OVERVIEW OF COMMON MOVEMENT DISORDERS

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ABSTRACT

Movement disorders are a diverse group of hypokinetic and hyperkinetic neurologic diseases characterized by abnormal function of the basal ganglia. In this chapter, we will discuss the four most common diagnoses encountered in subspecialty movement disorders clinics: Parkinson disease, essential tremor, dystonia, and spasticity. The presentation and natural history of each of these disorders varies widely in terms of age of onset, anatomic distribution, and severity. We will review the demographics, clinical characteristics, diagnostic criteria, natural history, and management of these diseases. The medical and surgical management of Parkinson disease will be covered in the chapters ''Update on the Medical Management of Parkinson Disease'' and ''Deep Brain Stimulation in Movement Disorders,'' respectively.

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KEY POINT

- Parkinson disease (PD) is the second most common neurodegenerative disease with 1 million to 2 million people diagnosed in the United States.

PARKINSON DISEASE

Parkinson disease (PD) is a chronic, progressive, neurodegenerative disorder characterized by pathologic intraneuronal α-synuclein-positive Lewy bodies and neuronal cell loss. Classically, this process has been described as involving the dopaminergic cells of the substantia nigra pars compacta, later becoming more widespread in the CNS as the disease progresses. However, recently there has been a growing awareness that the disease process may involve more caudal portions of the CNS and the peripheral nervous system *prior to* the clinical onset of the disease (Braak et al, 2002). We will discuss the well-known motor features of PD, as well as nonmotor aspects crucial to both the initial diagnosis and care of moderate and advanced PD.

Demographics

PD is the second most common neurodegenerative disorder after Alzheimer disease. Current studies estimate that 1 million to 2 million people in the United States suffer from PD. As the population ages, this number is expected to rise dramatically. The prevalence of PD steadily increases with age, affecting about 1% to 2% of the population older than 65 years, and over 3% of those older than 85 years. Most age-adjusted prevalence rates are reported to be between 100 and 200 cases per 100,000. Estimates of the incidence of PD are more variable. Age is the strongest risk factor for PD. Interestingly, a recent large prospective study found that incidence rates rise steeply through age 89; then lifetime risk plateaus after age 90 (Driver et al, 2009). The incidence of PD

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KEY POINTS

- PD usually presents asymmetrically with cardinal motor features of resting tremor, bradykinesia, rigidity, and postural instability.
- Parkinsonian tremor is typically a low frequency (4 Hz to 6 Hz) rest tremor that is temporally suppressed by action.
- Bradykinesia can present in a variety of ways, causing slowness of movement in fine and gross motor tasks.
- Tremor superimposed on rigidity results in the cogwheeling quality when passively moving a joint.

has been reported to be higher in men than in women but only among patients older than 60 years (Taylor et al, 2007). Several studies suggest a higher incidence of PD in whites than in African Americans or Latin Americans. This may be due to true biological differences in PD risk or underdiagnosis due to barriers to health care such as education or cultural beliefs about health and aging (Dahodwala et al, 2009).

Clinical Features and Diagnosis

Parkinsonism is a syndrome characterized by resting tremor, slowness of movement, rigidity, and/or postural instability. In PD, the most common form of parkinsonism, these features present asymmetrically. The contralateral side is eventually affected, but the asymmetry usually persists throughout the disease course.

Tremor is the major hyperkinetic movement seen in PD and is defined as a rhythmic, oscillatory, involuntary movement. Tremor is the most common presenting symptom in PD. It is the initial symptom in about 50% to 70% of patients, although a small proportion of patients with PD never develop tremor. The resting tremor of PD is typically asymmetric, low frequency (4 Hz to 6 Hz), and characterized by a pill-rolling (supination-pronation) movement. It most commonly affects the distal upper extremities but may also involve the lower extremities and face, with chin tremor being particularly specific for PD. In its early stages, the resting tremor of PD is frequently noted when speaking, walking, or being distracted and is brought out by stressful situations. Commonly, patients describe being able to suppress the tremor with concentration or with actions of the affected hand. With progression of the disease, the tremor becomes more constant, higher in amplitude, and more frequently associated with action. However, the action tremor of PD typically occurs at the same 4-Hz to 6-Hz frequency of the rest tremor and "reemerges" after a short latency period, distinguishing it from essential tremor (ET). Because many patients report tremor to be their most bothersome symptom, much of the focus of medical and surgical therapies for PD targets this symptom.

Bradykinesia is defined as a slowness or lack of movement. Patients with bradykinesia experience difficulty initiating and maintaining the velocity and amplitude of movement. Symptomatically, patients may report a loss of manual dexterity with fine motor tasks or an increase in time required to perform activities of daily living. Many common symptoms and signs of PD are direct manifestations of bradykinesia: micrographia (small handwriting), hypophonia (quiet monotone speech), hypomimia or masked facies (loss of facial expression), and the general lack of spontaneous movement. In addition to these signs, patients will frequently exhibit a decreased blink rate, shortened stride length, and decreased arm swing with walking. Patients with bradykinesia may also have a slower velocity and lower amplitude with rapid repetitive movements such as hand grips, finger taps, and heel stomps.

Rigidity is the increased resistance to passive movement of skeletal muscle across a joint. Symptomatically, rigidity is experienced as stiffness and can present as musculoskeletal concerns, such as a frozen shoulder. Rigidity is often severe enough to cause aching or cramping pain. On examination, unlike spasticity, resistance is consistent throughout the range of movement in all directions and is not velocity dependent. This gives rigidity its "lead-pipe" quality. In PD, the superimposition of tremor onto rigidity creates the sensation of cogwheeling. Distracting maneuvers (such as having the patient perform a task with the contralateral limb) can be helpful in detecting mild and otherwise subclinical rigidity in early PD.

Postural instability and gait disturbance are less prominent in early PD and

are rarely presenting symptoms. Early on, gait disturbance can manifest as dragging of one leg (which may be due to bradykinesia and rigidity) or stooped posture. Later in the course of PD, however, gait problems (such as loss of postural reflexes, festination, freezing, and more severe postural changes) can be severe, frequently becoming the major source of disability. Loss of postural reflexes can lead to instability, as even a slight perturbation may lead to falls. Even late in the disease course, gait remains narrow based, differentiating PD from many causes of unsteadiness such as cerebellar ataxia. Festination is the sense of the feet wanting to rush forward and the patient experiences hastening of the gait. Freezing of gait is an inability to take effective steps and is particularly disabling. Patients with freezing of gait will describe their feet feeling "stuck to the floor." Freezing of gait typically occurs with gait initiation, turning, and passing through narrow spaces. Gait disturbance is a disabling and dangerous problem for patients, commonly leading to falls and injuries. Postural stability can be evaluated using the pull test. The patient stands with feet separated and attempts to keep his or her balance when the examiner pulls the patient backward. A patient with mild instability may take three or more steps of retropulsion before recovering. More severe instability manifests as a complete loss of postural reflexes and may require the examiner to catch the patient.

Diagnosis

The clinical examination remains the criterion standard for diagnosis of idiopathic PD. The accuracy of diagnosis by general neurologists approaches 70% and by movement disorders specialists approaches 90% (Hughes et al, 2002). The most stringent and widely used diagnostic criteria, especially in research settings, are those of the UK Parkinson's Disease Society Brain Bank (Hughes et al, 1992). These criteria require presence of two of the four cardinal features of PD and the absence of certain features that would suggest other causes of parkinsonism (**Table 1-1**). Additionally, the presence of at least three supportive criteria is needed for a "definite" diagnosis of PD but may require several years of follow-up to confirm. A history of nonmotor symptoms (such as olfactory loss, REM-sleep behavior disorder, or constipation) can also be quite helpful in the early diagnosis of PD (**Table 1-2**).

The differential diagnosis of PD is broad (**Table 1-3**). Tremor itself has a large differential, the most common being ET. Interestingly, patients with ET, especially those with long-standing symptoms, have a higher risk of PD. When a tremor is more clearly a resting tremor and occurs with bradykinesia or rigidity, the differential of parkinsonism must be considered (**Table 1-3**). The most common mimics of PD include neurodegenerative conditions such as the atypical parkinsonian disorders and secondary causes of the syndrome such as drug-induced and vascular parkinsonism. In general, relative lack of tremor, symmetric presentation, lack of robust response to levodopa, and the early prominence of features usually seen later in idiopathic PD are concerning for atypical parkinsonism (**Table 1-4**). There are several caveats to these principles. First, few patients with PD will develop tremor. Thus, lack of tremor does not rule out PD. Second, one must remember that substantial doses of dopaminergic drugs (more than 300 mg/dose of levodopa or an apomorphine injection) must be tried before declaring a patient unresponsive. Furthermore, intolerance to PD medications does not equate with unresponsiveness.

Natural History

PD is a progressive neurodegenerative disorder in which a general decline in motor and nonmotor functions occurs,

KEY POINTS

- Postural instability and gait disturbance typically occur in more advanced PD, can be disabling, and can cause dangerous problems for patients.
- The main conditions in the differential of PD are essential tremor, atypical parkinsonian disorders, drug-induced parkinsonism, and vascular parkinsonism.
- Patients with PD typically have a robust response to levodopa.

TABLE 1-1 UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria

▶ **Inclusion Criteria**
Bradykinesia (and at least one of the following):
Muscular rigidity
4-Hz to 6-Hz tremor
Postural instability (not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction)
▶ **Exclusion Criteria**
History of repeated strokes with stepwise progression of parkinsonian features
History of repeated head injury
History of definite encephalitis
Oculogyric crisis
Neuroleptic treatment at onset of symptoms
More than one affected relative
Sustained remission
Strictly unilateral features after 3 years
Supranuclear gaze palsy
Cerebellar signs
Early severe autonomic involvement
Early severe dementia with disturbances of memory, language, and praxis
Babinski sign
Presence of cerebral tumor or communicating hydrocephalus on CT scan
Negative response to large doses of levodopa (if malabsorption excluded)
1-Methyl-4-phenyl-1,2,3, 6-tetrahydropyridine (MPTP) exposure
▶ **Supportive Criteria (Three or More for Diagnosis of "Definite" Parkinson Disease)**
Unilateral onset
Rest tremor present
Progressive disorder
Persistent asymmetry
Excellent response (70% to 100%) to levodopa
Severe levodopa-induced chorea
Levodopa response for 5 years or more
Clinical course for 10 years or more

CT = computed tomography.

Adapted 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(3):181–184. Copyright © 1992, with permission from BMJ Publishing Group.

leading to greater disability (**Table 1-5**). Wide variability exists in both the rate of progression and the development of symptoms from patient to patient. In general, younger patients who develop PD tend to have a slower rate of progression, have more tremor-predominant disease, and have less nonmotor disability, including less dementia. They do, however, generally develop more disabling dyskinesia. Older patients tend to have a faster rate of progression, with more postural instability, gait disturbance, and nonmotor disability, including more prominent dementia.

Preclinical or Premotor Parkinson Disease

Classically, PD has been thought of as a movement disorder with motor symptoms being the presenting symptoms and most prominent features. Yet, nonmotor features of the disease (eg, autonomic,

TABLE 1-2 Nonmotor Symptoms in the Premotor Phase of Parkinson Disease and Their Neuropathologic Substrates

Premotor Symptoms	Braak Stage/Presumed Brain Structures Involved
Olfactory Loss	
Hyposmia, with impairments in odor detection, identification, discrimination	Stage 1: Olfactory bulb, anterior olfactory nucleus, amygdala, perirhinal cortex
Dysautonomia	
Gastrointestinal disturbances: gastroparesis, constipation Urinary: frequency and urgency Sexual: erectile dysfunction, vaginal lubrication, ejaculation, orgasm	Stage 1: Dorsal nucleus of the vagus, sympathetic ganglia, enteric and abdominopelvic autonomic plexuses (amygdala, intermediolateral column of spinal cord)
Mood	
Depression Anxiety	Stages 2, 3: Locus ceruleus, raphe nuclei (amygdala, mesolimbic, mesocortical cortex)
Sleep	
REM behavior disorder Excessive daytime sleepiness Insomnia/sleep maintenance	Stage 2: Nucleus subceruleus, pedunculopontine nucleus (thalamus, hypothalamus)
Other Nonmotor	
Pain, apathy, fatigue, midlife obesity, impaired color discrimination, restless legs syndrome, rhinorrhea	Unclear

Data from Tolosa E, Gaig C, Santamaría J, Compta Y. Diagnosis and the premotor phase of Parkinson disease. Neurology 2009;72(7 suppl);S12–S20.

sensory, cognitive, behavioral, and sleep related) are also an important part of the disease and play a major role in disrupting quality of life for patients with PD. Nonmotor symptoms are frequently present early in the disease, quite often occurring prior to the presentation of motor symptoms (**Table 1-2**).

In recent years, it has become clear that a loss of olfaction (hyposmia), although not specific to PD, is a common symptom of premotor PD. In fact, 90% of patients with PD have measurable hyposmia (Katzenschlager and Lees, 2004). A recent prospective study showed that subjects in the lowest quartile of olfaction testing had the highest risk of subsequently developing PD (Ross et al, 2008). This relation to hyposmia is not present in other forms of parkinsonism. Even when loss of olfaction is severe it can be asymptomatic and therefore may require objective measurement for detection.

Abnormal sleep can also be present in the premotor phase of PD. REM sleep behavior disorder (RBD), the pathologic acting out of one's dreams, is the most common sleep disturbance in PD.

TABLE 1-3 Differential Diagnosis in Parkinsonism

- **Other Neurodegenerative (Atypical Parkinsonism, Parkinson-Plus Syndromes)**
  - Multiple system atrophy (MSA)
    - Striatonigral degeneration (MSA-P)
    - Olivopontocerebellar atrophy (MSA-C)
    - Shy-Drager syndrome
  - Progressive supranuclear palsy
  - Corticobasal degeneration
  - Dementia with Lewy bodies (and other dementia syndromes)
- **Secondary**
  - Drug-induced parkinsonism
    - Dopamine receptor–blocking agents (antipsychotics, antiemetics)
    - Dopamine depleting agents (reserpine, tetrabenazine)
    - Other agents less commonly responsible (eg, valproic acid, phenytoin, lithium, calcium channel blockers, amiodarone, lithium, immunosuppressants)
  - Vascular parkinsonism (''lower half'' parkinsonism)
  - Infectious (postencephalitic)
  - Structural (hydrocephalus, trauma, brain tumor, hemiparkinsonism/hemiatrophy)
    - Toxic/Metabolic (eg, Wilson disease, manganese, 1-methyl-4-phenyl-1,2,3, 6-tetrahydropyridine (MPTP), organophosphates, mercury, cyanide)

One study found RBD in 60% of patients with PD when cases were ascertained by formal sleep studies (Gagnon et al, 2002).

Bed partners will describe the patient thrashing around in bed, sometimes violently. The movements can be complex and appear purposeful. Grabbing and striking the bed partner or falling out of bed may result in injury. RBD is not specific to PD and is also frequently seen in other neurodegenerative synucleinopathies,

TABLE 1-4 Red Flags for Atypical Parkinsonism

- **Early Prominence of Features Usually Not Seen Until Advanced Stages of Parkinson Disease**
  - Postural instability and falls
  - Dementia
  - Psychosis (hallucinations, delusions)
  - Dysphagia
  - Dysautonomia (especially urinary symptoms, orthostatic hypotension)
- **Symmetric Presentation**
- **Relative Lack of Tremor**
- **Poor or Transient Response to Levodopa and Other Dopaminergic Agents**
- **Presence of Other Atypical Features**
  - Cerebellar features (ataxia, dysmetria)
  - Pyramidal signs (spasticity, Babinski sign, hyperreflexia)
  - Atypical tremor (postural, jerky) and myoclonus
  - Neuropathy
  - Cortical signs (astereognosis, agraphesthesia, aphasia, apraxia)
  - Focal neurologic deficits
  - Oculomotor deficits (gaze palsies)

including multiple system atrophy and dementia with Lewy bodies.

Autonomic symptoms are usually not disabling early in the course of PD. However, constipation is frequently present in the years prior to PD diagnosis. A large prospective study in Hawaii showed that men who had fewer than one bowel

TABLE 1-5 Natural History of Parkinson Disease, With Typical Signs and Symptoms at Each Stage

Rating Scale and Symptomology	Premotor	Early	Moderate	Advanced
Hoehn and Yahr stage (approximate)[a]	0	1, 2	2, 3, 4	4, 5
Presumed Braak stage (pathologic)	1, 2, 3	3, 4	4, 5	4, 5, 6
Typical UPDRS III score:	0–5	10–35	20–50	30–60
Motor	None Subtle, such as stiff shoulder Restless legs syndrome	Resting tremor, rigidity, bradykinesia, mild gait disturbance Very dopamine responsive: sustained, predictable Some secondary features (stooped postures, hypomimia, hypophonia, micrographia)	Motor complications: wearing off, dyskinesias, on/off phenomena Less consistent dopamine response More gait disturbance, some falls, increased axial symptoms Off period freezing of gait	Severe motor complications[b] Axial symptoms become most disabling feature (dysphagia, hypophonia, dysarthria, postural instability, balance, frequent falls, freezing of gait, etc)
Autonomic	Constipation	→	→	→
	Urinary symptoms should be mild	Urinary symptoms (mild)	Urinary symptoms more common (urgency, frequency, nocturia)[b]	Urinary incontinence
		Nausea[b]		
		Sexual dysfunction	→	→
		Sweating disturbance	Orthostatic hypotension/ lightheadedness[b]	Worsening orthostatic hypotension[b]
				Sialorrhea (drooling)
Cognitive	Subtle attention deficits, executive dysfunction	→	More pronounced frontal executive dysfunction and decreased verbal fluency	Psychosis including visual hallucinations, delusions, decreased attention, dementia

continued on next page

TABLE 1-5 *Continued*

Rating Scale and Symptomology	Premotor	Early	Moderate	Advanced
Behavioral	Anxiety	→	→	Severe anxiety, panic
	Depression	→	→	Severe depression
	Apathy	→	→	Severe apathy
		Impulse control disorder[b] (gambling, etc)		
Sleep	REM sleep behavior disorder	→	→	→
	Excessive daytime sleepiness[b]	→	→	→
		Vivid dreams[b]	→	→
		Sleep maintenance	→	→
Other (sensory, pain, skin, systemic)	Olfactory loss	→	→	→
	Seborrhea	→	→	→
		Pain	→	→
		Paresthesia	Change in vision/ bright lights	Weight loss[b]

UPDRS = Unified Parkinson's Disease Rating Scale.
→ = Sign or symptoms continue to the next stages of disease.

[a]Hoehn and Yahr staging:
Stage 1: Symptoms on one side of the body only.
Stage 2: Symptoms on both sides of the body. No impairment of balance.
Stage 3: Balance impairment. Mild to moderate disease. Physically independent.
Stage 4: Severe disability, but still able to walk or stand unassisted.
Stage 5: Needing a wheelchair or bedridden unless assisted.
[b]Can be worsened, complicated by medications.

movement per day had a fourfold higher risk for developing PD when compared with men who had two or more bowel movements per day (Abbott et al, 2001). Early constipation may reflect PD pathology in the autonomic plexuses of the gastrointestinal (GI) tract. Importantly, GI symptoms are significantly more common than genitourinary (GU) symptoms early in the disease. Early prominent GU symptoms (such as urinary urgency and incontinence) are more suggestive of multiple system atrophy. Cardiovascular symptoms are uncommon in early PD. However, using ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy, cardiac sympathetic denervation is common, even at the time of PD diagnosis.

The cognitive-behavioral profile of PD is complex. Even at the time of PD diagnosis, subtle executive or attention problems may be present as mild symptoms or detected by detailed cognitive testing. From a behavioral standpoint, depression and anxiety are common, even in the premotor stage of the disease.

Early Parkinson Disease

In the early stages of PD, the cardinal motor features of the disease, especially

resting tremor, bradykinesia, and rigidity, predominate. At this stage, patients may be symptomatic only unilaterally. Dopaminergic medications (both dopamine agonists and levodopa) provide excellent relief of motor symptoms. Tremor can be an exception to this, as it is sometimes resistant to dopaminergic medications, especially if high in amplitude and occurring during action. During the course of a day, the period of time when dopaminergic medications relieve the parkinsonian symptoms is commonly referred to as the *on* state. Patients are frequently able to function independently (if not close to normally) in their occupation and social activities. The *off* state is the period of time when the effect of medications has worn off, and parkinsonian symptoms return. In early PD, the effect of medications will last until the next dose, and patients experience a consistent effect from their medications. Nonmotor symptoms are not prominent at this stage, but loss of olfaction, RBD, constipation, and mood disorders may all be present and require attention and screening (**Case 1-1**).

Moderate Parkinson Disease

Decreases in the consistent and sustained response to levodopa, termed *motor complications*, are the hallmark of moderate-stage PD. A "wearing-off" phenomenon occurs when the duration of effect of levodopa decreases, requiring more frequent dosing of levodopa and at times the addition of agents that extend the effect of levodopa (catechol-*O*-methyltransferase inhibitors and monoamine oxidase type B inhibitors). During these off times, the cardinal features return, and the patient gradually spends more time in a disabled off state. The other major complication

KEY POINTS

- Nonmotor PD features occurring preclinically or before motor symptoms include hyposmia, REM sleep behavior disorder, constipation, depression, and anxiety.
- In early PD, patients have measurable asymmetric motor impairment and robust response to PD medications, which provide consistent benefit throughout the day.

Case 1-1

A 54-year-old man presented with a 6-month history of intermittent right hand tremor. The tremor concerned him but did not interfere with his daily activities. It was worse when he was speaking or was in a stressful situation. If he concentrated on the tremor, it stopped. He also developed pain in his right shoulder for which he received a cortisone injection with minimal relief. When asked how well he slept, his wife mentioned that over the past 4 years he frequently thrashed around in bed, at times violently, and seemed to be acting out his dreams. On review of systems, he had trouble with constipation during the past decade, requiring daily stool softeners, and he reported a decreased sense of smell. On examination, a constant, low-frequency, pill-rolling tremor was noted in his right hand as it rested in his lap, especially when he was speaking. When asked to hold his hands outstretched in front of him, the tremor stopped briefly, then after a few seconds reemerged. Rapid repetitive movements such as finger tapping and opening and closing of the hand were slow and lower in amplitude on the right. Tone at first seemed normal, but mild rigidity was noted in his right wrist when the left hand was given a task. No tremor, bradykinesia, or rigidity was noted on the left side. When walking, there was less dramatic arm swing on the right and the tremor worsened.

Comment. This case is consistent with presentation of parkinsonism. The asymmetric presentation of his characteristic resting tremor and the pretremor history of constipation and sleep disturbance (likely RBD) make early idiopathic PD the likely diagnosis. When the patient was started on a dopamine agonist, his symptoms improved. Three months later, his examination revealed no rigidity and a lower-amplitude, intermittent, right hand tremor.

KEY POINT

- In moderate PD, response to medications is variable with motor fluctuations and dyskinesia commonly encountered.

of PD therapy is dyskinesia. Dyskinesias are hyperkinetic, typically choreoathetoid, movements that usually occur at the peak level of levodopa. More rarely, they occur in a biphasic pattern (as the medication is kicking in or wearing off). In early stages, when mild, dyskinesias can be unnoticed or not bothersome to the patient and are frequently more disconcerting to friends and family. In fact, most patients would prefer to be dyskinetic than off. However, when more intense, dyskinesias can be severely disabling and even painful. Dyskinetic intrusions can interfere with gait, throwing the patient off balance.

In moderate PD, nonmotor symptoms can be more prominent and bothersome to the patient. Constipation becomes progressively worse over time, requiring escalating doses of stool softeners and motility agents. GU symptoms include erectile dysfunction and urinary symptoms such as urinary urgency and eventually incontinence. Cardiovascular symptoms such as orthostatic hypotension become more prominent and can be exacerbated by PD medications. Depression is seen in 40% to 50% of patients with PD (Reijnders et al, 2008). PD-related depression is not fully explained by the patient's level of disability and can be refractory to medications. Therefore, depression and anxiety in PD may be the result of PD pathology, leading to multiple neurotransmitter deficiencies (**Case 1-2**).

Advanced Parkinson Disease

In advanced PD, motor and nonmotor symptoms continue to progress. The response to levodopa is less robust, less consistent, and less sustained. Further titration of levodopa can be restricted, as it commonly exacerbates or causes many underlying nonmotor symptoms, such as visual hallucinations, orthostatic

Case 1-2

A 66-year-old woman with PD for 8 years presented to clinic for follow-up. Her initial symptoms of left hand resting tremor and left foot dragging responded very well to a dopamine agonist. However, during the next 5 years she required higher doses and the addition of carbidopa/levodopa to control the tremor and keep her mobile. For the past 3 years, her medications seemed to be wearing off before she was scheduled for the next dose. During this off time, she experienced more disability from her tremor and gait disturbance. To prevent this wearing off, she required 4-times-daily dosing of levodopa and the addition of a catechol-*O*-methyltransferase inhibitor. During the follow-up visit, she described a new involuntary, wiggling, dancelike movement of her head, trunk, and left leg when her medicines were peaking. She also reported awakening in the morning with painful toe curling of the left foot, uncomfortable stiffness, and difficulty getting out of bed. She felt fatigued and frequently dozed off while watching television. For 2 years, she had struggled with depression, but felt better after she was switched from a selective serotonin reuptake inhibitor to a selective serotonin-norepinephrine reuptake inhibitor. Initially, she denied cognitive impairment, but then admitted to more difficulty keeping track of multiple home duties. In addition to her long-standing constipation, she developed urinary urgency and had occasional incontinence, especially during off periods. Last year, she had to retire earlier than planned because her symptom control was too inconsistent and her work performance was affected.

Comment. This patient demonstrates a typical case of moderate PD. She is experiencing the common motor complications of wearing-off and peak-dose dyskinesias. These fluctuations have caused increasing disability and more complicated fine-tuning of her medication regimen (higher frequency, lower doses, and additional agents). Nonmotor symptoms (eg, mild cognitive impairment, depression, pain, fatigue, and urinary urgency) have become more bothersome and have required more attention and multidisciplinary care.

hypotension, nausea, and urinary dysfunction. The combination of worsened motor fluctuations, decreased levodopa response, and need to lower PD medication doses results in more motor disability. Furthermore, gait disturbance becomes more prominent with significant postural instability, change in posture, freezing of gait, and festination leading to more frequent falls. Dementia, incontinence, and behavioral problems also become a major source of disability. In cases in which motor features continue to be well controlled by medications or deep brain stimulation (DBS), these nonmotor features become the main source of disability (**Case 1-3**).

ESSENTIAL TREMOR

Demographics

ET is widely considered the most common movement disorder with prevalence studies suggesting ET occurs at a rate of 5% in the general population. A population-based study conducted in Papua New Guinea reported prevalence rates of 4% among patients older than 40 years (Dogu et al, 2003). In a similarly designed study in Finland, a prevalence of 5.6% was reported for this same age group (Rautakorpi et al, 1982). Advancing age is a clear risk factor for development of ET. In patients older than 60 years, the prevalence of ET has been reported to be 9%, with the highest incidence occurring in the sixth through eighth decades of life (Rautakorpi et al, 1982). Genetics also play a significant role in the age of onset of ET. A positive family history of tremor is highly correlated with a younger age of onset (Louis and Ottman, 2006). Conflicting reports have been published in terms of the role of sex with some suggesting ET is more common among men and others showing no sex differences (Das et al, 2009).

KEY POINTS

- In advanced PD, motor symptoms progress and gait dysfunction becomes more prominent. Worsening cognitive and other nonmotor symptoms complicate management.
- Essential tremor (ET) is the most common movement disorder with increased incidence as age increases.

Case 1-3

A 77-year-old man with PD for 16 years presented from a skilled nursing facility. His medications continued to partially control his tremor and stiffness, but they wore off quickly, requiring doses every 2 hours. Most of his on time was spent with bothersome dyskinesia. He was able to feed himself but had difficulty swallowing and needed frequent redirection to sit up and chew slowly. He lost 5.4 kg in the past 2 years. He spent most of his time in a wheelchair, as poor postural stability and freezing of gait had led to frequent falls. His dementia worsened to the point that he was fully dependent on caregivers for most activities of daily living. Despite discontinuation of a dopamine agonist and amantadine, he continued to struggle with visual hallucinations. He also had paranoid delusions that his wife placed him in the nursing facility so that she could have extramarital affairs. The sequential lowering of his levodopa dose, addition of a cholinesterase inhibitor, and an atypical neuroleptic finally brought his psychosis under better control. On examination, he was seated in his wheelchair, with little spontaneous speech or movement. He was emaciated. Due to palilalia, hypophonia, and dysarthria, he had difficulty conversing. He had very prominent masked facies, with mouth parted open and drooling onto his shirt. He was hunched over and leaned to the right. A prominent tremor was present, and he moved very slowly. On gait examination, he was stooped forward, flexed at the waist, used a four-point walker, and had frequent freezing, requiring cues to take his next step. With mildly strong pull test, he had to be caught by the examiner to prevent a fall.

Comment. This case typifies advanced PD. Dopaminergic medications continue to be of some benefit, decreasing tremor, slowness, and stiffness, but doses have had to be drastically decreased because of exacerbation of psychosis. Gait disturbance and nonmotor problems (including dementia, psychosis, orthostatic hypotension, and incontinence) have become the main source of disability. He now requires full assistance with all activities of daily living and had to enter a skilled nursing facility, as his family could no longer care for him at home.

Clinical Features and Diagnosis

Tremor is an involuntary, rhythmic, oscillatory movement, which can present as a resting tremor, action tremor, or intention tremor (**Table 1-6**). *Resting tremor* occurs when a limb is relaxed, without voluntary activity. *Action tremor* can be either postural (when the affected body part is maintained in a certain posture) or kinetic (when the body part is moving voluntarily). *Intention tremor* is a type of kinetic tremor that worsens as the limb approaches the target, classically seen in the setting of cerebellar dysfunction.

The tremor seen in ET is classically a 4-Hz to 12-Hz postural tremor, most commonly seen in the upper extremities, head, and voice. The severity of the tremor varies widely. Some patients have only a fine, low-amplitude, postural tremor in their hands, while others are severely disabled by a high-amplitude, sometimes more proximal, tremor that interferes with most activities of daily living. It is typically seen as an adduction-abduction of the fingers or flexion-extension of the wrist. Pronation-supination of the wrist can also occur but is seen more often in PD. The tremor may start unilaterally but over time typically becomes bilateral. A kinetic tremor is common, whereas a resting tremor is usually not seen except in more severe long-standing cases. A head tremor results in a vertical "yes-yes" tremor or a horizontal "no-no" tremor. The voice, tongue, and chin can also develop tremor. Clinically, tremor can impair daily activities such as feeding (eg, using a spoon, drinking from a cup), writing, typing, and maintaining self-hygiene (**Case 1-4**). Tremor may also interfere with occupational motor tasks. Alcohol can reduce tremor amplitude in 50% to 90% of cases (Koller et al, 1994; Lou and Jankovic 1991), but rebound tremor may occur after the effect has worn off. Archimedes spirals can demonstrate the tremor and can be useful in

TABLE 1-6 Tremor Phenomenology

Type of Tremor	Definition	Example
Rest	Occurs when body part is completely supported against gravity	Hand resting on one's lap or dangling freely while walking
Action	Occurs during voluntary contraction of muscle	
Postural	Occurs when voluntarily maintained against gravity	Hand extended out in front of the body
Kinetic	Occurs when voluntary movement is made	While drinking from a cup
Intention	Tremor has increased amplitude at the end of a goal-directed movement	When performing finger-to-nose testing
Task specific	Occurs only during specific activities or postures	While writing (primary writing tremor)
Isometric	Results when muscle contraction occurs against a rigid object	While making a fist

Case 1-4

A 68-year-old woman with a history of hypertension presented to clinic with worsening tremor in her hands. She reported the tremor started about 10 years ago but was only present when she was under stress or she drank an excessive amount of caffeine. Gradually, over the years the tremor started to interfere with her activities of living. Her handwriting became messy and difficult to read. She could no longer drink from a glass using one hand without spilling, and she had difficulty applying her make-up in the morning. Some nights she drank a glass of wine to relax the tremor, before making dinner. She recalled that her mother had tremor in her hands when she got older. The patient was embarrassed by her tremor and considered quitting her long-time card group. On examination, she had a10-Hz low-amplitude action tremor in her upper extremities. No tremor was present in her head, trunk, or legs, and she had a normal neurologic examination otherwise except for mild hearing loss and slight difficultly with tandem gait. She was initially prescribed propranolol for tremor treatment with the thought of also treating her hypertension. When taking propranolol, she saw mild tremor improvement but developed bradycardia and fatigue at higher doses. Primidone was then prescribed, starting at a very low dose and gradually increasing over months. At 150 mg twice a day, she noticed a 50% improvement in her tremor and was able to drink from a glass again without spilling. Her writing also improved, and she no longer drank wine to control her tremor. Higher doses resulted in intolerable fatigue and mild forgetfulness.

Comment. This case highlights the typical history, examination, and related disability patients with ET report. She clearly meets diagnostic criteria for ET. The case also describes a typical approach to treatment. A balance must always be reached between the development of side effects and trying to achieve the most efficacy and relief for the patient.

documenting progression or response to treatment over time (**Figure 1-1**). **Table 1-7** lists the current diagnostic criteria for ET.

Although in the past ET has been thought of as a pure tremor disorder, recently several other motor and non-motor signs and symptoms have been

KEY POINT

- ET affects the upper extremities bilaterally, resulting in a 4-Hz to 12-Hz postural tremor. It can also result in head and voice tremor and significant disability.

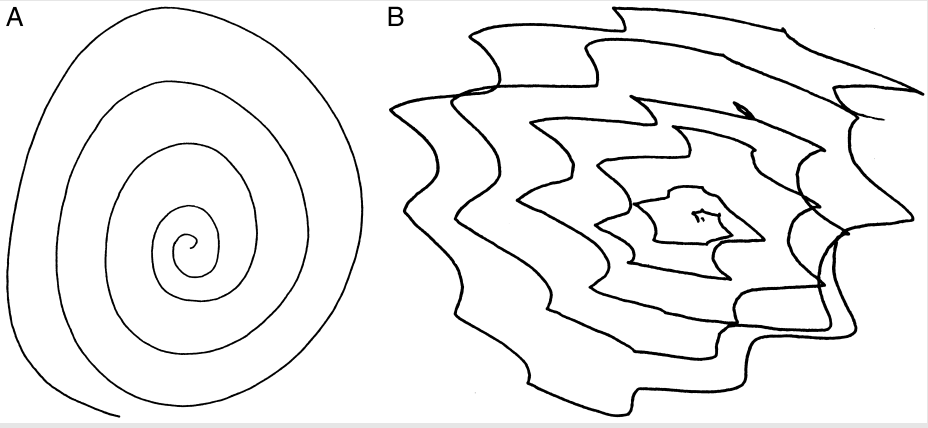

FIGURE 1-1 Archimedean spirals drawn by individuals with and without essential tremor. *A*, A spiral drawn by an individual without tremor. *B*, A spiral drawn by a patient with severe essential tremor.

KEY POINTS

- ET is newly recognized to have a higher association with cognitive decline, anxiety, gait abnormalities, and hearing loss.
- Differential diagnosis for action tremor includes physiologic tremor, ET, PD, dystonia, and Wilson disease.

TABLE 1-7 Core Criteria and Secondary Supporting Criteria in Essential Tremor

▶	**Core Criteria**
	Bilateral action tremor of the hand and forearms (not rest tremor)
	Absence of other neurologic signs (except for cogwheel phenomenon)
	May have isolated head tremor with no signs of dystonia
▶	**Secondary Criteria**
	Long duration (>3 years)
	Positive family history
	Beneficial response to alcohol

Adapted with permission from Bain P, Brin M, Deuschl G, et al. Criteria for the diagnosis of essential tremor. Neurology 2000;54(11 suppl 4):S7. Copyright © 2000, AAN Enterprises, Inc. All rights reserved.

associated with ET. Patients with ET have been shown to have an increase in anxiety symptoms (Tan et al, 2005), cognitive decline (Benito-Leon et al, 2006), tandem gait abnormalities (Singer et al, 1994), and hearing loss (Benito-Leon et al, 2007a), suggesting that ET may be a less focal disease than once appreciated.

Differential Diagnosis

An estimated 30% to 50% of patients with ET are misdiagnosed with PD or other tremor disorders (Jain et al, 2006). When evaluating a patient with action tremor, the most common differential diagnosis includes enhanced physiologic tremor, PD, adult-onset idiopathic dystonia, and Wilson disease. **Table 1-8** describes the prevalence, features, and differential diagnoses of action tremor. Quantitative computerized analysis of tremor is available at some tertiary care centers and may guide the clinician in distinguishing ET from other types of tremor, but its diagnostic validity has not been established.

Everyone has a normal, underlying physiologic tremor (usually only detected with electrophysiologic techniques) that can be more pronounced in times of stress or fatigue. Enhanced physiologic tremor should be considered in the differential diagnosis for a postural tremor, especially when encountered in the setting of certain drugs. The most common drugs to consider are caffeine, nicotine, lithium, prednisone, β-adrenergic bronchodilators, valproate, and selective serotonin reuptake inhibitors.

Patients with tremor should be screened for hyperthyroidism, especially in the setting of associated weight loss, diarrhea, or other supportive features. In patients who present with action tremor before the age of 40, the possibility of Wilson disease should be considered with a measurement of serum ceruloplasmin. If other clinical features suggestive of Wilson disease, such as dysarthria, dystonia, and parkinsonism, are present, an experienced ophthalmologist should perform a careful slit-lamp examination of the eye, looking for Kayser-Fleischer rings on Descemet membrane.

Natural History

Patients with ET experience a slowly progressive course usually presenting in adulthood, although some patients will experience symptoms in childhood. As the disease progresses, the tremor usually increases in amplitude, decreases in frequency, and spreads proximally (Elble et al, 1994). Women tend to develop more head tremor than men. One recent study reported that patients with asymmetric tremor have a worse prognosis over time (Putzke et al, 2006). As symptoms worsen and impairment increases in the dominant limb, patients are more likely to seek medical treatment. In the past, ET has been referred to as "benign ET" because ET does not

TABLE 1-8 **Prevalence, Features, and Differential Diagnosis of Action Tremor**

Variable	Essential Tremor	Enhanced Physiologic Tremor	Parkinson Disease	Adult-Onset Idiopathic Dystonia	Wilson Disease
Overall prevalence (9%)	0.4–6.0	Unknown[a]	0.01–0.4	0.03	0.003
Age at onset (year)[b]	>70	Any age	>70	<50	<20[c]
Type of tremor	Action	Action	Resting and action	Action	Resting and action
Other characteristics	Distal tremor, with the greatest amplitude at the wrist joint and the least at the shoulder; usually mildly asymmetric, with an average 30% difference between sides	In contrast to essential tremor, may be present equally in the outstretched arms and legs; signs of the underlying cause of enhanced tremor may be present (eg, physical manifestations of hyperthyroidism including tachycardia and exophthalmos)	Resting tremor often has a pill-rolling quality; other signs of Parkinson disease usually present (eg, slow finger taps, minimal arm swing, rigidity, and flexed posture)	Tremor often irregular and jerky rather than regularly oscillatory; there may be a null point, a hand or arm position that will result in temporary resolution of the tremor; other signs of dystonia typically present (eg, abnormal flexion or extension of the fingers or wrist while arms are extended, or torticollis)	A wing-beating tremor (a proximal tremor at the shoulder when it is adducted, the elbow flexed, and the fingers of each hand pointed toward one another in the midline); other neurologic abnormalities present (eg, dystonia, dysarthria, parkinsonism)
Progressive	Yes	No	Yes	Yes	Yes
Familial form (% of cases)	30–50	0	1	5–30	100
Mode of inheritance	Autosomal dominant	Not applicable	Autosomal dominant	Autosomal dominant	Autosomal dominant

[a] Although the prevalence is unknown, most medications acting on the central nervous system can produce tremor as a side effect.
[b] This is the age at which 50% of cases occur.
[c] Virtually all patients have neurologic manifestations by the age of 40 years.

KEY POINT

- Propranolol and primidone are the most effective medications in treating ET and have differing side effect profiles.

reduce life expectancy and was believed to be relatively asymptomatic other than the presence of a tremor. However, ET can be quite severe and result in significant physical and social disability (Koller et al, 1986). Of patients with ET who seek medical attention, 15% to 25% retire early and 60% choose not to apply for a job or promotion because of tremor (Bain et al, 1994).

Pharmacologic Treatment

Several medication options are available when tremor causes enough disability or social embarrassment to justify pharmacologic intervention. The choice of medication must balance efficacy in reducing tremor with avoidance of intolerable side effects. In general, arm/hand tremor is more effectively treated by medications than is head or voice tremor.

Propranolol is the most well-studied beta-blocker used in the treatment of ET. It was the first medication to be shown effective against ET. Between 45% and 75% of patients will have some improvement in arm tremor compared with placebo; thus, it is one of the criterion standard therapies of ET. Other selective beta-antagonists such as sotalol and nadolol also appear to be effective but have not been as well studied compared with the nonselective beta-antagonist. Propranolol can be dosed as a standard or long-acting formulation and is usually initiated with 20 mg/d. It can be titrated weekly to an effective dosage, typically 120 mg/d, and as high as 320 mg/d. Patients who develop side effects to propranolol usually do not develop tolerance over time, and this often limits the effectiveness of this medication. Elderly patients, in particular, may experience symptomatic hypotension or bradycardia. Other common side effects include impotence, drowsiness, confusion, headache, and exercise intolerance (Benito-Leon et al, 2007b). Because beta-blockade can cause bronchoconstriction, asthma and chronic obstructive pulmonary disease are relative contraindications to propranolol.

Primidone, a structural analog of phenobarbital, is the other criterion standard medication for ET. It has similar efficacy to propranolol but with a different side effect profile. The most bothersome side effects with primidone are somnolence and fatigue. The typical starting dose is 25 mg nightly. To avoid side effects, the medication dose is titrated slowly. It may take 6 to 8 weeks for patients to achieve an effective dose (average 750 mg/d divided into three doses a day), and patients should be encouraged to continue titrating up if side effects are not a limiting factor. Twenty percent of patients cannot tolerate this medication because of nausea, drowsiness, and unsteadiness, even starting at very low doses (Findley et al, 1985). This often leads to the discontinuation of the medication. Unlike propranolol, the early mild side effects of primidone are habituating and, therefore, may be tolerated with slow upward titration in dose.

Propranolol and primidone are frequently used as combination therapy and in some patients may provide even greater relief of tremor. For patients who have failed these two medications, other less well-studied oral agents may be used to treat ET, including benzodiazepines, topiramate, and gabapentin (Zesiewicz et al, 2005). These medications have varying effectiveness but may be worth a trial in persistently symptomatic patients (**Table 1-9**).

Botulinum toxin injections into the forearm muscles for hand tremor, cervical muscles for head tremor, or vocal cords for voice tremor can sometimes help dampen tremor. The challenge with this approach is to appropriately target the muscles (sometimes difficult to do in arm and head tremor as it may involve a complicated pattern of muscles) and to inject the appropriate amount of toxin for clinical effect without causing significant muscle weakness. Please refer to

TABLE 1-9 Doses and Side Effects of Medications for Essential Tremor

Agent	First-Line Agent	Level of Evidence	Usual Starting Dose	Usual Therapeutic Dose	Side Effects
Propranolol (Inderal)	Yes	A	20 mg/d	160 mg/d to 320 mg/d	Fatigue, impotence, headache, breathlessness, bradycardia, depression, confusion, reduced arterial pressure
Propranolol LA (Inderal LA)	Yes	A		80 mg/d to 320 mg/d	Skin eruptions, transient dizziness
Primidone (Mysoline)	Yes	A	25.0 mg/d to 62.5 mg/d	62.5 mg/d to 1000.0 mg/d	Sedation, nausea, vomiting, ataxia, dizziness, confusion, vertigo
Atenolol (Tenormin)	No	B		50 mg/d to 150 mg/d	Lightheadedness, nausea, cough, dry mouth, sleepiness
Gabapentin (Neurontin)	No	B	300 mg/d	1200 mg/d to 3600 mg/d	Drowsiness, fatigue, slurred speech, imbalance, nausea, dizziness
Sotalol (Sotacor)	No	B		75 mg/d to 200 mg/d	Decreased alertness
Alprazolam (Xanax)	No	B	0.75 mg/d	0.75 mg/d to 2.75 mg/d	Sedation, fatigue, tolerance, potential for abuse
Topiramate	No	B		Up to 400 mg/d	Appetite suppression, weight loss, paresthesias, anorexia, concentration difficulties
Clonazepam (Klonopin)	No	C		0.5 mg/d to 6.0 mg/d	Drowsiness
Nadolol (Corgard)	No	C		120 mg/d to 240 mg/d	None
Nimodipine (Nimotop)	No	C	120 mg/d	120 mg/d to 300 mg/d	Orthostatic hypotension, headache, heartburn

Adapted with permission from Louis ED. Clinical practice: essential tremor. N Engl J Med 2001;345(12):887–891. Copyright © 2001, Massachusetts Medical Society. All rights reserved.
Adapted with permission from Zesiewicz TA, Elble R, Louis ED, et al. Practice parameter: therapies for essential tremor: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2005;64(12):2008–2020. Copyright © 2005, AAN Enterprises, Inc. All rights reserved.

the chapter ''Neurotoxin Injection for Movement Disorders'' for more details on the treatment of ET with neurotoxin injections.

For patients with severe tremor refractory to medications, surgical procedures may be considered and are usually highly effective. Thalamotomy (lesioning of the thalamus) is a very effective approach. However, thalamotomy has increasingly been replaced by DBS of the ventralis intermedius nucleus. DBS has

KEY POINTS

- Dystonia is a neurologic symptom dominated by involuntary, sustained or spasmodic, repetitive, and patterned contractions of muscles, causing twisting and other abnormal movements or postures.
- Patients with dystonia frequently have a sensory trick (*geste antagoniste*) that improves dystonia and can aid in the diagnosis.

the advantage of being a reversible, nondestructive, adjustable therapy that can be better tolerated when performed bilaterally. Please refer to the chapter "Deep Brain Stimulation for Movement Disorders" for more details on DBS therapy.

DYSTONIA

Phenomenology

Dystonia is a neurologic disorder dominated by involuntary, stereotyped, patterned (sustained or spasmodic) contractions of muscles. These movements frequently cause twisting and other abnormal movements or postures. Dystonia causes involuntary simultaneous cocontraction of both agonist and antagonist muscles, resulting in the "twisted" movements with unintended spread to adjacent muscles. Dystonic contractions are usually sustained at the peak of the movement, differentiating dystonic contractions from the brief contractions seen in chorea or myoclonus. In addition, dystonic contractions involve the same pattern of muscles, whereas in chorea the involved muscles are more random.

Dystonia is characterized as a hyperkinetic movement disorder because of the development of excessive movements. However, dystonic movements may be slow or fast and can be associated with tremor (dystonic tremor). Dystonic movements typically worsen with action and can be very task specific in some patients. As the dystonic syndrome progresses, actions in one body region can induce dystonic movements in another region; this is referred to as *overflow dystonia*.

One fascinating feature of dystonia is the sensory trick (*geste antagoniste*) in which a specific touch to an affected body part can help improve the dystonia. Identification of this phenomenon can be helpful in making the diagnosis of dystonia and may offer a unique way to modulate the movements. Dystonia is frequently misdiagnosed as spasticity

TABLE 1-10 Classification of Dystonia

Classification and Type	Description
Age of Onset	
Early-onset (childhood-adolescent-onset) dystonia	<26 years
Late-onset (adult-onset) dystonia	>26 years
Distribution	
Focal	Single body region
Segmental	Contiguous body regions
Hemibody	Ipsilateral arm and leg
Multifocal	> Two noncontiguous body parts
Generalized	Entire body
Etiology	
Primary dystonia	
Secondary dystonia	

or rigidity, or thought to be due to psychogenic causes. A greater awareness of the disorder is needed.

Classification of Dystonia

Dystonia is a heterogeneous disorder with multiple etiologies and varying clinical presentations.

Dystonia can be classified based on the age of onset (childhood/adulthood), distribution of affected body regions (focal, segmental, multifocal, or generalized), etiology (primary/idiopathic or secondary), or genetics (Tarsy and Simon, 2006) (**Table 1-10**). Classification based on age is clinically useful in predicting progression of disease. Typically, the earlier the dystonia begins, the more likely it is to be severe and subsequently generalize. Classification based on the affected body part is useful in describing the physical appearance of the dystonia. Examples of classic focal dystonias can be seen in **Figure 1-2**.

Historically, dystonia has been largely classified into two groups based on etiology: (1) primary (or idiopathic) and (2) secondary (or symptomatic). Secondary dystonia refers to dystonia occurring as a result of a known injury or destructive process (**Table 1-11**). Primary dystonia, originally termed *idiopathic* because no clear cause of the dystonia could be determined, is now a less accurate term because several genes have now been recognized in association with this type of dystonia. Recently the term *primary torsion dystonia*, instead of *primary dystonia*, has been proposed if the following three criteria are met: (1) dystonia is the sole abnormality directly attributable to the condition; (2) no laboratory or imaging abnormalities suggest an acquired or degenerative cause of dystonia, and no dramatic response to levodopa suggests dopa-responsive dystonia; and (3) historical information fails to implicate a known acquired or environmental cause of dystonia (Bressman, 2004).

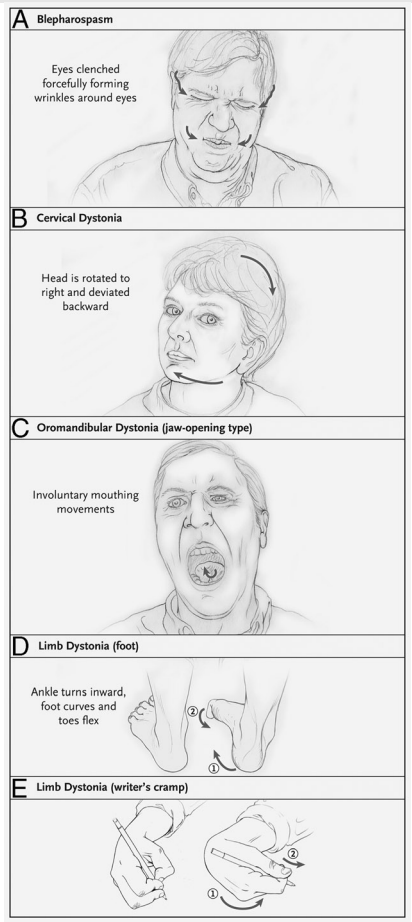

FIGURE 1-2 Examples of focal abnormal postures in dystonia. *Panel A* shows blepharospasm causing involuntary eye closure with reactive lower facial grimacing. *Panel B* shows cervical dystonia causing combined head rotation and backward head deviation. *Panel C* shows oromandibular dystonia causing involuntary jaw opening. *Panel D* shows lower limb dystonia causing involuntary ankle inversion and toe flexion. *Panel E* shows upper limb dystonia causing flexion dystonia of the wrist and digits while the patient is writing.

Childhood-/Adolescent-Onset Primary Dystonia

Early-onset dystonia usually begins with symptoms in a limb, most commonly a leg, during activities such as running or walking. Over time, the dystonia can

KEY POINTS

- Dystonia can be classified based on age of dystonia onset, distribution of the body part(s) affected, etiology (primary or secondary), or genetics.
- Childhood-/adolescent-onset primary dystonia typically begins in a limb and often progresses to generalized dystonia.

become less specific to a certain action and eventually occur at rest and result in a sustained posture. The dystonia often spreads to other body regions, including the other leg, trunk, and arms within 5 years. The average age of onset is around 9 years. When the age of onset is late childhood or adolescence, the

TABLE 1-11 Secondary Dystonias

Types of Secondary Dystonia	Subtypes	Examples
Dystonia plus	Dopa-responsive dystonia	GTP cyclohydrolase-1 mutations and tyrosine hydroxylase mutations (DYT5), other biopterin deficiencies, dopamine agonist-responsive dystonia (aromatic acid decarboxylase deficiency)
	Myoclonic-dystonia (DYT11)	
	Rapid-onset dystonia and parkinsonism (DYT12)	
Heredodegenerative dystonias/metabolic	Autosomal dominant	Huntington disease
		Machado-Joseph disease (SCA3)
		Dentatorubral-pallidoluysian atrophy (DRPLA)
	Autosomal recessive	Wilson disease
		G_{M1} and G_{M2} gangliosidosis
		Metachromatic leukodystrophy
		Homocystinuria
		Hartnup disease
		Glutaric acidemia
		Methylmalonic aciduria
		Pantothenate kinase–associated neurodegeneration (PKAN)
		Dystonia lipidosis
		Ceroid lipofuscinosis
		Ataxia telangiectasia
		Neuroacanthocytosis
		Intraneuronal inclusion disease
		Juvenile parkinsonism (Parkin)
	X-linked	Lubag (X-linked dystonia-parkinsonism or DYT3)
		Lesch-Nyhan syndrome
	Mitochondrial	Myoclonic epilepsy with ragged red fibers
		Myopathy, encephalopathy, lactic acidosis, and strokelike episodes syndrome
		Leber disease

continued on next page

TABLE 1-11 *Continued*

Types of Secondary Dystonia	Subtypes	Examples
Acquired structural lesions	Perinatal ischemic injury	
	Ischemic and hemorrhagic infarcts	
	Brain infection	Viral encephalitis, encephalitis lethargic, Reye syndrome, subacute sclerosing panencephalitis, Creutzfeldt-Jakob disease, HIV infection
	Trauma	
	Toxin exposure	Manganese, carbon monoxide, carbon disulfide, cyanide, methanol, disulfiram, 3-nitroproprionic acid
	Brain tumor	
Other neurodegenerative conditions	Parkinson disease	
	Corticobasal degeneration	
	Multiple system atrophy	
	Progressive supranuclear palsy	
Tardive syndromes, drug induced	Levodopa, dopamine agonist, dopamine receptor–blocking agents, fenfluramine, anticonvulsants, ergots, some calcium channel blockers	

HIV = human immunodeficiency virus.

Adapted with permission from Fernandez HH. Classification, presentation, medical and surgical treatment of dystonia. Presented at: 61st Annual Meeting of the American Academy of Neurology: May 1, 2009; Seattle, WA.
Adapted with permission from Fahn S, Bressman SB, Marsden CD. Classification of dystonia. Adv Neurol 1998;78:1–10.

dystonia may begin in the arm and is less likely to become generalized. Patients with early-onset primary dystonia usually have normal cognitive functioning.

In recent decades, several gene loci have been found for childhood-onset dystonias. In 1989, the DYT1 gene locus for idiopathic torsion dystonia was mapped to chromosome 9q. A GAG deletion mutation in the DYT1 gene (which encodes for the protein torsin A) has been associated with early-onset dystonia. This autosomal dominant condition has only a 30% penetration rate (Ozelius et al, 1997) and is more common among Ashkenazi Jews (Bressman et al, 1994). The dystonia phenotype can vary widely within families and may include pure focal dystonia. The function of torsin A is still not well understood, but it is a member of the AAA+ family of chaperone proteins (McLean et al, 2002). Torsin A is widely expressed in the CNS and periphery and may have a possible role in neurotransmitter release (Balcioglu et al, 2007) (**Case 1-5**). The test for the DYT1 mutation is now commercially available and should be performed in patients with generalized dystonia with age of onset less than 26 years of age (or if the patient has an affected family member with early-onset generalized dystonia, the test may

KEY POINT

- Patients presenting with generalized dystonia before the age of 26 should be tested for the DYT1 gene mutation.

Case 1-5

A 10-year-old girl of Ashkenazi Jewish descent presented with increasing difficulty walking. When in a seated position she felt fine, but as she tried to walk, her left foot inverted, causing her to walk on the outside of the foot. Interestingly, when she walked backward, the foot straightened out and was flat on the ground. She also reported having more difficulty in school with writing. Her hand tired after 10 minutes, and she had to press very hard on the paper to achieve the proper hand control. When writing, her right hand flexed at the wrist, her forearm muscle appeared tense, and she elevated her right shoulder. Subtle inversion of the left foot occurred when she concentrated. The patient was the product of a normal pregnancy and delivery. She achieved normal developmental milestones. Family history was positive for a grandfather with an abnormal gait starting in childhood who had been diagnosed with mild cerebral palsy. The patient was treated with carbidopa/levodopa titrating up slowly to 300 mg 3 times a day with no benefit, ruling out the possibility of dopa-responsive dystonia as a diagnosis. MRI of the brain was normal, decreasing the likelihood of secondary dystonia. The patient then tested positive for the DYT1 gene. She started taking trihexyphenidyl 8 mg 3 times a day, and her walking and handwriting were moderately improved.

Comment. This case illustrates a classic example of a patient with young-onset primary generalized DYT1-positive dystonia. Treatment with trihexyphenidyl was effective in improving her symptoms at high doses. If medication therapy had not been helpful, then DBS surgery would have been the next treatment option to consider.

be performed after age 26) (Bressman et al, 2000).

Adult-Onset Primary Dystonia

The clinical spectrum of adult-onset dystonia is quite different from young-onset dystonia. It often begins as a focal dystonia in the upper body, usually affecting the arms, neck, or cranial muscles. Symptoms may worsen over time and spread to adjacent body parts, resulting in segmental dystonia, but rarely does the dystonia generalize. Idiopathic adult-onset focal dystonias are usually sporadic, although, on occasion, more than one member of the family may have a focal dystonia. **Table 1-12** highlights the common adult-onset focal dystonias; these are also described in more detail later in this chapter.

The prevalence of idiopathic adult-onset dystonia is much more common than previously recognized, estimated from 3.4 to 6.2 per 100,000. Adult-onset dystonia usually begins in the fourth or fifth decade of life but may develop earlier or later. Women are affected 3 times more frequently than men. The severity of symptoms greatly varies. Some patients experience only mild spasms with relatively stable symptoms, while others have more progressive, severe, disabling spasms. A small percentage of patients (usually younger patients with cervical dystonia) experience remission, but remission is often transient.

Blepharospasm is the result of involuntary contraction of the orbicularis oculi muscles causing intermittent or sustained bilateral eyelid closure. Spasms are made worse by stress, exposure to bright light, or wind. Actions such as looking upward, walking, reading, and, less commonly, watching television or driving may also exacerbate spasms. Patients will frequently wear dark glasses to help

TABLE 1-12 Primary Adult-Onset Focal Dystonias

Type of Dystonia	Main Clinical Features	Common Misdiagnoses
Cervical dystonia (spasmodic torticollis)	Abnormal head posture, head tremor, head pain	Muscle strain, cervical disk disease, osteoarthritis
Blepharospasm	Increased blink rate, forced eye closure, difficulty opening eyes	Myasthenia gravis, dry eyes
Oromandibular dystonia	Jaw clenching (bruxism), jaw in open position, lateral jaw shift	Temporomandibular joint syndrome, myasthenia gravis, dental malocclusion, edentulous movements
Spasmodic dysphonia		
Adductor type	Voice breaks and strain	Chronic laryngitis, vocal cord polyps, voice tremor, psychogenic causes
Abductor type	Breathy voice	
Mixed type	Features of both	
Limb dystonia	Action dystonias affecting writing, playing musical instruments, handling tools, and walking	Nerve entrapment, overuse syndromes, muscle cramps
Axial dystonia	Movements of shoulders, back, or abdomen	Myoclonus, motor tic, psychogenic causes

alleviate the symptoms and often use sensory tricks, such as touching the upper eyelid on one side, to help relieve the spasms. In some patients with blepharospasm, the dystonia can spread to the lower face or cervical area. A history of head trauma with loss of consciousness, older age of onset, and female sex are all thought to be risk factors for the spread of dystonia (Defazio et al, 1999).

Oromandibular dystonia occurs in the region of the jaw, lower face, and mouth. Spasms can result in jaw closing, opening, protrusion, or lateral deviation. Spasms may also involve the tongue or other adjacent muscle groups. Frequently, patients have contractions of the orbicularis oris muscles, resulting in oromandibular spasms. Patients with oromandibular dystonia will often report symptoms such as difficulty and pain with chewing, eating, or speaking.

Laryngeal dystonia, or spasmodic dystonia, occurs when dystonic spasms affect the vocal cords. There are two types—adductor and abductor spasmodic dystonia—although mixed types may also occur. The most common type, adductor spasmodic dystonia, results in overadduction of the vocal cards, leading to a strangled-sounding speech with abrupt initiation and termination. Abductor spasmodic dystonia is seen with overabduction of the vocal cards and results in a breathy, whispering quality of speech.

Cervical dystonia, or spasmodic torticollis, affects the muscles of the neck, causing stereotyped abnormal head and neck posturing. This is the most common adult-onset focal dystonia with an

estimated prevalence of 5.7 to 8.9 per 100,000 persons (Epidemiological Study of Dystonia in Europe (ESDE) Collaborative Group, 2000; Nutt et al, 1988). The head can deviate in various directions, including rotation (torticollis), tilt to the side (laterocollis), pulling forward (anterocollis), or pulling backward (retrocollis). Elevation or anterior displacement of the shoulder is also common. Many patients will have a combination of these abnormal postures. Unlike other focal dystonias, pain is extremely common in cervical dystonia and is a source of significant disability in these patients. Common sensory tricks used in cervical dystonia include lightly touching the chin, face, or back of the head (**Case 1-6**).

Focal limb dystonia occurs when a limb develops involuntary twisting repetitive muscular contractions, causing abnormal posturing. Limb dystonia is typically task specific, occurring primarily when the patient performs a certain action. Writer's cramp is an example of limb dystonia that only occurs when a patient is writing. When a patient with writer's cramp picks up a pencil and puts it to the paper, the fingers and wrist develop abnormal posturing. The fingers generate an abnormal forceful grip, or the fingers may hyperextend, preventing the grip of the pencil. The wrist will also frequently overflex or extend.

Primary focal limb dystonia occurring in the lower extremities is rare in

Case 1-6

A 55-year-old woman presented with an 8-year history of painful neck spasms. She had been previously diagnosed with fibromyalgia. Her symptoms began with a slight pulling of the chin to the right, which became more pronounced over time. She had increasing trouble looking to the left, which also resulted in a no-no head tremor. She developed severe stabbing pain in her right posterior neck region. The head posture would improve if she gently touched her right chin, leaned her head against a wall while sitting, or laid down. The patient had experienced a minor whiplash injury a few years before the onset of her condition. She had been taking no medications except ibuprofen at times. Recently she developed pain and numbness radiating down her right arm in the C6 distribution, which prompted her to see a neurologist. By that time she was no longer able to read or drive long distances and was considering an early retirement and applying for disability insurance because of the painful spasms and associated head tremor. At presentation, the patient was diagnosed with cervical dystonia with severe right torticollis, dystonic head tremor when looking to the left, and right C6 radiculopathy. A cervical spine MRI scan confirmed moderate degenerative cervical spine changes and C6-C7 neuroforaminal narrowing. The patient was treated with botulinum toxin injections; and after the dose and muscles targeted were refined, she experienced a 50% improvement in her symptoms in head position, range of motion, and pain, but still required a C6-C7 laminectomy for her radicular symptoms.

Comment. This is a classic example of a patient with cervical dystonia who went undiagnosed and untreated for a number of years before getting relief from botulinum toxin therapy. Unfortunately, she developed significant degenerative cervical spine disease as a result of the chronic muscle spasms, which is not uncommon. This case illustrates how important it is to arrive at a correct diagnosis and initiate treatment to prevent secondary problems and avoid greater disability.

adulthood. When it does occur, it usually affects the distal leg, causing ankle inversion, foot plantar flexion, and toe flexion, and it often worsens when walking. Over time, the leg may develop a fixed dystonic posture and dystonia may spread up the leg. Patients with adult-onset who develop focal leg dystonia should be evaluated for a focal CNS lesion or early parkinsonism.

Dystonia-plus syndromes include dystonia as well as other neurologic findings on examination. In general, these are rare disorders that are different from heredodegenerative disorders or other secondary dystonias since they are not associated with known neuropathologic findings (Fahn et al, 1998). The most common forms of dystonia-plus syndromes include the following:

(1) *Dopa-responsive dystonia (DRD, DYT5, Segawa disease*) presents in children with previously normal motor and cognitive development. It typically begins with foot dystonia, gait abnormalities, and hyperreflexia, progressing to generalized dystonia (Nygaard et al, 1991). The disorder may be confused with the dystonia seen in spastic cerebral palsy. A unique feature of DRD is its diurnal fluctuation, with worsening of symptoms late in the day. It is usually inherited in an autosomal dominant fashion, caused by a point mutation in the gene for guanosine triphosphate cyclohydrolase 1 (a gene involved in the synthesis of tetrahydrobiopterin, a cofactor in dopamine synthesis). The disease may also occur in autosomal recessive forms due to a mutation in the tyrosine hydroxylase gene. DRD is extremely sensitive to treatment with levodopa, and the effect is sustained over time. Interestingly, 18F-flurodopa PET scans are normal.

(2) *Myoclonus-dystonia (DYT11)* is a condition that usually begins in childhood or adolescence, presenting with dystonia of the arms, trunk, and oromandibular region, and is associated with brief myoclonic muscle jerks. It is made worse with alcohol ingestion (Quinn, 1996). Myoclonus-dystonia is caused by a mutation in the ϵ-sarcoglycan gene. The mutation is inherited in an autosomal dominant pattern (Zimprich et al, 2001).

(3) *Rapid-onset dystonia-parkinsonism (DYT12)* is an autosomal dominant condition presenting in adolescence with rapid development of dystonia and parkinsonism, followed by a plateau of symptoms. Interestingly, it is not associated with nigrostriatal neural loss or clinical response to levodopa (Dobyns et al, 1993).

Secondary Dystonia

Secondary dystonias, also known as symptomatic dystonias, represent a large and diverse group of disorders. They include neurodegenerative/metabolic dystonias, dystonias of acquired structural lesions, and tardive dystonia (**Table 1-11**). Compared with primary dystonias, secondary dystonias are often associated with other neurologic symptoms. Secondary dystonia tends to occur more commonly at rest and is associated with known environmental or hereditary causes. The most common cause of secondary dystonia is perinatal brain injury, whereas most cases of hemidystonia are caused by focal brain lesions. Brain imaging is extremely helpful in confirming the diagnoses in these cases.

Tardive dystonia should be considered in patients with chronic dystonia and a history of exposure to dopamine-blocking medications, certain anticonvulsants, or antidepressants. Patients with tardive dystonia typically have prominent oromandibular, lingual, and cervical

KEY POINTS

- Adult-onset primary dystonia typically is a focal dystonia usually affecting cranial or cervical areas, resulting in blepharospasm, oromandibular dystonia, laryngeal dystonia, cervical dystonia, or upper limb dystonia.
- Dystonia-plus syndromes are rare heredodegenerative disorders in which dystonia occurs in addition to other neurologic findings on examination and are not associated with any known neuropathologic findings.
- Secondary dystonia includes dystonia from heredodegenerative and metabolic causes of dystonias, dystonia due to acquired structural lesions, and tardive dystonia.

KEY POINT

- Paroxysmal dystonia syndromes are associated with episodes of dystonia followed by complete resolution of symptoms between episodes.

involvement (including the characteristic lip smacking and prominent retrocollis), although some will develop generalized dystonia. Some patients have a mixed movement disorder with both dystonia and chorea, tremor, or tics. Tardive dystonia is difficult to treat and often develops into a chronic lifelong condition. Withdrawing the offending medication is usually the first step to prevent worsening of symptoms. In patients with unstable psychiatric conditions, withdrawal of medications may not be safe and can present a management challenge. Fortunately, newer atypical neuroleptics are associated with a lower incidence of tardive dystonia (**Case 1-7**).

Paroxysmal Dystonia

These disorders usually begin in childhood or young adulthood and are associated with episodes of dystonia and other involuntary movements followed by complete resolution of the symptoms between episodes. They are divided into the following categories:

(1) *Kinesigenic dystonia* in which the dystonia is brought about by movement
(2) *Nonkinesigenic dystonia* in which the dystonia is not brought about by movement and can occur at rest or during activities
(3) *Exercise-induced dystonia* in which the abnormal movements occur after prolonged exercise

Recent data have now identified several genes that are associated with paroxysmal dystonia (**Table 1-13**). Treatment with carbamazepine may be especially helpful for patients with kinesigenic paroxysmal dystonia.

Genetic Classification of Dystonia

Many advances have recently occurred in the area of dystonia genetics. Recent

Case 1-7

A 37-year-old woman with a history of bipolar disorder treated with risperidone gradually developed intermittent facial grimacing, back arching, and neck extension. She subsequently developed difficulty reading, driving, and eating because of her abnormal head posture and difficulties with chewing. She had difficulty sitting in a chair and preferred to lie down. She experienced significant neck and back spasms and was very concerned and embarrassed by the abnormal movements. On examination, she had phasic lingual and oromandibular dystonic movements, opisthotonic posturing of her back, and retrocollis. The patient had a complete workup, including a normal brain MRI, which failed to reveal a cause of her symptoms. She was diagnosed with tardive dystonia. Reduction of the risperidone resulted in the development of a manic episode. She was admitted to an inpatient psychiatric unit where lithium was initiated, resulting in improved mood control. Her dystonia improved only slightly. Once her mood stabilized, her dystonia was treated with a low dose of trihexyphenidyl and baclofen. Her cervical dystonia was successfully treated with botulinum toxin injections. The patient still had mild symptoms but considerably less disability.

Comment. This case highlights the unfortunate development of tardive dystonia in a patient treated chronically with a neuroleptic medication to control her bipolar disorder. This case describes a classic tardive dystonia, with retrocollis being especially common. Treatment of tardive dystonia is often challenging and often managed by a multidisciplinary team, in this case psychiatry and neurology, for best results.

TABLE 1-13 DYT Genetic Classification

DYT Locus	Other Names	Chromosome	Gene	Mutation	Clinical Features
DYT1	Primary torsion dystonia: idiopathic torsion dystonia, Oppenheim dystonia, dystonia musculorum deformans 1, TOR1a	9q34	Torsin A	GAG deletion	Symptoms start in childhood or young adulthood in the limb and then often become generalized
DYT2	Autosomal recessive primary torsion dystonia	Unknown	Unknown	Unknown	Childhood onset with segmental or generalized symptoms
DYT3	X-linked dystonia—parkinsonism, Lubag	Xq13.1	TAF1	Unknown	Male patients develop focal dystonia followed by segmental or generalized dystonia followed by parkinsonism in 50% of cases; endemic in Panay, Philippines
DYT4	Torsion dystonia 4, non-DYT1 primary torsion dystonia	Unknown	Unknown	Unknown	Primarily laryngeal dystonia; sometimes cervical; often generalized; psychiatric symptoms in some; described in one large Australian family
GCH1 (formerly DYT5)	Dopa-responsive dystonia, Segawa disease, hereditary progressive dystonia with marked diurnal variation	14q22.1-14q22.2 11p15.5 for tyrosine hydroxylase	Guanosine triphosphate cyclohydrolase, rarely tyrosine hydroxylase	Variable (>60 mutations reported)	Dystonia and parkinsonism usually begin in childhood and have diurnal variation and dramatic response to levodopa

continued on next page

TABLE 1-13 *Continued*

DYT Locus	Other Names	Chromosome	Gene	Mutation	Clinical Features
DYT6	Adolescent-onset primary torsion dystonia of mixed type	8p21-8p22	Unknown	Unknown	Focal dystonia or segmental; may become generalized; reported in Amish families
DYT7	Adult-onset focal primary torsion dystonia	8p11.3	Unknown	Unknown	Onset in adulthood presenting with focal dystonia, hand tremor; reported in German families
DYT8	Paroxysmal dystonic choreoathetosis; paroxysmal nonkinesigenic dyskinesia; Mount-Reback syndrome	2q33-2q36	Unknown	Unknown	Onset in childhood or early adulthood with episodes of dystonia and chorea lasting 2 minutes to 4 hours triggered by stress, alcohol, caffeine, or nicotine
DYT9	Paroxysmal choreoathetosis with episodic ataxia and spasticity; choreoathetosis, spasticity, and episodic ataxia	1p13.3-1p21	Unknown	Unknown	Childhood onset with chronic spastic paraplegia plus episodes of dystonia, choreoathetosis, paresthesias, and diplopia triggered by exercise, stress, or alcohol
DYT10	Paroxysmal kinesigenic dystonia/ dyskinesia with episodic ataxia and spasticity	16p11.2-q12.1	Unknown	Unknown	
DYT11	Myoclonus-dystonia syndrome	7q21-q23 (ε-sarcoglycan)	Unknown	Unknown	Myoclonus and dystonia, with alcohol responsiveness

continued on next page

TABLE 1-13 *Continued*

DYT Locus	Other Names	Chromosome	Gene	Mutation	Clinical Features
DYT12	Rapid-onset dystonia parkinsonism	19q	Unknown	Unknown	Childhood, adolescent onset
DYT13		1p36.13-p36.32	Unknown	Unknown	Single family with cervical dystonia
DYT14	Dopamine-responsive dystonia	14q14	Unknown	Unknown	Childhood onset, responsive to dopamine, same as DYT5
DYT15	Myoclonus-dystonia	18p11	Unknown	Unknown	Myoclonus and dystonia
DYT16	Young-onset dystonia-parkinsonism	2q	PRKRA	Unknown	Childhood-onset generalized dystonia, bulbar involvement, mild parkinsonism
DYT17	Autosomal recessive primary torsin dystonia	20pq	Unknown	Unknown	Segmental or generalized dystonia, dysarthria
DYT18	Paroxysmal exertion-induced dyskinesia 2	1p	SLC2A1	Unknown	Similar to DYT9
DYT19	Episodic kinesigenic dyskinesia 2	16q	Unknown	Unknown	
DYT20	Paroxysmal nonkinesigenic dyskinesia 2	2q	Unknown	Unknown	

Data from Klein C. The twists and turns of dystonia gene and loci: an update. The Movement Disorders Society Web Site Edition: February/March 2009. *www.movementdisorders.org/monthly_edition/2009/02/twists_and_turns.php*. Accessed September 18, 2009.

data now suggest that about 20 genetic subtypes of dystonia exist, each designated as a unique dystonia type by the Human Genome Organisation/Genome Database. This classification system assigns locus names (DYT) for each newly identified subtype, starting with DYT1, discovered in 1989. This classification assignment strategy is somewhat problematic in that it includes dystonias of different etiologies. Six of these genetic subtypes are primary forms of dystonia (DYT 1, 2, 4, 6, 7, and 13), and the others are secondary dystonias. Researchers have now identified eight genes associated with these genetic subtypes and determined

KEY POINTS

- The genetic classification of dystonia is growing and now includes 20 genetic subtypes of dystonia, each given a DYT designation.
- All children and adolescents presenting with dystonia should be given a trial of levodopa to rule out dopa-responsive dystonia.
- Trihexyphenidyl is the best-studied systemic medication in dystonia. Baclofen and benzodiazepines can also be helpful.
- Botulinum toxin therapy should be considered as a treatment option in focal dystonia.

the chromosome location in 18 of these subtypes. Two subtypes (DYT2 and 4) have been designated as a DYT based only on clinical description (**Table 1-13**). Despite these limitations, this classification system will likely prove increasingly valuable as new dystonia gene loci are added and better defined in the genome database (Klein, 2009).

Pharmacologic Treatment

Few medications are effective for the treatment of dystonia. The exception to this is the treatment of DRD (otherwise known as DYT5 dystonia or Segawa disease), which is extremely responsive to levodopa therapy. All children or adolescents who present with dystonia should be given a trial of levodopa to determine whether this is the diagnosis. Typically, carbidopa/levodopa at 300 mg/d will improve symptoms of DRD, but the dose should be increased up to 1000 mg/d for 1 month to effectively rule out DRD (Jankovic, 2006).

If levodopa is ineffective, the patient should next be tried on an anticholinergic medication. Trihexyphenidyl (Artane) is the best-studied medication for use in dystonia, but other anticholinergic medications are sometimes used. Patients with young-onset generalized dystonia appear to have the most benefit from this class of agents and are able to tolerate a much higher dose than adults. Trihexyphenidyl should be started at 1 mg/d to 2 mg/d and gradually titrated up to effective doses. Younger patients may be able to tolerate up to 120 mg/d. Its effectiveness is limited in adults, however, as they frequently develop intolerable side effects, including memory loss, dry mouth, confusion, sedation, and hallucinations, at much lower doses.

Typically, the next medication prescribed for dystonia is baclofen, a γ-aminobutyric acid agonist. Baclofen is typically less potent compared with anticholinergic medications but is better tolerated. A trial of baclofen is worthwhile, as this has been shown to improve lower extremity dystonia, especially among children. Anticholinergic medications and baclofen are often used as combination therapy.

Benzodiazepines (typically clonazepam) are also used in dystonia treatment, usually as a supplementary medication in generalized dystonia. In adult-onset dystonia, it may be effective in treating blepharospasm.

Other medications, including muscle relaxants, anticonvulsants, dopamine-depleting agents, and dopamine antagonists have also been used to treat dystonia. However, these medications have been associated with more side effects and lower efficacy (**Table 1-14**).

In patients with focal dystonia, botulinum toxin may be helpful. In patients with blepharospasm and cervical dystonia, botulinum toxin injections are considered first-line therapy. For other forms of focal dystonia, if patients fail to achieve adequate symptom relief after oral medication therapy, botulinum toxin injection with appropriate muscle selection and dosing should be considered. If the patient fails reasonable medical therapy, the patient may need to be considered for surgical candidacy. Botulinum toxin therapy and surgical therapies for patients with dystonia will be covered in later chapters.

SPASTICITY

Spasticity classically results from upper motor neuron (UMN) dysfunction and thus cannot be formally classified as a movement disorder. However, as movement disorder neurologists are increasingly called on to manage this symptom, especially with the administration of botulinum toxin, we felt it appropriate to briefly discuss spasticity in this overview chapter.

Clinical Features and Etiology

Spasticity, like rigidity, is a form of increased tone, seen on examination as

TABLE 1-14 Dystonia Medications

Medication	Typical Starting Dose (mg/d)	Typical Therapeutic Dose (mg/d)	Side Effects/Comments
Carbidopa/levodopa	25/100	Up to 800	Nausea; dramatic response in dopa-responsive dystonia at low doses
Anticholinergic/antihistaminic			
Trihexyphenidyl (Artane)	1–2	Up to 120	Dry mouth, blurred vision, urinary retention, memory problems, sedation, confusion; effective in 40% of patients but benefit limited by side effects; requires slow upward titration
Benztropine (Cogentin)	0.5–1.0	Up to 8	Same as above
Procyclidine (Kemadrin)	2.5–7.5		Same as above
Diphenhydramine (Benadryl)	25		Same as above
Ethopropazine (Parsidol)	50		Same as above
Baclofen (Lioresal)	5–10	Up to 120	Nausea, sedation, muscle weakness; effective in 20% of patients; intrathecal baclofen minimally successful; withdrawal effects on sudden discontinuation
Clonazepam (Klonopin)	0.5–1.0	Up to 5	Sedation, depression, confusion, dependence; effective in 15% of patients, withdrawal effects on sudden discontinuation
Muscle relaxants			
Tizanidine	2	24	Sedation, dysphoria; limited benefit
Cyclobenzaprine			
Anticonvulsant medications			
Carbamazepine	100		Ataxia, sedation; very helpful in paroxysmal kinesigenic dyskinesia
Gabapentin	100		
Dopamine-depleting agents			
Tetrabenazine	25	Up to 75	Depression, dysphoria, parkinsonism; requires slow upward titration
Reserpine	0.1		
Dopamine antagonists			Effective in 25% of patients; possibility of tardive dyskinesia and other adverse effects limits greatly this class of medications in dystonia treatment

KEY POINTS

- Spasticity, like rigidity, is a form of increased tone, seen on examination as increased resistance to passive movement of skeletal muscle.
- Spasticity is velocity dependent (increasing with faster movement of the limb) and varies in terms of direction of the stretch (with arm flexors and leg extensors being more affected).
- For patients with localized spasticity, botulinum toxin injections can be very helpful.
- For patients with generalized spasticity, oral medications such as baclofen, dantrolene, tizanidine, and benzodiazepines are often helpful and can be used as monotherapy or together as combination therapy.

increased resistance to passive movement of skeletal muscle. However, unlike rigidity, spasticity is velocity dependent (increasing with faster movement of the limb) and varies in terms of direction of the stretch (with arm flexors and leg extensors being more affected). This variation gives spasticity its ''clasp-knife'' quality. It may interfere with range of motion, cause considerable pain, and limit mobility, resulting in impairment of activities of daily living and significant disability.

Spasticity results from dysfunction or injury of the UMN of the corticospinal tract. It is commonly associated with other UMN signs such as weakness (usually distal), hyperreflexia, clonus, and the Babinski sign. As many processes commonly affect the UMNs, spasticity has a broad differential that varies widely according to age. Common causes include cerebral palsy in childhood, multiple sclerosis in young adults, stroke in older adults, and spinal cord processes at any age. While the incidence of spasticity is not known with certainty, it likely affects more than half a million people in the United States and more than 12 million people worldwide.

Although the pathophysiology of spasticity is incompletely understood, the changes in muscle tone likely result from alternation in the balance of inputs from the reticulospinal and other descending pathways to the motor and interneuronal circuits of the spinal cord and the absence of an intact corticospinal system. Loss of the descending tonic or phasic excitatory and inhibitory control, denervation supersensitivity and neuronal sprouting are likely involved.

Natural History

After an acute injury to the UMN, the affected limb may have little clinical evidence of spasticity and may appear flaccid and hyporeflexic. Over time (days to weeks) spasticity and hyperreflexia develop, usually resulting in the affected limb assuming one or more stereotyped positions listed below:

- Shoulder flexion/internal rotation/adduction
- Elbow flexion/pronation
- Wrist flexion
- Finger flexion
- Hip flexion/adduction
- Knee flexion
- Knee hyperextension
- Ankle and foot inversion/equinovarus posturing
- Toe flexion/extension

Once spasticity is established, the chronically affected muscle often develops physical changes such as shortening and contracture that further worsen muscle stiffness, immobility, and disability.

Management

Not all patients with spasticity will require treatment, but many will. When spasticity leads to significant pain and disability, management typically involves a multimodality approach (**Table 1-15**). The primary goal is to improve quality of life. Rehabilitative therapies such as physical and occupational therapy improve muscle tone, range of motion, mobility, comfort, and strength and enhance independence and the performance of activities of daily living. Prolonged stretching and splinting of the affected joint, ultrasound, and massage are often used. Management of spasticity is often different for patients with focal or generalized spasticity. For patients with localized spasticity, botulinum toxin injections can be very helpful (see the chapter ''Neurotoxin Injection for Movement Disorders''). For more semipermanent effects, phenol injections (the effect of which can last up to 9 months) can be considered for larger muscles. Orthopedic procedures, such as muscle denervation and tendon release/lengthening/transfer, can be performed in severe cases. For patients with generalized spasticity, oral

TABLE 1-15 Treatment Modalities Useful in Spasticity

Modalities	Treatment	Typical Dose	Side Effects
Rehabilitative therapies	Prolonged splinting/stretching		
	Ultrasound		
	Range-of-motion exercises		
Oral medications	Baclofen (Lioresal, Kemstro)	5 mg 3 times a day initial Up to 20 mg 3 times a day to 4 times a day	Sedation, downiness, weakness, decreased muscle tone, confusion, fatigue, nausea, dizziness, and lowered seizure threshold
	Dantrolene (Dantrium)	25 mg every day initial Up to 100 mg 2 times a day to 4 times a day	Diarrhea, sleepiness, weakness, nausea, liver damage (requires liver function monitoring)
	Tizanidine (Zanaflex)	1 mg to 2 mg every day initial 8 mg in the evening every 8 hours 36 mg/d (maximum)	Sedation, low blood pressure, dry mouth, dizziness, hallucinations, liver damage (requires liver function monitoring)
	Benzodiazepine (Valium and Klonopin)	Valium 2 mg to 10 mg 3 times a day Klonopin 0.5 mg to 1.0 mg each bedtime	Sedation, low blood pressure, nausea, confusion, depression, clumsiness, poor balance, memory and behavior problems
Injection therapy	Botulinum toxin	See the chapter ''Neurotoxin Injection for Movement Disorders''	See the chapter ''Neurotoxin Injection for Movement Disorders''
	Phenol	Varies	Dysesthesia and pain from nonselective tissue destruction to muscles or nerves
Surgical therapy	Intrathecal baclofen pump	20 μg/d to 800 μg/d	Infection of device, other device-related failures
	Orthopedic procedures		

medications such as baclofen, dantrolene, tizanidine, and benzodiazepines are often helpful and can be used as monotherapy or together as combination therapy. It is not uncommon for systemic side effects, such as sedation or cognitive dysfunction, to limit their efficacy. Intrathecal baclofen (ITB) is another therapeutic option associated with fewer cognitive side effects than the oral form. Patients treated with ITB can have surgical and mechanical complications; the pump needs to be refilled every 3 to 12 months. ITB is more helpful for lower extremity spasticity and has been shown to be effective in patients with cerebral palsy (Brochard et al, 2009) and stroke (Ivanhoe et al, 2006). Overall, early and thorough treatment of spasticity

is important, as long-standing severe or incompletely managed spasticity can lead to fixed-position spastic contractures, which are notoriously difficult to treat.

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