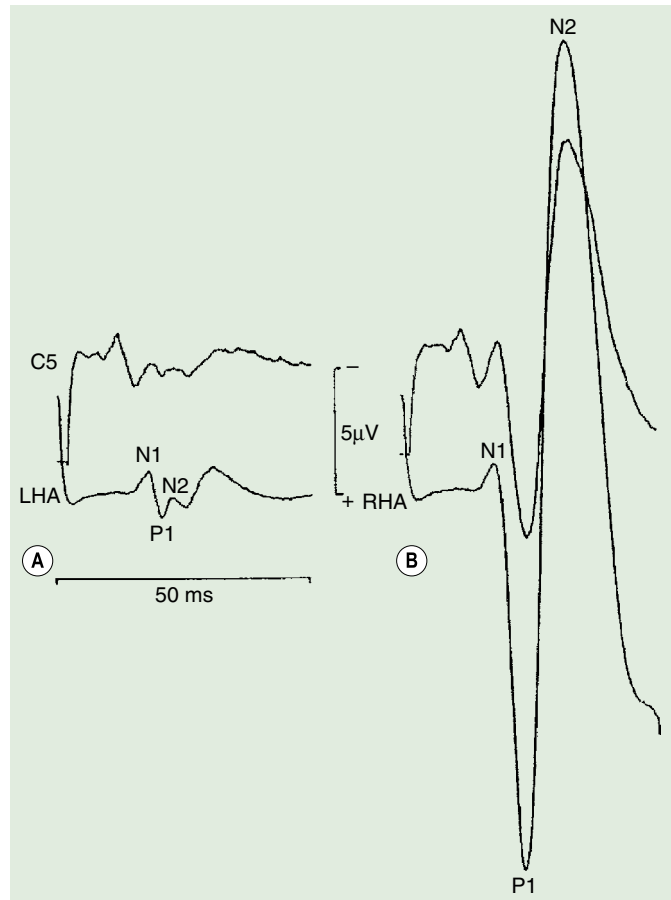


Fig. 18.5 Focal cortical myoclonus. Details of short-latency components of somatosensory evoked potentials in cervical (C5; top traces) and cortical hand area of the left and right hand (LHA, RHA; bottom traces) after electrical stimulation of the index finger of the left (A) and right (B) hand. The patient, a 34-year-old woman, had an undiagnosed left hemisphere lesion. For some 6 years she had experienced rare grand mal seizures but continuous flexor jerking of the right hand and forearm while awake. These jerks occurred spontaneously, on action, or in response to touch of the fingers or a tap with a tendon hammer. On examination, apart from the focal myoclonus of the right hand, there were no other neurologic signs. Brain imaging was normal, as was a carotid arteriogram and cerebrospinal fluid examination. Routine electroencephalogram showed a focal abnormality over the region of the left sensorimotor area, with spike-sharp-wave discharges. The early cervical potentials, with a peak latency of 13 ms, and the first major cortical response (N1), with a latency of 20 ms, are the same size on both sides. The later components are much enlarged after right hand stimulation (B). Traces are the average of 999 sweeps, with the stimulation given at the beginning of the sweep. Electrodes referred to a reference at Fz. The apparent large late responses recorded at the cervical electrode in B are due to activity at the Fz reference. (From Rothwell JC, Obeso JA, Marsden CD. Electrophysiology of somatosensory reflex myoclonus. *Adv Neurol*. 1986;43:385–398, with permission.)

tended to be worse when lying down and at wake-sleep transitions (Antelmi and Provini, 2015). A premonitory sensation might be present before the jerks. The cause of many of these cases is not clear, although injury to the spinal cord from trauma, infection, tumor, and disk herniation has been described (Capelle et al., 2005; Shprecher et al., 2010; Jang et al., 2012). Diffusion tensor imaging with fiber tracking of the spinal cord was said to reveal abnormalities (Roze et al., 2009), but some of these findings might be artifactual. The EMG pattern of propriospinal myoclonus

Video 18.5 Cortical tremor. This patient has a rhythmic myoclonus on action that has an appearance similar to essential tremor. That it is cortical myoclonus is proven by physiologic recordings.

Video 18.6 Examples of propriospinal myoclonus. (A) Propriospinal myoclonus is characterized by occasional flexions of the trunk. They can be spontaneous or induced by sensory stimuli. (B) In the second patient, the myoclonus is induced by tapping on the knee. (A and B, From Brown P, Thompson PD, Rothwell JC, et al. Paroxysmal axial spasms of spinal origin. *Mov Disord.* 1991;6:43-48, with permission.)

can be mimicked voluntarily, indicating that psychogenic myoclonus should be in the differential diagnosis in these cases (Kang and Sohn, 2006), and such cases have now been reported (Williams et al., 2008; Slawek et al., 2010). Indeed, in a series of 35 patients referred with axial jerks, 34 of them were considered to be psychogenic (van der Salm et al., 2010). In another series of 65 patients, 86%

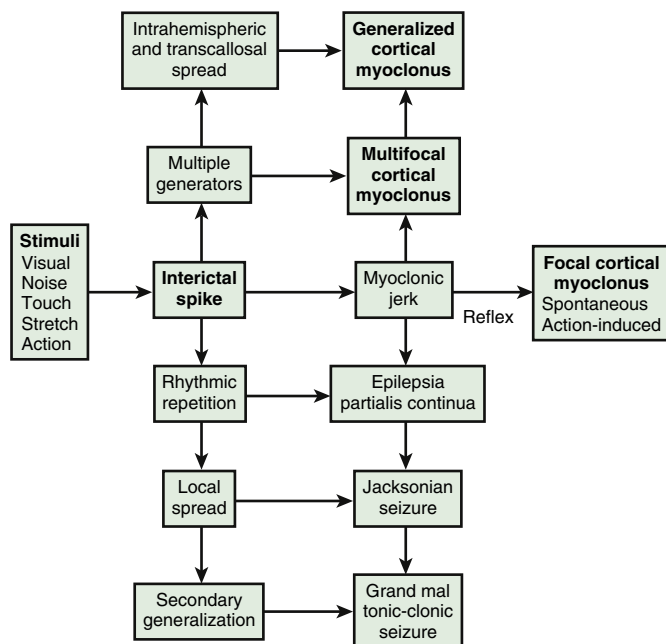


Fig. 18.7 Cortical myoclonus. The various manifestations of spike discharges in the motor cortex and their interrelationships are depicted. The physiologic correlate of the focal cortical myoclonic jerk is a cortical positive wave (an interictal spike) that represents a volley of pyramidal cell discharge in motor cortex. This can occur spontaneously, on voluntary movement, or in response to stimuli. Multiple spikes can cause multifocal myoclonus. The cortical discharge can also spread throughout the motor strip and, via the corpus callosum, to the opposite motor cortex to cause multifocal or generalized cortical myoclonus. If the spike discharge occurs repetitively, the result is epilepsy partialis continua. If it propagates locally it may cause a simple Jacksonian motor seizure, or if it becomes secondarily generalized, a tonic-clonic grand mal seizure occurs.

had a Bereitschaftspotential preceding the jerk, implying a psychogenic origin (Erro et al., 2013). Esposito and colleagues (2014) have reviewed the literature on apparent symptomatic cases and concluded that even these might well be mostly psychogenic. Thus, it may well be that the most frequent cause of this clinical syndrome is psychogenic, but that does not mean that there are not rare bona fide cases (Brown, 2014). A literature review concluded that 58% were psychogenic (van der Salm et al., 2014). The differential diagnosis can be tricky (Antelmi and Provini, 2015), and clearly more work is needed in this area. The most effective drug for treatment has been clonazepam (Roze et al., 2009).

Brainstem reticular myoclonus (Table 18.7 and Fig. 18.10) may follow cerebral anoxia, and probably is responsible for the generalized muscle jerks that occur in a number of toxic myoclonic syndromes, as, for example, in uremia (Chadwick and French, 1979) and other metabolic disturbances and those precipitated by drugs. It is characterized by a generalized axial myoclonic jerk that starts in muscles innervated by the lower brainstem, then spreading up the brainstem and down the spinal cord (Hallett, Chadwick, Adam et al., 1977). There is no time-locked cortical correlate, and sensory evoked potentials are normal. Such brainstem reticular myoclonus may occur after cerebral anoxia and can be seen in some patients with the stiff-person syndrome (Leigh et al., 1980). Brainstem lesions, such as occur in multiple sclerosis, also may be responsible (Smith and Scheinberg, 1990).

Exaggerated startle syndromes (hyperekplexia) consist of an excessive motor response, or jump, to unexpected auditory and, sometimes, somesthetic and visual stimuli (Tables 18.7 and 18.8) (Suhren et al., 1966; Andermann and Andermann, 1988; Brown, Rothwell, Thompson et al., 1991; Matsumoto et al., 1992; Matsumoto and Hallett, 1994; Bakker et al., 2006). The jump consists of a blink, contortion of the face, flexion of the neck and trunk, and abduction and flexion of the arm (Fig. 18.11). Such patients jump in response to sound and crash to the ground, injuring themselves. There is no loss of consciousness. An exaggerated startle syndrome may be due to local brainstem pathologic conditions (anoxia, inflammatory lesions including

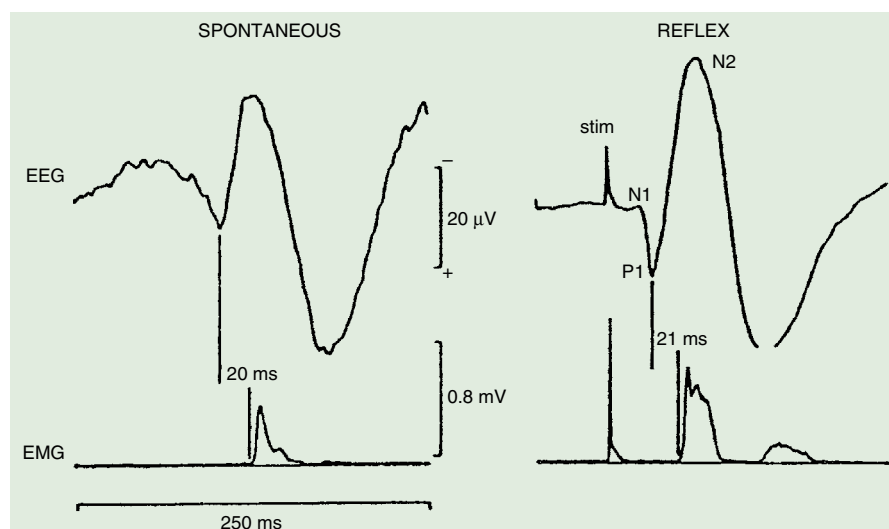


Fig. 18.6 Focal cortical myoclonus.

Average (of 128) electromyogram (EMG) and electroencephalogram (EEG) events associated with spontaneous (left traces) and reflex-evoked (right traces) cortical myoclonus in a patient with a focal dysplastic lesion of the right sensorimotor cortex. The EEG during spontaneous jerks was back-averaged from a trigger point on the rectified EMG record. Reflex jerks were elicited by giving electrical stimuli (stim) to the left forefinger, 50 ms after the start of the recording sweep. The time interval between the large P1 positive wave in the EEG and the start of the myoclonic EMG burst is indicated. EMGs taken from the left first dorsal interosseous; EEG records from the contralateral sensorimotor hand area, referred to a linked mastoid reference. (From Rothwell JC, Obeso JA, Marsden CD. On the significance of giant somatosensory evoked potentials in cortical myoclonus. *J Neurol Neurosurg Psychiatry*. 1984;47[1]:33–42, with permission.)

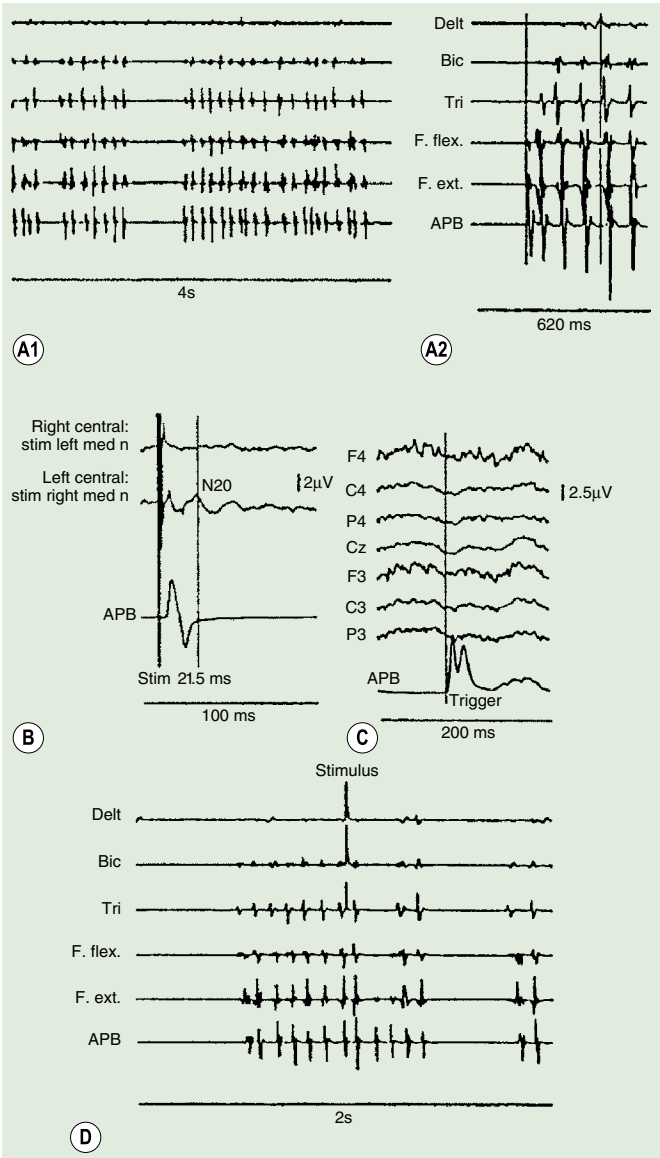


Fig. 18.8 Epilepsia partialis continua. (A1) Pattern of spontaneous jerking in the left arm of a case as a result of cerebral infarction. Hypersynchronous bursts of electromyography (EMG) activity occur at the same time in virtually all muscles of the arm (Delt, deltoid; Bic, biceps; Tri, triceps; F. flex., flexor muscles in the forearm; F. ext., extensor muscles in the forearm; APB, abductor pollicis brevis). The jerks occur in short runs with pauses of 0.5 second or so between each. (A2) Shows the start of a run of activity after one of these pauses. Note that the first jerk of the run occurs only in forearm and hand muscles; the second jerk involves most of the muscles of the left arm (B). Lack of enlarged somatosensory evoked potential (SEP) and reflex muscle jerk after stimulation of the left median nerve at the elbow. The top two traces are average (of 256 trials) Electroencephalogram (EEG) records from the right central (C4) and left central (C3) electrodes, referenced to linked earlobes. The bottom trace is the EMG from APB. The N20 component of the SEP is present and of normal size and latency. (C) Lack of any back-averaged EEG correlate preceding spontaneous jerks of the left APB muscle (rectified EMG record in bottom trace); 350 trials averaged. Linked earlobe reference. (D) Effect of a submotor threshold magnetic stimulus over the right motor cortex on an ongoing run of spontaneous jerking. The stimulus occurs at the time of the stimulus artifact. No short-latency muscle response is evident (on this time scale it would merge into the stimulus artifact). A spontaneous jerk of all arm muscles follows the stimulus, but then the upper arm muscles pause for the following two jerks. (From Cockerell OC, Rothwell J, Thompson PD, et al. *Clinical and physiological features of epilepsia partialis continua: Cases ascertained in the UK Brain*. 1996;119[Pt 2]:393–407, with permission.)

Table 18.6 Causes of focal cortical myoclonus and epilepsia partialis continua

Etiology	Number	
	Thomas et al. (1977)	Cockerell et al. (1996)
Infarct or cerebral hemorrhage	8	9
Tumor Astrocytoma Hemangioma Lymphoma Uncertain	5	4
Encephalitis (including Rasmussen encephalitis)	5	7
Trauma	2	1
Hepatic encephalopathy	2	—
Subarachnoid hemorrhage	1	—
Unknown	9	9
Total	32	30
Others		
Subdural hematoma		
Abscess		
Granuloma (tuberculosis)		
Multiple sclerosis		
Meningitis		
Nonketotic hyperglycemia		
Focal gliosis		
Spinocerebellar degeneration		
Mitochondrial disease		

sarcoidosis and multiple sclerosis, and hemorrhage) and also occurs as an inherited condition (hereditary hyperekplexia), usually transmitted as an autosomal dominant trait (Video 18.7). The first abnormal gene found for this disorder was a point mutation in the $\alpha 1$ subunit of the glycine-receptor (Shiang et al., 1993, 1995; Tijssen et al., 1995). This may lead to altered ligand binding or disturbance of the chloride ion-channel part of the receptor. Subsequently other mutations were found in the glycine receptor and glycine receptor complex (Davies et al., 2010). Additionally, responsible mutations are also found presynaptically in the glycine transporter 2 (Rees et al., 2006; Carta et al., 2012). Glycine is an inhibitory neurotransmitter in several spinal interneurons, including Renshaw cells, Ia inhibitory interneurons, and some Ib inhibitory interneurons. Physiologic studies suggest normal recurrent inhibition, but abnormal Ia reciprocal inhibition in hyperekplexia (Floeter et al., 1996). Affected babies are hypertonic and stiff when handled and have difficulty subsequently with walking. They develop excessive

Video 18.7 Hereditary hyperekplexia. This young girl is from a large family with hereditary hyperekplexia. Taps to the nose produce head retraction. Noises, such as a clap, induce a whole-body startle that does not habituate. She was well treated with clonazepam and only partially withdrew from medication for this taping.

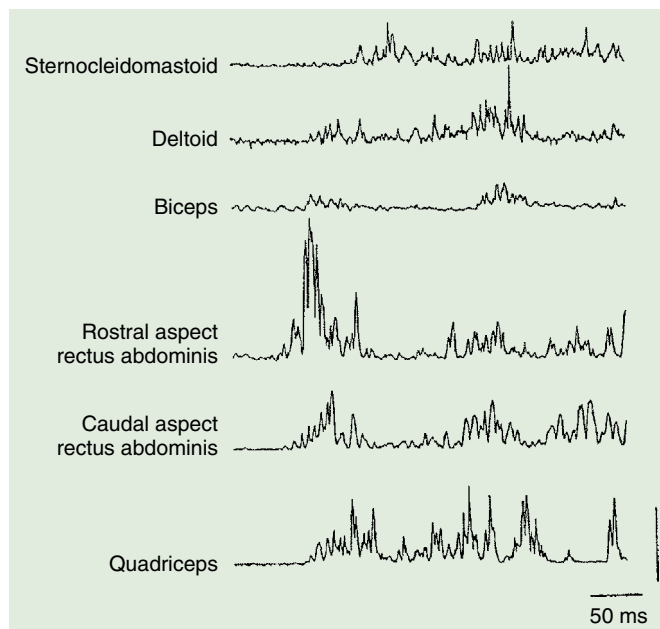


Fig. 18.9 Propriospinal myoclonus. Electromyogram (EMG) record of a single spontaneous jerk in a patient with propriospinal myoclonus. Muscles are sternocleidomastoid, deltoid, biceps, rostral aspect of rectus abdominis, caudal aspect of rectus abdominis, and quadriceps. EMG activity occurred first in rectus abdominis. Contraction of sternocleidomastoid, rectus abdominis, and quadriceps occurred in all jerks, but activity in deltoid and biceps (evident here) was variable. Vertical calibration line = 200 μ V and 100 μ V for bottom and top three channels, respectively. (From Brown P, Thompson PD, Rothwell JC, et al. Axial myoclonus of propriospinal origin. *Brain*. 1991;114:197–214, with permission.)

startle, which takes two forms: the minor form is a simple brief startle jerk, and the major form is a more prolonged tonic startle spasm. In these situations, the normal startle reflex is exaggerated, both in amplitude and in its failure to rapidly habituate (Brown, Rothwell, Thompson et al., 1991; Matsumoto et al., 1992; Matsumoto and Hallett, 1994). The afferent and efferent systems of the startle reflex in hyperreflexia are identical to those of the normal startle response, involving a similar or the same generator in the lower brainstem, probably in the medial bulbopontine reticular formation. However, there may be differences between the minor form and major forms of hyperreflexia. First, only the major

Table 18.7 Two types of brainstem reticular myoclonus

In both types, the myoclonus originates in the caudal brainstem, and muscles are activated up the brainstem and down the spinal cord. The myoclonus is generalized and mainly axial to cause neck flexion, shoulder elevation, and trunk and knee extension.

1. Exaggerated startle response

Bulbospinal pathways are slow conducting
Evoked by sudden noise or light, or by sensory stimuli to the mantle area
Spontaneous jerks not prominent

2. Reticular reflex myoclonus

Bulbospinal pathways are fast conducting
Stimulus sensitivity greatest over the limbs
Spontaneous jerks common

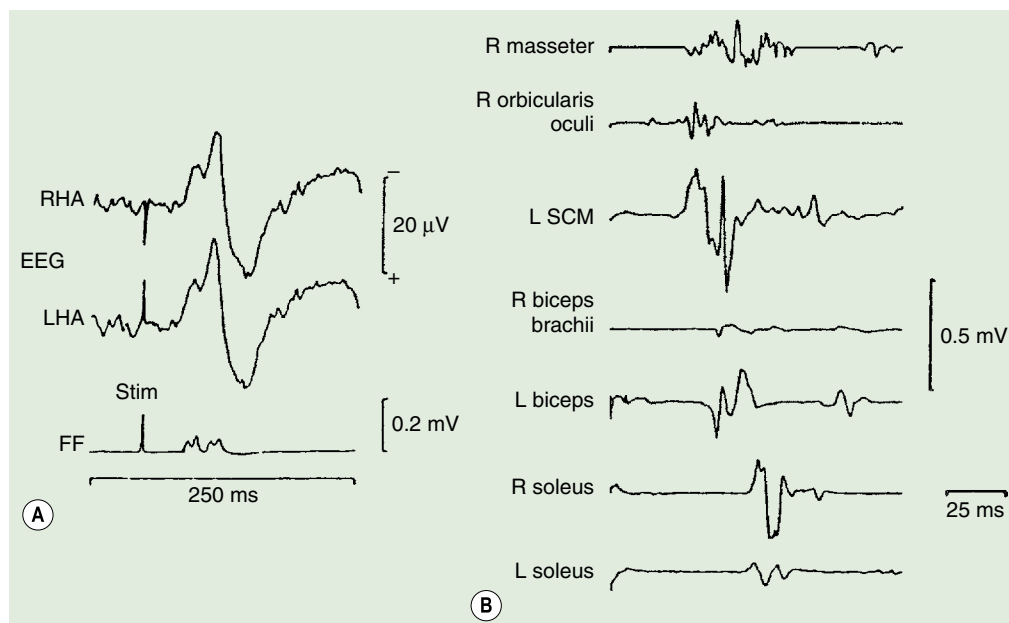


Fig. 18.10 Brainstem reticular myoclonus. (A) Average of 128 electroencephalographic (EEG) and electromyographic (EMG) responses to electrical stimulation (Stim) of the index finger of the right hand in a patient with reticular reflex myoclonus. EEG recorded monopolarly from over the sensorimotor hand area (RHA, right-hand area; LHA, left-hand area) referred to a linked mastoid reference. Rectified EMG from surface electrodes placed over the flexor carpi radialis (FF). No enlargement of the EEG response is evident preceding the myoclonic muscle jerk. The bilateral late response probably is produced by movement artifact from the generalized muscle jerk. (B) Order of muscle activation on a single generalized myoclonic jerk in the same patient, produced by a light tap with a tendon hammer to the forehead at the start of the sweep. The jerk begins in the sternocleidomastoid (SCM) and travels up the cranial nerves and down the spinal cord. This 41-year-old man developed increasing generalized muscle stiffness and jerks over a period of about 1 year. Eventually, he became bedridden with severe rigidity but remained alert and, according to his relatives, suitably responsive. On examination, although alert, he was severely dysarthric and he could not move voluntarily. His limbs were held in flexion and exhibited extreme rigidity. Tendon reflexes were brisk, and the plantar responses were flexor. Any stimulus, including visual menace, loud noise, light touch, or a tap with a tendon hammer, evoked massive generalized muscle jerking. All investigations failed to reveal a pathologic diagnosis, although clinically it was suspected that he had a diffuse encephalomyelitis. (From Rothwell JC, Obeso JA, Marsden CD. *Electrophysiology of somatosensory reflex myoclonus*. *Adv Neurol*. 1986;43:385–398, with permission.)

Table 18.8 Causes of the startle syndrome**A. Pathologic exaggeration of the normal startle reflex**

1. Hereditary hyperekplexia
2. Idiopathic hyperekplexia
3. Symptomatic startle syndromes

Static encephalopathies

- a. Static perinatal encephalopathy with tonic spasms
- b. Postanoxic encephalopathy
- c. Posttraumatic encephalopathy

Brainstem encephalitis

- a. Sarcoidosis
- b. Viral encephalomyelitis
- c. Encephalomyelitis with rigidity
- d. Multiple sclerosis
- e. Paraneoplastic

Structural

- a. Brainstem hemorrhage/infarct
- b. Cerebral abscess

B. Unknown physiology

1. Hexosaminidase A deficiency
2. Static perinatal encephalopathy with epileptic tonic spasms (startle epilepsy)
3. Gilles de la Tourette syndrome
4. Jumping Frenchmen, lath, and myriachit
5. Functional

From Brown P, Rothwell JC, Thompson PD, et al. The hyperekplexias and their relationship to the normal startle reflex. *Brain*. 1991;114:1903–1928.

form appears to be linked to the glycine receptor gene (Tijssen et al., 1995, 2002). Second, the physiologic abnormalities in the minor and major forms appear to differ (Tijssen et al., 1996, 1997). Treatment with clonazepam may be very effective in some patients (Matsumoto and Hallett, 1994). Others have responded to sodium valproate or piracetam. ▶

An exaggerated startle response is a component of the motor manifestations of “jumping Frenchmen” and other culturally determined startle syndromes such as lath (Andermann and Andermann, 1988; Brown, Rothwell, Thompson et al., 1991; Matsumoto and Hallett, 1994). In these syndromes the startle is followed by stereotyped behaviors such as a vocalization or striking out, and it is the exaggeration of these secondary behaviors that is the most important feature (Bakker et al., 2013) (Video 18.8). Hyperekplexia must be distinguished from startle-evoked epileptic seizures (Matsumoto and Hallett, 1994; Manford et al., 1996). ▶

Orthostatic myoclonus is a myoclonus of the legs when standing and is a source of unsteadiness. It is described in Chapter 19 in the discussion of gait and balance difficulties. Its nature is unknown, but it is not an uncommon presentation (Gasca-Salas et al., 2013; van Gerpen, 2014).

Multifocal and generalized cortical myoclonus

Multifocal myoclonus of cortical origin typically affects many parts of the body bilaterally, but not synchronously. Each myoclonic jerk involves only a few adjacent muscles. The movements of the fingers or toes may be small twitches

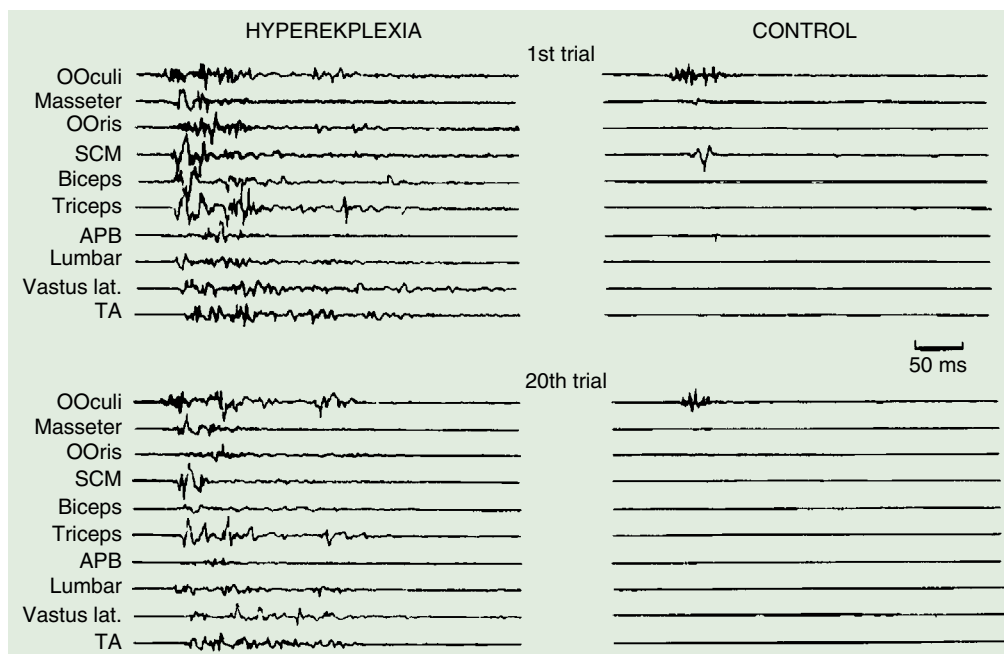


Fig. 18.11 Electromyogram (EMG) in hereditary hyperekplexia. Multichannel surface EMG recordings of startle responses in a 13-year-old girl with hereditary hyperekplexia compared with a normal subject. Top left: An initial 103-dB acoustic stimulus given at the time indicated by the arrow is followed by a generalized EMG startle response. Note the early activation of the orbicularis oculi (OOculi) followed by the sternocleidomastoid (SCM). Bottom left: The twentieth startle response after repetitive acoustic stimuli given at 1-minute intervals shows little habituation. The control subject's recordings on the right show a much more subdued response that reveals marked habituation at the twentieth trial. APB, Abductor pollicis brevis; TA, Tibialis anterior. (From Matsumoto J, Hallett M. Startle syndromes. In: Marsden CD, Fahn S, eds. *Movement Disorders 3*. Oxford: Butterworth-Heinemann; 1994, pp. 418–433, with permission.)

Video 18.8 Latah. This is a sequence of four patients with latah from a long videotape produced by Indiana University. In the first two segments, there are four people, of whom only one has latah. (From a videotape entitled "Latah," Producer, director, ethnographer: Ronald C. Simons. Distributor: Instructional Support Services, Indiana University, Bloomington, IN 47405, with permission.)

Table 18.9 Characteristics of major primary epileptic myoclonus syndromes**Cryptogenic myoclonic epilepsy**

1. Massive myoclonic jerks as the only or major seizure type
2. Bursts of bilateral irregular slow spike/wave at 2.5 Hz or more
3. Onset 6 months to 5 years
4. No signs of brain damage prior to seizures
5. Tonic-clonic seizures, but no tonic seizures
6. Relatively good prognosis

Eyelid myoclonus with absences

1. Photosensitive attacks
2. Marked eyelid jerking, with upward eye deviation, during absences
3. Irregular 3-Hz spike/wave in EEG

Infantile spasms

1. Flexor (extensor) spasms
2. Hypsarrhythmic EEG
3. Onset in first year of life
4. Many causes recognized
5. Learning disability

EEG, Electroencephalogram.

Juvenile myoclonic epilepsy (Janz)

1. Myoclonus, mainly in arms, especially in the morning
2. Spikes, polyspikes and slow waves in EEG
3. Onset around puberty
4. No signs of brain damage
5. Tonic-clonic seizures, especially at night. Absences in 10%
6. Very good response to sodium valproate

Absences in petit mal

1. Eyelid myoclonus, and more rarely massive myoclonic jerks, with absences
2. 3-Hz spike/wave in EEG

Lennox–Gastaut syndrome

1. Massive myoclonic jerks, tonic spasms and atonic attacks
2. Atypical slow (less than 2.5 Hz) spike/wave in EEG
3. Onset after infantile spasms, and other brain insults, around 2–8 years
4. Tonic-clonic and other seizures
5. Poor prognosis

(minipolymyoclonus) (Wilkins et al., 1985); those of more proximal and axial muscles cause bigger movements. Multifocal cortical myoclonus is due to a generalized excitability of the cerebral cortex, particularly of the sensorimotor cortex. The EEG may show multifocal spike discharges, and back-averaging reveals the typical cortical correlate to each focal myoclonic jerk. Somatosensory evoked potentials often are enlarged. The jerks are frequently stimulus-sensitive.

Many patients with multifocal cortical myoclonus also exhibit generalized myoclonic jerks, synchronous in many muscles at the same time. Some of these are of brainstem origin (brainstem reticular myoclonus), perhaps driven by a cortical origin. However, discharge in the sensorimotor cortex may produce a generalized jerk as a result of transcallosal and intracortical spread (Brown, Day, Rothwell et al., 1991).

Many conditions cause multifocal and generalized cortical myoclonus. These include myoclonus of epilepsy, in which epilepsy dominates and there is no progressive disease of the brain, progressive myoclonus epilepsy and progressive myoclonic ataxia, postanoxic myoclonus, viral encephalopathies, metabolic disease, and toxic encephalopathies (see Table 18.2).

Myoclonus of epilepsy

Myoclonus of epilepsy refers to those epilepsies characterized exclusively, or predominantly, by brief myoclonic, atonic, or tonic seizures. Such myoclonus can be positive (with active muscle contractions) or negative (lapses of postural tone) (Guerrini et al., 1993; Tassinari et al., 1995, 1998). Conditions subsumed under this category include infantile spasms, the Lennox–Gastaut syndrome, cryptogenic myoclonic epilepsy, the myoclonus associated with petit mal, and juvenile myoclonic epilepsy (JME) of adolescence (Janz). The key features of these various conditions are summarized in Table 18.9 (Aicardi, 1986; Shields, 2004; Nabbut and Dulac, 2008; Caraballo and Dalla Bernardina, 2013; Caraballo et al., 2013).

Of these conditions, JME is the most frequent epileptic syndrome manifesting with myoclonus, usually in adolescence

(Serafini et al., 2013). The main symptom is myoclonic jerks, usually without loss of consciousness, predominantly in the morning after awakening from sleep. Generalized tonic-clonic seizures also tend to occur in the morning. JME appears to be a complex genetic trait, and although a susceptibility gene has been identified, no single responsible gene is yet known (Pal and Greenberg, 2012; Thomas et al., 2013).

Progressive myoclonus epilepsy and progressive myoclonus ataxia

Progressive myoclonus epilepsy refers to a combination of severe myoclonus (spontaneous, action, and stimulus-sensitive), severe generalized tonic-clonic and other seizures,

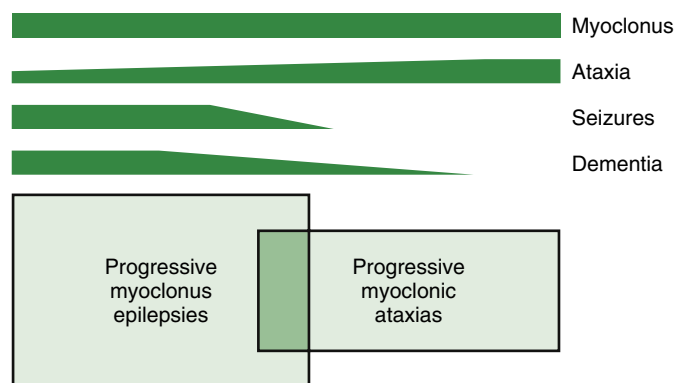


Fig. 18.12 Schematic representation of the clinical features and relationship of the syndromes of progressive myoclonic epilepsy (PME) and of progressive myoclonic ataxia (PMA). The bars in the upper part of the figure give a general indication of the prominence of the key clinical signs in the PME and PMA syndromes. Initial recognition of either syndrome then demands an attempt to reach a specific diagnosis. A specific diagnosis can now usually be made in patients with PME, whereas a larger proportion of cases with PMA remain undiagnosed. Previous authors have used the term Ramsay Hunt syndrome to describe different groups of patients within this spectrum. (From Marseille Consensus Group. *Classification of progressive myoclonus epilepsies and related disorders*. *Ann Neurol*. 1990;28(1):113–116, with permission.)

Table 18.10 Major causes of progressive myoclonus epilepsy

Condition	Age at onset (years)	Diagnostic features		
		Clinical	Laboratory	Diagnostic test
Unverricht–Lundborg disease	6–15	Severe myoclonus Dementia absent or mild	EEG	Clinical
Lafora body disease	11–18	Occipital seizures Dementia	EEG	Lafora bodies (skin, liver, brain)
Neuronal ceroid lipofuscinosis (Batten) Late-infantile (Jansky–Bielschowsky)	2.5–4 (dead by 6–10)	Severe seizures Rapid regression Macular degeneration	EEG ERG VER	EM of skin, muscle Rectum or brain
Juvenile (Spielmeyer–Vogt)	4–10 (dead by 15–25)	Visual failure Macular degeneration	Dolichols	
Adults (Kufs)	12–50 (long course)	Behavioral change Dementia		
Sialidosis				
Type I	8–20	Cherry-red spot	Storage in lymphocytes, etc.	Alpha-N-acetyl-neuraminidase
Type II	10–30	Cherry-red spot Dysmorphic	Urinary sialyl-oligosaccharides	
Mitochondrial encephalomyopathy (MERRF)	5–42	Short stature	Blood and CSF lactate	“Ragged-red” fibers on muscle biopsy Deafness DNA tests

EEG, electroencephalogram; EM, Electron microscopy; ERG, electroretinogram; VER, visual evoked responses; MERRF, myoclonus epilepsy and ragged-red fibers. Genetic testing is now available for many of these disorders

After Berkovic SF, Andermann F. The progressive myoclonic epilepsies. In: Pedley TA, Meldrum BS, editors. Recent Advances in Epilepsy 3. Edinburgh: Churchill Livingstone; 1986, pp. 157–187.

and progressive neurologic decline, particularly dementia and ataxia (Berkovic and Andermann, 1986; Berkovic et al., 1986, 1990; Zupanc and Legros, 2004; Shahwan et al., 2005; Ramachandran et al., 2009; Kalviainen, 2015; Malek et al., 2015). Progressive myoclonic ataxia (sometimes known as the Ramsay Hunt syndrome) (Marsden et al., 1990; van der Veen et al., 2018; Rossi et al., 2021) is distinguished from progressive myoclonus epilepsy by seizures being mild or absent and dementia being mild or nonexistent, but myoclonus and ataxia are the major problems (Fig. 18.12).

The differential diagnosis of progressive myoclonus epilepsy (Table 18.10) and progressive myoclonic ataxia (Table 18.11) is dominated by five main conditions (Girard et al., 2013; Franceschetti et al., 2014; Knupp and Wirrell, 2014; Bhat and Ganesh, 2018).

Lafora body disease and neuronal ceroid lipofuscinosis generally produce severe neurologic decline with dementia or neurologic regression, along with myoclonus and fits. Lafora body disease (EPM2), inherited as an autosomal recessive trait, is characterized by polyglucosan accumulation in cells identified as periodic-acid–Schiff (PAS)-positive inclusions in cells of brain, liver, muscle, and skin (eccrine sweat glands) (Singh and Ganesh, 2009; Serratosa et al., 2012; Nitschke et al., 2018). Onset usually is in childhood with behavioral and cognitive change, dementia and seizures, and myoclonus; late-onset forms with a more benign onset also occur. Two genes have been identified as etiologic (Nitschke et al., 2018).

Table 18.11 Causes of progressive myoclonic ataxia**Major causes**

Unverricht–Lundborg disease
Mitochondrial encephalomyopathy
Sialidosis
Lafora body disease*
Neuronal ceroid lipofuscinosis*
Spinocerebellar degenerations

Rarer causes

Gaucher disease (noninfantile neuronopathic form)
GM₂ gangliosidosis*
Biotin-responsive encephalopathy
Neuroaxonal dystrophy (juvenile form)*
Pantothenate kinase–associated neurodegeneration
Atypical inclusion-body disease
Action myoclonus–renal failure syndrome (mutation in *SCARB2/LIMP2*)
Dentatorubral–pallidoluysian atrophy
Progressive myoclonic epilepsy and deafness (May–White syndrome)PME-ataxia syndrome (mutation in *PRICKLE1*)
Progressive myoclonic epilepsy and lipomasNorth Sea PME (mutation in *GOSR2*)
Celiac disease
Whipple disease

*Dementia often prominent, so not typical of progressive myoclonic ataxia.

The gene responsible in about 75% of cases encodes a protein tyrosine phosphatase (PTP) called laforin; this version of the disorder is called EPM2A (Singh et al., 2008). Laforin localizes at the plasma membrane and the endoplasmic reticulum (Minassian et al., 2001). A second gene is associated with Lafora body disease, *NHLRC1* (*EPM2B*), which encodes malin, a putative E3 ubiquitin ligase with a RING finger domain and six NHL motifs (Singh and Ganesh, 2009, 2012). Laforin is a substrate for malin (Gentry et al., 2005). These two proteins work together, and several functions have been identified for them. They seem to regulate cellular glucose uptake by preventing plasma membrane targeting of glucose transporters (Singh et al., 2013), function in the degradation of polyglucosan bodies (Liu et al., 2014), regulate glycogen accumulation (Rubio-Villena et al., 2013), and facilitate the astrocytic glutamate transporter (Perez-Jimenez et al., 2020). A third form of Lafora body disease has been identified with early onset with early dysarthria and somewhat longer course. The mutation is in a gene called *PRDM8*, and its protein appears to regulate the amount of laforin and malin (Turnbull et al., 2012). With some mutations, the disorder is mild with slow progression (Ferlazzo et al., 2014). In the end, the myoclonus may arise from loss of GABAergic cortical neurons (Ortolano et al., 2014). There is a mouse model of the disorder (Ganesh et al., 2002). Zonisamide has been described as very useful for the myoclonus and epilepsy in these patients (Yoshimura et al., 2001). In the long run, understanding of the cell biology may lead to rational etiologic therapy (Pederson et al., 2013; Singh et al., 2013; Gayarre et al., 2014; Turnbull et al., 2014).

Neuronal ceroid lipofuscinosis (Batten disease), inherited as an autosomal recessive condition, also manifests with seizures and myoclonus with cognitive impairment and dementia, along with blindness in the late infantile and juvenile forms (Jalanko and Braulke, 2009; Lehesjoki and Gardiner, 2012; Jadav et al., 2014). The adult form is often dominated by psychiatric and cognitive impairment. Lipopigment accumulates in lysosomes in brain, eccrine glands, skin, muscle, and gut with characteristic inclusions (curvilinear bodies and finger print profiles). Both Lafora body disease and neuronal ceroid lipofuscinosis usually can be diagnosed in axillary skin biopsies with electron microscopy.

Unverricht–Lundborg disease (EPM1) is characterized by stimulus-sensitive myoclonus, tonic-clonic seizures, a characteristic EEG (paroxysmal generalized spike-wave activity, and photosensitivity), and a progressive course with ataxia but only mild intellectual decline (Kalviainen et al., 2008; Lehesjoki and Gardiner, 2012; Hypponen et al., 2015). In some patients there might be oculomotor apraxia, dystonia, or rapidly progressive dementia (Chew et al., 2008). It is inherited as an autosomal recessive trait, with onset around the age of 6 to 15 years, and occurs worldwide. Autopsy shows widespread degeneration, with prominent loss of cerebellar Purkinje cells without the presence of storage material. The gene for Unverricht–Lundborg disease has been linked to the long arm of chromosome 21q22.3 in a number of Finnish and Mediterranean families, and the gene involved codes for cystatin B, a small protein that is a member of a superfamily of cysteine protease inhibitors (Lehesjoki, 2003). The most common mutation is an unstable expansion of a dodecamer minisatellite repeat unit in the promoter region of the cystatin B gene. The exact role of cystatin B is not known, but it has been found primarily localized in the nucleus (Riccio et al., 2001). Cystatin B interacts with a variety of proteins, and these multiprotein complexes

are found in the cerebellum (Di Giaimo et al., 2002). One possible pathophysiologic mechanism is sensitization to oxidative stress (Lehtinen et al., 2009). An animal model has been developed (Shannon et al., 2002). In an Arab family with similar clinical appearance, a cystatin B mutation was ruled out, linkage was identified on chromosome 12, and the disorder named EPM1B (Berkovic et al., 2005).

It is of critical importance in these cases to recognize that phenytoin treatment may be associated with worsening of the condition (Eldridge et al., 1983). Patients can be treated successfully with other anticonvulsants, as described later.

Mitochondrial encephalomyopathy may manifest in many forms or guises (Mancuso et al., 2014). One phenotype is the myoclonus epilepsy and ragged-red fiber syndrome (MERRF) (Canafoglia et al., 2001; Bindoff and Engelsens, 2012). Symptoms typically commence in the second decade, but onset as late as the age of 40 has been described. Myoclonus and ataxia are typical features, and tonic-clonic seizures and dementia often also occur. Deafness and short stature may be a clue to the diagnosis. Muscle weakness is variable. A raised blood or cerebrospinal fluid (CSF) lactate concentration may suggest the diagnosis. Muscle biopsy reveals the characteristic “ragged-red” fibers. Maternal inheritance can sometimes be evident, and a number of mutations of mitochondrial genes have been identified.

Sialidosis (cherry-red spot myoclonus syndrome) also is inherited as an autosomal recessive condition with onset in childhood or adolescence (Canafoglia et al., 2011; Vieira de Rezende Pinto et al., 2013; Sobral et al., 2014; Coppola et al., 2020). However, cases are described with onset in the third decade without retinal changes or high sialic acid excretion in the urine (Canafoglia et al., 2014). The sialidoses are lysosomal storage disorders associated with a deficiency of alpha-N-acetylneuraminidase and, in some, with additional deficiency of alpha-galactosidase.

In adults, another group of conditions, namely spinocerebellar degenerations, may cause myoclonus. For example, one presentation of dentatorubro-pallidoluysian atrophy (DRPLA) occurs with myoclonus and epilepsy (Tsuji, 2012). Some patients with the autosomal dominant spinocerebellar ataxias also may have prominent myoclonus. So, too, may patients with multiple system atrophy, in which the myoclonus tends to affect the fingers and toes and is stimulus-sensitive (Rodriguez et al., 1994).

Some patients with progressive myoclonic ataxia will have celiac disease (Bhatia et al., 1995; Burk et al., 2009). The onset of the neurologic syndrome in these cases follows the gastrointestinal and other manifestations of celiac disease even while on a gluten-free diet, in the absence of overt features of malabsorption or nutritional deficiency. It may well be that the neurologic features are caused by antibodies cross-reacting in the central nervous system. The neurologic syndrome is dominated by action and stimulus-sensitive myoclonus of cortical origin with mild ataxia and infrequent seizures (Swinkin et al., 2020). The condition may progress despite strict adherence to diet. This disorder is a variant of gluten ataxia, discussed in more detail in Chapter 20, and is likely due to an antibody related to, but not exactly the same, as the one producing celiac disease itself.

Action myoclonus–renal failure syndrome (AMRF) is a distinctive form of progressive myoclonus epilepsy associated with renal dysfunction. Badhwar and associates (2004) have described 15 individuals who presented with either renal or neurologic features. Segregation analyses suggested autosomal recessive inheritance. Tremor (onset 17–26 years), action

myoclonus (onset 14–29 years), infrequent generalized seizures (onset 20.28 years), and cerebellar features were characteristic. Brain autopsy in two patients revealed extraneuronal pigment accumulation. Proteinuria, detected between ages 9 and 30 years in all cases, progressed to renal failure in most patients within 8 years. Renal biopsies showed collapsing glomerulopathy, a severe variant of focal glomerulosclerosis. Dialysis and renal transplantation were effective for the renal but not the neurologic features, which continued to progress even when kidney function was improved.

Biotin, which is vitamin H, can have a role in myoclonus and can be depleted by insufficient dietary intake, but also as a result of several genetic abnormalities such as an abnormal biotinidase, which has roles in intestinal absorption and plasma transport of biotin (Zempleni et al., 2008). Biotin deficiency can cause neurologic features such as seizures, hypotonia, ataxia, and myoclonus (Said, 2012). The syndrome can be responsive to administration of biotin (Bressman et al., 1983).

Other causes of progressive myoclonus epilepsy and progressive myoclonic ataxia are much rarer (see Table 18.11). Investigation of patients with these clinical syndromes can include neurophysiology, white cell enzyme assays, and muscle and axillary skin biopsy, although all of these types of tests are being replaced by genetic analysis and ability to reach the right diagnosis is improving (Kravljanc et al., 2020). As the genetics and cell biology of these disorders is better understood, it will become possible to treat these disorders etiologically (Riva et al., 2020).

Posthypoxic myoclonus

Myoclonus after cerebral hypoxia (anoxia) is usually the result of an anesthetic accident, cardiac arrest, or respiratory failure often due to asthma (Lance and Adams, 1963; Werhahn et al., 1997; Frucht, 2002) (Table 18.12). In acute posthypoxic myoclonus, there is an initial period of coma, sometimes with myoclonic storms. The first 3 days are crucial to long-term prognosis; generalized myoclonic status epilepticus carries a very poor prognosis (Wijdicks et al., 1994). In recent years with the use of hypothermia, prognosis is better (Bouwes et al., 2012). The myoclonus can be of cortical or brainstem origin, but it is difficult to differentiate solely on a clinical basis. Clinical neurophysiologic testing can aid the diagnosis and prognosis (Dhakar et al., 2018; Reynolds et al., 2018; van Zijl et al., 2018).

Table 18.12 Causes of posthypoxic myoclonus

Cause	Number of patients
Associated with anesthesia and surgery	32
Myocardial infarct	12
Obstructed airway	11
Drug intoxication	9
Miscellaneous	21
Not stated	3
Total	88

From Fahn S. Posthypoxic action myoclonus: literature review update. *Adv Neurol*. 1986;43:157–169.

For example, patients who have a continuous EEG background with narrow spikes have a much better prognosis than those with burst suppression (Elmer et al., 2016). An animal model has been developed that should be useful in understanding the pathophysiology of this disorder (Tai et al., 2007).

In those who survive, spontaneous, action-induced and stimulus-sensitive myoclonus may emerge on recovery (Video 18.9). The chronic clinical syndrome as reported by Lance and Adams (1963) noted the precipitating feature of action and the association with cerebellar ataxia, postural lapses, gait disturbance, and grand mal seizures. Intellect may be normal, but there may be additional cerebellar ataxia along with the disabling myoclonus. Seizures may persist. Posthypoxic myoclonus may consist of multifocal jerks of cortical origin, generalized jerks resulting from intrahemispheric and transcallosal spread, brainstem reticular myoclonus, or a mixture of all these types (Werhahn et al., 1997; Hallett, 2000). Many patients have prominent negative myoclonus particularly of the legs, resulting occasionally in sudden falls (Video 18.10). Werhahn and colleagues (1997) reported the clinical and neurophysiologic features of 14 patients with chronic posthypoxic myoclonus. All patients had experienced cardiorespiratory arrest, most caused by an acute asthma attack. All patients had multifocal action myoclonus, and 11 had additional stimulus-sensitive myoclonus. There was late improvement in the myoclonic syndrome and the level of disability in all but one patient. Cognitive deficits were found in seven patients and were usually mild. Electrophysiologic investigation confirmed cortical action myoclonus in every case, although this could be combined with cortical reflex myoclonus, an exaggerated startle response, or brainstem reticular reflex myoclonus. The site of the responsible lesion in the brain is not certain, but there does appear to be a disorder of serotonin metabolism supported not only by the therapeutic response to 5-hydroxytryptophan, but also by the reduction in CSF levels of 5-HIAA, which improves with successful therapy. A study using glucose PET showed a bilateral hypermetabolism in the ventrolateral thalamus and pontine tegmentum relative to controls, but the significance of this is not clear (Frucht et al., 2004). ▶

Infectious and autoimmune myoclonus

Multifocal and generalized myoclonus also may occur in a variety of acute encephalitic illnesses or postinfectious disseminated encephalomyelitis (Bhatia et al., 1992). It is characteristic of subacute sclerosing panencephalitis (SSPE) (Shibasaki et al., 1981; Prashanth et al., 2006; Jafri et al., 2018) and Creutzfeldt–Jakob disease (Brown et al., 1986). In SSPE the myoclonus is often periodic at long intervals (Video 18.11), but not all patients with SSPE will have myoclonus (Jagtap et al., 2013). Carbamazepine might be considered for the myoclonus of SSPE (Yigit and Sarikaya, 2006; Ravikumar and Crawford, 2013). In these latter conditions, the myoclonus often has a characteristic hung-up jerk, and periodic EEG discharges are evident in the majority of patients. Myoclonus also is seen in patients with the AIDS–dementia complex (Maher et al., 1997). ▶

The myoclonic encephalopathy of infants (opsoclonus–myoclonus, or dancing eyes–dancing feet syndrome) appears between the ages of 6 and 18 months and can respond to immunologic treatment (Tate et al., 2012; Blaes and Dhar-malingam, 2016; Saini et al., 2020) (Table 18.13). Features other than myoclonus include loss of speech, drooling, limpness, and inability to walk or sit (Pranzatelli et al., 2017).

Video 18.9 Posthypoxic myoclonus. These two patients are some of the originals from the series by Lance and Adams. Note the large-amplitude positive and negative action myoclonus. (From Lance JW, Adams RD: Negative myoclonus in posthypoxic patients: Historical note. *Mov Disord.* 2001;16:162–163, with permission.)

Video 18.10 Negative myoclonus and bouncy gait from posthypoxic myoclonus. This patient with posthypoxic myoclonus has positive and negative myoclonus with arm movements. When the patient is standing and trying to walk, it is primarily the negative myoclonus that produces the bouncy gait.

Video 18.11 Subacute sclerosing panencephalitis (SSPE). This young boy has SSPE. He has whole-body jerks at long intervals. The jerk has a long duration but rapid onset. (Courtesy C.D. Marsden.)

Table 18.13 Opsoclonus–myoclonus syndrome (dancing eyes–dancing feet)

Opsoclonus: Continuous, arrhythmic, multidirectional, large saccades
Myoclonus: Trunk, limbs, diaphragm, larynx, pharynx, and palate
Causes: Viral infections, postinfectious encephalitis, trauma, tumor (paraneoplastic), toxic, drugs
 50% of children have a neuroblastoma (chest or abdomen)
 Only 2% of those with a neuroblastoma have opsoclonus–myoclonus syndrome
 20% of adults have an underlying cancer (see Table 18.14)

Table 18.14 “Brainstem encephalitis”

Subacute onset of ataxia, dysarthria, diplopia and ophthalmoplegia, nystagmus, opsoclonus, vertigo, deafness, and myoclonus
 Viral infection (e.g., herpes simplex), bacterial infection (e.g., *Listeria*), postinfectious, demyelination, vascular disease, tumor, or paraneoplastic syndromes
 Paraneoplastic cases have normal imaging, but often have an active cerebrospinal fluid with oligoclonal bands. Many have anti-Purkinje cell (e.g., anti-Yo) or anti-Ri antibodies. Common cancers are of ovary and lung

An autoimmune origin seems likely because it is associated with a distinctive pattern of serum immunoglobulin M (IgM) and IgG binding to neural tissues and antigens (Blaes et al., 2008; Raffaghelli et al., 2009). For some cases, an antibody was detected against the cerebellar antigen glutamate receptor delta2 (Berridge et al., 2018). There are a variety of causes, including infectious, postinfectious, paraneoplastic, toxic, and drugs (Blaes and Dharmalingam, 2016). About half of such cases have an underlying neuroblastoma (De Grandis et al., 2009), and, of course, in this circumstance the tumor should be removed. Although this can be curative, it is not necessarily the case, perhaps because the autoimmunity has already been triggered and patients may have relapses of the disorder (Kirkham et al., 2011). Variations in therapy have been compared over a 20-year period in a large series of 74 children. Corticotropin-based therapy is better than “conventional” therapy with corticosteroids, and the addition of more aggressive agents such as cyclophosphamide or rituximab bring even better improvement (Tate et al., 2012; Pranzatelli et al., 2018). Reduced levels of the metabolites of serotonin (5-HIAA) and dopamine (homovanillic acid [HVA]) have been observed in the CSF (Pranzatelli et al., 1995), and some patients may benefit symptomatically from treatment with the serotonin precursor 5-hydroxy-L-tryptophan. The incidence of subsequent developmental or neurologic disturbance is high (Krug et al., 2010; Brunklaus et al., 2011).

A similar syndrome of opsoclonus and myoclonus may occur in adults, mostly parainfectious or paraneoplastic (Markakis et al., 2008; Sabater et al., 2008; Klaas et al., 2012; Oh et al., 2019) (Table 18.14) (Video 18.12). In a series of 21 patients, 3 had cancer and the rest were thought to be parainfectious (Klaas et al., 2012). Adding their 21 patients to 116 literature review patients, the most common cancers were lung and breast, the most common paraneoplastic antibody was antineuronal nuclear antibody type 2 (anti-Ri). Of parainfectious causes, HIV was notable. Whipple disease also may produce such a clinical picture (Schwartz et al., 1986), as can West Nile virus (Cooper

and Said, 2014). Opsoclonus-myoclonus can also be seen as a post-infectious complication of COVID-19 (Emamikhah et al., 2021; Foucard et al., 2021); myoclonus by itself can also be seen (Anand et al., 2020; Rabano-Suarez et al., 2020). Cases have been observed in women with anti-N-methyl-D-aspartate receptor encephalitis (Kurian et al., 2010; Smith et al., 2011), and other single cases were seen in patients with antibodies directed to the GABA_B receptor (Hoftberger et al., 2013) and glutamic acid decarboxylase (GAD) (Bhandari, 2012). Rarely, there might be a toxic cause (Blaes and Dharmalingam, 2016). If there is a cancer, of course it should be dealt with first and the opsoclonus–myoclonus may resolve. Immunologic therapy can be very effective. Trazadone or clonazepam also may be helpful for the myoclonus symptomatically. Symptomatic benefit for the opsoclonus has been described with clonazepam, gabapentin, topiramate, and chlormethiazole (Blaes and Dharmalingam, 2016). ▶

The origin of the opsoclonus in the opsoclonus–myoclonus syndrome is not known, but there is one suggestion that it might be due to antibodies directed to the parallel fiber–Purkinje cell synapses in the cerebellum (Jen et al., 2012).

Antibodies to voltage-gated potassium channels (VGKCs) also may be found in patients with myoclonus. In a study from the Mayo Clinic in which they screened sera from 130,000 patients for markers of paraneoplastic neurologic autoimmunity, 80 patients were identified with VGKC immunoreactivity and 29% manifested myoclonus (Tan et al., 2008). As in the stiff-person syndrome (see Chapter 23), such antibodies are probably mostly directed to proteins associated with the VGKC and not the channel itself (Balint et al., 2013).

Degenerative disorders

Myoclonus and dementia in adults occurs not only in Creutzfeldt–Jakob disease but also in Alzheimer disease (Wilkins et al., 1984; Schmidt et al., 2010). Parkinson disease (PD) rarely manifests myoclonus. Although the myoclonus appears to be cortical in origin, there is no reflex myoclonus or a giant somatosensory evoked potential (Caviness et al., 2002). Myoclonus is a well-described feature of dopa-dyskinesias (Luquin et al., 1992), and this would be its most frequent cause in patients with PD. Patients with PD and unsteadiness when standing may have orthostatic myoclonus (Leu-Semenescu et al., 2007; Gasca-Salas et al., 2013). Myoclonus is more common in multiple system atrophy. Myoclonus can be observed in patients with dystonia, the myoclonus in this situation being a short “burst” of dystonia (Kinugawa et al., 2008; Roze, Lang and Vidailhet, 2018) (Video 18.13). It may also be a feature of Huntington disease, and physiologically is cortical myoclonus (Caviness and Kurth, 1997; Rossi et al., 2012). Myoclonus is a prominent, characteristic feature of corticobasal degeneration (Kompolti et al., 1998; Ouchi et al., 2014). The myoclonus is stimulus-sensitive, with a short latency that may be helpful in differential diagnosis. Its pathophysiology is debated as to whether it is cortical or subcortical in origin (Carella et al., 1997; Strafella et al., 1997; Notturmo et al., 2011). ▶

Drugs and toxins

A wide variety of drugs and toxins may provoke multifocal and generalized myoclonus (Gordon, 2002; Burkhard, 2014; Zutt et al., 2015; Janssen et al., 2017). Among drugs, antidepressants

Video 18.12 Opsoclonus–myoclonus syndrome. (A and B) These two patients have the opsoclonus–myoclonus syndrome. Note the chaotic, but conjugate, movement of the eyes.

Video 18.13 Dystonic myoclonus. This patient has a focal hand dystonia, a writer's cramp. In addition to the dystonic posturing, there are many myoclonic jerks. (Courtesy Hiroshi Shibasaki, MD.)

Table 18.15 Appropriate dosages of agents for the treatment of myoclonus

Drug	Dosage (mg/day)
Baclofen	15–80
Benztropine	2–8
Brivaracetam	50–150
Clonazepam	3–20
Diazepam	4–40
5-Hydroxytryptophan	Up to 1500*
Levetiracetam	1000–3000
Perampanel	8–12
Phenobarbital	60–180
Piracetam	2400–16 800
Primidone	500–1000
Tetrabenazine	25–100
Trihexyphenidyl (benzhexol)	Up to 35
Valproic acid (sodium valproate)	1000–2000
Zonisamide	100–600

*In combination with a peripheral aromatic amino acid decarboxylase inhibitor (such as carbidopa 100–300 mg/day). Heavily modified from Brown P. Myoclonus: A practical guide to drug therapy. CNS Drugs. 1995;3:22–29.

(particularly the selective serotonin reuptake inhibitors [SSRIs]), opiates, anesthetics, anticonvulsants (particularly at toxic levels), antipsychotics, antibiotics, withdrawal of benzodiazepines and propranolol, lithium (Caviness and Evidente, 2003), monoamine oxidase inhibitors, and levodopa can all cause myoclonus. Among toxins, bismuth, heavy metals, glue and gasoline sniffing, and toxic cooking oil in Spain can cause prominent myoclonus. Myoclonus is prominent in the “serotonin syndrome,” along with confusion, agitation, diarrhea, fever, and sweating. This syndrome has been reported after treatment with tryptophan, monoamine oxidase inhibitors, SSRIs, and tricyclic antidepressants, alone or in combination (Mason et al., 2000; Pedavally et al., 2014). Myoclonus, positive and negative, is associated with the use of gabapentin, but can be mild and may not cause any symptomatic problem (Asconape et al., 2000; Ege et al., 2008; Kim et al., 2017).

Essential myoclonus (Myoclonus dystonia)

Essential myoclonus refers to a syndrome of nonprogressive multifocal myoclonus, without other cognitive or neurologic symptoms or signs, or fits. It may be inherited as an autosomal dominant trait in a family (Fahn and Sjaastad, 1991), although sporadic cases also occur (Bressman and Fahn, 1986). Essential myoclonus usually manifests in the first or second decade, and the course is benign. There are no seizures, dementia, or ataxia, and the EEG is normal. In some with essential myoclonus the physiologic abnormality appeared to be that of overflow of ballistic movement patterns (Hallett, Chadwick and Marsden, 1977; Borges et al., 2000).

Likely in most families with essential myoclonus, there also are manifestations of dystonia; some individuals have both,

and others have myoclonus or dystonia. The myoclonus in such families may be very responsive to alcohol—hence, the description as alcohol-sensitive myoclonus dystonia (Quinn, 1996). Most families with myoclonus dystonia have an abnormal gene for ϵ -sarcoglycan (Carecchio et al., 2013; Ghosh and Indulkar, 2013). The clinical presentation is relatively homogeneous with this gene defect with myoclonus predominantly of neck and upper limbs and dystonia manifesting as cervical dystonia and/or writer’s cramp (Roze et al., 2008; Vanegas et al., 2020). Epilepsy is also seen in some families (Haugarvoll et al., 2014). Myoclonus–dystonia is also caused by a mutation in *KCTD17* (Mencacci et al., 2015) and by a mutation in *CACNA1B* (Groen et al., 2015). See also Chapter 11 for more details on myoclonus–dystonia.

Functional myoclonus

Myoclonus is a frequent manifestation of a functional movement disorder, and it is important to keep this in mind in the differential diagnosis (Video 18.14). Functional movement disorders are discussed in Chapter 27, but in the context of discussing myoclonus, it is noteworthy that the clinical neurophysiology is distinctive and can help resolve the differential diagnosis (Hallett, 2010). There is evidence that antidepressant therapy can be useful (Voon and Lang, 2005) and that psychotherapy (Hinson et al., 2006) and physical therapy (Czarnecki et al., 2012) can be useful. Patients typically need a thoughtful multidisciplinary approach that mirrors the complex biopsychosocial cause of their problem (Hallett et al., 2011). ▶

Drug treatment of generalized or multifocal myoclonus

Myoclonus, particularly action myoclonus, can be very disabling. It distorts speech, interferes with manual function, and prevents walking. The drugs used to treat myoclonus generally possess anticonvulsant properties (Table 18.15) (Brown, 1995; Obeso, 1995; Pranzatelli and Nadi, 1995; Frucht, 2000; Chang and Frucht, 2008; Caviness and Truong, 2011; Kojovic et al., 2011; Caviness, 2014; Holmes, 2020; Pena and Caviness, 2020), usually by enhancing gamma-aminobutyric acid (GABA) inhibitory activity. In epilepsy, it is currently fashionable to try to manage patients using a single drug rather than polytherapy. However, there are good reasons for the opposite approach in the treatment of myoclonus. Electrophysiologic evidence suggests that anti-myoclonic drugs may exert different actions on the sequence of events responsible for myoclonus, at least for those concerned with cortical myoclonus. Some drugs that decrease cortical myoclonus increase the size of the giant sensory evoked potential, whereas others have the opposite effect. Myoclonus thus often responds best to a combination of drugs.

Table 18.16 summarizes the drugs used to treat specific types of myoclonus arising in different parts of the neuraxis (see also Mills and Mari, 2015; Levy and Chen, 2016).

Epileptic myoclonus and cortical myoclonus respond best to drugs such as sodium valproate and clonazepam, often used in combination in maximum tolerated anticonvulsant doses (Obeso, 1995). Sodium valproate is the drug of choice to treat JME (Mantoan and Walker, 2011).

Video 18.14 Psychogenic myoclonus. This patient has psychogenic myoclonus. Note that the movements are not simple in nature.

Table 18.16 Drug treatment for specific types of myoclonus

Type of myoclonus	Drug(s) of first choice	Other agents
Cortical myoclonus	Valproic acid (sodium valproate) or clonazepam	Primidone or phenobarbital, levetiracetam, piracetam, zonisamide, 5-HTP*
Brainstem reticular myoclonus	Valproic acid or clonazepam [†]	5-HTP*
Hyperekplexia	Clonazepam	Carbamazepine, phenytoin
Ballistic overflow myoclonus	Benztropine or trihexyphenidyl (Benzhexol)	Alcohol (ethanol), clonazepam, 5-HTP*
Palatal myoclonus	Phenytoin, carbamazepine, clonazepam, diazepam, trihexyphenidyl or baclofen [†]	5-HTP*, sumatriptan
Propriospinal myoclonus	Clonazepam	
Segmental spinal myoclonus	Clonazepam	Diazepam, carbamazepine, tetrabenazine

*Combined with a peripheral aromatic amino acid decarboxylase inhibitor (such as carbidopa). Usefulness limited by poor tolerability.

[†]Treatment with any agent is often unsuccessful.

5-HTP, 5-Hydroxytryptophan.

It is conventional to start with sodium valproate in patients with severe myoclonus, then to add clonazepam. If disability is not adequately improved, piracetam or levetiracetam then can be added. The mechanism of action of piracetam is uncertain, but it undoubtedly possesses antimyoclonic activity (Genton et al., 1999). Levetiracetam, a molecule related to piracetam that has been approved for the treatment of epilepsy, also can be effective for myoclonus and has mostly replaced piracetam (Caviness and Truong, 2011; Espay and Chen, 2013). Brivaracetam is a newer similar drug for epilepsy (Strzelczyk et al., 2016) and also may be useful for myoclonus (Pena and Caviness, 2020). There is one negative trial for EPM1 (Kalviainen et al., 2016), but the drug should be further studied. There is a report of tizanidine helping two of three patients (Mukand and Giunti, 2004).

Primidone also may be of value as an additional drug in severely affected patients, as may clobazam and acetazolamide. Zonisamide has been useful in some patients, including those with myoclonus–dystonia (Hainque et al., 2016). The potential antimyoclonic activity of newer anti-convulsants, such as vigabatrin, gabapentin, and lamotrigine, remains to be established. There are, however, some early studies suggesting that perampanel may be useful (Pena and Caviness, 2020). Note that both vigabatrin and

gabapentin may, paradoxically, worsen some types of myoclonus (Asconape et al., 2000). Some patients may respond to gamma-hydroxybutyric acid (Frucht et al., 2005; Arpesella et al., 2009). Phenytoin, carbamazepine, and gabapentin, should be avoided because they can cause myoclonus.

Unfortunately, although spontaneous action and reflex positive myoclonus often is helped by drug therapy, negative myoclonus frequently is resistant. As a result, disabling postural lapses in antigravity leg muscles usually persist to cause the typical bouncy unsteady stance and gait, often with falls. Two patients have been described with an excellent response to levetiracetam (Gelisse et al., 2003; Yu et al., 2009). Epileptic negative myoclonus in atypical benign partial epilepsy of childhood can be managed with combinations of valproate, clonazepam, and corticosteroids (Yang et al., 2009). Ethosuximide also has been found useful in some cases (Oguni et al., 1998; Capovilla et al., 1999; Rubboli and Tassinari, 2006).

The antioxidant N-acetylcysteine has been claimed to have considerable beneficial effect on the myoclonus in Unverricht–Lundborg disease (Hurd et al., 1996), but this generally has not been useful (Edwards et al., 2002). Alcohol also has been found to be a potent antimyoclonic agent in post-hypoxic myoclonus and Unverricht–Lundborg disease (Genton and Guerrini, 1992).

Patients with brainstem myoclonus seem to respond best to clonazepam (Chadwick, Hallett, Harris et al., 1977).

Spinal and other segmental myoclonus also responds best to treatment with clonazepam (Obeso, 1995; Devetag Chalaupka and Bernardi, 1999), but tetrabenazine and baclofen occasionally may be helpful. Levetiracetam can be useful (Keswani et al., 2002) or topiramate (Siniscalchi et al., 2004). One case responded to valproate and serotonergic therapy (Jimenez-Jimenez et al., 1991). Two patients responded to intrathecal baclofen (Chiodo and Saval, 2012). If all else fails, botulinum toxin can be used (Laguëny et al., 1999).

Deep brain stimulation (DBS) is not ordinarily undertaken for posthypoxic myoclonus, but there are some successful cases reported that have responded to bilateral globus pallidus internus (GPi) stimulation (Asahi et al., 2015; Kim et al., 2020).

Essential myoclonus sometimes improves with alcohol, a beta-blocker such as propranolol, or an anticholinergic agent (Chokroverty et al. 1987; Lee et al., 2011). In myoclonus–dystonia syndrome, alcohol can be of benefit to the myoclonus, but not to the dystonia with which it may be associated (Quinn, 1996). Some patients respond to levodopa (Luciano et al., 2009), one patient responded to oral zolpidem (Park et al., 2009), and two siblings responded to tetrabenazine (Luciano et al., 2014). Myoclonus–dystonia can be improved with bilateral DBS of the GPi and the ventralis intermedius nucleus (Azoulay-Zyss et al., 2011; Rughani and Lozano, 2013; Krause et al., 2021).

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Gait disorders

Pathophysiology and clinical syndromes

Chapter contents

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Introduction

Gait is a fundamental human skill. It permits movement from place to place, and, as anthropologists are fond of pointing out, that humans do it on two legs frees up the arms for other skilled tasks. The ability to walk is basic to human quality of life. However, walking on two legs is a difficult motor task involving the ability to balance and execute a complex motor program at the same time. Many movement disorders affect gait, and this becomes an important aspect of the disorder. The nature of the gait disorder, conversely, of course, can be a clue to the diagnosis of the movement disorder. This chapter will first briefly review the physiology of balance and gait, and then consider the many different gait disorders.

Balance

It is important to distinguish between balance and stance. Stance is the posture of standing. It is normally upright on two legs with a distance between the feet approximately equal to pelvic width. An example of abnormal stance would be the stooped posture seen in Parkinson disease (PD). Balance is the ability to maintain stance without falling or excessive lurching (Benvenuti, 2001). If balance is poor, sometimes persons modify their stance; the most common manifestation is increasing the distance between the feet to widen the base of support (BOS).

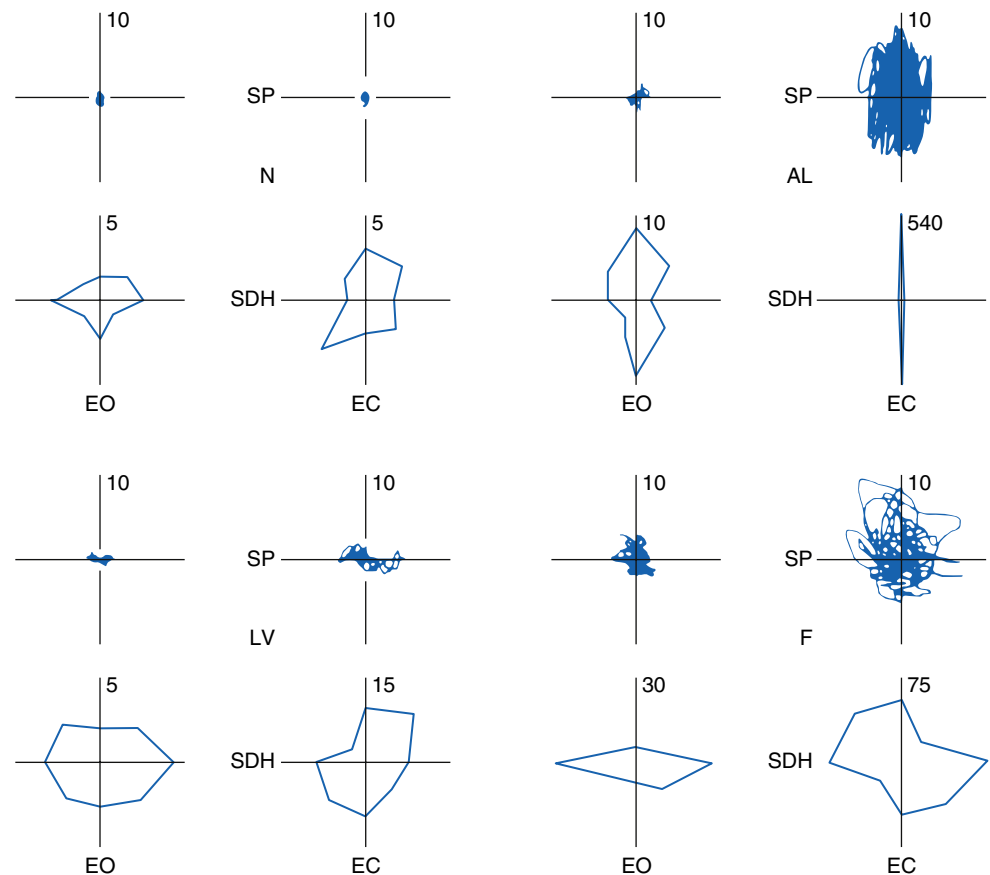
From standard Newtonian physics, for an object to maintain its position, its center of mass (COM) must be over its BOS. In the case of a human standing, the COM is generally somewhere in the abdomen and the BOS is the area between and including the feet. Because the BOS is relatively small and the COM relatively high above the BOS, it takes considerable skill to maintain the BOS above the COM. The ability to remain upright cannot be explained best by just the simple need to maintain the BOS above the COM. This is a static requirement, and the body or body parts are constantly moving. This movement must be taken into account. A “dynamic model” of balance includes consideration of the velocity of

COM (Pai et al., 1998). The general principle is that the balance mechanisms of the body (such as the postural muscles) must be able to counteract any large velocities of the COM, even if the COM is currently over the BOS, because if they cannot, the COM will soon be beyond the BOS.

The body is constantly moving, and this movement is called sway. Each body part can have its own movement, but the important “summary” of these movements would be movement of the COM for the reasons already described. Neurologists are used to doing a visual analysis of sway, but this is not very exact, of course. Instrumental methods have been developed. The position of the COM can be estimated, although it is generally somewhat difficult. The position of the different body parts can be determined with video methods, and if their individual masses are estimated, the COM can be calculated. This is generally performed only in research laboratories. An alternative method, generally called posturography, uses the ability to record forces that the body exerts on the floor with devices called force plates (Kaufman et al., 2001; Chaudhry et al., 2011). The devices measure force in three directions, vertical, forward/backward, and side-to-side, and the two-dimensional center of action of the forward/backward and side-to-side force is called the center of pressure (COP). In the static situation (static posturography), the COM is directly over the COP. Movements of the COM cause deviance of the matching of the COM and COP, but if the movements are small and slow, the deviance is not much. For this reason, sway is often measured with movements of the COP. Recent advances in mobile devices are making balance measurements easier (Gawronska et al., 2020).

Generally, it is thought that more sway means less good balance. This is often but not always true. In some circumstances, because the balance is bad, patients stiffen up, voluntarily or involuntarily, and the sway might decrease. This might be true in PD, for example (Panzer et al., 1990). When a patient is “off,” balance is poor and patients are very stiff, often swaying little. When the patient is “on,” balance is better, the patient is more relaxed, and sway might increase. Sway markedly increases with dyskinesias (characteristic of the “on” state and good balance). In most circumstances,

Fig. 19.1 Examples of posturography, the path of the center of pressure while standing. In each part of the figure, SP is the sway path and SDH is the sway direction histogram. The upper left, N, is the normal pattern; the upper right, AL, is from a cerebellar patient with anterior lobe dysfunction; the lower left, LV, is from a cerebellar patient with lower vermis dysfunction; the lower right, F, is from a patient with Friedreich ataxia. EO, eyes open; EC, eyes closed. (From Diener HC, Dichgans J, Bacher M, Gompf B. Quantification of postural sway in normals and patients with cerebellar diseases. *Electroencephalog Clin Neurophysiol.* 1984;57:134–142, with permission.)



however, increased sway does indeed indicate poor balance and posturography can be employed to make this assessment quantitatively. A more accurate way to assess balance is to see what happens with a perturbation to stance (Visser et al., 2008; Chaudhry et al., 2011; Nonnekes et al., 2013). There are instrumental methods available for quantitative assessment of increases in sway with various perturbations; this is referred to as dynamic posturography (Petro et al., 2017). Grossly, clinically, if patients can remain upright with a big perturbation, then balance is good; if they fall, balance is defective. This is the logic of the pull test.

The pull test is performed by having the patient stand and having the investigator stand behind the patient and give a sudden pull backward (Hunt and Sethi, 2006). The patient is told to maintain balance. The best ability is to deal with the perturbation by body movements without moving the feet. A second-level ability is to maintain balance by taking a timely step backward. Failure, of course, is a fall, and that is the reason that the test is a pull rather than a push; the patient can fall into the examiner. Balance is virtually always better in the forward direction than the backward direction. With poor balance, patients tend to fall backward. All the reasons for this are not clear, but one is likely that when standing, the COM is closer to the back of the foot than the front. In any event, because of this, the pull test is often only performed in the backward direction. A related test called the push and release test has been suggested, and it might be more sensitive and consistent than the pull test (Jacobs et al., 2006; Valkovic et al., 2008).

Good balance depends on good motor control abilities, but also good sensory feedback about what the exact body position and velocity are at any time. Feedback comes from vision, proprioception, and vestibular sensation. When one sensory modality is impaired, generally the others can compensate. When two modalities are impaired, there is more of a problem. This is the source for the popular Romberg test. Sway is assessed when the eyes are closed. If there is a problem with proprioception, in the absence of vision, sway will be increased.

Abnormalities in posturography have been reported in many disorders. The best studied has been cerebellar disturbances (Diener et al., 1984; Gatev et al., 1996; Schwabova et al., 2012); the findings are reviewed in detail in Chapter 2 and illustrated as an example here (Fig. 19.1). PD also has been studied (Nonnekes et al., 2013; Bekkers et al., 2018; Panyakaew et al., 2019; Kamieniarz et al., 2021).

Gait

Human gait is a complex, rhythmical, cyclical movement (Winter, 1991). The movements are generated to some extent by a locomotor generator in the spinal cord, but they are under control by supraspinal mechanisms. The spinal cord generator can produce only simple, primitive stepping and react to perturbations in stereotypic fashion (Burke, 2001). Supraspinal mechanisms are required for a person to go in desired directions, with desired velocities and to deal well with perturbations. An important supraspinal control center

is the mesencephalic locomotor region, which includes the pedunculopontine nucleus (PPN). The PPN is an important integrator of activity from basal ganglia, cerebellum, and motor cortex and projects to reticular nuclei in the brainstem (see [Chapters 2 and 3](#)). Although there is evidence for the PPN to be involved in gait ([Grabli, Karachi, Folgoas et al., 2013](#)), there is some question as to whether it is the PPN itself that is involved or other nearby regions ([Ferraye et al., 2010](#); [Snijders et al., 2016](#); [Garcia-Rill et al., 2019](#)). The cerebellum is also important ([Mori, Matsuyama, Mori et al., 2001](#); [Fasano et al., 2017](#)). Supraspinal control signals are conveyed to the spinal cord by reticulospinal and vestibulospinal tracts.

Although the spinal and brainstem mechanisms are important, walking is ultimately under control of the cerebral cortex. A person must know where to go, how fast to go, how to get there, and how to avoid obstacles in the path. Thus, there is a chain of command from cortex (and basal ganglia) to brainstem (and cerebellum) to spinal cord—the whole brain is involved ([Fig. 19.2](#)) ([Nutt et al., 2011](#); [Weiss et al., 2020](#)). Multiple neurotransmitter systems are also involved as illustrated in the figure.

A number of terms are useful in describing gait, and many of them are defined here.

Stance phase: When the foot is on the floor.

Swing phase: When the foot is in the air.

Stance time: The time that the foot is on the floor, measured as the time between heel strike and toe or heel off, whichever is last.

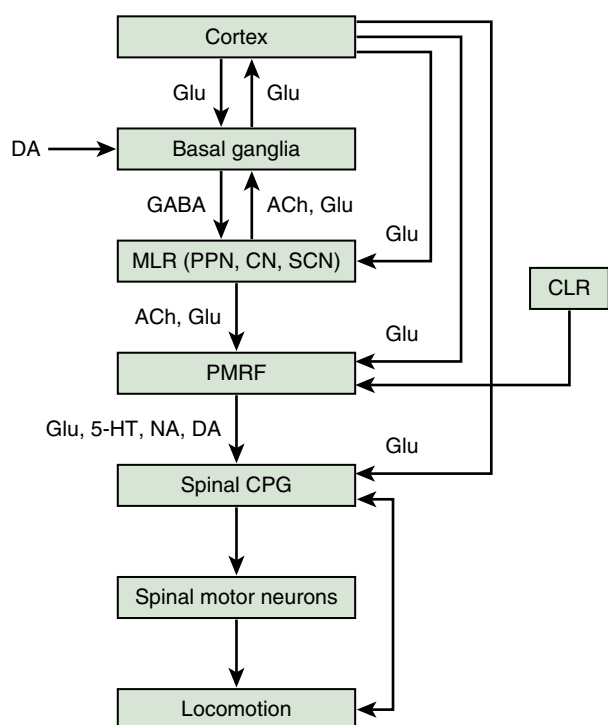


Fig. 19.2 Central nervous system circuitry controlling locomotion and balance. 5HT, Serotonin; ACh, acetylcholine; CLR, cerebellar locomotor area; CN, cuneiform nucleus; CPG, central pattern generator; DA, dopamine; GABA, gamma-aminobutyric acid; Glu, glutamate; MLR, mesencephalic locomotor region; NA, noradrenaline; PMRF, pontomedullary reticular formation; PPN, pedunculopontine nucleus; SCN, subcuneiform nucleus. (Modified from Nutt JG, Bloem BR, Giladi N, Hallett M, Horak FB, Nieuwboer A. Freezing of gait: Moving forward on a mysterious clinical phenomenon. *Lancet Neurol.* 2011;10:734–734.)

Swing time: The time that the foot is in the air, measured as the time between toe off and heel strike.

Cadence: The number of steps per minute.

Step length: The distance advanced by one foot compared with the position of the other.

Stride length: The sum of two consecutive step lengths, one with each leg, or the distance advanced by one foot compared with its prior position.

Step time: The time from heel strike of one foot to the subsequent heel strike of the contralateral foot.

Gait cycle: One complete cycle of events, often looked at as the time between two consecutive heel strikes of the same foot. Hence, a gait cycle would begin at the beginning of stance phase of one foot, go through stance and swing, and end at the end of swing (which is the beginning of the next stance phase).

Stride time: The time for a full gait cycle.

Average gait velocity: The stride length divided by the stride time.

A gait cycle for the right leg is illustrated in [Fig. 19.3](#). Note that the gait cycle for the left leg is not exactly 180 degrees out of phase. For this reason, and because stance phase is longer than swing phase, there are several periods in which both feet are on the ground, and these are called double support. (In normal walking, there are no periods of simultaneous swing; that is, no “flying,” although this may occur with running.) With normal gait, when the foot contacts the ground, the heel contacts first and then the foot rotates to flat with the heel as the point of rotation. When the foot leaves the floor for swing, the foot rotates over the toe and the heel leaves the ground first.

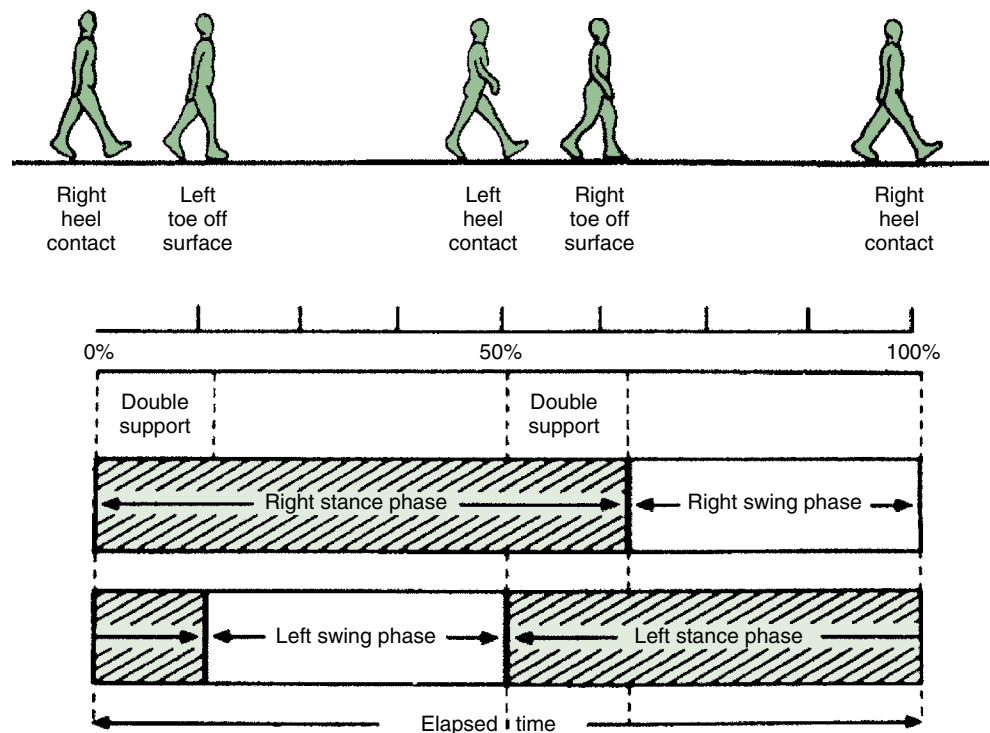
The joint angles of a normal gait cycle are illustrated in [Fig. 19.4](#). The ankle shows a brief plantar flexion at heel strike, followed by a gentle dorsiflexion in stance as the body moves over the foot. The ankle then shows a brisk plantar flexion producing push-off lasting from heel off to toe off. During swing there is a dorsiflexion of the ankle to avoid hitting the toe on the ground and to prepare for heel strike. The knee shows a slight flexion during stance and a more pronounced flexion during swing. The hip extends in stance and flexes during swing.

Muscle activities during gait are illustrated in [Fig. 19.5](#). During the gait cycle, the triceps surae (gastrocnemius-soleus) is active primarily at the end of stance to push off for the swing phase. The tibialis anterior muscle is active in the beginning of stance to slow the plantarflexion of the foot so that it does not slap onto the floor. Then it is active again during swing to produce the dorsiflexion of the ankle mentioned above.

Gait initiation

The initiation of gait is a special problem ([Elble et al., 1994](#); [Stansfield et al., 2018](#)). Not only does it pose a unique biomechanical problem but it also causes some patients particular difficulty ([Mancini et al., 2009](#)). The task is to get the body moving forward and to get the first foot off the ground into a “swing phase.” In quiet standing, there is a very slight tonic activation of the triceps surae. This prevents the body from falling forward because the COM is anterior to the ankle joints. The first event is a diminution of activity in the triceps surae muscles, more prominent on the side

Fig. 19.3 Diagram of the gait cycle; see text for detailed description. (From Sudarsky L. *Geriatrics: Gait disorders in the elderly*. *N Engl J Med*. 1990;322[20]:1441–1446, with permission.)



of the leg that will become the stance leg for the first step. This by itself would cause the body to start moving forward, rotating around the ankle. Then, the tibialis anterior muscles contract, which actively rotates the body forward around the ankle. These events get the body moving.

The next set of events is like a ministep. The leg that will become the stance leg briefly flexes slightly at the knee and hip, just like in a swing phase. This helps drive the COP toward the swing leg. Then, the swing leg makes a large burst of electromyographic (EMG) activity in the triceps surae producing the push-off force for the swing phase. This force, coupled with a slight abduction of the hip, drives the COP toward the stance leg, which it accepts as it serves a full stance function during the swing of the other leg.

Gait disorders

Epidemiology

Gait problems are a major neurologic issue, particularly in elderly people (Sudarsky, 2001; Snijders et al., 2007; Axer et al., 2010; Pirker and Katzenschlager, 2017). In this population, common causes for problems are stroke, peripheral neuropathy, brain or spinal cord trauma, and PD. The term “senile gait” is sometimes used, but it likely does not exist as a distinct entity. Multiple medical problems accumulate with age, including visual difficulties and arthritis, and these may become additive. There is, however, a relationship between gait speed and cognitive ability in the elderly (Montero-Odasso et al., 2014; Ojagbemi et al., 2015; Ohlin et al., 2021).

Sudarsky (1997) evaluated a series of patients referred for an unknown gait disorder. After careful neurologic evaluation, he was able to make a diagnosis in most (Table 19.1).

The most frequent entities were sensory deficits, myelopathy, multiple infarcts, parkinsonism, and unknown.

Evaluation of gait

Of course, the gait itself should be observed, but special attention should be paid to different aspects, including nature of the steps, which includes stride length and cadence, deviations from the direction of progression, width of the feet from each other during periods of double support, variability of the stepping, and angular movements at the joints. Any stiffness of motion should be indicated. Additionally, the ability to initiate stepping and the ability to turn should be noted. Looking for more subtle abnormalities, individuals can be asked to walk a straight line, heel to toe. In the case of dystonia, the patients might be asked to walk backward to see if this improves performance. Balance should be assessed as well, observing quiet standing with eyes open and eyes closed, and performing the pull test. Of course, it is critical to evaluate patients for nonneurologic features such as arthritis, limitation of motion, pain (antalgic gait), and asymmetries of leg length.

A number of important observations have implications for the differential diagnosis (Nutt et al., 1993):

Weakness. Weakness should ordinarily be noted on general neurologic examination. Depending on the muscles affected, there will be certain patterns identified such as steppage and waddling, which will be described further later. Weakness is commonly due to neuropathy or myopathy.

Dysmetria of stepping. Steps that are abnormal by virtue of being the wrong length or direction and are also highly variable. This is characteristic of ataxia and chorea. Ataxia

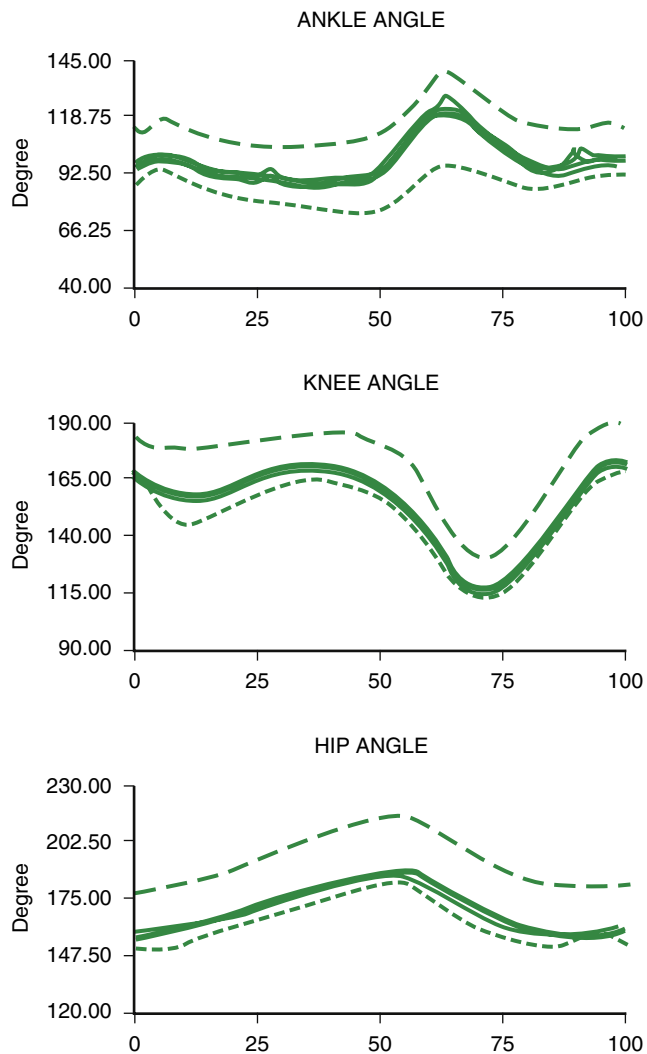


Fig. 19.4 Changes of the ankle, hip, and knee angles during a full gait cycle beginning with the start of stance phase. The solid lines are multiple trials from a single, healthy subject showing the excellent reproducibility from cycle to cycle. The dashed lines are the normal limits from a group of 10 healthy subjects. (Modified from Palliyath S, Hallett M, Thomas SL, Lebedowska MK. *Gait in patients with cerebellar ataxia. Mov Disord.* 1998;13[6]:958–964, with permission.)

looks mostly clumsy, whereas chorea often has a dancing quality.

Stiffness or rigidity. This is characterized by reduction of joint movement. It is seen with spasticity, parkinsonism, and dystonia.

Veering. Deviations from a direct line of progression are due to either vestibular or cerebellar disorders.

Freezing. Freezing is also known as motor blocks and is characterized by lack of movement with the feet looking like they are glued to the floor (Snijders et al., 2008, 2016; Browner and Giladi, 2010; Nutt et al., 2011; Paramanandam et al., 2018; Weiss et al., 2020). Patients often look like they are trying to move, but they cannot. This may be due to inability to generate sufficient postural shifting to initiate forward movement (Elble et al., 1996; Mancini et al., 2009). Freezing can occur when trying to initiate gait, in which circumstance it also has been called “start hesitation.” Freezing can also interrupt walking, and in

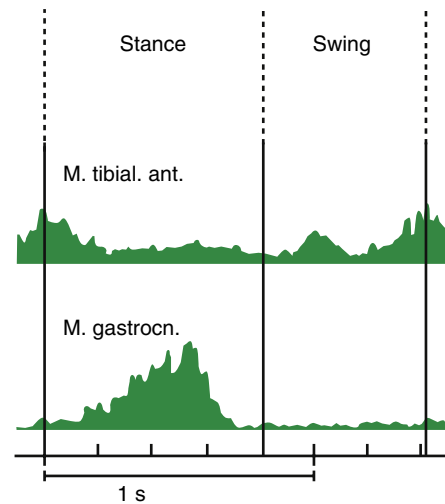


Fig. 19.5 Electromyogram activity in the tibialis (M. tibial. ant.) and gastrocnemius (M. gastrocn.) muscles during a full gait cycle. The figure shows rectified activity in a healthy subject. (Modified from Conrad B, Meinck HM, Benecke R. *Motor patterns in human gait: Adaptation to different modes of progression.* In: Bles W, Brandt T, eds. *Disorders of Posture and Gait.* Amsterdam: Elsevier Science Publishers BV; 1986: pp. 53–67, with permission.)

Table 19.1 Frequency of causes of neurologically referred undiagnosed gait disorders

Causes	Percentage
Sensory deficits	18.3
Myelopathy	16.7
Multiple infarcts	15.0
Unknown	14.2
Parkinsonism	11.7
Cerebellar degeneration	6.7
Hydrocephalus	6.7
Psychogenic	3.3
Other	7.5

“Other” causes include metabolic encephalopathy, antidepressant and sedative drugs, toxic disorders, brain tumor, and subdural hematoma.

From Sudarsky L. Clinical approaches to gait disorders of aging. In: Masdeu J, Sudarsky L, Wolfson L, eds. *Gait Disorders of Aging: Falls and Therapeutic Strategies.* Philadelphia: Lippincott-Raven; 1997, pp. 147–158, with permission.

this circumstance is sometimes precipitated by a sensory stimulus such as a doorway, the ring of a doorbell, or a street light changing color. Curiously, sensory stimuli also can be used to improve freezing. They appear to act in this regard by providing external triggers for movement.

The pathophysiology of freezing is not clear, but there are a number of associated abnormalities (Nutt et al., 2011; Heremans et al., 2013; Nieuwboer and Giladi, 2013; Ehgoetz Martens et al., 2020; Lichter et al., 2021). Patients show defective bilateral coordination of stepping (Plotnik et al., 2008), increased variability of gait variables (Barbe et al., 2014), and postural instability (Bekkers et al., 2018). There is an association of freezing with loss of frontal lobe executive function (Amboni et al., 2008; Ferraye et al., 2013; Shine et al., 2013). Another possible factor is the sequence effect in which sequential movements become progressively smaller (Ianssek et al., 2006; Chee et al., 2009). One study showed that freezing would

occur when the demands for rapid stepping were high (Moreau, Defebvre, Bleuse et al., 2008). Yet another factor contributing to freezing is the loss of automaticity and excessive dependence on external stimuli in patients with PD (Hallett, 2008; Vandenbossche et al., 2012; Wu et al., 2015). Imaging studies suggest that freezing is associated with abnormalities of the mesencephalic locomotor region (Snijders et al., 2011; Fling et al., 2013; Seville et al., 2018), but other regions as well (Herman et al., 2013; Fasano et al., 2015). Given all the various factors that can affect freezing, it is reasonable to consider that there are really multiple subtypes (Ehgoetz Martens et al., 2018).

In addition to the absence of movement, another form of freezing is characterized by rapid, side-to-side shifting of weight and trembling of the knees, but no lifting of the feet and no forward progression. This has been called the “slipping clutch syndrome.” In this situation, physiologic studies show co-contraction activity in antagonist muscles, perhaps not permitting effective forward movement (Yanagisawa et al., 2001). There is evidence that this repetitive activity is a series of anticipatory postural adjustments (Jacobs et al., 2009). Ordinarily, only one such adjustment is needed to allow a step to take place.

Freezing is very common in idiopathic PD, but is also seen in other parkinsonian states such as progressive supranuclear palsy (PSP), vascular parkinsonism, and normal pressure hydrocephalus. It seems less common in multiple system atrophy and drug-induced parkinsonism (Giladi, 2001).

Marché à petit pas. Walking with very short, often shuffling, steps. This is most typical of a multi-infarct state, but can be seen with parkinsonism.

Festination. This is a gait in which short steps become progressively more rapid. This extension of *Marché à petit pas* is also characteristic of parkinsonism. The stepping may even become much more rapid than normal. This can also be called a propulsive gait. It has been proposed that there are two phenotypes of festination (Nonnekes, Giladi, Guha et al., 2018).

Anatomic/physiologic classification

Gait disorders, like gait itself, are very complex. This chapter will follow the classification of Nutt and colleagues, proposed in 1993, because that has been the most commonly used (Nutt et al., 1993). Some more recent refinements have been suggested to this classification (Jankovic et al., 2001; Nutt, 2001). Other newer classifications focus on “neurologic signs” (Nonnekes, Goselink, Ruzicka et al., 2018) or “unusual gait disorders” (Paramanandam et al., 2018).

Lowest level

The lowest level refers to elemental disorders such as those resulting from muscle, nerve, or root disorders. This would also include the consequences of sensory deficits such as peripheral neuropathy and vestibular or visual disorder. Severe sensory loss can produce a gait similar to that of cerebellar ataxia; these patients have particular difficulty walking in the dark. An example is the GALOP syndrome, characterized by gait “ataxia” and peripheral neuropathy associated with a monoclonal immunoglobulin M (IgM) specific for galopin, a central nervous system white matter antigen (Alpert, 2004).

One set of examples relates to disturbances generated by particular patterns of weakness. For example, the steppage gait is the result of a foot drop. The hip and knee have to be excessively flexed to bring the leg up high enough so the toes do not scrape the floor. Another example is the Trendelenburg gait, or waddling gait, in which weakness of the hip abductors during stance leads to dropping of the pelvis on the contralateral side (the swing leg). The compensated Trendelenburg gait is characterized by a lean (or lurch) toward the stance leg to attempt to avoid the pelvic drop.

Middle level

The middle level refers to central nervous system disorders arising from standard parts of the motor system.

Hemiparetic gait

Because of a unilateral lesion of the corticospinal tract, most commonly observed with stroke, there is a stiff extended leg that circumducts during swing with scraping of the toe (Video 19.1). This is also called spastic gait. Typically, of course, there should be some weakness in a “pyramidal” distribution and increased reflexes. The earliest sign might be reduced knee flexion during swing (Kerrigan et al., 2001). Other findings would be increased stance time on the good leg and decreased step length of the affected leg (Vachranukunkiet and Esquenazi, 2013). ▶

Treatment of the spasticity might be useful, but this must be done carefully because without spasticity, the leg might collapse and not provide support. Oral agents, dorsal rhizotomy, or intrathecal baclofen can be used. Botulinum toxin directed to the rectus femoris or triceps surae has been used very successfully, particularly in the setting of cerebral palsy (Love et al., 2010; Dunne et al., 2012; Tok et al., 2012; Esquenazi et al., 2013; Lampire et al., 2013; Wang and Gao, 2013; Esquenazi et al., 2020).

Paraparetic gait

The paraparetic gait is a bilateral hemiparetic gait and shows stiffness of both legs with scissoring (excessive hip adduction) (Video 19.2). Conditions in which this is prominent include spinal cord injury, hereditary spastic paraparesis, and primary lateral sclerosis. ▶

Stiff-legged gait

The term stiff-legged gait includes the spastic syndromes of hemiparetic and paraparetic gait and also the disorder seen with the stiff-person syndrome (Video 19.3). There is primary stiffness of the spine with hyperlordosis, but all joints of the lower extremity will have reduced range of motion as well. ▶

Ataxic gait

Patients with cerebellar ataxia have difficulty with motor control by virtue of dysmetria, dyssynergia, variability of performance, and poor balance. All these features contribute to their disorder of gait (Ilg et al., 2008; Ilg and Timmann, 2013). Clinically, the gait is characterized by irregularity of stepping, in direction, distance, and timing. Patients may lurch in different directions. Stability of upright stance is poor, and patients may fall (Schniepp et al., 2014). Just as with standing balance, the base, or distance between the feet, is said to be broad (Video 19.4). ▶

Video 19.1 Hemiplegic gait secondary to a stroke. This patient has a left hemiparesis. He walks with a stiff left leg. The leg circumducts to avoid hitting the ground in swing, and the landing of the foot is flat.

Video 19.2 Paraplegic gait secondary to hereditary spastic paraplegia. This patient has hereditary spastic paraplegia. There is scissoring of the legs with bilateral circumduction of the legs in the swing phase. (Courtesy Mary Kay Floeter, MD, National Institutes of Health.)

Video 19.3 Two examples of gait in stiff-person syndrome. (A) The first patient with stiff-person syndrome is clearly very stiff in all joints and can barely walk, needing some support to aid her balance. She was filmed while having a gait study, and there are markers on her joints. (B) The second patient is also very stiff, but his balance is better. (A, Courtesy Marinos Dalakas, MD, National Institutes of Health.)

Palliyath and colleagues (1998) studied the gait pattern in 10 patients with cerebellar degeneration. Gait at natural speed was studied using a video-based kinematic data acquisition system for measuring body movements. Patients showed a reduced step and stride length with a trend to reduced cadence. Heel off time, toe off time, and time of peak flexion of the knee in swing were all delayed. Range of rotation of ankle, knee, and hip were all reduced, but only ankle range of rotation reached significance. Multijoint coordination was impaired as indicated by a relatively greater delay of plantar flexion of the ankle compared with flexion of the knee and a relatively late knee flexion compared with hip flexion at the onset of swing. The patients also showed increased variability of almost all measures. Although some of the deviations from normal were due simply to the slowness of walking, the gait pattern of patients with cerebellar degeneration showed incoordination similar to that previously described for their multijoint limb motion. A wide base was not seen in this study, but it was seen in another one (Hudson and Krebs, 2000). There is excessive antagonist muscle coactivation in these patients as well (Mari et al., 2014).

Patients with essential tremor have a mild gait abnormality that is ataxic in type (Stolze, Petersen, Raethjen et al., 2001; Arkadir and Louis, 2013; Roemmich et al., 2013; Louis and Faust, 2020). This observation forms part of the evidence that essential tremor results from cerebellar dysfunction.

Parkinsonian gait

Parkinson patients often have a stooped posture and stand and walk on a narrow base (Morris, Huxham, McGinley et al., 2001a,b; Ebersbach et al., 2013). Sometimes there is marked flexion of the trunk, called camptocormia, a condition also seen in dystonia and in functional conditions (Azher and Jankovic, 2005). Balance is poor, and patients often fall (Kerr et al., 2010). They develop short, shuffling steps, the *marché à petit pas*, and this can be associated with festination (Video 19.5). They turn en bloc, and important associated signs are lack of arm swing and tremor of the hands. There is difficulty taking the first step at gait initiation (Rahimpour et al., 2020; Bayot et al., 2021). Freezing is common and can occur in both the “off” and “on” states. Freezing is seen in about one-quarter of patients by 4 years (Rascol et al., 2000). Abnormalities of EMG pattern have been described (Nieuwboer et al., 2004; Nutt et al., 2011). 🕒

Gait speed in PD is slow and progressively slows as the disease progresses (Vila et al., 2021). If trying to walk faster, patients increase step rate proportionately more than stride length (compared with normal subjects) (Morris et al., 1998). EMG and kinematic studies have illuminated the pathophysiology (Albani et al., 2003; Svehlík et al., 2009; Nanhoe-Mahabier et al., 2011; Creaby and Cole, 2018; Marquez et al., 2020; Zanardi et al., 2021).

Variability of stride length is a gait feature that has been associated with falls (Ma, et al., 2020). Stride time and variability were studied in patients with PD and compared with other clinical measures (Schaafsma et al., 2003). Variability was independent of tremor, rigidity, and bradykinesia, but somewhat responsive to levodopa. Gait variability markedly increases with a simultaneous cognitive task, and this certainly would make patients more prone to falls (Hausdorff, Balash, and Giladi, 2003). Those patients with more freezing also have more variability, suggesting that this might be a factor in the cause of freezing (Hausdorff, Schaafsma, Balash et al., 2003; Gilat et al., 2013).

Because gait does require some attention, if patients are asked to do a second task while walking, the gait performance can deteriorate (Plotnik et al., 2009; Yogev-Seligmann et al., 2013; Vitorio et al., 2020). Patients can even fall. Patients realize this, at least subconsciously, and may well stop walking to answer a question. This is the basis of the “stops walking when talking” test (Lundin-Olsson et al., 1997).

Treatment of the parkinsonism with dopaminergic therapy or deep brain stimulation (DBS) improves gait, but often not as much as other motor symptoms (Lubik et al., 2006; Feray et al., 2008; Szlufik et al., 2018). Freezing particularly is generally difficult to treat, but off-freezing may well improve with dopaminergic medication and in some cases with DBS. Another approach is the use of methylphenidate (Auriel et al., 2006; Devos et al., 2007, 2013; Pollak et al., 2007; Moreau et al., 2012; Devos et al., 2013), although there is some negative evidence (Espay et al., 2011). There is also some evidence for the utility of amantadine (Malkani et al., 2012). On-freezing is a particularly difficult problem and may respond to lowering the dopaminergic medication. It was suggested that botulinum toxin might improve gait freezing (Giladi et al., 2001), but this was not confirmed in a double-blind trial (Wieler et al., 2005). Parkinsonian gait also can be improved by rhythmical visual or auditory cues (Suteerawattananon et al., 2004; Ledger et al., 2008; Arias and Cudeiro, 2010; Thaut et al., 2018). Mental singing while walking may also improve gait performance (Satoh and Kuzuhara, 2008). Physical therapy can help, but may have only a short-term benefit especially if not continued (Frazzitta et al., 2009; Morris et al., 2010; Tomlinson et al., 2013; Rutz and Benninger, 2020; Alatawi, 2021). On the other hand, it seems very clear that exercise in general is very good for patients with PD (Grazina and Massano, 2013; Tollar et al., 2018). A meta-analysis concluded that although all exercise is good, if improved gait is the goal, some type of gait training might be best (Ni et al., 2018). One component of therapy should have the patients concentrate on making “big” steps (Werner and Gentile, 2010). Action observation may improve freezing of gait in PD patients (Pelosin et al., 2010; Di Iorio et al., 2018). Treadmill training can be helpful as well (Bello et al., 2010; Mehrholz et al., 2010), and this might be augmented by combining with visual clues (Schlick et al., 2016). Dance therapy may have some longer lasting effects; much work has been done particularly with the tango (Hackney and Earhart, 2009, 2010; de Dreu et al., 2012; Foster et al., 2013). Gait training in water (hydrotherapy) appears to have value (Volpe et al., 2017; Masiero et al., 2019). Transcranial magnetic stimulation may have benefit when used by itself (Lomarev et al., 2006; Lefaucheur et al., 2020), but may have even greater benefit if used to prime behavioral training (Chung et al., 2020). A comprehensive approach to gait freezing includes an algorithm to guide thinking (Nonnekes et al., 2015).

Spinal cord stimulation also has been occasionally used to help patients with freezing (Samotus et al., 2018), including patients already receiving DBS (Pinto de Souza et al., 2017), although evidence for this treatment is mixed (García et al., 2020).

It is now often the case that problems with balance and gait continue despite improvements in bradykinesia after DBS. This has led to attempts to improve DBS (Potter-Nerger and Volkmann, 2013). One approach is to change the stimulation parameters in the subthalamic nucleus (STN) or globus pallidum internus (GPi) (Moreau, Defebvre, Destee et al., 2008;

Video 19.4 Ataxic gait in a patient with degenerative ataxia. This patient has a degenerative ataxia and walks with poor balance, a wide base, and irregular steps. There is also an occasional lurch.

Video 19.5 Six examples of Parkinson gait. (A) This woman has only a subtle problem with decreased swing of the left hand and intermittent tremor.

(B) This man shows bilateral decreased arm swing and en bloc turns. (C). This man has a slow gait, with bilateral arm tremor, much more on the right. (D) This man, who has some balance difficulty, freezing, decreased swing of right arm, and en bloc turns. (E) This man has a significant problem with freezing that is brought out on turns. (F) This woman has very severe freezing.

Ramdhani et al., 2015; Su et al., 2018). There also has been considerable interest in the PPN as a DBS target (Stefani et al., 2007, 2013; Pereira et al., 2008; Ferraye et al., 2010; Morita et al., 2014; Welter et al., 2015; Snijders et al., 2016; Thevathasan et al., 2018; Garcia-Rill et al., 2019; Lin et al., 2020; Yu et al., 2020). Some patients certainly respond, but others do not, and the evidence overall is that the effect is only mild to moderate. One issue with PPN DBS is the exact target in the PPN area; this remains controversial, and the cuneiform nucleus might be the relevant target (Fournier-Gosselin et al., 2013; Snijders et al., 2016; Goetz et al., 2018, 2019). Another issue has been disease progression in other functions, especially balance, even when improvement is noted in gait and freezing parameters.

Dystonic gait

An early common manifestation of dystonic gait is the inversion of the foot with walking. The great toe can be flexed or extended. It is an action dystonia and would not be present at rest. As the dystonia worsens, there can be more abnormal posturing of the legs, trunk, and arms. Sometimes there is so much abnormal movement that the gait looks like the dancing gait of chorea. The disorder is task-specific so that walking backward in some cases may be much better than walking forward, and running can be spared (Video 19.6). Dystonic gaits can look very unusual, and care is needed to distinguish them from psychogenic. Camptocormia, flexion of the spine, is one such abnormal posture in which a principal differential diagnosis is psychogenic. ►

Choreic gait

The choreic gait is often called dancing gait and represents the superimposition of chorea on the locomotor movements. Stepping is also uncoordinated and appears dysmetric like an ataxic gait (Video 19.7). ►

Bouncing gait (myoclonus)

When myoclonus affects stance and gait, it gives rise to a characteristic bouncing (Video 19.8). The appearance is due more to frequent negative myoclonus than to positive myoclonus. ►

Highest level

The highest level disorders come from malfunction of the cerebral hemispheres. These disorders are not completely distinct from each other; patients may have characteristics of more than one or may progress from one to another (Jankovic et al., 2001; Nutt, 2001; Thompson, 2001). This level also includes functional (psychogenic) gait and disorders arising from psychiatric origin, such as cautious gait.

Subcortical disequilibrium

Subcortical disequilibrium is a severe impairment of balance (Masdeu, 2001). The disorder arises from dysfunction at midbrain, basal ganglia, or thalamic levels, and is often a feature of parkinsonism-plus disorders. It has been called thalamic astasia. This entity, by its etiology, is really misplaced and belongs in the middle-level category. Perhaps it really represents a combined basal ganglionic and cerebellar balance disorder.

The next three conditions, frontal disequilibrium, isolated gait ignition failure, and frontal gait disorder, are frequently difficult to separate from each other and might be considered varied manifestations of a frontal lobe dysfunction of gait (Fig. 19.6).

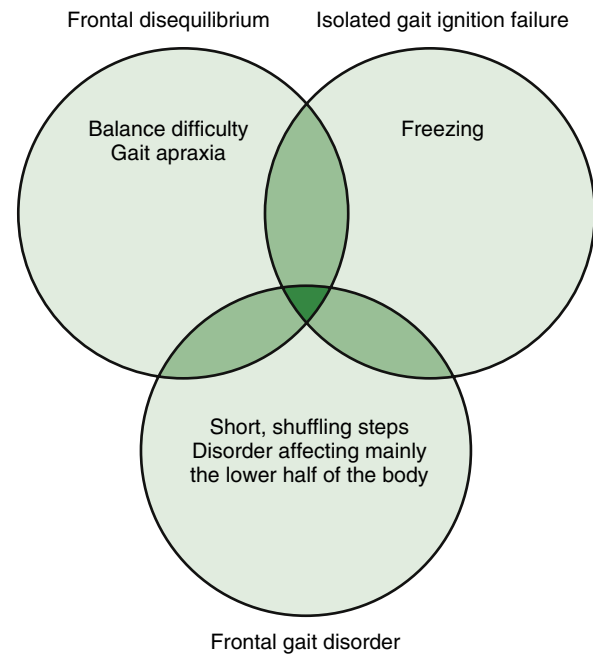


Fig. 19.6 Relationship of the three different types of higher level gait disorders arising from frontal lobe dysfunction. See text for more detail.

Frontal disequilibrium

Frontal disequilibrium is also characterized by a loss of balance, but is accompanied by disordered stepping that is difficult to describe. Some have called the stepping disorder “apraxia” (Gerstmann and Schilder, 1926) and others have called it “ataxia” (Bruns, 1892). The concept of apraxia comes from the observation that leg movements unrelated to walking seem reasonably good. It is also associated with frontal lobe signs, and it is this feature that suggests the frontal origin.

Isolated gait ignition failure

Isolated gait ignition failure is the difficulty in initiating and sustaining locomotion (Taskapilioglu et al., 2009). The patient has freezing, particularly of the type getting started. The term primary progressive freezing gait has also been used (Factor et al., 2002). Balance can be good, and although steps begin short, they gradually increase in amplitude. Thus, patients may say that they walk normally once they get started. This gradual increase differs from festination in that with festination, the stepping never appears normal.

Frontal gait disorder

Patients with frontal gait disorder at first look like they have a parkinsonian gait, with short, shuffling steps, poor balance, initiation failure, and hesitations on turns (Video 19.9). Differentiating features are a more upright stance, lack of tremor, frontal lobe signs, and apparent involvement of only the lower part of the body (Thompson, 2001). This last feature gives rise to the term “lower half parkinsonism” or “lower body parkinsonism.” The disorder can evolve to a frontal disequilibrium with the difficult-to-describe stepping disorder. The disorder does not respond to levodopa. ►

As noted, frontal disequilibrium, isolated gait ignition failure, and frontal gait disorder often overlap. Their causes are also similar and include subcortical arteriosclerotic

Video 19.6 Two examples of gait in patients with dystonia. (A) This first patient has neuroacanthocytosis. There is obvious dystonic posturing of the legs during walking. As is common in dystonia, she walks much better backward. (B) The second patient is a young boy with an intermittent abnormal movement of the legs when walking, including occasional toe walking. A walking abnormality is often the opening symptom of childhood dystonia. (A, Courtesy Adrian Danek, MD, National Institutes of Health. B, Courtesy Leon Dure, MD.)

Video 19.7 Gait in a patient with Huntington disease (HD). This patient with HD presented with a gait abnormality, called the dancing gait. Because this patient was a longtime dancer, the movement disorder was not recognized at first.

Video 19.8 Myoclonic gait. This patient has posthypoxic myoclonus. He has considerable negative and positive myoclonus while trying to walk; this is called the bouncy gait. The backpack carries physiologic recording equipment.

Video 19.9 Three examples of frontal gait. (A) The first patient has a frontal gait disorder that is characterized by slowness and freezing while walking. She has particular difficulty with turns. (B) The second patient also has a frontal gait disorder, but the freezing has a different character, with the legs rapidly moving in place. This is called the slipping clutch gait. (C) The third patient has normal pressure hydrocephalus as the cause of his frontal gait disorder. Balance is poor, turning is difficult, and stepping is slow. (D) The next segment shows this same patient after shunting. His walking has clearly improved considerably, and his turning is faster. (B–D, Courtesy William Weiner, MD.)

encephalopathy (Binswanger disease), multi-infarct state, anterior cerebral artery stroke, normal pressure hydrocephalus, Pick disease, Alzheimer disease, frontotemporal dementia, subdural hematoma, brain tumor, multiple sclerosis, PSP, and corticobasal degeneration (Thompson, 2001). Older patients are more likely to have gait dysfunction if they have more white matter lesions on MRI (Franch et al., 2009). Two patients have been described with lesions predominant in the supplementary motor area (SMA) (Nadeau, 2007). PSP might be the most common cause.

The gait in normal pressure hydrocephalus has been the most studied, although the diagnosis is controversial (Saper, 2017; 2017; Brautigam et al., 2018) and other causes might be relevant in many of the diagnosed patients (Espay et al., 2017; Macki et al., 2020). Many of the patients have abnormal striatal dopamine reuptake transporter binding (Pozzi et al., 2021). Patients have freezing and gait apraxia. Quantitative gait studies show decreased stride length and reduced foot floor clearance (Stolze et al., 2000; Stolze, Kuhtz-Buschbeck, Drucke et al., 2001; Torsnes et al., 2014). Compared with a group of PD patients, those with normal pressure hydrocephalus were slower and had shorter stride length (Bugalho et al., 2013). It is, of course, critical to make this diagnosis because it is potentially a treatable disorder (McGirt et al., 2008; Williams and Relkin, 2013, 2018). The diagnosis is difficult, and patients should have clear clinical features (Agerskov et al., 2018), and laboratory data must be used thoughtfully (Relkin et al., 2005; Kiefer and Unterberg, 2012; Verny and Berrut, 2012). An evidence-based review suggested that the best test is prolonged external lumbar drainage in excess of 300 mL, which is associated with high sensitivity (50%–100%) and high positive predictive value (80%–100%) (Marmarou et al., 2005). A study of 90 patients with 1-day drainage confirmed this test with 12-month benefit of surgery with 100% sensitivity and 75% specificity (2018). The features of gait most responsive to lumbar drainage are walking speed, number of steps for turning, and balance (Ravdin et al., 2008; Gallagher, 2018). Anatomic MRI can be helpful, but may not be as good as lumbar drainage (Lee et al., 2010). However, a “small” callosal angle can be helpful in patients who will respond to shunting (Virhammar et al., 2014a,b). Identification of increased pulsatility of intracranial pressure has been suggested to be of value (Eide and Sorteberg, 2010), but there is negative evidence (Ringstad et al., 2015). Diffusion tensor imaging (DTI) may be predictive of which patients will respond to therapy (Jurcoane et al., 2014; Younes et al., 2018). One study has shown that the white matter lesions in patients will improve with shunting, suggesting that this aspect may play a role in the pathophysiology of the disorder (Akiguchi et al., 2008).

Increased ventricular dilation, even independent of a formal diagnosis of normal pressure hydrocephalus, is associated with gait impairment (Palm et al., 2009). An increased ratio of ventricular volume compared with sulcal cerebrospinal fluid volume predicted gait speed. This finding was independent of white matter hypertensity volume.

In the series of 30 patients reported by Factor and associates (2002) under the name of primary progressive freezing gait, they found a clinically distinct, progressive neurologic disorder that primarily affected gait, initially resulting in freezing and later in postural instability. A wheelchair-bound state often developed within 5 years. It was accompanied by other parkinsonian features, particularly bradykinesia, but was unresponsive to dopaminergic medications. Because of

its stereotyped manner, they suggested that it be considered a specific entity within the parkinsonism-plus disorders. Such patients may well have PSP (Williams et al., 2007), but other entities can be etiologic, such as corticobasal syndrome and even primary lateral sclerosis (Fasano et al., 2012).

Another classification of frontal gait disorders has been proposed, with three main types based on presumptive sites of anatomic damage: (1) ignition apraxia, in which damage is predominantly in the SMA and its connections, with good responses to external clues; (2) equilibrium apraxia, in which damage is predominantly in the premotor area and its connections, with poor responses to external clues; and (3) mixed gait apraxia (Liston et al., 2003). The authors of this proposal studied 13 patients with cerebral multi-infarct states and higher level gait disorder and diagnosed 7 with ignition apraxia and 6 with equilibrium apraxia.

In some patients with frontal gait disorder at least one component of the difficulty may be due to orthostatic myoclonus–jerking of the legs only when standing (Glass et al., 2007; van Gerpen, 2014; Hassan and van Gerpen, 2016). In 13 of 15 patients with postural unsteadiness due to this type of myoclonus, there was also a frontal gait disorder. Some of these patients improved with clonazepam or levetiracetam (Hassan and van Gerpen, 2016). In another study, looking for this entity, 16 of 93 patients with gait impairment and unsteadiness were thought to have this disorder (Gasca-Salas et al., 2013).

Although the term frontal gait disorder is used, the location of the relevant pathologic features is not completely clear. There is, in fact, some evidence for frontal dysfunction. For example, relevant white matter lesions leading to poor gait were largely in the frontal lobe (Srikanth et al., 2010). One study looked at single-photon emission computed tomography in patients with subcortical chronic vascular encephalopathy with and without walking. In those patients with gait dysfunction, there was less activation of the medial frontal gyrus bilaterally (and the anterior lobes of the cerebellum) (Carboncini et al., 2009). Dysfunction of the basal ganglio-thalamo-cortical loop may also play a role (Iseki et al., 2010).

Cautious gait

This is a common disorder, particularly in the elderly or with patients who have already experienced a fall for some reason (Kurlan, 2005; Sudarsky, 2006). The term “space phobia” has been used. Patients become cautious because of anxiety that they will fall. The gait is like what it would be for normal persons who are walking on ice. There is a wide base with slow, short steps; turns are en bloc. Arms are tense. Patients try to find support, and when they have it there is marked improvement (Video 19.10). These individuals do not have overt freezing or shuffling. ►

Functional (psychogenic) gait

A gait disorder is a common way for psychogenic movement disorders to manifest (Lempert et al., 1991; Hayes et al., 1999; Bhatia, 2001; Morris et al., 2006; Sudarsky, 2006; Baik and Lang, 2007; Jordbru et al., 2012; Fung, 2016; Sokol and Espay, 2016; Edwards, 2018; Nonnekes et al., 2020) (Video 19.11). This is also called astasia–abasia or acrobatic gait. There are unusual patterns of stance and gait, often inconsistent, often dramatic, with lurching, but only rarely falls (and then

Video 19.10 Cautious gait. When walking on her own, this patient walks very carefully, with small slow steps and hands outstretched, but when supported by her husband, she walks perfectly normally.

Video 19.11 Two examples of functional gait. (A) The first patient has a classic functional gait. Stepping is very irregular, and the knee buckling is a

very frequent manifestation. Despite the claim of poor balance, her balance is clearly very good. She occasionally falls but never hurts herself. (B) The second patient has a functional tremor and a functional gait. It appears that he is periodically pushed backward as he walks.

without hurting themselves). Sudden knee buckling without falling is a common pattern (Lempert et al., 1991). Extreme slow motion can be seen, and there is a sense that energy is being wasted. Camptocormia can be another manifesting feature (Skidmore et al., 2007), but there are many organic causes as well. Careful observation will show that the person typically demonstrates excellent balance. There may well be wide fluctuations over short periods of time, and quantification of the variation can be helpful (Merello et al., 2012). Another possible clue is a suffering or strained facial expression, with moaning and hyperventilation (Lempert et al., 1991; Laub et al., 2015). It is important to recognize that this can well be a treatable condition (Jordbru et al., 2014). See also Chapter 27. ●

It was mentioned earlier, but is worth noting again at this point, that disorders of gait are often multifactorial, particularly in elderly patients. It is useful to continue searching for causes even after one has been identified. This is certainly true of functional gait as well, because many of these patients have an organic neurologic disturbance.

Therapeutic considerations

As with other aspects of movement disorders, etiologic considerations come first. Is there a treatable neuropathy? Can vision be improved? PD can be treated, as can normal pressure hydrocephalus. The second consideration would be symptomatic treatments. Physical therapy can help with strengthening exercises or practice with elemental coordination. There are a variety of walking aids from canes to walkers (Edelstein, 2013). There are weighted walkers and rolling walkers that help in special circumstances. It is also critical to know when to suggest that the patient no longer should be trying to walk without assistance. Falls are potentially disastrous, with broken hips and subdural hematomas as possible consequences.

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Ataxia

Pathophysiology and clinical syndromes

Chapter contents

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Introduction

Ataxia is the type of clumsiness produced by dysfunction of the cerebellum or cerebellar pathways. The pathophysiology of the signs and symptoms has been detailed in the earlier chapter on motor control ([Chapter 2](#)) and have been reviewed ([Bodranghien et al., 2016](#); [Marsden, 2018](#)). The core symptoms are difficulty with balance and gait, clumsiness of the hands, and dysarthria. The differential diagnosis is very long and includes all types of neurologic pathologic processes. Although most patients presenting with ataxia will have a sporadic disorder, there has been increased attention on the genetic ataxias because of rapid advances in research. In a study from Japan of 10,487 patients there were 67.2% sporadic ataxia, 28.8% hereditary ataxia, 4.7% with more prominent hereditary spastic paraplegia, and 1.5% unknown ([Tsuji et al., 2008](#)). A population-based study in South East Wales in the United Kingdom identified 178 patients, 55 familial cases, and 123 sporadic cases ([Wardle et al., 2009](#)). In a study from northern France of 204 patients, identified after eliminating known (sporadic) secondary causes such as alcoholism and multiple system atrophy (MSA), 47% had autosomal dominant ataxia, 33% had sporadic ataxia, and 8% had recessive ataxia ([Degardin et al., 2012](#)). In a report of 167 childhood ataxias from Canada, 89% were sporadic and only 11% genetic ([Benini et al., 2012](#)). A study of 1500 patients from Sheffield, United Kingdom over 20 years had 1205 sporadic and 295 familial ataxia cases ([Hadjivassiliou, Martindale, Shanmugarajah et al., 2017](#)). A study from France of 80 patients with ataxia, with onset after the age of 40, identified the cause in 52 ([Gebus et al., 2017](#)). The most frequent was MSA (29), 9 had genetic causes, and 14 had a variety of acquired causes.

Sporadic ataxia

[Table 20.1](#) lists the principal categories. A series of 112 patients with sporadic ataxia in the United States were reported in 2002 ([Abele et al., 2002](#)). Thirty-two patients met the clinical criteria of possible or probable MSA. With genetic testing, Friedreich ataxia (FA) was found in 5 patients and dominant spinocerebellar ataxias (SCAs) in 11. The disease remained unexplained in 65 patients, although anti-gliadin antibodies were present in 14 patients (see later for detailed discussion of this entity). In the larger, more recent study of 1205 patients ([Hadjivassiliou, Martindale, Shanmugarajah et al., 2017](#)), 302 were thought to have gluten ataxia, no cause was found in 291, a genetic cause was identified in 157, 147 were alcohol related, and 128 were likely MSA; other causes were less than 3% each. Of the genetic causes, FA was by far the most frequent.

Degenerative ataxia

MSA is likely the most common disorder, certainly in adults ([Fanciulli and Wenning, 2015](#); [Laurens et al., 2017](#)). In the large series from Japan, of the sporadic ataxias, 64.7% were MSA ([Tsuji et al., 2008](#)). In addition to ataxia, patients have parkinsonism and autonomic dysfunction (including impotence). The disorder also has been called olivopontocerebellar atrophy or MSA-C when the emphasis is on ataxia, striatonigral degeneration, or MSA-P when the emphasis is on bradykinesia and rigidity, and Shy-Drager syndrome when the emphasis is on autonomic dysfunction. Early falls are a prominent feature. Variable clinical features include pyramidal signs, tremor, dysarthria, dystonia, and mild dementia. There is typically a poor response to levodopa, but clearly at times there is some response, and this can be

Table 20.1 Categories of sporadic ataxia

Degenerative
Stroke
Tumor
Toxic/metabolic
Paraneoplastic
Autoimmune
Infectious/postinfectious
Demyelinating
Other
Ataxia of noncerebellar origin

confusing. Responses are rarely dramatic and typically unsustainable. The pathologic hallmark of the disorder, in addition to neuronal cell loss, is the glial cytoplasmic inclusion (GCI) (Yoshida, 2007). Although common, MSA is often misdiagnosed. A study of 134 clinically diagnosed patients found that 68% were correctly diagnosed (Koga et al., 2015). MSA is described in detail in Chapter 9.

Laboratory findings of value include autonomic abnormalities (Pellecchia et al., 2020). Studies include the skin sympathetic response, the Valsalva maneuver, and heart rate variation. Rectal sphincter electromyography (EMG) shows denervation, but this test must be performed with caution. Women who have been through childbirth may have denervation secondary to their delivery. The specificity of this finding has been called into question. Magnetic resonance imaging (MRI) can show cerebellar and pontine atrophy. The hot-cross bun sign in the pons is due to degeneration of corticocerebellar fibers. Magnetic resonance spectroscopy (MRS) can show decreased N-acetyl aspartate signal in the cerebellum, and positron emission tomography (PET) can show decreased cerebellar metabolism.

Another degenerative cause is progressive myoclonic epilepsy because ataxia is typically a part of this syndrome. Often myoclonus and ataxia become difficult to separate. These syndromes are described in Chapter 18.

Strokes

A variety of strokes can produce ataxia. These can be due to lesions of the cerebellum or the cerebellar pathways (Pandolfo and Manto, 2013).

Ataxic hemiparesis is characterized by both weakness and incoordination. Lesions can be in the thalamus and posterior limb of the internal capsule, upper basis pontis and cerebral peduncle, parietal lobe, and (debated) anterior internal capsule and frontal lobe.

Hemisensory loss and hemiataxia is typically the result of a thalamic lesion.

Isolated gait ataxia can be seen with a lesion of the pontomedullary junction.

Ataxia (hemiataxia and/or gait ataxia) with variable cranial nerve involvement can be seen with involvement of several arteries. The superior cerebellar artery affects the upper pontine tegmentum; the anterior inferior cerebellar artery leads to damage of the lateral pontomedullary junction; and the posterior inferior cerebellar artery gives rise to the well-known lateral medullary syndrome.

Table 20.2 Tumors producing ataxia

Medulloblastoma
Astrocytoma
Ependymoma
Hemangioblastoma
Metastatic tumor
Meningioma
Cerebellopontine angle schwannoma

Tumors

The tumors commonly affecting the cerebellum are listed in Table 20.2.

Toxic and metabolic

Toxic damage to the cerebellum can be caused by alcohol, both acute and chronic (Manto, 2012; Hammoud and Jimenez-Shahed, 2019). The acute effects of alcohol appear to cause a true ataxia as measured by physiologic studies. In the chronic state, there can be irreversible cerebellar damage, particularly to the cerebellar vermis, leading to particular difficulties with stance and gait. There is also a characteristic prominent anterior-posterior sway when standing.

Hypoxia damages the cerebellum with a particular propensity for the Purkinje cells. These patients may also get myoclonus. Hyperthermia is another cause for Purkinje cell loss.

The childhood hyperammonemias are a cause of intermittent ataxia.

Although it remains somewhat controversial, ataxia can be a gluten-related disorder, that is, a consequence of the ingestion of gluten, a component of wheat (Hadjivassiliou et al., 2014; Hadjivassiliou, Sanders and Aeschlimann, 2015; Mearns et al., 2019). Celiac disease or sprue, the best-known gluten-related disorder (Ludvigsson et al., 2013), is an enteropathy with malabsorption and has been long known to sometimes be associated with ataxia and possibly also myoclonus (Burk et al., 2009). It is now considered that there are three main forms of autoimmunity to gluten, celiac disease, gluten ataxia, and dermatitis herpetiformis (Sapone et al., 2012; Taraghihkah et al., 2020); however, there continue to be reports of antibodies associated with a variety of neurologic diseases, even including amyotrophic lateral sclerosis (Gadoth et al., 2015). The different manifestations likely arise from different spectra of antibodies. Celiac disease can be treated with a gluten-free diet. The ataxia in the setting of celiac disease may persist despite a good diet (Burk et al., 2009).

The notion of gluten ataxia arose after finding a higher than expected incidence of antigliadin antibodies in patients with sporadic ataxia. Curiously, it is now clear that up to 40% of patients with sporadic ataxia have antigliadin antibodies, but no sign of celiac disease (Burk et al., 2001; Bushara et al., 2001; Hadjivassiliou et al., 2003; Hadjivassiliou, Boscolo, Tongiorgi et al., 2008; Hadjivassiliou, Sanders, Woodroffe et al., 2008). This has been supported by a 2018 meta-analysis (Lin et al., 2018). In some of these patients, there are abnormalities of the white matter and prominent headache; at least a few of these patients have some symptomatic response to a gluten-free diet (Hadjivassiliou et al., 2001). Antibodies to gangliosides were found in 64% of patients with mixed ataxias, suggesting

that the increase in antigliadin antibodies may not be specific (Shill et al., 2003). In gluten-associated ataxia, there also can be antibodies directed to tissue transglutaminase, either type 2, which is expressed in the gut (Hadjivassiliou et al., 2006), or, likely more specifically, type 6, which is expressed in neural tissue (Hadjivassiliou, Aeschlimann, Strigun et al., 2008). In a series of 100 patients with sporadic ataxia, 35 of 48 (73%) who had antigliadin antibodies had antibodies to transglutaminase type 6, whereas the antibodies were present in 21 of 65 (32%) patients without antigliadin antibodies (Hadjivassiliou et al., 2013). In that same series, neurologic controls had 5% incidence of the antibodies. Antigliadin antibodies in patients with ataxia also bind to the neural antigen synapsin I (Alaeldini et al., 2007), giving another autoimmune pathway to neurologic damage.

Some patients have symptoms of celiac disease but no demonstrable enteropathy, called nonceliac gluten sensitivity (NCGS). In a study of 228 patients with celiac disease and 334 with NCGS, there was about 40% ataxia in both groups and a similar high incidence of transglutaminase type 6 antibodies and a similar response to a gluten-free diet (Hadjivassiliou, et al., 2016).

There is open-label evidence that a gluten-free diet (Ghazal et al., 2012; Mulder et al., 2013) may benefit patients with antigliadin antibodies, but still no double-blind study. Additionally, magnetic resonance spectroscopy (MRS) of the cerebellum can improve on a gluten-free diet (Hadjivassiliou, Grunewald, Sanders et al., 2017). Intravenous immunoglobulin (IVIG) has improved the ataxia in three patients with overt celiac disease and ataxia (Souayah et al., 2008). IVIG therapy has been observed to help two patients and two other patients with anti-GAD antibodies (see later for discussion of this entity), suggesting a role for immunotherapy (Nanri et al., 2009).

A patient has been reported with long-standing slowly progressive ataxia who developed palatal tremor, and hence the syndrome of progressive ataxia with palatal tremor (PAPT) (Kheder et al., 2012). She had antigliadin antibodies. On a gluten-free diet, the palatal tremor resolved and the ataxia stabilized. Additionally, there was, typically, hypertrophy of the inferior olivary nuclei, and this regressed to some extent when on the diet.

There is a large report of 68 neurologic patients with celiac disease biomarkers that found that most had a strong alternative cause identified, some with other autoimmunity (McKeon et al., 2014). Hence, it might be that antigliadin antibodies are a frequent bystander and not often directly pathogenic.

Vitamin deficiencies can cause cerebellar dysfunction, including thiamine (vitamin B₁), vitamin B₁₂, and vitamin E. Zinc deficiency also may be a culprit of cerebellar dysfunction.

In the endocrine area, hypothyroidism, hypoparathyroidism, and hypoglycemia (insulinoma) have been associated with ataxia.

Toxic drugs include thallium, bismuth subsalicylate, methyl mercury, methyl bromide, and toluene. Drugs include phenytoin, carbamazepine, barbiturates, lithium, cyclosporine, methotrexate, and 5-fluorouracil. Ataxia can be a component of the serotonin syndrome, from selective serotonin reuptake inhibitors (SSRIs).

Table 20.3 Paraneoplastic antibodies seen in cerebellar syndromes

Antibody	Commonly related tumors
Anti-Yo (PCA1)	Ovary, breast
Anti-Tr	Hodgkin disease
Anti-PCA2	Small cell lung cancer
Anti-GAD	Thymoma, renal cell carcinoma
Anti-mGluR1	Hodgkin disease
Anti-Hu (ANNA-1)	Small cell lung cancer, neuroendocrine tumors
Anti-Ri (ANNA-2)	Breast, small cell lung cancer
Anti-Zic4	Small cell lung cancer
Anti-VGCC	Small cell lung cancer
Anti-CV2 (CRMP5)	Small cell lung cancer
Anti-Ma1	Testicular cancer
Anti-Ma2 (Ta) (rare)	Testicular cancer
Anti-amphiphysin (rare)	Small cell lung cancer

Paraneoplastic

The paraneoplastic causes are very important to keep in mind (Blaes and Tschernatsch, 2010; Sioka et al., 2010; Panzer and Dalmau, 2011; Graus and Dalmau, 2012; Greenlee, 2013). The clinical syndrome is often rapidly progressive over a relatively short period and then plateaus. What appears to be happening in most cases is a rapid destruction of Purkinje cells. Even if the cancer is found and successfully treated, the disorder may not improve because the cells are irreversibly damaged. Nevertheless, it is clearly important to treat the cancer.

In many cases, there will be detectable antibodies in the serum (Table 20.3). These antibodies are markers of the cancer and are not specific for cerebellar syndromes. Some cases of paraneoplastic ataxia have no defined associated antibody, so the disorder should not be ruled out just because one of the known antibodies is not found.

A number of the antibodies react against intracellular neuronal antigens, and many of those are specific to the Purkinje cell. These include anti-Yo (also called PCA1), seen with ovary and breast cancers; anti-Tr, seen with Hodgkin disease; and anti-PCA2, seen with small cell lung cancer. Two antibodies can be seen with or without neoplasms. These are anti-GAD (Arino et al., 2015), which can be seen with thymoma or renal cell carcinoma, and anti-mGluR1, which can be seen with Hodgkin disease. Anti-mGluR2 antibodies have now also been found in two patients with tumors (Ruiz-Garcia et al., 2020).

There are antibodies directed against neurons, not specific to the Purkinje cell. Anti-Hu (ANNA-1) can be seen with small cell lung or neuroendocrine tumors. Because the antibody may have a wide impact, other neurologic conditions may occur, such as encephalomyelitis. Anti-Ri (ANNA-2) is found with tumors of the breast and small cell lung cancer. Patients might also have brainstem encephalitis.

Antibodies to Zic4 are directed mostly to cerebellar granule cells and are seen with small cell lung cancers.

An antibody directed to a neuronal cell surface antigen is the anti-voltage-gated calcium channel (VGCC), which is also seen with small cell lung cancers.

Anti-CV2 (CRMP5) antibody is associated with a syndrome of ataxia often together with retinal or optic nerve symptoms (Honnorat et al., 2009; Porto et al., 2013). It has been seen with small cell lung carcinoma. The CV2 antigen is expressed by oligodendrocytes. This is one syndrome in which improvement has been seen with removal of the tumor.

Antibodies directed to a serum protein, Ma1, have been found in patients with testicular and other tumors (Gultekin et al., 2000; Dalmau et al., 2004). A related antibody is anti-Ma2 (or anti-Ta). These patients more likely will have limbic or brainstem encephalitis. Ma1 is a phosphoprotein highly limited to brain and testis.

Antibodies directed to amphiphysin are rarely associated with a cerebellar syndrome (Saiz et al., 1999; Coppens et al., 2006). This is often a marker for small cell lung carcinoma.

Tests that are currently commercially available include Hu, Ma, Ta, Yo, Ri, amphiphysin, Zic4, and CV2. Guidelines for screening have been published by the European Federation of Neurologic Societies (EFNS) (Titulaer et al., 2011).

In a series of 50 patients with paraneoplastic cerebellar degeneration out of 137 with any neurologic syndrome, 19 had anti-Yo, 16 anti-Hu, 7 anti-Tr, 6 anti-Ri, and 2 anti-mGluR1 (Shams'ili et al., 2003). Whereas 100% of patients with anti-Yo, anti-Tr, and anti-mGluR1 antibodies had ataxia, 86% of anti-Ri and 18% of anti-Hu patients had paraneoplastic cerebellar degeneration. In 42 patients (84%), a tumor was detected; the most common were gynecologic and breast cancer (anti-Yo and anti-Ri), lung cancer (anti-Hu), and Hodgkin lymphoma (anti-Tr and anti-mGluR1). All patients received antitumor therapy, and 7 had some neurologic improvement. The functional outcome was best in the anti-Ri patients, with 3 of 6 improving neurologically; 5 were able to walk at the time of last follow-up or death. Survival was worse with anti-Yo and anti-Hu compared with anti-Tr and anti-Ri.

In relation to treatment, it is critical to move as rapidly as possible. In addition to removing the tumor, immunologic therapy might be considered (Greenlee, 2013).

Autoimmune

Ataxia can be associated with antibodies not related to an underlying cancer (Mitoma et al., 2016). As noted earlier, one such antibody is anti-GAD (Dayalu and Teener, 2012; Alexopoulos and Dalakas, 2013; Nanri et al., 2013; Arino et al., 2014; Manto et al., 2018) (although it can be cancer related [Arino et al., 2015]). There can be a pure ataxia syndrome and one with an associated peripheral neuropathy. In one series of 14 patients, 13 were women and 11 had late-onset diabetes (Honnorat et al., 2001). Another series had 34 patients, 28 were women and 13 had diabetes (Arino et al., 2014). Anti-GAD antibodies are better known for association with stiff-person syndrome, but why one patient has one disorder or the other is not clear. It could be that the pathologic process is actually mediated by subtypes of GAD65-specific CD4(+) T cells, and the anti-GAD antibodies are only a marker (Costa et al., 2002; Burton et al., 2010). In the series by Arino and colleagues (2014), 9 of the 34 also had stiff-person syndrome.

In one case with antibodies in the cerebrospinal fluid, the antibody blocked GABAergic transmission in the rat cerebellum (Mitoma et al., 2000). As with stiff-person syndrome, patients can exhibit other forms of autoimmunity. IVIG or other immunotherapy may be useful (Nanri et al., 2009; Arino et al., 2014; Georgieva and Parton, 2014).

Patients also have been described with autoimmunity directed to the metabotropic glutamate receptor type 1 (mGluR1) (Lopez-Chiriboga et al., 2016). The symptoms and settings were highly variable.

Autoimmunity in general is a bad prognostic finding; guidelines for diagnosis have been suggested (Hadjivassiliou et al., 2020). The presence of one or more systemic, non-neuronal antibodies correlates with a faster evolution and shorter survival (Sivera et al., 2012). On the other hand, in anti-GAD ataxia, prompt recognition and immunotherapy led to long-term improvement in 35% (Arino et al., 2014). General guidelines have been suggested for treating immune-mediated ataxias (Mitoma et al., 2015; Mitoma et al., 2021). In a series of 118 patients with various types of autoimmunity, a number of patients did respond well, particularly those with GAD65 or plasma membrane protein (PMP) autoimmunity (Jones et al., 2015).

Infectious and postinfectious

Infectious causes include rubella and *Haemophilus influenzae* (Klockgether, 2010). Ataxia is also common in neurocytomegalovirus (Rissardo et al., 2020). Acute postinfectious cerebellitis is generally a childhood condition, most common after varicella. Creutzfeldt-Jakob disease may have an ataxic form. Acute cerebellitis can be due to SARS-CoV-2 (Fadakar et al., 2020).

Demyelinating

Ataxia is common in multiple sclerosis. A patient with leukoencephalopathy with neuroaxonal spheroids (LENAS), a rare disease of cerebral and cerebellar white matter, had a 14-year course of progressive neurologic decline consistent with a clinical diagnosis of probable MSA, with prominent cerebellar dysfunction and dysautonomia (Moro-De-Casillas et al., 2004).

Other

Other syndromes include Chiari malformation, abscess, hydrocephalus, and superficial central nervous system hemosiderosis (Klockgether, 2010). Ataxia can be a feature of high-altitude cerebral edema (Bird et al., 2011).

Ataxia of noncerebellar origin

What looks like cerebellar ataxia can come from dysfunction outside the cerebellum. Most common causes include neuropathies such as the Miller Fisher form of Guillain-Barré syndrome (Lo, 2007; Aranyi et al., 2012; Pandolfo and Manto, 2013) and spinocerebellar tract lesions.

Genetic ataxia

One of the most active areas in movement disorders and genetics is in determining the genes for numerous types of

hereditary ataxias. Additionally, we are beginning to understand some of the mechanisms of neurodegeneration. On the other hand, specific therapies are still in the future. Many of the genes can be tested commercially. This is helpful, but it is important to remember that genetic testing can have significant consequences, both emotionally and socially, and not only for the individual tested, but also for the family. Therefore, testing should be done with care and clear informed consent (Tan and Ashizawa, 2001). The worldwide prevalence of dominant ataxia averages 2.7 per 100,000, and autosomal recessive ataxia averages 3.3 per 100,000 (Ruano et al., 2014). The situation is rapidly changing, however, and with the availability of next generation sequencing and special analysis techniques, more patients will likely be identified with genetic causes (Ohba et al., 2013; Sawyer et al., 2014; Keogh et al., 2015; Pyle et al., 2015; Rafehi et al., 2020).

Moseley and colleagues (Moseley et al., 1998) determined the incidence of SCA types 1, 2, 3, 6, and 7 in 178 dominant kindreds in the United States with adult-onset ataxia of unknown cause. They found SCA1 expansion at a frequency of 5.6%, SCA2 expansion at a frequency of 15.2%, SCA3 expansion at a frequency of 20.8%, SCA6 expansion at a frequency of 15.2%, and SCA7 expansion at a frequency of 4.5%. The incidence of the SCAs also has been explored in other countries, such as Australia (Storey et al., 2000), Taiwan (Soong et al., 2001), Thailand (Sura et al., 2009), Portugal (Coutinho et al., 2013), and Argentina (Perez Maturo et al., 2020). The pattern does differ somewhat in different countries (Schols et al., 2004; Pandolfo and Manto, 2013; Klockgether et al., 2019). The epidemiologic patterns are summarized in Wardle and associates (2009) and Ruano and colleagues (2014). In those reviews, the most common autosomal dominant condition is SCA3, followed by SCA2 and SCA6, and the most common autosomal recessive condition is FA, followed by ataxia with oculomotor apraxia and ataxia-telangiectasia. Looking specifically at patients with onset at age 18 or later (late onset), a study in the southeast Wales population showed the most frequent defined diagnoses to be SCA6, dentatorubral-pallidoluysian atrophy (DRPLA), and SCA8 (Wardle et al., 2009).

In the large review of 1500 patients from Sheffield, United Kingdom (Hadjivassiliou, Martindale, Shanmugarajah et al., 2017) of the 295 familial cases, 40 were episodic ataxia type 2 (EA2), 30 SCA6, 22 FA, 12 SPG7, and 9 SCA2, and other entities had 7 or fewer. Of the 1205 sporadic cases, 295 were genetic and included 51 with FA, 26 with mitochondrial cause, 20 with spastic paraplegia 7 (SPG7), 14 with SCA6, 5 with fragile X-associated tremor/ataxia syndrome (FXTAS), and others with 3 or fewer. It is important to note SPG7, which is categorized as a hereditary spastic paraplegia (HSP). The HSPs will not be considered here, but there can be an overlap of the SCAs and the HSPs (see for review Blackstone, 2018a,b).

A very detailed compendium of the genetic ataxic disorders can be found at <http://neuromuscular.wustl.edu/ataxia/aindex.html>. There are a number of ataxia mutation databases (Hersheson et al., 2012).

Here, the principal disorders will be reviewed. There are many good reviews (Durr, 2010; Verbeek and van de Warrenburg, 2011; Sailer and Houlden, 2012; Subramony, 2012; Jayadev and Bird, 2013; Pandolfo and Manto, 2013; Rossi et al., 2014; van de Warrenburg et al., 2014; Teive and Ashizawa, 2015; Sun et al., 2016).

Dominant ataxia

The dominant ataxias were divided into three clinical syndromes by Anita Harding, the autosomal dominant cerebellar ataxias (ADCAs) I, II, and III. ADCA I is a cerebellar syndrome plus other neurologic degenerations such as corticospinal, basal ganglia, ophthalmoplegia, and dementia. ADCA II is a cerebellar syndrome with a pigmentary maculopathy. ADCA III is largely a pure cerebellar syndrome, with possible mild corticospinal signs. Subsequently, the genes were identified for these disorders, and they have been called the SCAs. This terminology is much more common now in clinical use. The identified SCAs are growing rapidly, and clearly there are more to be determined (Mundwiler and Shakkottai, 2018; Soong and Morrison, 2018). Alternative nomenclature has been proposed by a task force of the Movement Disorder Society (Marras et al., 2016).

Table 20.4 gives the identified SCAs and their known genetic disorder. Many of them are due to expanded trinucleotide repeats. SCA3 is Machado–Joseph disease and is often referred to as SCA3/MJD. DRPLA is often included in such lists. It shares the mutation disorder of CAG expansion and may have prominent ataxia as part of its manifestation. Some details about the proteins are known, and these are listed in Table 20.5. There is a bewildering array of mutations and likely multiple mechanisms of cerebellar degeneration. Using transcriptomic analysis, it was possible to demonstrate a number of specific functional modules for the involved genes (Bettencourt et al., 2014). The most significant module involved calcium signaling and homeostasis, and another involved the ubiquitin-proteasome system.

Commercial tests are available for many of the SCAs including DRPLA (and this list is likely to expand). The situation with genetic testing is changing rapidly however, and, in many circumstances, it may well make more sense to get a whole exome or whole genome analysis rather than individual genetic tests (Jacob, 2013; Jacob et al., 2013; van de Warrenburg et al., 2014; Coutelier et al., 2018). Whole exome analysis does not identify triple repeat disorders, and these are common, those should be tested for before the whole exome.

Generally, the cerebellar syndrome is similar in the different disorders. Patients experience gradual onset of balance and gait difficulty, dysarthria, and clumsiness of the hands. There may be visual symptoms such as blurry vision or diplopia. Age of onset is highly variable. MRI usually shows cerebellar atrophy (Klaes et al., 2016). Sometimes clinical features can help differentiate the different disorders. SCA12, for example, may be somewhat unique in that it may manifest with an action tremor that may look like essential tremor (O’Hearn et al., 2001). Other manifestations may help predict the genotype, but virtually any constellation of signs and symptoms can occur with any phenotype. Some guidelines are noted later. A longitudinal study has identified survival estimates for SCA1, 2, 3, and 6 (Diallo et al., 2018).

Lining up the ADCAs and the SCAs offers a starting point for the clinician (Table 20.6). A number of phenotypic clues are listed in Table 20.7.

DRPLA is most common in the Japanese (Tsuiji, 2012). It is also known as the Haw River syndrome from an African American family in North Carolina. In addition to ataxia, there may be myoclonus, epilepsy, chorea, athetosis, dystonia, dementia, psychiatric disorders, and parkinsonism.

Table 20.4 The spinocerebellar ataxias

Name	Chromosome	Mutation	Normal repeat number	Range of repeats in the disorder
SCA1	6p23	CAG expansion	6–44	40–83
SCA2	12q24	CAG expansion	14–31	34–59
SCA3	14q32	CAG expansion	12–38	56–86
SCA4	16q22			
SCA5	11q13	Deletion or point mutation		
SCA6	19p13	CAG expansion	4–20	21–31
SCA7	3p14	CAG expansion	7–17	38 to >200
SCA8	13q21	CTG expansion	15–91	100–155
SCA9	Not linked			
SCA10	22q13	ATTCT repeat	10–22	800–3800
SCA11	15q14			
SCA12	5q31	CAG expansion	<29	66–93
SCA13	19q13			
SCA14	19q13.4–qter	Point mutation		
SCA15, 16, 29?	3p26	Deletion or point mutation		
SCA17	6q27	CAG expansion	25–42	45–63
SCA18	7q31			
SCA19, 22	1p21–q21	Point mutation		
SCA20	11q.12			
SCA21	1p36.33	Point mutation		
SCA23	20p13	Point mutation		
(SCA24)	Now SCAR4			
SCA25	2p15–p21			
SCA26	19p13	Point mutation		
SCA27	13q34	Point mutation		
SCA28	18p11			
SCA30	4q34			
SCA31 (SCA4)	16q22	Penta-nucleotide (TGGA)n repeat insertion		
SCA32	7q32			
SCA35	20p13	Point mutation		
SCA36	20p13	expansion of intronic GGCCTG repeat, or a point mutation		1500–2500
SCA37	1p32			
SCA 38	6p12.1	Point mutation		
SCA 40	14q32.11	Point mutation		
SCA 41	4q27	Point mutation		
SCA 42	17q21	Point mutation		
SCA 43	3q25	Point mutation		
SCA 44	6q24	Point mutation		

Continued

Table 20.4 Continued

Name	Chromosome	Mutation	Normal repeat number	Range of repeats in the disorder
SCA 45	5q32	Point mutation		
SCA 46	19q13	Point mutation		
SCA 47	1p35	Point mutation		
SCA 48	16p13	Point mutation		
DRPLA	12p13	CAG expansion	<26	49–88

Table 20.5 Proteins affected in the spinocerebellar ataxias

Name	Protein
SCA1	Ataxin-1
SCA2	Ataxin-2
SCA3 (Machado–Joseph disease)	Ataxin-3
SCA4 (with sensory axonal neuropathy)	
SCA5 (Lincoln ataxia)	Beta III spectrin (SPTBN2)
SCA6	α_{1a} Component of the voltage-dependent calcium channel: CACNL1A4
SCA7	Ataxin-7
SCA8	(Mutation is in noncoding region)
SCA9	
SCA10	Ataxin-10
SCA11	Tau tubulin kinase 2 (TTBK2)
SCA12	Protein phosphatase 2A, regulatory subunit B (PPP2R2B)
SCA13	KCNC3
SCA14	Protein kinase C γ (PRKCG)
SCA15, 16, 29?	Inositol 1,4,5-triphosphate receptor, type 1 (ITPR1)
SCA17 (also called HDL4) (with intellectual deterioration)	TATA binding protein (TBP)
SCA18 (with sensorimotor neuropathy)	
SCA19, 22	KCND3
SCA20 (with dysphonia and dentate calcification)	
SCA21 (with extrapyramidal features)	Transmembrane protein 240
SCA23	Prodynorphin (PDYN)
(SCA24) Now SCAR4	
SCA25 (with sensory neuropathy)	
SCA26 (pure cerebellar ataxia)	Eukaryotic translation elongation factor 2 (EEF2)

Name	Protein
SCA27 (with tremor and dyskinesia)	Fibroblast growth factor 14 (FGF14)
SCA28 (with ophthalmoparesis and hyperreflexia)	ATPase family gene 3-like 2 (AFG3L2)
SCA30 (pure cerebellar ataxia)	
SCA31 (Japanese form of SCA4)	Brain-expressed, associated with NEDD4 (BEAN)
SCA32 (cerebellar ataxia with azospermia and mental impairment)	
SCA35 (cerebellar ataxia with upper motor neuron features)	Protein-glutamine gamma-glutamyltransferase 6 (TGM6)
SCA36 (cerebellar ataxia with motor neuron involvement)	Nuclear protein 56 (NOP56; NOL5A)
SCA37 (cerebellar ataxia with abnormal vertical eye movements)	
SCA38	Elongation of very long chain fatty acids–like 5 (ELOVL5)
SCA40	Coiled-coil domain-containing protein 88C (CCDC88C; Daple)
SCA41	Transient receptor potential cation channel, subfamily C, member 3 (TRPC3)
SCA42	Haploinsufficiency of T-type calcium channel (CACNA1G)
SCA43	Haploinsufficiency of neprilysin, a zinc-dependent metalloproteinase (MME)
SCA44	Toxic gain-of-function metabotropic glutamate receptor 1 (GRM1)
SCA45	FAT2
SCA46	Haploinsufficiency of phospholipase D activity (PLD3)
SCA47	Haploinsufficiency of PUM1
SCA48	STUB1
DRPLA	Atrophin-1 or DRPLA protein

Table 20.6 Relationship between autosomal dominant cerebellar ataxias and spinocerebellar ataxias

ADCA type	SCA type
I (ataxia plus)	1, 2, 3, 4, 8, 9, 12, 17, 27, 28, 35, 42, 43, 44, 46, 47, DRPLA
II (with pigmentary maculopathy)	7
III (pure ataxia)	5, 6, 11, 14, 15, 22, 26, 30, 31, 37, 41, 45
Ataxia and epilepsy	10
Early onset with learning disability	13

Table 20.7 Clues to the spinocerebellar ataxias

Age at onset	Young adult: SCA1, 2, 3, 21 Older adult: SCA6, 35, 36, 37 Childhood onset: SCA2, 7, 13, 25, 27, DRPLA
Prominent anticipation	SCA7, DRPLA
Upper motor neuron signs	SCA1, 3, 7, 9, 12, 35 Some in SCA6, 8 Rare in SCA2
Slow saccades	Early, prominent: SCA2, 7 Late: SCA1, 3, 17, 28 Rare: SCA6
"Basal ganglia" signs	Early chorea: DRPLA, SCA 17, 27 Akinetic-rigid, Parkinson: SCA2, 3, 9, 12, 17, 21
Generalized areflexia	SCA2, 4, 19, 21, 22
Visual loss	SCA7
Dementia	Prominent: SCA17, DRPLA Early: SCA2, 7 Otherwise: rare
Myoclonus	DRPLA, SCA2, 14, 19
Tremor	SCA2, 8, 12, 15, 16, 19, 27
Seizures	SCA10, DRPLA

The pathologic features of the SCAs have been comprehensively reviewed (Seidel et al., 2012). The pathologic processes of cell loss and atrophy are overlapping in the different entities, but some patterns are common. The disease proteins may aggregate into cytoplasmic or intranuclear inclusions. A few have some specific features such as tau aggregation in SCA11 and protein deposition in the Purkinje cell layer in SCA31.

The pathophysiologic processes of the triplet repeat ataxias have been extensively studied (Zoghbi and Orr, 2009; Durr, 2010; Rub et al., 2013). Generally, the longer the length of the repeat, the earlier is the age of onset (Schols et al., 2004) and the more severe the disorder (Durr, 2010). These fall into a category of disorders called the polyQ diseases that also includes Huntington disease and spinal and bulbar muscular atrophy (Kennedy disease) (Nalavade et al., 2013; Stoyas and La Spada, 2018). A well-supported hypothesis is that the

mutated protein aggregates and is toxic to the cell (Hands and Wyttenbach, 2010; Papaleo and Invernizzi, 2011; Perez Ortiz and Orr, 2018). For example, in a mouse model of SCA1, the gene was made conditional; when the gene was turned off, the animals improved (Zu et al., 2004). Similarly, treatment of a mouse model of SCA1 with RNA interference (RNAi) or antisense oligonucleotide can improve the disorder (Friedrich et al., 2018). Recombinant adeno-associated virus vectors expressing short hairpin RNAs were injected into the cerebellum with marked benefit (Xia et al., 2004). The SCA1 RNA itself also can be toxic (Nalavade et al., 2013).

There are likely many pathologic causes for the ataxias. Reviewing a large number of genes, the shared mechanisms include abnormalities of synaptic transmission, transcription regulation, toxic RNA gain-of-function, mitochondrial dysfunction, channelopathies, and autophagy (Nibbeling et al., 2017; Sullivan et al., 2018).

There is no treatment for the SCAs. Lithium improved neurologic function and hippocampal dendritic arborization in a mouse model of SCA1 (Watase et al., 2007). The mode of action of lithium in this circumstance is not clear, but it could function as a histone deacetylase (HDAC) inhibitor. Perhaps also working as an HDAC inhibitor, valproic acid has ameliorated neurodegeneration in an animal model of SCA3 (Yi et al., 2013). Human studies have been initiated. Ultimately, gene therapy will be developed (Pulst, 2016).

There are other autosomal dominant disorders that may manifest with ataxia or have ataxia as a frequent component of a mixed picture. One such example is adult-onset Alexander disease that in addition to ataxia may have bulbar dysfunction and pyramidal signs (Pareyson et al., 2008; Prust et al., 2011). Patients can have the syndrome of PAPT. The MRI scan shows a very thin medulla and a thin cervical spinal cord, and these findings are an important clue to the diagnosis. As demonstrated by pathologic findings, another cause of PAPT is a tauopathy (Mari et al., 2014). The syndrome of cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss is referred to as CAPOS (Maas et al., 2016). It may manifest in childhood as a paroxysmal disorder in the setting of a febrile illness or in adult life as a slowly progressive ataxia. It has been found to be due a mutation in the *ATP1A3* gene, and acetazolamide might be useful in preventing the paroxysms.

Episodic ataxias

The episodic ataxias (EAs) are autosomal dominant (Table 20.8) (Tomlinson et al., 2009; Baloh, 2012; Choi and Choi, 2016; Piarroux et al., 2020). See also Chapter 24.

EA1 is associated with interictal myokymia. There are brief attacks of ataxia and dysarthria lasting seconds to minutes precipitated by exercise or startle. Onset is in childhood or early adolescence. The myokymia is prominent around the eyes or lips or in the fingers. The myokymia may respond to phenytoin and the ataxia to acetazolamide.

EA2 has intermittent attacks of ataxia, dysarthria, nausea, vertigo, diplopia, and oscillopsia lasting minutes to days. There may be interictal nystagmus or mild ataxia. Episodes are provoked by stress and exercise, but not startle. About half of the patients also have migraine. The attacks may respond to acetazolamide. The potassium channel blocker 4-aminopyridine also can be effective (Strupp et al., 2004). The gene for EA2 is the same as the gene for SCA6, but

Table 20.8 The episodic ataxias

Name	Chromosome	Mutation	Protein
EA type 1 (with myokymia)	12p13	Missense	Potassium channel, KCNA1
EA type 2 (with nystagmus)	19p13	Missense	α_{1a} Component of the voltage-dependent calcium channel: CACNL1A4
EA type 3 (with vertigo and tinnitus)	1q42		
EA type 4 (PATX)			
EA type 5	2q22		CACNB4 β 4
EA type 6 (with migraine)	5p13		SLC1A3 (EAAT1 protein)
EA type 7	19q13		
EA type 8	1p36-p34		
EA type 9 (same gene as SCA27)	13q34		FGF-14
EA with paroxysmal choreoathetosis and spasticity (CSE, also DYT9)	1p34		SLC2A1 (GLUT1)

the nature of the mutation differs. A different missense or truncation mutation in this gene causes familial hemiplegic migraine. There can be phenotypic overlaps among all three conditions. Two patients have been described that progressed to a late life dystonia (Spacey et al., 2005). Such patients may also have weakness; a disorder at the neuromuscular junction has been demonstrated with single-fiber EMG (Jen et al., 2001; Maselli et al., 2003). Ataxia attack frequency probably can be reduced with 4-aminopyridine 15 mg/day (Zesiewicz, Wilmot, Kuo et al., 2018).

EA3, called periodic vestibulocerebellar ataxia, is an autosomal dominant disorder characterized by defective smooth pursuit, gaze-evoked nystagmus, ataxia, and vertigo (Damji et al., 1996).

EA4 is characterized by vestibular ataxia, vertigo, tinnitus, and interictal myokymia; attacks are diminished by acetazolamide (Steckley et al., 2001). EA5 has been identified in one family and is due to a mutation in a calcium channel gene (Escayg et al., 2000). In other families with a mutation in this gene, there is epilepsy. EA6, EA7, EA8, and EA9 have been identified.

EA with paroxysmal choreoathetosis and spasticity has age of onset of 2 to 15 years (Auburger et al., 1996). There are attacks of ataxia, with involuntary movements and dystonia of extremities, paresthesias, and headache. Episodes last about 20 minutes and occur twice per day to twice per year. Precipitating factors include alcohol, fatigue, emotional stress, and physical exercise. In some there is spastic paraplegia which may persist between attacks. This is now identified also as DYT9 resulting from an abnormality of the GLUT1 protein (see Chapter 11). Treatment is with acetazolamide.

Recessive ataxia

A large number of recessive ataxias have been identified (Vermeer et al., 2011; Anheim et al., 2012; Filla and De Michele, 2012; Pandolfo and Manto, 2013; Fogel, 2018). The most common of these are discussed here, but many of these are rare. The ones discussed in this chapter are summarized in Table 20.9. Others can be found in the genetics table in

Chapter 1 (Table 1.5). The full list of designated autosomal recessive ataxias (SCAR) and ataxias with spasticity (SPAX) can be found there. The terminology is rather complex, and some disorders have multiple names from appearing in multiple lists. Another abbreviation for autosomal recessive cerebellar ataxia is ARCA, and later it will be noted that ARCA1 is SCAR8 and ARCA2 is SCAR9.

A clinical classification has been suggested based on clinical features (Beaudin et al., 2017). An alternative nomenclature has been proposed by a task force of the International Parkinson and Movement Disorder Society that is also based in part on clinical features (Rossi et al., 2018). This list includes 62 entities with the prefix ATX followed by the gene name, 30 disorders with mixed ataxia with another movement disorder with a prefix such as ATX/HSP for a spastic ataxia, and 89 additional entities that may have some ataxia but do not merit an ATX prefix.

Friedreich ataxia (FA)

The major autosomal recessive ataxia to consider is FA, the most common cause of hereditary ataxia, with a prevalence of about 1 in 50,000 persons (Collins, 2013; Pandolfo and Manto, 2013; Parkinson et al., 2013; Burk, 2017; Cook and Giunti, 2017). Age of onset is generally before 20 years. The clinical features, in addition to ataxia, are dysarthria, sensory loss, and corticospinal tract signs with absent reflexes. There is an axon loss peripheral neuropathy. There may be skeletal abnormalities such as kyphoscoliosis, cardiomyopathy, and diabetes. The cardiomyopathy is hypertrophic with possible associated muscular subaortic stenosis or a hypokinetic-dilated left ventricle. Abnormal electrocardiogram (ECG) findings are common.

The genetic abnormality is usually an expanded trinucleotide repeat of GAA in the first intron of a gene on chromosome 9q coding for the protein called frataxin, and a commercial genetic test is available. Normal repeat length is 6 to 28, and patients have 66 to 1700. Six percent of the time there is a point mutation. Frataxin is a mitochondrial protein encoded by nuclear DNA. Frataxin is involved in iron transport, and in FA there is excessive iron accumulation in mitochondria.

Table 20.9 Some recessive ataxias

Name	Chromosome	Mutation	Protein
Friedreich ataxia (FA)	9q13	Trinucleotide repeat of GAA (some point mutations)	Frataxin
Friedreich ataxia 2 (FA2)	9p23		
Ataxia with isolated vitamin E deficiency (AVED)	8q13	Point mutations and deletions	α -Tocopherol transfer protein (TTP1)
Abetalipoproteinemia	4q22	Point mutation, deletion	Microsomal triglyceride transfer protein (MTP)
Ataxia telangiectasia	11q22	Chromosome breaks	ATM gene that codes for the protein kinase PI-3
(Early onset) ataxia with oculomotor apraxia type 1 (AOA1)	9p13	Insertion, deletion, point mutation	Aprataxin (APTX)
(Early onset) ataxia with oculomotor apraxia type 2 (AOA2) (SCAR1)	9q34	Point mutation, deletion	Senataxin (SETX)
Autosomal recessive spastic ataxia of Charlevoix–Saguenay (ARSACS)	13q12	Deletions, point mutations	SACS gene that codes for saccin
Cayman ataxia (ATCAY)	19p13	Point mutations	ATCAY gene that codes for caytaxin
Marinesco–Sjögren Syndrome (MSS)	5q31	Various	SIL1
Mitochondrial recessive ataxia syndrome (MIRAS)	15q25	Point mutation	POLG1, a catalytic subunit of the mitochondrial DNA polymerase gamma
Spinocerebellar ataxia with axonal neuropathy (SCAN1)	14q31	Point mutation	Tyrosyl-DNA phosphodiesterase (TDP1)
ARCA1 (SCAR8) or SYNE1 ataxia	6q25	Point mutation, deletions	Synaptic nuclear envelope protein 1 (SYNE1)
ARCA2 (SCAR9)	1q41	Point mutations	CABC1 (ADCK3)
Familial cerebellar ataxia with muscle coenzyme Q10 deficiency			Some patients have AOA1 or ARCA2

There are abnormalities of iron-sulfur biogenesis and cellular iron metabolism (Pandolfo, 2012; Alsina et al., 2018). Using functional MRI, apparent increased iron has been detected in patients in the dentate nucleus (Waldvogel et al., 1999). (Pathologic studies have shown that total iron is not abnormal, and the MRI signal change may be due to shift of iron to ferritin [Koeppen et al., 2007].) The excess iron may lead to toxic free radicals and oxidative stress (Pandolfo, 2012; Gomes and Santos, 2013) and mitochondrial pathology (Gonzalez-Cabo and Palau, 2013). There are significant problems in the heart (Bradley et al., 2000; Lane et al., 2013) and in the brain.

Now that the gene can be identified, the phenotype has widened: (1) Late-onset FA (LOFA) with age of onset more than 25 is characterized by a more benign course (Lecocq et al., 2016); (2) FA with retained reflexes (FARR); and (3) the Acadian or Louisiana form with slower progression (Evidente et al., 2000). Generally, these phenotypes are related to shorter GAA expansions. FA can even manifest with peripheral neuropathy alone, without ataxia (Panas et al., 2002).

A second gene was identified whose mutation can lead to a clinically classic FA. This has been localized to chromosome 9p (Christodoulou et al., 2001), and although on the same chromosome as in the frataxin gene, it is not linked to it.

Many basic and clinical studies have attempted to develop a treatment for FA (Mancuso et al., 2010; Perlman, 2012; Pandolfo and Manto, 2013; Richardson et al., 2013; Strawser et al., 2014; Tai et al., 2018). Nothing is yet approved, although there are many approaches and some promising leads. There are four main directions for therapy (Wilson, 2012; Tai et al., 2018): increase the expression of frataxin, reduce the mitochondrial iron load, reduce the oxidative stress, and modulate frataxin-controlled metabolic pathways. In relation to increasing expression of frataxin, the mutation is in an intron; exons are generally intact, and hence an approach such as an HDAC inhibitor might produce more frataxin (Sandi et al., 2014).

For clinical treatment trials, there has been the most work with antioxidants, including coenzyme Q10 and idebenone, a molecule structurally related to coenzyme Q10. This large literature has been reviewed in the Cochrane Database, and the conclusion is that there is no demonstrated benefit (Kearney, Orrell, Fahey et al., 2012) (for any other type of therapy either). Subsequent to the Cochrane review, the first study of another antioxidant, A0001 (alpha-tocopheryl quinone) reported a dose-dependent improvement in ataxia (Lynch et al., 2012). There is also an open-label study of resveratrol reporting improvement (Yiu et al., 2015). A double-blind,

randomized trial of EPI-743, another antioxidant, did show some improvement (Zesiewicz, Salemi, Perlman et al., 2018).

In relation to iron chelation, most work has been done with deferiprone. The guideline review of the American Academy of Neurology concluded that it actually worsens ataxia (Zesiewicz, Wilmot, Kuo et al., 2018).

A promising early trial has been reported with high-dose nicotinamide (Libri et al., 2014). This is vitamin B₃ and an HDAC inhibitor. Over 8 weeks, an increase in frataxin concentration was found, and the medication was well tolerated. No clinical changes were seen, but longer treatment would seem necessary. Aminobenzamides are also promising HDAC inhibitors (Gottesfeld et al., 2013).

Gene therapy would seem to be the best approach in the long run. The mutation is in an intron, not in an exome, so if the abnormal region could be skipped or cut out, the protein might be normal (Li et al., 2018; Tai et al., 2018; Rocca et al., 2020).

Ataxia with isolated vitamin E deficiency (AVED)

AVED is a rare, but important, disorder that has a phenotype similar to that of FA (Di Donato et al., 2010; Hentati et al., 2012; El Euch-Fayache et al., 2014; Bonello and Ray, 2016). Additionally, there can be ophthalmoplegia and retinitis pigmentosa. This disorder is due to a defect in the *TTP1* gene coding for alpha-tocopherol transfer protein. This protein incorporates alpha-tocopherol into lipoproteins secreted by the liver. As in the conditions when vitamin E is deficient because of malabsorption, this disorder can be treated with vitamin E (Gabsi et al., 2001; Doria-Lamba et al., 2006). It should not be missed!

Abetalipoproteinemia (ABL)

ABL is a rare autosomal recessive deficiency of apoB-containing lipoproteins caused by a microsomal triglyceride transfer protein (MTP) deficiency (Burnett et al., 1993; Hentati et al., 2012; Lee and Hegele, 2014). Typically manifesting in infancy (Burnett et al., 1993), when occurring in teenage years or early adulthood, the syndrome is due to vitamin E deficiency. The main characteristics are ataxia and polyneuropathy, as well as acanthocytosis, celiac syndrome, and retinal degeneration. It should be treated with high doses of vitamin E.

Ataxia telangiectasia (AT)

AT is due to a mutation in the *ATM* gene that codes for a protein kinase that plays an important role in cell cycle control, apoptosis, and DNA double-strand break repair (Teive, Moro, Moscovich et al., 2015; Riboldi and Frucht, 2018). This abnormality leads to an increased incidence of malignancy and neurodegeneration. The mutations are scattered over the gene. The disorder begins early in childhood, often age 1 to 2 years (Hoche et al., 2012). There is ataxia, truncal more than appendicular, and dysarthria. Oculomotor apraxia—difficulty in initiating saccades—occurs early. Many other features are associated, such as dystonia, masked facies, choreoathetosis, myoclonus, tremor, long tract signs, and, eventually, peripheral neuropathy and cognitive decline (Levy and Lang, 2018a,b). There are also the well-known oculocutaneous telangiectasias and immunodeficiencies with reduced immunoglobulins and T-cell deficiencies, recurrent sinopulmonary infections, and malignancies, particularly

leukemia or lymphoma. Alpha-fetoprotein levels are elevated and chromosome breaks can be identified.

Early-onset ataxia with ocular motor apraxia and hypoalbuminemia (EAOH or AOA1 and AOA2)

Two disorders recognized in Japan, early-onset ataxia with hypoalbuminemia and ataxia with ocular motor apraxia (EAOH or AOA1 and AOA2) are now considered the same clinical entity because of the identification of a common mutation in the aprataxin gene (*APTX*) (Tada et al., 2010). The protein is relevant in DNA repair. In six patients from four families, cerebellar ataxia and peripheral neuropathy were noted in all, ocular motor apraxia was observed in five patients, and choreiform movements of the limbs and mental deterioration were observed in five patients (Shimazaki et al., 2002). All patients had hypoalbuminemia and hypercholesterolemia; brain MRI or computed tomography (CT) showed marked cerebellar atrophy. Nerve biopsy revealed depletion of large, myelinated fibers in three of the five patients examined. Many other patients have been described (D'Arrigo et al., 2008; Yokoseki et al., 2011; Renaud et al., 2018). A biomarker in many patients is a mild elevation of the blood level of alpha-fetoprotein (Renauds et al., 2018).

Ataxia with oculomotor apraxia type 2 (AOA2) also has been identified with a similar clinical picture but with mutations in the senataxin (*SETX*) gene (Criscuolo et al., 2006; Choudry et al., 2018). In a series of 19 patients, other features noted were a frequent polyneuropathy and elevation of the serum alpha-fetoprotein (Tazir et al., 2009). The alpha-fetoprotein level is higher than in AOA1, but less than that in AT (Mariani et al., 2017). The *SETX* gene is also mutated in ALS4, a motor neuron disorder with early onset, and some patients may share this phenotype (Schols et al., 2008). AOA2 is the second most common recessive ataxia after FA in Europe (Choudry et al., 2018).

Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS)

ARSACS with ataxia and pyramidal signs has a high prevalence in northeastern Quebec and is due to a mutation in the gene *SACS*, which codes for the protein saccin (Duquette et al., 2013; Gagnon et al., 2018). The protein regulates intermediate filament assembly and dynamics (Gentil et al., 2019). The clinical syndrome is clinically and genetically heterogeneous (Thiffault et al., 2013). There can be associated psychiatric manifestations (Mignarri et al., 2014).

Although this entity was originally thought to be geographically distinct, patients have been reported, for example, in Tunisia (Mrissa et al., 2000), Italy (Gregianin et al., 2013), Norway (Tzoulis et al., 2013), and Turkey (Incecik et al., 2018). Moreover, the phenotype is actually very broad, with some patients having neuropathy without ataxia (Vill et al., 2018).

Cayman ataxia

Cayman ataxia is a recessive congenital ataxia restricted to one area of Grand Cayman Island that appears to be due to one of two mutations (Bomar et al., 2003). The gene *ATCAY* or *Atcay* encodes a neuron-restricted protein called caytaxin. Caytaxin contains a CRAL-TRIO motif common to proteins that bind small lipophilic molecules. Mutations in

caytaxin are also responsible for the jittery mouse. A CRALTRIO domain is also in the alpha-tocopherol transfer protein (TTPA), mutations that cause a vitamin E-responsive ataxia.

Marinesco–Sjögren syndrome (MSS)

MSS is characterized by ataxia, cataracts from infancy, learning disability, myopathy, and short stature (Krieger et al., 2013; Ezgu et al., 2014). Mutations in the gene for SIL1, a protein in the endoplasmic reticulum, cause the disorder.

Mitochondrial recessive ataxia syndrome (MIRAS)

Mutations in POLG1, a catalytic subunit of the mitochondrial DNA polymerase gamma, can produce a wide variety of neurologic manifestations leading to various syndromes (Tzoulis et al., 2010; Isohanni et al., 2011; Rahman and Cope-land, 2019). There can be weakness, encephalopathy, seizures (including Alpers syndrome), progressive external ophthalmoplegia, dysphagia, and even Parkinson disease (Ylonen et al., 2013). Mutations can also cause ataxia (Palin et al., 2012; Mignarri et al., 2015; Nuzhnyi et al., 2021), likely due, at least in part, to sensory axonal peripheral neuropathy. One phenotype is sensory ataxia, neuropathy, dysarthria, and ophthalmoparesis (SANDO) (Gati et al., 2011; Lovan et al., 2013).

Spinocerebellar ataxia with axonal neuropathy (SCAN1)

SCAN1, a disorder of late childhood appears as a result of a mutation in tyrosyl-DNA phosphodiesterase (TDP1), a protein in the DNA repair pathway (Fam et al., 1993; Hirano et al., 2007).

Autosomal recessive cerebellar ataxia type 1 (ARCA1) or SYNE1 ataxia

ARCA1 syndrome has been characterized by middle-age onset, slow progression and moderate disability, significant dysarthria, mild oculomotor abnormalities, occasional brisk reflexes in the lower extremities, normal nerve conduction studies, and diffuse cerebellar atrophy on imaging; that is, a relatively pure ataxia syndrome. SYNE1 mutations are causative (Dupre et al., 2007; Noreau et al., 2013). Further analysis using next-generation sequencing in a large number of recessive ataxia families have found that this mutation is present in about 5% of families, but those families often have other important manifestations, particularly motor neuron disease (Mademan et al., 2016; Synofzik et al., 2016; Wiethoff et al., 2016). There also can be muscle and cardiac involvement (Indelicato et al., 2018).

Autosomal recessive cerebellar ataxia type 2 (ARCA2)

Patients with ARCA2 present with a slowly progressive ataxia characterized by cerebellar atrophy and seizures, with studies suggestive of coenzyme Q10 deficiency, including mildly elevated lactate levels and ubiquinone deficiency (Mignot et al., 2013). Mutations in the same gene were found by two groups, one that called it the *CABC1* gene (Mollet et al., 2008) and the other referring to it as the *ADCK3* gene (Lagier-Tourenne et al., 2008).

Familial cerebellar ataxia with muscle coenzyme Q10 deficiency

Familial cerebellar ataxia with muscle coenzyme Q10 deficiency is a complicated syndrome but important because it might be treatable in some circumstances (Artuch et al., 2006; Montero et al., 2007). In the original report, six patients with muscle CoQ10 deficiency (26%–35% of normal) presented with cerebellar ataxia, pyramidal signs, and seizures (Musumeci et al., 2001). All six patients responded to CoQ10 supplementation; strength increased, ataxia improved, and seizures became less frequent. Subsequently, in a study of muscle biopsies in 135 patients with undefined cerebellar ataxia, 13 were found to have deficient CoQ10 (Lamperti et al., 2003). The mutation in one family was in the aprataxin gene (*AOA1*) (Quinzii et al., 2005), and some of these patients certainly have *ARCA2* (Lagier-Tourenne et al., 2008; Liu et al., 2014). Another family had a mutation in *COX20*, but the phenotype here included dystonia and ataxia (Doss et al., 2014). Another mutation that leads to dystonia and ataxia is *COQ8a* (Galosi et al., 2019). Yet another cause is a *COQ4* gene defect (Bosch et al., 2018). The bottom line is that there appear to be many causes of the Q10 deficiency, but that identification of the deficiency is important.

Cerebellar ataxia with neuropathy and vestibular areflexia syndrome (CANVAS)

CANVAS is not a rare disorder (Szmulewicz et al., 2016; Infante et al., 2018). In one family, in whom the disorder appears to be dominant, there was a missense variant in *ELF2*, a gene that regulates expression of *ATXN2* and *ELOVL5*, other genes known to be involved in genetic ataxia (Ahmad et al., 2018). The principal mutation has now been identified as an intronic AAGGG repeat expansion in the replication factor complex subunit 1 (*RFC1*) gene (Cortese et al., 2020). It is indeed very common with some patients not exhibiting all the manifestations (Aboud Syriani et al., 2020). Another clinical clue to the disorder is a dry cough. The disorder can also be a mimic of early MSA (Sullivan et al., 2021).

Other autosomal recessive ataxias

There are a very large number of other recessive ataxias. There are a few entities worth mentioning, in which ataxia is typically only a minor part of the syndrome but can be treated (Anheim et al., 2012). Thus, they should come to mind in the differential diagnosis so as not to be missed by the clinician. Refsum disease has peripheral neuropathy, retinitis pigmentosa, deafness, loss of smell, and dry skin and can be treated with a phytanic acid-free diet and plasmapheresis. Niemann–Pick type C has hepatosplenomegaly, supranuclear gaze palsy, dystonia, cognitive decline, and possible epilepsy and should be treated with miglustat. Cerebrotendinous xanthomatosis has xanthomas on tendons, cataracts, brittle bones, dementia, and seizures and should be treated with chenodeoxycholic acid (Stelten et al., 2019; Islam et al., 2021).

Other entities are continuously being discovered. Two families were seen with early-onset ataxia and tonic upgaze, and the mutation was identified as a deletion in *GRID2*, a protein in the synapse between parallel fibers and Purkinje cells (Hills et al., 2013). A family was reported with slowly progressive ataxia, axonal neuropathy, and pyramidal signs with a mutation in *PEX10*

producing a peroxisomal biogenesis disorder. There is virtually no way to remember all of these entities, and, after common entities are ruled out, the next step is to perform comprehensive genetic testing and consult with up-to-date databases.

Frequency of the autosomal recessive ataxias

In a review of 102 patients with autosomal recessive (or sporadic) ataxia, a diagnosis was made in 57 of them; 36 were affected with FA, 7 with AOA2, 4 with AT, 3 with AOA1, 3 with MSS, 2 with ARSACS, 1 with AVED, and 1 with ARCA2 (Anheim et al., 2010). In the study from Northern France, of 13 patients, 6 had FA, 3 AT, 2 had AVED, 1 had ARCA2, and 1 had xeroderma pigmentosum (Degardin et al., 2012). Genetic testing is currently available for FA, AT, AVED, MSS, AOA1, AOA2, ARSACS, and MIRAS. Some clinical clues to the identification of the recessive ataxias are offered in Table 20.10. Given the pleomorphic manifestation of many gene mutations, it is important to think broadly. In a recent series, 18.6% of adult patients who also had some pyramidal signs had a mutation in SPG7 (Pfeffer et al., 2015), and SPG7 should be considered in other situations with a complex ataxia (Casari and Marconi, 1993). Since a number of the autosomal recessive ataxias have etiological treatments, it is important not to miss the diagnosis (Kwei and Kuo, 2020).

X-linked ataxia

Fragile X-associated tremor/ataxia syndrome (FXTAS)

Attention has been drawn to the fact that the fragile X premutation has been associated with tremor with appearance similar to that of essential tremor (Aparis et al., 2012; Leehey and Hagerman, 2012; Hagerman and Hagerman, 2013, 2016; Hall and O'Keefe, 2013; Hall and Berry-Kravis, 2018). Ataxia and executive dysfunction are also prominent in this disorder, and there can be some parkinsonism. Both women and men can be affected. An increased signal in the middle cerebellar peduncle can sometimes be seen by MRI. FXTAS has a clinical appearance similar to that of MSA, but in a review of 77 patients with an MSA diagnosis, only one person was identified with FXTAS (Biancalana et al., 2005); in another review of 426 patients, 4 had the premutation (Kamm et al., 2005). Continuing studies show this disorder to be rare (Reis et al., 2008). The abnormality is a premutation in the fragile X mental retardation type 1 (FMR1) gene, which leads to a gain of FMR1 mRNA function (Kong et al., 2017; Mila et al., 2018). The premutation is a 55 to 200 CGG repeat expansion. The neuropathology of this syndrome is characterized by intranuclear inclusions (Greco et al., 2006; Hagerman, 2013).

Diagnostic plan

In the evaluation of a patient with ataxia, Table 20.11 outlines a reasonable approach. After a good history and physical examination, laboratory tests should be performed to follow up clinical suspicions. More detailed algorithms can be found in the literature (Anheim et al., 2010; Klockgether, 2010; van Gaalen and van de Warrenburg, 2012). A highly successful algorithm for recessive ataxias, called RADIAL, makes use of all the clinical

Table 20.10 Clues to the recessive ataxias

Clinical feature	Ataxias to consider
Peripheral neuropathy	FA, AVED, SANDO, AT, AOA1, AOA2, ABL, SCAN1
Spasticity	ARSACS, LOFA
Oculomotor apraxia	AT, AOA1, AOA2
Motor neuron disease	SYNE1 ataxia
Retinitis pigmentosa	AVED, Refsum
Chorea	AT, AOA1, AOA2
Dystonia	AT, AOA2, Niemann–Pick type C
Seizures	ARCA2, MIRAS
Myopathy	MSS, MIRAS, ARCA2
Cataract	MSS, cerebrotendinous xanthomatosis
Intellectual disability	AOA1, ARCA2, MSS, Niemann–Pick type C

Modified from Vermeer S, van de Warrenburg BP, Willemsen MA, et al. (2011). Autosomal recessive cerebellar ataxias: The current state of affairs. *J Med Genet* 2011;48(10):651–659.

Table 20.11 Evaluation of the ataxic patient

Good history and physical examination, including a careful family history
Standard laboratory tests, including lipids and thyroid function
MRI (and PET and/or MRS if available)
Autonomic testing
Genetic testing
Toxic screen, vitamin levels (especially E)
Paraneoplastic antibodies, Other antibodies including antigliadin antibodies

MRI, Magnetic resonance imaging; MRS, magnetic resonance spectroscopy; PET, positron emission tomography.

and laboratory data (Renaud et al., 2017). MRI findings in different types of ataxias can be useful in diagnosis (Vedolin et al., 2013; Mascalchi and Vella, 2018). Currently, genetic testing is proving to be very effective in identifying the diagnosis. Whole exome methods have a high yield after checking for the triple-repeat disorders, which cannot be identified with such methods (Coutelier et al., 2018). It is also problematic that whole exome methods do not detect abnormalities in the noncoding regions (Aydin et al., 2018). However, with whole genome sequencing and new methods of analysis, these problems are being overcome, and finding responsible mutations is becoming more successful (Bogdanova-Mihaylova et al., 2021).

Recovery from cerebellar injury; therapy

Chronic signs and symptoms of cerebellar injury differ from those of the acute phase, and signs may disappear entirely, especially when cerebellar damage is sustained early in life or is limited in extent. In general, recovery from lesions

limited to regions of the cerebellar cortex, especially of the lateral hemispheres, is potentially greater than lesions that affect the deep nuclei. This may be due to plasticity at other sites within and outside the cerebellum, combined with the fact that cerebral repercussions of cerebellar injury may not be especially apparent on conventional testing.

Weakness, deconditioning, and spasticity are often seen in conjunction with ataxia and contribute substantially to its morbidity. All other factors being equal, stronger, more athletic individuals tend to tolerate moderate ataxia better. Specific physical treatments for ataxia with the application of weights might be helpful. The use of added mass to treat certain tremors has a sound mechanical basis. Because the addition of mass lowers the resonant frequency of a limb, it reduces its response to high-frequency oscillating driving signals. Indeed, [Hewer and colleagues \(1972\)](#) found better results in patients who had a tremor frequency greater than 7 Hz. In general, the more severe the tremor in terms of amplitude, the more weight that was needed to obtain improvement. With regard to ataxia, up to a point, additional mass also improved ataxia of arm movement and gait. However, beyond this, increased weight was associated with poorer performance. The optimal weight value varied by individual and was not clearly related to the severity of ataxia. Within the limits of fatigue tolerance, which unfortunately may pose a significant restriction, weight therapy remains a reasonable treatment option for some patients. It is also possible to use devices with incorporated viscous damping ([Aisen et al., 1993](#)). Physical therapy might be helpful, at least for balance and gait ([Marquer et al., 2014](#); [van de Warrenburg et al., 2014](#); [Marsden, 2018](#); [Milne et al., 2020](#)). The guideline review from the American Academy of Neurology could conclude only that 4-week in-patient rehabilitation probably improves ataxia and function ([Zesiewicz, Wilmot, Kuo et al., 2018](#)).

Pharmacologic therapy has been reviewed ([Trujillo-Martin et al., 2009](#); [Ilg et al., 2014](#); [Martineau et al., 2014](#); [Zesiewicz, Wilmot, Kuo et al., 2018](#); [Perlman, 2020](#)). Unfortunately, there are no excellent treatments and the evidence itself is generally limited.

Riluzole has shown some efficacy in a randomized, double-blind, placebo-controlled trial of 40 patients presenting with cerebellar ataxias of different causes ([Ristori et al., 2010](#)). Patients were treated with riluzole (100 mg/day) or placebo for 8 weeks. Results of a second randomized, double-blind, placebo-controlled trial of 60 patients for 1 year were also positive ([Romano et al., 2015](#)). Half of the treated group showed an improvement during the trial. A guideline of the American Academy of Neurology concluded that riluzole probably improves ataxias of mixed causes ([Zesiewicz, Wilmot, Kuo et al., 2018](#)). The guideline also noted that thyrotropin-releasing hormone possibly improves ataxia, but the evidence was only over 2 weeks. An additional conclusion is that, specifically for SCA type 3, valproic acid 1200 mg/day possibly improved ataxia at 12 weeks.

Acetyl-DL-leucine was given open-label to 13 patients with various generative ataxias over 1 week with significant improvement ([Strupp et al., 2013](#)). Controlled studies are underway ([Kalla et al., 2016](#); [Kalla and Strupp, 2019](#)). Other drugs are in the pipeline ([Perlman, 2020](#)).

Surgical ablation or high-frequency electrical stimulation of the ventral intermediate nucleus of the thalamus (VIM) can be effective in reducing cerebellar tremor and somewhat improve function ([Narabayashi, 1992](#); [Nguyen and Degos, 1993](#); [Shahzadi et al., 1995](#)); however, these procedures do not significantly lessen ataxia. Transcranial magnetic stimulation of the cerebellum possibly improves cerebellar signs at 3 weeks ([Zesiewicz, Wilmot, Kuo et al., 2018](#)).

In the end, there are so many mechanisms for ataxia that the exact cause will likely guide personalized treatment, either genetic or symptomatic ([Bushart et al., 2016](#); [Pulst, 2016](#); [Perlman, 2020](#)). In regard to the future development of clinical trials, it may be that neuroimaging will provide the most robust biomarkers ([Coarelli et al., 2018](#)).

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Stiffness syndromes

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Introduction

Muscle stiffness may be the presenting symptom in many disorders of the motor nervous system and muscles ([Table 21.1](#)). Spasticity is the most common, and the others must be distinguished from it. In this chapter, therefore, spasticity is the primary topic and considered first. The pathophysiologic process of rigidity, muscle stiffness in parkinsonism, is discussed in [Chapter 2](#). The important entities of stiff-person syndrome and its variants and neuromyotonia, syndromes of continuous muscle activity, are both autoimmune in nature and are considered in [Chapter 23](#). Continuous muscle activity can also arise from situations in which the pathophysiologic features lie in the muscle, nerve, or anterior horn cell. These conditions will also be considered in this chapter.

Stiffness is assessed by the amount of force required to make an object move. Tone, the more general clinical term, can be defined as the resistance to passive stretch of a joint. Stiffness is a sign and not a symptom. Patients may well mistake their weakness or bradykinesia as being stiff. Normal tone is very low, and it is difficult to appreciate a decrease in tone, but some authorities say that they can detect hypotonia in cerebellar dysfunction. Increased tone, hypertonia, is characteristic of several different states and can come from three theoretical mechanisms: (1) altered mechanical properties of the muscle or joint, (2) background co-contraction of muscles acting on the joint, and (3) increase in reflex response to the stretch opposing the movement ([Hallett, 2012](#)). Background muscle activity is often the most important of the three. The mechanical characteristic of muscle that describes its resistance to stretch is thixotropy. The most severe change of altered mechanical properties is contracture. Increased background contraction is often seen with difficulty in relaxation, such as commonly characterizes Parkinson disease. In most patients with dystonia, there is increased tone only when there is dystonic activity of a muscle. Background contraction is also obviously the main cause

of increased tone in patients with continuous muscle activity syndromes. There are many different reflexes that can occur in response to stretch, and these can help differentiate different states of hypertonia. In differentiating spasticity and rigidity, in simple terms, spasticity shows exaggerated short latency reflexes and rigidity shows exaggerated long latency reflexes ([Table 21.2](#)).

Spasticity

Spasticity is a form of hypertonia with a number of characteristic features ([Sheean, 2002](#); [Sanger et al., 2003](#); [Dietz & Sinkjaer, 2012](#); [Burke, Wissel, & Donnan, 2013](#); [Trompetto et al., 2014](#); [Li & Francisco, 2015](#); [Rivellis & Morice, 2018](#)). The increased resistance to stretch is velocity sensitive; there is more resistance the faster the joint is moved. There also might be a spastic catch, in which there is a sudden increase in tone in the middle of a fast stretch. There may be a clasped-knife phenomenon in which the resistance increases and then suddenly gives way. There are also several other “positive” features such as increased tendon jerks, clonus, increased flexor reflexes, spontaneous flexor spasms, and abnormal postures (spastic dystonia) ([Lorentzen et al., 2018](#)). Importantly, there are also “negative” features, including weakness (in a “pyramidal distribution”), fatigue, loss of coordination, and a decrease of some cutaneous reflexes. It can be noted that the increased stiffness can be valuable to a patient with significant weakness, because it might, for example, allow the patient to stand.

Loosely, neurologists usually say that spasticity arises from a lesion in the pyramidal tract or that it is from damage to the “upper motor neuron.” The first is false, and the second is vague. Supraspinal control of movement is complicated and consists of many tracts. Briefly, those fibers that go through the pyramid arise from the cortex and go to the spinal cord also can be called the corticospinal tract ([Davidoff, 1990](#)).

Table 21.1 Causes of muscle stiffness, cramps, spasms, rigidity, or contracture**Cerebral—brainstem**

Spasticity
 Parkinson disease (PD) (rigidity)
 Akineti–rigid syndromes other than PD
 Dystonia

Spinal cord

Stiff-person syndrome (also supraspinal abnormalities)
 Toxins
 Tetanus
 Strychnine poisoning
 Black widow spider bite
 Inflammatory myelitis
 Progressive encephalomyelitis with rigidity and myoclonus (PERM)
 Borrelia burgdorferi infection
 Traumatic myelopathy
 Spinal cord neoplasm (intrinsic)
 Ischemic myelopathy
 Spinal arteriovenous malformation
 Cervical spondylotic myelopathy

Peripheral nerve

Neuromyotonia (myokymia with impaired muscle relaxation)
 Idiopathic
 Paraneoplastic syndrome
 Peripheral neuropathies
 Hereditary motor and sensory neuropathies
 Inflammatory neuropathies
 Toxic neuropathies
 Radiation plexopathies
 Morvan syndrome (Morvan fibrillary chorea)
 Schwartz–Jampel syndrome
 Satoyoshi syndrome
 Hereditary distal muscle cramps without neuropathy

Tetany (hypocalcemia, hypomagnesemia)
 Cramps
 Postexertion
 Dehydration/salt depletion
 Pregnancy
 Denervation (motor neuron disease, motor neuropathies)

Muscle

Myotonic syndromes
 Myotonic dystrophy
 Myotonia congenita
 Paramyotonia congenita
 Metabolic myopathies
 Myophosphorylase deficiency (McArdle disease)
 Phosphofructokinase deficiency
 Ca⁺⁺ ATPase deficiency (Brody disease)
 Inflammatory myopathies
 Polymyositis
 Endocrine myopathies
 Hypothyroidism
 Addison disease
 Congenital myopathies
 Stiff-spine syndrome
 Emery–Dreifuss muscular dystrophy
 Bethlem muscular dystrophy
 Other conditions presumed to be muscular in origin
 Rippling muscle disease
 Rolling muscle disease

Contracture

Bone (ankylosis)
 Arthritis
 Ankylosing spondylitis
 Soft tissue
 Volkmann ischemic contracture

Table 21.2 Features differentiating spasticity and rigidity

Feature	Spasticity	Rigidity
Change in mechanical properties	Possible contracture	Increased thixotropy
Failure to fully relax	Yes	Yes
Response to phasic stretch	Increased short latency reflex (tendon jerk) and possible clonus	Increased long latency reflexes
Velocity sensitivity	Yes	No

Approximately 30% of those fibers arise from the primary motor cortex; but there are also significant contributions from premotor cortex and sensory cortex. The fibers largely cross in the pyramid, but some remain uncrossed. Some terminate as monosynaptic projections onto alpha-motoneurons, and others terminate on interneurons, including those in the dorsal horn. Other cortical neurons project to basal ganglia, cerebellum, and brainstem; these structures can also originate spinal projections. Particularly important is the reticular formation that originates several tracts with different functions (Nathan, Smith, & Deacon, 1996). The dorsal reticulospinal

tract may have particular relevance for spasticity and is normally inhibitory onto the spinal cord (Takakusaki et al., 2001, 2003; Habaguchi et al., 2002). There is cortical innervation of the reticular formation, and this is called the cortico-reticulo-spinal tract. Lesions of the primary motor area alone and lesions of the pyramid alone do not cause spasticity (Sherman, Koshland, & Laguna, 2000). It appears that premotor damage is necessary and likely involvement of cortico-reticulo-spinal pathways. Dysfunction of the dorsal reticulospinal tract will disinhibit the spinal cord and may give rise to the hyperexcitability characteristic of spasticity (Li & Francisco, 2015). Then there could be secondary changes in the spinal cord itself (Trompetto et al., 2014). The term “corticofugal syndrome” has been suggested to indicate that “spasticity” has important negative and positive features and that the lesions involve descending tracts other than the corticospinal tracts (Thilmann, 1993). This term, however, has not been commonly used.

The clinical and physiologic features of spasticity differ to some degree depending on whether the lesion is cortical or spinal. Spasticity observed in hemiparesis differs from that seen with spinal cord lesions. For example, exaggeration of flexor reflexes is much more likely with spinal lesions. This certainly must be derived from the difference in the exact pattern of damage to the descending tracts.

Clinical features of spasticity that help with the diagnosis, in addition to the velocity-dependent increased tone, include brisk tendon reflexes, the Babinski sign, the Hoffman reflex (indicating brisk finger flexor reflexes), and loss of cutaneous abdominal reflexes. The negative features often will be seen as well, with weakness in the lower extremities of flexors more than extensors and in the upper extremities of extensors more than flexors. In the clinical neurophysiology laboratory, there will be increased H reflexes, identified with an increase of the maximum amplitude H reflex compared with the M wave (muscle response to direct supramaximal stimulation of the nerve), called the H/M ratio (Hallett, 2012). There is also a diminished decrease of the H reflex with vibration of the body part. Characteristics of the tonic stretch reflex also can be assessed for threshold and gain to stretches of varying velocity. In spasticity, there is some controversy, but both lowered velocity threshold and an increased gain have been found (Thilmann, Fellows, & Garms, 1991; Ibrahim et al., 1993; Musampa, Mathieu, & Levin, 2007). It is important to recognize that there are both reflex and nonreflex contributions to spastic hypertonia (Chung et al., 2008). As noted earlier there are both neural and nonneural components; there are instrumental methods that can help in this differentiation (Bar-On et al., 2015).

The neurologic syndromes in which spasticity can be seen are numerous. These include stroke (Zeng et al., 2020), spinal cord injury, brain trauma, cerebral palsy, and demyelinating illnesses such as multiple sclerosis. Spasticity also can be a part of degenerative disorders, such as amyotrophic lateral sclerosis, and is the major symptom in primary lateral sclerosis. In the hereditary spastic paraplegias (HSPs) spasticity is the primary feature, and it is interesting to note the important overlap between the HSPs and the ataxias (Bereznyakova & Dupre, 2018). Indeed, some mutations can cause spasticity, ataxia, or both, and some of the cell biologic pathways for the two entities are shared (Synofzik & Schule, 2017). SPG7 is particularly common in complex ataxias.

More than 80 mutations have been identified for the HSPs (Murala et al., 2021). The entities have been divided into pure HSP and complicated or complex HSP (de Souza et al., 2017). Pure cases have slowly progressive weakness and spasticity with possible sphincter disturbance and/or sensory loss. Complex forms have additional ataxia, neuropathy, cognitive impairment, epilepsy, myopathy, external ophthalmoplegia, parkinsonism, dystonia, or psychiatric disorders. Nonneurologic manifestations may be ophthalmologic abnormalities, such as cataracts or retinitis pigmentosa, dysmorphic features, and orthopedic abnormalities. There can be a wide variety of magnetic resonance imaging (MRI) findings from mild white matter changes to leukodystrophy, thin corpus callosum, spinal cord or cerebellar atrophy, brain iron accumulation, and hydrocephalus (de Souza et al., 2017), and these changes can be genotype specific (Servelhere et al., 2021). Genetically, they can be dominant, recessive, X-linked, and mitochondrial (Murala et al., 2021). The most common autosomal dominant entities are SPG4, SPG3A, and SPG31, and the most common autosomal recessive entities are SPG11 and SPG15. The protein products of all of these genes have function in relation to organelle shaping (Blackstone, 2018). Looking over all the HSPs, the defective genes seem to play key roles in axon development and maintenance, including organelle shaping and biogenesis,

Table 21.3 Treatment of spasticity

Focus on negative symptoms before positive symptoms
Physical therapy
Oral agents
• GABAergic: benzodiazepines, baclofen, gabapentin • Alpha-2 adrenergic: tizanidine • Block calcium release in muscle: dantrolene • Uncertain: tolperisone (block sodium channels?) • Cannabinoids (experimental)
Injection therapy
• Botulinum toxin, phenol, alcohol wash
Surgery
• Intrathecal baclofen, rhizotomy

membrane and cargo trafficking, mitochondrial function, nucleotide metabolism, and lipid/cholesterol metabolism (Blackstone, 2018).

Many methods are used to treat spasticity (Table 21.3), but this must be done carefully because correction of the positive features may not be all that helpful, and, as noted before, may even be detrimental (Dietz & Sinkjaer, 2012; Burke et al., 2013). For many patients, the much more important aspects of their corticofugal syndrome are the negative features, such as the weakness, and these cannot be dealt with easily. Increased tone can be improved with a variety of oral agents, including benzodiazepines, baclofen, and tizanidine (Ronan & Gold, 2007; Kamen, Henney, & Runyan, 2008; Rivelis & Morice, 2018). Baclofen can be given intrathecally by pump, and this can be much more efficacious, likely because of the ability to increase the dose at the target tissue without side effects (Dykstra et al., 2007; Rietman & Geertzen, 2007; Saval & Chiodo, 2010; Furstimming, Boyle, & Schiess, 2014; Overgard et al., 2015; Winter, Beni-Adani, & Ben-Pazi, 2018). Tolperisone has been evaluated in patients after stroke (Stamenova et al., 2005) and might be another consideration (Quasthoff et al., 2008). Medical cannabis might be useful in some circumstances (Borgelt et al., 2013; Syed, McKeage, & Scott, 2014; Contin et al., 2018; Flachenecker, Sacca, & Vila, 2018), and systematic reviews, including one from the American Academy of Neurology, concluded that oral cannabis extract is, and tetrahydrocannabinol probably is, effective in the treatment of spasticity in the setting of multiple sclerosis (Koppel et al., 2014; Whiting et al., 2015; Rice & Cameron, 2018; Patel, 2021). Approach to pharmacological management of spastic cerebral palsy has received specific attention (Reilly et al., 2020).

Direct blockade of muscle contraction with agents such as phenol has been used for some time, and the introduction of botulinum toxin (BTX) for this purpose has been welcomed with enthusiasm (Mohammadi et al., 2010). Evidence-based reviews give BTX high recommendation for treatment in both adults and children (Simpson et al., 2008, 2016; Esquenazi et al., 2013; Moeini-Naghani, Hashemi-Zonouz, & Jabbari, 2016). For poststroke spasticity, there is very good evidence for reduction of spasticity (Francisco et al., 2021; Li and Francisco, 2021). Evidence is developing for an increase in functional ability (Foley et al., 2010; Fridman et al., 2010; Sun et al., 2010; Rosales, Kanovsky, & Fernandez, 2011), and can be enduring (Kanovsky et al., 2021), but this

benefit might be only short term (Rosales et al., 2016) or limited (Kaji et al., 2010; Levy et al., 2018). Improvement might be better with higher doses than have commonly been used (Santamato et al., 2015). Children with cerebral palsy can be much improved (Kanellopoulos et al., 2009; Lukban, Rosales, & Dressler, 2009; Baird & Vargus-Adams, 2010; Coutinho dos Santos et al., 2011; Pin, Elmasry, & Lewis, 2013; Strobl et al., 2015; Mirska et al., 2019; Satila, 2020), but are a vulnerable population and need to be treated with care (Albavera-Hernandez, Rodriguez, & Idrovo, 2009). Several evidence-based reviews document the utility of BTX for this indication (Delgado et al., 2010; Hoare et al., 2010). It is interesting to note that the effect of BTX is mediated not only on the alpha-motoneuron neuromuscular junction but also via the gamma-motoneuron effect on the muscle spindle (Trompetto et al., 2008). Reduction of gamma-motoneuron activity will lead to slackness of the muscle spindle, reduction of muscle afferent activity, and reduced reflex contribution to increased tone. Surgical methods such as rhizotomy also can be used in some cases for symptomatic relief of severe spasticity (Lazorthes et al., 2002; Dudley et al., 2013; Ailonr et al., 2015; Aquilina, Graham, & Wimalasundera, 2015; Deltombe, Lejeune, & Gustin, 2018; Abbott, 2020).

Of course, physical therapy is also important. In the end, a multifaceted approach with a multidisciplinary team may well be necessary (Kheder & Nair, 2012; Narayanan, 2012; Graham, 2013; Prazeres et al., 2018).

Syndromes of continuous muscle activity

A variety of disorders causing stiffness and cramps arise from peripheral nerve or muscle origin. These produce continuous muscle activity with special clinical and electrophysiologic features that allow separation from disorders arising in the central nervous system (see Table 21.1). Neuromyotonia is the most important of these entities, and, as noted earlier, this is discussed in Chapter 23. A few examples of genetic cause will be considered here.

Schwartz–Jampel syndrome

Schwartz–Jampel syndrome (chondrodystrophic myotonia) is a rare autosomal recessive condition (Schwartz & Jampel, 1962; Mallineni, Yiu, & King, 2012; Arya et al., 2013; Basiri, Fatehi, & Katirji, 2015; Chandra et al., 2015). The typical picture is of continuous muscle fiber activity and muscle stiffness, especially of the face, with an abnormal facial appearance (blepharophimosis, a small jaw and a puckered chin, and low-set ears), skeletal abnormalities (spondylo-epiphyseal dysplasia), and short stature (Fig. 21.1) (Naharajakumar et al., 2006). Percussion myotonia may be present. The muscle stiffness is due to semicontinuous motor unit discharges, with high frequency and after-discharges of muscle fibers (Fig. 21.2). The abnormality is due to mutations in the *HSPG2* gene, which encodes perlecan, the major proteoglycan of basement membranes (Stum et al., 2006). Although there were some data showing that the abnormalities persisted after curare (Spaans et al., 1990), suggesting a muscle origin for the hyperactivity, detailed studies now demonstrate the abnormality to be of the distal axon. Studies have been done in humans and a



Fig. 21.1 Schwartz–Jampel syndrome. Characteristic facial appearance of a patient with Schwartz–Jampel syndrome with myotonia of orbicularis oris, orbicularis oculi, and muscles of facial expression. There are also low-set ears, long philtrum, and recessed chin. (From Naharajakumar, Subbulakshmi C, John E et al. Crying or smiling? The Schwartz–Jampel syndrome. *J Pediatr.* 2006;148:702, with permission.)

mouse model that show similar findings. There is distal hypomyelination of the nerve axon with denervation and reinnervation and loss of acetylcholinesterase at the neuromuscular junction (Echaniz-Laguna et al., 2009; Bangratz et al., 2012; Bauche et al., 2013). A very detailed study in one human patient shows normal nerve conduction and neuromuscular transmission, indicating the sole abnormality of hyperexcitability of the distal axon (Bauche et al., 2013). BTX can be used to improve the blepharospasm in this condition (Vargel et al., 2006; Aburahma et al., 2009). The myotonia can sometimes be improved with anticonvulsants, for example, carbamazepine and phenytoin (Gurbuz and Albayrak, 2019), and antiarrhythmic drugs, for example, mexiletine and procainamide (Basiri et al., 2015).

Satoyoshi syndrome

Satoyoshi syndrome (Satoyoshi, 1978) begins in childhood or adolescence with severe intermittent painful muscle spasms and twitches, twisting the body into abnormal postures. The spasms last up to a few minutes and occur frequently, up to hundreds per day. They are precipitated by movement or stimulation of the affected area. At the same time, complete alopecia and intestinal malabsorption with diarrhea develop. There also is metaphyseal dysplasia with growth retardation. It may also affect adults (Ikeda et al., 1998). Manifestations may be only unilateral (Uddin et al., 2002; Ishihara et al., 2014). The pathophysiologic feature is hyperexcitability of the motor neurons or axons (Aghoram, Sri-jithesh, & Kannoth, 2016). The cause is not completely clear, although there does seem to be a systemic autoimmune disorder (Heger et al., 2006; Matsuura et al., 2007). In one case, antibodies to the voltage-gated potassium channel complex were identified, making a link to neuromyotonia (Dhamijatock et al., 2011). On the other hand, genetic mutations have been suspected (Solera et al., 2017); however, these must somehow trigger an immune disorder. Cerebrospinal fluid glycine was elevated in the one case studied (Solera et al., 2015).

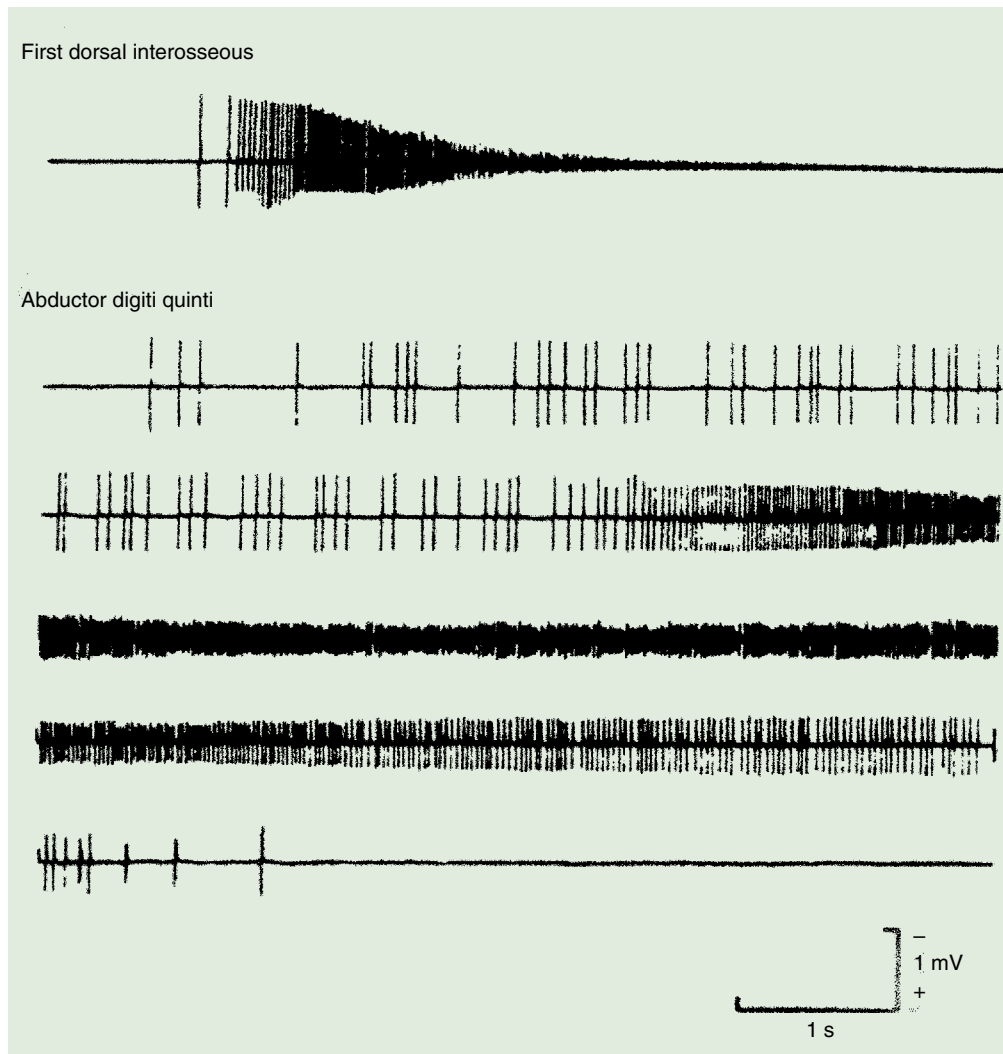


Fig. 21.2 Example of electromyographic discharge from a patient with Schwartz–Jampel syndrome. The discharge is triggered by stimulation of the seventh nerve. (From Thompson PD. *Stiff people*. In: Marsden CD, Fahn S, eds. *Movement Disorders 3*. Oxford: Butterworth-Heinemann; 1994, pp. 373–405, with permission.)

Treatment with corticosteroids can be effective (Wisuthsarewong, Likitmaskul, & Manonukul, 2001; Endo et al., 2003), as can intravenous immunoglobulin (IVIG) (Arita et al., 1996), methotrexate (Heger et al., 2006), plasmapheresis (Aghoram et al., 2016), and azathioprine (Montanaro et al., 2017). These different approaches have been reviewed (Solis-Garcia Del Pozo et al., 2019). Botulinum toxin can be used symptomatically (Bledsoe, 2020).

Rippling muscle disease

Rippling muscle disease manifests with muscle cramps; pain; stiffness, especially on exercise; and a characteristic lateral rolling movement of muscle after contraction and balling of muscle on percussion (Torbergesen, 2002; Sundblom et al., 2010). It may have several causes, but is most commonly an autosomal dominant inherited disorder of skeletal muscle. In one family with 11 affected members, muscle stiffness and myalgia were the most prominent symptoms (So et al., 2001). Muscle rippling was present in 6 affected family members, whereas persistent muscle contraction to

muscle percussion was present in all affected adults. Phenotypes clearly vary in the same family (Jacobi et al., 2010). Some of the time, the muscle contractions are electrically silent, and one hypothesis is that the abnormal muscle contractions are evoked by “silent” action potentials traveling in the muscle’s tubular system (Lamb, 2005). However, myotonic-like activity is more commonly seen (Maki et al., 2011; Milone et al., 2012).

The disorder is now known to be due to mutations in *CAV3* (encoding caveolin 3) (Betz et al., 2001; Lorenzoni et al., 2007; Traverso et al., 2008). Mutations in *CAV3* also have been described in limb-girdle muscular dystrophy type 1C (LGMD1C) and other neuromuscular syndromes, again demonstrating that different phenotypes can come from mutations in the same gene (Gazzerro et al., 2010; Ishiguro et al., 2018). This disorder can be associated with myasthenia gravis and might be improved with immunosuppression (Schoser et al., 2009; George et al., 2010; Bettini et al., 2016). Indeed, it appears that rippling muscle disease can be immune-mediated without a mutation in the *CAV3* gene (Schulte-Mattler et al., 2005; Ducci et al., 2017).



Fig. 21.3 Rigid spine syndrome. Patients with *BIN1* mutation leading to centronuclear myopathy. Dorsal (A) and lumbar (B) spine stiffness, respectively. (From Cabrera-Serrano, Mavillard, Biancalana, et al. A Roma founder *BIN1* mutation causes a novel phenotype of centronuclear myopathy with rigid spine. *Neurology*. 2018;91:e339–3348, with permission.)

Rigid spine syndrome

Several congenital and hereditary myopathies can manifest with rigidity of the spine as an important and often early feature before much weakness becoming evident (Koul et al., 2014). The abnormality is due to contractures of the spinal extensor muscles leading to abnormal postures and scoliosis (Fig. 21.3). Respiratory insufficiency is common. Depending on the myopathy, there can be hypotonia and variable patterns of weakness, including neck muscle weakness. There also can be an associated sensorimotor neuropathy resembling Charcot–Marie–Tooth disease (Noury et al.,

2018). Whole body muscle MRI can be helpful in making the diagnosis (as can genetic testing) because the different myopathies have different patterns if the whole body pattern of involvement is considered (Tordjman et al., 2018). Disorders include Pompe disease and mutations in *RYR1*, *Collagen VI*, *LMNA*, *SEPN1*, *LAMA2*, *MYH7*, *TTN*, and *BIN1* genes (Yue et al., 2015; Cabrera-Serrano et al., 2018; Tordjman et al., 2018).

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Wilson disease

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Wilson disease

Wilson disease is an inborn error of copper metabolism manifested by hepatic cirrhosis and damage to the basal ganglia, brainstem, and other subcortical and cortical regions (Wilson, 1912). Wilson disease is one of the few curable movement disorders, but the good outcome is critically dependent on early diagnosis. It presents in so many guises that any patient younger than 50 years of age with a movement disorder should be considered to possibly have Wilson disease. It is sufficiently rare that the diagnosis is often missed. In a review of 307 patients, the average delay to diagnosis was 2 years and misdiagnoses included schizophrenia, juvenile polyarthritis, rheumatic chorea, nephrotic syndrome, metachromatic leukodystrophy, congenital myopathies, subacute sclerosing panencephalitis, and neurodegenerative disease (Prashanth et al., 2004).

Wilson disease is inherited as an autosomal recessive trait. The gene responsible for Wilson disease lies on chromosome 13q14.3, whereas that for ceruloplasmin is located on chromosome 8 (Wang et al., 1988). The Wilson disease gene encodes for a copper-transporting P-type ATPase (ATP7B) (Petrukhin et al., 1993; Tanzi et al., 1993). Over 600 mutations of the gene have been detected, and more continue to be found (Bem et al., 2013; Coffey et al., 2013; Das et al., 2013; Gu et al., 2013; Li et al., 2013; Simsek Papur et al., 2013; Mukherjee et al., 2014; Chang and Hahn, 2017; Lorincz, 2018). The enzyme binds copper in its large N-terminal domain and aids in intracellular processing in the hepatocyte (Ala et al., 2007).

The prevalence of Wilson disease is now best estimated at 142 per million, but the prevalence will certainly vary depending on the population (Lo and Bandmann, 2017). Consanguinity will increase the incidence (Samanci et al., 2021). Earlier estimates that were solely clinically based were generally lower. The current figure takes into account the addition of genetic testing. The rate of heterozygote carriers is estimated at 1 in 25 (Coffey et al., 2013). Heterozygotes do not develop Wilson disease, but may exhibit mild abnormalities of copper metabolism.

Because there is such a variation in the phenotype and even penetrance of Wilson disease, it is thought that there must be modifier genes and/or important epigenetic and environmental factors (Medici and Weiss, 2017). Curiously,

monozygotic twins might be discordant for Wilson disease, further suggesting that epigenetic or environmental factors must also be important (Czlonkowska et al., 2009).

Intestinal absorption of copper is normal in Wilson disease (normal adults absorb about 1 mg of copper daily), as is subsequent transport into the hepatocyte. Because absorption is about 1 mg per day, and the requirement is for 0.75 mg per day, about 0.25 mg must be excreted from the body each day (Lorincz, 2010). There are two pathways for copper excretion from the hepatocyte aided by ATP7B. One is the attachment to ceruloplasmin in the Golgi apparatus and subsequent delivery of the copper-ceruloplasmin complex into the serum. A second is promotion of copper excretion into the bile. The mutations lead to failure to excrete copper by both routes, causing build-up of copper in the hepatocyte and eventual spillover of free copper into the circulation. This leads to a substantial positive net copper balance and systemic copper poisoning (Cuthbert, 1998; Loudianos and Gitlin, 2000; Scheiber et al., 2017). There is increased circulating free copper and excessive urinary excretion of copper, but this is insufficient to prevent copper accumulation (the normal human body contains 80 mg of copper). Excess copper in the liver causes progressive liver damage. Copper also accumulates in the brain and other sites (the eye, kidney, bones, and blood tissues being particularly vulnerable to copper toxicity). Some of the toxicity of copper may be due to oxidative mechanisms. Different pathological processes are more prominent at different phases of the disease (Zhou et al., 2021).

In most cases, Wilson disease can be diagnosed by measuring the serum concentration of the copper protein ceruloplasmin. Ceruloplasmin (molecular weight 132,000), an alpha-2 globulin glycoprotein, contains six atoms of copper per molecule. Ceruloplasmin contains 0.3% copper in a fixed ratio of metal to protein (330 mg ceruloplasmin carries 1000 µg copper/L). In Wilson disease, ceruloplasmin is not normally produced because there is defective incorporation of copper. However, it is clear that there is no defect in ceruloplasmin in Wilson disease; indeed, some patients have normal levels, and the gene for the disease lies at a different site for that responsible for ceruloplasmin synthesis.

The pathologic abnormalities in the brain are primarily in the basal ganglia, with cavitory necrosis of the putamen



Fig. 22.1 Postmortem brain of a patient with Wilson disease showing the cavitory necrosis of the basal ganglia. (From Wilson SAK. *Progressive lenticular degeneration: A familial nervous disease associated with cirrhosis of the liver. Brain.* 1912;34:295–507.)

and caudate, associated with neuronal loss, axonal degeneration, and astrogliosis with a cell type called Opalski cells (Poujois et al., 2017) (Fig. 22.1). Other subcortical and cortical regions can be affected. In a pathologic study of eight patients, six had neurologic manifestations clinically (Meenakshi-Sundaram et al., 2008). Of these six, five had central pontine myelinolysis, five had subcortical white matter cavitations, four had putaminal softening, and six had variable ventricular dilatation. The liver in Wilson disease develops cirrhosis, and although the nodular type is common, there are a variety of presentations (Pronicki, 2017).

Clinical manifestations

The initial manifestations of the illness (Table 22.1) are neurologic in about 40% of patients (usually after the age of 12 years) (Brewer, 2000; Lorincz, 2010; Lin et al., 2014; Czlonkowska et al., 2017; Lorincz, 2018). The remainder present with symptoms of liver disease (about 40%) (usually at an earlier age) (Manolaki et al., 2009) or a psychiatric illness (about 15%). The psychiatric picture may show a change in personality or mood (Biswas et al., 2017). Psychosis is rare. In a series of 282 patients from India, where the disorder is very common, neurologic presentation was 69.1%, hepatic 15.9%, hepato-neurologic 3.5%, pure psychiatric 2.4%, osseomuscular 2.1%, and presymptomatic 5.3% (Taly et al., 2007). Different percentages are reported in a series from Greece (Tampaki et al., 2020). What determines these individual variations in clinical presentation is not clear. In part this clearly depends on the referrals of particular clinics. A population based study was reported from South Korea but applicability to other countries is not certain (Choe et al., 2020). One biological factor has been determined for different presentations; patients with ApoE epsilon3/3 genotype have delayed onset of symptoms compared with all other ApoE genotypes (Schiefermeier et al., 2000). Symptoms usually appear between the ages of 11 and 25 years, but can occur as early as 4 and as late as

Table 22.1 Presentation of Wilson disease

Liver disease (40%)

95% present under the age of 20 years (usually 7–15)
Acute hepatitis
Fulminant hepatitis
Chronic active hepatitis
Cirrhosis

Neurologic (40%)

30% present over the age of 20 years
Isolated tremor, dysarthria, drooling, clumsiness or gait disturbance (rarely, seizures)
A parkinsonian syndrome
A generalized dystonic syndrome
A “pseudosclerotic” syndrome (postural and intention tremor)

Psychiatric (15%)

Conduct disorder
Cognitive impairment
Dementia
Psychosis

Others (5%)

Ocular: Kayser–Fleischer ring, sunflower cataract
Renal: Aminoaciduria, renal tubular acidosis, calculi
Skeletal: Osteomalacia and rickets (blue nails)
Hematologic: Hemolytic anemia

50+ years (Starosta-Rubinstein et al., 1987; Stremmel et al., 1991; Walshe and Yealland, 1992; Ferenci et al., 2007). Some patients with Wilson disease have autonomic nervous system abnormalities (Bhattacharya et al., 2002; Meenakshi-Sundaram et al., 2002; Li et al., 2017).

A detailed analysis of the psychiatric presentation of 15 patients showed an affective disorder spectrum abnormality in 11 and a schizophreniform illness in 3 (Srinivas et al., 2008). Note was made that whereas psychiatric symptoms improved in 5 patients with de-coppering therapy, 7 patients needed symptomatic treatment as well. The literature about psychiatric features has been extensively reviewed (Zimbren and Schilsky, 2014; Zimbren and Seniow, 2017). Initial presentation was psychosis in 36%, depression in 22%, personality change in 8%, and learning problems in another 8%.

Those with neurologic abnormalities usually present in the second or third decade, with (1) an akinetic-rigid syndrome resembling parkinsonism, (2) a generalized dystonic syndrome (pure chorea is uncommon), or (3) postural and intention tremor with ataxia, titubation, and dysarthria (pseudosclerosis) (Table 22.2) and (Video 22.1). The tremor may be mild, but is classically a slow, high-amplitude proximal tremor with the appearance of “wing-beating” when the arms are elevated and the hands placed near the nose. Dysarthria and clumsiness of the hands are common manifesting features. The speech abnormality may include rapid speech, hypophonia, and slurring. It is most unusual for the illness to manifest with a gait disorder. No two patients with Wilson disease are ever quite the same. The facile grinning face (sometimes referred to as risus sardonicus or rictus grin) with drooling saliva is characteristic. Early pseudobulbar features are common. Eye movements can be disordered, with slow saccades (Kirkham and Kamin, 1974) and occasionally ophthalmoplegia (Gadoth and Liel, 1980). Besides the presence

Table 22.2 Number (percentage) of Wilson disease patients with different initial symptoms and signs

	Juveniles (n = 65)	Adults (n = 71)
Symptoms		
Personality change	21 (32)	23 (32)
Speech defect	63 (41)	42 (30)
Drooling	31 (20)	22 (16)
Dysphagia	14 (9)	7 (5)
Hand tremor	48 (31)	55 (39)
Hand clumsy	32 (21)	20 (14)
Abnormal gait	34 (22)	18 (13)
Fall at work or school	40 (26)	
Signs		
Personality disorder	14 (21)	13 (18)
Dysarthria	34 (52)	19 (27)
Gait abnormal	8 (12)	5 (7)
Eye movement abnormal	4 (6)	4 (6)
Drooling	18 (28)	11 (15)
Parkinsonian facies	15 (23)	5 (7)
Open mouth	10 (15)	0 (0)
Bradykinesia	6 (9)	3 (4)
Tongue abnormal	11 (17)	9 (13)
UL tremor	17 (26)	23 (32)
UL dystonia	14 (21)	13 (18)
UL spontaneous movements	8 (12)	0 (0)
LL tremor	2 (3)	6 (8)
LL dystonia	12 (18)	0 (0)
LL spontaneous movements	1 (1)	1 (1)
Liver disease	19 (29)	8 (11)

UL, Upper limb; LL lower limb.

From Walshe JM, Yealland M. Wilson's disease: The problem of delayed diagnosis. *J Neurol Neurosurg Psychiatry*. 1992;55(8):692–696.

of Kayser–Fleischer rings, other neuro-ophthalmologic abnormalities in patients with Wilson disease include sunflower cataracts, slow and dysmetric saccades, impaired pursuit (vertical before horizontal), apraxia of eyelid opening, and oculogyric crises (Waln and Jankovic, 2018). Vision and sensation are not affected, and paralysis does not occur although pyramidal signs may be evident. Sphincter control is spared. Seizures are infrequent (Smith and Mattson, 1967). Cognitive changes are common, even to the extent of a frank dementia. Changes in school or work performance are often the initial indication of the illness. Impulsiveness or antisocial behavior and other indices of personality change are common (Denning and Berrios, 1989; Denning, 1991; Akil and Brewer, 1995). ▶

Many of those with neurologic complaints give a history of prior or concurrent liver disease. This may consist of a previous episode of acute hepatitis, chronic active hepatitis,

Table 22.3 The diagnosis of Wilson disease (WD)

1. Low serum ceruloplasmin (<20 mg/dL)
False negatives in:
5% of WD patients
Pregnancy or birth control pills
False positives in:
Heterozygotes
Severe protein loss
Severe liver disease
Menkes disease
2. Kayser–Fleischer ring
False negatives in:
Liver WD
Local eye disease
False positives in primary biliary cirrhosis
3. Raised 24-hour urinary copper excretion (>100 µg)
False positives in cholestasis (NB: drugs)
4. Raised liver copper concentration (>250 µg/g dry weight)
False positives in:
Biliary cirrhosis
Cholestasis
(NB: histology is essential)
5. Magnetic resonance imaging
6. Identification of known mutation

portal hypertension, or asymptomatic hepatosplenomegaly (Scheinberg and Sternlieb, 1984). An unexplained hemolytic anemia, renal disease with hematuria, amino-aciduria, renal tubular defects, calculi (Wiebers et al., 1979), or skeletal disease with osteoporosis/osteomalacia (Carpenter et al., 1983) are other clues.

Untreated, the condition progresses inexorably to death either from the complications of the liver disease, or from severe neurologic involvement, within a few years.

Laboratory confirmation

Laboratory testing can make a definitive diagnosis (Mak and Lam, 2008). When the diagnosis of Wilson disease is suspected (Table 22.3) screening for reduced serum ceruloplasmin should be the initial laboratory investigation. However, 5% of those with Wilson disease have a normal serum ceruloplasmin. The concentration of ceruloplasmin also may be low in heterozygotes, severe protein loss, severe liver disease of other cause, Menkes disease, copper deficiency, and ceruloplasmin (see later). Serum ceruloplasmin may be increased by pregnancy and estrogens. Serum total copper is low in many patients, but nonspecific (Kumar et al., 2007); however, using a new method for “exchangeable copper” (CuEXC) and a ratio between CuEXC and total serum copper called relative exchangeable copper (REC) enables a diagnosis with high sensitivity and specificity (Poujois and Woimant, 2018). Urinary copper excretion is nearly always raised. However, anything causing cholestasis (particularly drugs) may raise serum copper and increase urinary copper excretion. When an expert examines the cornea with a slit lamp, virtually all patients with neurologic Wilson disease show Kayser–Fleischer rings in the Descemet membrane (Fig. 22.2) (Wiebers et al., 1977). However, patients with neurologic Wilson disease but no Kayser–Fleischer rings have been described (Ross et al., 1985; Demirkiran et al., 1996; Youn et al., 2012). Occasionally, a Kayser–Fleischer ring is only

Video 22.1 Examples of Wilson disease.

seen in one eye (Madden et al., 1985). The yellow and brown copper deposits are seen at the limbus of the cornea, usually first visible and most dense at the upper and lower poles of the eye. Kayser–Fleischer rings are not present in all patients with the liver manifestations of Wilson disease, and other liver disease can produce them (Fleming et al., 1977).

Computed tomography (Harik and Post, 1981; Williams and Walshe, 1981) or magnetic resonance imaging (MRI) (Alanen et al., 1999; Giagheddu et al., 2001) of the brain usually reveals changes in the basal ganglia that are reversible with treatment. Caudate and putamen show increased T2 signal, and there may be similar changes in the substantia nigra (SN) pars compacta, periaqueductal gray, pontine tegmentum, and thalamus (Fig. 22.3A) (Saatci et al., 1997). Particularly striking are the putaminal lesions with a pattern of symmetrical, bilateral, concentric-laminar T2 hyperintensity. Hyperintensity of the mesencephalon with sparing of the red nuclei and lateral aspect of the SN gives rise to the “face of the giant panda sign” (see Fig. 22.3B) (Giagheddu et al., 2001). A “double panda sign” also has been described (Jacobs et al., 2003; Liebeskind et al., 2003).



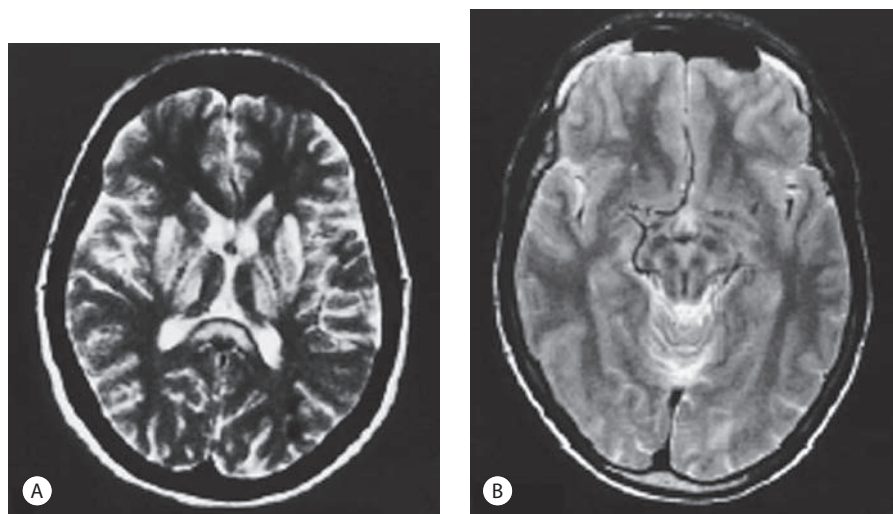
Fig. 22.2 Kayser–Fleischer ring in a patient with Wilson disease. The ring is composed of the brown pigment at the outer circumference of the iris. (From Scheinberg IH, Sternlieb I. *Wilson's disease*. Philadelphia: WB Saunders; 1984.)

There can be hyperintensity of the middle cerebellar peduncle (Uchino et al., 2004). Another change has a similar appearance to central pontine myelinolysis, and this will improve with therapy (Sinha, Taly, Prashanth et al., 2007; Sinha, Taly, Ravishankar et al., 2007). Diffusion-weighted MRI also might be useful (Favrole et al., 2006). In a study of 100 patients with various basal ganglia diseases, the magnetic resonance imaging (MRI) features most useful to diagnose Wilson disease were the face of giant panda sign (seen in 14.3%), tectal plate hyperintensity (seen in 75%), central pontine myelinolysis–like abnormalities (seen in 62.5%), and concurrent signal changes in basal ganglia, thalamus, and brainstem (seen in 55.3%) (Prashanth et al., 2010). As MRI methods have been improved, making the diagnosis of Wilson disease is getting more dependent on neuroimaging (Tinaz et al., 2020).

Positron emission tomography using ^{18}F -fluorodopa shows reduced uptake in the striatum indicating loss of the dopaminergic nigrostriatal pathway (Snow et al., 1991). Transcranial brain parenchyma sonography (TCS) detects lenticular nucleus hyperechogenicity, likely to be caused by copper accumulation, in neurologically symptomatic and asymptomatic Wilson disease patients (Walter et al., 2005; Tribi et al., 2018). Magnetic resonance spectroscopy is also abnormal (Lucato et al., 2005; Tarnacka et al., 2009). Seven-tesla MRI using quantitative susceptibility mapping can identify copper in brain regions, including the basal ganglia (Fritsch et al., 2014), but this is not routinely available.

If there is any doubt about the diagnosis of Wilson disease in a patient under the age of 50 presenting with neurologic problems, the first test would be a 24-hour urine copper excretion. In Wilson disease, excretion is typically more than 100 $\mu\text{g}/24$ hours and less than 50 $\mu\text{g}/24$ hours would exclude the diagnosis (Brewer and Yuzbasiyan-Gurkan, 1992; Brewer, 2000). The definitive investigation is a liver biopsy with histologic assessment of tissue and measurement of copper concentration (Madakshira et al., 2018). Guidelines for diagnosis have been published by the American Association for the Study of Liver Diseases (Roberts and Schilsky, 2008) and by the Hepatology Committee of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (Socha et al., 2018). An algorithm for the diagnosis is presented in Fig. 22.4 (Brewer, 2008).

Fig. 22.3 Magnetic resonance imaging scans in Wilson disease. (A) T2-weighted image showing hyperintensity of the basal ganglia. (B) T2-weighted image showing the “face of the giant panda sign” resulting from hyperintensity of the mesencephalon sparing the red nuclei and the lateral part of the substantia nigra. (Modified from Giagheddu M, Tamburini G, Piga M, et al. *Comparison of MRI, EEG, EPs and ECD-SPECT in Wilson's disease*. *Acta Neurol Scand*. 2001;103[2]:71–81.)



SCREENING AND DIAGNOSIS IN PATIENTS WITH THE NEUROLOGIC/PSYCHIATRIC PRESENTATION

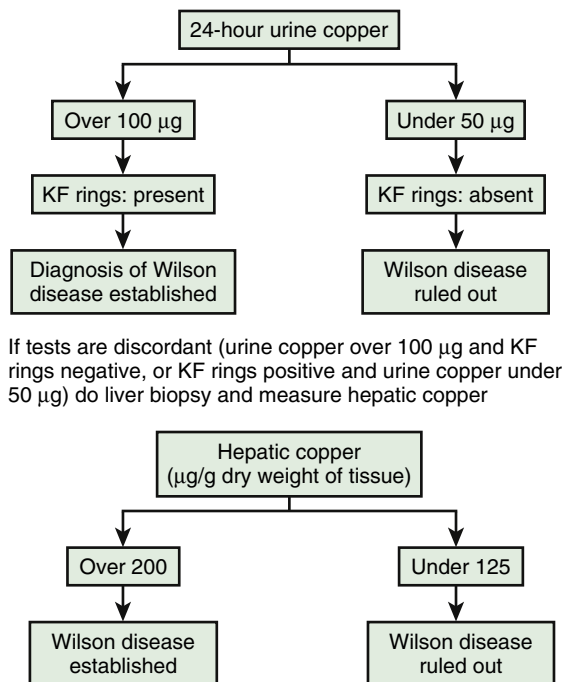


Fig. 22.4 An algorithm for screening and definitive diagnosis in patients with suspicion of Wilson disease. KF, Kayser–Fleischer. (From Brewer GJ. *Wilson's disease*. In: Hallett M, Poewe W, eds. *Therapeutics of Parkinson's Disease and Other Movement Disorders*. Chichester, UK: Wiley-Blackwell; 2008, pp. 251–261.)

SCREENING AND DIAGNOSIS OF PRESYMPTOMATIC SIBLINGS

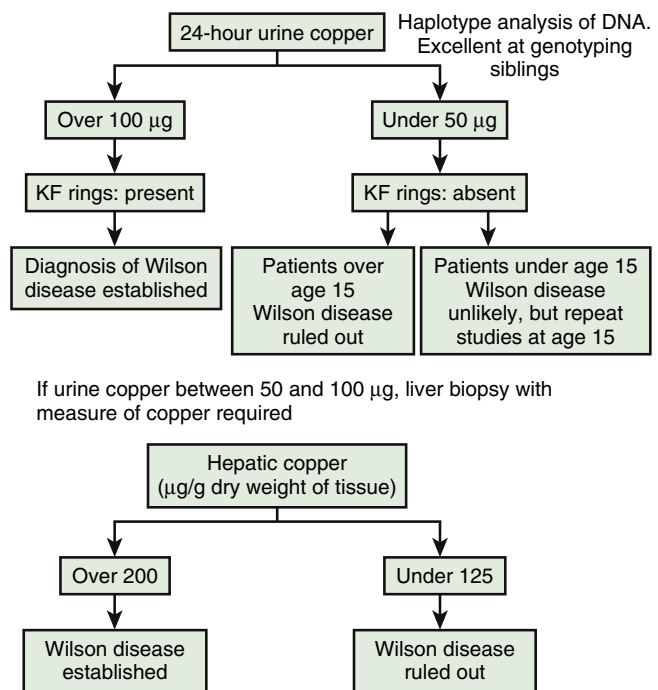


Fig. 22.5 An algorithm for screening and diagnosis of presymptomatic siblings. KF, Kayser–Fleischer. (From Brewer GJ. *Wilson's disease*. In: Hallett M, Poewe W, eds. *Therapeutics of Parkinson's Disease and Other Movement Disorders*. Chichester, UK: Wiley-Blackwell; 2008, pp. 251–261.)

Genetic linkage studies to chromosome 13 may be valuable if other family members are available, and the gene can be closely searched for a mutation (Farrer et al., 1991; Caca et al., 2001; Davies et al., 2008). With genetic information of the parents, even prenatal testing is possible (Lv et al., 2015). With modern sequencing methods and database availability, such studies are becoming better (Seo, 2012), but care should be taken because some findings could be nonpathogenic variants (Collet et al., 2018). Certainly if you know the high-frequency mutations in a population, it is possible to focus on those (Schilsky and Ala, 2010; Garcia-Villarreal et al., 2021). A database with 656 known pathogenic variants is available (Kumar et al., 2020).

All siblings, who have a one in four chance of developing the illness, and cousins of known patients, should be screened for Wilson disease even when there are no symptoms or signs of the disease (Li et al., 2018; Socha et al., 2018). Clinical signs, the presence of a Kayser–Fleischer ring, and abnormalities of serum and urine copper metabolism indicate the need for prophylactic treatment. If there is doubt, a liver biopsy may be undertaken, although molecular genetic techniques may prove diagnostic. An algorithm for evaluating presymptomatic siblings is presented in Fig. 22.5 (Brewer, 2008).

Treatment

The treatments for Wilson disease have been reviewed (Gouider-Khouja, 2009; Lorincz, 2010; 2012; Weiss and Stremmel, 2014; Czlonkowska and Litwin, 2017; Litwin et al., 2017; Aggarwal and Bhatt, 2018). Guidelines for treatment have been published by the American Association for the Study of

Liver Diseases (Roberts and Schilsky, 2008) and by the Hepatology Committee of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (Socha et al., 2018). Patients can be monitored with the Wilson-Disease-Specific global assessment scale (Aggarwal and Bhatt, 2013) or the Unified Wilson Disease Rating Scale (Czlonkowska et al., 2018). Outcome can be very good, but it depends on compliance and severity of neurologic and psychiatric features when therapy is initiated (Hefter et al., 2018).

The gold standard of treatment (Table 22.4) has been the metal chelator D-penicillamine (Walshe, 1999), building up to around 1 g/day, along with pyridoxine 25–50 mg/day. D-Penicillamine should be introduced gradually because about 20% of patients may develop early side effects (Litwin et al., 2015). The most common are fever, rash, and lymphadenopathy. Gradual reintroduction of D-penicillamine in low dosage under corticosteroid cover may overcome these problems. More serious is the development of bone marrow depression. Unfortunately, 20% to 40% of those with neurologic disability will exhibit deterioration in the initial months of penicillamine treatment (Brewer, 1999; Kalita et al., 2013). The neurologic deterioration can be severe; in an exemplary report the patient developed marked dystonia (status dystonicus) and died (Svetel et al., 2001). However, clinical improvement usually occurs within about 3 months, but it may take 6 months to a year before noticeable change takes place.

Reducing copper intake obviously is wise (Shimizu et al., 1999), but strict diets are rarely followed. Copper-rich foods include liver, nuts, chocolate, coffee, and shellfish.

Table 22.4 Treatment of Wilson disease

1. D-Penicillamine
 - Low and slow: 1 g/day (0.5–2.0) before food
 - Pyridoxine 25–50 mg/day
 - Avoid copper-rich foods
 - Monitor blood count and liver function tests, serum and urinary copper, Kayser–Fleischer ring
 - Early side effects: Allergy (20%)—fever, rash, glands; marrow depression; neurologic deterioration (20%–40%)
 - Late problems: Nephrotoxicity (proteinuria, nephrotic syndrome), systemic lupus erythematosus, thrombocytopenia, Goodpasture syndrome, dermatopathy, myasthenia
2. Trientine
 - 1–2 g/day (250–500 mg four times per day)
 - Iron deficiency
3. Zinc (sulfate or acetate)
 - 50–200 mg/day in divided doses
 - Gastrointestinal side effects
4. Liver transplant

Successful de-coppering can be monitored by an initial increase in urinary copper excretion, which subsequently falls, a reduction in the concentration of free copper in serum, and the fading of Kayser–Fleischer rings (Pfeiffenberger et al., 2018).

Late reactions to penicillamine treatment are usually seen after a year or so of therapy. The most common is penicillamine dermatopathy, a result of damage of collagen and elastin causing weakness of subcutaneous tissue so that slight trauma may cause bleeding, leaving brown papules with excessive wrinkling and thinning of the skin. A minority may develop proteinuria which can progress to a frank nephrotic syndrome. Other problems include the emergence of a form of systemic lupus erythematosus, thrombocytopenia, Goodpasture syndrome, and myasthenia gravis.

An alternative to d-penicillamine is trientine (triethylene tetramine dihydrochloride) (Brewer, 1999; Shimizu et al., 1999), another chelator. Trientine undoubtedly is a valuable alternative in those intolerant to the latter, but it has advantages in that the initial worsening may not occur (Brewer, 1999). It also can be used in children, in whom it can be effective with fewer side effects than with penicillamine (Taylor et al., 2009). Trientine is relatively safe (it can cause a sideroblastic anemia and can reactivate penicillamine-induced lupus), but is expensive, poorly absorbed, and not universally available. In a retrospective review of 405 patients treated with either penicillamine or trientine, the results were comparable, but there were fewer side effects with trientine (Weiss et al., 2013).

Zinc and tetrathiomolybdate prevent the absorption of copper and are other alternatives. Zinc is an excellent agent for chronic use for mild cases and prevention (Hoogenraad, 2006; Linn et al., 2009) but may not be rapid enough for initiating therapy in someone with severe illness. Zinc is also the treatment of choice during pregnancy. Zinc can be given safely in the pediatric age group (Brewer et al., 2001; Ranucci et al., 2014). For pediatric cases, a high-dose zinc and low-dose penicillamine combination has been proven safe and effective (Chang et al., 2013). In a systematic review of the literature, for neurologic Wilson disease, zinc was best

tolerated and had good efficacy (Wiggelinkhuizen et al., 2009). Zinc monotherapy may fail, however, and chelators would be needed (Weiss et al., 2011).

In a study of 143 patients, penicillamine and zinc sulfate were compared as initial therapy (Czlonkowska et al., 2014). Improvement was about the same, but there were fewer side effects with zinc.

Tetrathiomolybdate is not available except experimentally (Brewer, Hedera, Kluin et al., 2003; Brewer, Askari, Lorincz et al., 2006; Brewer, 2009; Brewer, Askari, Dick et al., 2009), and, although it showed efficacy with low rate of side effects, it seems that it will not get approval. Bis-choline tetrathiomolybdate (WTX-101), an oral copper-protein-binding agent that forms tripartite complexes with albumin and increases biliary copper excretion, is a newer version of tetrathiomolybdate (Weiss et al., 2017; Weiss et al., 2018). After a positive phase II study, this drug is being evaluated in a 48-week multicenter phase III trial (ClinicalTrials.gov: NCT03403205).

A new approach is the combination of zinc with dimer-captosuccinic acid (DMSA), a copper chelator. Good experience has been reported in a group of 60 patients who were intolerant to penicillamine (Zhu et al., 2020). Another trial compared zinc combined with sodium 2, 3-dimercapto-1-propane sulfonate (DMPS) to penicillamine with slightly better results (Zhang et al., 2020). There are also experimental therapies being developed (Aggarwal and Bhatt, 2020).

It is, of course, important to treat identified asymptomatic patients. Long-term follow-up of neurologically asymptomatic children treated for 10 years shows that zinc is well tolerated; liver disease improves, neurologic disorders do not develop, and growth is normal (Marcellini et al., 2005). Zinc monotherapy is safe and effective for completely presymptomatic children (Abuduxikuer and Wang, 2014). Another study of 87 patients showed that d-penicillamine and zinc can prevent overt disease over a median of 12 years, but the authors note that compliance with therapy is critical (Dziezyc et al., 2014).

With therapy, in addition to clinical improvement, there is also radiologic improvement (Sinha, Taly, Prashanth et al., 2007). Magnetic resonance spectroscopy, particularly measuring N-acetylaspartate (NAA), can be helpful in assessment of treatment efficacy (Tarnacka et al., 2008).

In desperate cases, injection of dimercaprol (BAL) still may be life-saving (Scheinberg and Sternlieb, 1995). But because injections are painful, this cannot be used chronically (Walshe, 1999).

Liver transplantation also has been employed, and may cure Wilson disease (Podgaetz and Chan, 2003; Arnon et al., 2011; Schilsky, 2014; Choudhary et al., 2018). The neurologic manifestations can be reversed in about 80% of cases, and liver transplantation can be undertaken for the neurologic disorder even with stable liver disease (Stracciari et al., 2000; Geissler et al., 2003). A series of 21 patients had a mean follow-up of 5.2 years and an actuarial follow-up of 10 years (Schumacher et al., 2001). All patients did well with the neurologic functioning, improving over 1 to 1.5 years. In a series of 24 patients with a mean follow-up period of 92 months, quality of life improved to the same level as controls in the general population (Sutcliffe et al., 2003). In a series of 13 patients, all did well, and those without neurologic manifestations before transplant did not develop them (Pabon et al., 2008). Other series also report good results (Marin et al.,

2007; Cheng et al., 2009; Yoshitoshi et al., 2009). A large series of 121 patients was reported concerning experience in France with a median follow-up of 72 months (Guillaud et al., 2014). Most of their cases were transplanted for severe liver disease, and again note that there can be excellent long-term outcome. The French group have reported their patients specifically selected for neurologic deterioration refractory to chelation again with good results (Poujois et al., 2020).

Liver transplantation is also a first-line treatment in fulminant Wilson disease, but it is also possible to consider plasma exchange, continuous hemodiafiltration, and copper chelation (Motobayashi et al., 2014; Pawaria et al., 2020).

Symptomatic treatment with antiparkinsonian drugs such as levodopa, dopamine agonists, and anticholinergics may be of benefit. For refractory neurologic symptoms, deep brain stimulation has been rarely employed with some benefit (Sidiropoulos et al., 2013; Hedera, 2014).

Hereditary deficiency of ceruloplasmin

A rare condition, hereditary deficiency of ceruloplasmin or aceruloplasminemia, can cause a movement disorder. In this autosomal recessive disorder caused by gene defects in the ceruloplasmin gene (Yazaki et al., 1998; Fasano et al., 2008; Pelucchi et al., 2018), homozygotes develop iron overload (Miyajima et al., 1987, 1995; Harris et al., 1995). The disorder is estimated to occur in 0.5 persons per million in Japan (Miyajima et al., 1999). Ceruloplasmin oxidizes ferrous iron to ferric iron (so some call it ceruloplasmin “ferroxidase”), which is stored in ferritin and hemosiderin. Ferric iron can be transported out of cells. Absence of ceruloplasmin leads to a low serum iron level with normal total iron binding capacity and sometimes to anemia. Serum ferritin and liver and brain iron concentrations are increased. Brain MRI shows increased iron deposition in the striatum, SN, red nuclei, and dentate nuclei. T2 hypointensities can be marked, including in the cerebral cortex (Grisoli et al., 2005). Clinical presentation has been with insulin-dependent diabetes (Calder et al., 2017), anemia, retinal degeneration, subcortical dementia, and a movement disorder, which typically is a facial dyskinesia (blepharospasm and oral dystonia) and torticollis, rigidity, and sometimes ataxia (Miyajima et al., 1987; Kawanami et al., 1996; Vroegindeweij et al., 2017). One patient has presented with parkinsonism (Kohno et al., 2000). A review of 33 patients found the age at diagnosis to be 16 to 71, and there was cognitive impairment in 42%, craniofacial dyskinesia in 28%, cerebellar ataxia in 46%, and retinal degeneration in 75% of patients

(McNeill et al., 2008). Treatment has been described with iron chelation (Miyajima et al., 1997; Skidmore et al., 2008). One patient was successfully treated with repeated infusions of fresh frozen plasma (containing ceruloplasmin) (Yonekawa et al., 1999). Combination of chelation and fresh frozen plasma also has been successfully used (Poli et al., 2017).

Hypoceruloplasminemia-related movement disorder

There is one report of hypoceruloplasminemia-related movement disorder without Kayser–Fleischer rings and without the Wilson disease mutation (Lironga et al., 2009). Patients presented with parkinsonism, tremor, dystonia, ataxia, and a tic disorder. It is not clear what these patients have and whether this is even a homogeneous entity.

Dystonia-parkinsonism, cirrhosis, and hypermanganesemia

Another autosomal recessive condition been recognized, which, similar to Wilson disease, is characterized by early-onset dystonia or parkinsonism with cirrhosis (Tuschl et al., 2008; Mukhtiar et al., 2016; Gulab, 2018; Zaki et al., 2018). It has been called “hypermanganesemia with dystonia 1” (HMNDYT1) (Aggarwal and Bhatt, 2020). MRI of the brain shows hyperintense T1 signal in the anterior pituitary, caudate, lentiform and dentate nuclei, and cerebellar white matter, but normal T2 signal, consistent with manganese deposition. This disorder has hypermanganesemia and polycythemia, which will separate it from Wilson disease, but the similarities have led to referring to it as the “new” Wilson disease (Stamelou and Bhatia, 2012). Genetic studies in a number of families have determined that the disorder is due to mutations in *SLC30A10*, a manganese transporter (Quadri et al., 2012; Tuschl et al., 2012, 2016). Like Wilson disease, the disorder can be treated with considerable benefit with chelation therapy (calcium sodium edetate and oral iron) (Quadri et al., 2012; Stamelou and Bhatia, 2012); thus it is important to keep in mind.

This disorder can also be produced by mutations in related genes dealing with manganese transport, *SLC39A14* (HMNDYT2) and *SLC39A8* (Marti-Sanchez et al., 2018). Other mimics have been described (Aggarwal and Bhatt, 2020).

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www.expertconsult.com.

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Autoimmune movement disorders

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Introduction

Advances in immunology over the past few decades have led to the discovery of a variety of new antibodies and improved the diagnosis and understanding of mechanisms underlying autoimmune disorders of the nervous system. This may in part explain the marked increase in the incidence of autoimmune disorders. Some of these disorders are associated with underlying tumors or cancers (paraneoplastic), others have antibodies that can be detected in the serum or cerebrospinal fluid (CSF), and yet others have no identifiable antibodies (Table 23.1). In one study of 41 adolescents and adults with nonparaneoplastic autoimmune encephalitis, 21 (51.2%) presented with a movement disorder as a part of their clinical presentation. The movement disorders encountered in the prospectively followed cohort included orofaciolingual dyskinesia (57.1%), tremor (38.1%), choreoathetosis (33.3%), paroxysmal dyskinesia (23.8%), stereotypies (14.3%), bradykinesia (13.1%), dystonia (13.1%), catatonia (4.7%), neuromyotonia (4.7%), ballism (4.7%), ataxia (4.7%), and stiff-person syndrome (4.7%) (Dash et al., 2018). On follow-up, 17 (80.1%) patients had good response to immunomodulatory therapy with total remission of the movement disorder.

Early recognition and institution of appropriate immunotherapy are critical to favorable outcomes. Besides multiple sclerosis, which has been well established as an immunologic disorder, autoimmune movement disorders have emerged as a growing category of neurologic disorders, typically characterized by acute or subacute onset of hyperkinetic disorders, although parkinsonism also may be a manifestation in some of these autoimmune disorders (McKeon and Vincent, 2016; Baizabal-Carvallo and Jankovic, 2018; Damato et al., 2018). Indeed, the role of immunologic mechanisms is increasingly being recognized in Parkinson disease (PD) and other neurodegenerative disorders (Sulzer et al., 2018; Jankovic, 2018, 2019; Tan et al., 2020). This is discussed further in Chapter 5.

Pathogenesis

The pathogenesis of autoimmune movement disorders is not well understood, but it is often determined by the location of the antigen (McKeon and Vincent, 2016; Balint et al., 2018, 2020; Damato et al., 2018). Whereas in many cases the detected antibodies, termed neuroglial surface autoantibodies, are directed against cell surface proteins, in other cases the antigens are located in intracellular (cytoplasmic or nuclear) compartments. The neuroglial surface autoantibodies may be pathogenic by interfering with normal physiologic processes or transmembrane channel functions (e.g., voltage-gated potassium channels). In autoimmune disorders with autoantibodies (e.g., Hu, Yo, Ri, CRMP5, and Ma2) directed against intracellular antigens, the autoantibodies may serve only as surrogate markers or bystanders and the observed pathologic changes may be mediated by microglia proliferation and infiltration of CD8⁺ cytotoxic T cells. In such cases, drugs that inhibit T-cell function (e.g., sirolimus) may improve outcomes more than immunomodulatory therapies (de Jongste et al., 2015). In some cases, intracellular antigens, such as those directed against the synaptic vesicle protein glutamic acid decarboxylase (GAD) may transiently reach the cell surface, such as during vesicle fusion, and trigger an immune (autoantibody) response.

Parainfectious movement disorders

Sydenham chorea

Sydenham chorea (SC) is a subacute, childhood-onset movement disorder that occurs as a result of infection with group A beta-hemolytic streptococcus (GABHS) typically in the setting of rheumatic fever (RF). RF, an autoimmune, multiorgan inflammatory disease, is associated with carditis (50%–78%), arthritis (35%–88%), chorea (2%–30%), erythema marginatum (less than 6%), and subcutaneous nodules (less

Table 23.1 Clinical features, antibody profile, and treatment of autoimmune conditions associated with movement disorders

Disorder	Typical age at onset/sex predilection	Antibodies	Tumor frequency	Main neuropsychiatric manifestations	Movement disorders
Sydenham disease	5–15 y/female preponderance	Lysoganglioside Tubulin D1 and D2 dopamine receptor	0%	Obsessive-compulsive behavior, abnormal verbal fluency and prosody, seizures, dysexecutive syndrome	Chorea (F) Tics Hypotonia Oculogyric crises
PANDAS or PANS	3 y to puberty/male preponderance	Same as Sydenham disease	0%	Obsessive-compulsive behavior, separation anxiety, enuresis, night fears, anorexia, etc.	Tics (F) Chorea minima (F)
Basal ganglia encephalitis	<1–15 y/equal sex distribution	Dopamine-2 receptor	0%	Emotional lability, attention deficit, psychosis	Dystonia (F) Parkinsonism (F) Chorea (F)
Anti-NMDA receptor encephalitis	23 y/4 times more common in females, except in extremes of life	NMDA receptor (NR1 subunit)	58% in women >18 years (ovarian > testicular teratoma)	Delusions, agitation, hallucinations, speech dysfunction, memory deficits dysautonomia, seizures, central hypoventilation, decreased level of consciousness, hemiparesis	Chorea, stereotypies, catatonia, dystonia, myorhythmia (F) Cerebellar ataxia (U)
Postherpes simplex encephalitis	24–79 y/equal sex distribution	NMDA receptor (NR1 subunit) D2 dopamine receptor GABA _A receptor	0%	Psychiatric manifestations	Choreoathetosis (F)
Encephalitis (diffuse or limbic)	64 y/male twice more commonly affected	LG11	5%–10% (thymoma)	Behavioral changes Seizures (several types) Amnesic syndrome Hyponatremia REM sleep behavior disorder	Faciobrachial dystonic seizures (F)
	40 years/male preponderance	GABA _B receptor	50% (SCLC)	Encephalopathy, seizures	Ataxia, opsoclonus, chorea, lingual dyskinesia (U)
	56 y/ women 70% of cases	AMPA receptor	65% (SCLC, thymoma)	Encephalopathy, seizures	Ataxia (U) SPS phenomena (U)
	40 y/male sex (more common)	GABA _A receptor	<5% (Thymoma)	Encephalopathy, seizures	SPS phenomena (U) Opsoclonus-myoclonus (U) Catatonia (U)
Morvan syndrome	57 y/almost exclusively in males	CASPR2 LG11 (less common) Contactin-2 (less common)	20%–50% (thymoma)	Psychosis, insomnia, agrypnia excitata, dysautonomia (hyperhidrosis, cardiovascular instability), peripheral neuropathy	Neuromyotonia, cramps, fasciculations (F)
Progressive encephalomyelitis with rigidity and myoclonus (PERM)	50 y/male preponderance	Glycine1 receptor DPPX-6	<20%	Encephalopathy, brainstem dysfunction, dysautonomia, sensory symptoms	Stiffness/rigidity (F) Stimulus-sensitive spasms (F) Myoclonus (F) Hyperekplexia (F) Ataxia (F)
Parasomnia associated with IgLON5 antibodies	64 y/equal sex distribution	IgLON5	0%	Abnormal non-REM and REM sleep, stridor, obstructive sleep apnea, dysphagia, vocal cord paresis, dysarthria, hypoventilation, altered ocular movements, dysautonomia	Severe gait instability (F) Rapid periodic leg movements (F) Chorea (F) Mandibular spasms (U)

Continued

Table 23.1 Clinical features, antibody profile, and treatment of autoimmune conditions associated with movement disorders—Continued

Disorder	Typical age at onset/sex predilection	Antibodies	Tumor frequency	Main neuropsychiatric manifestations	Movement disorders
Hashimoto encephalopathy (SREAT)	45–55 y/ 5 times more common in females	Thyroid peroxidase Thyroglobulin Alpha-enolase	0%	Confusion, seizures, stroke-like episodes, REM sleep behavior disorder	Myoclonus (F) Tremor (F) Ataxia (F)
Opsoclonus-myoclonus syndrome	45 y/slight female preponderance	Ri/ANNA2 Glycine1 receptor NMDA receptor GABA _B receptor GABA _A receptor Human natural killer (HNK-1)	40% (lung and breast cancer)	Opsoclonus	Myoclonus (F) Tremor (F) Gait ataxia (F)

Frequent (F): present in ≥25% of patients in most series; uncommon (U): present in <25 of cases in most series.

AMPA, α-Amino-3-hydroxyl-5-methyl-4-isoxazole-propionate; dipeptidyl-peptidase-like protein 6; GABA_B, gamma-aminobutyric acid B; NMDA, N-methyl-D-aspartic acid; REM, rapid eye movement; SCLC, small cell lung carcinoma; SPS, stiff-person syndrome; SREAT, steroid-responsive encephalopathy associated with autoimmune thyroiditis.

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than 1%–13%) (Szczygielska et al., 2018). Chorea is associated with RF in about 26% of cases, but in 20% of cases it may be the sole manifestation (Cardoso, 2017). Chorea is usually asymmetrical, and it may manifest as pure hemichorea in about 20% of cases. Although usually not disabling, in about 8% of cases it may be associated with severe hypotonia resulting in the patient being bedridden (chorea paralytica). Other motor phenomena include motor imperistence (“milkmaid grip” and “darting tongue”), phonic or motor tics, altered ocular fixation and oculogyric crises, dysarthria, and impaired verbal fluency (Baizabal-Carvallo and Jankovic, 2018). Chorea may also recur during pregnancy (chorea gravidarum). In one study, 15 of 20 (75%) SC patients developed chorea gravidarum, which also may be triggered by the use oral contraceptives (Maia et al., 2012).

In SC the individual contractions are slightly longer (longer than 100 ms) compared with those in Huntington disease (50–100 ms), but both have reduced corticospinal excitability. Some have postulated that reduced excitability, as demonstrated by transcranial magnetic stimulation (TMS) studies, may be compensatory (Hallett and Obeso, 2015; Khedr et al., 2015).

In most cases of SC, various neuropsychiatric manifestations, such as obsessive-compulsive symptoms, attention deficit disorder, personality changes, emotional lability, anxiety, age-regressed behaviors, anorexia, and dysexecutive syndrome, follow the onset of or accompany chorea, and these behavioral problems may persist for years or decades after chorea resolves (Cardoso, 2017). Typically, SC is a self-limited condition with a spontaneous remission after a course of 8 to 9 months, but up to 50% of patients may remain with chorea for years or decades. Despite regular use of secondary prophylaxis, recurrences are observed in up to 30% of patients (often without association with streptococcus infection or even anti-basal ganglia antibodies (Cardoso, 2017).

A major concern in patients with SC is cardiac involvement, particularly mitral valve insufficiency, present in 60% to 80% of cases (Cardoso, 2017). Because of the many neurologic, psychiatric, rheumatologic, cardiac, and other comorbidities the condition should be called Sydenham disease rather

than Sydenham chorea (analogous to Huntington disease rather than Huntington chorea), but the term Sydenham chorea has been traditionally used in the medical literature.

The diagnosis of SC is supported by demonstration of a previous infection with GABHS using throat cultures, positive antistreptolysin O, or anti-DNAse antibodies. Magnetic resonance imaging (MRI) is usually normal, although an increase in basal ganglia volume has been reported using volumetric methods.

The pathogenic mechanism of SC is not well understood, but molecular mimicry and cross-reactivity between GABHS and certain components of the basal ganglia have been proposed. For example, rats immunized with GABHS developed antibodies against D1 and D2 receptors and clinically showed compulsive-like behaviors (Brimberg et al., 2012). In addition, passively transferred serum obtained from GABHS-immunized mice caused behavioral disturbances (Yaddanapudi et al., 2010). Furthermore, anti-basal ganglia antibodies have been observed with a high sensitivity in patients with acute SC (Cunningham, 2014; Cardoso, 2017). It has been postulated that some of these antibodies activate the CaM-KII pathway of neurons leading to an increase in dopamine release, possibly explaining the chorea and some of the neuropsychiatric manifestations of SC. Some of the antibodies cross-react with various brain components besides the basal ganglia, and thus they should be referred to antineuronal, rather than anti-basal ganglia antibodies.

A full 10-day course of oral penicillin V therapy or an injection of benzathine penicillin G because penicillin prophylaxis is advisable in all patients for at least 10 years after RF or carditis. A brief course of prednisone, based on findings of beneficial effects in a double-blind, placebo-controlled study, has been also recommended (Oosterveer et al., 2010). Symptomatic treatment with a short course of fluphenazine or other dopamine receptor-blocking agent may improve chorea. Other drugs such as vesicular monoamine 2 inhibitors (tetrabenazine, deutetrabenazine, valbenazine) (Jankovic, 2016), valproic acid, and carbamazepine may also provide relief until the condition resolves spontaneously.

The terms PANDAS (pediatric autoimmune neuropsychiatric disorder associated with streptococcus) and PANS

(pediatric acute-onset neuropsychiatric syndrome) have been proposed to explain disorders triggered by GABHS infections and are manifested by young-onset obsessive-compulsive behavior, followed by tics and choreiform movements of fingers and toes that may be associated with poor handwriting skills (in PANDAS) (Nielsen et al., 2018; Siga et al., 2018). These patients share a set of antibodies similar to those with SC. Although the concept of PANDAS is controversial and its existence has been questioned because of the lack of consistent link with GABHS infections, other microorganisms such as *Mycoplasma* or influenza viruses, and Lyme disease have been proposed to be associated with a similar disorder, which has led to coin the term PANS. Despite the separate terminology, the existence of PANDAS and PANS as nosologically distinct disorders is doubtful.

Anti-N-methyl-D-aspartate receptor encephalitis

Anti-N-methyl-D-aspartate receptor encephalitis (anti-NMDAR) encephalitis is considered the most common autoimmune encephalitis in childhood, but it also can occur in adults (Titulaer et al., 2013a; Dalmau, 2016). It affects predominantly young individuals with a mean age at onset of 23 years; women are affected four times more frequently than men, but female predominance is less prominent in individuals younger than 12 years and older than 45 years (Titulaer et al., 2013b). A substantial proportion of young females with NMDAR encephalitis have underlying ovarian teratomas, but testicular tumors and various carcinomas have been reported, especially in adults. The diagnosis is usually suspected by subacute manifestation of behavioral and neurologic (encephalopathic) symptoms and is supported by an abnormal electroencephalogram (EEG) and CSF with pleocytosis and oligoclonal bands. Definite diagnosis is based on the detection of immunoglobulin G (IgG) against the NR1 subunit of the NMDA receptor, particularly in the CSF (Graus et al., 2016). In contrast to IgG NMDAR antibodies, which are highly specific for anti-NMDAR encephalitis (Hara et al., 2018), IgA or IgM antibodies occur infrequently and nonspecifically (Gresa-Arribas et al., 2014). The higher the antibodies in the serum and CSF, the worse the prognosis. CXCL13, a B-cell-attracting chemokine, is a relatively sensitive and specific biomarker for anti-NMDAR encephalitis, as high concentrations in the CSF have been associated with relatively poor treatment response and poor outcome (Leypoldt et al., 2015).

Anti-NMDAR encephalitis is characterized by the onset of neuropsychiatric manifestations, followed by dysarthria, memory deficits, dysautonomia, insomnia followed by somnolence that can lead to altered consciousness, seizures, and a broad variety of movement disorders (Titulaer et al., 2013b; Dalmau, 2016; Ariño et al., 2020). The following movement disorders have been described in patients with anti-NMDAR encephalitis: chorea, stereotypies, dystonia, catatonias, myoclonus, tremor, opsoclonus-myoclonus, and cerebellar ataxia (Florange et al., 2009; Baizabal-Carvallo et al., 2013; Duan et al., 2016; Varley et al., 2019). Orofacial dyskinesia is typically manifested by dystonia, stereotypy, or myorhythmia (Mohammad et al., 2014; Baizabal-Carvallo et al., 2015) (Video 23.1).

The pathological abnormalities in the brains of patients with NMDAR encephalitis have not been well described but the presence of concurrent anti-glial antibodies including antibodies directed against oligodendrocytes, causing a decrease of expression of GLUT1, may related to white matter alterations

reported in patients with NMDAR encephalitis (Matute et al., 2020; Martinez-Hernandez et al. 2020). The latter is characterized by slow (1–4 Hz), repetitive, rhythmical movements affecting cranial or limb muscles (Baizabal-Carvallo et al., 2015). The hyperkinetic movement disorders, particularly stereotypies, associated with anti-NMDAR encephalitis usually respond to dopamine-depleting drugs, such as tetrabenazine, deutetabenazine, and valbenazine (Baizabal-Carvallo et al., 2013; Jankovic, 2016). Although the movement disorders usually resolve after appropriate treatment, many patients have persistent behavioral abnormalities such as impaired attention and cognition, and fatigue (de Bruijn et al., 2018). ●

Postherpes simplex encephalitis

A relapsing form of herpes simplex encephalitis, occurring in about 20% of patients after the initial illness, has been shown to be associated with the presence of anti-NMDA receptor antibodies in the serum or, more likely, in the CSF (Prüss et al., 2012; Armangue et al., 2014; Hachohen et al., 2014). Antibody synthesis of several isotypes (IgG, IgA, or IgM) usually starts 1 to 4 weeks after the initial viral infection and may precede the onset of neurologic symptoms associated with the relapse. The most common manifestation is subacute, childhood-onset choreoathetosis, with or without orofacial and lingual stereotypies (Mohammad et al., 2014). Most patients with this form of anti-NMDAR encephalitis, triggered by prior herpes simplex encephalitis, improve with immunotherapy.

Basal ganglia encephalitis

Basal ganglia encephalitis typically manifests with a subacute, childhood-onset hyperkinetic or hypokinetic movement disorder associated with psychiatric manifestations (Marques-Matos et al., 2018). Although an MRI scan may be initially normal, in about half the cases it shows diffusion-weighted imaging (DWI) and T2-flair symmetrical bilateral hyperintensity in the striatum that progresses to hypointensity and striatal atrophy (Dale et al., 2012). Dystonia with dystonic tremor is the most frequent movement disorder, observed in 10 of 17 patients in one series, followed by parkinsonism, chorea, and oculogyric crises (Dale et al., 2012). Most cases occur after an infection (particularly beta-hemolytic streptococcus, mycoplasma, or enterovirus) or vaccination. Anti-dopamine 2 receptor (D2R) antibodies are often present in the CSF, but not necessarily in the serum. Some have suggested that encephalitis lethargica represented a form of autoimmune basal ganglia encephalitis (Dale et al., 2004). D2R antibodies have been detected in most children with basal ganglia encephalitis (Dai et al., 2020). These may be directed primarily to the striatum, the nucleus accumbens, and the olfactory tubercle, and patients with D2R encephalitis may benefit from immune therapy. Most patients fully recover when treated early with corticosteroids, intravenous immunoglobulin (IVIG), plasmapheresis, rituximab, or cyclophosphamide.

Limbic encephalitis

Limbic encephalitis is characterized clinically by subacute onset of rapidly progressive cognitive decline, confusion, mood changes, and seizures (Graus et al., 2016). The MRI typically shows bilateral hyperintensities in the medial temporal lobes on T2-weighted images (Wang et al., 2017). The

Video 23.1 Anti-NMDAR encephalitis. This 3-year-old boy with subacute onset of myalgias, frontal headaches, malaise, and vomiting; followed by confusional state, insomnia, hallucinations, dysarthria, and motor aphasia. He was admitted with diagnosis of viral encephalitis. During the hospitalization he developed generalized seizures, dysautonomia, repetitive orofacial stereotypies, dystonic contractions of the left side of his face, blepharospasm, dystonic flexion of the right hand and generalized chorea. He improved markedly with tetrabenazine.

following antibodies have been identified in patients with limbic encephalitis: paraneoplastic antibodies such as ANNA-1 (anti-Hu) and anti-Ma2 and neuronal cell surface antibodies directed against the VGKC complex. These antibodies are not directed against potassium channels but to the associated proteins LGI1 and contactin-associated protein-like 2 (Caspr-2) and less commonly to contactin-2, and they interfere with protein–protein interactions between these proteins and presynaptic A disintegrin and metalloproteins (ADAMs) (van Sonderen et al., 2016, 2017; Gadoth et al., 2017). Anti-LGI1 encephalitis typically manifests with faciobrachial dystonic seizures manifested by repetitive, brief, dystonic movements affecting mainly the arm and ipsilateral face (Irani et al., 2011). EEG does not always show abnormal epileptiform activity, and antiepileptic drugs are usually ineffective. Most patients fully recover with appropriate immunotherapy but residual cognitive deficit and relapses are common; the 2-year case fatality rate was 19% (van Sonderen et al., 2016).

Peripheral nervous system manifestations, including pain, and paroxysmal episodes of dizziness are commonly associated with LGI1 antibodies (Gadoth et al., 2017). Patients with antibodies against Caspr-2 have a more variable manifestation with central and peripheral nervous system manifestations (van Sonderen et al., 2016). Neuromyotonia (Isaacs syndrome) is part of the LGI1 or Caspr-2 syndrome, typically manifested by stiffness, spontaneous muscle contractions with cramps, fasciculations, myokymia, and impaired relaxation (Irani and Vincent, 2016). Electromyography (EMG) usually shows bursts of high-frequency random muscle discharges, after-discharges on nerve conduction studies, fasciculation potentials, myokymic discharges, neuromyotonic discharges, and other types of abnormal spontaneous activity on needle examination (Ahmed and Simmons, 2015; van Sonderen et al., 2017; Quian et al., 2019). In some cases, particularly in males, neuromyotonia, myokymia, burning pain, weight loss, hyperhidrosis, and dysautonomia are followed by encephalopathy (Morvan syndrome) (Irani et al., 2012). Morvan syndrome is one of three syndromes associated with the presence of antibodies against Caspr-2 and/or LGI1; the other two are acquired neuromyotonia and limbic encephalitis. (Muñiz-Castrillo et al., 2020; Michael et al., 2020).

Other antibodies directed against membrane receptors such as α -amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA), gamma-aminobutyric acid B (GABA_B), and GABA_A may be associated with encephalopathy and seizures (Lancaster et al., 2010; Höftberger et al., 2013; Kruer et al., 2014; Petit-Pedrol et al., 2014; Dogan Onugoren et al., 2015; Joubert et al., 2015; Spatola et al., 2017; Petit-Pedrol et al., 2018) (see Table 23.1). In one study of GABA encephalitis involving 26 patients, median age 40.5 years, the following clinical features were present: seizures (88%), alteration of cognition (67%), behavior (46%), consciousness (42%), or dyskinesia (35%)—orofacial dyskinesias, dystonic postures, or generalized choreoathetosis, especially in children (Spatola et al., 2017). Multifocal cortical-subcortical MRI abnormalities were noted in 23 (88%) patients, and 7 had tumors (mostly thymomas). The main epitope targets were the $\alpha 1/\beta 3$ subunits of the GABA_AR. GABA_AR encephalitis may overlap with herpes and anti-NMDAR encephalitis (Galli et al., 2017). LGI1 forms a trans-synaptic complex that includes the presynaptic disintegrin and metalloproteinase domain-containing

protein 23 (ADAM23), which interacts with voltage-gated potassium channels Kv1.1, and the postsynaptic ADAM22, which interacts with AMPA receptors. Anti-LGI1 antibodies seem to interfere with the interaction of LGI1 with ADAM23 and ADAM22, resulting in neuronal hyperexcitability. Many patients with clinical presentation characteristic of limbic encephalitis have no detectable antibodies.

IgLON5 syndrome

The IgLON5 syndrome, characterized by sleep disorders resembling restless legs syndrome, with rapid periodic leg movements during sleep onset and wakefulness, and by brainstem and hypothalamic manifestations has been found to be associated with antibodies against the neuronal cell adhesion protein IgLON5 (Sabater et al., 2014). Patients with anti-IgLON5 antibodies also often have cognitive decline, chorea, orofacial dyskinesia (stereotypy), and oculomotor abnormalities with severe gait difficulty and postural instability resembling progressive supranuclear palsy (Sabater et al., 2014; Gaig et al., 2017). Many patients with IgLON5 syndrome respond well to immunotherapy, but many develop severe symptoms including status epilepticus and sudden death. Brain MRI often shows abnormalities midbrain, hippocampus and cerebellar peduncles (Chen et al., 2020).

Abnormal accumulation of tau protein in the brainstem tegmentum, hypothalamus, and hippocampus (Sabater et al., 2014). In contrast to the other autoimmune disorders, this syndrome often fails to respond to immunotherapy and may have a fatal outcome with sudden death.

Stiff-person syndrome

Stiff-person syndrome (SPS), initially referred to as stiff-man syndrome until Blum and Janković's publication in 1991, is characterized by increased tone of axial and limb muscles, with superimposed muscle spasms leading to lumbar hyperlordosis and stiff gait (Video 23.2). It is nearly always associated with other autoimmune disorders, such as type 1 diabetes mellitus, thyroid disease, pernicious anemia, and vitiligo (Baizabal-Carvallo and Jankovic, 2015; Martínez-Hernández et al., 2016). Rarely, SPS may occur as paraneoplastic syndrome, mainly in women with breast cancer. ●

Typically manifesting between the fourth and sixth decade of life, with women outnumbering men 5 to 1, SPS also has been described in children (Fekete and Jankovic, 2012). In addition to muscle stiffness, SPS is often accompanied by autonomic crises with profuse diaphoresis, tachycardia, and hypertension. Muscle rigidity and spasms may result in several complications, including dyspnea, poor exercise tolerance, joint dislocation, or bone fractures. Some patients may manifest prominent stimulus-sensitive myoclonus affecting axial and proximal limb muscles, known as jerking stiff-man syndrome. Other features include paroxysms of transient but intense muscle spasms, frequently triggered by emotional upset, sudden movements, or external stimuli, may be accompanied by dysphoria, hyperreflexia, downbeat nystagmus, and ophthalmoplegia.

Diagnosis of SPS is usually considered based on clinical presentation, but electrophysiologic and immunologic studies are usually necessary to confirm the diagnosis. EMG typically shows continuous motor unit activity in agonist and antagonist muscles, presumably as a result of decrease in GABAergic

Video 23.2 Stiff-person syndrome. This 61-year-old woman with a long history of insulin-dependent diabetes started having progressive stiffness in both legs 6 months before our initial evaluation. On examination she had marked rigidity in both legs and paraspinal muscles that interfered with her ability to arise from chair and walk. She had brisk reflexes, ankle clonus, and bilateral extensor plantar response. The clinical presentation was characteristic of stiff-person syndrome, coupled with diabetic polyneuropathy. The patient tested positive for anti-GAD65 antibody (greater than 30 units/mL; normal less than 1.2) and responded well to low-dose diazepam and intravenous immunoglobulin infusions.

tone in the spinal cord interneurons and supraspinal disinhibition (Floeter et al., 1998; Sandbrink et al., 2000; Khasani et al., 2004; Levy et al., 2005; Dalakas, 2013). Antibodies to the following antigens have been detected in patients with SPS: GAD65, GAD67, glycine α -subunit receptor, amphiphysin, gephyrin, dipeptidyl-peptidase-like protein-6, GABAA and GABAB receptors, glycine receptor β -subunit, glycine transporter 2/SLCA5, Ri protein, and cardiolipin and β 2 glycoprotein 1 (Balint and Bhatia, 2016; Budhram et al., 2021).

Although there are few randomized controlled trials (RCTs) of these drugs in patients with SPS, IVIG showed improvement in stiffness and heightened sensitivity scores in patients in a crossover trial versus placebo; where patients received each therapy for 3 months (Dalakas et al., 2001). Benefit of IVIG was sustained for 6 weeks up to 1 year. A placebo-controlled trial of rituximab with 2 biweekly infusions of 1 g each in 24 patients with SPS showed no changes in the stiffness index at 6 months, although improvements in quality of life were noted at 3 but not at 6 months (Dalakas et al., 2017). Long-term immunotherapy may be needed to maintain remission.

Progressive encephalomyelitis with rigidity and myoclonus

Progressive encephalomyelitis with rigidity and myoclonus (PERM) is characterized by relapsing-remitting course of altered level of consciousness, dysautonomia, and brainstem manifestations with myoclonus, stimulus-sensitive spasms, hyperekplexia, cerebellar ataxia, and axial and limb rigidity (Carvajal-González et al., 2014; Mas, 2017). The latter may resemble features observed in SPS; therefore PERM has been considered within the spectrum of this disorder. However, more recent evidence links it with antibodies against the α 1 subunit of the glycine receptor (GlyR) and with GAD antibodies (Hutchinson et al., 2008; Piotrowicz et al., 2011; Carvajal-González et al., 2014). Furthermore, patients with PERM usually show pathologic signs of encephalomyelitis with perivascular lymphocytic cuffing, which contrasts with paucity of inflammatory changes in autopsy studies of SPS patients; although with little evidence of inflammation on neuroimaging. Most patients affected by PERM are in their fifth or sixth decades of life, although SPS can affect any age group, including children (Fekete and Jankovic, 2012). A syndrome similar to PERM, but frequently accompanied by diarrhea and other gastrointestinal symptoms, has been associated with antibodies against DPPX-6, which is a regulatory subunit of the Kv4.2 potassium channel, a protein highly expressed in the enteric plexus that can become hyperexcitable after exposure to these antibodies (Boronat et al., 2013; Balint et al., 2014; Piepgas et al., 2015).

Cerebellar ataxia

Autoimmune cause should always be considered in patients with sporadic, nongenetic, ataxias, particularly of subacute onset (see Chapter 22). In one prospective study of 1500 patients with sporadic progressive ataxia, gluten ataxia, associated with anti gliadin and antitransglutaminase antibodies, was most common (Hadjivassiliou et al., 2017). Enteral pathologic features typically found in celiac disease, however, is uncommon. In addition to ataxia, other movement disorders have been described in patients with gluten

sensitivity, including myoclonus, chorea, dystonia, tremor, and parkinsonism. Moderate improvement can be achieved with a gluten-free diet (Mitoma et al., 2016; Vinagre-Aragón et al., 2018). For some unknown reason, most reports of gluten ataxia come from the same geographic area in the United Kingdom, although gluten sensitivity is a world-wide disorder (Table 23.2).

Anti-GAD cerebellar ataxia is the second most common neurologic syndrome associated with positive serum anti-GAD antibodies after SPS and is the second most common autoimmune ataxia (Baizabal-Carvallo and Alonso-Juarez, 2017). Women represent more than 80% of cases, with a median age at onset of 59 years. Most patients have a subacute (between 3 and 6 months) or chronic (more than 6 months) course. Patients usually present with a pancerbellar syndrome and prominent oculomotor dysfunction, including nystagmus. In 20% of cases the cerebellar ataxia is preceded by transitory episodes of brainstem dysfunction, the so-called brainstem attacks (Ariño et al., 2014). About 50% to 70% of patients have a coexistent autoimmune disorder such as type 1 diabetes mellitus, thyroiditis, polyendocrine autoimmune disease, vitiligo, pernicious anemia, and myasthenia gravis, similar to what is observed in patients with SPS. Some patients may have modest improvement in their ataxia with immunosuppression.

In addition to SPS, PERM and cerebellar ataxia there are many other syndromes associated with anti-GAD antibodies, including epilepsy and limbic encephalitis (Budhram et al., 2021). Of these, cerebellar ataxia was the least responsive to immunotherapy and predicted poor outcome.

Movement disorders in autoimmune diseases

Systemic lupus erythematosus and antiphospholipid syndrome

Chorea occurs in 1% to 3% of patients with systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS), and it may be the initial manifestation in these autoimmune diseases (Baizabal-Carvallo et al., 2013; Cardoso, 2017; Garcia and Erkan, 2018) (Videos 23.3, and 23.4). Women represent more than 90% of cases of SLE chorea, with a median age at onset between 15 and 26 years. In addition to generalized chorea the patients may have dysarthria and loss of balance. Neither the antigen nor the pathogenesis of chorea in SLE are understood. Antiphospholipid (aPL) antibodies, positive in up to 90% of patients with lupus chorea, have been thought to disrupt the blood-brain barrier, allowing other antibodies to reach the brain. In addition, arterial thrombotic events may occur in the brains of these patients (Reiner et al., 2011). Anti-NMDAR antibodies against subunits NR2a and NR2b have been implicated in behavioral and cognitive changes in patients with SLE, but not in chorea or other involuntary movements (Baizabal-Carvallo et al., 2013). Positron emission tomography (PET) scans using ^{18} F-deoxyglucose (FDG) have shown increased metabolism in the striatum, but it is not clear whether this has any pathogenic implications for chorea. ●

Parkinsonism, the second most common movement disorder reported in patients with SLE, typically starts much earlier than idiopathic PD, and SLE-related parkinsonism is often associated with neuropsychiatric manifestations such as hallucinations, delirium, and mutism (Baizabal-Carvallo et al., 2013). Antidopaminergic antibodies have been detected in

Video 23.3 Lupus chorea. This 19-year-old woman with a history of meningitis at age 10 and subsequent arthralgias, myalgias, and pericarditis at age 18 years. She presented with a butterfly erythematous facial rash and a 10-day history of involuntary movements and incoordination. Anti-DS DNA antibody titer was 160 (normal less than 10). Her chorea markedly improved with tetrabenazine.

Video 23.4 Chorea associated with antiphospholipid antibody syndrome. This 70-year-old woman with a 2-year history of rapidly progressive but fluctuating generalized abnormal movements was found to have high titers of anticardiolipin immunoglobulin G (IgG) antibodies and high IgG phosphatidyl serine. She markedly improved with prednisone and tetrabenazine.

Table 23.2 Differential diagnosis of autoimmune cerebellar ataxias.

	Anti-GAD	Gluten sensitivity	Cerebellar type of HE	SLE ataxia
Gender	85% female	50% (female)	50% (female)	>90% (female)
Age at onset	58 y	48 y	53 y	20–40 y
Evolution	Subacute or chronic	Chronic	Acute to chronic	Acute or subacute
Clinical manifestations	Gait and limb ataxia, nystagmus is frequent. SPS phenomena and epilepsy may coexist	Gait and limb ataxia, nystagmus, sensorimotor axonal neuropathy, myoclonus, palatal tremor, opsoclonus, chorea	Gait ataxia (main), nystagmus infrequent (17%); neuropsychiatric symptoms	Pancerebellar syndrome, brainstem or cranial nerve dysfunction
Antibodies	GAD	Gliadin Transglutaminase-2 Transglutaminase-6	Thyroglobulin, thyroid peroxidase, NH ₂ -terminal alpha-enolase	Purkinje cell (75 kDa) nuclear dsDNA cardiolipin (IgG and IgM)
Investigations	MRI: Mild cerebellar atrophy Intrathecal production of GAD antibodies	MRI: Mild cerebellar atrophy, white matter hyperintensities. MRS: Reduction of NAA/Cr ratio in the vermis	MRI: Mild cerebellar atrophy EEG: Slow waves	MRI: Cerebellar atrophy, ischemic lesions in the brainstem and cerebellum; small hyperintensities in the white matter
Associated autoimmune disease	DM1, thyroiditis, pernicious anemia	DM1, thyroiditis, pernicious anemia	Thyroiditis	APS
Therapy	Corticosteroids, IVIG, rituximab, azathioprine	Gluten-free diet IVIG in refractory cases MM for myoclonic ataxia	Corticosteroids (highly effective)	Corticosteroids, azathioprine Cyclophosphamide (monthly pulses) Anticoagulation (in case of ischemia)

APS, Antiphospholipid syndrome; dsDNA, double-stranded DNA; EEG, electroencephalogram; GAD, glutamic acid decarboxylase; HE, Hashimoto encephalopathy; Ig, immunoglobulin; IVIG, intravenous immunoglobulin; MM, mycophenolate mofetil; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAA/Cr, N-acetylaspartate/creatine.

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some of these patients, thus suggesting the possibility that they represent basal ganglia encephalitis. Other movement disorders identified in these patients include cerebellar ataxia, tremor, focal dystonia, tics, paroxysmal nonkinesigenic dyskinesia, and corticobasal-like syndrome (see [Table 23.2](#)).

Other autoimmune disorders

Hashimoto disease

Hashimoto disease, also known as steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT), is defined by the combination of neuropsychiatric symptoms, laboratory evidence of antithyroid antibodies, and prominent clinical improvement with corticosteroids, along with lack of evidence of other disorders. Because encephalopathy is not always present, the term Hashimoto disease is now preferred. Onset is usually between 45 and 55 years of age, and females are five times more commonly affected. Typical clinical presentation includes seizures, stroke-like episodes, cognitive decline, and neuropsychiatric symptoms. Movement disorders, observed in up to 80% of patients, include tremor, chorea, athetosis, myoclonus, palatal myoclonus, and ataxia. Presentations with prominent cerebellar ataxia and limbic encephalitis also have been described ([Nakagawa et al., 2007](#); [Kishitani et al., 2017](#)).

Elevated titers of CSF antithyroxine peroxidase (TPO) antithyroglobulin (ATG), and alpha-enolase antibodies are more specific than serum antibodies. Most patients are euthyroid or have subclinical hypothyroidism; overt hypothyroidism occurs in 20% of cases ([Ferracci and Carnevale, 2006](#)). Antibodies reacting with the amino-terminal portion

of alpha-enolase are detected in about 50% of cases. Alpha-enolase is a cytoplasmic glycolytic enzyme, but it is also present in the surface of several cell types, where it acts as a plasminogen receptor ([Díaz-Ramos et al., 2012](#)). Alpha-enolase antibodies may not be specific for Hashimoto disease because they also have been detected in SLE, multiple sclerosis, and other autoimmune disorders ([Pratesi et al., 2000](#)). Back-averaged EEG does not show a cortical correlate with myoclonus, suggesting a subcortical origin ([Ferracci and Carnevale, 2006](#)).

Pathologic samples of patients with Hashimoto disease have demonstrated mild perivascular lymphocytic infiltration of small vessels. These vasculopathic changes have been related to stroke-like episodes and regional hypoperfusion assessed with single-photon emission computed tomography (SPECT) ([Mocellin et al., 2007](#)). MRI is usually normal. Response to corticosteroids is characteristic; improvement is usually observed within 4 to 6 weeks after treatment initiation. Replacement with thyroid hormones does not modify the course of the disease.

Opsoclonus-Myoclonus syndrome

This disorder is characterized by chaotic, multidirectional, conjugate, saccades (opsoclonus) ([Waln and Jankovic, 2018](#)). Myoclonus affecting predominantly the limbs, but also axial and craniocervical muscles, is one of the core features of this syndrome (see [Chapter 18](#)). In addition, tremor and gait ataxia are frequently observed. The disorder has a slight female preponderance, with bimodal peaks of age at presentation. In children, this disorder is commonly associated with neuroblastoma, but a wide variety of neoplasms such as breast or lung cancer and onconeural antibodies

(particularly ANNA-2/Ri) have been found in adults. In some patients a parainfectious cause is assumed (Klaas et al., 2012). In a series of 114 patients, 61% were considered idiopathic and 39% were paraneoplastic (Armangué et al., 2016). Neuronal surface antibodies such as anti-GlyR antibodies (associated with lung cancer), anti-HNK-1, and other antibodies have been detected (Armangué et al., 2016).

Paraneoplastic movement disorders

Cerebellar ataxia is the most common paraneoplastic neurologic syndrome, typically associated with small cell lung carcinoma. It has been associated with a variety of antibodies, including ANNA-1 (anti-Hu), ANNA-2 (anti-Ri), PCA-1 (anti-Yo), PCA-2, PCA-Tr, or ZIC4 (Graus et al., 2004; Jones et al., 2015). A group of IgG antibodies binding to the somatodendritic part of the Purkinje cell located in the molecular layer of the cerebellum, collectively known as “medusa head ataxia,” may be associated with antibodies directed against antigens involved in the glutamate/calcium pathway: mGluR1, Homer-3, SJ/ITPR 1, CARP VIII, PKCγ, ARHGAP26, GluRδ2, DNER, VGCC, Nb/AP3B2, CDR2, and PCA-2 (Jarius and Wildemann, 2015a,b,c). Parkinsonism has been associated with Ma1/Ma2 antibodies (Dalmau et al., 2004). Most of these patients present with limbic, diencephalic, or brainstem encephalitis, frequently accompanied by supranuclear gaze palsy, sometimes evolving to complete ophthalmoplegia, rapid eye movement (REM) sleep behavior disorders, or narcolepsy; testicular germ cell tumor is the most common underlying cancer. Paraneoplastic chorea, which is often volitionally suppressible, is most frequently associated with antibodies against CRMP5-IgG, followed by ANNA-1 (Vigliani et al., 2011) (Video 23.5). The patients may also exhibit dystonia, orobuccal dyskinesia, and comorbid polyneuropathy. Small cell lung carcinoma is the most common underlying cancer (Honnorat et al., 2009).

Clinical approach and diagnosis

An autoimmune pathogenesis should be suspected in patients with acute or subacute onset of movement disorders, especially when accompanied by psychiatric manifestations, brainstem dysfunction, dysautonomia, or encephalitis. Fluctuating neurologic manifestations may be observed in patients with PERM, and paroxysmal dizziness has been associated with LGI1 antibodies (Gadoth et al., 2017). “Brainstem attacks” may precede the onset of anti-GAD-associated ataxia (Matsumoto et al., 2002; Ariño et al., 2014).

The phenomenology of presenting movements may be helpful in diagnosing a specific autoimmune disorder. Onset of chorea or dyskinesia in children or young adults should raise suspicion of SC, NMDAR encephalitis, SLE, or APS. Facial dyskinesia such as orofacial stereotypy, although typically a manifestation of tardive dyskinesia, has been characteristically associated with anti-NMDAR encephalitis. In adults, autoimmune chorea is most frequently paraneoplastic; male sex, older age, severe chorea, comorbid peripheral neuropathy, and weight loss increase the likelihood of cancer (O’Toole et al., 2013). Dystonia is not commonly reported in the context of autoimmune disease, but jaw dystonia and laryngospasm have been described in patients with ANNA-2 antibodies (Pittcock

et al., 2010). Limb dystonia may be observed in patients with anti-NMDAR encephalitis, basal ganglia encephalitis, or SC. Faciobrachial dystonic seizures have been most typically associated with anti-LGI encephalitis.

Parkinsonism is not a common manifestation of autoimmune disease, although there is growing interest in the role of autoimmunity (Sulzer et al., 2017; Tan et al., 2020) and autoantibodies directed against alpha-synuclein in patients with PD (Shalash et al., 2017; Akhtar et al., 2018). Furthermore, monoclonal antibodies targeting alpha-synuclein are currently studied as potential disease-modifying therapy (Jankovic, 2019). Autoimmune parkinsonism usually manifests with encephalopathy, in patients with Ma1/Ma2 antibodies, anti-basal ganglia encephalitis, or SLE. In a series of 10 patients, mean age 63.7 years, presenting with multiple system atrophy, progressive supranuclear palsy, or atypical parkinsonism, 2 had LGI1 antibodies and 8 had unidentified neuronal antibodies (Kannoth et al., 2016). Marked clinical improvement with oral corticosteroids has been used as additional evidence of autoimmune cause in these cases. Although REM sleep behavior disorder often precedes a variety of parkinsonian disorders, its presence also has been noted in patients with limbic encephalitis associated with VGKC-complex antibodies (Iranzo et al., 2016), anti-IgLON5, or Hashimoto disease.

It should be noted that in many cases clinically suspected of being of autoimmune origin no specific antibodies are detected either the serum or CSF. Although in most cases serum determination of antibodies is sufficient for diagnosis of anti-NMDAR encephalitis, CSF examination may be necessary when negative results are obtained in the serum. In the case of positive serum and negative CSF antibodies, a false-positive result should be suspected and additional tests may be needed to confirm the diagnosis. This is also true for patients suspected of having GAD-associated autoimmunity, such as SPS or ataxia. CSF in patients with autoimmune movement disorders may show mild pleocytosis, increased protein, and positive oligoclonal bands, although these findings are not specific. There are no laboratory tests that can identify individuals at risk for autoimmune movement disorders, but one study showed association of anti-LGI1 encephalitis with certain human leukocyte antigen (HLA)-II haplotypes and anti-NMDAR encephalitis with HLA-I allele B*07:02 ($P=0.039$) (Mueller et al., 2018).

MRI studies are usually unremarkable, except in patients with limbic and other encephalitis, in which focal hyperintensities may be observed, particularly with VGKC-complex antibodies (Heine et al., 2015). PET computed tomography (CT) may show increased metabolism of basal ganglia or areas of inflammation detected on MRI. In one study, ^{18}F -FDG PET/CT showed higher sensitivity than MRI to detect abnormalities in patients with autoimmune encephalitis, particularly lobar hypometabolism (Solnes et al., 2016).

Suspicion of a paraneoplastic movement disorder is based on age, sex, hereditary background, environmental risk factors, and subacute onset. Certain autoimmune movement disorders, such as anti-NMDAR encephalitis, opsoclonus-myoclonus syndrome, or Morvan syndrome, are nearly always associated with underlying neoplasm. The following cancers are most frequently associated with paraneoplastic movement disorder: small cell lung carcinoma, breast cancer, ovarian teratoma, testicular seminoma, neuroblastoma, and thymoma (Fig. 23.1).

Video 23.5 Chorea associated with anti-CRMP antibodies. This 60-year-old man presented with progressive weight loss and subacute confusion. He was hospitalized because of marked hyponatremia and while in the hospital was noted to also have generalized chorea that was temporarily suppressible and rapidly progressive gait and balance difficulties. He had a positive titer (1:245,760) of collapsin response-mediator protein-5 (CRMP-5) immunoglobulin G (by immunofluorescence). He was found to have metastatic lung cancer and died within 3 months after initial evaluation.

ALGORITHM FOR DIAGNOSIS AND TREATMENT OF AUTOIMMUNE MOVEMENT DISORDERS

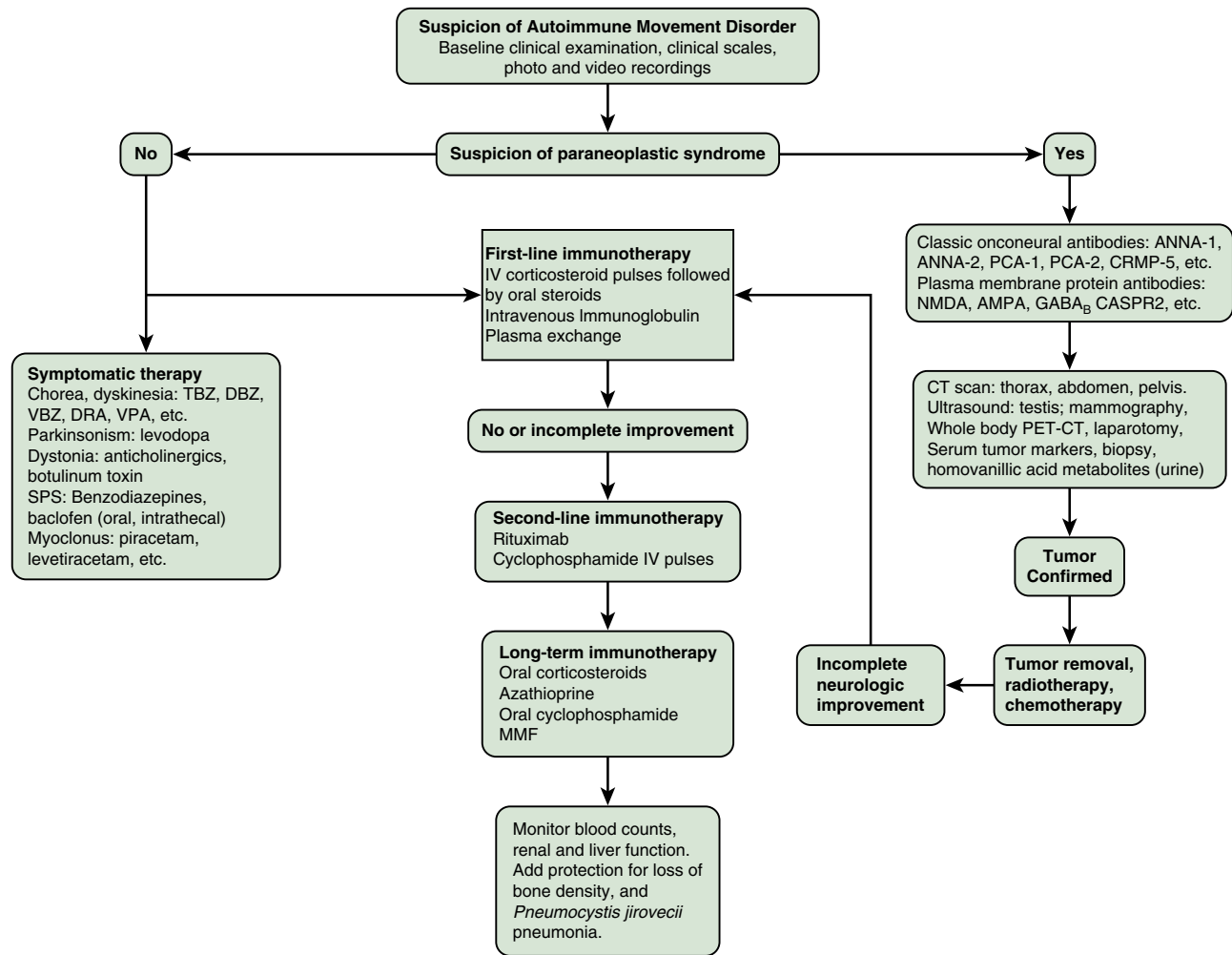


Fig. 23.1 Algorithm for diagnosis and treatment of autoimmune movement disorders. CT, Computed tomography; DBZ, deutetrabenazine; DRA, dopamine receptor antagonists; MMF, mycophenolate mofetil; PET, positron emission tomography; TBZ, tetrabenazine; VBZ, valbenazine; VPA, valproic acid. (Reproduced with permission from Baizabal-Carvallo JF, Jankovic J. Autoimmune and paraneoplastic movement disorders: An update. *J Neurol Sci.* 2018;385:175–184.)

Therapy

In addition to symptomatic therapy, such as vesicular monoamine transporter 2 inhibitors (VMAT2) in patients with chorea (Jankovic, 2016; Bashir and Jankovic, 2018), patients with autoimmune disorder should be aggressively investigated for underlying tumor (Table 23.3). Many studies have shown that early detection and treatment of an underlying cancer with tumor removal or chemotherapy not only ameliorates the movement disorder but markedly improves the long-term outcome.

Antibiotic therapy is recommended for patients with SC to prevent long-term complications, such as RF. Penicillin G benzathine intramuscular 1.2 million units every 21 days is recommended for patients who weigh more than 27 kg and 0.6 million units for those weighing less than 27 kg until the age of 21 years; sulfa drugs can be used in the case of allergy to penicillin (Cardoso, 2017). Despite prophylaxis, SC may recur in up to 40% of patients (Korn-Lubetzki et al., 2004). Some have advocated corticosteroids for patients with SC (Teixeira et al., 2005). This recommendation is supported by

an RCT of prednisone that showed meaningful improvement in the duration and intensity of chorea (Paz et al., 2006). Corticosteroids also may be associated with improvement in swallowing, chewing, and language (Fusco et al., 2012).

Most patients with autoimmune movement disorders should receive immunotherapy, including intravenous corticosteroids followed by a course of oral prednisone, IVIG, and plasma exchange. If these measures fail, anti-CD20 therapy with rituximab or intravenous pulses of cyclophosphamide should be considered, although an increasing number of centers use rituximab as the first line of treatment (Gastaldi et al., 2016).

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Table 23.3 Selected drug therapy for autoimmune movement disorders

Drug class	Doses	Comments and side effects
Immunotherapy		
Immunoglobulins	IVIg 2 g/kg in 2–5 days every month	Doses can be administered on a monthly basis Acute SE: Headache, fever, chest tightness, back pain, blood pressure changes, tachycardia, anaphylactic reactions (IgA deficient patients) Late SE: Renal failure, thromboembolic events, hemolytic anemia
Corticosteroids	Methylprednisolone 1 gr IV for 3–5 days followed by prednisone 50–60 mg/day with progressive dose reduction	Monthly pulses of corticosteroids are necessary in some conditions SE: Hyperglycemia, hypertension, weight gain, and osteoporosis Add oral calcium 1500 mg/day, vitamin D 1000 international units/day, sulfa, dapsone, or pentamidine for <i>Pneumocystis jiroveci</i> prevention
Plasma exchange	1.0–1.5 plasma volume per exchange	Invasive and time-consuming SE: Hypotension, arrhythmias, infections, hemolysis
Anti-CD20	Rituximab 375 mg/m ² IV over 90 min in 4 wky doses or subcutaneous rituximab over 5–7 min	SE: Allergic infusion reactions (premedication is necessary), infections, neutropenia B-cell count can be used as biomarker
Intravenous immunosuppressive agents	Cyclophosphamide 750 mg/m ² IV	Monthly pulses of CF are necessary in some conditions SE: Infections, ovarian failure, neutropenia, hemorrhagic cystitis
Oral immunosuppressive agents	Azathioprine 2–3 mg/kg/day, MMF 1.5–3 g/day in two doses	Target doses guided by the ALC. Measure TPMT activity for azathioprine (low activity increases the risk for SE) SE: Fatigue, GI symptoms, myelotoxicity, and liver toxicity
Symptomatic therapy		
Dopamine depleters	Tetrabenazine 12.5–50 mg tid Deutetrabenazine 6, 9, 12 mg bid Valbenazine 40, 80 mg daily	Useful for several hyperkinetic MDs, such as chorea or tics Monitor for drug-induced sedation, insomnia, depression, akathisia, parkinsonism, no risk for TD
Antagonists of dopamine receptors	Risperidone 2–8 mg/day (oral), Haloperidol 2–20 mg/day IM	Useful for several hyperkinetic MDs but only for <2 weeks of treatment Risk for acute dystonic reaction, TD, and drug-induced parkinsonism.
Muscle relaxants	Baclofen (oral) 10–60 mg/day or (intrathecal) 50–150 mcg/day	Useful for stiffness and muscle spasms of SPS, PERM, etc. SE: Drowsiness, dry mouth, ataxia, decreased cardiac output. Catheter dysfunction (intrathecal) may lead to severe withdrawal.
Benzodiazepines	Clonazepam 2.5 mg/day or diazepam 5 mg/day (starting doses)	Useful for opsoclonus, myoclonus, stiffness and muscle spasms. SE: Drowsiness, fatigue, ataxia, hypotonia, dry mouth.
GABAergic drugs	Gabapentin 300–900 mg tid Levetiracetam 500–100 mg bid Piracetam 7.2–24 g/day bid or tid	Useful for myoclonus, or muscle spasms SE: Drowsiness, dizziness, ataxia, peripheral edema, or nervousness (with levetiracetam)
Antiepileptics	Valproate 600–1800 mg/day Carbamazepine 200–1600 mg/day	Useful for Sydenham chorea or myoclonus (valproate). Several SE, including ataxia, hyponatremia, liver toxicity, etc.

First-line therapies include IVIg, corticosteroids, and PE; in case of poor response, escalation to rituximab or cyclophosphamide can be tried; maintenance therapy with oral prednisone/prednisolone with or without steroid-sparing agents: azathioprine or mycophenolate mofetil may be necessary.

ALC, Absolute lymphocyte count; CF, ***; GI, gastrointestinal; IgA, immunoglobulin A; IM, intramuscularly; IV, intravenously; IVIg, intravenous immunoglobulin; MDs, movement disorders; MMF, mycophenolate mofetil; PERM, progressive encephalomyelitis with rigidity and myoclonus; SE, side effects; SPS, stiff-person syndrome; TD, tardive dyskinesia; TPMT, thiopurine methyl transferase.

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Paroxysmal dyskinesias

Chapter contents

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Introduction

Paroxysmal dyskinesia refers to a group of diverse disorders that have as a salient clinical feature the occurrence of episodes of abnormal movements lasting variable periods of time that may or may not be triggered by a stimulus. The episodes are often separated by intervals of normal neurologic function, although in some of these disorders there may be baseline deficits that persist. Other paroxysmal neurologic disorders include migraine and epilepsy. In some cases the paroxysm is not of known neurologic origin, such as functional or psychogenic movement disorders (Bressman et al., 1988; Erro et al., 2018). There are a variety of movement disorders that, although sometimes occurring intermittently, are not considered with the paroxysmal movement disorders. These are listed in Table 24.1. The pathophysiologic processes of paroxysmal dyskinesias (PXD) is not understood, and epilepsy of the basal ganglia has been a serious consideration but difficult to prove. Some PXDs are supplementary sensorimotor seizures, including many of the hypnogenic variety (Lüders, 1996).

Definitions: Transient, paroxysmal, episodic, and periodic

Some pediatric neurologists have used the term “transient” for a number of movement disorders in children, but the concept of PXDs is becoming more widely recognized among pediatric neurologists (Lotz and Jankovic, 2003). Excluding tic disorders, Fernandez-Alvarez (1998) reviewed the 356 movement disorder cases under the age of 18 years that had been seen in his department’s clinic and reported that 19% of them were classified as transient dyskinesias (Table 24.2). In some

of these disorders, such as essential palatal myoclonus, the movements are not transient. The diagnosis depends on the clinical features; diagnostic tests are normal and unnecessary.

Kotagal and colleagues (2002) evaluated their cases of paroxysmal nonepileptic events. These are reviewed in Chapter 22. These were most common in adolescents and the school-age group. In the preschool group, the most common diagnoses were stereotypies, hypnic jerks, parasomnias, and Sandifer syndrome.

It is not clear how the label “paroxysmal” became the most common terminology applied to the group of dyskinesias of the choreoathetotic and dystonic type and the label “episodic” became commonly used for the ataxic variety. According to *Dorland’s Medical Dictionary*, a paroxysm is defined as (1) a sudden recurrence or intensification of symptoms and (2) a spasm or seizure. *Webster’s Third New International Dictionary* gives a similar definition. “Episodic” is not listed in *Dorland’s*; Webster’s defines “episodic” as occurring, appearing, or changing at usually irregular intervals. This definition is not very different from the definition of paroxysmal, except for the word “sudden.” Both terms are reasonable and acceptable.

The term “periodic” is defined by both *Dorland’s* and Webster’s as recurring at regular intervals of time. Because the PXDs do not recur at regular intervals, the term “periodic” would not be appropriate. Despite this, in neurology this term is used for the condition of familial periodic paralysis (Rowland and Gordon, 2005) and familial periodic ataxia (e.g., Vighetto et al., 1988, even though muscle weakness and ataxia, respectively, in these disorders do not occur at regular intervals. Some authors (e.g., Griggs et al., 1978) used the term “paroxysmal ataxia” in preference to “periodic ataxia,” and others use the term “episodic ataxia” (Zasorin et al., 1983). But the literature today uses “episodic ataxia (EA).”

Table 24.1 Classic movement disorders that usually appear in bursts or with specific actions, but are not considered paroxysmal dyskinesias

1. Action dystonia
2. Action myoclonus
3. Action and intention tremors
4. Arrhythmic myoclonus
5. Hyperekplexia
6. Periodic movements in sleep
7. Restless legs syndrome
8. Sandifer syndrome
9. Akathitic movements
10. Stereotypies
11. Tics

*The movements usually occur so frequently that they are not distinguished with a "paroxysmal" label.

Table 24.2 "Transient" movement disorders in children (not all are transient) (clinic of [Fernandez-Rivasa, 1990](#))

Benign paroxysmal torticollis in infancy
Benign paroxysmal tonic upgaze
Benign myoclonus of the newborn
Benign myoclonus of infancy
Essential palatal myoclonus
Jitteriness
Shuddering
Spasmus nutans
Transient idiopathic dystonia of infancy
Transient tic

According to dictionary definitions, either "paroxysmal" or "episodic" would be an appropriate term for the dyskinesias that are under discussion here. By common usage, and with few exceptions (e.g., [Margolin and Marsden, 1982](#)), "paroxysmal" has been chosen in preference over "episodic" for the choreoathetotic and dystonic types and is used in this syllabus. The term "episodic" is also applied here to the ataxias in keeping with the current trend in the literature. The term "paroxysmal" has been used to indicate that the symptoms occur suddenly out of a background of normal motor behavior. It does not define the frequency, severity, duration, aggravating factors, or type of dyskinesia of the attack. These features vary and are important in the current nosology and classification of the PxDs.

Historical aspects

This is a condensed review of historical highlights of the paroxysmal and episodic dyskinesias. For a more complete discussion, see the review by [Fahn \(1994\)](#) and reviews by [McGuire and colleagues \(2018\)](#) and [Menert and Roze \(2016\)](#).

Earliest descriptions: Reported as epilepsy

Although [Gowers \(1885\)](#) is often credited with the first report of movement-induced seizures, it is possible that his cases actually represented PxD. One of his patients was a boy whose attack lasted 15 seconds, but the boy was said to

be unconscious during his initial attack. Later, he remained awake during the attacks. Another patient was a girl whose attacks started at the age of 11 years and occurred when she arose suddenly after prolonged sitting. But at least one of her attacks was said to be associated with a terrified expression, flushed facies, and dilated pupils. After Gowers, a number of reports of "movement-induced seizures" appeared in the literature. Many of these reports have been published under the designation of reflex epilepsy and tonic seizures induced by movement. However unlike most motor convulsions, there was no alteration in the state of consciousness. Moreover, some of these reports had more than tonic contraction, namely, they included sustained twisting, athetosis, and chorea. These characteristics are today referred to as paroxysmal dystonia and paroxysmal choreoathetosis, rather than convulsive seizures. Even the presence of choreoathetosis did not lead the earliest interpreters of these brief attacks to conclude they were a movement disorder; instead, they were considered to be a form of epilepsy, the cerebral site of these "seizures" being in the basal ganglia or in the subcortical region.

After the report of Gowers, the next report of movement-induced paroxysmal movements appears to be that of Spiller in 1927. Spiller described two patients with brief tonic spasms that were brought on by voluntary movement of the involved limbs and, in one of them, also by passive manipulation. Spiller called this "subcortical epilepsy." [Wilson \(1930\)](#) described a 5-year-old boy who had brief attacks of unilateral torsion and tonic spasm that lasted up to 3 minutes and were precipitated by fright or excitement. There was no loss of consciousness. The attacks could be preceded by pain. Wilson considered this to be reflex tonic epilepsy and thought it also to be subcortical in origin. The concept that these attacks of tonic, often twisting, contractions without loss of consciousness are uncommon seizure disorders was continued ([Whitty et al., 1964](#); [Burger et al., 1972](#)). It would appear that today these movement-induced involuntary movements would be considered paroxysmal choreoathetosis/dystonia rather than convulsive movements of the reflex epilepsy type. Differentiation of the attacks between cortical seizures and PxDs is sometimes difficult. Clouding of consciousness, if it occurs, would point to a seizure disorder.

By 1966 and 1967, when papers using the term "paroxysmal choreoathetosis" began regularly to appear ([Stevens, 1966](#); [Kertesz, 1967](#); [Mushet and Dreifuss, 1967](#)), particularly those cases induced by movements, there were still occasional papers referring the condition to a seizure disorder. As is discussed in the section on paroxysmal hypnogenic dyskinesias PHDs, nocturnal epilepsy is now considered to be the leading cause for that specific entity.

Reported as a paroxysmal disorder of involuntary movements

In 1940, [Mount and Reback \(1940\)](#) introduced a new concept, that of labeling attacks of tonic spasms plus choreic and athetotic movements as a paroxysmal type of movement disorder. They described a 23-year-old man who had experienced both large and small "spells" since infancy. Both types were preceded by a sensory aura of tightness in parts of the body or by a feeling of tiredness. The movements involved the arms and legs and were usually a combination

of sustained twisted posturing and chorea and athetosis. The small attacks lasted from 5 to 10 minutes. Longer attacks were considered large and also involved the neck (retrocollis), eyes (upward gaze), face (ipsilateral to the limbs if the limb involvement was unilateral), and speech. These large attacks lasted for as long as 2 hours, and the movements were considered to resemble those seen in Huntington disease. There was never a loss of consciousness or clonic convulsive movements, biting of the tongue, or loss of sphincter control. Drinking alcohol, coffee, tea, or cola would usually bring on an attack. Fatigue, smoking, and concentrating were other precipitating factors. The attacks would clear more rapidly if the patient would lie down and would be aborted by sleep. The patient had an average of one large and two small attacks a day. Between attacks, the neurologic examination was normal. Phenytoin and phenobarbital had no effect, and scopolamine was the only drug found to reduce the frequency, severity, and duration of the attacks. The family history revealed 27 other members who had similar attacks; the pedigree showed autosomal dominant inheritance with what appears to be complete penetrance. [Mount and Reback \(1940\)](#) called this disorder “familial paroxysmal choreoathetosis.”

Mount and Reback’s paper (1940) became the seminal paper in the field of PXDs. After its publication, most of the reports in the literature referenced it over the next five decades. However, the next report of a large family with similar attacks of muscle spasms did not refer to it. In 1961, Forssman described a family with autosomal dominant inheritance in which there were attacks lasting from 4 minutes to 3 hours.

The next large family was described in 1963 by [Lance \(1963\)](#). Like [Forssman \(1961\)](#), Lance also did not relate this to nor refer to Mount and Reback’s report, nor did he mention the report by Forssman. In fact, Lance considered his patients to have a form of epilepsy. Later, [Lance \(1977\)](#) was to write one of the definitive papers in this field, containing a useful classification scheme in which he related his family to those of [Mount and Reback \(1940\)](#), [Forssman \(1961\)](#), and [Richards and Barnett \(1968\)](#).

Although there were reports of patients whose PXDs were induced by sudden movement, they were not denoted by any special terminology until 1967, when [Kertesz \(1967\)](#) introduced the label “paroxysmal kinesigenic choreoathetosis” (PKC). This label has developed into a most useful and widely accepted designation because the kinesigenic feature has proven to be so characteristic. Kinesigenicity has an important place in the classification of the PXDs, and [Demirkiran and Jankovic \(1995\)](#) recommended that the term “paroxysmal kinesigenic dyskinesia” (PKD) be used instead, because the movements can be other than choreoathetotic. That suggestion is followed in this chapter. As is pointed out later, the PKD designation can be applied to some patients who do not have the dyskinesias triggered by sudden movement (or startle).

Kertesz (1967) reported 10 new cases of PXD and reviewed the literature. Among the important features of his paper, Kertesz differentiated the kinesigenic variety (induced by sudden movement) from that described by Mount and Reback, by Forssman, and by Lance, which were aggravated not by movement but by alcohol, caffeine, and fatigue. (It should be noted that Kertesz differentiated the kinesigenic

type from that reported by [Mount and Reback \[1940\]](#) and by [Lance \[1963\]](#), but he failed to mention the paper by [Forssman \[1961\]](#).)

Although phenytoin was recognized earlier as a very useful agent for PKD, carbamazepine was later found to be as useful and was introduced as a treatment by [Kato and Araki \(1969\)](#). This drug currently appears to be the one that is most commonly used for this disorder.

After the 1963 paper by Lance, [Richards and Barnett \(1968\)](#) reported the next big family with the same type of PXD as Mount and Reback’s case and thought that Lance’s family (1963) represented a variant because there were only tonic spasms and no movements in that family. Richards and Barnett emphasized the nonkinesigenic nature of the attacks and thought that the terms rigidity, tremor, dystonia, torsions, spasm, athetosis, chorea, and hemiballism could all be used for such movements, often blending into each other. To emphasize the postural and increased tone, they added “dystonic” to the label. They recommended avoiding the term “epilepsy” until the pathophysiology is better known. Richards and Barnett coined the term “paroxysmal dystonic choreoathetosis” (PDC), which was later adopted by Lance in 1977. The terms “paroxysmal non-kinesigenic choreoathetosis” and “paroxysmal dystonia” are sometimes used instead of PDC ([Bressman et al., 1988](#)). We have adopted the term “paroxysmal nonkinesigenic dyskinesia” (PNKD) proposed by [Demirkiran and Jankovic \(1995\)](#).

The original cases that were reported as PNKD were idiopathic and usually familial. It was not long before symptomatic cases began to be reported in which the attacks of movements were reported as a PNKD: perinatal encephalopathy ([Rosen, 1964](#)), encephalitis ([Mushet and Dreifuss, 1967](#)), and head injury ([Whitty et al., 1964](#); [Robin, 1977](#)). However, earlier reports of symptomatic PNKD had been described as a manifestation of multiple sclerosis, but considered as a form of epilepsy ([Matthews, et al., 1958](#); [Joynt and Green, 1962](#); [Verheul and Tyssen, 1990](#)). Many other causes have been reported since the cases in the 1950s and 1960s (see later).

One of the most enlightening papers ([Lance, 1977](#)) achieved the following:

1. It discovered Forssman’s paper (1961).
2. It placed together as one syndrome the families that [Mount and Reback \(1940\)](#), [Forssman \(1961\)](#), [Lance \(1963\)](#), and [Richards and Barnett \(1968\)](#) had reported, bringing them all in under the term “familial paroxysmal dystonic choreoathetosis” (PDC), which has a duration of attacks from 5 minutes to 4 hours.
3. It expanded the description of Lance’s own previously reported family (1963), which he now classified as having this disorder instead of the seizure disorder that he had originally considered.
4. It added another family with PXD that had attacks induced by continuous exercise rather than sudden movement that affected the legs with a duration between 5 and 30 minutes. (These were the first cases of what is now recognized as paroxysmal exertional dyskinesia.)
5. It classified the PXDs into three groups separated primarily by duration of action (prolonged, intermediate, and brief attacks) and secondarily by precipitating factors.
6. It reported the therapeutic response to clonazepam in some patients with the prolonged attacks.

7. It mentioned normal autopsy findings in two individuals with the prolonged attacks.
8. It summarized the literature to that date.
9. It pointed out that the Forssman and Lance families with the prolonged attacks had dystonic postures without choreoathetosis, whereas the Mount and Reback and the Richards and Barnett families had choreoathetosis.
10. It explained that over time, patients with sustained spasms can eventually develop writhing movements, thereby linking these phenotypes together.
11. It commented that in all types of PXDs, males are more affected than females.

Instead of Lance's proposed classification (item 5 in the preceding list) based on duration of the attacks, the classification scheme that is adopted here is the one based on precipitating factors suggested by [Demirkiran and Jankovic \(1995\)](#).

The next historical advances were the recognition that (1) idiopathic PNKD can occur sporadically and not just in families ([Bressman et al., 1988](#)) and (2) sporadic PNKD is often psychogenic in origin ([Bressman et al., 1988](#); [Fahn and Williams, 1988](#)).

Paroxysmal hypnogenic dyskinesia

[Horner and Jackson \(1969\)](#) described two families in which several members had attacks of involuntary movement that occurred during sleep. These appear to be the first cases of PHD to be reported. Family W is of particular interest because some affected members had classic PKD, some had hypnogenic, and others had a combination. Case 3 in this family began with the hypnogenic variety at age 8. By age 11, daytime attacks also occurred, sometimes triggered by sudden movement. Gradually, the hypnogenic episodes disappeared, leaving the patient with kinesigenic dyskinesia that responded to anticonvulsants. [Lugaresi and colleagues \(Lugaresi and Ciri-gnotta, 1981; Lugaresi et al., 1986\)](#) independently rediscovered and eventually popularized the syndrome of PHD.

In addition to these short-duration attacks, [Lugaresi and colleagues \(1986\)](#) reported long-duration hypnogenic attacks. Such long-duration attacks occur in a minority of individuals with PHD. These longer attacks last from 2 to 50 minutes and do not respond to medication, including anticonvulsants, tricyclics, benzodiazepines, and antipsychotics.

There has long been considerable speculation as to whether the short-duration hypnogenic attacks could be a manifestation of epilepsy, because they respond so well to anticonvulsants. The lack of abnormal electroencephalogram (EEG) findings during the attack has been used to argue against this concept. However, there is accumulating evidence that many PHDs are indeed the result of seizures. [Tinuper and colleagues \(1990\)](#) described three patients with this disorder who had EEG evidence for frontal lobe seizures as a cause of the attacks. [Sellal and colleagues \(1991\)](#) and [Meierkord and colleagues \(1992\)](#) studied a series of patients with hypnogenic dystonia and concluded that these represent seizure disorders, particularly of frontal lobe epilepsy because repeated nocturnal EEG recordings often reveal epileptic patterns of abnormalities. Seizures arising near the mesial posterior frontal supplementary sensorimotor area may be a particular culprit in inducing PHDs in children

([Bass et al., 1995](#)). These types of seizures tend to be brief and frequent, with bilateral tonic posturing, gross proximal limb movements, and preserved consciousness. Dystonic and other dyskinetic features may result from spread of epileptic activity from the mesial frontal region to the basal ganglia because there are close anatomic connections between them. It appears that the short-lasting attacks of PHDs are most likely the result of seizures, but the question remains whether patients without abnormal EEGs and more prolonged hypnogenic attacks could have something more akin to the PXDs. In a family with autosomal dominant nocturnal frontal lobe epilepsy, interictal EEGs were normal, but ictal video EEG studies showed that the attacks were partial seizures with frontal lobe origin ([Scheffer et al., 1995](#)). [Fish and Marsden \(1994\)](#) reviewed epilepsy masquerading as a movement disorder, and they concluded that most cases of hypnogenic dyskinesias are considered to be due to epilepsy, as did [Lüders \(1996\)](#), with cyclic alternating EEG pattern thought to be a provocative factor ([Terzano et al., 1997](#)).

The genetics of hypnogenic dyskinesias/seizures has been explored. A large autosomal dominant Australian family ([Oldani et al., 1998](#)) and a Norwegian family ([Nakken et al., 1999](#)) have been described with mutations in the nicotinic acetylcholine receptor alpha4 subunit (*CHRNA4*) gene, located on chromosome 20q13.2–q13.3. A second acetylcholine receptor subunit, *CHRNA2*, is also associated with autosomal dominant nocturnal frontal lobe epilepsy ([Phillips et al., 2001](#)). Another family with autosomal dominant hypnogenic frontal lobe epilepsy has been mapped to 15q24 ([Phillips et al., 1998](#)).

In addition to epilepsy mimicking hypnogenic PXDs, there is a syndrome of infantile convulsions and PXDs, referred to as the infantile convulsions with choreoathetosis (ICCA) syndrome ([Lee et al., 1998](#)). The gene for this disorder has been mapped to the pericentromeric region of chromosome 16 (see the discussion in the section on PKD and also in the section on molecular genetics of paroxysmal dyskinesias). Single-photon emission computed tomography (SPECT) studies revealed alterations in local cerebral perfusion in the sensorimotor cortex, the supplementary motor areas, and the pallidum ([Thiriaux et al., 2002](#)).

Transient paroxysmal dyskinesias in infancy

[Snyder \(1969\)](#) introduced a new type of PXD that he called "paroxysmal torticollis in infancy." He described 12 cases of intermittent head tilting in young infants. The age at onset was between 2 and 8 months of age, except for three cases, in which the first attacks occurred at 14, 17, and 30 months. The attacks would occur about two or three times a month and last from 10 minutes to 14 days, usually 2 to 3 days. The head would tilt to either side and often rotate slightly to the opposite side. There is no distress unless a parent attempts to straighten the head, upon which the baby cries. In some cases, the head tilting is associated with vomiting, pallor, and agitation for a short period. The infant is normal between attacks, which disappear after months or years, usually around age 2 or 3 years. Subsequently, several similar cases have been described ([Gourley, 1971](#); [Santer and Bergstrom, 1979](#); [Bratt and Menelaus, 1992](#)), including familial cases ([Lipson and Robertson, 1978](#)). [Santer and Bergstrom \(1979\)](#) reported a patient whose father had a similar condition in early infancy, suggesting that this disorder is hereditary.

The clinical picture of paroxysmal torticollis in infancy (Video 24.1) that has evolved is that the trunk also can be involved, with lateral curvature concave to the same side as the head tilting, and the ipsilateral leg can be flexed. Onset can be as early as the first months of life and can recur every couple of weeks until they disappear before the age of 2 years. Each attack can last a couple of hours to a couple of weeks. In between attacks, the child is normal. The main differential diagnosis is a posterior fossa tumor and Sandifer syndrome (in which head tilt is due to gastroesophageal reflux) (Menkes and Ament, 1988). ▶

In 1988, the clinical spectrum expanded with the report by Angelini and colleagues (1988) under the name “transient paroxysmal dystonia in infancy.” They described nine patients who had onset of the PXDs between 3 and 5 months of age, except for one patient who had an onset at age 1 month. Three had a history of perinatal brain damage, and six did not. The attacks consisted of opisthotonus, increased muscle tone with twisting of the limbs, and, in three, neck and trunk twisting, thereby linking this with paroxysmal torticollis in infancy. The attacks last several minutes, with a maximum of 2 hours in one patient. They would occur from several times per day (Video 24.2) to once a month. Remission occurred between the ages of 8 and 22 months, with two not yet having reached a remission. ▶

Dunn (1981) described an infant with head turning and posturing of the right arm lasting from 45 minutes to 18 hours. There were six attacks from age 26 months to age 40 months. The author did not mention the possible diagnosis of paroxysmal torticollis in infancy and made a diagnosis of PDC instead. One should consider the possibility that PNKD may occur in infancy and disappear over several months. If so, then the paroxysmal torticollis in infancy of Snyder and the paroxysmal dystonia in infancy of Angelini may represent the lowest age spectrum of PNKD and a benign form of the disorder.

Some patients with benign paroxysmal torticollis of infancy come from kindreds with familial hemiplegic migraine linked to CACNA1A mutation, and after recovering from these episodes as they reach childhood, they might have migraines (Giffin et al., 2002). In fact, a family with individual members of the kindred having one or more of paroxysmal tonic upgaze, benign paroxysmal torticollis of infancy, and EA with familial migraine and a CACNA1A mutation (as in EA-2) has been reported (Roubertie et al., 2008). The clinical picture of benign paroxysmal torticollis of infancy has been summarized to consist of attacks usually lasting less than a week, recurring from every few days to every few months, improving by age 2 years, and ending by age 3; there is very frequently a family history of migraine (Rosman et al., 2009).

Intrauterine cocaine exposure can be associated with multiple transient dyskinesias. Beltran and Coker (1995) described four infants who tested positive for cocaine metabolite at birth with subsequent transient dystonic reactions, beginning at 3 hours to 3 months of age and persisting for several months.

The clinical syndrome of transient PXD of infancy appears distinct from the syndrome referred to as “benign paroxysmal tonic upgaze of childhood” (Ouvrier and Billson, 1988; Deonna et al., 1990; Echenne and Rivier, 1992; Campistol et al., 1993), which is a sustained tonic conjugate upward deviation of the eyes that begins in infancy and eventually

disappears in childhood. This appears to be an autosomal dominant disorder (Guerrini et al., 1998). An infant with tonic upgaze was found to have a partial tetrasomy of 15q (Joseph et al., 2005). Ataxia may be present, and there can be clumsiness and delayed walking. The ocular deviations lessen in the morning hours and disappear with sleep. Acetazolamide is not effective; however, Campistol and colleagues (1993) reported levodopa to be effective. Perhaps the tonic upgaze with diurnal fluctuations would be a better term than “paroxysmal.” Not all cases of infantile transient tonic upgaze disturbance are benign, although the mean age of offset is 2.5 years (Hayman et al., 1998). Ouvrier and Billson (2005) published a review of this disorder. The family reported by Roubertie and colleagues (2008) suggests that tonic upgaze and transient torticollis and EA-2 may be related. A secondary cause of paroxysmal tonic upgaze has been reported. A 1-year-old girl with a hypomyelinating leukoencephalopathy, who presented in the neonatal period with episodes of sustained paroxysmal tonic upward gaze, roving eye movements, pendular nystagmus, and severe hypotonia, with the later appearance of pyramidal and extrapyramidal signs and no development (Blumkin et al., 2007).

Another paroxysmal ocular disorder, known as paroxysmal ocular downward deviation, has been described in normal and brain-damaged infants (Yokochi, 1991; Miller and Packard, 1998). The ocular displacement was accompanied by closure of the upper eyelids, and the episode lasted seconds.

The syndrome of benign myoclonus of infancy can be mistaken for infantile spasms, but the benign EEG and clinical course allow for a clear distinction. The movements are sudden myoclonic and shuddering episodes of the head and shoulders (Lombroso and Fejerman, 1977; Fejerman, 1984). The jerks often repeat in a series, and consciousness remains intact.

Another benign paroxysmal disorder in infants is spasms nutans. It consists of a slow (2.4 Hz) tremor of the head, usually horizontal, and often an associated pendular nystagmus (Antony et al., 1980). It tends to disappear within 6 months.

Episodic (paroxysmal) ataxias and tremor

Intermittent ataxia can be due to metabolic defects such as Hartnup disease (Baron et al., 1956), pyruvate decarboxylase deficiency (Lonsdale et al., 1969; Blass et al., 1970, 1971), and maple syrup urine disease (Dancis et al., 1967). Fever often triggers the attacks of ataxia. In one case with pyruvate decarboxylase deficiency (Blass et al., 1971), choreoathetosis tended to accompany the ataxia. Paroxysmal ataxia and dysarthria also have been reported to occur in multiple sclerosis (Andermann et al., 1959; Espir et al., 1966; DeCastro and Campbell, 1967; Miley and Forster, 1974; Gorard and Gibberd, 1989), which, as remarked previously, is a disorder that also can cause paroxysmal choreoathetosis/dystonia. The attacks of paroxysmal ataxia in multiple sclerosis last seconds and are thus much shorter than the attacks described later. They also can respond to carbamazepine. Paroxysmal ataxia also has been reported in Behçet disease (Akmandemir et al., 1995).

An important advance was the discovery by Griggs and colleagues (1978) that acetazolamide can effectively prevent attacks. These authors showed this benefit in one kindred with familial paroxysmal ataxia. The following year, Donat

Video 22.1 Paroxysmal torticollis in infancy.

Video 22.2 Paroxysmal dystonia in infancy.

and Auger (1979) had similar results in another kindred. Fahn (1983, 1984) reported a woman who had paroxysmal tremor, both intention and resting, associated with ataxia and postural instability during the attack; acetazolamide eliminated the attacks. Factor and colleagues (1991) reported an infant who had three attacks of coarse tremor and an orofacial dyskinesia that resembled that seen with tardive dyskinesia. Each attack lasted several hours before spontaneously clearing. Tetrahydrobiopterin, the cofactor for the enzymes tyrosine hydroxylase and phenylalanine hydroxylase, was reduced. The child responded to levodopa.

Mayeux and Fahn (1982) reported a patient with PNKD in a background of hereditary ataxia. Onset of PNKD was at age 10; onset of ataxia was at age 19. During an attack, which could last from 10 minutes to 4 hours, there was an accompanying increase of ataxia. Initially there was an 8-month response to acetazolamide. After the drug was no longer effective, the patient's PNKD responded to clonazepam. This patient might be a link between familial PNKD and paroxysmal ataxia.

Several other reports of acetazolamide-responsive familial paroxysmal ataxia have been reported (Aimard et al., 1983; Zasorin et al., 1983; Koller and Bahamon-Dussan, 1987). Although CT has been normal, magnetic resonance imaging (MRI) studies have revealed selective atrophy in the anterior cerebellar vermis (Vighetto et al., 1988).

Families with a combination of periodic ataxia and persistent, continuous electrical activity in several muscles, reported either as myokymia (Van Dyke et al., 1975; Hanson et al., 1977; Gancher and Nutt, 1986; Brunt and Van Weerden, 1990) or as neuromyotonia (Vaamonde et al., 1991), have been described. Description of the attacks, which are brief and are sometimes preceded by sudden movement, include dyskinetic movements and sustained posturing, ataxia, dysarthria, and vertigo. This type of paroxysmal ataxia is now called EA 1 (EA-1).

In 1986, Gancher and Nutt (1986) classified the hereditary EAs into three syndromes. In one group are those cases associated with persistent myokymia or neuromyotonia (now called EA-1). They described the attacks being precipitated by fatigue, excitement, stress, and physical trauma, but the family reported by Vaamonde and colleagues (1991) had attacks triggered by sudden movement, and kinesigenicity is now recognized as a feature. There is no dizziness or vertigo. The attacks last 2 minutes or less. Acetazolamide and anti-convulsants are usually ineffective. The gene for this type of paroxysmal ataxia has been located at chromosome 12p13 (Litt et al., 1994). Subsequently this mutation was found in the *KCNA1* gene and is a potassium channelopathy referred to as EA-1 (D'Adamo et al., 2015).

The second group (now known as EA-2) is featured by attacks of ataxia (with or without interictal nystagmus and with or without persistent ataxia), responding to acetazolamide or amphetamines. The attacks are precipitated by exercise, fatigue, or stress and occasionally by carbohydrate or alcohol ingestion. In addition to ataxia, the attacks are accompanied by vertigo, headache, nausea, and malaise. The attacks last for several hours or until the patient falls asleep. Additional families have been reported with these features (Bain et al., 1991; Baloh and Winder, 1991; Hawkes, 1992). The siblings reported by Bain and colleagues (1991) had persistent diplopia secondary to superior oblique paresis as part of the syndrome. Using (^{31}P)

nuclear magnetic resonance spectroscopy, Bain and colleagues (1992) found the pH levels in the cerebellum to be increased in untreated subjects with acetazolamide-responsive paroxysmal ataxia; the pH dropped to normal with treatment. The gene for this type of paroxysmal ataxia has been mapped to chromosome 19p13, with a mutation in the *CACNA1A* gene related to calcium channels (Vahedi et al., 1995; Von Brederlow et al., 1995; Choi et al., 2017).

Gancher and Nutt (1986) listed a third group, which is kinesigenic. Typical PKD can occur in some members of the family. The attacks of ataxia last minutes to hours, whereas the PKD lasts seconds. The disorder can resolve with time. Acetazolamide appears to be ineffective, but phenytoin is effective for both the kinesigenic ataxia and the PKD. In their review, Griggs and Nutt (1995) place this third type with associated PKD in the first group of paroxysmal ataxias. Genotyping has now definitively placed this as EA-1 (Nutt and Gancher, 1997).

Miscellaneous paroxysmal disorders

Keane (1984) reported two patients with posttraumatic periodic, rhythmical movements of the tongue. The attacks occurred about every 20 seconds, and each attack lasted 10 seconds. They consisted of three undulations per second. Eventually, the movements diminished. Other cases of episodic lingual dyskinesias were associated with epilepsy (Jabbari and Coker, 1981) and pontine ischemia (Postert et al., 1997).

A few PxDs are mentioned here but are not discussed further. These are Sandifer syndrome (prolonged head tilting in children after eating, as a result of gastroesophageal reflux) (see the review by Menkes and Ament [1988]); hyperekplexia (excessive startle syndrome with complex movements) (see the review by Andermann and Andermann [1986] and Chapter 18 on myoclonus); stereotypy (Chapter 16) (Duchowny et al., 1988; Tan et al., 1997), and paroxysmal bursts of myoclonus and tics. Classically, stereotypy, myoclonus, and tics are each recognized as a specific class of movement disorders, and they characteristically manifest as paroxysmal bursts of their type of movement. As a result, their discussion should be separated from discussion of conditions labeled as "paroxysmal." Shuddering attacks in children (Holmes and Russman, 1986) are brief bursts of rapid shivering-like movements of the head and arms, occurring up to 100 times per day; they can begin in infancy or in older children, and they resolve over time. The attacks last several seconds without impairment of consciousness. The frequency of shuddering movements as seen on electromyogram (EMG) or EEG was similar to that of essential tremor (Kanazawa, 2000).

Classification of the paroxysmal dyskinesias

The PxD are classified here according to the presence of an inciting triggering event. The three types of PxD described are PKD, paroxysmal nonkinesigenic dyskinesia (PNKD) and paroxysmal exercise-induced dyskinesia (PED) (Demirkiran and Jankovic, 1995). A fourth classification, PHD, is now considered to be a manifestation of mesial frontal lobe epilepsy. PKD is elicited by a sudden movement and often involves the limbs, although other body regions can be affected. The episodes are brief, lasting from

seconds to minutes, without loss of consciousness and complete resolution. There can be multiple episodes during a day. PNKD is elicited by stress, startle, fasting, sleep deprivation, anxiety, and other stressors. These episodes are of longer duration (from minutes to hours) and occur less frequently than PKD. PED includes movements triggered by sustained exercise and are typically dystonic, affecting the legs. These can last up to 30 minutes and are not associated with change in consciousness. It is estimated that from 40% to 70% of PXDs are familial. Over the past several years, numerous genetic mutations have been found. Often the phenotype is overlapping. These are described in more detail later. A review of 500 patients with PXD describes each of the PXDs and provides a suggested classification scheme that is based on the common trigger factors for each (Erro et al., 2014a).

A case series that included 145 patients with PXD and 53 patients with familial EA assessed mutations in three genes (*PRRT2*, *SLC2A1*, and *PNKD* (*MR1*)) (Gardiner et al., 2015). This study showed that pathologic mutations were present in 47% of patients. The most frequent was mutations of *PRRT2* identified in 35%, *SLC2A1* mutations in 10% and *PNKD* in 2%. There were variable phenotypes associated with each of these, with considerable phenotype-genotype variability. The most frequent clinical characteristics associated with each is described in the following section.

Paroxysmal kinesigenic dyskinesia

Duration: Seconds to 5 minutes

Characteristic trigger factor: Sudden movement

Precipitant: Startle

Precipitant: Hyperventilation

Treatment: Responds well to anticonvulsants

Cause:

Primary—familial, sporadic

Secondary

Genetics (Erro and Bhatia 2018, McGuire et al., 2018, Tian et al., 2018):

PRRT2

ADCY5

SCN8A

SLC16A2

EKD2

Note that the effectiveness of anticonvulsants correlates with brief duration of the paroxysms rather than their being triggered by sudden movement. Diagnostic criteria for PKD have been proposed (Bruno et al., 2004a).

A family of paroxysmal kinesigenic atonia has been reported (Fukuda et al., 1999). There was no alteration of consciousness or EEG findings of epilepsy. Anticonvulsants were effective in reducing the attacks. This has not been replicated; thus, it is not clear whether the atonia could have been functional

Paroxysmal nonkinesigenic dyskinesia (Mount-Reback type)

Duration: 2 minutes to 4 hours

Characteristic trigger factors: Coffee, alcohol, and other non-kinesigenic factors

Treatment: Not sensitive to anticonvulsants

Cause:

Primary—familial, sporadic

Secondary

Psychogenic

Genetics (Erro and Bhatia 2018, McGuire et al., 2018):

PKND (*MR1*)

PRRT2

ADCY5

SLC2A1

ATP1A3

KCNMA1

FGF14

GAD-1

Paroxysmal exercise-induced dyskinesia

Duration: 5 to 30 minutes

Characteristic trigger factor: Prolonged exercise

Cause:

Idiopathic—familial, sporadic

Symptomatic

Psychogenic

Genetics (Erro and Bhatia 2018, McGuire et al., 2018):

SLC2A1 (also known as GLUT1 deficiency)

GCH-1

ADCY5

PRRT2

ATP1A3

PARK2

PDHA1

ECHS1

Benign dyskinesias in infancy and childhood

1. Paroxysmal dystonia/torticollis in infancy
2. Paroxysmal tonic upgaze or downgaze
3. Paroxysmal myoclonus of infancy
4. Shuddering attacks
5. Spasmus nutans
6. Sandifer syndrome
7. Stereotypies

Paroxysmal dyskinesias and epilepsy

1. Hypnogenic PXDs as frontal lobe epilepsy (see earlier)
2. Infantile convulsions and paroxysmal dyskinesias (ICCA) on chromosome 16p12–q12 and 16q13–q22.1.

Paroxysmal ataxia (Choi and Choi, 2016)

1. EA-1 Autosomal dominant
 - Attacks: Ataxia, dysarthria, or behavioral changes or feeling strange
 - Duration: Brief; less than 2 minutes
 - Precipitant: Sudden movement or startle
 - Treatment: Sometimes sensitive to acetazolamide and to anticonvulsants
 - Interictal: Persistent myokymia/neuromyotonia
 - Other feature: May be accompanied by PKD
 - Genetics: Point mutations *KCNA1* gene, involving voltage-dependent potassium channels
2. EA-2 Autosomal dominant

Attacks: Ataxia and dysarthria

Duration: Hours

Precipitant: Exercise, fatigue, stress, alcohol

Treatment: Sensitive to acetazolamide

Interictal: Nystagmus

Other features: Headache, malaise, may develop persistent ataxia

Genetics: Mutation *CACNA1A* (calcium channel)

3. EA-3 Unknown inheritance

Attacks: Ataxia, tinnitus, falling, headache, blurred vision, vertigo, nausea

Duration: 10 to 30 minutes

Precipitants: None

Treatment: Acetazolamide

Other features: Myokymia

Genetics: Mapped to 1q42: unknown mutation

4. EA-4 Unknown inheritance

Attacks: Ataxia, diplopia, oscillopsia, vertigo, nausea, tinnitus

Duration: Minutes to hours

Precipitants: Sudden change in head position, fatigue, and an environment in which objects are moving past the patient

Treatment: Lying quietly with eyes closed for 15 to 30 minutes; no response to acetazolamide

Other features: The episodes become more frequent and then become constant with progressive ataxia

Genetics: Genetically distinct from other EAs

5. EA-5 Autosomal dominant

Attacks: Ataxia, vertigo

Precipitants: None

Treatment: Acetazolamide

Other features: Juvenile epilepsy; interictal nystagmus

Genetics: Mapped to 2q22–q23, *CACNB4* gene

6. EA-6 Autosomal dominant or sporadic

Attacks: Ataxia, alternating hemiplegia, photophobia, phonophobia

Precipitants: Excitement, exercise

Treatment: Acetazolamide

Other features: Hemiplegic migraine, vertigo, weakness, seizures

Genetics: Mapped to 5p13, glutamate transporter, *SLC1A3* gene

7. EA-7: Mixed inheritance

Attacks: Ataxia

Precipitants: Excitement, exercise

Treatment: None

Other features: Attacks accompanied by vertigo, weakness, and dysarthria

Genetics: Mapped to 19p3

8. EA-8 Autosomal dominant

Attacks: Slurred speech, weakness, unsteadiness

Precipitants: None

Treatment: Clonazepam

Other features: Eye twitching, nystagmus, myokymia, and persistent tremor

Genetics: Mutations in *UBR4*

unilateral—always on one side or on either side—or bilateral. Unilateral episodes can be followed by a bilateral episode. The attacks are brief, usually lasting only seconds, but rarely can last up to 5 minutes. They are precipitated by a sudden movement or a startle, usually after the patient has been sitting quietly for some time (Video 24.3). The attacks can be severe enough to cause a patient to fall. There can be as many as 100 attacks per day. After an attack, there is usually a short refractory period before another attack can take place. Speech can sometimes be affected, with inability to speak because of dystonia, but there is never any alteration of consciousness. The attacks can sometimes be aborted if the patient stops moving or warms up slowly. Very often, patients report variable sensations at the beginning of the paroxysms. These can consist of paresthesias, a feeling of stiffness, crawling sensations, or a tense feeling. ▶

Equivalent to PKD are equally brief attacks that are not precipitated by sudden movement or startle. Because the duration and therapeutic response are the same as in PKD, they are listed here under the PKD rubric rather than in an entirely new category. Often, these attacks, lasting a few seconds, can be triggered by hyperventilation.

Kinast and colleagues (1980) reported as Case 4 a patient with typical brief dyskinesias occurring many times a day, preceded by paresthesias, and responding to anticonvulsants but not induced by sudden movement. Although this was technically not PKD, because sudden movements did not trigger any attacks, the clinical features otherwise resemble the attacks that are seen in PKD. As was mentioned previously, this type of PKD is placed in this category of PKD. Since the attacks of PNKD are usually prolonged and because they do not ordinarily respond to anticonvulsants, this case does not fit into the PNKD category. See the discussion on the classification of these brief attacks as symptomatic PKD later.

Plant (1983) emphasized the focal and unilateral nature of PKD in many patients. Of the 73 cases of PKD in the literature reviewed by him, he found the following types of laterality:

Laterality of attacks	N
Unilateral—one side only	25
Unilateral—either side	12
Unilateral and bilateral	11
Bilateral only	22
Not stated	3
Total	73

In the literature there are many reports of PKD without distinguishing kinesigenic from nonkinesigenic. These episodes have occurred with or without accompanying epilepsy. Without videotapes of the episodes and without a clear clinical description, the placement into PKD or PNKD is done with a degree of uncertainty. This caveat is provided here and applies to the rest of this chapter, including the molecular genetics.

Paroxysmal kinesigenic dyskinesia

Clinical features

The attacks of PKD consist of any combination of dystonic postures, chorea, athetosis, and ballism. They can be

Paroxysmal kinesigenic dyskinesia

The cause in most case reports of PKD has been idiopathic and predominantly hereditary, inheritance being autosomal dominant. Males are more often affected than females, with a ratio of 3.75:1 (75 males and 20 females reported by

Video 22.3 Primary paroxysmal kinesigenic dyskinesia.

Fahn [1994]). A large series of 150 cases were reported from a questionnaire in Japan. This gender imbalance was supported by the additional 26 cases reported by Houser and colleagues (1999), consisting of 23 men and 3 women, and another 150 cases from Japan (Nagamitsu et al., 1999). Adding all these cases together brings the total to 218 men and 53 women, or a ratio of 4.1:1. Age at onset shows a wide range, usually starting in childhood between the ages of 6 and 16 years, but can range from 6 months to 40 years (Frucht and Fahn, 1999; Li et al., 2005). Excluding the cases by Nagamitsu and colleagues (1999), the mean age at onset is 12 years; the median age is 12 years. Familial cases might be more common among the Japanese (Kishimoto, 1957; Fukuyama and Okada, 1967; Kato and Araki, 1969) and Chinese (Jung et al., 1973). The survey reported by Nagamitsu and colleagues (1999) found 53 sporadic cases and 97 familial ones.

There is one report of PKD developing in a patient who had essential tremor (Nair et al., 1991). EEGs are generally normal, and CT scans are also normal (Goodenough et al., 1978; Kinast et al., 1980; Suber and Riley, 1980; Bortolotti and Schoenhuber, 1983; Lou, 1989) with a few exceptions, such as the case reported by Watson and Scott (1979) with suggested brainstem atrophy, and the one by Gilroy (1982) with an ill-defined unilateral hemispheric lesion. However, Hirata and colleagues (1991) demonstrated an abnormal EEG with rhythmic 5-Hz discharges over the entire scalp during episodes of PKD, raising the possibility that the PKD might have an epileptogenic basis. A patient was reported who developed PKD shortly after initiation of therapy with methylphenidate for attention deficit-hyperactivity disorder. Attacks persisted long after methylphenidate was discontinued and responded to treatment with carbamazepine (Gay and Ryan, 1994). The authors think that the patient had a hereditary susceptibility for PKD that was triggered by the drug.

The attacks tend to diminish with age. Fortunately, PKD responds dramatically to anticonvulsants. The early literature indicates that phenytoin was the most popular, followed by phenobarbital and primidone. Carbamazepine appears to be the drug that is most commonly used. Valproate also has been effective (Suber and Riley, 1980), although Hwang and colleagues (1998) report that both carbamazepine and phenytoin were superior to valproate. Other anticonvulsants are effective, including oxcarbazepine (Gokcay and Gokcay, 2000; Tsao, 2004; Chillag and Deroos, 2009), lamotrigine (Pereira et al., 2000; Ueberall and Wenzel, 2000), levetiracetam (Chatterjee et al., 2002), and topiramate (Huang et al., 2005b). There is one report in which high dosage of only phenytoin was effective (Bonakis et al., 2009). There is a report of response to levodopa (Loong and Ong, 1973), but another report of lack of effect with this drug (Garello et al., 1983). Analogously, there is one report of three patients with PKD worsening with haloperidol (Przuntek and Monninger, 1983), but Garello and colleagues (1983) reported no effect from this drug (or from levodopa) in two brothers. The calcium channel blocker flunarizine, which is also a neuroleptic, was effective in a 7-year-old girl who did not respond to carbamazepine or methylphenidate (Lou, 1989).

Homan and colleagues (1980) reported that children with PKD need doses of phenytoin that are similar to those used to treat epilepsy, whereas adults can respond to lower

doses. These authors also describe a patient who might have had interictal chorea (the patient was described as fidgety) and suggested that this might represent a possible link to benign hereditary chorea. However, the fidgetiness that was described might not have been chorea. Perhaps these movements might be interictal myoclonus, similar to that in two patients with PKD (Cochen De Cock et al., 2006). Another report of interictal movements was by Bird and colleagues (1978) in which a woman had anxiety-induced dystonia/choreoathetosis and random, adventitious small jerky movements when she was not having an attack (first reported by Perez-Borja and colleagues in 1967); her daughter had delayed milestones and persistent choreoathetosis. However, it seems likely that the daughter's choreoathetosis was not idiopathic but secondary, so it seems that PXDs and hereditary benign chorea should not be linked on the basis of a couple of these cases.

The pathophysiology of PKD is still unclear, and its relationship with epilepsy remains speculative. Because movement-induced seizures can occur (e.g., the case of Falconer et al., 1963) and because PKD responds dramatically to anticonvulsants, these are not sufficient reasons to consider PKD a form of epilepsy. The retention of consciousness, lack of postictal phenomena, and the presence of dystonia and choreoathetosis should be sufficient to disqualify PKD from the epilepsies. However, Beaumanoir and colleagues (1996) described a boy with PKD and normal EEGs and consciousness, who later had a longer attack with clouding of consciousness and recording of postictal abnormalities on the EEG to support the diagnosis of reflex epilepsy. There is emerging a syndrome of infantile epilepsy, referred to as the ICCA syndrome, followed by childhood PXDs, as was mentioned earlier in the chapter (Lee et al., 1998; Thiriaux et al., 2002).

Franssen and colleagues (1983) investigated the contingent negative variation (CNV) in one patient with PKD. CNV is a slow cerebral potential that follows a warning stimulus that prepares the subject to expect an imperative stimulus requiring a decision or motor response. The slow negative wave component of the CNV was more pronounced than that in control subjects. It returned to normal after phenytoin treatment. Mir and colleagues (2005) later demonstrated reduced intracortical inhibition, reduced early-phase transcallosal inhibition, and reduced first phase of spinal reciprocal inhibition in PKD patients; treatment with carbamazepine normalized the abnormality of transcallosal inhibition.

The differential diagnosis of PKD is focal epilepsy, tetany, hyperekplexia, tics, stereotypies, and hysteria, as was noted in the misdiagnosis of the case reported by Waller (1977). The clinical features are so distinctive, particularly if triggered by sudden movement, that there is little likelihood of not diagnosing the condition correctly once one is aware of its existence. Similarly, the markedly effective response to anticonvulsants sets PKD apart from the other disorders. One case of primary PKD that has been observed to be the result of a consistent ictal discharge arising focally from the supplementary sensorimotor cortex, with a concomitant discharge recorded from the ipsilateral caudate nucleus without spread to other neocortical areas (Lombroso, 1995), suggests that some primary PKDs could be epileptic in origin. The nonkinetic, brief attacks of hemidystonia, often precipitated by hyperventilation and controlled with anticonvulsants,

has been considered a sign of epilepsy (Kotagal et al., 1989; Newton et al., 1992). So each case of such suspected non-kinesigenic PKD needs to be evaluated for a convulsive disorder.

In addition to the cases of PKD described in the historical highlights and earlier in the syllabus, a number of other reports should be cited to make the review complete (Zacchetti et al., 1983; Boel and Casaer, 1984; Lang, 1984). One case of paroxysmal torticollis induced by sudden movement or stimulus appeared 5 years after the onset of classic spasmodic torticollis that had begun at the age of 20 years (Laguëny et al., 1993). After failing to respond to alcohol, tiapride, haloperidol, carbamazepine, clobazam, and valproate, the patient was treated effectively with injections of botulinum toxin.

There have been reports of two autopsies in PKD. Case 4 of Kertesz (1967) died, apparently by suicide, and a postmortem examination revealed no clear-cut brain abnormality, just the presence of some melanin pigment in macrophages in the locus coeruleus. Stevens (1966) had earlier reported the postmortem findings of one of his patients, which were also essentially normal, showing only a slight asymmetry of the substantia nigra.

SPECT scans measuring cerebral blood flow were studied in two children with PKD, revealing increased perfusion in the contralateral basal ganglia at the onset of an attack in one (Ko et al., 2001) and in the contralateral thalamus in the other (Shirane et al., 2001). Physiologic studies indicate that there is surround inhibition in PKD (Shin et al., 2010).

Genetics (see table 24.6)

The genetic mutations associated with PKD have been rapidly expanding. Despite early theories that these disorders were predominantly channelopathies, the genetic mutations that give rise to these disorders have a wide range of actions. These include synaptic function (*PRRT2* and *MR1*), transportopathies (*SCL2A1*), and channelopathies (*KCNMA1*) (Erro and Bhatia, 2018).

Proline-rich transmembrane protein 2 (*PRRT2*) (Wang et al., 2011; Lee et al., 2012) is a gene located at 16p11.2 (Depienne and Brice, 2011). *PRRT2* mutations are frequently associated with PKD, accounting for up to 90% of familial PKD. Typical symptoms begin in childhood. Activity, stressors, and prolonged exercise can initiate attacks. Although beginning focally, the movements tend to generalize. Episodes are very brief and can occur very frequently, up to 100 times per day. In the interictal periods, there are no neurologic deficits. Low doses of carbamazepine are usually very effective. The episodes tend to wane and sometimes resolve in adulthood. Other disorders associated with this mutation include benign infantile seizures, infantile convulsions with choreoathetosis (Tomita et al., 1999; Bennett et al., 2000; Swoboda et al., 2000), EA, and hemiplegic migraine (Nobile and Striano, 2014). The most common associated clinical features include migraine and hemiplegic migraine (Gardiner et al., 2015). Other phenotypes included EA, benign epilepsy, and PED (Gardiner et al., 2015).

SLC2A1 is a gene encoding GLUT1. The initial clinical description included infantile spasticity, epilepsy and paroxysmal nonepileptic ataxia, chorea, dystonia, and alternating hemiplegia. This was associated with microcephaly

and developmental delay (Wang et al., 1993) (Erro et al., 2014b). In a series of 91 patients with GLUT1 deficiency, most had onset before 6 months of age with seizures as the first manifestation followed by eye movement abnormalities. Cerebrospinal fluid shows low glucose with normal serum glucose values (Akman et al., 2016). This disorder can respond well to a ketogenic diet, providing improved long-term outcomes and making it critical to diagnose early in life (Alter et al., 2015).

Other genes that have been associated with PKD include *KNCMA-1*, a gene associated with calcium-activated potassium channels. *SCN8A* mutations associated with PKD resemble the clinical manifestations of the *PRRT2*-associated PKD (Erro and Bhatia, 2018). Enoyl coenzyme A hydratase short chain 1 (*ECHS1*) mutations manifest with dystonia and bilateral lesions of the globus pallidus that can manifest as a Leigh-like syndrome in infancy or a milder form consisting of PED (Olgiati et al., 2016). Adenyl cyclase 5 (*ADCY5*) mutations gives rise to a range of movement disorders, including PKD and PKND. It may be associated with facial myokymia, delayed motor milestones, axial hypotonia, and intellectual impairment. The paroxysmal disorders are often triggered by drowsiness, setting them apart from most of the previous PKDs (Chang et al., 2016).

Secondary paroxysmal kinesigenic dyskinesia

The overwhelming majority of reported cases of PKD are idiopathic or familial. Although not reported as often, symptomatic PKD is probably more common. Table 24.3 lists the most common causes of symptomatic PKD, the most common being associated with multiple sclerosis and head injury. Pseudohypoparathyroidism is also on this list (Huang et al., 2005a). In one family with X-linked mutations in the thyroid hormone transporter gene *MCT8*, PKDs accompanied global mental retardation (Brockmann et al., 2005).

In symptomatic PKD, like primary PKD, attacks that last seconds are sometimes induced not by sudden movement but by hyperventilation. These usually respond to anticonvulsants, such as carbamazepine, and are also seen in multiple sclerosis (Verheul and Tyssen, 1990; Sethi et al., 1992). Fahn (unpublished) encountered a patient who had attacks

Table 24.3 Symptomatic paroxysmal kinesigenic dyskinesia

Multiple sclerosis
Head injury
Perinatal hypoxic encephalopathy
Idiopathic hypoparathyroidism
Pseudohypoparathyroidism
Basal ganglia calcifications
Hemiatrophy
Putaminal infarct
Thalamic infarct
Moyamoya disease
Medullary lesion (hemorrhage, subarachnoid cyst)
HIV infection
Hyperglycemia in the presence of a lenticular vascular malformation
Progressive supranuclear palsy
Spinal cord lesion
Huntington disease
Peripheral trauma

lasting seconds, induced by hyperventilation and without being induced by sudden movement, after a mild cerebral ischemic episode, that also responded to carbamazepine. These pharmacologic responses suggest that the briefness of the attack is more important than the sudden movement to distinguish the classification of the PXDs. Sethi and colleagues (1992) reported success in treating three patients with paroxysmal dystonia (not induced by movement, but triggered by hyperventilation and lasting many seconds) with acetazolamide with or without a combination of carbamazepine.

Multiple sclerosis

Although few of the PXDs that are associated with multiple sclerosis are triggered by sudden movement, an occasional patient with multiple sclerosis will manifest typical PKD (Matthews, 1958). In fact, the presenting symptom of multiple sclerosis can be PKDs as in the case reported by Roos and colleagues (1991); these attacks were associated with a lesion in the caudate nucleus and responded to phenytoin. In three of the eight patients reported by Berger and colleagues (1984) with PXD associated with multiple sclerosis, the attacks were induced by sudden movement; they were relieved by anticonvulsants. The patient with PKD with multiple sclerosis reported by Burguera and colleagues (1991) had a lesion in the left thalamus demonstrated by MRI. The PKD was the presenting symptom, as in other cases of demyelinating disease. Gatto and colleagues (1996) reported medullary lesions in multiple sclerosis and bilateral paroxysmal dystonia.

Head trauma

Case 3 of Whitty and colleagues (1964) was a 13-year-old boy with onset 9 months after mild head trauma. Robin (1977) reported a 33-year-old man with severe head injury who developed PKD 8 months later. In two of the three cases of posttraumatic PXDs reported by Drake and colleagues (1986), the movements were induced by sudden movement of the affected body part. Richardson and colleagues (1987) reported another posttraumatic case. These posttraumatic cases of PKD responded to anticonvulsants, similar to idiopathic PKD. Attacks of dystonia lasting several seconds and induced by tactile stimulation were reported secondary to a head injury; they disappeared within 2 months without treatment (George et al., 1990). Nijssen and Tijssen (1992) reported another case of tactile-induced dyskinesias as a result of a thalamic infarct.

Perinatal hypoxic encephalopathy

Rosen (1964) appears to have been the first to report a case of PKD associated with perinatal hypoxic encephalopathy, with the onset at age 12. This boy's attacks were usually triggered by a combination of startle and body contact. Mushet and Dreifuss (1967) described a 9-year-old boy who developed brief attacks of athetosis and dystonia. They usually occurred when he was startled but also could occur after sudden movement. At age 6 months, he had a febrile illness, which was retrospectively thought to be encephalitis. He had considerable motor regression and was not able to walk,

nor did he gain syntactical speech. His dyskinetic attacks were not suppressed by anticonvulsants but did respond to anticholinergics.

Basal ganglia calcifications

PKD has been reported to occur with basal ganglia calcifications with or without hypoparathyroidism (Arden, 1953). Subsequent cases of hypoparathyroidism were reported (Tabaei-Zadeh et al., 1972; Barabas and Tucker, 1988). The clinical syndrome resembles that of primary infantile convulsions and childhood PKD (Hattori and Yorifuji, 2000). Calciferol was effective in controlling these attacks. The case reported by Soffer and colleagues (1977) was not noted to have the attacks induced by sudden movement, but the briefness of the attack resembles that of PKD.

Hemiatrophy

Case 2 of the 5 cases described by Kinast and colleagues (1980) had attacks of left hemidystonia lasting 1 minute and occurring up to 50 times a day. The major precipitating factor was not sudden movement, but stress and the anticipation of movement (also reported in one patient by Franssen et al., 1983). Technically, like their Case 4 described previously, this patient does not fulfill the criterion of attacks induced by sudden movement. This is another example, because of the brief duration, the frequency of the attacks, and their response to phenytoin, that otherwise resembles PKD and again points out why such nonkinesigenic cases are placed under the PKD rubric in the classification scheme used here. Examination of this patient revealed left-sided hemiatrophy and hyperreflexia with a normal CT scan. Because the hemiatrophy syndrome can be associated with a delayed-onset movement disorder (Buchman et al., 1988), it seems reasonable to consider it an etiologic factor in this particular case.

Gilroy (1982) reported a 32-year-old man with an abnormal right hemisphere on CT scan who had multiple daily brief attacks of left hemidystonia present since the age of 5 that were typical of PKD. The speculation is that the PKD was secondary to pathologic processes in the involved hemisphere. An arteriogram and cortical biopsy did not shed further light on the pathologic features.

Cerebral infarcts and hemorrhages

With the advent of MRI, more cases of PKD have been reported as a result of cerebral infarcts with putaminal infarct (Merchut and Brumlik, 1986), thalamic infarct (Video 24.4) (Camac et al., 1990; Nijssen and Tijssen, 1992; Milandre et al., 1993), an infarct probably in the cortex (Fuh et al., 1991), and medullary hemorrhage (LeDoux, 1997). As was mentioned earlier, the case of Nijssen and Tijssen (1992) had attacks stimulated by touch of the affected limb. The attacks secondary to infarcts (Merchut and Brumlik, 1986; Fuh et al., 1991) or multiple sclerosis (Sethi et al., 1992) can be painful tonic spasms. Riley (1996) reported a case of paroxysmal attacks of tightening of the throat muscles and elevation of the tongue to the roof of the mouth associated with a remote hemorrhage in the medulla. Moyamoya disease has been reported to cause PKD (and PNKD) (Gonzalez-Alegre et al., 2003). ●

Video 22.4 Secondary paroxysmal kinesigenic dyskinesia.

Other causes

PKD also has been reported to occur in a patient with progressive supranuclear palsy (Adam and Orinda, 1986) in hyperglycemia in the presence of a lenticular vascular malformation (Vincent, 1986), in subacute sclerosing panencephalitis (Ondo and Verma, 2002), and in spinal cord lesion (Cosentino et al., 1996). A case of spinal cord glioma was associated with paroxysmal kinesigenic segmental myoclonus (Marrufo et al., 2007). Another case of spinal cord compression was associated with PKD (Yulug et al., 2008). A case of PKD was reported in which it was the first symptom in a patient who developed Huntington disease (Scheidtmann et al., 1997). Human immunodeficiency virus (HIV) infection has been reported to be associated with PKD and PKND (Mirsattari et al., 1999). A lesion in the medulla has been associated with PKD (Jabbari et al., 1999). Peripheral trauma to a foot was subsequently followed by paroxysmal hemidystonic episodes (Chiesa et al., 2008). An adult with PKD and cramp-fasciculation syndrome was associated with voltage-gated potassium channel-complex protein antibody encephalitis; with the patient responding to plasma exchange and intravenous immunoglobulin (Aradillas and Schwartzman, 2011).

Paroxysmal nonkinesigenic dyskinesia

Clinical features

As with PKD, the attacks of PNKD consist of any combination of dystonic postures, chorea, athetosis, and ballism. They can be unilateral—always on one side or on either side—or bilateral. Unilateral episodes can be followed by a bilateral one. They can affect a single region of the body or be generalized. Involvement of the neck can be a combination of torticollis and head tremor (Hughes et al., 1991). The major distinctions from PKD are the longer duration of each attack, the smaller frequency of the attacks, and a host of different aggravating factors for the attacks. The attacks last minutes to hours, sometimes longer than a day. Usually, they range from 5 minutes to 4 hours (Video 24.5). They are primed by consuming alcohol, coffee, or tea; by psychological stress or excitement; and by fatigue. There are usually no more than three attacks per day, and attacks may be months apart. The attacks can be severe enough to cause a patient to fall. Speech is often affected, with inability to speak because of dystonia, but there is never any alteration of consciousness. The attacks can sometimes be aborted if the patient goes to sleep. As with PKD, patients very often report variable sensations at the beginning of the paroxysms. These can consist of paresthesias, a feeling of stiffness, crawling sensations, or a tense feeling. ●

A form of PNKD, known as intermediate PDC and more recently as paroxysmal exercise-induced dyskinesia (PED), is triggered only by prolonged exercise and not the other precipitants. This was first described by Lance (1977) and subsequently reported in another family by Plant and colleagues (1984) and in a sporadic case by Nardocci and colleagues (1989). This form will be discussed separately. Under the classification scheme of Demirkiran and Jankovic (1995), this form, which is discussed separately, is called PED.

Paroxysmal Nonkinesigenic Dyskinesia (Mount-Reback syndrome)

The initial reports of PNKD were familial (Mount and Reback, 1940; Forssman, 1961; Lance, 1963, 1977; Weber, 1967; Richards and Barnett, 1968; Horner and Jackson, 1969; Tibbles and Barnes, 1980; Walker, 1981; Mayeux and Fahn, 1982; Przuntek and Monninger, 1983; Jacome and Risko, 1984), with hereditary transmission being autosomal dominant. In 1980 Kinast and colleagues (1980) (Case 4) and Dunn in 1981 each described a child with PNKD without a positive family history. Since then Bressman and colleagues (1988) later described seven sporadic cases of PNKD, and Nardocci and colleagues (1989) added another one. The familial cases of idiopathic PNKD still greatly outnumber sporadic cases, according to the reports in the literature. However, the sporadic cases are much more difficult to diagnose, and they have the difficulty of the need to be differentiated from a psychogenic cause (Bressman et al., 1988; Fahn and Williams, 1988). On the basis of the experience of Bressman and her colleagues (1988), the sporadic form may actually be more common than the familial form but is just rarely reported.

For some unexplained reason males are slightly more often affected than females, with a ratio of 1.4:1 (32 males and 23 females reported in the reviewed English literature) (see Fahn, 1994). Age at onset shows a wide range, usually in childhood between the ages of 6 and 16 years, but can range from 2 months to 30 years. The mean age at onset is 12 years, and the median is 12 years. CT scans are normal (Mayeux and Fahn, 1982; Jacome and Risko, 1984).

The EEGs are generally normal, but the case of Jacome and Risko (1984) may be of interest. The patient had unilateral PNKD and had normal interictal EEGs. Photoc stimulation at low frequencies induced paroxysmal lateralized epileptiform discharges from the contralateral hemisphere. From this the authors suggest that the disorder might have some epileptogenic basis.

Sleep aborted the episodes in one family that had myokymia in addition to the PNKD (Byrne et al., 1991). The presence of myokymia links this particular family to several with paroxysmal ataxia, in which myokymia is a feature (Van Dyke et al., 1975; Vaamonde et al., 1991).

A family reported by Kurlan and colleagues (1987) had some atypical features for classic PNKD. The long-duration attacks were painful dystonic spasms that were not precipitated by alcohol, caffeine, or excitement, but could follow exposure to cold or heat or result from exertional cramping. Other members of the family had only exertional cramping without PNKD. The authors suggested that exertional cramping might be a forme fruste of PNKD. It is also possible that the PNKD in this family falls into the category of the intermediate form of PXD that was reported by Lance (1977) and Plant and colleagues (1984). Also unusual was the presence of some fixed dystonia, which had not been reported previously. Bressman and colleagues (1988) also described some sporadic cases of PNKD, in which the patients had some interictal dystonia.

Lance (1977) mentioned that autopsies performed on two patients with PNKD revealed no pathologic findings. His Case II.4 had normal macroscopic findings. His Case IV.2 died of sudden infant death syndrome; macroscopic and microscopic findings were normal.

Video 22.5 Primary paroxysmal nonkinesigenic dyskinesia (PNKD).

The attacks can diminish spontaneously with age (Lance, 1977; Kinast et al., 1980; Bressman et al., 1988). Unfortunately, most patients have persistence of their attacks, and they are difficult to treat. As a general rule, PNKD does not respond to the same type of anticonvulsants that so effectively treat PKD. An occasional patient will respond to such agents as carbamazepine, valproate, and gabapentin (Chudnow et al., 1997). Clonazepam, as introduced for PNKD by Lance (1977), appears to be the most successful agent for both primary PNKD and symptomatic PNKD. A number of other drugs have been tried, sometimes with success. These include antimuscarinics (Mount and Reback, 1940), chlorthalidopoxide (Perez-Borja et al., 1967; Walker, 1981), acetazolamide (Mayeux and Fahn, 1982; Bressman et al., 1988), oxazepam and other benzodiazepines (Kurlan and Shoulson, 1983; Kurlan et al., 1987), sublingual lorazepam (Dooley and Brna, 2004), and L-tryptophan (Kurlan et al., 1987).

Kurlan and Shoulson (1983) treated one patient with familial PNKD on alternate-day oxazepam. He had marked benefit from diazepam but only for 4 weeks. Clonazepam and oxazepam gave relief for 2 to 3 weeks each. Eventually he was placed on a regimen of 40 mg oxazepam given on alternate days. The concept was that the benzodiazepine receptors became desensitized on daily doses. Alternate-day administration prevented this desensitization.

Przuntek and Monninger (1983) and Coulter and Donofrio (1980) carried out trials of the dopamine receptor antagonist, haloperidol, and reported benefit. In the obverse, Przuntek and Monninger (1983) found that levodopa worsened one patient.

MR1 mutations previously referred to as mutations in the *PNKD* gene, were described in two families with PNKD (Rainier et al., 2004). The attacks occur typically with stressors, especially coffee and alcohol. The episodes can last for hours and combine chorea and dystonia. In about half the cases, the movements generalize. The onset is usually in childhood, and the familial pattern is autosomal dominant. One family with PNKD and the *MR1* mutation had reduced oxygen consumption and altered homeostasis in fibroblasts (Ghezzi et al., 2015). In contrast to PKD, PKND does not respond to anticonvulsants and may benefit from benzodiazepines, such as clonazepam. The episodes often decrease in later adulthood. Although there is no epilepsy associated with this mutation, migraines are frequent (Kim et al., 2018).

Chronic stimulation of the ventral intermediate nucleus (Vim) of the thalamus was effective in reducing the frequency, duration, and intensity of attacks in one patient with PNKD (Loher et al., 2001). At least one patient with PNKD has been treated successfully with deep brain stimulation of the globus pallidus interna (Yamada et al., 2006).

In contrast to idiopathic PKD, which is so distinctive, the major difficulty in the diagnosis of sporadic PNKD is to differentiate it from a psychogenic movement disorder. The problem is that the disappearance of the movements with placebo or psychotherapy could be coincidental because the attacks disappear spontaneously. However, if the paroxysms are frequent and the attacks are prolonged, repeated trials with placebo can be informative. If such trials consistently produce remissions, one can be convinced that the diagnosis is a psychogenic disorder (see Chapter 27).

Three different genetic mappings have been made for PNKD. The first type, originally described by Mount and Reback

(1940), is referred to genetically as familial paroxysmal dyskinesia type 1 (FPD1) which was mapped to 2q33–35 (Fink et al., 1996; Fouad et al., 1996; Hofele et al., 1997; Matsuo et al., 1999). One of these families (Pzuntek and Monninger, 1983; Hofele et al., 1997) shows a fair response to diazepam. The gene for this disorder has been identified as myofibrillogenesis regulator 1 also called the *PNKD* gene (*MR1*) (Lee et al., 2004). Bruno and colleagues (2007) analyzed 14 families with PNKD, and 8 had *MR1* mutations. Patients with PNKD with *MR1* mutations had their attack onset in youth (infancy and early childhood). Typical attacks consisted of a mixture of chorea and dystonia in the limbs, face, and trunk, and typical attack duration lasted from 10 minutes to 1 hour. These attacks resembled the phenotype presented by Mount and Reback (1940). Caffeine, alcohol, and emotional stress were prominent precipitants. Attacks had a favorable response to benzodiazepines, such as clonazepam and diazepam. Attacks in families without *MR1* mutations were more variable in their age at onset, precipitants, clinical features, and response to medications. Several were induced by persistent exercise. A Serbian family with PKND and the *MR1* mutation had similar clinical features, with attacks starting in the first 6 months of life (Stefanova et al., 2006).

In a large study of 14 kindreds with PKND, 8 pedigrees had the PKND (*MR1*) mutation. The gene penetrance was 98%, with onset of attacks at an average age of 4 years. Almost half reported premonitory sensations preceding an attack. The attacks were characterized as a combination of dystonia and chorea. Speech involvement occurred in almost half the patients. The duration of the episode lasted 10 minutes to 1 hour and occurred at least once a week in most patients. These attacks tended to diminish in frequency with aging. The most frequent precipitants were caffeine and alcohol. The most effective treatment for these patients was clonazepam, with no response to anticonvulsants. There was no gender predominance (Bruno et al., 2007).

The second type of PNKD has additional clinical features, including perioral paresthesias, double vision, and headache during attacks, and some also have a constant spastic paraparesis; this type was mapped to chromosome 1p (Auburger et al., 1996) and has been called choreoathetosis/spasticity episodica (CSE). The locus is very close to the *SLC2A1* gene locus at 1p34.2, suggesting that the family might be positive for a *GLUT1* mutation. The third type of PNKD has been seen in familial infantile convulsions, in which the gene has been mapped to the pericentromeric region of chromosome 16 (Szepietowski et al., 1997). This has been called ICCA. The gene has been identified as the sodium/glucose cotransporter (Roll et al., 2002). A fourth type is linked to chromosome 2q31 and has been designated PNKD2 and also listed with the dystonias as DYT20. A fifth type is a family with PNKD and epilepsy, found to be due to a mutation in the calcium-sensitive potassium channel gene on chromosome 10q22 (*KCNMA1* gene) (Du et al., 2005). Further discussion about the genetics of the PxDs is in a later section in this chapter.

Secondary paroxysmal nonkinesigenic dyskinesia

The overwhelming majority of reported cases of PNKD are idiopathic or familial, but a number of cases of symptomatic

Table 24.4 Symptomatic paroxysmal nonkinesigenic dyskinesia

Multiple sclerosis
Perinatal hypoxic encephalopathy
Psychogenic
Encephalitis
Idiopathic hypoparathyroidism
Pseudohypoparathyroidism
Basal ganglia calcifications
Thyrotoxicosis
Transient ischemic attacks
Infantile hemiplegia
Cystinuria
Succinic semialdehyde dehydrogenase deficiency (Leuzzi et al., 2007)
Head injury
Hypoglycemia
AIDS
Diabetes
Anoxia
Brain tumor
Tardive syndrome?
Alternating hemiplegia of childhood
Antiphospholipid syndrome
Moyamoya disease
Celiac disease
Allan–Herndon–Dudley syndrome (impaired transporter of thyroid hormones)
Streptococcal infection
Sjögren syndrome

PNKD have been reported. Table 24.4 lists the most common causes of symptomatic PNKD.

The most common cause of symptomatic PNKD, just like PKD, is multiple sclerosis (Matthews, 1958; Joynt and Green, 1962; Lance, 1963; Berger et al., 1984; Verheul and Tyssen, 1990; Sethi et al., 1992). In multiple sclerosis, the paroxysmal movements may be only ocular, lasting several minutes (MacLean and Sassini, 1973). One patient with paroxysmal hemidystonia associated with multiple sclerosis later developed psychogenic PNKD (Morgan et al., 2005). Another patient had paroxysmal laughter in addition to PXDs (Aguirregomez et al., 2008).

The next two most common causes are perinatal encephalopathy (Lance, 1963; Erickson and Chun, 1987; Bressman et al., 1988), and psychogenic (Video 24.6) (Bressman et al., 1988; Fahn and Williams, 1988; Lang, 1995). A longer discourse of psychogenic PNKD is presented in the syllabus on psychogenic movement disorders. ▶

Other causes of PNKD are encephalitis (Video 24.7) (Mushet and Dreifuss, 1967; Bressman et al., 1988), cystinuria (Cavanagh et al., 1974), succinic semialdehyde dehydrogenase deficiency (improved with vigabatrin) (Leuzzi et al., 2007), hypoparathyroidism (Soffer et al., 1977; Yamamoto and Kawazawa, 1987; Dragasevic et al., 1997), Pseudohypoparathyroidism (Prashantha and Pal, 2009); basal ganglia calcifications without altered serum calcium (Micheli et al., 1986); thyrotoxicosis (Fischbeck and Layzer, 1979); transient ischemic attacks (Margolin and Marsden, 1982; Bennett and Fox, 1989), including basilar ischemia causing episodic tongue and alternating limb movements (Li and Lee, 2009); infantile hemiplegia (Huffstutter and Myers, 1983); head trauma (Perlmutter and Raichle, 1984; Drake et al.,

1986); hypoglycemia (Newman and Kinkel, 1984; Winer et al., 1990; Schmidt and Pillay, 1993), acquired immunodeficiency syndrome (AIDS) (Nath et al., 1987); diabetes (Haan et al., 1988); anoxia (Bressman et al., 1988); brain tumor (Bressman et al., 1988); hypoglycemia induced by an insulinoma (Shaw et al., 1996; Debruyne et al., 2009); post-streptococcal autoimmune neuropsychiatric disease (PANDAS) (Dale et al., 2002; Senbil et al., 2008); celiac disease (Hall et al., 2007); Sjögren syndrome (Alonso-Navarro et al., 2009); and the Allan–Herndon–Dudley syndrome, which is an X-linked recessive disorder resulting from a mutation in the monocarboxylate transporter 8 (MCT8) gene and resulting in decreased transport of thyroid hormone into neurons (Fuchs et al., 2009). The patient with AIDS (Nath et al., 1987) had two attacks of dystonia, but details are lacking in regard to the duration or characteristics of the attacks. Moyamoya disease has been reported to cause PNKD (and PKD) (Gonzalez-Alegre et al., 2003).

There is a case report of one person who developed paroxysmal hemidystonia after starting fluoxetine, which cleared on discontinuing the drug (Dominguez-Moran et al., 2001). Related to transient ischemic attacks mentioned previously is the case of one patient who had paroxysmal hemidystonia precipitated by assuming an upright position after sitting or lying, associated with occlusion of the contralateral internal carotid artery and near-total occlusion of the ipsilateral internal carotid artery (Sethi et al., 2002). The authors called this orthostatic paroxysmal dystonia. A SPECT study demonstrated decreased perfusion in the contralateral frontoparietal cortex during the typical dystonic spell. PNKD has now been reported in the antiphospholipid syndrome (Engelen and Tijssen, 2005). A series of 17 cases of secondary PXDs was reported by Blakeley and Jankovic (2002), who found that 9 patients had PNKD, 2 patients had PKD, 5 patients had mixed PKD/PNKD, and 1 patient had PHD.

PNKD caused by endocrine disorders responds to appropriate treatment. But in general, treatment of symptomatic PNKD is not often effective.

Micheli and colleagues (1987) reported an interesting case of a mentally retarded youth who had received dopamine receptor-blocking drugs since the age of 3. At age 16 he developed paroxysmal dystonia. The attacks could be precipitated by stress but not by movement, caffeine, cold, fatigue, or hyperventilation. The episodes lasted from 30 minutes to 3 hours. They did not respond to anticonvulsants but were abolished with trihexyphenidyl 20 mg/day. It is possible that the PNKD in this youth represented a variant of tardive dystonia (Burke et al., 1982; Kang et al., 1986).

A positron emission tomography study was performed on one patient with posttraumatic paroxysmal hemidystonia (Perlmutter and Raichle, 1984). Decreased oxygen metabolism, decreased oxygen extraction, increased blood volume, and increased blood flow in the contralateral basal ganglia were found.

The syndrome commonly known as alternating hemiplegia of childhood typically contains periods of prolonged dystonic attacks, along with other elements of the syndrome (Bourgeois et al., 1993). The syndrome begins before 18 months of age. In addition to prolonged periods of dystonia, there are attacks of nystagmus, dyspnea, and autonomic phenomena. Episodes of quadriplegia appear either when a hemiplegia shifts from one side to the other or as an isolated

Video 22.6 Psychogenic paroxysmal nonkinesigenic dyskinesia (PNKD).

Video 22.7 Secondary paroxysmal nonkinesigenic dyskinesia (PNKD).

manifestation. The episodes were often followed by developmental deterioration. Eventually, there is cognitive impairment and a choreoathetotic movement disorder. Sleep relieves the weakness and other paroxysmal phenomena, but they can reappear after awakening. The attacks can last from a few minutes to several days. Flunarizine and aripiprazole can be partially effective (Haffejee and Santosh, 2009). Some infants manifest paroxysmal dystonia before the classic features of alternating hemiplegia develop (Andermann et al., 1994). Magnetic resonance spectroscopy was normal in the case reported by Nezu and colleagues (1997). A review of the phenotypic data on 103 patients with this syndrome has been published (Sweeney et al., 2009). Paroxysmal eye movements were the most frequent early symptom, manifesting in the first 3 months of life in 83% of patients. Paroxysmal episodes of focal dystonia or flaccid, alternating hemiplegia appeared by 6 months of age in 56% of infants. A European consortium reported that the natural history of alternating hemiplegia is highly variable and unpredictable, and the course is not always steadily progressive and degenerative (Panagiotakaki et al., 2010).

Paroxysmal exercise-induced dyskinesia

Lance (1977) was the first to describe what he called an intermediate form of PDC (now called PNKD). Today, this family would appear to have PED. The family had attacks that were briefer than those in classic PNKD, lasting from 5 to 30 minutes, and in which the attacks were precipitated by prolonged exercise and not by cold, heat, stress, ethanol, excitement, or anxiety. The spasms affected mainly the legs. Plant and colleagues (1984) reported a second family. In both families, the inheritance pattern was that of autosomal dominant transmission. In neither family did anyone derive any benefit from barbiturate, levodopa, or clonazepam. Sporadic cases are also seen (Video 24.8), as in Case 3 reported by Nardocci and colleagues (1989). This patient also had interictal chorea without any family history of a similar condition. This patient was helped by clonazepam. Wali (1992) reported another sporadic case; this was an 18-year-old man in whom attacks of right hemidystonia lasting about 10 minutes were precipitated by prolonged running (about 10 minutes) or cold. The EEG and the CT scan were normal; anticonvulsants were not helpful. Demirkiran and Jankovic (1995) mentioned seeing 5 patients, 3 being females. The largest series of sporadic cases is that by Bhatia and colleagues (1997). Familial cases appear to be autosomal dominant (Kluge et al., 1998). A large family with PED with 4 affected members had onset at 9 to 15 years of age and a male-to-female ratio of 3:1 (Munchau et al., 2000). The 26 reported cases consisted of 13 women and 13 men. The age at onset ranged from 2 to 30 years, all but 6 beginning in childhood.

Some patients labeled as PKD (e.g., Cases 1 and 3 of Jung and colleagues [1973] and PNKD (e.g., the family of Kurlan and colleagues [1987]) have attacks that occur after prolonged exercise. It is possible that such patients have a variant of PNKD or a combination of PNKD and one of the other PXDs. However, if the attacks last only seconds and respond to anticonvulsants, they fit clinically with these features of PKD.

The family reported by Schloesser and colleagues (1996) supports the notion that PED is a variant of PNKD. The father of the proband was affected by exertional cramping, and two other men in the family had PED. Women in the family had more prolonged attacks, fitting those of PNKD.

Ictal and interictal cerebral perfusion SPECT studies have been conducted (Kluge et al., 1998). During the motor attacks, decreased perfusion of the frontal cortex and increased cerebellar perfusion were observed. The perfusion of the basal ganglia also decreased. No cortical hyperperfusion indicative of an epileptic nature was seen. The authors conclude that PED represents a paroxysmal movement disorder rather than epilepsy. However, an opposite finding in a case of PED also has been reported (Yoon et al., 2007). In this 16-year-old boy, there was increased perfusion in the somatosensory cortex.

In a patient with familial PED, different stimuli, and maneuvers in triggering dystonic attacks in the arm were studied. Motor paroxysms could be provoked by muscle vibration, passive movements, transcranial magnetic stimulation, magnetic stimulation of the brachial plexus, and electrical nerve stimulation but not by sham stimulation (Meyer et al., 2001). The authors conclude that dystonic attacks are triggered by proprioceptive afferents.

Guerrini and colleagues (1999) described a family with PED and autosomal recessive rolandic epilepsy, with the gene mapped to chromosome 16p12–11.2. That family's dystonia resembles the ICCA syndrome, and the genetic mapping overlaps with that syndrome. Perniola and colleagues (2001) described another family with autosomal dominant PED and epilepsy; fasting and stress were also precipitating factors.

In a study in which CSF monoamine metabolites were measured before and after the attack, a 2-fold increase in the concentration of homovanillic acid and 5-hydroxyindoleacetic acid was detected after the attack (Barnett et al., 2002).

A case of PED foot dystonia in an adult was found to be due to the earliest symptom of Parkinson disease, as established by dopamine transporter binding and SPECT and effectively treated with dopaminergic medication (Katzenschlager et al., 2002). Two other adults (second cousins) who presented with PED later developed clinical features of Parkinson disease (Bruno et al., 2004b).

Autosomal dominant PED accompanied by epilepsy was found to be due to GLUT1 deficiency arising from mutations in *SLC2A1* (Wang et al., 1993; Weber et al., 2008; Suls et al., 2008; Zorzi et al., 2008; Leen et al., 2010; Gardiner et al., 2015; Meneret and Roze, 2016; Tchapyjnikov and Mikati, 2018). The syndrome also includes mild developmental delay, reduced CSF glucose levels, hemolytic anemia with echinocytosis, and altered erythrocyte iron concentrations. The GLUT1 deficiency syndrome arises from defective glucose transport across the blood-brain barrier. The clinical spectrum of GLUT1 deficiency was evaluated by videotape in 57 patients, and a wide range of movement disorders are seen (Pons et al., 2010). These include abnormal gait (ataxic-spastic and ataxic), action limb dystonia (86%), mild chorea (75%), cerebellar tremor (70%), myoclonus (16%), and dyspraxia (21%). Nonepileptic paroxysmal events were encountered in 28% of patients and included episodes of ataxia, weakness, parkinsonism, and nonkinesogenic dyskinesias. Alternating hemiplegia also has been reported with GLUT1

 **Video 22.8** Paroxysmal exertional dyskinesia.

deficiency (Rotstein et al., 2009). A pair of homozygous twins with GLUT1 deficiency had PED, migraine, absence seizures, and writer's cramp with an excellent response to a ketogenic diet (Urbizu et al., 2010).

PEDs are difficult to treat. Those with GLUT1 deficiency can be treated with a ketogenic diet. Posteroventral pallidotomy has been reported to ameliorate attacks of PED (Bhatia et al., 1998).

Table 24.5 lists the major distinguishing features of non-epileptic PKD, PNKD, and PED.

Episodic ataxias

The paroxysmal ataxias, called EAs, have been distinguished by their clinical features and genotypes. These characteristics are presented and summarized in Table 24.6.

The genes for four of the hereditary EAs have been determined. In one of them, EA-1, the type associated with myokymia or neuromyotonia, has been found to be due to point mutations in the gene *Kv1.1* for the voltage-gated potassium channel (*KCNA1*) (Browne et al., 1994; Comu et al., 1996). The gene is located on chromosome 12p13 (Litt et al., 1994).

Different mutations have been found in different families (D'Adamo et al., 1998; Zerr et al., 1998; Eunson et al., 2000). The attacks are brief, lasting seconds to minutes; myokymia is present during and between attacks. The attacks can be triggered by sudden movement (Nutt and Ganther, 1997), and these can respond to anticonvulsants. Some families have episodes of myokymia without ataxia (Eunson et al., 2000). In one family, mutations in the *KCNA1* gene can cause severe neuromyotonia resulting in marked skeletal deformities without EA and others in the family had the ataxia (Kinali et al., 2004).

Another EA, EA-2, is the type that has a vestibular component and does not have myokymia as an associated feature. The attacks last between 15 minutes and a few days and respond to acetazolamide. The gene was mapped to chromosome 19p13 (Vahedi et al., 1995; Von Brederlow et al., 1995), and the syndrome was found to be mutations in the gene for the calcium channel *CACNA1A* (Spacey et al., 2005). Spontaneous mutations (Yue et al., 1998) and familial cases have been described. There is clinical heterogeneity, with attacks varying from pure ataxia to combinations of symptoms that suggest involvement of the cerebellum, brainstem, and cortex. Oculographic findings were localizing to the vestibulocerebellum and posterior vermis. Some

Table 24.5 Clinical features of paroxysmal kinesigenic (PKD), nonkinesigenic (PNKD), and exertional dyskinesia (PED)

FEATURE	PKD	PNKD	PED
Male-to-female	4:1	1.4:1	1:1
Inheritance	AD	AD	AD
Genetic mapping	16p11.2–12.1 (also designated as DYT10); with infantile convulsions <i>PRRT2</i> gene <i>PRRT2</i> protein 16q12.1–16q21 (gene designated as <i>EKD2</i>); PKD without convulsions; (also designated as DYT19)	- Mount-Reback syndrome 2q34 (FPD1) (PNKD1) (also designated as DYT8) myofibrillogenesis regulator 1 gene (<i>MR1</i>). New name is PNKD for gene and protein. - With diplopia and spasticity (CSE); chromosome 1p21; (also designated as DYT9) (now thought to be GLUT1 and the same as DYT18) - With familial infantile convulsions; ICCA, chromosome 16, pericentric, sodium/glucose cotransporter - Linkage on chromosome 2q31; (PNKD2); (DYT20) - With epilepsy; chromosome 10q22; calcium-sensitive potassium channel (<i>KCNMA1</i>) (Du et al., 2005)	- With autosomal recessive rolandic epilepsy–PED–writer's cramp. 16p12–p11.2 RE–PED–WC - GLUT1 autosomal dominant; developmental delay; hemolytic anemia echinocytosis (DYT18) (<i>SLC2A1</i>), 1p34.2
Age at onset	<1–40	<1–30	2–30
Range:	12	12	11.5
Median:	12	12	12
Mean:			
Attacks	<5 min	2 min–4 h	5 min–2 hr
Duration	100/day–1/mo	3/day–2/y	1/day–2/mo
Frequency			
Trigger	Sudden movement, startle, hyperventilation	Nil	Prolonged exercise; muscle vibration; nerve stimulation; TMS of motor cortex
Precipitant	Stress	ETOH, stress, caffeine, fatigue	Stress
Movement pattern	Any combination of dystonic postures, chorea, athetosis, and ballism; unilateral or bilateral	Any combination of dystonic postures, chorea, athetosis, and ballism; unilateral or bilateral	Any combination of dystonic postures, chorea, athetosis, and ballism; unilateral or bilateral
Treatment	Anticonvulsants	Clonazepam, benzodiazepines, acetazolamide, antimuscarinics	Acetazolamide, antimuscarinics, benzodiazepines

CSE, choreoathetosis/spasticity episodica; ETOH, ethanol; GLUT1, glucose transporter 1; ICCA, infantile convulsions with choreoathetosis; TMS, ...

affected individuals exhibited a progressive ataxia syndrome that is phenotypically indistinguishable from the dominantly inherited spinocerebellar ataxia (SCA) syndromes. SCA6 has been found to be due to an expanded CAG repeat on the same gene (Zhuchenko et al., 1997). Two patients with childhood-onset EA-2 developed adult-onset dystonia (Spacey et al., 2005). About half of the affected individuals have migraine headaches, and several have episodes that are typical of basilar migraine (Baloh et al., 1997). Both familial hemiplegic migraine and EA-2 are caused by mutations in the Ca^{++} channel gene *CACNL1A4* and can be considered as allelic channelopathies (Ophoff et al., 1996). When progressive ataxia is present, there is cerebellar atrophy on MRI scans, and not all cases have a CAG expansion (Yue et al., 1997). On the other hand, cases with the CAG expansion and cerebellar atrophy also can have EA-2 (Jodice et al., 1997). A family with the phenotype of EA-2 was found not to have a mutation of the *CACNL1A* gene on chromosome 19p13, indicating genetic heterogeneity for this disorder (Hirose et al., 2003). EA-2 is responsive to acetazolamide and aminopyridine (Choi and Choi 2016).

EA-8 was described in a large Irish family. This syndrome is autosomal dominant and marked by an early age of onset, typically before the age of 2 years. The attacks include ataxia, slurred speech, nystagmus, and myokymia. The episodes are more prolonged, lasting minutes to days, and there may be up to two episodes per day. Interictally, there may be ataxia. In contrast to some of the other EAs, this genetic form does not include epilepsy. There is no response to acetazolamide but a good response to clonazepam. The genetic mutation identified was UBR4 on chromosome 1:19277109 (Conroy et al., 2014).

EA-1, EA-2, and EA-8 were described earlier. Not all families with migraine and episodic vertigo could be linked to the EA-2 markers on chromosome 19p, indicating genetic heterogeneity for this type of EA (Baloh et al., 1996). EA-3 is autosomal dominant EA manifested by vestibular ataxia, vertigo, tinnitus, and interictal myokymia; attacks are diminished by acetazolamide (Steckley et al., 2001). EA-1 and EA-2 genetics were excluded. The fourth type of paroxysmal ataxia with ocular motility problems can be precipitated by sudden head movement (Damji et al., 1996). The gene for this fourth type of EA has not yet been mapped but is

Table 24.6 Clinical and genetic features of episodic ataxias

Type	Age at onset	Clinical	Acetazolamide response	Precipitant	Frequency/duration	Interictal	Gene
Myokymia, neuromyotonia (EA-1)	2–15	Aura of weightless or weak then ataxia, dysarthria, tremor, facial twitching	In some kindreds, anticonvulsants may help	Startle, movement, exercise, excitement, fatigue	Up to 15/day; usually ≤ 1 /day; seconds to minutes usually 2–10 min	Myokymia, shortened Achilles tendon; PKD	12p13, K^+ channel, differed point mutations in <i>KCNA1</i>
Vestibular (EA-2)	0–40 usually 5–15	Ataxia, vertigo, nystagmus, dysarthria, HA, ptosis, ocular palsy, vermis atrophy	Very effective	Stress, alcohol, fatigue, exercise, caffeine	Daily to every 2 mo; usually hours; 5 min to wk	Nystagmus, mild ataxia, less common: dysarthria, cerebellar and progressive	19p13, Ca^{++} channel, <i>CACNA1A4</i> , familial hemiplegic migraine
Tinnitus (EA-3) (Steckley et al., 2001)	1–41	Ataxia, tinnitus, falling, headache, blurred vision, vertigo, nausea	Effective	None	Daily; 10–30 min	Myokymia; some with ataxia	1q42
Ocular (EA-4) (Damji et al., 1996)	20–50	Ataxia, diplopia, vertigo, nausea	No response	Sudden change in head position	Daily to year; minutes to hours	Symptoms gradually become constant	Unknown
Vertigo (EA-5) (Escayg et al., 2000)	20–30	Ataxia, vertigo, juvenile epilepsy	Effective	None	Daily; hours	Nystagmus, mild ataxia, dysarthria	2q22–q23, Ca^{++} channel, <i>CACNB4</i>
Photophobia (EA-6) (Jen et al., 2005)	Birth to 20	Ataxia, dysarthria, hemiplegic migraine, photophobia	Effective	Fever, emotional stress, fatigue, alcohol, caffeine	Daily; 2–3 h	Ataxia, nystagmus	5p13 <i>SLC1A3</i> ; glutamate transporter EAAT1
EA-7 (Kerber et al., 2007)	<20	Ataxia weakness, dysarthria	Unknown	Excitement, exercise	Monthly to yearly; hours to days	Normal	19p13
EA-8 (Conroy, McGettigan et al., 2014)	<2	Ataxia, myokymia, response to clonazepam; nystagmus, slurred speech	No response stress		Minutes to hours	Ataxia	UBR4 ubiquitin ligase protein
HA, ...							

genetically distinct from EA-1 and EA-2. The fifth type was seen in a French-Canadian family. The attacks began after age 20 years, but earlier in life there was epilepsy (Escayg et al., 2000). The sixth type ranges from more severe with younger onset with episodes of ataxia, seizures, migraine, and alternating hemiplegia from birth (Jen et al., 2005) to milder forms with attacks accompanied by nausea, vomiting, photophobia, phonophobia, vertigo, diplopia, and dysarthria (de Vries et al., 2009). The seventh type maps to the same region as EA-2, without any interictal symptoms and without mutations in the potassium channel gene (Kerber et al., 2007). In a study of 39 Korean patients with EA, whole exome sequencing was done. This revealed 16 pathogenic mutations, with 9 having *CACNA1*, 3 with *SLC1A3*, and 4 with mutations in *UBR4*. In 7 patients without an identified EA gene, other pathogenic mutations were found, including *ATP1A2*, *SCN1A*, *TTBK2*, *TGM6*, *FGF14*, and *KCND3*. This study highlights the genetic heterogeneity of EA in Korea and suggests that whole exome sequencing may be a valuable tool in this population (Choi et al., 2017).

Another family with EA that does not map to the disorders labeled EA-1 to EA-8 has been described (Damak et al., 2009). This family has not been linked to any chromosomal site yet. It appears to be autosomal dominant, onset between 48 and 56 years of age, the most severely affected had daily attacks with slowly progressive and disabling permanent cerebellar ataxia and a poor response to acetazolamide. Sporadic cases of EAs occur. Four patients with autopsies had ataxia resembling EA-2, but did not respond to acetazolamide, nor did their molecular genetics workup fit EA-2 (Julien et al., 2001).

Molecular genetics of paroxysmal dyskinesias

Overall, there is a phenotypic overlap for the genes associated with the paroxysmal movement disorders. The *PRRT2* gene, although mostly causing classic PKD and associated with hemiplegic migraine and infantile seizures, can be found with EA and PNKD. Patients with the *PNKD* (*MR1*) mutation, mostly reported associated with PNKD, may also present with PED. Patients with the *SLC2A1* mutation, most associated with PED, can demonstrate PNKD (Erro et al., 2014).

A number of PXDs have been mapped to chromosome 16. PKD with infantile convulsions has been mapped to 16p11.2–q12.1 and called EKD1 and designated as DYT10 (Tomita et al., 1999; Bennett et al., 2000; Swoboda et al., 2000). PKD without convulsions has been mapped to 16q13–q22.1 with the gene referred to as EKD2 and designated as DYT19 (Valente et al., 2000). The ICCA syndrome has been reported without linkage to these two loci (Spacey et al., 2002). A family with infantile convulsions has an associated PNKD, and the abnormal gene has been mapped to chromosome 16 (Szepe-towski et al., 1997). The gene in this region that appears to be responsible for ICCA is the sodium/glucose cotransporter gene (*KST1*) (Roll et al., 2002). It also appears to be responsible for benign familial infantile convulsions. Perhaps this disorder with its genetic mapping has been referred to by others as PKD with infantile convulsions. Guerrini (2001) proposed that disparate reports of families suggest that the same gene could be responsible for autosomal recessive rolandic epilepsy, PED, writer's cramp (RE-PED-WC), and PNKD, with

specific mutations accounting for each of these mendelian disorders. Evidence is for a major gene or a cluster of genes for epilepsy and PXD to the pericentromeric region of chromosome 16. These families need to be tested for the *KST1*. Caraballo and colleagues (2001) have diagrammed where the gene loci for these different disorders have been mapped on chromosome 16 (Fig. 24.1).

Six pedigrees with PKD have been found on the Chinese mainland, and they were not linked to the two known loci and so represent another familial form of PKD (Zhou et al., 2008).

An autosomal dominant form of PED with developmental delay and erythrocyte changes has been found to be due to GLUT1 deficiency (Weber et al., 2008). There is a cation

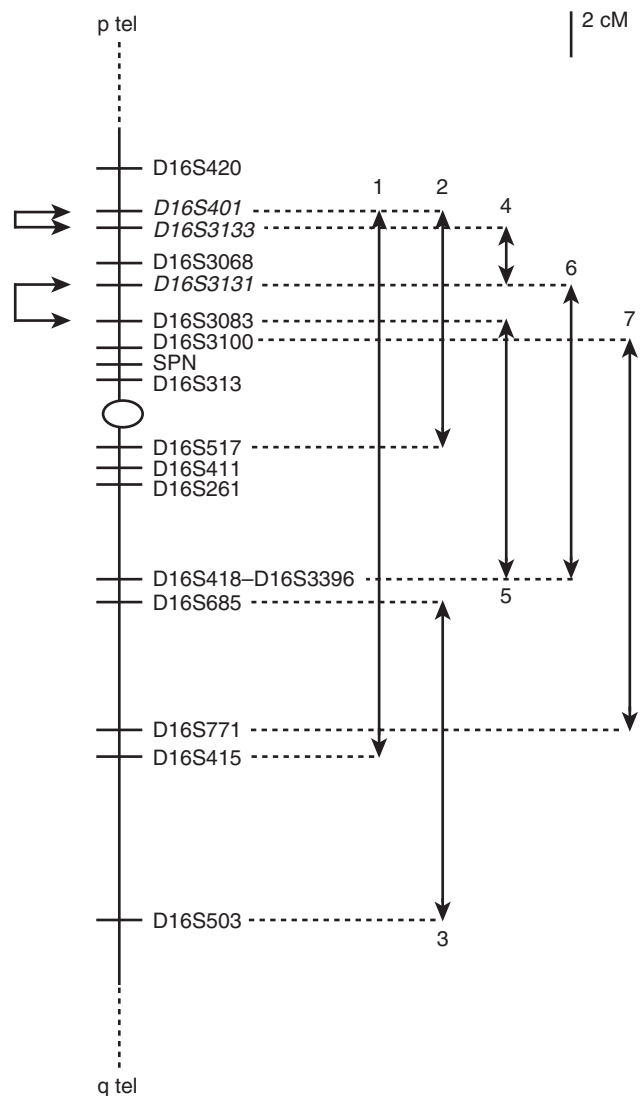


Fig. 24.1 Schematic representation of the genetic map of human chromosome 16p12–q12. Critical regions are indicated: 1, benign familial infantile convulsions (BFIC) (7 families, present study); 2, infantile convulsions with choreoathetosis (ICCA) (Szepe-towski et al., 1997); 3, paroxysmal kinesigenic dyskinesia (PKD) (Valente et al., 2000); 4, reflex epilepsy–PED–writer's cramp (RE-PED-WC) syndrome (Guerrini et al., 1999); 5, PKD and BFIC (Tomita et al., 1999); 6, PKD and BFIC (Swoboda et al., 2000); PKD (Bennett et al., 2000). (From Caraballo R, Pavak S, Lemainque A, et al. Linkage of benign familial infantile convulsions to chromosome 16p12–q12 suggests allelism to the infantile convulsions and choreoathetosis syndrome. *Am J Human Genet.* 2001;68[3]:788–794.)

leak from the erythrocytes that alters the intracellular concentration of sodium, potassium, and calcium. This leads to hemolytic anemia and echinocytosis as detected by electron microscopy. Many more papers have reported GLUT1 deficiency causing PED (Suls et al., 2008; Zorzi et al., 2008; Schneider et al., 2009; Leen et al., 2010). The most frequent gene mutation identified is *SLC2A1* (Silveira-Moriyama et al., 2018).

Two papers independently reported the mapping of a gene for PNKD to chromosome 2q31–36 (Fink et al., 1996; Fouad et al., 1996), and the region was narrowed to 2q33–q35 by Fink and associates (1997). Another family was mapped by Raskind and colleagues (1998), who narrowed the region to 2q34. Jarman and colleagues (1997) mapped the gene to a large British family. Although a cluster of sodium channel genes is near the PNKD locus, the mutated gene has now been found to be myofibrillogenesis regulator 1 (*MR1*) (Lee et al., 2004), which has been renamed the *PNKD* gene (Silveira-Moriyama et al., 2018). The mutations in this gene were associated with PNKD in 50 individuals from 8 families; they cause changes (Ala to Val) in the N-terminal region of two *MR1* isoforms. The *MR1L* isoform is specifically expressed in the brain and is localized to the cell membrane, and the *MR1S* isoform is ubiquitously expressed and shows diffuse cytoplasmic and nuclear localization. The *MR1* gene is homologous to the hydroxyacylglutathione hydrolase (*HAGH*) gene, which functions in a pathway to detoxify methylglyoxal, a compound that is present in coffee and alcoholic beverages and is produced as a by-product of oxidative stress. The finding of the *MR1* gene locus suggests a mechanism whereby alcohol, coffee, and stress may act as precipitants of attacks in PNKD. However, there is genetic heterogeneity in PNKD, because there is a Canadian family without this mutation, with links to a separate locus at 2q31 instead (Spacey et al., 2006); it has been designated as PNKD2 and also DYT20; the *MR1* gene disorder is called PNKD1 and DYT8.

A large Australian family with autosomal dominant hypnogenic frontal lobe seizures/dystonia has been found to have a missense mutation in the second transmembrane domain of the nicotinic acetylcholine receptor alpha4

subunit (*CHRNA4*) gene, located on chromosome 20q13.2–13.3 (Oldani et al., 1998). A second locus has been found on chromosome 15q24 (Phillips et al., 1998, 2001), and a third locus has been found on chromosome 1 in a large Italian family (Gambardella et al., 2000).

Miscellany

There are a number of other types of PXDs that do not fit well into the classification scheme listed previously (Pourfar et al., 2005). For example, a case of truncal flexion spasms that persist repeatedly in attacks lasting several hours has been described (Brown et al., 1991). These were considered to have a spinal origin, presumably involving the propriospinal pathways, and is now called propriospinal myoclonus. We have seen a patient with multiple brief dystonic spasms, lasting seconds, after cardiac arrhythmias. These attacks have all the clinical features of symptomatic PKD, except that they were not precipitated by sudden movement or startle. Like PKD, they responded dramatically to low dosages of carbamazepine. Perhaps the major delimiter in classifying the PXDs should not be whether they are kinesigenic but rather the duration of the attacks. Like tics, stereotypies can occur episodically (Video 24.9). ▶

A syndrome in infant girls is self-stimulatory (previously called masturbatory) behavior that occurs episodically (Fleisher and Morrison, 1990; Mink and Neil, 1995; Nechay et al., 2004; Yang et al., 2005). The episodes appear between 3 and 14 months of age and consist of the child's applying her suprapubic region to a firm edge of furniture, such as the arm of a sofa (Video 24.10). There is often stiffening of the lower extremities. The episodes last less than a minute to hours at a time. Most commonly this behavior is misdiagnosed as epilepsy or paroxysmal dystonia. This is now generally classified as a stereotypy. ▶

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Video 22.9 A burst of stereotypic arm and hand wiggling.

Video 22.10 Paroxysmal self-stimulatory behavior.

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Restless legs syndrome

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Restless legs syndrome and periodic movements of sleep

Clinical features

The term “restless legs” has been applied to a number of conditions. [Ekbom \(1960\)](#) originally applied this term to unpleasant crawling sensations in the legs, particularly when sitting and relaxing in the evening, which disappeared on walking. The syndrome was probably first described by Thomas Willis in 1685. In honor of these two physicians, and to indicate that the syndrome is a disease, some now refer to restless legs syndrome as Willis-Ekbom disease (WED) ([Chokroverty, 2014](#)). “Restlessness” is also a characteristic feature of akathisia, but here the feeling is of inner restlessness not specifically referred to the legs, although this inner feeling can be dissipated by activity. “Inner tension” is also a feature of the urge preceding tics, relieved by the involuntary movement..

The restless legs syndrome (RLS) is characterized by a deep, ill-defined discomfort or dysesthesia in the legs that arises during prolonged rest or when the patient is drowsy and trying to fall asleep, especially at night ([Trenkwalder et al., 2009](#); [Trenkwalder and Paulus, 2010](#); [Rye and Trotti, 2012](#); [Allen, 2014](#); [Chokroverty, 2014](#); [Comella, 2014](#); [Garcia-Borreguero and Williams, 2014](#); [Ferre et al., 2018](#)). The disorder is truly diurnal; the symptoms are worse during the night, even when the person tries to stay awake for long periods. The discomfort may be difficult to describe—terms such as crawling, creeping, pulling, itching, drawing, or stretching are used, and the feeling usually is felt in the muscles or bones. The most frequent words and phrases used are tabulated in several large series ([Karroum Golmard et al., 2012](#); [Kerr et al., 2012](#)) and the most common anatomic sites diagrammed ([Fig. 25.1](#)) ([Karroum, Leu-Semenescu et al., 2012](#); [Koo et al., 2013](#)). These intolerable sensations are relieved by movement of the legs or by walking. The feeling usually is bilateral and symmetrical in the legs. The arms are occasionally involved, and a restless arms syndrome variant has been described ([Ruppert et al., 2012](#)). Standardized criteria have been put forward by the International Restless Legs

Syndrome Study Group ([Table 25.1](#)) ([Allen, Picchietti et al., 2014](#)) that have been integrated with considerations for the diagnosis of pediatric RLS ([Picchietti et al., 2013](#)). Symptoms in children are similar to those in adults, but children often choose different words to describe them ([de Weerd et al., 2013](#)). In some patients there is overt pain ([Cho et al., 2015](#)).

Complaints of restless legs are common, with an estimated prevalence of 3% to 10% ([Hening et al., 2004](#); [Bjorvatn et al., 2005](#); [Budhiraja et al., 2012](#)). A large population study (over 16,000 adults) showed a prevalence of any restless symptoms to be 7.2% and moderately or severely distressing symptoms to be 2.7% ([Allen et al., 2005](#)). RLS is generally a condition of middle to old age, but at least one-third of patients experience their first symptoms before the age of 20 years ([Kotagal and Silber, 2004](#)). There may be increased mortality among men with RLS ([Li et al., 2013](#)). Most patients have mild symptoms to begin with, but these worsen with time, so that they seek aid in middle life. Remission is uncommon, occurring in about 15% ([Walters et al., 1996](#)). RLS can even affect a phantom limb ([Skidmore et al., 2009](#); [Vetrugno et al., 2010](#)). The differential diagnosis conditions for RLS are called mimics, and it is necessary to rule them out specifically to make the diagnosis ([Picchietti et al., 2013](#); [Ondo, 2014](#)). Specifically noted in the criteria are myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, and habitual foot tapping.

The majority of those with RLS also exhibit periodic leg movements of sleep (PLMS) ([Rye and Trotti, 2012](#)) ([Table 25.2](#)). These consist of brief (1–2 seconds) jerks of one or both legs, consisting of, at its simplest, dorsiflexion of the big toe and foot. Initially there is a jerk, but subsequently there is sustained tonic spasm. Such events tend to occur in runs every 20 seconds or so for minutes or hours, and there should be more than five per hour to be considered significant. Sometimes the whole leg or both legs may flex ([Fig. 25.2](#)). The movement resembles a flexion reflex ([Bara-Jimenez et al., 2000](#)). Such periodic movements can wake the sleeping partner. There also may be arousals in the affected individual, in which case there may be excessive daytime drowsiness. The arousals often appear to be related to the PLMs ([Ferri et al., 2015](#)), but there is some evidence that they are not directly associated with the PLMs, but instead with

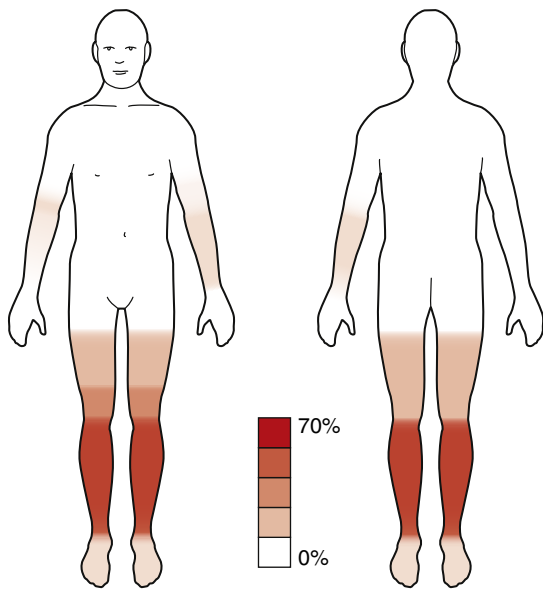


Fig. 25.1 Topography of restless leg syndrome sensory symptoms. Color density indicates the percentages of participants with sensory symptoms involving that area. (From Koo YS, Lee G-T, Lee SY et al. Topography of sensory symptoms in patients with drug-naïve restless legs syndrome. *Sleep Med.* 2013;14:1369–1374, with permission.)

Table 25.1 Restless legs syndrome

Essential diagnostic criteria for restless legs syndrome

1. An urge to move the legs usually but not always accompanied by or felt to be caused by uncomfortable and unpleasant sensations in the legs
2. The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting
3. The urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues
4. The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity occur only or are worse in the evening or night than during the day
5. The occurrence of the above features is not solely accounted for as symptoms primary to another medical or a behavioral condition (e.g., myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping).

Supportive clinical features of restless legs syndrome

The following features, although not essential for diagnosis, are closely associated with RLS and should be noted when present:

1. Periodic limb movements (PLMs): presence of periodic leg movements in sleep (PLMS) or resting wake (PLMW) at rates or intensity greater than expected for age or medical/medication status.
2. Dopaminergic treatment response: Reduction in symptoms at least initially with dopaminergic treatment.
3. Family history of RLS/WED among first-degree relatives.
4. Lack of profound daytime sleepiness

From Allen RP, Picchietti D, Garcia-Borquero D, et al. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: Updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria-history, rationale, description, and significance. *Sleep Med.* 2014;8:860–873, with permission.

Table 25.2 Periodic movements of sleep

Runs (every 30 seconds or so) of brief (1–2 seconds) jerks in one or both legs
Initial jerk followed by tonic spasm
Dorsiflexion of big toe and foot (or flexion of whole leg)
More common during stage I and II sleep
May occur in awake, drowsy individual
Asymptomatic, may wake sleeping partner or can be associated with arousals
Prevalence increase with age: rare under 30 years; 5% 30–50 years; 29% over 50 years

an electroencephalography phenomenon called the cyclic alternating pattern (Manconi et al., 2012). Generally, they appear during periods of arousal during sleep in stages I and II, and decrease during deep sleep during stages III and IV; they are unusual during rapid eye movement (REM) sleep. Sometimes such flexion movements of one or both legs can occur in the waking subject, particularly when drowsy (Hening et al., 1986) (Video 25.1). Note should be made that some patients with RLS have propriospinal myoclonus just before falling asleep (Vetrugno et al., 2005).

Although most people with restless legs have PLMS (at least in the sleep laboratory), a proportion do not complain of restless legs. The combined syndrome of restless legs and PLMS is an age-related condition; its incidence increases in adult and late life. It usually manifests after the age of 30, and it is said to affect 5% of those between the ages of 30 and 50 years and as many as 30% of those over the age of 50. However, in a large proportion of cases, the PLMS do not cause complaints and are found incidentally during sleep studies. In many with restless legs, the condition is not disabling. A revised scoring system for PLMs has been developed, increasing the sensitivity of measurement. (Elena, Leslie et al., 2020).

There is an indication that RLS may adversely affect the cardiovascular system through sympathetic activation, leading to autonomic instability an increased risk of cardiovascular events (Duarte, Alves et al., 2020; Chenini, Barateau et al., 2021).

Genetics

Evidence suggests that the disorder in many if not most patients, particularly early-onset cases, is transmitted as an autosomal dominant trait (Xiong et al., 2010; Jimenez-Jimenez, 2018), yet, despite promising linkages, no genes with strong mendelian influence have been found. Association studies in large populations have now identified several common sequence variants (single nucleotide polymorphisms [SNPs]) that convey substantial risk for the disorder (Rye and Trotti, 2012; Dauvilliers and Winkelmann, 2013). These variants explain a considerable amount of the familial incidence. Risk alleles have been identified in *MEIS1*, *BTBD9*, *MAP2K5*, *S*, and *PTPRD* (Schormair et al., 2017; Jimenez-Jimenez, 2018). Large genome wide sequencing and whole exome sequencing have demonstrated several new loci associated with RLS (Schormair, Zhao et al., 2017; Tilch, Schormair et al. 2020; Ergun, Say et al., 2021; Roy, Earley et al., 2021).

The biologic function of the *KCOR1*, *PTPRD*, *TOX3*, and *BC034767* genes is not clear. *MEIS1* may play a role in brain development (Spieler et al., 2014; Ferre et al., 2018).

Video 25.1 Periodic limb movements.

Fig. 25.2 Polysomnography recording from a patient with periodic limb movements of sleep. Note the periodic electromyographic bursts in leg muscles coming about every 20 seconds. (From Lugaresi E, Cirignotta F, Coccagna G, Montagna P. Nocturnal myoclonus and restless legs syndrome. *Adv Neurol.* 1986;43:295–307, with permission.)

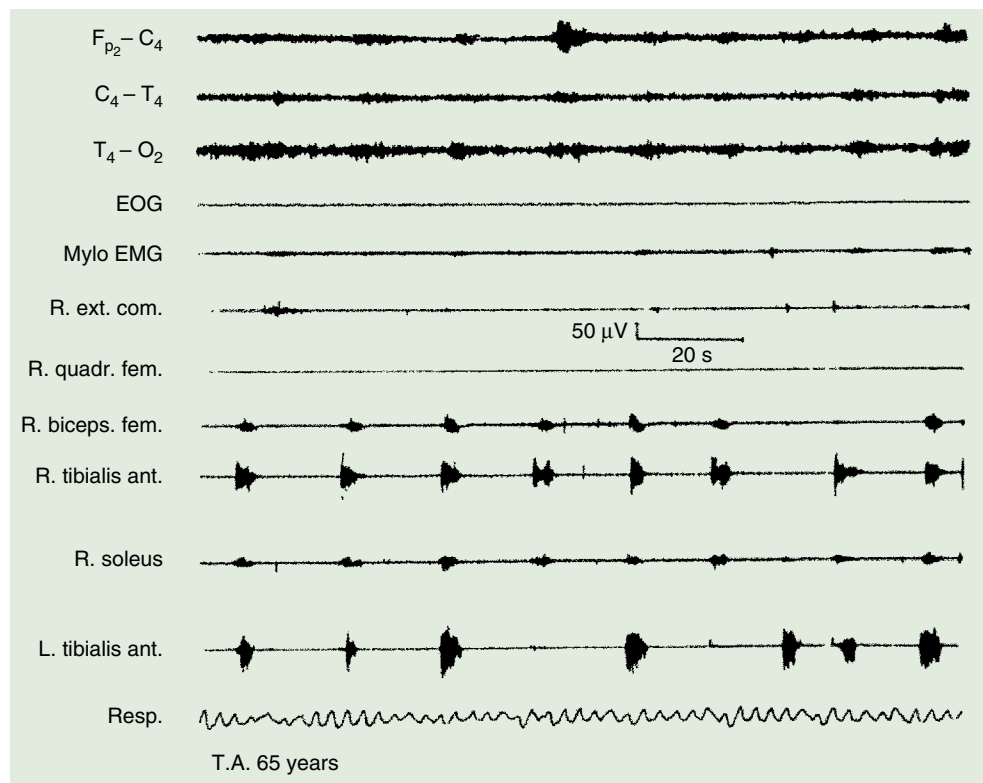


Table 25.3 Nonpharmacologic treatments of restless legs syndrome

Iron replacement if serum ferritin low.
Discontinue caffeine
Consider changing medications that may exacerbate RLS
Serotonergic antidepressants
Antihistamines
Dopamine receptor–blocking agents
Good sleep hygiene
Pneumatic compression
Vibrating pads
Data from Silber MH, Becker PM, Earley C, et al.; W.G. & F. Medical Advisory Board of The Willis-Ekbom Disease. Willis-Ekbom Disease Foundation revised consensus statement on the management of restless legs syndrome. <i>Mayo Clinic Proc.</i> 2013;88(9):977–986; Garcia-Borreguero D, Silber MH, Winkelman JW, et al. Guidelines for the first-line treatment of restless legs syndrome/Willis-Ekbom disease, prevention and treatment of dopaminergic augmentation: A combined task force of the IRLSSG, EURLSSG, and the RLS-foundation. <i>Sleep Med.</i> 2016;21:1–11; and Winkelman J, Allen R, Hogl B, et al. Treatment of restless leg syndrome: Evidence-based review and implications for clinical practice (revised 2017). <i>Mov Disord.</i> 2018;33(7):1077–1091.)

From linkage studies, there are eight susceptibility loci for familial RLS that have been identified (RLS1–RLS8). These loci have not been consistently identified, and no specific gene mutation has yet been identified.

Secondary restless legs syndrome

Whereas many patients have a genetic or primary cause, some are secondary. Important such causes are iron-deficiency anemia, pregnancy (Srivanitchapoom et al., 2014; Tuna Oran, Yuksel et al., 2021), migraine headaches (Yang et al., 2018), chronic myelopathies and peripheral neuropathies, gastric surgery, uremia, chronic lung disease, and anxiety and depression

Table 25.4 Pharmacologic treatment of restless legs syndrome

Intermittent RLS
Carbidopa levodopa
Low-potency opioids (codeine, tramadol)
Benzodiazepines
Initial treatment chronic RLS
Alpha2delta ligands: Reduced risk for augmentation
Gabapentin
Gabapentin encarbil
Pregabalin
Nonergot dopamine agonists at lowest effective dose
Rotigotine patch
Ropinirole
Pramipexole
Treatment of refractory RLS, augmentation
Combination therapy of alpha2delta ligands and dopamine agonists
High-potency opioids at low doses
Oxycodone/naltrexone
Methadone
Data from Silber MH, Becker PM, Earley C, et al.; W.G. & F. Medical Advisory Board of The Willis-Ekbom Disease. Willis-Ekbom Disease Foundation revised consensus statement on the management of restless legs syndrome. <i>Mayo Clinic Proc.</i> 2013;88(9):977–986. Garcia-Borreguero D, Silber MH, Winkelman JW, et al. Guidelines for the first-line treatment of restless legs syndrome/Willis-Ekbom disease, prevention and treatment of dopaminergic augmentation: A combined task force of the IRLSSG, EURLSSG, and the RLS-foundation. <i>Sleep Med.</i> 2016;21:1–11; and Winkelman J, Allen R, Hogl B et al. Treatment of restless leg syndrome: Evidence-based review and implications for clinical practice (revised 2017). <i>Mov Disord.</i> 33(7):1077–1091.

(Comella, 2014; Ondo, 2014). RLS in pregnancy affects from 15% to 30% of women and is most prevalent during the third trimester (22%). After delivery, the prevalence decreased to 4%. Although iron deficiency has been proposed as the underlying related cause, the finding that symptoms quickly resolve with delivery suggests a multifactorial cause (Minaret

al., 2015; Chen et al., 2018). Other potential associations with RLS in pregnancy include a family history, low ferritin levels, high estrogen levels, and possibly vitamin D deficiency (Gupta et al., 2016). In patients with iron-deficiency anemia, there is a high prevalence of RLS (25%–35%) that is improved by iron replacement (Trenkwalder et al., 2016). It is not uncommon in Parkinson disease and many epidemiologic studies show an increased prevalence compared with the general population (Krishnan et al., 2003; Rijsman et al., 2014). A point of confusion in this regard is that wearing-off phenomena may mimic RLS symptoms (Peralta et al., 2009). There is good evidence that males with RLS are slightly more likely to develop Parkinson disease than those without RLS (Wong et al., 2014) although presynaptic dopamine imaging in RLS shows no abnormalities, there is no Lewy body pathologic process in RLS. In the 16,636 participants in the Health Professional Follow-Up Study, having RLS was associated with a higher risk for constipation and self-reported REM sleep behavior disorder (RBD) but not with hyposmia (Iwaki et al., 2018). Looking from the other direction, there is an increased incidence of RLS in patients with PD (Calzetti et al., 2013; Ylikoski et al., 2015). Occasionally, drugs such as neuroleptics and antidepressants, lithium, antihistamines, and anticonvulsants may precipitate intense restlessness of the legs.

Pathophysiology

Interestingly, in the idiopathic form of the disorder, Earley and colleagues (2000) found low cerebrospinal fluid (CSF) ferritin levels and high CSF transferrin levels. There was no difference, however, in serum ferritin and transferrin levels. The findings suggest that there might be low brain iron in these patients. Further investigations by this group have shown that the CSF ferritin is low only in the early-onset RLS patients and that levels are lower at night than during the day (Earley et al., 2005). Neuroimaging studies of iron reveal low levels in the substantia nigra (SN), thalamus, putamen, and pallidum (Rizzo, Mannes et al., 2013). A subsequent study found reduced iron in the thalamus and dentate of RLS compared with controls (Li et al., 2016). A neuropathologic evaluation of seven brains has demonstrated decreased iron and H-ferritin in the SN (Connor et al., 2003). There was a positive correlation between the serum and CSF ferritin levels in both patients with RLS and normal controls, but the slope of the regression lines for the RLS group was lower. These results indicate low brain iron concentration might be caused by the dysfunction of iron transport from serum to central nervous system (CNS) in patients with idiopathic RLS (Mizuno et al., 2005), and now there is good evidence for this. The total iron regulatory protein binding activity in the brain microvasculature is reduced in patient brains (Connor et al., 2011). Another observation is that the number of mitochondria and the mitochondrial ferritin is increased in the SN; the authors suggest that the mitochondria also might be partially responsible for the low cytosolic iron (Snyder et al., 2009). Hfe levels have been proposed as an even more sensitive measure than ferritin levels (Chenini, Delaby et al., 2020). Iron deficiency could well influence dopamine metabolism (Connor, 2008; Connor et al., 2009; Earley et al., 2014).

An alternative hypothesis for the generation of RLS symptoms is that they are caused by peripheral hypoxia in the legs. Although there had been some indirect evidence, there is now direct evidence showing decreased partial

pressure of oxygen in the legs (and not in the chest wall) that is reversed with dopaminergic therapy (Salminen et al., 2014).

Periodic movements of sleep should be distinguished from hypnic jerks or “sleep starts,” which consist of whole-body sudden jerks on falling asleep, and from fragmentary sleep myoclonus. This consists of multifocal myoclonus, which is perhaps more common in sleeping dogs. RLS must be distinguished from the syndrome of painful legs and moving toes and from painful night cramps.

That dopaminergic mechanisms are involved in RLS is strongly suggested by the amelioration of symptoms with dopaminergic therapy. A critical role for the basal ganglia is suggested by the observation that pallidotomy or deep brain stimulation (DBS) of the pallidum for Parkinson disease ameliorated the sensory symptoms of restless legs (Rye and DeLong, 1999; Okun et al., 2005). In relation to surgery for Parkinson disease, some patients with DBS of the subthalamic nucleus will develop RLS (Kedia et al., 2004). This might be due to the fact that dopaminergic drug therapy is reduced, and this might unmask the disorder, but in one series those patients who developed RLS had less reduction of medication (Marques et al., 2015). There is some evidence for abnormalities in the dopaminergic system with single-photon emission computed tomography (SPECT) and positron emission tomography (PET) scanning, but the abnormalities are not consistent across studies (Rizzo, Tonon et al., 2013). Importantly, there is a strong relationship between iron and dopamine, with iron deficiency causing a dopamine deficiency (Allen, 2004).

Voxel-based morphometry (VBM) studies in RLS have produced conflicting results. Etgen and colleagues (2005) found bilateral increase in gray matter in the pulvinar of the thalamus bilaterally. Unrath and associates (2007) found a decrease in cortical gray matter in the sensorimotor cortex, and the degree of abnormality appeared to correlate with the severity of the disorder. This has some interest because the primary symptom of RLS is sensory. Another study found multiple abnormal areas (Chang et al., 2015). On the other hand, other reports found no apparent relevant abnormality (Hornyak et al., 2008; Celle et al., 2009). Diffusion tensor imaging reveals some white matter abnormalities, but the meaning is not really clear (Chang et al., 2014). Recently, alterations in functional magnetic resonance imaging suggests alterations in functional connectivity in untreated patients with RLS (Tuovinen, Stefani et al., 2021).

Opioid receptor availability evaluated with PET and [¹¹C] diprenorphine, a nonselective opioid receptor radioligand, showed no difference between patients and controls (von Spiczak et al., 2005). However, patients' symptoms were inversely proportional to the binding in the brain medial pain system.

The calcium channel $\alpha_2\delta$ subtype 1 protein regulates the influx of calcium into the neuron. The ligands for this protein result in a reduction of calcium channels at the nerve terminal leading to a reduced release of neurotransmitters such as glutamate, norepinephrine, and substance P. This alteration in neurotransmitters has been hypothesized to improve sleep and reduce arousals (Ferre, Earley et al., 2017). Adenosine receptors also have been implicated in the pathophysiology of RLS. Adenosine interacts with dopamine receptors and has effects on glutamate release. This has been hypothesized to lead to hyperarousal, restlessness, and periodic limb movements of sleep (Ferre et al., 2018; Quiroz et al., 2016; Ferre, Quiroz et al., 2017).

Treatment

The first step in the treatment of RLS is the consideration of secondary causes. A ferritin (and transferrin saturation) will allow assessment of body iron stores. If the ferritin is low (this value depending on the reference values of the laboratory), replacement therapy is indicated. In addition, if the value is low and there is no explanation for iron deficiency, one should consider causes for blood loss, including gastrointestinal disorders and cancers. Iron should improve symptoms in those cases associated with iron deficiency. For example, patients with low ferritin levels, oral ferrous sulfate 325 mg twice daily improved symptoms more than placebo (Wang et al., 2009). Iron should be given with vitamin C to enhance absorption (Silber et al., 2013). Iron seems particularly efficacious in children with low ferritin and RLS (Amos et al., 2014). Intravenous iron also can be used for faster repletion (Mehmood et al., 2014). Using parenteral iron bypasses the issues associated with oral iron, including gastritis and constipation. Four preparations are available. High molecular weight iron dextran can cause anaphylaxis and its use is largely abandoned. Low molecular weight iron dextran, ferric carboxymaltose, ferumoxytol, and iron maltose do not carry this risk and have long half-lives. These parenteral preparations have been tested in RLS without overt iron deficiency, and this makes some sense if the problem is iron transport into the CNS. Most such studies are negative (Trotti et al., 2012), but there are some studies in which intravenous iron had some efficacy, either with ferric carboxymaltose (Allen et al., 2011) or lower molecular weight iron dextran (Cho et al., 2013) (Ferre, Earley et al., 2017). In a retrospective study of 164 RLS patients administered intravenous ferric carboxymaltose, 65% experienced benefit. The predictors of benefit included idiopathic RLS, those with iron deficiency anemia and gastrectomy. The percent transferrin saturation was found to be highly associated with response. (Park, Choi et al., 2020).

There are many nonpharmacologic approaches to the treatment of RLS (Table 25.3). Nonpharmacologic treatments should be considered, but the evidence for these is largely anecdotal (Rye and Trotti 2012; Comella, 2014). A meta-analysis of studies evaluating the effects of these treatments showed some effect of pneumatic compression devices, acupuncture, and possibly repetitive transcranial magnetic stimulation. Electrical stimulation, vibratory stimulation, and enhanced external counter pulsation were not effective. Exercise and yoga had some promising results. Most of these studies are of limited quality with small numbers of patients (Xu et al. 2018). Caffeine or drugs such as antidepressants might be contributing to the disorder and should be considered for discontinuation (Silber et al., 2013). Other patients report improvement with warm compresses, vibratory pads, and other nondrug treatments. The effects of these interventions is likely due to the robust placebo effect as described later (Rye and Trotti, 2012; Comella, 2014; Ondo, 2014; Wijemanne and Jankovic, 2015). In a small, controlled study, cognitive behavioral therapy was demonstrated to improve sleep parameters in RLS. (Song, Park et al., 2020).

In addition to these, surgical interventions such as DBS have been anecdotally reported to improve symptoms of RLS both in idiopathic and in RLS secondary to PD. This is not yet confirmed by controlled studies and evidence is based on only a small number of patients (Klepitskaya, Liu et al., 2018; Casoni, Galbiati et al., 2020; Zuzuarregui and Ostrem, 2020).

Pharmacologic interventions (Table 25.4)

Levodopa was the first agent identified and can be very effective, but the dopamine agonists seem better tolerated, particularly over the long term. Ropinirole, pramipexole, and the rotigotine transdermal patch are most commonly used and are efficacious. Pathologic gambling and other impulse control disorders have been reported in RLS patients on dopamine agonists similar to that seen in Parkinson disease (Pourcher et al., 2010; Voon et al., 2011; Silber et al., 2013). There are some data on the long-term use of pramipexole over 12 years, which is generally well tolerated; early drop outs relate to efficacy and augmentation, whereas late drop outs can be due to impulse control disorders (Lipford and Silber, 2012). The rotigotine patch, with its longer duration of action is preferred by some experts as the first line dopaminergic therapy for RLS (Karapinar, Yunusoğlu et al., 2020; Lv, Wang et al., 2020; Gao, Ba et al., 2021). Interestingly, dopaminergic therapy has efficacy even in patients with complete spinal cord lesions, suggesting some action at the level of the spinal cord (de Mello et al., 1999).

A problem with dopaminergic therapy of RLS is augmentation, an increase in the severity of symptoms, a shift in time for the start of symptoms to earlier in the day, a shorter latency to symptoms when resting, and sometimes spread of symptoms to other body parts (Hogl et al., 2010). The explanation is not completely clear, but one hypothesis is that there is an increase of dopamine concentration in the CNS with dopaminergic overstimulation, particularly of the D1 receptor (Paulus and Trenkwalder, 2006). This suggests that dopaminergic therapeutic levels should be low for optimal therapy (Williams and Garcia-Borreguero, 2009). It is possible to give the dopaminergic therapy earlier in the day to combat this, but this may provoke an even earlier onset of symptoms. In the face of augmentation, there are some strategies that might be employed (Mackie and Winkelman, 2015), but it might be reasonable to switch to a different class of agents. Patients will do better with gradual switching of medication (Rosenstein et al., 2015).

Another class of drugs with efficacy are those that bind to the $\alpha_2\delta$ subunit of the voltage-dependent calcium channel. These include gabapentin, gabapentin enacarbil (Bogan et al., 2015), and pregabalin. Gabapentin enacarbil has Level 1 evidence for efficacy and has been approved by the U.S. Food and Drug Administration for the indication of RLS. Because of the lack of augmentation associated with the use of gabapentin and gabapentin enacarbil, these are now considered first line for the treatment of RLS (Winkelmann et al., 2018). In one retrospective study, RLS patients responded optimally to gabapentin if not previously on long term therapy with a dopamine agonist (Garcia-Borreguero, Cano-Pumarega et al., 2019). When compared to placebo, the strong placebo effect in RLS was problematic. (Winkelman and Jaros, 2018). However a recent systematic review of controlled study clearly demonstrate the efficacy of this agent. (Ahmed, Bachu et al., 2019). How these drugs influence RLS is not clear, but they reduce the release of a variety of neurotransmitters. A large trial comparing pramipexole and pregabalin found that pregabalin was more efficacious and caused less augmentation (less than 3%) (Allen, Chen et al., 2014; Garcia-Borreguero et al., 2014).

A third class are the opioids, but these have not been as intensively investigated as the others. Drugs such as codeine, tramadol, oxycodone, and methadone have been used (Silber et al., 2013; Ferini-Strambi and Marelli,

ALGORITHM FOR MANAGEMENT OF RLS

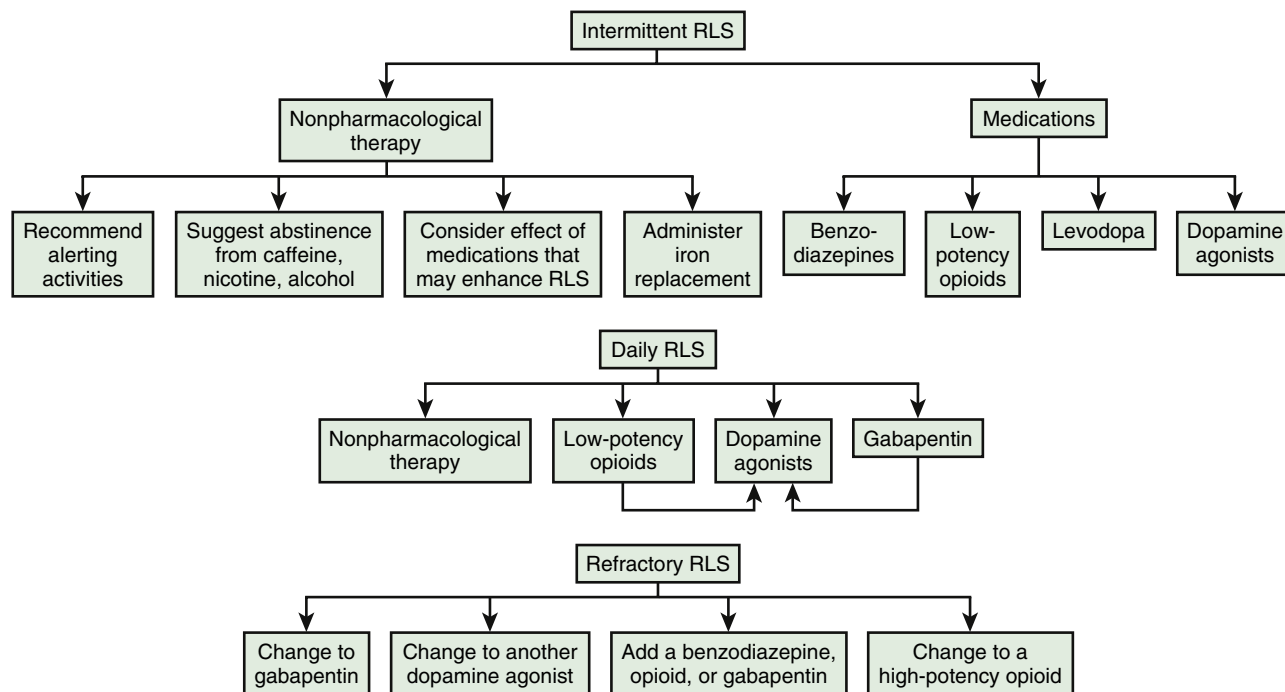


Fig. 25.3 Algorithm for therapeutic management of restless syndrome. (From Silber MH, Becker BM, Earley C, et al. Willis-Ekbom Disease Foundation revised consensus statement on the management of restless legs syndrome. *Mayo Clin Proc.* 2013;88[9]:977–986, with permission.)

2014). A large group of patients who had failed previous drugs were studied with a fixed dose of prolonged-release oxycodone-naloxone in a double-blind fashion over 12 weeks and then in an open extension of 40 weeks (Trenkwalder et al., 2013; Frampton 2015). There was significant efficacy but also a number of side effects. Note that opioids rarely cause augmentation (Earley and Allen, 2006). Opioids are considered the last line of treatment. However, if RLS is refractory to other medications (alone or in combination) and no underlying exacerbating factor is identified (such as iron deficiency), or if there is severe augmentation, low doses of opioids (oxycodone 10 mg, methadone 2.5 mg) slowly titrated to efficacy may be useful (Silber et al., 2018; Winkelmann et al., 2018).

A variety of other drugs also have been used, but generally the evidence is less and the efficacy is also less. These drugs include clonazepam, carbamazepine, baclofen, clonidine, magnesium, and vitamins (Comella, 2014). Advice about how to manage RLS in pregnancy is available (Srivanthapoom et al., 2014).

One of the limitations of treatment studies in RLS is the occurrence of a robust placebo effect (positive outcome with placebo) and nocebo effect (reduced benefit with the active drug). A meta-analysis of randomized placebo-controlled studies demonstrated a clinically important benefit associated with placebo treatment. These effects are greater in studies with a longer duration, industry-funded studies, and unpublished studies (Fulda and Wetter 2008; Silva et al., 2017).

In patients with low ferritin levels, oral ferrous sulfate 325 mg twice daily improved symptoms more than placebo (Wang et al., 2009). Iron should be given with vitamin C to enhance absorption (Silber et al., 2013). Iron seems

particularly efficacious in children with low ferritin and RLS (Amos et al., 2014). Intravenous iron also can be used for faster repletion (Mehmood et al., 2014). Iron also has been suggested even without overt iron deficiency, and this makes some sense if the problem is iron transport into the CNS. Most such studies are negative (Trotti et al., 2012), but there are some studies in which intravenous iron had some efficacy, with either ferric carboxymaltose (Allen et al., 2011) or lower molecular weight iron dextran (Cho et al., 2013; Ferre, Earley et al. 2017).

Nonpharmacologic treatments also should be considered, but the evidence for these is largely anecdotal (Rye and Trotti, 2012; Comella, 2014; Xu et al., 2018). Such treatments include exercise, yoga, acupuncture, and cognitive behavioral therapy. Caffeine or drugs such as antidepressants might be contributing to the disorder and should be considered for discontinuation (Silber et al., 2013).

Practice parameters for treatment have been published by the American Academy of Sleep Medicine (Aurora et al., 2012a,b). Evidence-based reviews have been published by many authors, which all basically agree on the principles as outlined previously (Garcia-Borreguero et al., 2012; Wilt et al., 2013; Hornyak et al., 2014; Winkelmann et al., 2018). Useful algorithms have been presented for patients with intermittent symptoms, chronic persistent symptoms, and refractory symptoms (Fig. 25.3) (Silber et al., 2013; Wijemanne and Jankovic, 2015). Specific guidelines for treatment of patients during pregnancy and lactation have been published (Picchietti et al., 2015).

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Peripheral movement disorders

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Introduction

Abnormal involuntary movements (dyskinesias) usually are caused by brain damage or dysfunction. Occasionally, however, lesions of the spinal cord, spinal roots, cervical or lumbar plexus, or even peripheral nerves appear to cause a variety of dyskinesias (Table 26.1). Sometimes the relationship between the trauma and the movement disorder is not definite, and there are no proven rules to relate them. Jankovic and colleagues have proposed some criteria that can be used as guidelines while waiting for more definitive rules (Table 26.2) (Jankovic, 1994; Cardoso and Jankovic, 1995). An example of a definitive peripheral disorder is hemifacial spasm, in which compression of the facial nerve by an aberrant vessel or cerebellopontine angle mass lesion in the posterior fossa produces repetitive clonic and tonic contractions of one side of the face. Focal myoclonus is sometimes the result of damage to spinal roots, the plexus, or peripheral nerves. Such lesions also rarely cause other dyskinesias, such as dystonia and other forms of muscle spasms, sometimes associated with complex regional pain syndrome. Pathophysiologically, a peripheral injury may act as the trigger for the appearance of dyskinesias thought to arise in the brain; the peripheral injury alters central nervous system (CNS) activity to generate involuntary movements.

Hemifacial spasm

Hemifacial spasm (HFS) is a rare condition that is more frequent in women than men and may be more common in Asians compared to Whites (Wu et al., 2010), characterized by synchronous spasms of one side of the face. It is more frequent in women than men (Table 26.3). Most cases are primary, but some are secondary after recovery from facial nerve palsy (Colosimo et al., 2006; Yalitho and Jankovic, 2011).

The spasms are usually very brief, but can occur in runs and are occasionally tonic. The disorder typically begins around the eye, and this often is the most symptomatic aspect to the disorder (Fig. 26.1) (Video 26.1). The disorder can be bilateral, but then the two sides of the face do not spasm in synchrony. Cases seem to be more common in persons of Asian origin (Poungvarin et al., 1995; Wu et al., 2010). Twitching is mostly spontaneous and can be brought out by facial muscle contraction. When someone closes the eyes, ordinarily the brow moves down, but in hemifacial spasm, the brow moves up because of the synergistic involvement of the frontalis muscle. This is known as the "other Babinski sign" (Devoize, 2001), and it is a reliable diagnostic feature (Stamey and Jankovic, 2007; Pawlowski et al., 2013). The differential diagnosis includes synkinesis after Bell palsy, stroke, demyelination, psychogenic, tic, myoclonus, parotid gland tumors, Chiari malformation and posterior fossa anomalies, and hemimasticatory spasm (Yalitho and Jankovic, 2011; Chaudhry et al., 2015). The distinction among these usually can be made using electromyography (Lefaucheur et al., 2018) and magnetic resonance imaging. The latter is recommended for the assessment of HFS (Banerjee, et al., 2021).

The disorder clearly involves the facial nerve, and the cause appears to be most frequently (94%) a compression of the nerve by a blood vessel just as the nerve leaves the brainstem (Tan and Chan, 2004; Naraghi et al., 2007). About 4% of cases are due to a tumor compressing the nerve (Han et al., 2010). Biopsy of the compressed nerve shows demyelination.

Definitive treatment can be by surgery to decompress the nerve (Hyun et al., 2010; Miller and Miller, 2012; Sekula et al., 2013; Soriano-Baron et al., 2015). This procedure of posterior fossa microvascular decompression was initially developed by Peter Jannetta and is often referred to as the Jannetta procedure (Kaufmann and Price, 2019). The vessels most frequently implicated are the posterior inferior

Video 26.1. Hemifacial spasm.

Table 26.1 Peripheral movement disorders

Hemifacial spasm
 Jumpy stumps
 Belly dancer's dyskinesia
 Painful legs and moving toes
 Peripheral myoclonus and dystonia
 Complex regional pain syndrome (CRPS) and movement disorders

Table 26.2 Criteria for a movement disorder to be related to trauma

1. Injury must be severe enough to cause local symptoms persisting for at least 2 weeks or requiring medical evaluation within 2 weeks of the injury
2. The onset of the movement disorder must have occurred within a few days or months (up to 1 year) after the injury
3. The onset of the movement disorder must have been anatomically related to the site of the injury

From Jankovic J. Post-traumatic movement disorders: Central and peripheral mechanisms. *Neurology*. 1994;44:2006–2014; and Cardoso F, Jankovic J. Peripherally induced tremor and parkinsonism. *Arch Neurol*. 1995;52:263–270.

Table 26.3 Hemifacial spasm

Unilateral clonic jerks, with tonic spasm of all facial muscles
 Starts around eye, spreads to mouth and platysma
 Spasms lift eyebrow, the other Babinski sign
 Irregular and unpredictable; triggered by facial movement; may occur in flurries
 Mild facial weakness develops, with paradoxical synkinesis
 Adults; females more than males (3:2)

cerebellar artery and the anterior inferior cerebellar artery. The vertebro-basilar artery has been implicated in a small percentage of cases (Mercier, 2018). In this procedure, the offending artery is transposed away from the cranial nerve exit zone, thus alleviating the pressure on the nerve. In a retrospective studies, approximately 75%-85% (Compagnon, et al., 2020) of patients with HFS have complete resolution, and improvement occurred in 16%. The features that most predicted a good outcome included male sex, mild HFS, indentation of the facial nerve, and delayed, reversible facial palsy (Lee, 2019). The adverse effects of the procedure include hearing loss and permanent facial nerve palsy (Bartindale, 2018). There are some reports of improved efficacy and reduced adverse effects using endoscopic guidance (Feng, et al., 2020; Cai, et al., 2021). Given the risk of permanent side effects, most patients prefer botulinum toxin treatment, which can be highly effective and can improve quality of life without the risk for permanent sequelae (Czyz et al., 2013; Hallett et al., 2013; Ababneh et al., 2014; Streitova and Bares, 2014; Chaudhry et al., 2015; Sorgun et al., 2015). The dose of botulinum toxin is typically very low but improves symptoms in approximately 85% of patients (Simpson et al., 2008) although there is an absence of randomized controlled clinical trials (Duarte, et al. 2020). In some patients receiving botulinum toxin unilaterally for HFS, facial asymmetry can be cosmetically unacceptable. These patients can benefit from bilateral injections to reduce the asymmetry (Xiao, 2018). With the lower doses used in HFS, the occurrence of neutralizing antibodies is rare (Walter, et al., 2020).



Fig. 26.1 Left-sided hemifacial spasm. Note the elevation of the left brow with the spasm because of contraction of the frontalis muscle. Elevation of the brow with closing of the eye is not easily possible voluntarily. The phenomenon was noted by Babinski and has been referred to as the “other Babinski sign.” (From Devoize JL. “The other” Babinski’s sign: Paradoxical raising of the eyebrow in hemifacial spasm. *J Neurol Neurosurg Psychiatry*. 2001;70[4]:516, with permission.)

Although the cause is relatively clear, the pathophysiologic processes are still not certain. There are two main hypotheses, and there are good data to support each.

Nerve origin hypothesis

This hypothesis proposes that the abnormal discharges producing the spasms come from the region of demyelinated nerve under the compression (Nielsen, 1984a,b; Nielsen and Jannetta, 1984). It is known that demyelinated nerve can produce spontaneous discharges, called ectopic discharges. In addition, there can be lateral transmission of activity between demyelinated nerve axons, called ephaptic transmission. Ephaptic transmission can be responsible for involvement of much of the face (Kameyama, 2016). It is also possible in the case of activity in demyelinated axons with ephaptic transmission for trains of activity to be produced after a single action potential. These phenomena could explain many of the clinical features. Another possibility is that the nerve compression or stretch leads to ion channel changes that increase the nerve excitability, and that demyelination is not necessary (Lefaucheur, et al., 2018). Finally, there is evidence in some patients with HFS of indentation of the facial nerve, leading to more persistent symptoms and an increased likelihood of recurrence after decompression (Ko, et al., 2021).

Additionally, there are physiologic studies that are consistent. If a branch of the seventh nerve is stimulated, in these patients there will be late responses seen in muscles innervated by other branches at latencies consistent with ephaptic transmission at the site of demyelination. This phenomenon is not influenced by botulinum toxin treatment (Geller et al., 1989). Studies of the variability of transmission of this effect, using the technique of jitter, are consistent with only the neuromuscular junction and no intervening synapses (Sanders, 1989). A more recent

suggestion is that the cross-transmission between nerve fibers is by sympathetic nerves in the arterial wall of the compressing vessel (Zheng et al., 2012; Dou et al., 2015).

The final argument in favor of the nerve origin hypothesis is the fact that the disorder very rapidly ameliorates after decompression. However, there has been some evidence of either primary or secondary changes in subcortical structures associated with HFS, including enlargement of the caudate and pallidum (Xu, et al., 2019).

Facial nucleus hypothesis

According to this the facial nucleus hypothesis, the peripheral lesion leads to hyperexcitability of the facial nucleus and the discharges arise there. There is a rat model in which such a phenomenon has been demonstrated. Perhaps the most persuasive argument for this hypothesis is that there is hyperexcitability of the blink reflex in hemifacial spasm, and this must involve brainstem synaptic circuitry. By this theory, the late responses seen with stimulation of branches of the nerve are enhanced F-waves (Roth et al., 1990; Ishikawa et al., 1994). Finally, although the calculations deal in differences of only a millisecond or two, conduction times may be more consistent with transmission all the way to the brainstem and back, rather than just to the site of demyelination (Moller and Jannetta, 1984; Moller, 1987). It is possible that both are true and play a role in most cases.

Jumpy stumps

Not only did S. Weir Mitchell (1872) describe causalgia after gunshot wounds of peripheral nerves, but he also recorded tremor, jerks, and spasms of the remaining stump after amputation, sometimes associated with severe phantom pain. The “painful, jumpy stump” has since been described by others (Marion et al., 1989; Kulisevsky et al., 1992; Tyvaert et al., 2009). A jumpy stump has been seen as a manifestation of tardive dyskinesia (Alencar et al., 2013), and even a phantom dyskinesia induced by metoclopramide has been recorded (Jankovic and Glass, 1985) (Video 26.2). There have also been some reports of jumpy stump as a feature of a functional or psychogenic movement disorder (Davis, et al., 2017). ▶

Jerking of the amputation stump (jactitation), coinciding with lancinating neuralgic stump pains, frequently occurs in the postoperative period but settles over weeks or months (Russell, 1970). The cases referred to previously, however, experienced spasms and jerks of the stump for prolonged periods, for example, up to 40 years in one of the patients reported by Marion and colleagues (1989), who also reviewed many similar cases described in the earlier literature. Jerking of the stump frequently was preceded by severe pain in the stump, appearing weeks or months after the surgery. Upper or lower limb stumps could be affected. The stump jerks could be induced by voluntary movement or, sometimes, by cutaneous stimuli.

Steiner and associates (1974) considered involuntary stump movements to be a form of segmental myoclonus, caused by afferent impulses arising from the severed nerves. Marion and colleagues (1989) concluded that they were due to either “the result of functional changes in spinal (or cortical) circuitry leading to redirection of afferent information through different spinal neurons, or structural reorganization of local neuronal circuitry by axonal sprouting after nerve injury.” Note that a case of psychogenic jumpy stump has been reported (Zadikoff et al., 2006).

One patient responded to pramipexole (Seidel et al., 2011).

Belly dancer’s dyskinesia

Belly dancer’s dyskinesia, or the moving umbilicus syndrome, is another bizarre condition sometimes related to abdominal trauma. Iliceto and associates (1990) described five patients with odd abnormal movements of the abdomen (Video 26.3). One had diaphragmatic flutter (repetitive contractions at about one per second were seen on diaphragmatic screening), but the remainder did not. The latter exhibited regular rhythmic contractions of the abdominal wall, which had a sinuous, writhing, flowing character, often moving the umbilicus from side to side or in a circular rotatory fashion. The intensity of the abnormal movement may vary with respiration. Three of these four patients dated the onset of their abdominal dyskinesia to trauma (cholecystectomy and anal fistula, cystoscopic removal of a renal calculus, and cystectomy), and two had severe pain. Botulinum toxin can be helpful (Lim and Seet, 2009). One patient responded to bilateral deep brain stimulation of the globus pallidus interna (Schrader, Capelle, Kiefe et al., 2009). ▶

Painful legs and moving toes

There is another condition in which injury to peripheral nerves and roots may cause the combination of pain in the leg and abnormal involuntary movement of the toes (Table 26.4). Spillane and colleagues (1971) described six patients with severe pain in one or both feet accompanied by characteristic writhing movements of the toes and sometimes of the feet. Three of these patients had a history suggestive of lumbosacral root damage. Subsequently, further patients were described with local peripheral nerve damage, L5 herpes zoster, S1 root compression and cauda equina lesions (Nathan, 1978), generalized peripheral neuropathy (Montagna et al., 1983), and minor trauma to the legs (Schott, 1981). It may be associated with the neuropathy of acquired immunodeficiency syndrome (AIDS) (Pitagoras de Mattos et al., 1999).

Dressler and associates (1994) reviewed a series of 18 patients with the syndrome of painful legs and moving toes (Table 26.5). Of them, 1 case followed a bullet injury to the spinal cord and cauda equina; 4 cases were due to spinal nerve root injury (herpes zoster, 2 with lumbar disk prolapses, and an L5 hemangioma); 4 cases were due to peripheral leg trauma; 3 cases were associated with an axonal peripheral neuropathy; and in 6 cases no definite cause could be identified (although lumbosacral radiculopathies were suspected in at least 4 of these patients). Three other patients with identical toe movements but no other pain were also described. There is a report of 76 patients from

Table 26.4 Painful legs and moving toes

Adults 30–80 years: males and females
Unilateral or bilateral
Pain in feet first, followed days or years later by movements
Deep ache, burning, throbbing, crushing, tearing
Hyperpathia and allodynia
Sinuous, writhing, athetoid toe movements
Complex 1–2 Hz movement patterns of central origin
Treatments usually fail:

Video 26.2. Jumpy stumps.

Video 26.3. Belly dancer's dyskinesia.

Table 26.5 Clinical features of patients with painful legs and moving toes

	<i>n</i> = 29*	<i>n</i> = 18†
Average age of onset (years)	57.7 (30–80)	60.3 (28–76)
Male/Female	11:18	3:15
Bilateral/unilateral	15:14	10:8
Lesions identified		
Cord	0	0
Cauda equina‡	14	8
Peripheral neuropathy	7	3
Peripheral trauma	6	4
Unknown	2	3

*Twenty-nine cases from various sources (Spillane et al., 1971; Nathan, 1978; Barnett et al., 1981; Schott, 1981; Wulff, 1982; Montagna et al., 1983; Schoenen et al., 1984).

†Cases from Dressler et al. (1994).

‡Includes disk compression, herpes zoster, sacral cyst, hemangioma, and trauma.

the Mayo Clinic (Hassan et al., 2012), and the clinical features and causes were similar to those earlier described (Reich, 2011). One of the largest retrospective studies of painful legs and moving toes included 76 patients, 66% women with a mean age of onset of 58 years. In 91% only the lower limb was affected, and up to 58% had bilateral symptoms. Of these total group, 42% did not have an identifiable etiology, the remaining had either peripheral neuropathy, trauma or radiculopathy as associated (Hassan et al., 2012).

The age of onset usually is in middle or late life. Pain usually is the first symptom, preceding the movements by days to years. The pain has been described as a deep dull ache, burning, throbbing, crushing, searing, surging, or bursting. Sometimes there are associated sensations of pins and needles in the affected limb. The pain is very severe, leading patients to put their feet into refrigerators, wrap them with flannels, or other major measures. The onset may be unilateral, with subsequent spread to the opposite limb, or bilateral. In many patients the pain and the movements appeared to be linked, with increasing pain associated with worsening movements. The pain typically is diffuse, not limited to a peripheral nerve or segmented dermatomal pattern. The characteristics of the pain and the common coexistence of hyperpathia and allodynia may suggest causalgia (Schott, 1986).

The moving toes symptom refers to sinuous, athetoid-like dystonic movements of the toes and rarely of the feet. The patient may complain that the toes are working inside the shoe, rubbing to cause blisters. The toe movements consist of complex sequences of flexion, extension, abduction, and adduction, in various combinations at frequencies of 1 to 2 Hz (Alvarez et al., 2008) (Video 26.4). In the Mayo Clinic report, the electromyogram showed irregular 50-ms to 1-s bursts of normal-appearing motor units firing at 2 to 200 Hz. The electromyographic (EMG) characteristics of such muscle contractions cannot be explained by a peripheral nerve mechanism alone, but point to an origin in the CNS. ►

The mechanism proposed to explain this condition again is that of peripheral injury to nerves, plexuses, or roots,

causing an alteration in spinal and/or supraspinal sensory (the pain) and motor (the movements) machinery. However, the nature of the movements (slow, writhing, and sustained, i.e., dystonic) is quite different to the type of movements seen in hemifacial spasm (myoclonic jerks) or, indeed, in spinal myoclonus. Whether the movements in this condition arise in the spinal cord, as suggested by Nathan (Nathan, 1978) and Schott (Schott, 1981, 1986), or supraspinally is unknown.

It is the pain that causes the major disability, and, unfortunately, this is very difficult to treat. There are only anecdotal reports of any improvement (Hassan et al., 2012). A few patients have responded to sympathetic blockade, but in the majority this is ineffective. A course of guanethidine blocks into the affected limb has been successful. Transcutaneous electrical nerve stimulation (TENS) applied to the leg or foot may help the pain. Carbamazepine, diphenylhydantoin, amitriptyline, and phenothiazines occasionally help. There are reports of utility of adenosine (Guieu et al., 1994), gabapentin (Villarejo et al., 2004; Aizawa, 2007), and pregabalin (Rossi et al., 2015). Epidural block may be helpful (Okuda et al., 1998), as may epidural spinal cord stimulation (Takahashi et al., 2002). Botulinum toxin injection has been reported useful for both movement and pain in two patients (Eisa et al., 2008).

The syndrome can very rarely involve the upper extremity, in which case it is referred to as painful arm and moving fingers (Supiot et al., 2002) (Video 26.5). One case was due to a brachial plexus lesion associated with a breast carcinoma and radiotherapy (Verhagen et al., 1985). ►

Focal myoclonus caused by root, plexus, or peripheral nerve lesions

Myoclonic jerking of the paraspinal muscles caused by a malignant tumor involving the fifth thoracic root, without long tract signs of spinal cord involvement, has been described (Sotaniemi, 1985). Similar focal myoclonus of the legs has also occurred with lumbosacral radiculopathy and after lumbar laminectomy for lumbar stenosis and root lesions (Jankovic and Pardo, 1986). Rhythmical myoclonus of the quadriceps muscle has been reported as a result of a Schwann cell sarcoma of the femoral nerve (Said and Bathien, 1977).

Focal myoclonus of the right arm due to a brachial plexus lesion has been described after radiotherapy for carcinoma of the breast followed by abduction trauma of the right shoulder (Banks et al., 1985). The latter case exhibited rhythmical muscle jerks at about five per second in the distribution of the axillary and radial nerves, but not in other muscles innervated by the lateral and medial cords of the brachial plexus. Electromyographic analysis of this case indicated that the myoclonus arose from a generator located in a segment of the posterior cord of the brachial plexus, between the departure of the axillary nerve and distal to the emergence of the suprascapular nerve. Other patients developed myoclonus of one arm after an electrical injury to the left brachial plexus and after a thoracic sympathectomy (Jankovic and Pardo, 1986). Two patients had myoclonus restricted to ulnar muscles with lesions of the ulnar nerve (Tyvaert et al., 2009; Ross et al., 2013).

Video 26.4. Painful feet and moving toes.

Video 26.5. Painful arm and moving fingers.

The clinical characteristics of myoclonus as a result of spinal cord, root, plexus, or peripheral nerve diseases are:

1. It is focal, being confined to the muscles innervated by the affected spinal cord segments or peripheral lower motor neurons.
2. It is usually spontaneous and rhythmic, and it often persists in sleep.

These observations suggest that it is the result of repetitive, spontaneous discharge of groups of anterior horn cells.

Swanson and associates (Swanson et al., 1962) suggested two mechanisms that might be responsible for spinal segmental myoclonus: (1) enhanced neuronal excitability as a result of direct cellular excitation by inflammation or tumor, or (2) enhanced neuronal excitability because of removal of inhibition. The former seems unlikely, because spinal segmental myoclonus can occur without evidence of damage to anterior horn cells. Loss of inhibition of anterior horn cell pools seems more probable.

Posterior rhizotomy or hemicorpectomy leads to abnormal spontaneous discharge of some spinal neurons in the deafferented segments, which tend to fire in bursts at high frequency (Loeser and Ward, 1967). However, these bursting spinal neurons are found in the dorsal, not the ventral, horns. Nevertheless, such spontaneous bursting of spinal interneurons after deafferentation might drive anterior horn cells to produce focal myoclonus.

Alternatively, loss of inhibitory spinal interneurons might liberate anterior horn cells to fire spontaneously in a rhythmic burst fashion. In the case described by Davis and colleagues (1981) spinal myoclonus occurred after ischemic damage to the cord, which at autopsy was found to have caused extensive loss of small and medium-sized interneurons, with relative preservation of large anterior horn cells. The loss of inhibitory spinal interneurons could release anterior horn cells to discharge spontaneously, but what then determines their tendency to fire repetitively and rhythmically is less clear (Kiehn, 1991; Kiehn and Eken, 1997). Loss of spinal interneurons also is the pathologic change thought to be responsible for alpha spinal rigidity.

It is clear that spinal lesions, particularly with loss of interneurons, can give rise to spontaneous activity underlying myoclonus. Lesions of peripheral nerves or roots, although possibly giving rise to spontaneous activity similar to that in hemifacial spasm, appear to be able to induce secondary changes in the spinal cord, which can then be responsible for the involuntary movements as if the lesion were in the cord itself. The case described by Shin and associates (2007) provides evidence for this. Myoclonus of the quadriceps muscle occurred after a femoral nerve injury that was abolished by spinal anesthesia.

Dystonia induced by peripheral injury

This is a controversial area with many experts thinking that many of these patients have psychogenic disease. There have been a number of case reports of peripheral trauma with or without nerve lesions with subsequent dystonia. There were some early reports of nerve lesions that “appeared to cause” typical arm dystonia (Schott, 1985; Scherokman et al., 1986). Other cases with the association of trauma and the onset of dystonia did not have nerve lesions (Video 26.6).

Sheehy and Marsden (1980) described three trauma-induced cases in a series of 60 patients with torticollis and calculated that 9% of 414 cases of this focal dystonia had suffered preceding injuries. These authors (Sheehy and Marsden, 1982) subsequently reported that writer’s cramp could be precipitated by local hand injury, and identified 5 such cases among 91 patients (Sheehy et al., 1988). Schott (1985) described 4 patients with axial or arm dystonia after local trauma, and later Schott (1986) described 10 additional patients with movement disorders that appeared to have been precipitated by peripheral trauma; 6 of these had developed dystonia, including writer’s and pianist’s cramps, cranial segmental dystonia, axial segmental dystonia, and focal foot dystonia. The interval from injury to development of dystonia ranged from 24 hours to 3 years. Brin and colleagues (1986) briefly reported 23 patients in whom trauma precipitated dystonia in the injured region after an interval of between 1 day and 8 weeks. Jankovic and van der Linden (1988) also described a number of patients with dystonia and tremor induced by peripheral trauma; of 28 cases, 13 had persistent dystonia (4 of a hand, 5 of a foot, 1 of an arm, 1 of a leg, and 2 of craniocervical musculature) developing within 1 day to 12 months after a relevant injury. One report focused on post-traumatic cervical dystonia (Tarsy, 1998). In some patients, oromandibular dystonia has appeared after dental treatment (Thompson et al., 1986; Koller et al., 1989; Sankhla et al., 1998; Schrag et al., 1999). Two patients with task-specific musician’s cramp have been described after trauma (Frucht et al., 2000). Ulnar nerve injury has been suggested to be frequent before piano player’s dystonia (Charness et al., 1996). Immobilization also has been described as an antecedent (Okun et al., 2002; Singer and Papapetropoulos, 2005). Reviews of reported cases have been published (van Rooijen et al., 2011).

Although the dystonia in association with trauma is often similar to that without trauma, there are some differences in many cases (Schrag et al., 2004; Jankovic, 2009). The dystonia tends to be fixed, and this may lead to early contractures. Sensory tricks are not common. These differences have been some of evidence for thinking that the disorder is psychogenic.

There is at least one point of caution in attributing dystonia to a peripheral nerve injury because nerve entrapment may be secondary to dystonia. Thus, for example, some 7% of patients with writer’s cramp subsequently develop carpal tunnel compression of the median nerve as a consequence of their dystonia (Sheehy et al., 1988), and secondary entrapment neuropathies are not uncommon in those with any form of dystonia, including athetoid cerebral palsy (Alvarez, 1982).

There is no proof that trauma is formally causal for dystonia. Of course, it makes sense only if there is a “reasonable” temporal and spatial relationship. Jankovic and colleagues have proposed a set of arbitrary rules in this regard: (1) the trauma is severe enough to cause local symptoms for at least 2 weeks or requires medical evaluation within 2 weeks after trauma; (2) the initial manifestation of the movement disorder is anatomically related to the site of injury; and (3) the onset of the movement disorder is within days or months (up to 1 year) after the injury (Jankovic, 2009).

There are some controlled epidemiologic studies of this issue, and these are both negative and positive. A multicenter

Video 26.6. Peripheral dystonia.

case-control study was performed using a semistructured interview in five Italian referral centers (Martino et al., 2007). The presence of a history of head trauma and of posttraumatic sequelae was recorded from 177 patients with primary adult-onset cranial dystonia and 217 controls with hemifacial spasm. No association was found between vault/maxillofacial trauma and cranial dystonia. Another case-control study was done with 104 consecutive patients with writer's cramp and matched controls (Roze et al., 2009). The risk for writer's cramp increased with the time spent writing and also with head trauma with loss of consciousness, but it was not significantly associated with peripheral trauma. Recently a large epidemiologic study was carried out in a population insurance database in Taiwan (Macerollo, 2019). The authors identified 65,704 people with peripheral injuries and an equal number of controls. Those with trauma had three times the likelihood of developing dystonia.

The matter remains controversial, however, and it is often debated whether the majority of the cases are organic or psychogenic (Jankovic, 2001; Weiner, 2001). There are movement disorders other than dystonia in the setting of trauma, and these are similarly difficult (Pandey et al., 2014).

Of course, the vast majority of those subjected to local injury do not develop dystonia, so trauma alone is unlikely to be the sole cause. Rather, it seems more probable that trauma acts as a trigger to the appearance of dystonia in those predisposed to develop this illness. One such patient, where this seems to be the case, developed foot dystonia after trauma (Bohlhalter et al., 2007). His brother was already known to have craniocervical dystonia, and both he and the brother had increased cortical excitability with transcranial magnetic stimulation similar to that in patients with primary focal dystonia. Moreover, on occasion, trauma may trigger a focal dystonia in patients who subsequently progress to develop generalized dystonia.

In blepharospasm, there is often a history of preceding local ocular disease (Grandas et al., 1988; Martino et al., 2005), and in spasmodic dysphonia, there is often a preceding history of sore throat (Schweinfurth et al., 2002). These results do seem to support the idea that local trauma can be a trigger.

Isolated generalized dystonia is usually genetic in origin, so trauma may be a significant trigger to onset of the illness in those carrying the abnormal gene. Fletcher and associates (1991) examined the relationship between trauma and dystonia in 104 patients with isolated generalized, multifocal, or segmental dystonia. Genetic analysis of this population had indicated that the illness was caused by an autosomal dominant gene with reduced (40%) penetrance in about 85% of cases (Fletcher et al., 1990). Of these 104 cases, 17 (16.4%) reported that their dystonia had been precipitated (14 cases) or exacerbated (5 cases) by local trauma. The dystonia appeared in the injured part of the body within days or up to 12 months after the trauma. Subsequently, the dystonia spread to other body regions. Some patients experienced a new dystonia in a different body part after a subsequent injury to that distant structure. Of these 17 patients, 8 had affected relatives, so were genetically at risk for developing dystonia before the injury. Brin and colleagues (1986) and Jankovic and Van der Linden (1988) also noted familial cases among patients with trauma-induced dystonia (i.e., 9 of 23, and 3 of 13 cases, respectively). All this evidence is

consistent with the hypothesis that peripheral injury might precipitate dystonia in those carrying a gene for isolated generalized dystonia gene, although trauma among those with isolated generalized dystonia is no more frequent than in a matched control population (Fletcher et al., 1991).

The dystonia associated with trauma in these cases was similar in all respects to that occurring spontaneously. Inherited isolated dystonia is thought to be due to basal ganglia dysfunction. If this is also the case in those who develop dystonia after injury, it would seem that trauma may trigger abnormalities of the brain and spinal cord.

There are possible mechanisms whereby peripheral injury might alter basal ganglia function. A major projection of the spinothalamic tract is to the ventrobasal nucleus of the thalamus, which projects to the somatosensory cortex. This system probably subserves discriminative pain perception, and spinoreticular pathways may be involved in large-scale somatic and autonomic responses to pain. The main projection of the nociceptive component of the spinoreticular tract is to the nucleus gigantocellularis in which (in the rat) nearly all cells respond to noxious stimuli (Benjamin, 1970). Neurons in the nucleus gigantocellularis project principally to the centrum medianum and parafascicular thalamic nuclei, which are a major source of projections to the striatum (Guilbaud, 1985). Thus, nociceptive stimuli can gain access to the basal ganglia.

There also is direct experimental evidence that peripheral injury can alter basal ganglia chemistry. De Ceballos and colleagues (1986) found that a thermal injury to one hind limb in the rat causes early (24 hours) bilateral reduction of leu-enkephalin immunoreactivity in the globus pallidus, and later (1 week) bilateral (but most marked contralaterally) reduction of both met-enkephalin and leu-enkephalin immunoreactivity in globus pallidus and of met-enkephalin immunoreactivity in caudate and putamen. These late changes in basal ganglia enkephalin content may reflect alterations in basal ganglia function that conceivably may be responsible for peripheral trauma precipitating dystonia in genetically susceptible individuals.

Whether or not the basal ganglia are involved, peripheral injury certainly can lead to CNS plastic changes (Hallett, 1999; Navarro et al., 2007; Davis et al., 2011; Quartarone and Hallett, 2013), and some of these might be directly pathologic or interact with other factors to cause dystonia.

Muscle spasms associated with complex regional pain syndrome

This situation is one step more complex than the last topic, in that there are now muscle spasms associated with complex regional pain syndrome (CRPS) in addition to dystonia or other movement disorder. CRPS is a complex syndrome characterized by a posttraumatic pain syndrome including allodynia, hyperalgesia, edema, and autonomic dysregulation (Borchers and Gershwin, 2014; Bussa et al., 2015). There are a variety of formal criteria for its diagnosis; the Budapest Research Criteria are noted here (Table 26.6). CRPS I is what has been called reflex sympathetic dystrophy, and CRPS II is what has been called causalgia. They are similar except for overt nerve injury in CRPS II. In 1984, five patients were described who developed abnormal involuntary movements

Table 26.6 The Harden/Bruehl criteria for complex regional pain syndrome (CRPS) that with minor modifications have become the Budapest Research Criteria.

1. Continuing pain disproportionate to any inciting event
2. Must report at least one symptom in each of the four following categories.

Sensory: Report of hyperesthesia

Vasomotor: Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry

Sudomotor/edema: Reports of edema and/or sweating changes and/or sweating asymmetry

Motor/trophic: Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

3. Must display at least one sign in two or more of the following categories:

Sensory: Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch)

Vasomotor: Evidence of temperature asymmetry and/or skin color changes and/or asymmetry

Sudomotor/edema: Evidence of edema and/or sweating changes and/or sweating asymmetry

Motor/trophic: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

4. There must be no other diagnosis that better explains the signs and symptoms.

From Borchers AT, Gershwin ME. Complex regional pain syndrome: A comprehensive and critical review. *Autoimmunity Rev.* 2014;13:242–265, with permission.

of a limb after injury (Marsden et al., 1984). All developed “reflex sympathetic dystrophy” and then abnormal muscle spasms or jerks of the affected limb, lasting years. Two exhibited myoclonic jerks of the injured leg, and one had both jerks and more prolonged muscle spasms of the injured foot; the remaining two patients developed more complex dystonic spasms of the injured arm. All had severe persistent pain in the damaged limb and the vasomotor, sudomotor, and trophic changes typical of CRPS. Jankovic and van der Linden (Jankovic and Van der Linden, 1988), Robberecht and colleagues (1988) and Schwartzman and Kerrigan (1990) also have drawn attention to a variety of involuntary movements associated both with CRPS I and CRPS II. These include fixed abnormal dystonic postures as a result of sustained muscle spasms and tremor. Schwartzman and Kerrigan (1990) collected 43 patients with “dystonia,” spasms, or tremor from 200 cases of CRPS. Another large series has been published by van Rijn and colleagues (2007).

Bhatia and colleagues (1993) reviewed 18 patients with CRPS and dystonia, triggered by injury (usually trivial) in 15, and occurring spontaneously in 3 cases, calling this the causalgia-dystonia syndrome. Most were young women. All had the typical burning causalgic pain with hyperpathia and allodynia, along with the vasomotor, sudomotor, and trophic changes in skin, subcutaneous tissue, and bone, typical of CRPS. All these patients developed deforming and often grotesque dystonic postures in the affected limb (the arm in 6, the leg in 12 cases), coincident with or after the CRPS. The dystonic spasms typically were sustained, producing a fixed dystonic posture, in contrast to the mobile spasms characteristic of primary torsion dystonia. Both the dystonia and the

CRPS spread to affect other limbs in 7 patients. All investigations were normal, and all modes of conventional treatment failed to relieve either the pain or the dystonia, but two patients recovered spontaneously. Thus, there appeared to be a relationship among causalgia, CRPS, and a variety of involuntary movements, all precipitated by peripheral injury.

The classic clinical features of CRPS are nicely reviewed (Borchers and Gershwin, 2014). The mechanisms responsible for CRPS have been the subject of much study and speculation but are still not certain (Maihofner et al., 2010). One view is that some persisting peripheral abnormality must be responsible, such as a small fiber neuropathy (Oaklander and Fields, 2009). Others think that this is an inadequate explanation and that altered central mechanisms, triggered by peripheral trauma, are most important (Birklein and Schlereth, 2015; Birklein et al., 2015). There is strong evidence that peripheral nerve injury can give rise to plastic changes at multiple levels of the CNS (Davis et al., 2011; Blom et al., 2014). How this relates to CRPS, however, is not clear.

It is important to note that the whole issue of CRPS is muddled in controversy. Certainly, the early notion of a primary sympathetic dysfunction seems unlikely. This whole area has been marked by anecdotal reports and poor science. The view opposing reflex sympathetic dystrophy has been eloquently stated by Ochoa (Ochoa, 1995, 1999; Ochoa and Verdugo, 1995). Many patients with this syndrome have significant psychiatric disease and many of the movement disorders appear to be psychogenic. Verdugo and Ochoa (2000) prospectively studied 58 patients with CRPS I or II and a movement disorder. The patients exhibited various combinations of dystonic spasms, coarse postural or action tremor, irregular jerks, and choreiform movements. No case of CRPS II but only cases of CRPS type I displayed abnormal movements. In addition to an absence of evidence of structural nerve, spinal cord, or intracranial damage, all CRPS I patients with abnormal movements typically exhibited pseudoneurologic (nonorganic) signs. In some cases, malingering was documented by secret surveillance. A detailed psychological investigation was carried out in a group of patients with CRPS I patients with dystonia (Reedijk, van Rijn, Roelofs et al., 2008). Compared with patients with conversion disorder and affective disorder, the CRPS I and dystonia group had elevated scores on somatoform dissociation, traumatic experiences, general psychopathologic findings but lower scores on some other scales.

Schrag and associates (Schrag et al., 2004) reported a large series of 103 patients with fixed dystonia. Most patients were female (84%) and had a mean age of onset of 29.7 years. A peripheral injury preceded onset in 63%, and spread of dystonia to other body regions occurred in 56%. Pain was present in most patients and was a major complaint in 41%, and 20% had CRPS. No consistent investigational abnormalities were found, and 37% of patients fulfilled classification criteria for documented or clinically established psychogenic dystonia, 29% fulfilled criteria for somatization disorder, and 24% fulfilled both. However, 10% of the prospectively studied and 45% of the retrospectively studied patients did not have any evidence of psychogenic dystonia. Treatment was largely unsuccessful. Some of these patients were followed up after a mean of 7.6 years. About 23% improved and 31% worsened, and there continued to be high rates of neuropsychiatric features (Ibrahim et al., 2009).

Table 26.7 Clinical features of different etiologic types of dystonia

Clinical feature	Idiopathic focal or genetic dystonia	Trauma-Induced "dystonia"	CRPS dystonia	Psychogenic dystonia
Associated pain	Occasional	Common	Severe	Common
Fixed postures	Rare	Common	Common	Common
Muscle hypertrophy	Not uncommon, particularly cervical	Uncommon	Uncommon	Uncommon
Sensory tricks	Common	Rare	Rare	Rare
Onset of symptoms	Slow	Abrupt	Abrupt to subacute	Abrupt to subacute
Response to treatment	Good for focal dystonia ^{*,†} ; moderate for genetic dystonia ^{†,‡}	Poor [*]	Poor [*]	Poor [‡]

CRPS, Complex region pain syndrome.
^{*}Treatment with botulinum toxin.
[†]Treatment with anticholinergics, dopaminergic therapy, deep brain stimulation.
[‡]Psychological treatment and rehabilitation.
 From Hawley JS, Weiner WJ. Psychogenic dystonia and peripheral trauma. *Neurology*. 2011;77:496–502, with permission.

Controversies continue. Reports of dystonia in the setting of CRPS appear (Oaklander, 2004; Oaklander and Fields, 2009) and are challenged (Morgan et al., 2005; Reich and Weiner, 2005; Lang and Chen, 2010). A large systematic review of 133 publications and 713 patients of peripheral trauma and movement disorders, in whom more than one-third had CRPS, concluded that some patients had psychogenic and some organic conditions (van Rooijen et al., 2011). Hawley and Weiner (2011) have pointed out that trauma-induced dystonia, CRPS dystonia, and psychogenic dystonia are all very similar and differ from idiopathic focal or genetic dystonia (Table 26.7).

Abnormalities in clinical neurophysiologic testing have been found by one group (van de Beek et al., 2002), but another study reported that changes are not dissimilar to findings that are seen in normal individuals mimicking an abnormal posture (Koelman, Hilgevoord, Bour et al., 1999). In a physiologic analysis of myoclonus in CRPS, EMG burst lengths ranged from 25 to 240 ms, and in two patients there was coherence between the EMG on the two sides of the body (Munts et al., 2008). These elements are consistent with a psychogenic origin (Lang et al., 2009). A study of

cortical plasticity in patients with CRPS and fixed posture of the hand showed no difference from normal, also suggesting a psychogenic origin, because patients with dystonia have increased plasticity (Morgante, 2017).

The treatment of this disorder is very difficult. The approach to CRPS that is generally accepted includes physical rehabilitation, desensitization, graded motor imagery, and functional restoration (Galve Villa, 2016, 2019). There are reports that intrathecal baclofen can be efficacious (van Hilten et al., 2000; van Rijn et al., 2009). Botulinum toxin can help, including reduction of pain (Kharkar et al., 2011). Recently deep brain stimulation has been reported to be an effective treatment in posttraumatic dystonia in five patients, but this needs confirmation in a larger controlled study (Li, 2019). Of course, if the disorder is psychogenic, a psychiatric approach would be appropriate.

The bottom line when there are patients with CRPS and dystonia is to be careful and thoughtful.

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Functional (psychogenic) movement disorders: Phenomenology, diagnosis, and treatment

Chapter contents

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Introduction

The terminology for functional movement disorders (FMDs) has changed over the years. Originally called hysteria, Freud called them conversion disorders based on his view of the cause. In recent years, the term *psychogenic movement disorder (PMD)* was most common, based on the idea that they are caused by psychological factors rather than by an organic cause. *Psychogenic* was the preferred term in the second edition of this book. Another term used was medically unexplained symptoms (MUS), which was a diagnosis made (rather unfortunately) when no known neurologic disorder could be identified. Most recently, there has been a shift to the use of functional movement disorder (Edwards et al., 2014). This is based on the idea that the disorder arises from a dysfunction of the brain that is structurally normal, and that the cause is multifactorial and might not necessarily be psychological. Additionally, patients seem more receptive to functional rather than psychogenic, and it is critical to get them to accept the diagnosis for therapy to be successful.

Commonly, FMD is contrasted with “organic disorders,” which was already done in the first paragraph. This would make FMD “nonorganic.” Because, as will be discussed later, there are some anatomic and physiologic changes in the patients, this is not really a fully appropriate distinction. However, no alternative terminology is available. Although perhaps better to just say FMD versus “other” neurologic disorders, we will continue to use organic as shorthand in order to be easily understood.

FMD is the movement disorder variety of functional neurologic disorder (FND) (Espay et al., 2018; Perez DL et al., 2020; Thenganatt and Jankovic, 2019; Perez DL, 2021). Functional disorders are common in all fields of neurology, and, for that matter, in all fields of medicine. FMD can be defined

as “a movement disorder caused by a brain network dysfunction that does not exclude the possibility of normal function, sometimes due in part to a psychological cause, and not explained by other neurologic pathology that may or may not be present.” Most neurologic disorders lead to network dysfunction; thus, it is only with FMD that function can be normal without medication or other medical intervention.

In the current psychiatric classification *Diagnostic and Statistical Manual of Mental Disorders (DSM) V*, FMD falls into the category of “somatic symptom and related disorders” and is listed as “Conversion disorder (functional neurologic symptom disorder).” This is characterized as follows:

- Symptoms or deficits are present that affect voluntary motor or sensory function
- Evidence of internal inconsistency or incongruity with recognized neurologic or medical disease.
- The symptom or deficit is not better explained by another recognized medical or DSM disorder.
- The symptom or deficit is associated with clinically significant distress or impairment in social, occupational, or other important areas of function or warrants medical evaluation.

There have been two books on FMDs (Hallett et al., 2006, 2011) and one book on FNDs (Hallett et al., 2016). After many years of neglect (Hallett, 2006), the field is now growing rapidly, with an increasing number of publications (Hallett, 2019). There is now also a society focusing on FND, the Functional Neurologic Disorder Society.

Differential psychiatric diagnosis

“Somatic symptom and related disorders” also includes factitious disorder; this is defined as when the physical symptoms

are *intentionally produced* (hence are under voluntary control) owing to psychological need. This group includes Munchausen syndrome. Factitious disorders are due to a mental disorder. They are generally associated with severe dependent, masochistic, or antisocial personality disorders.

Malingering is in the differential diagnosis but is not considered to be a mental disorder. It refers to *voluntarily produced* physical symptoms in pursuit of a goal such as financial compensation, avoidance of school or work, evasion of criminal prosecution, or acquisition of drugs. It is similar to factitious disorder in that it is voluntary rather than involuntary, but the person has no mental disorder.

When a physician is faced with a patient who has an apparent FMD, it is often not possible to distinguish with certainty among functional (conversion), factitious, and malingering disorders (Bass and Wade, 2019). A patient's volitional intent is often impossible to determine with certainty. Normal function when the patient does not think he or she is being observed will make a diagnosis of factitious disorder or malingering. Doctors sometimes make this observation by chance; lawyers might be employed in some situations for secret surveillance (Kurlan et al., 1997).

Frequency

Movement disorder specialists appear to be seeing increasing numbers of patients with FMD, although this may be just a matter of recognition. Bradykinetic disorders, given the large number of patients with parkinsonism, are less likely than hyperkinetic ones to be functional unless one were to consider the phenomenon of deliberate slowness to be a bradykinetic disorder. Although deliberate slowness is common in FMD, it is not usually the dominant feature, but when it is pure and without accompanying abnormal movements, it is considered in the category of functional parkinsonism. Fixed postures, characteristic of functional dystonia, are also common.

Functional disorders in neurology are estimated to be approximately 6% of neurology outpatient visits with a putative community incidence rate of 4 to 12 per 100,000 per year (Carson and Lehn, 2016). In a large study of 3781 new patients referred to neurology clinics in Scotland, 16% had functional or psychological symptoms and 5.5% had FND (Stone et al., 2010).

Functional disorders are present at virtually all ages and can affect persons of all socioeconomic classes and amount of education. For likely many reasons, women are affected three time more than men (Stone et al., 2009). One factor is that women are more likely to have sexual abuse than men, and there is an association between sexual abuse and functional movement disorders in women (odds ratio, 4.821), but not men (Kletenik et al., 2020).

Like other subspecialties in neurology, functional patients are not uncommon. In one large movement disorder clinic, such patients account for 10% of all nonparkinsonian new patient visits (Portera-Cailliau et al., 2006). Typically, patients are diagnosed by the predominant movement feature (e.g., functional tremor, functional dystonia, functional myoclonus, etc.). When evaluated this way, tremor was the most common functional phenomenology, followed by dystonia. In a review of 321 successive patients in a movement disorder clinic in Korea, 31 (10%) had an FMD (Park, 2018).

There were 27 females and 4 males, and tremor was the most common phenotype.

Neurologists usually and appropriately recognize patients with FMD, but the patients often do not accept this diagnosis and seek other opinions, going from physician to physician, seeking a diagnosis that is more to their liking. Therefore, a strategy is necessary for the best way to inform the patients of the diagnosis. This issue is discussed later in this chapter. Another common situation is that many neurologists do not offer the time-consuming care that is necessary to restore such patients to normality, preferring instead merely to diagnose the condition and have the referring physician or a psychiatrist deal with treatment.

Importance of an accurate diagnosis

The diagnosis of an FMD requires making a positive diagnosis that the movements are functional and not the result of an organic illness (Barbey and Aybek, 2017). The identification of a psychiatric disorder or the psychodynamics that could explain the cause of the abnormal movements is not necessary but can be helpful. It is critical to recognize that patients with organic illness may also have psychiatric disorders, so overemphasis of psychiatric features can be misleading. Deciding between abnormal movements with a functional cause and an organic one can be difficult. Never having seen strange movements before and pronouncing them to be functional therefore is not a satisfactory method because not even senior movement disorder specialists have seen the whole gamut of organic abnormal movements. An organic cause of the movements needs to be excluded. But this alone is insufficient; making a diagnosis of a functional disorder depends on finding positive criteria and not simply failing to find an organic cause (for historical review, see Fahn, 2006a).

An accurate diagnosis of an FMD is often one of the most difficult tasks there is in the movement disorder specialty. It is important to be correct in the diagnosis because only then can the appropriate therapy be initiated. The results of an incorrect diagnosis are detrimental. If a patient has a functional disorder that is misdiagnosed, the patient will be given inappropriate and potentially harmful medication and is also denied the proper treatment to overcome the disabling symptoms. By postponing the appropriate treatment, the cycle of disability is perpetuated. Untreated patients with FMD are at risk for becoming career invalids with chronic disability.

If the obverse occurs—that is, if a patient is given a diagnosis of FMD when, in fact, he or she suffers from an organic one—again the wrong treatment is given. In this situation, patients might be directed to inappropriate psychiatric treatments. Moreover, a diagnosis of a functional disorder can create emotional trauma for the patient and his or her family. It is important to point out that no matter how much experience a clinician has had, encountering a new type of movement disorder for the first time does not automatically make this an FMD. For example, task-specific jaw tremor (Miles et al., 1997) is rare, and even when it is encountered for the first time, a wise clinician should consider it to be organic (Video 27.1) and not functional (Video 27.2).▶

Neurologic symptoms and signs are a common result in functional disorders, and neurologists have long been fascinated by the brain's ability to be able to produce such clinical expressions on the basis of psychological (or other) disturbances.

Video 27.1 Task-specific jaw tremor.

Video 27.2 Head shaking.

Many great neurologists, such as Charcot and Freud, intensively studied conversion reactions, using hypnosis as a tool in their investigations and treatment (Goetz, 1987). In their training, neurologists are taught to differentiate the clinical findings of functional cause from those of organic. However, textbooks in the past often considered some dyskinesias, recognized today as organic, such as tics, writer's cramp and other occupational cramps, and some other forms of dystonia, to be examples of functional disorders. As medicine advances, we hope we can make more accurate diagnoses.

Although in the great majority of patients with an FMD all their clinical features result from the same cause, some may have the FMD on top of an organic movement disorder. Early reports of this, for example, are Patient 5 in the series of functional dystonias reported by Fahn and Williams (1988) and the cases of Ranawaya and colleagues (1990). Perhaps 10% to 15% of patients with an FMD have an underlying organic movement disorder as well. This overlap is also seen in patients with functional seizures; 10% to 37% of patients have organic seizures as well (Krumholz and Niedermeyer, 1983; Lesser et al., 1983).

Perhaps the movement disorders with the highest prevalence rate of a functional origin are the nonfamilial, "idiopathic," paroxysmal nonkinesigenic dyskinesias, as surveyed by Bressman and colleagues (1988). They found that of 18 patients with paroxysmal nonkinesigenic dystonias and with no known symptomatic cause or positive family history for a paroxysmal dyskinesia, the dystonias were due to functional causes in 11 patients, representing 61% of patients. The age at onset in these patients ranged from 11 to 49 years; 8 of the 11 patients were female. Thus, unless accompanied by a clear-cut family history, these paroxysmal dystonias are commonly functional, and their diagnosis is extremely difficult to make for reasons that are explained later in the chapter.

Kotagal and colleagues (2002) conducted a study of paroxysmal events in children. Over a 6-year period, 883 patients were monitored in their pediatric epilepsy monitoring unit; 134 patients (15.2%) were documented to have paroxysmal nonepileptic events. Children in the preschool group (age: 2 months to 5 years) ($n = 26$) were eventually diagnosed with stereotypies, hypnic jerks, parasomnias, and Sandifer syndrome. The school-age group (age: 5–12 years) ($n = 61$) had diagnoses of functional seizures, inattention or daydreaming, stereotypies, hypnic jerks, and paroxysmal dyskinesias. The adolescent group (age: 12–18 years) ($n = 48$) had a diagnosis of functional seizures in 40 patients (83%). The authors concluded that in patients with paroxysmal nonepileptic events, conversion disorder was seen in children older than 5 years of age, and its frequency increased with age, becoming the most common type of paroxysmal nonepileptic events among adolescents. In adolescents, conversion disorder was more common in females, whereas males predominated in the school-age group. Concomitant epilepsy with nonepileptic events occurred in all three age groups to a varying extent.

Mass hysteria or mass psychogenic illness

Neurologists encounter mostly individual patients with FMD. However, historically, mass hysteria was common, probably more so than it is today. Mass hysteria still occurs, such as "shell shock" in wartime, and during current environmental events such as mass inoculations (Kharabsheh et al., 2001; Khien et al., 2003). Symptoms also can be generated from

mass concerns about medications and breast implants, in part owing to widespread publicity, although legal liability issues may also drive the development of symptoms. Mass hysteria resembling seizures occurred in 10 high school girls after the development of organic absence seizures in another student (Roach and Langley, 2004). Another similar event mainly in high school girls was characterized by movements resembling tics (Mink, 2013).

It is interesting to note on a historical level that the term *chorea*, meaning dancing in Latin, comes from the dancing mania (a mass hysteria) that was seen in the Middle Ages, and from which the term *St. Vitus dance* was coined; this term subsequently was applied by Sydenham to describe the condition now referred to as *Sydenham chorea*. For further information on this topic, there is a monograph devoted to hysteria (Halligan et al., 2001).

Physiologic basis for functional neurologic disorders

Understanding FND, like any illness, requires understanding of both cause and pathophysiologic features. The cause relates to the root sources, and the pathophysiologic processes relate to the genesis of the symptoms. The etiologic factors of FMD lead to changes in the brain that lead to the dysfunctional circuitry that produces the symptoms. There is progress in understanding both cause and pathophysiologic features of FMD.

The cause of FMD seems best explained with the biopsychosocial model (Hallett, 2018). This model is multifactorial, including biologic factors, psychological issues, and social situation, all three of which interact with each other. For example, persons with different underlying biology from genetic differences may react to a social situation differently and only in some circumstances lead to a psychiatric disorder. A genetic polymorphism has been identified that is more frequent in patients than controls in the TPH2 gene which is relevant in the metabolism of serotonin (Spagnolo et al., 2020). Different persons will develop different amounts of stress and anxiety in the same situation. The biopsychosocial model should be interpreted that each person will have different relevant factors in different proportions.

What we know is that patients with FMD have more depression and anxiety than nonaffected persons (Kranick et al., 2011). Additionally, the patients report more childhood trauma—physical, sexual, and psychological—compared with normal subjects (Ludwig et al., 2018). In one study of 64 patients compared with healthy volunteers and patients with a disease control, focal hand dystonia, the FMD patients had higher rates of total childhood trauma, greater fear associated with traumatic events, and a greater number of traumatic episodes (Kranick et al., 2011). Emotional abuse, physical neglect, fear with traumatic events, and the number of traumas were significant also after covarying for depression.

Early life stress, even stress of the mother when the child is in utero, can lead to problematic changes. Increased cortisol levels can lead to shrinkage of the hippocampus and epigenetic changes of specific genes that then predispose to psychiatric abnormalities (Ehlert, 2013; Alexander et al., 2018). Current stress is often thought to be a factor in the precipitation and maintenance of an FMD. Although patients often deny it, stress is often evident, although it must be noted that stress is common in today's world. An objective measure

of current stress is the 24-hour cortisol levels. In one study of 33 patients and matched controls with salivary cortisol levels at five times during the diurnal cycle, there was no difference between groups (Maurer et al., 2015). Thus, there was no objective evidence of higher amounts of stress in the patients. Stress may well play a role in some patients, but it might be the reaction to the stress rather than the “objective” amount of stress. This result also raises caution for neurologists to not insist that stress is a problem for the patient (particularly if the patient does not agree).

There is some evidence for a difficulty in dealing with stress. Heart rate monitoring for 14 to 24 hours revealed decreased root mean square of successive differences between adjacent NN intervals (Maurer, Liu, et al., 2016). This is indicative of deficient vagal tone, which correlates with impaired ability of the individual to adapt appropriately to environmental demands.

Neuroimaging studies of brain structure in patients reveal subtle anatomic abnormalities (Baizabal-Carvallo, Hallett et al., 2019; Roelofs et al., 2019). These would not be apparent in individual patients but show up as significant group differences. For example, in one study on 48 patients with clinically definite FMDs compared with 55 age- and sex-matched healthy controls, group differences in gray matter volume using voxel-based morphometry was studied (Maurer et al., 2018). Patients with FMD exhibited increased volume of the left amygdala, left striatum, left cerebellum, left fusiform gyrus, bilateral thalamus, and decreased volume of the left sensorimotor cortex.

Another social factor is secondary gain, and this is often noted in the patients’ situations. Sometimes it certainly seems that getting better from the disorder will put the person into a worse social situation, and this would reduce the motivation for getting well.

As to the pathophysiologic process, there are two main features to explain: (1) what is the genesis of the movements (or paresis or slowness) and (2) why are the movements experienced as involuntary. It is intellectually intriguing that the brain can create neurologic deficits—such as paralysis, sensory loss, blindness, seizures, and movement disorders—from psychological factors. This mysterious ability fascinated pioneers working on hysteria, such as Charcot and Freud. These issues are now being carefully investigated with clinical neurophysiologic testing and neuroimaging.

Analyzing functional myoclonus with clinical neurophysiology, the jerk-like movements are essentially identical to quick voluntary movements (Hallett, 2010; Baizabal-Carvallo, Hallett et al., 2019). The electromyographic (EMG) pattern is characteristic and quite different from most organic myoclonias such as posthypoxic myoclonus. Moreover, the movement is preceded in the electroencephalogram (EEG) by a slow potential called the Bereitschaftspotential, first described with voluntary movement and indicating preparatory activity in the premotor cortex and the supplementary motor area (SMA). Sensory evoked functional myoclonus behaves like voluntary reaction time movements. Functional tremor, with EMG, looks like voluntary repetitive movements, and like voluntary movements, the tremor can be affected by movements of another body part. For example, the frequency of the tremor can be entrained to the voluntary frequency. Such clinical neurophysiologic observations not

only make clear the physiologic features, they also have been used diagnostically to identify or confirm that a movement is functional.

Neuroimaging studies show significant abnormalities of brain function in these patients (Aybek and Vuilleumier, 2016; Baizabal-Carvallo, Hallett et al., 2019; Roelofs et al., 2019; Demartini et al., 2020; Drane et al., 2020). An early observation was a study of brain activation in patients with functional tremor, comparing their involuntary tremor with a voluntary mimicking of the tremor. The most prominent abnormality was a decrease of activation of the temporoparietal junction (TPJ) during the involuntary tremor (Voon, Gallea et al., 2010). This observation seemed to explain the sense of involuntariness, because the TPJ is a relevant region generating the sense of self-agency for movement (Nahab et al., 2011). This finding has been supported by other studies. A resting state functional magnetic resonance imaging (fMRI) study of 35 patients compared with healthy volunteers showed decreased functional connectivity between the right TPJ and the right sensorimotor cortex, cerebellar vermis, bilateral SMA, and right insula (Maurer, LaFaver, et al., 2016). Abnormal functioning of the TPJ and its related network was also shown with voluntary movements with experimenter externally varying the amount of agency (Nahab et al., 2017). Other evidence for a decrease in agency even with voluntary movements is that patients have decreased action-effect binding (Kranick et al., 2013). Specifically, the subjective times of button press and resultant tone did not move as much closer together for patients as it did for healthy volunteers.

There is also evidence for overactivity of the limbic system in these patients, with increased connection to the motor system. Two studies have shown increased amygdala response to emotional faces with increased activity or connection to the SMA (Voon, Brezing et al., 2010; Aybek et al., 2015). With motor preparation, there was greater activity in the amygdala in patients than matched controls (Voon, Brezing et al., 2011). Another study of 10 patients with matched controls looked at the ability to maintain a constant grip force while viewing emotional images (Blakemore et al., 2016). Normal subjects reduced force with unpleasant images, but patients preserved the force, perhaps indicating an effect of negative affect on movement. During this task, patients had greater activity in a cerebellar-limbic network than controls. The startle response was studied in 17 patients and 15 matched controls (Dreissen et al., 2017). The startle response was similar in form but had increased amplitude in patients. The startle response is under control of the amygdala, and, therefore, the result is compatible with increased limbic activity. Other studies show abnormal activation of the ventromedial prefrontal cortex (Aybek and Vuilleumier, 2016) and the anterior and midcingulate cortex (Ospina et al., 2019) giving more evidence for limbic abnormality.

The picture is far from complete, but the evidence is accumulating for aberrant movement generation from an overactive limbic system and a failure of the network for self-agency. Because there is not much evidence for any abnormality of feedback (sensory processing) in the patients, a failure of self-agency would likely derive from an abnormal feedforward signal. If the limbic system is indeed triggering movement in an abnormal fashion, there might not be a proper feedforward signal.

Degree of certainty of the diagnosis of a functional movement disorder

Fahn and Williams (1988) categorized patients into four levels of certainty as to the likelihood of their having “psychogenic dystonia”; these categories can be applied to all FMDs. These four degrees of certainty are: (1) documented, (2) clinically established, (3) probable, and (4) possible. Here the criteria have been expanded somewhat, taking into account additional observations since the original publication.

Documented functional movement disorder

Just being suspicious that the signs and symptoms are functional is insufficient for the diagnosis of documented FMD. For the disorder to be documented, the symptoms must be completely relieved by psychotherapy; by the clinician using psychological suggestion, including physiotherapy; or by administration of placebos (again with suggestion being a part of this approach). If the signs and symptoms disappear and do not return, that is fairly good evidence that the underlying psychiatric problem has been relieved. But it is not uncommon for the movement disorder to return if the patient does not obtain complete relief of the psychiatric factors.

A critical issue for using the relief of signs as a criterion for the definition is that most organic movement disorders rarely remit spontaneously and completely except for tics, tardive dyskinesia, infectious (e.g., Sydenham chorea), and drug-induced reactions. Other organic disorders, such as Parkinson disease (PD), Huntington disease (HD), and essential tremor, are persistent and even progressive. Isolated dystonia, except for cervical dystonia (**Jahanshahi et al., 1990**), rarely totally remits. On occasion, patients with other types of dystonia will show improvement, but this improvement is typically incomplete and temporary.

The degree of remission that is seen in cases with documented FMDs is usually the dramatic, sudden improvement that occurs within a few days with supportive suggestion or placebo treatment. In a few patients with more chronic symptoms, improvement can be more gradual, occurring over weeks to months of “physiotherapy.” Physiotherapy also can have physical benefits for patients who had developed weakness, spasms, or contractures based on chronic disuse and/or abnormal postures for extended periods, even though these were on a functional basis.

Clinically established functional movement disorder

When the movement disorder is inconsistent over time (the features are different when the patient is observed at subsequent examinations) or is incongruent with a classic movement disorder, one becomes suspicious that the movements are functional. If either inconsistency or incongruity is present, and in addition the patient has any of the manifestations listed in **Table 27.1**, one can feel comfortable in believing that the disorder is functional, and this has been referred to as clinically established FMD.

It should be noted that item 4 in **Table 27.1** (disappearance with distraction) by itself is insufficient for a diagnosis

Table 27.1 Additional manifestations besides inconsistency and incongruity for the diagnosis of clinically established functional movement disorder

1. Other neurologic signs are present that are definitely functional (e.g., false weakness, false sensory findings, and self-inflicted injuries)
2. Multiple somatizations are present
3. An obvious psychiatric disturbance is present
4. The movement disorder disappears with distraction
5. Excessive (appearing deliberate) slowness of movement is present
6. Excessive fatigue that is incompatible with the amount of motor activity.
7. The electrophysiologic analysis of the phenomenology of myoclonus or tremor does not fit with the organic pattern in these phenomenologies

of a documented or clinically established functional disorder. This is because some organic movement disorders can be temporarily and voluntarily suppressed. Similarly, akathitic movements and paradoxical dystonia (**Fahn, 1989**) also tend to disappear with active voluntary movement. The difficulty establishing functional paroxysmal dyskinesias that have a normal interictal pattern is covered later. Fortunately, myoclonus has such a short-duration contraction that it cannot be purposely produced, so electrophysiologic evidence against organic myoclonus could be one of the factors along with inconsistency and incongruity that can lead to a clinically established diagnosis of a functional myoclonus. Functional tremors have features such as a change in tremor frequency caused by entrainment by tapping the contralateral limb. These features would establish the tremor as functional.

Probable psychogenic movement disorder

The definition of probably psychogenic movement disorder contains the following four categories of patients:

1. Patients in whom the movements are inconsistent or are incongruent with any classic movement disorder, but there are no other features to provide further support for the diagnosis.
2. Patients in whom the movements are consistent and congruent with an organic disorder, and the movements can be made to disappear with distraction, when ordinarily distraction would not be expected to eliminate the movements if they were organic.
3. Patients in whom the movements are consistent and congruent with an organic disorder, but other neurologic signs are present that are definitely functional (e.g., false weakness, false sensory findings, or self-inflicted injuries).
4. Patients in whom the movements are consistent and congruent with an organic disorder, but multiple somatizations are present.

The last two subdivisions contain psychiatric manifestations that make the clinician highly suspicious that the movements also might be functional, but by themselves they are insufficient to give a higher degree of certainty to the diagnosis of an FMD.

Possible psychogenic movement disorder

One can be suspicious that the movements are psychogenic if an obvious emotional disturbance is present, but this is not as compelling as the psychiatric features listed earlier. For the category of a possible functional disorder, the movements would be consistent and congruent with those of an organic movement disorder.

Summary on the degree of certainty of the diagnosis of a functional paroxysmal movement disorder

Paroxysmal movement disorders present a special and difficult problem. Their natural history characteristically shows prolonged periods of cessation of the abnormal movements, so its disappearance with placebo or by suggestion cannot by itself establish the diagnosis of a functional disorder, because the remission could have been coincidental. However, if the paroxysms are frequent and the attacks are prolonged, repeated trials with placebo can be informative. If such trials consistently produce remissions, one can be convinced that the diagnosis is a documented functional disorder.

The criteria for clinically established, probable, and possible FMDs would be the same for paroxysmal movement disorders and continual movement disorders. It is likely when both a paroxysmal movement disorder and a continual movement disorder are present in the same patient that the cause is functional.

Updates to classification of degree of certainty

Fahn and colleagues (Williams et al., 1995) modified the classification to combine Documented and Clinically Established into Clinically Definite. Gupta and Lang (2009) suggested a further modification, dropping the probable and possible categories, and adding “laboratory-supported definite,” as follows:

1. Documented (as in original)
- 2a. Clinically established plus other features (as in original)
- 2b. Clinically established minus other features but having unequivocal clinical features incompatible with organic disease with no features suggesting another underlying neurologic or psychiatric problem
- 1+ 2a + 2b. Clinically definite
3. Laboratory-supported definite with electrophysiologic evidence proving a psychogenic movement disorder (primarily in cases of psychogenic tremor and psychogenic myoclonus)

Clues suggesting the presence of a functional movement disorder

Often, there are clues from the history and neurologic examination that lead the clinician to suspect a diagnosis of an FMD. Clues from early publications (Fahn and Williams, 1988; Koller et al., 1989; Factor et al., 1995) are noted in Tables 27.2 and 27.3 and some additional ones from more recent publications (Hallett, 2016; Espay et al., 2018; Perez et al., 2020).

Abrupt onset of the movement disorder is quite common. The presence of more than one type of dyskinesia (item 5

Table 27.2 Clues relating to the movements that suggest a functional movement disorder

1. Abrupt onset
2. Inconsistent movements (changing characteristics over time; pattern, body distribution, rapidly varying severity)
3. Incongruous movements and postures (movements that do not fit with recognized patterns or with normal physiologic patterns)
4. Presence of certain types of abnormal movements that are fairly common among individuals with functional movement disorders, such as:
 - Rhythmical shaking
 - Bizarre gait
 - Deliberate slowness carrying out requested voluntary movement
 - Bursts of verbal gibberish
 - Excessive startle (bizarre movements in response to sudden, unexpected noise or threatening movement)
5. Presence of additional types of abnormal movements that are not known to be part of the primary or principal movement pattern that the patient manifests
6. Manifesting exhaustion, excessive fatigue
7. Delayed, often excessive, startle response to a stimulus
8. Spontaneous remissions
9. Decrease or disappearance of movements with distraction
10. Disappearance of tremors when handling treasured objects
11. Entrainment of the tremor to the rate of the requested rapid successive movement the patient is asked to perform
12. Response to placebo, suggestion, or psychotherapy
13. Manifestation of a paroxysmal disorder
14. Dystonia beginning as a fixed posture
15. Twisting facial movements that move the mouth to one side or the other (note that organic dystonia of the facial muscles usually does not move the mouth sideways)

Table 27.3 Clues relating to other medical observations that suggest a functional movement disorder

1. False (give-way) weakness
2. False sensory complaints
3. Multiple somatizations or undiagnosed conditions
4. Self-inflicted injuries
5. Obvious psychiatric disturbances
6. Employed in the health profession or in health insurance claims
7. Presence of secondary gain, including continuing care by a devoted spouse
8. Litigation or compensation pending

in Table 27.2) is another important clue, often confounding clinicians (Video 27.3). Most of the time, patients with an organic movement disorder present with only a single type. A note of caution is warranted, however. Certain disorders progress to involve more than one type of abnormal movement. For example, HD can have chorea, bradykinesia, dystonia, and myoclonus. Neuroacanthocytosis often is manifested by both chorea and tics. Some patients with childhood-onset tics may later develop torsion dystonia. Often, patients with isolated dystonia will have dystonic tremor or rapid movements that resemble myoclonus or chorea. Patients with tardive dyskinesia may have a combination of rhythmical oral-buccal-lingual movements plus dystonia and akathitic movements. Table 1.17 in Chapter 1 lists the diseases that are composed of multiple types of movement disorders. ▶

Video 27.3 Shaking movements and abnormal postures.

The most common types of movements, whether isolated or in the presence of other types of movements, in patients with FMDs are shaking movements (item 4 in Table 27.2) that can resemble organic tremors or peculiar, atypical tremors (Video 27.4). This was the most common type of abnormal movement in the spectrum of FMDs reported by Lang (2006) and by Jankovic and associates (2006b). Another note of caution about unusual tremors is that Wilson disease can also manifest with unusual tremors. Utterances of gibberish can be another useful sign (Videos 27.5, 27.6).

Item 4 in Table 27.2 also lists bizarre gaits as a clue. After tremors and dystonia, bizarre gait disorders are the next most common type of unusual movement disorder encountered in patients with mixed features of movements. Functional gait can show posturing, excessive slowness, and hesitation. There could be pseudoataxia or careful walking (like walking on ice). The latter resembles the fear-of-falling syndrome, which is discussed in more detail later. There can be sudden buckling of a leg, as if there is weakness, but the failure to produce this dipping movement each time the patient steps on the leg would be evidence of inconsistency. Accompanying this bizarre gait would be a variability of impairment and excessive swaying when tested for the Romberg sign, without falling.

Another aspect of item 4 is excessive startle that could mimic hyperreflexia, excessive startle syndrome, the jumping Frenchmen syndrome (Video 27.7), or even reflex myoclonus. Thompson and colleagues (1992) determined the physiologic parameters that are typically seen in patients with psychogenic startles. There is a variable latency to the onset of the jerk; the latencies are greater than those seen in reflex myoclonus of cortical or brainstem origin; the latencies are longer than the fastest voluntary reaction time; there are variable patterns of muscle recruitment within each jerk; and there is significant habituation with repeated stimulation. This last point is probably not specific to functional startle, because organic startles may also show habituation. Noise stimuli can induce other abnormal movements besides startle. Walters and Hening (1992) reported a case with functional tremor after sudden, loud noise; the patient had a posttraumatic stress disorder.

Item 11 in Table 27.2 points out that in a patient with functional tremor, when asked to carry out rapid successive movements, such as tapping the index finger on the thumb, the rate of the tremor becomes the same as the rapid successive movements (i.e., the tremor has become entrained). In contrast, an organic tremor is the dominant rate; it will gradually force the voluntary movements to be the same rate as the tremor.

Isolated dystonia usually begins with action dystonia, but functional dystonia often begins with a fixed posture. Fixed postures are sustained postures that resist passive movement, and the presence of such fixed postures is highly likely to be due to a functional dystonia (Fahn and Williams, 1988; Lang and Fahn, 1990; Schrag et al., 2004; Schrag, 2006). The posture can manifest so much rigidity that it is extremely difficult to move the limb about a joint (Video 27.8). Often, the functional dystonia resembles complex regional pain syndrome (CRPS, reflex sympathetic dystrophy) because there is accompanying pain, tenderness (allodynia), and skin changes (Lang and Fahn, 1990; Bhatia et al., 1993; Schrag et al., 2004; Schrag, 2006). Nerve injury leading to pain, shiny red skin, and fixed postures was called causalgia by

Mitchell and associates (1864). Charcot (1892) considered the disorder hysterical (see Muntz and Koehler, 2010). The term “reflex sympathetic dystrophy” was coined by Evans (1946) because the phenotype could occur in the absence of trauma to a major nerve and might be due to sympathetic nerves. “Complex regional pain syndrome” became the recommended term in 1994, with type 1 being reflex sympathetic dystrophy and type 2 being causalgia (Merskey and Bogduk, 1994). Whether CRPS is organic or functional is constantly debated.

To make matters confusing, in many cases, functional dystonia of a limb follows a minor trauma to that limb, similar to the pattern of reflex sympathetic dystrophy. On the other hand, organic dystonia of a body part can be preceded by an injury to that body part (Schott, 1985, 1986; Scherokman et al., 1986; Goldman and Ahlskog, 1993), so it can be difficult to distinguish between organic and functional dystonia. Fixed painful postural torticollis after trauma is not uncommon and determining whether it is organic or functional is difficult, but analysis indicates that many of these cases appear to be functional in cause (Sa et al., 2003).

Although a fixed dystonic posture, in which the joint cannot be passively extended or flexed, is often functional, it also could be due to a contracture (which, of course also could be the result of a functional dystonia and an organic dystonia). The evaluation of such fixed postures in which the affected joint cannot be passively altered requires the aid of anesthesia to see if contractures are present (Fahn, 2006b). This technique not only aids the diagnosis but also guides the clinician and patient in what to expect during therapy (Video 27.9). The prognosis of fixed dystonia is often poor (Ibrahim et al., 2009), but it depends on recognizing this disorder as likely to be a functional one and then applying treatment according to the principles described later.

In addition to the clues in the history and examination related to the movements themselves presented in Table 27.2, there are often clues in the nonmovement history and examination that help the clinician consider a functional disorder. These are presented in Table 27.3. A large Italian multicenter study found frequency nonmotor symptoms including anxiety, fatigue, and pain as well as components of other FNDs (Tinazzi et al., 2020).

We have been impressed by the frequency with which patients with FMDs are employed in some capacity working in the health profession (item 6 in Table 27.3). Many are nurses; another large group are employed in the health insurance industry, processing medical claims.

Another point that is worth commenting on is that many of the affected individuals have a devoted spouse who responds readily to their pressing needs (item 7 in Table 27.3). Some spouses carry a pager so that the patient can easily call them while they are at work. Others pamper the patient, who might even be wheelchair bound, especially if the patient has functional dystonia. Such devotion could be a secondary gain from having the movement disorder.

Diagnostic approach and clinical features

FMDs are usually identified on the basis of (1) unusual motor phenomenology and other clues as listed in Tables 27.2 and 27.3 and (2) a discrepancy between the patient's

Video 27.4 Paroxysmal tremor.

Video 27.5 Delayed startle, utterances of gibberish.

Video 27.6 Bent gait, episodes of shaking, startle reaction with gibberish.

Video 27.7 Jumping Frenchman syndrome.

Video 27.8 Dystonic postures that persist in sleep.

Video 27.9 Dystonia with fixed contractures.

Table 27.4 Predominant movement features in functional movement disorders

Predominant movement feature	No.	Percent
Tremor	467	37.5
Dystonia	365	29.3
Myoclonus	146	11.7
Gait disorder	114	9.2
Parkinsonism	60	4.8
Tics	29	2.3
Other	64	5.1
Total	1245	100

A tabulation of functional movement disorders seen at eight centers; most centers report their patients by a single primary motor feature, but some report multiple features if more than one is present.

Data from Lang AE. General overview of psychogenic movement disorders: Epidemiology, diagnosis, and prognosis. In: Hallett M, Fahn S, Jankovic J, et al., eds. *Psychogenic Movement Disorders: Neurology and Neuropsychiatry*. Philadelphia: Lippincott Williams & Wilkins; 2006, pp. 35–41.

disability and objective signs of motor deficit. Whereas the presence of psychiatric abnormalities was considered important in the past, this is not the case now, although, when present, they certainly should be noted (Perez et al., 2020). The neurologist bases the suspected diagnosis on identifying the different types of abnormal movements that are present in a given patient. The type of movement disorder is assigned the basis of the phenomenology, which can consist of more than one type (item 5, Table 27.2). The neurologist must exclude possible organic causes for the abnormal movements so that both the neurologist and the patient feel comfortable that the diagnosis of an FMD has been made with confidence. Then a suggested strategy for treatment is presented to the patient. In fact, explaining to the patient that the condition has the potential for a more favorable outcome with proper treatment than would an organic movement disorder may help the patient more readily accept the diagnosis of a functional cause.

Functional neurologic symptoms are common. About one-third of neurology outpatients receive that diagnosis (Stone et al., 2009). It would appear that neurologists are quite accurate when diagnosing a functional disorder. Of 1144 patients diagnosed as having a functional condition, by 18 months only 0.4% had acquired an organic disease diagnosis that was unexpected at initial assessment and plausibly the cause of the patients' original symptoms (Stone et al., 2009).

The types of functional movements seen in a review of the publications from eight movement disorders centers are presented in Table 27.4. Tremor was found to be the most common functional phenomenology, followed by dystonia. Tics were the least common. Although it is not often emphasized, patients also may have functional speech or voice disorders (Chung et al., 2018).

Williams and colleagues from Columbia (1995) reviewed the records of 131 patients with FMDs and listed their motor phenomenologies (Table 27.5). In their experience, dystonia, tremor, gait disturbances, paroxysmal dyskinesias, and

Table 27.5 Principal motor phenomenology in 131 patients with functional movement disorders

Movements	No.	Percent of organic cases
Dystonia	82	2.5
Tremor	21	
Gait disorder	14	
Myoclonus	11	
Blepharospasm/facial movements	4	
Parkinsonism	3	<0.1
Tics	2	
Stiff person	1	
Paroxysmal and undifferentiated movements	14	

Total for types of movements = 152, because more than one type was equally prominent.

Data from Williams DT, Ford B, Fahn S. Phenomenology and psychopathology related to psychogenic movement disorders. *Adv Neurol*. 1995;65:231–257.

Table 27.6 Phenomenology of functional movements

Phenomenon	Percentage
Single type	21
Multiple types	79
Continuous movements	45
Intermittent/paroxysmal	55
15 patients with hand tremor: dominant hand	93
Abrupt onset (usually inciting event)	60%
Spread from initial site	43

Data from Williams DT, Ford B, Fahn S. Phenomenology and psychopathology related to psychogenic movement disorders. *Adv Neurol*. 1995;65:231–257.

myoclonus were the major motor types that were encountered. The difference from other centers that found tremor to be more common than dystonia may be because the Columbia group labeled movements on a hierarchical scale, whereby if any dystonia is present, regardless of whether other movements such as tremor are also present, the condition was coded as a dystonic one. Williams and colleagues found that 79% of patients had multiple types of abnormal movements and that only 21% had a single definable type (Table 27.6). Moreover, again in contrast with the vast majority of organic movement disorders, in 55% of the patients the movements were either intermittent or paroxysmal, whereas only 45% of the patients had only continuous movements. They also reported that the onset was abrupt in 60% of patients, usually with a specific inciting event. In 43% of patients, the movements spread beyond the initial site of involvement.

Factor and colleagues (1995) reviewed their 28 cases of FMDs. These represented 3.3% of all 842 consecutive movement disorder patients seen over a 6-year period. Tremor was

Table 27.7 Demographics of patients with functional movement disorders**Age at onset**

Range: 4–73 years

Mean: 36.9 years

Sex

Males to females = 22:109

Males = 13%

Females = 87%

Presence of some organic component

13%

Onset to correct diagnosis

Mean: 4.9 years

Trimodal:

<6 mo: 25%

2 y: 40%

23 y: 15%

Data from Williams DT, Ford B, Fahn S. Phenomenology and psychopathology related to psychogenic movement disorders. *Adv Neurol.* 1995;65:231–257.**Table 27.8** Clinical features in patients with functional movement disorders

Clinical features	Percentage
Previously erroneously diagnosed as organic (three with multiple sclerosis despite negative laboratory tests)	75
False weakness	37
False sensory examination results	8.7
Pain and tenderness	17.4
Startle	29
Functional seizures	11.6
Disabled	65
Head trauma	25
Peripheral trauma	12.5

Data from Williams DT, Ford B, Fahn S. Phenomenology and psychopathology related to psychogenic movement disorders. *Adv Neurol.* 1995;65:231–257.

most common (50%), followed by dystonia, myoclonus, and parkinsonism. Clinical clues included distractibility (86%) and abrupt onset (54%). Distractibility was more important in tremor and least important in dystonia. Other diagnostic clues included entrainment of tremor to the frequency of repetitive movements of another limb, fatigue of tremor, stimulus sensitivity, and a previous history of functional illness.

The demographic pattern of the 131 patients reported by Williams and colleagues (1995) is presented in Table 27.7. Of the 131 patients, 87% were females; the mean age at onset was 37 years, with a range of 4 to 73 years. An organic component of a movement disorder was present in 13%. The mean duration before a correct diagnosis was made was 5 years. An organic diagnosis was made originally in 75% of the patients

Table 27.9 Psychiatric aspects of functional movement disorders

Psychiatric aspect	Percentage
Conversion disorder	75
Somatization disorder	12.5
Factitious disorder	8.3
Malingering	4.2
Accompanying	
Depression	71
Anxiety	17
Hypnotizable	
Highly	36
Mild-moderately	41

Data from Williams DT, Ford B, Fahn S. Phenomenology and psychopathology related to psychogenic movement disorders. *Adv Neurol.* 1995;65:231–257.

with an FMD (Table 27.8), including three patients who carried a diagnosis of multiple sclerosis despite the lack of any positive laboratory data detected by the treating neurologist. A number of neurologic findings manifested as clues to the functional nature. The most common was the presence of give-way weakness (37%). Next most common was a startle reaction that was nonphysiologic (29%). Pain and false sensory findings on examination were also encountered (see Table 27.8). Surprisingly, functional seizures were concurrently present in 12% of the patients. The FMD was disabling in 65% of the patients. A preceding history and inciting event of head trauma and peripheral trauma occurred in 25% and 12.5% of patients, respectively.

Williams and colleagues (1995) found that the most common psychiatric diagnosis, using older terminology than that used currently, was a somatoform disorder, particularly a conversion disorder (Table 27.9). Briquet syndrome (somatization disorder) was diagnosed in 12.5%. A few patients were diagnosed with a factitious disorder (8%) or malingering (4%), because those entities were not separated out at that time. An accompanying depression or anxiety was found in 71% and 17% of patients, respectively.

Functional dystonia

It is, in some ways, ironic that isolated dystonia can sometimes be due to a functional cause. From its earliest beginnings, dystonia appeared to have been mistaken as a manifestation of a psychiatric disturbance (Schwalbe, 1908). Soon after Schwalbe's description in 1908 (see English translation by Truong and Fahn, 1988), however, Oppenheim (1911) and Flatau and Sterling (1911) set matters right by emphasizing the organic nature of this disorder. Although some early publications on dystonia mentioned the "functional" nature of the symptoms (Destarac, 1901) or used the label *neurosis* (Ziehen, 1911), these terms were employed in those days in a manner different from today. *Functional* referred to a physiologic activation of the abnormal movements with voluntary motor activity, which would otherwise disappear when the patient was quiet at rest. *Neurosis* was a term that was used to

Table 27.10 Reports on the misdiagnosis of organic dystonia as being functional

Report (y)	Cases (%)
Eldridge et al. (1969)	23/44 (52)
Marsden and Harrison (1974)	18/42 (43)
Cooper et al. (1976)	56/226 (25)
Lesser and Fahn (1978)	37/84 (44)

indicate a neurologic, rather than a psychiatric, disorder but one without a structural lesion. Today, it is common for the term *functional* to be equivalent to *psychogenic* and for *neurosis* not to be used at all in neurology but to refer to a certain type of psychiatric disorder.

Thus, for many decades, the organic nature of dystonia was emphasized. Yet possibly beginning in the 1950s, many patients with various forms of focal, segmental, and generalized dystonia began to be misdiagnosed as having a conversion disorder (Table 27.10). Among 44 patients with idiopathic dystonia reviewed by Eldridge and colleagues (1969), 23 patients (52%) previously had been referred for psychiatric treatment (without benefit). Marsden and Harrison (1974) had a similar experience; 43% of their 42 patients were previously diagnosed as suffering from hysteria. Cooper and colleagues (1976) reviewed their series of 226 patients and found that 56 patients (25%) had a diagnosis of psychogenic cause at some time during their illness. Lesser and Fahn (1978) reviewed the records of 84 patients with idiopathic dystonia seen at Presbyterian Hospital in New York from 1969 to 1974 and found that 37 patients (44%) had previously been given a diagnosis that their movement abnormalities were due to an emotional disorder. These 37 patients consisted of 11 with generalized dystonia, 14 with segmental dystonia, and 19 with focal dystonia (14 with torticollis, 2 with oromandibular dystonia, and 3 with blepharospasm).

Although some authors (Meares, 1971; Tibbets, 1971) suggested that an underlying psychiatric illness might exist in patients with cervical dystonia, others (Zeman and Dyken, 1968; Cockburn, 1971; Riklan et al., 1976) found no differences between dystonic patients and controls in regard to previous psychiatric history and current life adjustment or on psychiatric testing. Similarly, some authors (Crisp and Moldofsky, 1965; Bindman and Tibbets, 1977) considered hand dystonia (writer's cramp, occupational cramp) to be psychogenic. But Sheehy and Marsden (1982) studied 34 patients with writer's or other occupational cramps affecting the hand or arm. All patients underwent assessment by a psychiatric interview technique; these patients compared favorably with a control group, and the investigators concluded that their disorder was not psychiatric in origin. A more recent study involved psychiatric assessment in 20 subjects with focal hand dystonia and also concluded that none had any serious psychopathologic condition (Grafman et al., 1991). Furthermore, patients with writer's cramp do not have increased anxiety (Harrington et al., 1988).

At the time of the first international symposium on dystonia, held in 1975, Fahn and Eldridge (1976) noted that no case of proven psychological dystonia had been reported.

With the realization that patients with dystonia were being misdiagnosed as having a psychiatric disorder, knowledgeable neurologists became sensitive to this problem and, since then, seemed to avoid a diagnosis of hysterical dystonia. However, at the annual meeting of the American Academy of Neurology in 1983, Fahn and colleagues (1983) described 10 patients as having documented psychogenic dystonia, 5 of them identified after the abstract to the meeting was submitted. Batshaw and colleagues (1985) had followed a patient who had been misdiagnosed as having an organic dystonia and who had undergone a stereotactic thalamotomy based on that diagnosis; these authors eventually recognized that their patient had psychogenic dystonia and reported her as a case of Munchausen syndrome. Fahn and Williams (1988) have described 22 cases of documented or clinically established psychogenic dystonia, including a case of a young girl who underwent a stereotactic thalamotomy. Lang (1995) reported on 18 patients with documented or clinically established psychogenic dystonia, 14 of whom had a known precipitant. Involvement of the legs occurred in 12 patients, despite onset in adulthood. Of Lang's patients, 10 had paroxysmal worsening of dystonia or other abnormal movements. Pain was a prominent feature in 14 of 16 patients with this complaint.

Functional dystonia is difficult to diagnose, but there are some laboratory tests that might be helpful. A number of cortical and spinal reflex abnormalities have been reported in organic dystonia, all showing lack of inhibition or spread of cortical field (see Chapter 12). These abnormalities might have been a useful way to differentiate functional dystonia from organic dystonia, but when these tests were applied to both groups to see their differences, the results were similar in the two groups; that is, both groups showed a reduced inhibition (Espay et al., 2006). On the other hand, using a method called "paired associative stimulation," patients with organic dystonia show increased plasticity (Quartarone et al., 2003), and this increase is not seen in functional dystonia (Quartarone et al., 2009). This method might even be used on an individual basis, but it has not yet been reproduced. Another possible clinical neurophysiologic test is the blink reflex that might have utility in dystonias of the cranial region. Tested so far only in functional blepharospasm, the normal inhibition in the blink reflex recovery curve, which is lost in organic blepharospasm, is normal in functional blepharospasm (Schwingsenschuh, Katschnig et al., 2011). This also needs further confirmation.

With or without laboratory analysis, diagnosis depends on clinical skill to differentiate organic and functional dystonia. The clues listed in Tables 27.2 and 27.3 should help alert the clinician to the possibility of a functional cause. Clues that often point to an organic diagnosis, such as a sensory trick (*geste antagoniste*) that mitigates dystonia, can be very helpful, but also occasionally can be misleading (Munhoz and Lang, 2004).

In a survey of 22 patients reported by Fahn (1994) on documented and clinically established cases of functional dystonia, he found that 6 patients had paroxysmal dystonia, and 16 had continual dystonia. Females outnumbered males by a ratio of 20 to 2. The youngest age at onset was 8 years, and the oldest was 58 years. Those with paroxysmal dystonia were, as a general rule, older than patients with continual dystonia.

The presence of joint contractures does not exclude the diagnosis of functional dystonia (Fahn and Williams, 1988;

Ziegler et al., 2008). This feature would require examination under deep anesthesia to determine whether there is an actual contracture (Fahn, 2006b). Knowing this information allows one to calculate the maximum amount of motor improvement that can be expected. Arrangements are made with an anesthesiologist to carry out the evaluation.

Functional tremor

As mentioned previously, rhythmical movements are the most common abnormal movement in patients with functional movements, often appearing as shaking movements and often varying in frequency over time. However, functional tremors can resemble organic tremors. Functional tremor tends to be present equally with the affected limb at rest, with posture holding, and with action (Video 27.10). This helps differentiate it from organic tremors, which typically dominate in just one of these characteristic features. Also, functional tremor tends to vary in pattern (e.g., being vertical in the hands when the arm is at rest and being horizontal in the hands when the arm is held against gravity in front of the body) (Jankovic et al., 2006b). Campbell (1979) pointed out that the amplitude of functional tremor is more pronounced when attention is paid to it and that it lessens and may even disappear when the patient's attention is diverted to another subject or other part of the body. Distraction is a useful part of the examination and lessening of severity by distraction can be very helpful diagnostically in trying to establish a diagnosis of functional tremor. Distraction, however, does not always succeed in making the tremor disappear, and many patients with organic tremor can temporally suppress the tremor, even parkinsonian tremor. Entrainment of the tremor to a new frequency may sometimes be seen by having the patient touch thumb to the different fingers in a dictated pattern. Of 12 patients with functional tremor compared with 33 with organic essential tremor studied by Kenney and colleagues (2007), functional tremor was significantly more likely to start suddenly and was more likely associated with spontaneous remissions compared with essential tremor; family history of tremor was significantly more common in the essential tremor group, distraction with alternate finger tapping significantly decreased functional tremor, but entrainment did not differentiate the two groups. ●

Koller and colleagues (1989) diagnosed 24 patients with functional tremors. They described the tremors as complex; usually they were present at rest, with posture, and with action. The onset was abrupt, and in all but one the tremors lessened or were abolished with distraction. Fahn (1994) described that functional tremors are sometimes paroxysmal and not always continuous. Deuschl and colleagues (1998) reviewed 25 cases of functional tremor. Sudden onset and rare remissions were common. The "coactivation sign" and absent finger tremor were the most consistent criteria to separate them from organic tremors. Whereas most organic tremors show decreasing amplitudes when the extremity is loaded with additional weights, most functional tremors show an increase of tremor amplitude (i.e., coactivation sign). Overall, functional tremor in their series had a poor outcome. Kim and colleagues (1999) reviewed their series of 70 cases of functional tremor. They emphasized the abrupt onset (73%), often with the maximal disability at onset (46%), and then taking static (46%) or fluctuating (17%)

courses. Tremor usually started in one limb and spread rapidly to a generalized or mixed distribution. Other features were spontaneous resolution and recurrence, as well as easy distractibility together with entrainment and response to suggestion. McKeon and colleagues (2009) followed their 62 patients with functional tremor; 33 responded. The outcome was good (mild or no tremor) in 36%, moderate in 24% and poor in 40%. Five patients with the good outcome had spontaneous improvement without psychotherapy.

In addition to tremor in the limbs, functional palatal tremor has been reported (Pirio Richardson et al., 2006). Now it seems that what has been called essential palatal tremor is almost always functional (Stamelou et al., 2012; Baizabal-Carvallo and Fekete, 2015). Functional stridor was diagnosed in a boy who developed inspiratory stridor when trying to fall asleep (Vetrugno et al., 2009), but this seems more appropriately to be called anxiety-induced stridor.

Another electrophysiologic approach to aid in distinguishing between functional and organic tremors is with accelerometry. Tremor is measured in one hand, with the other hand either rested or tapped to an auditory stimulus at 3 and 4 or 5 Hz. Functional tremors showed larger tremor frequency changes and higher intraindividual variability during tapping (Zeuner et al., 2003). Motor control physiology can be useful to distinguish functional from organic tremor (Deuschl et al., 2006).

About half of the functional tremors are coherent between the two arms, suggesting to the authors that coherent tremors might be voluntary whereas noncoherent tremors are involuntary (Raethjen et al., 2004). Voluntary tapping of the contralateral limb usually results in either dissipating the tremor or shifting the tremor frequency to that of the metronome, called entrainment (O'Suilleabhain and Matsumoto, 1998).

Schwingschuh, Katschnig, and colleagues (2011) suggested a laboratory test battery to identify functional tremor. Tests include tremor recorded at rest, posture (with and without loading), action, while performing tapping tasks (1, 3, and 5 Hz), and while performing ballistic movements with the less-affected hand. Subsequently, this was validated with 38 patients with functional tremor and 73 patients with organic tremors (Schwingschuh et al., 2016). The battery has good inter-rater reliability and test-retest reliability. Patients with functional tremor had a higher average score on the test battery and the predefined cutoff score for laboratory-supported functional tremor yielded a test sensitivity of 89.5% and a specificity of 95.9%.

A patient who underwent deep brain stimulation for the treatment of essential tremor developed functional tremor after the surgery (McKeon et al., 2008). This is illustrative of the common situation of a functional disorder mimicking an organic one in the same patient.

Functional gait

An abnormal gait is a common feature in patients with an FMD. Of 279 patients, 118 (42%) had an abnormal gait (Baik and Lang, 2007); 102 (86%) of these 118 patients had other functional movements, and gait abnormalities included slowing of gait (18.6%), dystonic gait (17.8%), bizarre gait (11.9%), astasia-abasia (11.9%), and buckling of the knee (7.6%) as the most common types. Among the pure functional gait disorders, buckling of the knee was the

Video 27.10 Tremors of the hands.

Table 27.11 Types of functional gaits

Clinical feature	Mixed type	Pure type
Number of patients	102	16
Slowing	21	1
Dystonic	20	1
Bizarre	12	2
Astasia–abasia	11	3
Knee-buckling	4	5
Tight-rope walking	7	1
Trembling	4	1
Stiff-legged	5	0
Dragging	4	0
Scissoring	4	1
Truncal myoclonus	4	0
Fatigue	3	0
Waddling	2	1
Ataxic	1	0

Data from Baik JS, Lang AE. Gait abnormalities in psychogenic movement disorders. *Mov Disord.* 2007;22(3):395–399.

most common feature (31.3%), followed by astasia–abasia (18.8%) (Table 27.11).

Morris and colleagues (2006) described key features of functional gait in their experience. These include exaggerated effort, fatigue with groans and sighs, extreme slowness, appearance of pain with grimaces, knee-buckling, unusual postures, and astasia–abasia. Keane (1989) described 60 cases with functional gait abnormality out of 228 patients with functional neurologic problems. Among these abnormal gaits were 24 patients with “ataxia” (the most common gait abnormality), 9 patients with trembling, 2 patients with “dystonia,” 2 patients with truncal “myoclonus,” and 1 patient with camptocormia (markedly stooped posture). Among the myriad of associated functional signs were 8 patients with tremor. In a video review of functional gaits, Hayes and colleagues (1999) emphasized certain features of the gait: exaggerated effort, extreme slowness, variability throughout the day, unusual or uneconomic postures, collapses, convulsive tremors, and distractibility. On the other hand, it is possible to misdiagnose as functional an abnormal gait that is organic. For example, such happened to a patient with a gait disorder and episodic weakness that were thought to be functional who was subsequently diagnosed with status cataplecticus as a result of narcolepsy (Simon et al., 2004).

Baizabal-Carvalho and colleagues (2019) found that 39% of 153 FMD patients had a primary gait disorder. Patients with a functional gait disorders had a high frequency of slow-hesitant gait, astasia–abasia, bouncing, wide-based gait, and scissoring. Bouncing gait with knee buckling was more frequently observed in patients with isolated functional gait disorder. Nonnekes and colleagues (Nonnekes et al., 2020) proposed seven groups of signs that could help diagnostically: variable, scissoring, weak with give-way, antalgic-like, excessively slow, leg dragging, and abnormal posturing.

Fear of falling

Fear of falling is a syndrome in which the patient can walk perfectly well if he or she is holding onto someone but is unable to walk without leaning against furniture or walls if alone. Sometimes, this could be purely due to a psychiatric problem, such as agoraphobia. Most of the patients we have seen with this problem developed the condition after they had fallen, usually from organic causes (such as loss of postural reflexes or ataxia) and were left with a marked fear of falling when walking without holding on. The freezing phenomenon (or motor blocks) that is seen in parkinsonism and the gait in action myoclonus patients are the other major conditions in which the gait also normalizes when the patient holds on to someone. The fear-of-falling syndrome is usually separated from the list of FMDs (see later) and might be better characterized as a psychiatric movement disorder. But in many of these patients, the fear of falling is beyond what is rational, so there is a functional component. Women are more affected than men, and often the mistaken diagnosis is PD (Kurlan, 2005).

Patients complaining of balance disorders and dizziness with no or only minimal signs that can explain the symptoms, may have a form of functional dizziness called persistent postural perceptual dizziness (PPPD) (Popkirov et al., 2018). This is a common complaint in neurotology clinics seeing patients with dizziness.

Functional myoclonus

Functional myoclonus often appears different from organic myoclonus in that it is not a simple movement and it might be observably “long” in duration. The myoclonus often looks like exaggerated startle. If sensory provoked, the latency can be long. Sometimes the myoclonus will be produced even if the tendon hammer is stopped just short of contact (Hallett, 2016).

Monday and Jankovic (1993) reported 18 patients with functional myoclonus stating that this was the most common form of FMD encountered in their clinic. The myoclonus was segmental in 10 patients, generalized in 7 patients, and focal in 1 patient. Functional myoclonus accounted for 8.5% of the 212 patients with myoclonus in their clinic. Inconsistency with continuously changing pattern anatomically and temporally was common. The movements often increased with stress, anxiety, and exposure to noise or light.

Functional myoclonus should be relatively easy to distinguish from organic myoclonus if access to a motor control physiology laboratory is available (Hallett, 2010, 2016). Poly-EMG is very helpful in distinguishing functional myoclonus from organic myoclonus. The short duration of an organic myoclonic jerk (usually less than 50 ms) is almost impossible to duplicate voluntarily. The EMG pattern of functional jerks may exhibit a triphasic pattern of activity between antagonistic muscles, whereas cortical myoclonus consists of short-duration 25- to 50-ms bursts of co-contracting antagonists muscles. Furthermore, the latency of reflex myoclonus is physiologically short (40–50 ms) whereas abnormal reactive functional jerks are much longer and variable in latency.

A Bereitschaftspotential preceding muscle jerks was found in five of six patients with a diagnosis of functional myoclonus (Terada et al., 1995) and in 25 of 29 cases in subsequent series (van der Salm et al., 2012). This is a positive sign for

the diagnosis of functional myoclonus, but because some patients do not have a Bereitschaftspotential, its absence cannot be used to exclude the diagnosis.

Most cases of propriospinal myoclonus are now recognized as being functional (van der Salm et al., 2014). The diagnosis is made by the lack of the classic stereotyped pattern and the presence of a Bereitschaftspotential. The event-related desynchronization might be more sensitive than the Bereitschaftspotential in this (and other) circumstances (Meppelink et al., 2016).

Functional tics

Functional movements can sometimes resemble tics, but these are one of the least common manifestations of an FMD (Lang, 2006) (see Tables 27.4 and 27.5). Distinguishing functional from organic tics is not easy. The classic features of organic tics, such as waxing and waning of symptoms, tics moving from one body part to another, suggestibility, suppressibility, and the paroxysmal nature of tics, are those that are clues for other types of abnormal movements being functional in origin (see Table 27.2). These “clues” for functionality do not apply for the phenomenology of tics because they are congruent with organic tics. For functional tics, one depends on other evidence, including incongruous presence of other abnormal movements that are functional, clues in the general neurologic examination, such as the presence of give-way weakness, and the background leading to the development of tics, such as tic-like movements in the outbreak of mass hysteria seen in high school girls in New York State in 2011 as noted earlier (Mink, 2013).

Other helpful clues are the absence of urge preceding a tic and lack of suppressibility in functional tics. These are common features commonly seen in organic tics, but these are not a uniform feature of organic tics, so they are not absolute criteria. Thus, often there is still difficulty telling the two disorders apart (Ganos et al., 2019). The Bereitschaftspotential is typically present before functional movements and typically absent or short before tics, but this testing cannot be considered more than suggestive (van der Salm et al., 2012).

It is more complicated when organic tics are also present. Dooley and colleagues (1994) described two children with Tourette syndrome who also had functional tics, which were identified, in part, by their resolution when the stressful issues in their lives were addressed.

Functional parkinsonism

Functional parkinsonism is relatively uncommon (see Tables 27.4 and 27.5). Lang and colleagues (1995) reported 14 patients with this disorder; 11 patients had tremor at rest, but the tremor did not disappear with movement of the limb, and the frequency and rhythmicity varied. Rigidity was present in 6 patients but without cogwheeling. All 14 patients had slowness of movement (bradykinesia) without the typical decrementing feature of organic bradykinesia (sequence effect) (Video 27.11). One patient had evidence of some organic parkinsonism as well but required a fluorodopa PET scan to be certain. Other studies also reported the combination of organic and functional parkinsonism and found the dopaminergic SPECT imaging can help in distinguishing this diagnosis from pure functional parkinsonism (Benaderette et al., 2006; Gaig et al., 2006).

A meta-analysis of the literature was done for functional parkinsonism and for functional symptoms in organic PD (Ambar Akkaoui et al., 2019). There were 121 patients with functional symptoms in PD, 57% were women, and the mean age was 61.3 years. Psychiatric history, mostly depression, was seen in 60%. The most common symptom was tremor (33.8%), most often located on the side most affected by PD (50%). There were 20 patients with functional parkinsonism, 62% were women, and the mean age was 50.7 years. The first symptoms appeared on average 5 years before diagnosis, with an abrupt onset in half the cases and 67.6% had a psychiatric history. It does seem to be the case that patients with PD are prone to develop functional symptoms (Hallett, 2018).

Treatment of functional movement disorders

Of course, before embarking on treatment, the neurologist should be confident of the diagnosis or, at least, that the most important part of the syndrome is functional. The diagnosis needs to be made on positive grounds, not just rule-out of organic conditions, and can be supported by the laboratory as noted earlier. That being the case, the first step is delivery of the diagnosis (Stone and Hoeritzauer, 2019; Stone et al., 2020). Delivery of the diagnosis begins the therapeutic process because acceptance of the diagnosis is a predictor of positive outcome (Stone et al., 2016).

Patients should be informed of the diagnosis using clear language. The rationale behind the diagnosis also should be provided. Patients should be presented with the evidence supporting their diagnosis. Showing patients with FNDs the features of their neurologic examination that led to their diagnosis is likely helpful in convincing patients. For example, patients with functional tremor can have their attention drawn to the entrainment or suppression of their tremor with contralateral tapping (Stone and Edwards, 2012). If the patient does not believe the doctor, the patient is unlikely to engage in treatment. The patient may never return, will continue to have symptoms, and probably will see a number of other physicians, looking for an organic diagnosis.

Importantly, the potential for reversibility with treatment should be stressed. Given limited public awareness about functional disorders, it is helpful to provide the patient with additional educational resources to review after the consultation. Patients can be directed to online resources such as <http://www.neurosymbols.org> and to patient organizations such as <http://www.fndhope.org>.

Developing a sense of trust and partnership between the patient and physician at the time of initial diagnosis is important because it is likely best that the neurologist remain as the coordinator of care for the patient. In addition, symptoms may evolve over time, and patients should feel comfortable in returning for a reevaluation.

Generally speaking, treatment needs to be multidisciplinary. In addition to the neurologist, there may well be need for psychiatry, rehabilitation, psychology, physical therapy, occupational therapy, and social work. Although such teams can be put together for each patient, it is better if teams can be organized for such therapeutic purposes and then called into play as a group.

The participation of a psychiatrist who understands FMDs is often critical. Psychiatrists cannot make the diagnosis of

Video 27.11 Deliberate slowness, psychogenic parkinsonism.

FMD because they are not trained in the differential diagnosis of movement disorders, but they can help identify important and relevant underlying psychopathology processes that might help guide treatment. Many patients will recognize mood or anxiety disorders and can understand the need for psychiatry, but, if not, the patients could be told that, from our experience, psychiatrists are able to help regardless.

Psychological treatment has traditionally been considered the standard of care. Although data are limited for evidenced-based treatment of FMD, evidence is growing for psychological treatment for functional disorders collectively. For example, a meta-analysis demonstrated a substantial reduction in seizure frequency in over three-quarters of patients with functional seizures treated by psychological interventions (Carlson and Nicholson Perry, 2017). Various types of therapy have shown promise, including disorder-adapted cognitive behavioral therapy (CBT), multimodal cognitive behavioral-informed psychotherapy, CBT-oriented self-management, and interdisciplinary psychodynamic interpersonal therapy. The goals of psychological treatment are to explore and address unhelpful beliefs and behavior. Patients are taught to identify how their thinking affects their emotional state and their behavior and to identify triggers exacerbating symptoms (Lehn et al., 2016). Small studies have demonstrated benefit of CBT in treating FMDs, including functional tremor (Espay et al., 2019) and functional dystonia (Vizcarra et al., 2019). In addition to improvement in clinical symptoms, patients with functional tremor exhibited significant changes in activation within the emotion-processing network after a 12-week CBT program as assessed by fMRI during a basic-emotion processing task (Espay et al., 2019). A systematic review of CBT, as well as psychodynamic therapy, for all types of FND has shown that there appear to be beneficial effects for both, but most studies have been small (Gutkin et al., 2020).

Physical therapy has an important role in the multidisciplinary treatment of patients with prominent motor symptoms. A set of consensus recommendations has identified principles to guide this type of therapy (Nielsen, Stone et al., 2015). Physical therapy programs should work within the biopsychosocial model of FMDs, in which a patient's abnormal movements are involuntary but also represent learned habitual movements driven by abnormal self-directed attention. CBT and stress reduction techniques can be incorporated to normalize illness beliefs and change maladaptive behaviors. Physical therapy itself focuses on function and automatic movements, such as walking, rather than on impairments, such as weakness. Attention also should be on controlling movements, such as strengthening exercises. Using these principles, good improvement has been demonstrated (Nielsen, Stone et al., 2013; Nielsen, Ricciardi et al., 2015; Nielsen, Buszewicz et al., 2017). Physical therapy may be helpful even if done with telemedicine (Demartini et al., 2019).

If present, comorbid depression or anxiety should be treated pharmacologically. There is little formal evidence for this, but it seems logical. One open label study did show benefit of treating depression (Voon and Lang, 2005). Desensitization therapy is a mechanism of treatment for patients who are stimulus-sensitive, such as having excessive startle, shakes, or myoclonus after exposure to a sensory stimulus. Introducing the stimulus in a mild, subclinical form that

fails to induce the abnormal response is the starting point. Then the intensity of the stimulus should be increased over time until the patient is desensitized. A variety of nonpharmacologic interventions have been used, including transcutaneous nerve stimulation (TENS), transcranial magnetic stimulation (TMS), biofeedback, and therapeutic sedation (Lehn et al., 2016), but none are much beyond a pilot stage.

There is controversy about using placebos in the diagnosis or treatment of patients with psychogenic movement disorders (Jankovic et al., 2006a). Although their use can be an easy approach to make the correct diagnosis, their use also often angers patients, who state that they have been "tricked." If used to help make the diagnosis, disclosure is necessary afterward, explaining the rationale and that the physician wants to be certain with the diagnosis so that proper treatment can be initiated. Patients will not have further trust in the treating physician if the patients discover placebos on their own. Using placebos to treat the symptoms can lead to mistrust also; this approach is no substitute for important psychotherapy to get to the root cause and cure of the problem. If placebos were used to treat the condition, and the patient improves, it can be difficult to then explain to the patient what was done. Patients can have a serious clinical reversal when they learn what has happened. If placebos were used to treat the symptoms, it would, therefore, be important to inform the patient as soon as possible to keep the patient's confidence that you were working with the patient to help him or her to a speedy recovery. For many reasons, then, it is better to avoid the use of placebos and strive to obtain successful results without them (Ford et al., 1995).

Although most patients are treated as out-patients, in-patient treatment might be considered either to jump-start a primarily out-patient program or because the disorder is so severe. In one study, 32 FMD patients participated in a 1-week, multidisciplinary in-patient treatment program with daily physical, occupational, speech therapy, and psychotherapy (Jacob et al., 2018). The most common phenotypes were abnormal gait (31.2%), hyperkinetic movements (31.2%), and dystonia (31.2%). At discharge, 86.7% of patients reported symptom improvement on the Clinical Global Impression Scale (CGI), and self-reported improvement was maintained in 69.2% at 6-month follow-up.

Results of treatment

Until recently, patients were either neglected or given "routine" psychiatric therapy and prognosis was not good. With newer approaches prognosis is improving. Williams and colleagues (1995) reported on a large series of their patients treated with an in-patient program. They used psychotherapy in all patients, along with the following supplemental approaches: family sessions, 58%; hypnosis, 42%; physical therapy, 42%; and placebo therapy, 13% (Table 27.12). Psychotropic medication (antidepressants) was used in 71%. Two patients with treatment-resistant major depression received electroconvulsive therapy (ECT); one responded completely, and the other responded only partially. One-quarter of the patients required more extensive psychiatric hospitalization because of suicidal ideation or because there was a poor response in reversing the psychodynamic pathologic features while on the neurology service. Treatment resulted in a permanent, meaningful benefit in 52% of

Table 27.12 Treatment of functional movement disorders

Treatment	Percentage
Accepted diagnosis and treatment	70
Refused diagnosis and treatment	30
Psychiatrically treated patients	
Family sessions	58%
Hypnosis	88%
Physiotherapy	42%
Placebo	13%
Antidepressants	71%
Electroconvulsive therapy	8%

Data from Williams DT, Ford B, Fahn S. Phenomenology and psychopathology related to psychogenic movement disorders. *Adv Neurol.* 1995;65:231–257.

Table 27.13 Results of treatment of functional movement disorders

Results	Percentage
Permanent, complete relief	25
Permanent, considerable relief	21
Permanent, moderate relief	8
Relapse	4
Partial relapse	17
No improvement	12
Previously employed	
Now working full-time	25
Now working part-time	10
Functioning at home	15
Now disabled	30

Data from Williams DT, Ford B, Fahn S. Phenomenology and psychopathology related to psychogenic movement disorders. *Adv Neurol.* 1995;65:231–257.

patients, with complete relief, considerable relief, and moderate relief in 25%, 21%, and 8% of patients, respectively (Table 27.13). Some relapse occurred in 21% of patients, and no improvement was seen in 12%. Of those who had been previously employed, 25% were able to resume full-time work and 10% were able to work part time, with 15% functioning at home (see Table 27.13).

In the series of 28 cases of FMDs reported by Factor and colleagues (1995), 35% resolved and this subgroup had a shorter duration of disease than those who did not resolve. Of 56 patients with any type of FMDs other than functional seizures, Couprie and colleagues (1995) found that the long-term outcome was good in 96% of those who improved during a hospital stay and in 30% of others and that rapid improvement was related to recent onset of symptoms. In a longitudinal study of 228 patients evaluated in the Baylor College of Medicine Movement Disorders Clinic (Jankovic et al., 2006a), after a mean duration of follow-up of 3.4 ±

Table 27.14 Movement disorders that are symptoms of psychiatric conditions and not classified as functional movement disorders

Psychiatric condition	Psychiatric movement disorder
Schizophrenia, depression	Catatonia
Depression	Psychomotor slowness
Obsessive-compulsive disorder	Obsessional slowness, stereotypies
Agoraphobia, anxiety	Fear of falling
Schizophrenia, autism	Stereotypies

2.8 years, improvement of symptoms was noted in 56.6% patients, 22.1% were worse, and 21.3% remained the same at the time of follow-up. Positive social life perceptions, strong suggestion by the physician of effective treatment, elimination of stressors, and treatment with antidepressant medications contributed to a favorable outcome. Using a “blinded” review of videos, psychiatric rating scales, and psychogenic movement disorder scale, Hinson and colleagues (2006) demonstrated the efficacy of psychotherapy and medications in the treatment of patients with FMDs.

We can compare treatment of FMD with that of functional seizures. In a double-blind study of 66 patients, CBT was more effective than standard medical care in reducing seizure frequency (Goldstein et al., 2010). The median monthly seizure frequency in the CBT group went from 12 to 1.5 and in the standard care group from 8 to 5. In a randomized study of 34 patients with CBT informed psychotherapy, sertraline, both, or neither, both groups with the psychotherapy improve compared with the two others. In general, there is a sense in the field that psychological therapies are of value in these patients (Michaelis et al., 2018).

Movement disorders caused by psychiatric conditions but not regarded as functional

Some movement disorders are due to diseases that are classified as mental or psychiatric disturbances, in which the abnormal hypokinesia or hyperkinesia is not listed as an FMD. Table 27.14 lists these and the common underlying causes.

Table 27.14 shows that, basically, none of the aforementioned psychiatric conditions is a somatoform disorder, a factitious disorder, or a malingering state. Thus, we can distinguish the FMDs from the conditions listed in Table 27.14 on the basis of the underlying psychiatric state. It should be noted that even if a somatoform disorder, a factitious disorder, or a malingering state is only suspected and not officially diagnosed, the diagnosis of an FMD can still be made. Also, even if a psychiatric consultant cannot detect one of these disorders, a neurologist may still make the diagnosis on the grounds listed in Tables 27.2 and 27.3.

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