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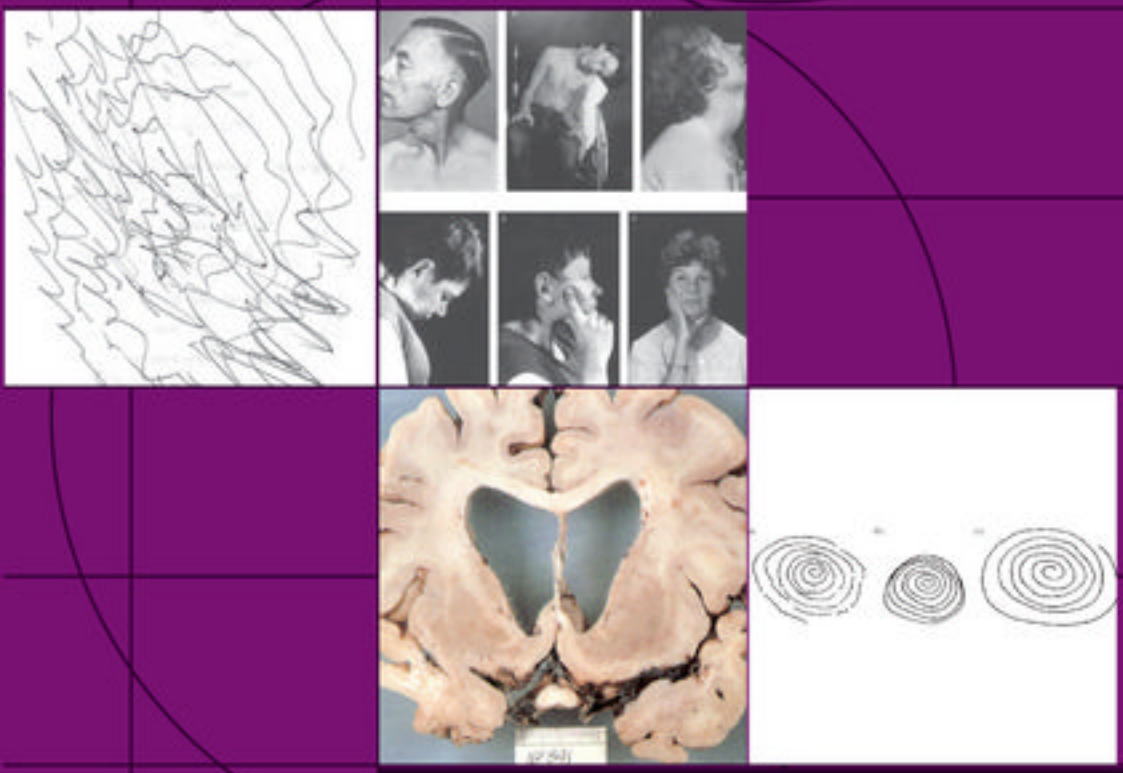

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Contents

Preface

The subspecialty of neurology termed "movement disorders" traditionally has focused on disorders of movement that are not due to pyramidal dysfunction (i.e., lesions of the corticospinal tract resulting in weakness or paralysis and spasticity). Rather, included are movement abnormalities resulting from dysfunction of the so-called extrapyramidal motor control system, largely the basal ganglia and their connections. Some movement disorders specialists also include the ataxias, disorders of the cerebellum.

We often say that the field of movement disorders involves patients who don't move enough and those who move too much. This highlights the traditional dichotomy between the hypokinetic (parkinsonian) movement disorders and the hyperkinetic (involuntary movements) movement disorders. It is the latter conditions that will be covered in this book.

The first step in approaching a patient with a hyperkinetic movement disorder is to accurately classify the abnormal movements. Hyperkinetic movement disorders can be conceptualized along a spectrum of speed or velocity of the movement. Fastest are the lightning-like jerks of myoclonus and then the quick jerks and twitches of tics. Next are the quick dance-like movements of chorea. Choreoathetosis is a slower version of chorea in which the dance-like movements become more sinewy. Athetosis itself involves slower writhing movements, and, finally, the slowest involuntary movement is the twisting and prolonged posturing of dystonia. Some hyperkinetic movements don't really fit within this spectrum based on velocity, including tremor and restless legs syndrome.

While the above represent the traditional neurological hyperkinetic movement disorders, there is another group of abnormal movements that have been historically classified along with psychiatric disorders. These include habits, mannerisms, compulsions, and stereotypies, and they will also be covered in this volume.

An individual movement is sometimes difficult to classify phenomenologically. For example, a head jerk could be a tic or myoclonus. A good rule of thumb in clinical movement disorders is to always consider the company a movement keeps. Thus, as discussed later, a simple motor tic such as a head jerk is often associated with more complex motor tics or vocal tics, revealing the nature of the movement.

In a given patient, it is common to see a variety of abnormal movements. For example, patients with Huntington's disease, mainly a disorder with chorea, often have evident tics or dystonia. Another principle of clinical movement disorders is to focus on the predominant movement disorder present when there is more than one.

Once the type of hyperkinetic movement disorder is appropriately classified, the second step in clinical evaluation is to consider the possible causes of the abnormal movements. Like other neurological signs, hyperkinetic movement disorders can result from a variety of disease processes. These etiologies can run the gamut of disease types, such as congenital, genetic, infectious, vascular, degenerative, and so forth. It is important to carefully consider the differential diagnosis of the movements and direct a clinical evaluation to appropriately diagnose any underlying condition. Thus, it is important to remember that the optimal treatment of a hyperkinetic movement disorder may not be simply suppressing the movement itself, but rather may require therapies directed toward a causative condition. In some cases, the underlying condition is unknown or untreatable. In these cases, treatment directed toward suppressing a disabling movement disorder would be rational.

Like other volumes in the Contemporary Neurology Series, *Hyperkinetic Movement Disorders* has been written to convey important, clinically valuable information in a clear and concise fashion. Useful summary tables are provided throughout the book, and for simplicity only key references are cited. Our authorship team hopes that *Hyperkinetic Movement Disorders* will be another successful volume in the Contemporary Neurology Series that has been so appreciated by the neurology community over the years.

Roger M. Kurlan, MD

Chapter 1

The Basal Ganglia

Roger M. Kurlan

GENERAL OVERVIEW

Movement disorders have been referred to as disorders of the basal ganglia because in most cases they result from or are associated with lesions or dysfunction in this anatomical brain region. The basal ganglia consist of an interconnected set of nuclei situated deep in the brain, in the diencephalon and midbrain, mostly lateral to the third ventricle bilaterally. Basal ganglia connections are complex and have not yet been fully elucidated, being made up of a variety of feedback loops. Basal ganglia functions are also varied and continue to be clarified, but for the most part this brain region can be viewed as a key motor control center, providing involuntary, unconscious (extrapyramidal system) input and influences to the voluntary corticospinal and corticobulbar motor pathways (pyramidal system). In a simplistic but clinically useful conceptualization, increasing basal ganglia output can be viewed as "applying the brakes" on movement. Excessive basal ganglia output results in slowed, rigid, and tremulous movement as seen in the hypokinetic parkinsonian disorders, while inadequate output causes excessive movement as displayed by the hyperkinetic involuntary movements discussed in this book. More recent evidence indicates that the basal ganglia braking function applies not only to motor control but also to the control of thoughts, emotions, impulses, motivation, and attention, with inadequate braking resulting in such problems as obsessions, mood disorders, impulse control problems, and attention deficits. This likely explains the frequent comorbidity of these nonmotor features with basal ganglia motor disorders.

The neurochemical anatomy of the basal ganglia has long been considered important in the development of rational pharmacologic

treatments for neurological movement disorders. More recently, the functional neuroanatomy of the basal ganglia has gained increased importance in contributing to the selection of optimal targets for deep brain stimulation therapy. Recognizing the complexity of basal ganglia anatomy, connections, pharmacology, and physiology, this chapter presents concise summary information, selected for clarity and practical clinical importance when approaching patients with neurological movement disorders, focusing on the hyperkinetic types.

ANATOMY

A commonly used model of basal ganglia circuitry is illustrated in Figure 1–1.[1–3] The major inputs to the basal ganglia most relevant to neurological movement disorders include (1) the highly topographically organized excitatory glutamatergic connection from the cerebral premotor and motor cortex to the caudate and putamen (striatum; corticostriatal pathway), (2) the excitatory glutamatergic connection from the thalamus to the striatum (thalamostriatal pathway), and (3) the dopaminergic pathway from the substantia nigra to the striatum (nigrostriatal pathway). There are also serotonergic inputs from the raphe nuclei and noradrenergic inputs from the locus ceruleus.

Outputs from the striatum originate from the cell bodies of medium spiny neurons and are composed of two major pathways. The so-called direct pathway includes inhibitory GABAergic projections from the putamen to the substantia nigra pars reticulata (SNpr) and the globus pallidus interna (GPi) and then to the thalamus. The indirect pathway involves inhibitory GABAergic projections from the putamen to the globus pallidus externa (GPe) then to the subthalamic nucleus, which has excitatory glutamatergic input to the GPi, which in turn has inhibitory connections with the thalamus. The dopaminergic nigrostriatal pathway appears to modulate these pathways. Putamenal neurons in the direct pathway have dopamine D1 receptors and are facilitated by dopamine, while putamenal neurons in the indirect pathway have D2 receptors and are inhibited. With two inhibitory synapses, the direct pathway has a net excitatory effect on thalamic output, while the indirect pathway with three inhibitory synapses produces a net inhibitory effect. The thalamus has largely GABAergic inhibitory input back to the premotor cerebral cortex. Taken together, this model describes two pathways that go from the cortex to the basal ganglia and then back to the cortex. Several other interconnections between the various structures have also been delineated.

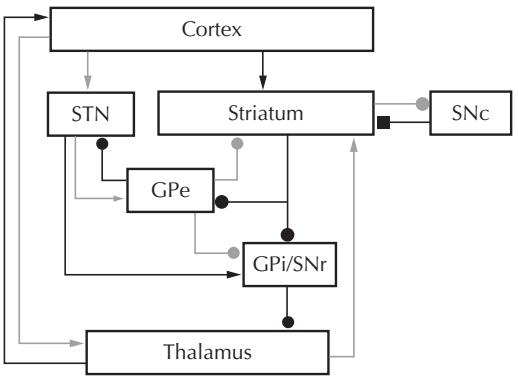

Figure 1–1. Model of basal ganglia circuitry.

CLINICAL IMPLICATIONS

Disturbances of the output from the striatum have largely been implicated as a primary contributor to neurological movement disorders. In some cases, current models have been useful in explaining the pathogenetic processes. A classic example is Parkinson's disease, in which degeneration of dopaminergic cells in the SNpc leads to dopamine deficiency in the striatum and in turn an increase in activity of the GPi by both direct and indirect pathways. The result is an increase in inhibitory thalamic output and decreased motor activity (slowness, rigidity). At the same time, although the exact mechanisms of stimulation remain unclear, deep brain stimulation of GPi or STN can be envisioned as reversing this situation and lessening parkinsonian features. As a related example, damage to the STN by stroke would result in a reduction of inhibitory thalamic output and explain the onset of the involuntary movement hemiballismus. Loss of intrinsic GABAergic striatal cells and cholinergic interneurons in Huntington's disease can similarly translate into differential dysfunction of direct and indirect pathways resulting in a decrease in inhibitory thalamic output, leading

to the excessive, involuntary movement of chorea. The model has proven insufficient at times, however, in explaining other hyperkinetic movement disorders, such as dystonia and tics, where specific neuropathological or neuropathophysiological localization is unknown. Undoubtedly there will be ongoing modifications to current models of basal ganglia circuitry and function that emerge over time to better explain the clinical phenomenology of movement disorders.

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Chapter 2

Tremor

Paul E. Greene

INTRODUCTION

Tremor is the rhythmic movement of a body part or body parts around a fixed point. No human tremor is precisely rhythmic, and physicians rarely provide precise standards for how much variation from precise rhythmicity is allowed before the movement is no longer categorized as tremor. This becomes even more complicated when two or more movement types are present, such as tremor and myoclonus, or when the movements are not limited to a single plane. Nonetheless, most experts agree on the diagnosis of tremor most of the time (this is one of those "I can't define it but I know it when I see it" diagnoses). The classification of tremor is relatively simple and is based on the condition when the tremor is present or exaggerated: at rest, during posture holding, during an action, or as the limb approaches a target (intention). In the case of action tremor, the tremor may be present only during one particular action—task-specific tremor, such as hand or wrist tremor while writing, lip or tongue

Table 2–1 **Conditions Associated with Tremor**

Rest tremor	Parkinson's disease
	Drug-induced parkinsonism
	Vascular parkinsonism (very rare)
	Holmes tremor
	Progressive supranuclear palsy (rare)
	Multiple system atrophy (<10% of cases)
	Spinocerebellar ataxia (esp. SCA2,3)
	Psychogenic tremor
Postural tremor	Enhanced physiological tremor
	Drugs*
	Toxins (mercury, toluene, solvents)*
	Metabolic disturbance (hyperthyroidism, Cushing's syndrome)
	Essential tremor
	Neuropathy*
	Dystonia*
	Task-specific tremors
	Parkinson's disease
	Multiple system atrophy (60% of cases)
	Spinocerebellar ataxia (esp. SCA 12)
	Fragile X
	Orthostatic tremor
	Psychogenic tremor
Kinetic tremor	Cerebellar disease (demyelination, hemorrhage, degenerative, toxic)†
	Holmes tremor†
	Wilson's disease†
	Psychogenic tremor
Head tremor	Essential tremor (uncommon)
	Dystonia
	Cerebellar disease
	Third ventricular cysts
	Spasmus nutans
	With congenital nystagmus
	Labyrinthine fistula
	As part of tic disorder
	Head banging in children
Chin tremor	Hereditary geniospasm
	Parkinson's disease
Jaw tremor	Parkinson's disease
	Dystonia
	Essential tremor (rare)

* Rest component to tremor may also occur.

† Rest and postural component to tremor may also occur.

Modified from: Parkinson's Disease and Other Movement Disorders. Mark Edwards, Niall Quinn, and Kailash Bhatia. Chapter 5 Tremor. Table 5.1.

tremor while playing a wind instrument, upper extremity tremor while holding a bow to play the violin, and others. There are a large number of causes of tremor. Drug-induced tremors are discussed in the chapter "Drug-Induced Movement Disorders." Here I will discuss the other significant and most common causes for tremor. For a list of most causes of tremor, see Table 2–1.

PHYSIOLOGIC TREMOR

Physiologic tremor is a tremor that is present in all people but is normally so small in amplitude that it does not interfere with function. Clinically, it may be barely apparent in the fingers of the outstretched hand but is not visible in handwriting or in spiral drawings. It has two components. There is a peripheral component of 8–12 Hz depending on the mass (and tension) of the part of the body that is shaking (called the mechanical-reflex tremor). The body does not put energy into sustaining this tremor, so if a weight is placed on the limb, the frequency drops. There is also a central component at the same frequency generated by a central oscillator that will maintain about the

Table 2–2 **Causes of Enhanced Physiological Tremor**

Drugs	Neuroleptics, metoclopramide, antidepressants (tricyclics), lithium, cocaine, alcohol, sympathomimetics, steroids, valproate, anti-arrhythmics (amiodarone), thyroid hormones, cytostatics, immunodepressants
Toxins	Mercury, lead, manganese, alcohol, DDT, lindan
Metabolic disturbances	Hyperthyroidism, hyperparathyroidism, hypoglycaemia, hepatic encephalopathy, magnesium deficiency, hypocalcaemia, hyponatraemia
Others	Anxiety, fatigue, sympathetic reflex dystrophy, withdrawal of alcohol or drugs

From: Oxford Textbook of Movement Disorders, Edited by David Burn, © 2013. Reprinted with permission from Oxford University Press.

Table 2–3 **Drugs With Tremor as a Possible Side Effect**

Group	Example
Beta-adrenergic drugs	Fenoterol, salbutamol
Phosphodiesterase inhibitors	Theophylline, caffeine
Anti-arrhythmic drugs	Amiodarone, mexiletine, procainamide
Calcium-channel inhibitors	Nifedipine, amlodipine
Immunotherapy	Cyclosporine, tacrolimus, interferon
Antidepressants	Tricyclic antidepressants, SSRIs
Lithium	
Neuroleptics, antidopaminergics	Haloperidol, metoclopramide
Antiepileptics	Valproate, lamotrigine
Anti-infective agents	Co-trimoxazole, amphotericin B, vidarabine
Hormone therapy	Thyroxine, calcitonin, progesterone, corticosteroids

same frequency even if the limb is weighted. In the presence of physical or emotional stress (such as increased adrenergic tone), the physiological tremor is exaggerated, may become symptomatic, and may be difficult to separate from essential tremor if the frequencies of the two tremors are similar.[1] If a patient tightens all muscles in an arm or a leg, physiologic tremor becomes exaggerated and apparent, a common symptom in psychogenic movement disorders. For conditions that can cause exaggerated physiological tremor, see Table 2–2. Many toxins and drugs can cause tremor, and it is not always clear if the tremor is exaggerated physiological tremor, enhanced essential tremor, or some other type of tremor (Table 2–3).

PARKINSONIAN TREMORS

Rest Tremor and Reemergent Tremor

Rest tremor should always suggest a dopamine deficiency state, but there are some exceptions. As described later in the chapter, some patients with essential tremor may have a tremor at rest. Rarely, patients with a tremor of cerebellar origin may have a rest tremor (see "Cerebellar Tremors"). Most patients with a rest tremor and dopamine deficiency will have Parkinson's disease (PD), although many patients with PD do not have a rest tremor. Rarely, rest tremor is present early in the course of one of the Parkinson-plus diseases such as multiple system atrophy (MSA) or even cortical-basal ganglionic degeneration (CBGD) or progressive supranuclear palsy (PSP). The rest tremor of parkinsonism usually disappears temporarily with movement but reappears if a posture is held or with repetitive movements. This has been called a reemergent tremor. Continually changing movements suppress this tremor. Although the rest tremor in PD usually improves with dopamine-replacement therapy, occasionally it does not, even when bradykinesia and rigidity improve markedly. Rest tremor and bradykinesia/rigidity in PD may progress independently: Occasional patients may have tremor as the major symptom for many years, and rest tremor may improve in some patients as bradykinesia and rigidity worsen.[2] On occasion the rest tremor may be worse on one side of the body and rigidity/bradykinesia worse on the other side. There is currently no physiologic explanation for these observations. Cells have been identified that fire synchronously with PD rest tremor in the thalamus and subthalamic nucleus, but there are several indirect lines of evidence suggesting that the tremor also involves a cerebellothalamocortical network.[2,3] Rest tremor does not correlate well with dopaminergic loss in the putamen, but it may correlate with dopamine depletion in the globus pallidus, and fMRI demonstrates activity in the basal ganglia predominately at the onset of the tremor, but ongoing tremor correlates with activity in the cerebellothalamocortical network (see Figure 2–1).[3] The phase difference between rest tremors in different muscles in

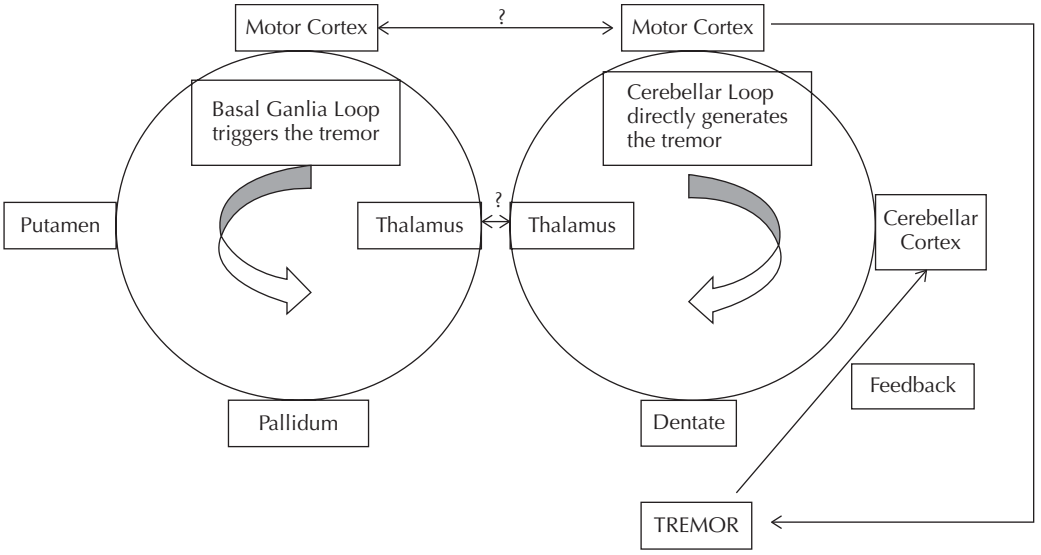

Figure 2–1. It has been proposed that a basal ganglia loop triggers rest tremor but a cerebellar loop is responsible for maintaining the tremor. The connections between the loops are not known. (From: Hallett M. Parkinson's disease tremor: pathophysiology. Parkinsonism Rel Disord 2012;18(S1):85–86.)

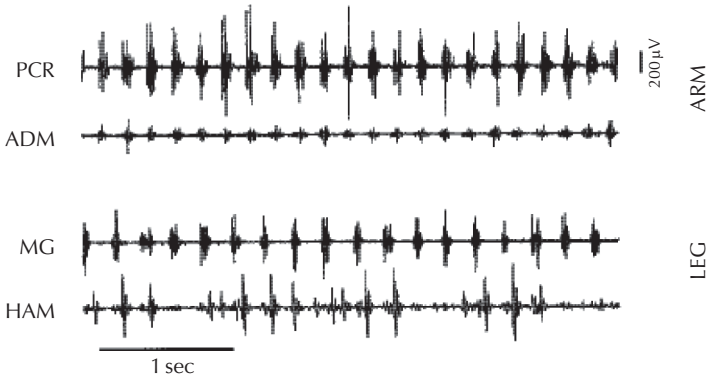

Figure 2–2. Lack of coherence of PD rest tremor between ipsilateral arm and leg in PD. Simultaneous EMG recordings from two muscles in the left arm and two in the left leg in a patient with PD. The activity is mainly synchronous from flexor carpi radialis (FCR) and abductor digiti minimi (ADM) in the same arm and between medial gastrocnemius (MG) and hamstrings (HAM) in the same arm but not between muscles in the arm and leg. (From: Hurtado JM, Lachaux J-P, Beckley DJ, Gray CM, Sigvardt KA. Inter- and intralimb oscillator coupling in Parkinsonian tremor. Mov Disord 2000;15:683–691. Figure 3.)

the same limb tends to be constant, whereas the phase difference between muscles in different limbs on the same side and between homologous muscles on opposite sides of the body tends to be random (see Figure 2–2).[4] This suggests that there may be independent tremor generators for each limb. The difficulty in elucidating the physiology of rest tremor is not surprising, as PD is a syndrome and the physiology of tremor may vary with the etiology.

Parkinson Action Tremor

Some patients with parkinsonism have a postural and action tremor distinct from the reemergent rest tremor.[5] It is not known whether

some or all of these patients have concurrent essential tremor. Patients with Parkinson-plus syndromes such as PSP and CBGD may have postural and action myoclonus that looks like a coarse, high-frequency tremor.[6] An unusual and rarely described tremor is a tremor of the lower extremities that occurs in some patients with PD and freezing of gait when they attempt to initiate walking. As they attempt to move one leg forward, that leg develops a moderate amplitude, moderate frequency vertical tremor that persists until they are able to move forward or stop trying to walk.

ESSENTIAL TREMOR

Phenomenology

Sometimes called benign essential tremor or familial tremor, essential tremor (ET) is a slowly progressive postural, action, and intention tremor. There are no electrophysiological, biochemical, or pathological features that define ET, so all classifications are primarily based on clinical features. Essential tremor is a syndrome. This is suggested by the great variations from patient to patient as noted later in the chapter, but the definitive evidence comes from the fact that at least three different genetic loci are associated with familial ET.[7] Generalizations about ET often vary from study to study, in part because it is a syndrome and in part because there are no universally agreed on criteria for ET. Other forms of action tremor, such as enhanced physiologic tremor, may be difficult to distinguish from mild ET and may contaminate even the most carefully designed studies. The frequency of the tremor in ET varies from about 4 Hz to about 12 Hz, with the youngest patients having the fastest tremor.[8] It has been demonstrated that the tremor frequency decreases over time in a single individual with ET (Table 2–4).[9]

In most patients with ET, the tremor is worse with action than with sustained posture, is worse as the limb approaches a target (intention tremor), and may be worse with some particular actions such as writing (Figure 2–3). It is not clear whether this is true task specificity or whether the tremor is exacerbated in actions requiring more dexterity (holding a paper cup full of water with a few fingers elicits more tremor than holding a ceramic cup with the entire hand). Most patients notice that they can steady the tremor by using both hands, as there is a varying phase difference between tremor in the left and right upper extremities. The tremor is usually bilateral at onset but asymmetric and sometimes dramatically asymmetric. The peak age at onset is in the 60s through the 80s, but cases in childhood and cases starting at ages above 90 years have been reported.[7] Essential tremor almost always starts in the upper extremities, but there can be clinically evident spread to the neck (about 30%), tongue and

Table 2–4 **Diagnostic Criteria for Essential Tremor**

Inclusion Criteria
1. Bilateral, largely symmetric postural or kinetic tremor involving hands and forearms that is visible and persistent
2. Additional or isolated tremor of the head may occur but in the absence of abnormal posturing

Exclusion Criteria
1. Other abnormal neurological signs, especially dystonia, in addition to the cogwheel sign and a mild gait impairment
2. The presence of known causes of enhanced physiological tremor, including current or recent exposure to tremorgenic drugs or the presence of a drug withdrawal state
3. Further exclusion criteria: evidence for psychogenic tremor, primary orthostatic tremor, isolated voice tremor, isolated position-specific or task-specific tremors (primary writing tremor), other isolated tremors (tongue, chin, leg)

Supportive Criteria
1. Tremor duration of >3 years
2. Positive family history
3. Reduction of tremor by alcohol (in 50–90% of patients with ET)

Figure 2–3. Patient with ET draws an Archimedes spiral. The oscillations in ET tend to have the same direction in all parts of the spiral (in this case, from lower right to upper left). (From: Martin Albert, MD, PhD, FAAN and Janice Knoefel, MD, MPH. Clinical Neurology of Aging, 3rd New York: Figure 1, Oxford University Press.)

vocal cords (20%), lower extremities (10%), and trunk (5%).[10] Jaw tremor is more common in PD but also occurs in 5%–10% of patients with ET.[7] Head tremor in ET is usually a horizontal "no-no" tremor, although in many patients a small vertical component is also present. Unlike in cervical dystonia, tremor amplitude is relatively constant in all head positions, although extreme head positions can dampen the tremor, presumably because the muscles are at mechanical disadvantage in these positions. Since ET is primarily a postural and action tremor, head tremor usually, but not always, disappears when patients lie in the supine position. Isolated head tremor is rare and raises suspicion of tremor related to cervical dystonia. It is not clear how many people with isolated head tremor really have ET: Studies examining the prevalence of head tremor related to ET usually start with patients identified as having ET, who as such must have at least mild arm tremor.[11] Voice tremor, when present, appears with all vocalizations (unlike the tremor of vocal cord dystonia, which may be present with speaking but not singing). When the frequency of voice tremor is very low, breaks in the voice may suggest adductor spasmodic dysphonia. Voice tremor may be difficult to detect in the presence of severe head tremor, and it may be necessary to lie the patient down to dampen the head tremor to exclude transmitted tremor. Occasionally, patients with ET have a tremor that appears at rest.[7] This can be difficult to determine clinically, as patients may have some muscle tone even with hands resting in their lap. The traditional teaching is that ET appears at rest only when the symptoms are severe and if rest tremor is present in mild to moderate ET there is probably early PD. It is not clear whether this is really the case. There is some data that the rest tremor of ET (unlike the postural and action tremors) involves synchronous activity in agonist and antagonist muscles whereas the rest tremor in PD consists of alternating activity in agonist and antagonist muscles.[12] Many patients with ET show marked improvement with alcohol consumption, although there may be rebound worsening of tremor during the alcohol withdrawal phase.

Essential tremor was originally conceived as a monosymptomatic condition. In recent years, there have been a growing number of associations between ET and various other signs and symptoms. In 1994, Singer et al. reported that patients with ET had difficulty with tandem gait.[13] In addition to cerebellar type deficits, several investigators found deficits in executive function and more widespread cognitive deficits meeting criteria for dementia.[14] Anxiety/depression, pessimism, and hearing and olfactory deficits have been found by some, but not all, investigators.[14] One group found a correlation between ET, large strokes, and cerebrovascular white matter disease, especially in the temporal lobe.[15] It is not clear whether patients with ET have a shorter life span than people without ET.[16] A longitudinal 3-year study in Spain found associations between ET and dementia, hearing impairment, alcohol consumption, depression (positive associations), and smoking (negative association).[17] In that study, subjects with ET were four times more likely to develop PD than controls.[17] Possible associations with ET are listed in Table 2–5. There is also controversy about the relationship between ET and PD. There are several epidemiologic studies that find increased prevalence of ET in people with PD compared with normal controls and increased prevalence of Lewy bodies in the subtantia nigra of patients with ET compared with controls.[7]

Table 2–5 **Associated Signs and Symptoms in Essential Tremor**

Subtle Neurological Deficits
Bradykinesia (mild)
Cerebellar Dysfunction
- Abnormal eyeblink reflex conditioning
- Deficits in paced finger typing
- Dysfunction in hand-eye coordination and ocular movements
- Mirror movements
- Mild dysarthria
- Tandem gait ataxia

Olfactory and hearing deficits

Non-Motor Deficits
Mild cognitive deficits
Neuropsychiatric symptoms
- Anxiety
- Depression
- Specific personality traits
- Sleep disorders
- Decreased body mass index

Nervous System Pathology
Pathology of the cerebellum and its brainstem connections

Association With Neurological or Neurodegenerative Disorders
Parkinson's disease
Dystonia
Myoclonus
Possibly associated with migraine, restless legs syndrome, Lewy body dementia, and Alzheimer's disease

From: Bermejo-Pareja F, Puertas-Martin V. Cognitive features of essential tremor: a review of the clinical aspects and possible mechanistic underpinnings. Tremor Other Hyperkinet Mov 2012;2: http://tremorjournal.org/article/view/74. Table 1.

Other studies have failed to find pathological overlap.[18] Because there is no pathophysiological marker for ET, as opposed to other potential causes for postural/action tremor, it is currently impossible to determine whether patients with PD and action tremor have another disease (ET) or whether the action tremor is an uncommon manifestation of their PD. Louis and Okun argued that ET may precede the development of PD by decades, making it unlikely that the tremor is a manifestation of PD.[16] However, there are nonmotor features linked to PD (such as loss of smell) that may also precede the onset of motor symptoms by decades and may be manifestations of the disease.

Epidemiology and Pathophysiology

Estimates of the prevalence of ET from around the world vary dramatically, from 80 to 220,000 per million.[19] It is not known how much of the variation results from methodological differences (including definition of tremor and ascertainment) and how much this reflects actual population differences. A meta-analysis in 2010 found an overall prevalence of 9,000 per million, with a prevalence of 46,000 per million in people aged 65 years and older.[19] The prevalence rises with age into the 90s: the prevalence was 20% in people aged 95 years and older in northern Manhattan.[19] It is probably more accurate to focus on community-ascertained studies. Even in these studies, there is substantial variation: In people over 60–65 years of age the prevalence varied from 1.9% to 14% in studies around the world (Table 2–6).[20–27]

Table 2–6 **Prevalence of ET in Community-Based Studies**

Reference	Country	Age Distribution, y	Prevalence Rate, %
Moghal et al., 1994	Canada	≥65	14.0
Louis et al., 1995	USA	≥65	3.9
Bergareche et al., 2001	Spain	≥65	4.8
Benito-Lean et al., 2003	Spain	≥65	4.8
Dogu et al., 2003	Turkey	≥60	6.3
Inzelberg et al., 2006	Israel	≥65	1.9
Mancini et al., 2007	Italy	≥61	2.1
Louis et al., 2009	USA	≥66	5.5
Present study	Brazil	≥64	7.4

From: Barbosa MT, Caramelli P, Cunningham MCQ, Maia DP, Lima-Costa MFF, Cardoso F. Prevalence and clinical classification of tremor in elderly—a community-based survey in Brazil. Mov Disord 2013;28:640–646. Table 1.

It has long been known that the frequency of the tremor in ET does not change much when weight is added to the limb, unlike physiologic tremor, where the frequency drops.[28] Because energy expenditure depends on frequency and mass, it is presumed that tremor generators in the nervous system expend energy to maintain pathological tremors, such as ET, but that no extra energy is expended in physiological tremor. Although this observation holds for most patients and provides a method for distinguishing physiological from pathological tremor, there are some exceptions. Patients with mild ET may have a drop in tremor frequency with limb weighting, a sort of transitional state between physiological tremor and ET.[28] Also, there may be no drop in frequency at all with limb weighting in patients with severe ET, as though the ET has overwhelmed the physiological tremor that should be present in all individuals.[28] There are also some normal individuals in whom the weighted limb demonstrates a drop in frequency indicating physiological tremor but in whom there is also a tremor that does not drop in frequency, perhaps indicating subclinical ET.[28] There is no fixed relationship between bursts of activity in agonist and antagonist muscles, and contractions in these muscles may be alternating but they may also cocontract in the same individual (see Figure 2–4).[28] There is no fixed phase relationship between the tremor on either side of the body.[8] This explains why people with ET can dampen their tremor by holding objects with two hands (the tremor on each side tends to cancel out the other side because they are out of phase).

There is increasing evidence that ET involves a disturbance of cerebellar circuits. As noted before, clinical signs such as imbalance, increase of tremor at a target, and eye movement abnormalities suggesting cerebellar dysfunction have been documented in patients with ET.[10] There are subtle similarities between physiological abnormalities in ET and in cerebellar dysfunction: intention tremor, hypermetria, abnormal conditioning of the blink reflex, and impaired rhythm generation.[29,30] In addition, the normal triphasic agonist/antagonist/agonist pattern of muscle contraction in ballistic movements is disturbed in ET in the same manner as in cerebellar dysmetria. Despite this, the physiological data is equivocal. There has been inconsistent pathological data that GABA may be reduced (in the dentate nucleus, cerebellar cortex, locus ceruleus, or pons), but PET imaging found increased GABA binding in the cerebellum.[31] There is a rodent model of ET generated by harmaline, an MAO-A inhibitor with complex biochemical effects. In this model, pacemaker cells in the inferior olivary nucleus are more synchronized, which could be a consequence of GABA deficiency.[31] However, the relevance of this model to human ET is unknown. The cerebellothalamocortical network has been linked to ET by PET scan, but this circuit has also been implicated in a variety of movement disorders.[31]

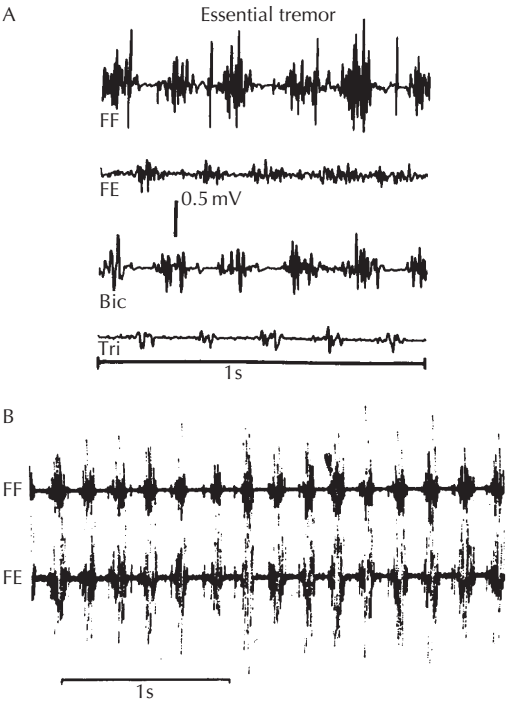

Figure 2–4. EMG recordings in two patients with ET. The patient in A has alternating contractions in the biceps (Bic) and triceps (Tri) and mostly alternating in the finger flexors (FF) and finger extensors (FE). The patient in B has cocontraction of FF and FE. (From: Marsden's Book of Movement Disorders. Ivan Donaldson, C. David Marsden, Susanne Schneider, and Kailash Bhatia. Chapter 17 Classical essential tremor. Figure 17.1.)

Until 2006, there was no consistent pathology for ET. Starting in 2006, Louis et al. published a series of papers describing subtle cerebellar pathology in patients with carefully defined ET, including decreased number of Purkinje cells, increased numbers of torpedo cells, increased Purkinje cell heterotopias, and increased density of basket cells.[32,33] In their

latest analysis, Louis et al. conclude there is a complex relationship between torpedo cell formation (indicating metabolic stress) and loss of Purkinje cells (when stress is severe enough to cause cell death). In ET, the formation of torpedo cells is more dramatic than the loss of Purkinje cells, indicating Purkinje cell stress in ET but not enough to create widespread cell loss.[32] Unfortunately, neither Purkinje cell loss nor torpedo cell formation correlated with duration of symptoms (and no direct correlation with symptom severity was provided), which is hard to explain, as ET is a slowly progressive disease. Other studies have failed to find such cerebellar pathology.[33] It is difficult to know whether these discordant findings come about because ET is a syndrome with many causes or because of differences in technique of measurement.[33]

As ET is overwhelmingly a genetic disease and large families with ET are available for study, it is remarkable that no gene has yet been identified as responsible for ET. Family-based studies identified three loci (labeled ET M1, M2, and M3 on chromosomes 3, 2, and 6 respectively) linked to inheritance of ET, but no mutation has yet been identified in genes within those loci. Some genome-wide association studies identified correlations between polymorphisms in the leucine-rich repeat and Ig domain containing one gene (*LINGO1*) on chromosome 15q24.3 and ET, but not all studies confirmed this and in some studies the correlation only held for young-onset or familial patients. LINGO1 protein levels were increased in the cerebellar cortex of patients with ET but not controls or patients with PD, although LINGO1 protein levels were increased in cerebellar white matter in patients with both PD and ET compared with controls.[34] LINGO1 is involved in neuronal survival and axonal regeneration, and there is a hypothesis that an increase in LINGO1 levels might lead to Purkinje cell death and thus to ET.[35]

Treatment

There is no single medication that helps the majority of patients with ET. As with most movement disorders, medications are started in low doses and increased gradually until there is benefit or significant side effects. Medications may produce limited benefit, or produce benefit that does not translate into improved quality of life. For that reason, some systematic scheme for evaluating both the tremor and the patient's quality of life are helpful before initiating treatment. A simple way to monitor tremor is to have the patient draw an Archimedes spiral with each hand as treatment progresses. There are more elaborate tremor rating scales and quality-of-life scales.[1,19] For detailed descriptions of the medications used to treat tremor, see Table 2–7.[36–38]

BETA BLOCKERS

Centrally acting beta blockers, primarily propranolol, have been used as the first drug for ET for a long time, and efficacy has been documented in many studies. Peripherally acting beta blockers generally are effective in studies but probably not as effective as the centrally acting agents. Although most studies show the drugs to be well tolerated, this may be misleading, as many men who develop impotence will not report it unless asked. If the dose is increased slowly, side effects from bradycardia (orthostasis, fatigue) are uncommon, although side effects such as depression and sleepiness may be significant at higher doses. Bronchial asthma and bradycardia are relative contraindications to usage of beta blockers, but these agents may be tolerated by many patients with heart failure. It is prudent to consult the cardiologist or internist in any patient with a history of heart disease. Doses over 300 mg/day have been used, but it is not clear whether increasing the dose is of value if there is no response at about 100 mg/day. For patients with mild ET that is symptomatic only in times of stress, as-needed doses of beta blockers in modest doses are well tolerated and may be sufficient to block the troublesome exacerbation of symptoms (e.g., 20 mg to 40 mg of propranolol half an hour before a scheduled stressful event). Time-release formulations are effective and may be indicated when compliance is a problem but probably produce more side effects than immediate-release versions.

ANTICONVULSANTS

Of the multiple anticonvulsants used to treat ET, the evidence is best for the efficacy of

Table 2–7 **Medical Treatments for the Tremor of ET**

Pharmacological Agent	Dosage	Potential Side-Effects
Alprazolam	0.75–2.75 mg/day	Sedation, fatigue, potential for abuse
Clonazepam	0.5–6 mg/day	Drowsiness
Atenolol	50–150 mg/day	Lightheadedness, nausea, cough, dry mouth, sleepiness
Nadolol	120–240 mg/day	None
Propranolol	60–320 mg/day	Reduced arterial pressure/pulse rate, tachy/bradycardia, impotence, drowsiness, exertional dyspnea, confusion, headache, lightheadedness
Long-acting propranolol	80–320 mg/day	Skin eruption, transient dizziness
Sotalol	75–200 mg/day	Decreased alertness
Clozapine	6.25–75 mg/day	Sedation, potential agranulocytosis (0.8% at 1 year)
Primidone	to 1000 mg/day	Sedation, fatigue, nausea, vomiting, ataxia, malaise, dizziness, unsteadiness, confusion, vertigo, acute toxic reaction
Gabapentin	1200–1800 mg/day	Lethargy, fatigue, decreased libido, dizziness, nervousness, shortness of breath
Topiramate	to 400 mg/day	Appetite suppression, weight loss, paresthesias, concentration difficulties
Zonisamide	100–200 mg/day	Ataxia, dizziness, somnolence, agitation, anorexia
l-octanol	to 64 mg/kg	Unusual taste
Nimodipine	120 mg/day	headache, heartburn, orthostatic hypotension
Botulinum toxin (head tremor)	40–400 units	Neck weakness, post-injection pain
Botulinum toxin (voice tremor)	0.6–15 units	Breathiness, weak voice, dysphagia

From: Benito-Leon J, Louis ED. Management of essential tremor, including medical and surgical approaches. In Handb Clin Neurol. Hyperkinetic Movement Disorders. W.J. Weiner and E. Tolosa, Eds. Elsevier B.V. 2011;100:449–456. Table 34.1.

topiramate (usually in doses of 25–400 mg daily) and primidone (usually in doses up to 750 mg daily). Both can have significant side effects: paresthesias, weight loss, fatigue, nausea, and others with topiramate and mainly sedation with primidone. Patients with ET seem to be especially sensitive to primidone and can develop profound sedation at typical anticonvulsant doses. Most ET patients will tolerate higher doses if the starting dose is 12.5 mg to 25 mg and the dose is increased gradually. Many patients with dramatic improvement with primidone improve at doses below 100 mg daily. Both zonisamide and gabapentin showed some benefit in lesser quality studies and probably can be used if other medications are inadequate.

BENZODIAZEPINES

Multiple benzodiazepines have been used to treat ET with modest benefit, possibly due to their antianxiety effect.

OTHER MEDICATIONS

An astonishing variety of other medications besides beta blockers, anticonvulsants, and benzodiazepines have been reported to help tremor in case reports and uncontrolled studies, including clozapine, isoniazid, trazodone, mirtazapine, calcium channel blockers, phenobarbital, theophylline, quetiapine, l-tryptophan, and others. It is not clear whether any of these are likely to help a patient with typical ET. In patients with alcohol-responsive ET, sodium oxybate was found to produce improvement comparable to alcohol, but some patients do not develop tolerance to the sedating effects even if the dose is increased gradually. Sodium oxybate is also difficult to obtain.[39] Acetazolamide and methazolamide in low doses have been reported to occasionally help tremor dramatically.[38] Despite the lack of prospective studies, I find those two medications worth trying in severe cases of ET. As noted, alcohol produces

dramatic temporary improvement in tremor in many patients with ET, and consumption of alcohol before meals seems to be an effective strategy for some. Apart from the obvious prejudices in our society, there is legitimate concern about chronic use of alcohol to treat ET. Patients seem to require increasing doses of alcohol to get the same relief (tachyphylaxis) and, after some level of alcohol consumption, there is a rebound worsening of tremor when the alcohol effect wears off. This raised concerns about possible alcohol dependency and abuse, but studies of rates of alcohol abuse among patients with ET have not yielded consistent results.[40]

BOTULINUM TOXIN

Botulinum toxin (BTX) has been used to treat ET of the hands, head, and vocal cords.[36] There is no question that the injections can reduce amplitude of hand tremor, but clinically useful benefit in our experience is usually accompanied by symptomatic weakness. This is less true for head and voice tremor, where a small percentage of patients get usable benefit without symptomatic weakness.

SURGERY

Stereotactic thalamotomy was effective in treating ET, but bilateral thalamotomy entailed significant risk of speech/swallowing impairment in addition to the risk of intracerebral hemorrhage, and the procedure is rarely used today. Thalamic deep brain stimulation (DBS) is highly effective for ET of the hands, but possibly less so for ET of the voice and head.[36] There is a small risk of hemorrhage, usually in the subcortical white matter and a large number of voltage-dependent side effects, such as paresthesias, ataxia, dysmetria, and dysarthria.[36,37] In general, the benefits of thalamic DBS are long-lasting, but there has been variation from center to center. (See Table 2–8.) Gamma knife thalamotomy and subthalamic nucleus DBS have been used in too small a number of patients to compare them with thalamic DBS.[36,37] Most recently, MRI-guided, focused ultrasound has been reported to benefit patients with ET, but the safety and efficacy of this technique are not yet known.[41]

The mean magnitude of improvement in tremor amplitude has been estimated for several of these interventions (Figure 2–5). Of course, a few patients will get much more benefit than the mean and many will get no benefit. One reasonable strategy is to use beta blockers (when possible) or primidone as the initial treatments. If this is unsuccessful or inadequate, substitute or add some of the other medications listed above. For neck tremor, BTX is worth a try. If none of the above are adequate and the symptoms are disabling, DBS is an option to be considered.

Table 2–8 **Long-Term Outcome of Deep Brain Stimulation for Essential Tremor**

Study No. of Cases	Mean Follow-up Duration (months)	Mean % Decrease in Overall Tremor Severity*	Mean % Improvement in Tremor-Related Disability**
Koller et al., 2001	12	40%	NR
N = 25	40	50%	NR
Sydow et al., 2003	12	53%	82%
N = 19	78	41%	39%
Blomstedt et al., 2007	13	53%	62%
N = 19	86	32%	4.9%
Mean of above	12.1	48%	72%
studies (N.3)	65.3	42%	22%

NR: Not reported.

* Calculated from items 1–9 in the ET Rating Scale (ETRS) using *% decrease in tremor* compared to baseline values;

** ADL calculated from items 15–21 in the ETRS using *% improvement in tremor-related disability.*

From: Deep Brain Stimulation. Edited by Peter Bain, Tipu Aziz, Xuguang Liu, and Dipankar Nandi. Publisher: Oxford University Press. Chapter 17. Table 17.1.

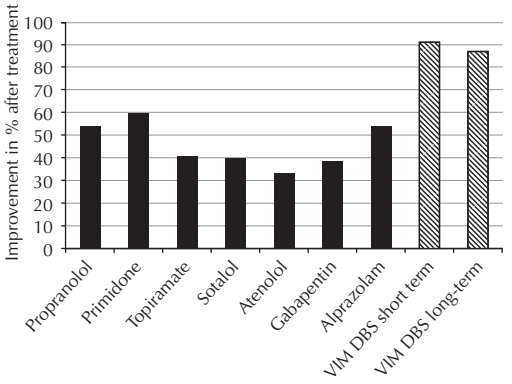

Figure 2–5. Estimated improvement in tremor amplitude for each intervention based on accelerometry and rating scales. (From: Schneider SA, Deuschl G. The treatment of tremor. Neurother 2014;11:128–138. Figure 1.)

ORTHOSTATIC TREMOR

In 1984, Heilman reported three patients with shaking or quivering of the trunk and legs that appeared shortly after standing and disappeared with sitting or walking, calling this orthostatic tremor (OT).[42] Patients with similar characteristics had previously been noted in movement disorder centers, and there had actually been a report (in Italian) in 1970 by Pazzaglia et al. of three such patients.[43] Shortly after Heilman's description, Thompson et al. reported the presence of a 16-Hz tremor in the legs of a patient with OT.[43] The presence of high-frequency tremor primarily with weight bearing is illustrated in Figure 2–6 No tremor at this high frequency had been reported before, thus providing convincing evidence that this was its own unique condition.[43] Since then, it has been discovered that some normal people do develop a 16-Hz tremor when they are off balance.[44]

Etiology and Physiology

Most reported cases of OT were sporadic, but this is an underreported condition, there are reports of familial cases and this may expand in the future.[43,46,47]

The pathophysiology of OT is unknown, and over the years hypotheses have placed the origin of OT throughout the entire neuraxis.[48] There is some evidence it originates in the cerebellum or posterior fossa, as the tremor can be reset by transcranial magnetic stimulation of the posterior fossa, there is increased activity detected by fMRI and PET in cerebellar circuits during the tremor, and some patients with secondary OT had pontine lesions or cerebellar atrophy.[43,45] However, other movement disorders such as dystonia also have evidence of cerebellar circuit overactivity, and some (but not all) studies have found abnormalities in dopaminergic systems in OT.[43] Attempts to find other physiological abnormalities have not been very successful. The acoustic startle reflex includes bursts of tremor at frequencies comparable to OT. An examination of acoustic startle and blink reflexes in a small number of patients with OT compared with controls found fewer patients with the startle reflex than controls.[48] The blink and startle reflexes were otherwise indistinguishable.[48] This suggests there may be abnormal excitability in the pontomedullary reticular system, but the number of patients was too small for this to be conclusive.

There is a continuing debate about the relationship between OT and ET. Some authors argue that OT is a task-specific form of ET because patients with OT often have upper extremity tremor consistent with ET and a family history of ET. Some patients with typical ET may develop an intermediate frequency (10–13 Hz) tremor of the legs on standing.[49,50] Others, however, point out that patients with OT do not always have postural tremor or a family history of ET, rarely improve with beta blockers or alcohol, more often improve with clonazepam than patients with ET, and have other neurological features atypical for ET, such as maximum symptoms in the legs, muscle cramps in the legs, broad-based stance, and so forth.[51,52] This controversy is unlikely to be resolved until a specific test is developed for ET or OT. There have been many cases of apparently secondary OT, including in patients with pontine stroke, cerebellar degenerations, diabetic neuropathy, head trauma, aqueductal stenosis, thiamine deficiency, chronic relapsing polyradiculoneuropathy (CRP), paraneoplastic syndromes, restless legs syndrome (RLS), Graves disease, stiff-person syndrome, mitochondrial disease, and others.[43,53–55] Some convincing cases of OT preceding PD have been reported, but OT in patients with PD is hard to separate from cases of PD postural tremor on standing that would be expected to improve with action. In one study of 26 patients with OT, four patients went on to develop

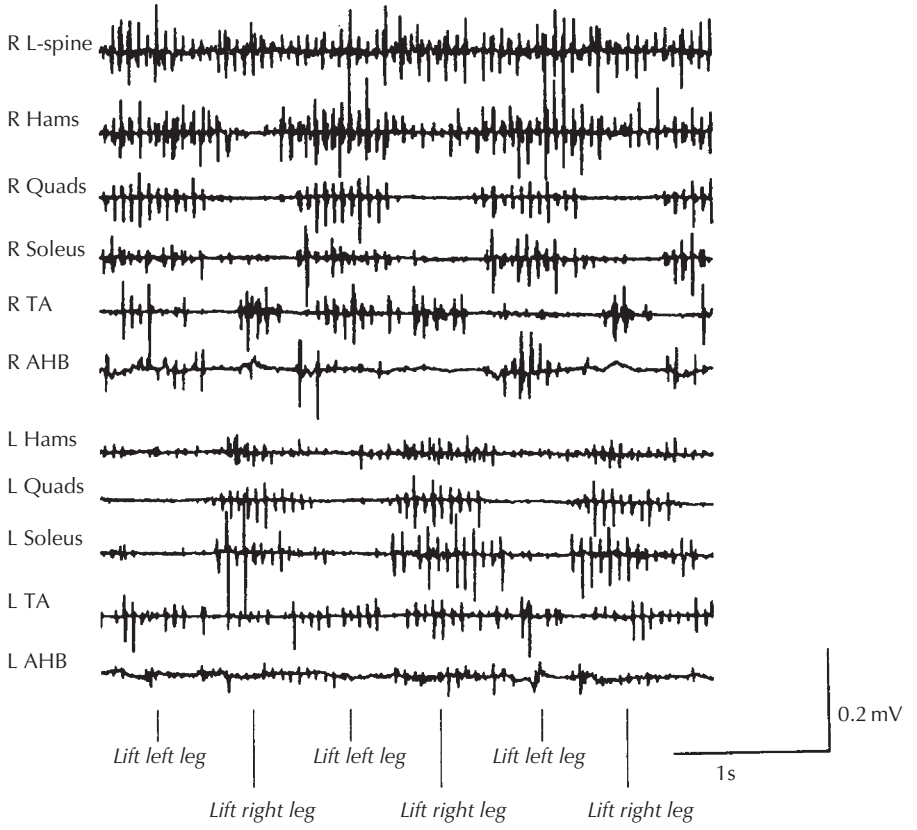

Figure 2–6. EMG recording from a patient with orthostatic tremor. A high-frequency (16-Hz) tremor is present in the paraspinal muscles and leg muscles. The tremor in the quadriceps, soleus, and hamstring muscles disappears when the ipsilateral leg is lifted from the ground. Tremor in the paraspinal and tibialis anterior muscles is less predictable. Quads = quadriceps femoris, TA = tibialis anterior, AHB = abductor hallucis brevis, Ham = hamstrings. (From: Marsden's Book of Movement Disorders. Ivan Donaldson, C. David Marsden, Susanne Schneider, and Kailash Bhatia. Chapter 18 Isolated site-specific or task-specific tremors. Figure 18.5.)

parkinsonism (including one autopsy-documented case of diffuse Lewy body disease) in 5–20 years after the onset of OT.[56] To make this even more bewildering, a small number of cases of secondary OT have had slow or intermediate frequency tremor.[57–59] In favor of an etiologic relationship between at least some of these conditions and OT is that in some cases, treatment of the underlying Parkinsonism, hydrocephalus, autoimmune disease, or CRP induced resolution of the OT.[58,60,61]

Clinical Features and Differential Diagnosis

The essential feature of OT is a high-frequency (13–18 Hz) tremor of the legs and trunk that appears on standing, usually after a delay of seconds to minutes, and is improved with sitting or walking. The tremor is so high frequency that it is usually not visible, although harmonics of the tremor may be visible. When the tremor is not visible, a high-frequency sound may be generated by placing a stethoscope on an affected muscle, called the "helicopter" sign.[43] The disease usually starts late in the seventh decade (range third to eighth decades), but the range is great, especially if you include secondary cases.[62] In most large series, there is a modest female predominance.[56,62] Patients have a sense of imbalance when standing and relieve their symptoms by walking, leaning against a wall, or rocking from side to side. Sometimes, just touching a wall is sufficient to provide relief. The sense of imbalance can be intense and is not reflective of actual severe impairment of balance as measured on a tilt

table.[43] As the disease worsens, the tremor appears sooner after standing and may even reappear with slow walking when the feet are on the ground.[43] Once it appears, the tremor worsens steadily with prolonged standing. If they are forced to stand, patients become anxious and may develop flushing, diaphoresis, tachycardia, and muscle tightness or pain. Many patients have a broad-based stance with narrow-based gait and difficulty with tandem walking. Despite the name, a high-frequency tremor can be reproduced in many patients if they exert moderate force with legs or arms while sitting or lying.[62]

Even in the recent past, patients with OT may go for years before the correct diagnosis is made.[43] Although it is not clear, I suspect that anxiety is the most common misdiagnosis, since the discomfort patients feel seems to far exceed their physical limitations. There is a syndrome of orthostatic myoclonus with a very similar clinical presentation, but it seems to be even less common than OT (see the chapter "Myoclonus"). As noted above, there is a special relationship between OT and PD, and a rare patient with PD may have a reemergent tremor of the legs that appears after prolonged standing and disappears with walking. That tremor may disappear with dopamine-replacement therapy (although rest, postural, and action tremors in PD may not respond to medication). The frequency of reemergent PD tremor will be much lower than the frequency of typical OT. Similarly, a rare patient with ET may have a visible lower extremity tremor, but that would not improve with walking and also would have lower frequency than the tremor of typical OT.

Treatment

The treatment of OT is unsatisfactory. Despite the lack of any controlled study, clonazepam is the medication most often cited as being effective in the treatment of OT. In two reviews published in the early 1990s, approximately 23/34 patients treated with clonazepam were reported to improve.[49,63] Benefit was described as ranging from mild improvement to almost complete resolution of symptoms. Doses required were from 1 to 8 mg/day. Benefit was limited by drowsiness, ataxia, or tachyphylaxis. In the largest series to date of 187 patients (published only in abstract form), clonazepam had some benefit in 57% of patients but marked benefit only in 17%.[62] There have been several controlled studies of gabapentin showing some benefit at doses from 1800 mg to 2400 mg/day.[8] Side effects in open-label studies were transient diplopia, drowsiness, unsteadiness, constipation, dry mouth, and nausea. Primidone, either alone or in combination with clonazepam, was reported to help OT with benefit ranging from modest to marked at doses from about 125 to 625 mg/day and few side effects.[43] Levodopa and the dopamine agonist pramipexole have been reported to help occasional patients (in at least one case the patient went on to develop PD), but small studies have not found consistent benefit.[43] Since BTX injections have been used to treat other tremors, it was tested in a double-blind study for OT and found not to be effective.[64] However, as with any other surgical-like procedure, it is possible that the injections might be effective with a change in technique (increased dose, other muscles, etc.) Other medications occasionally reported as beneficial include phenobarbital, valproic acid, and chlorazepate.[43] Levetiracetam was found to be ineffective in a small controlled study.[65] Finally, as with other forms of tremor, thalamic DBS was reported to provide long-term benefit in two cases of OT with bilateral stimulation but only short-term benefit in one case with unilateral stimulation.[66]

PRIMARY WRITING TREMOR

Primary writing tremor (PWT) is an ET-like upper extremity tremor that appears exclusively, or almost exclusively, with writing, which is very unusual for typical ET. The condition has been divided on clinical grounds into a subgroup with tremor only on writing and a subgroup with tremor even when the hand assumes the writing posture.[67] In one small series, most patients with PWT had slight postural or action tremor and some had lesser degrees of tremor with other activities.[68] The mean age at onset was about 50 years and about one-third of patients had a family history of PWT.[68] In some patients, the tremor increased with duration of writing (Figure 2–7). Patients with PWT may have relatives with typical ET and may improve with alcohol, suggesting a link with ET. Similarly, some patients with PWT may have slight dystonic

posturing when they write (Figure 2–8). It is not clear whether PWT is part of the ET spectrum in some patients and part of the spectrum of writer's cramp in other patients. Physiological studies seem to indicate a difference between writer's cramp and PWT, but this is based on small numbers of patients and PWT may be a heterogeneous condition.[67] For the moment, it is generally assumed that at least some patients with PWT have a unique underlying pathophysiology. One observation that suggests the conditions may be separate is that patients with PWT (unlike patients with ET) often have the tremor disappear if they write on a blackboard. This appears to be a consequence of the tremor primarily affecting the wrists, so that a similar improvement occurs if patients write with their wrists locked (Figure 2–9). Primary writing tremor has been treated with most medicines used to treat ET and with the anticholinergics used to treat dystonia. Multiple uncontrolled studies have reported success rates from 30% to over 50% with medicines such as propranolol, primidone, diazepam, and topiramate. Since these were uncontrolled, they are likely to be on the optimistic side. Botulinum toxin injection (to wrist flexors and extensors) has been reported to be beneficial, as has thalamic DBS.[67] Although PWT is the most commonly reported task-specific tremor, many other forms have been occasionally reported, including tremor of the hand while using a golf club, while holding a trowel, or while drinking tea; tremor of the head while playing a horn; and tremor of the lips while making an embouchure.[68] As with PWT, some of these were triggered by a posture and not necessarily just by a specific action.

Figure 2–7. Writing by a patient with Primary Writing Tremor. At the top, tremor increases as the patient continues to write with his dominant right hand. At the bottom, spiral is tremulous with his right hand but minimally tremulous with his left hand. (From: Bain PG. Task-specific tremor. Handb Clin Neurol 2011; 100:711–718. Figure 50.1.)

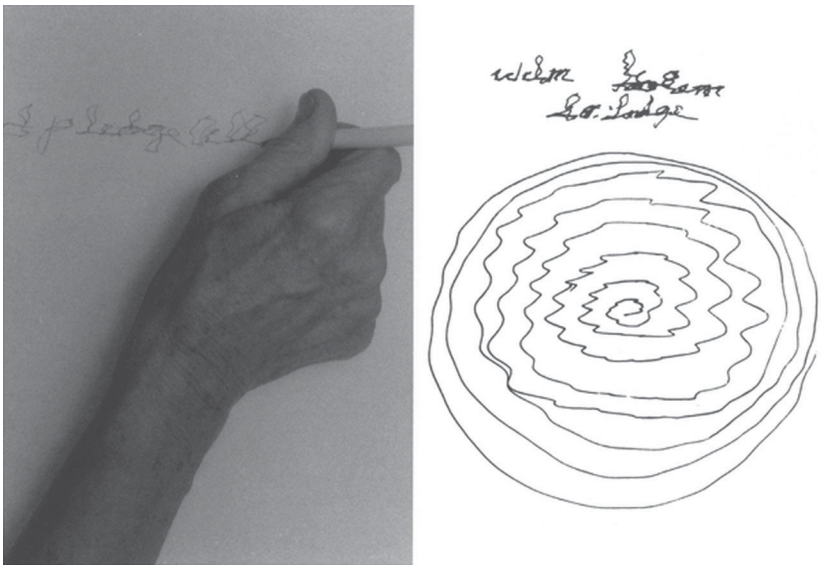

Figure 2–8. This patient with PWT also has dystonic wrist extension, forearm pronation, and tight grip, suggesting that the writing tremor is a form of task-specific dystonia. (From: Marsden's Book of Movement Disorders. Ivan Donaldson, C. David Marsden, Susanne Schneider, and Kailash Bhatia. Chapter 18 Isolated site-specific or task-specific tremors. Figure 18.2b.)

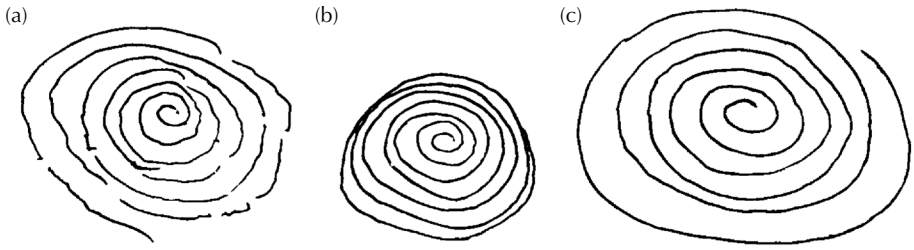

Figure 2–9. A patient with PWT draws an Archimedes spiral in the normal way (A), then draws the spiral with his wrist locked (B) and after a motor point block of the pronator teres (C). Interruptions in the spiral due to tremor improve markedly when movement at the wrist is inhibited. (From: Marsden's Book of Movement Disorders. Ivan Donaldson, C. David Marsden, Susanne Schneider, and Kailash Bhatia. Chapter 18 Isolated site-specific or task-specific tremors. Figure 18.1a.)

CEREBELLAR TREMORS

Cerebellar outflow tremors are low-frequency tremors (below 5 Hz and often 1–2 Hz) that worsen with intention when present in the limbs. The tremor can also affect the neck and trunk (titubation) and the voice. Although dysmetria is necessary to diagnose cerebellar tremor in the limbs, patients may have dysmetria without tremor, so there must be a different mechanism for these two phenomena. Most identified lesions for tremor have been in the dentato-rubro-thalamic or dentato-rubro-olivary pathways (triangle of Guillain-Mollaret). The typical cerebellar tremor in the arms is present with posture holding, and the amplitude increases over time with sustained posture. When the tremor is present at rest (Holmes or rubral tremor), there may or may not be parkinsonian signs present. Some lesions causing rubral tremor have included the substantia nigra, perhaps accounting for the rest tremor and other parkinsonian features, although other lesions may affect other parts of the nigrostriatal system.[29] This is one of the few non-Parkinson tremors that sometimes (but not always) improve with dopamine replacement with levodopa or dopamine agonists.[69] As with most tremors that go through the thalamus, ventral intermediate (VIM) thalamic DBS may help the tremor, but does not improve dysmetria.[70]

FRAGILE X-ASSOCIATED TREMOR ATAXIA SYNDROME

Fragile X–associated tremor ataxia syndrome (FXTAS) combines ataxia, progressive cognitive impairment, tremor, and a growing list of other neurological features. The tremor can mimic the tremor of ET, and the addition of tremor to the other symptoms is a key to the diagnosis.[71] Boys with greater than 200 CGG repeats in the Fragile X mental retardation 1 (FMR1) gene have developmental delay and progressive cognitive impairment (Fragile X syndrome). Their grandfathers may have intermediate-length (55–200) CGG repeats that may expand when their daughters give birth to sons. Carriers of intermediate repeat lengths are at risk for a syndrome the features of which are gradually expanding but consist at the core of ET-like tremor, cognitive decline, and ataxia usually starting over age 50. As more people were diagnosed with FXTAS, it became clear that parkinsonism (usually without rest tremor) is common, as are symptomatic peripheral neuropathy, impotence, bowel/bladder dysfunction, and dysphagia.[71,72] The risk of the full-blown syndrome increases with CGG repeat length and age. Even a repeat length below the intermediate range (40–55 repeats) may be a risk factor for other conditions, and these repeats seem to be more prevalent than expected in conditions such as PD, multiple system atrophy, various ataxias, and others.[72] More women are now being reported with a comparable syndrome. Some carriers (perhaps many) have mild parkinsonian features, and a few may have levodopa-responsive parkinsonism without evidence of presynaptic dopaminergic dysfunction.[72] Patients with FXTAS have brain MRI abnormalities including cortical atrophy, scattered white matter lesions, and, in about half of reported patients, hyperdense lesions in the middle cerebellar peduncle.[72] (see Figure 2–10).

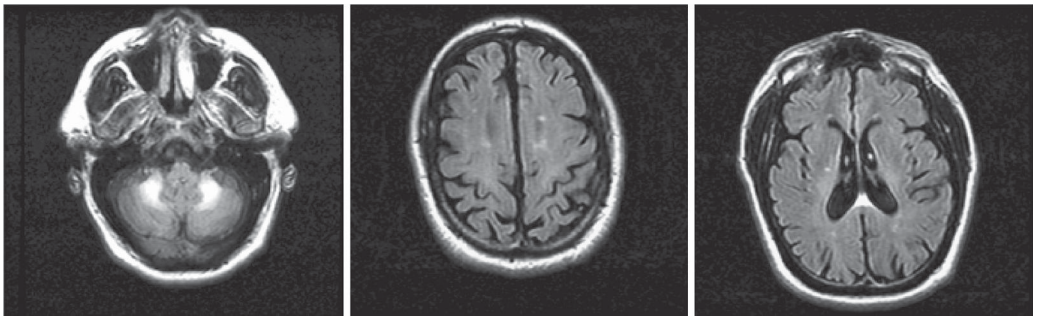

Figure 2–10. A. Axial flair MRI showing generalized atrophy and bilateral hyperintensities in the white matter and the splenium of the corpus callosum (white arrow). J. Axial flair MRI showing hyperintensity in both middle cerebellar peduncles (white arrows). K. Coronal T2-weighted MRI showing bilateral hyperintensity in the dentate nuclei (white arrows). L. Axial flair MRI showing hyperintense signals in the pons hyperintensities (white arrow).

DYSTONIC TREMOR

Although patients with dystonia may have an ET-like tremor, they also frequently have an unusual type of tremor only seen with dystonia. This tremor is like nystagmus, with a fast phase in the direction of the dystonic deviation followed by a slow phase in the opposite direction. Unlike ET, which responds poorly to BTX injections, dystonic tremor of the head in CD responds well to BTX treatment of the underlying dystonia (Table 2–9).

OTHER TREMORS

A posterior thalamic lesion (usually stroke or hemorrhage) may produce a tremor, usually after a delay of weeks to months.[8] The tremor may include postural, action, and even rest components. Some of these patients will also have dystonia, either jerky or fixed, that can dominate the picture.[8] Some patients with peripheral neuropathies develop tremor. The frequency of these tremors is 3 Hz to 6 Hz, and the evidence suggests that there is no central component to the tremor.[29] It is possible that delayed proprioceptive information and or delayed motor conduction play a role in generating the tremor. Inflammatory neuropathies may be particularly prone to generate tremor, but these conditions may also affect cerebellar circuits and contribute to the tremor.[29] There are a variety of tremors of unknown origin affecting isolated parts of the body, such as the lips, chin, or tongue. Some of these are genetic. Hereditary geniospasm is an autosomal dominant disease with no identified gene that causes high-frequency tremor (quivering) of the mentalis and other lower facial muscles. This is usually characterized

Table 2–9 **Factors That Help to Distinguish Between Essential and Dystonic Tremor**

	Essential Tremor	Dystonic Tremor
Amplitude	Small and constant	Large and variable—sometimes described as "jerky"
Symmetry	Symmetrical	Asymmetrical
Dystonia	Not present	Often present
Position specificity	Not present	Tremor often worse in particular positions
Task specificity	Not present	Tremor often worse in performance of particular tasks
Family history	Majority of cases	Not uncommon
Improvement with alcohol	Often dramatic	Can occur
Response to propranolol	Often good	Usually little response

Modified from: Parkinson's Disease and Other Movement Disorders. Mark Edwards, Niall Quinn, and Kailash Bhatia. Chapter 5 Tremor. Table 5.23.

as a tremor, although the quivering is actually irregular. The tremor is usually not disabling but it can be embarrassing and disappears with BTX injections.[73,74] There is evidence the geniospasm is associated with hyperexcitability of the facial nucleus, at least in some patients.[73] A variety of drugs induce tremor. Some are dopamine-receptor blockers and induce parkinsonism, others may enhance physiological tremor, but the mechanism for many drug-induced tremors is not known. For a list of drugs reported to cause tremor, see Table 10–1 in the chapter "Drug-Induced Movement Disorders."

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Chapter 3

Dystonia: Part 1

Paul E. Greene

HISTORY

It was not until the end of the 1800s and early 1900s that athetosis and dystonia were separated from the hyperkinetic choreas.[1] In 1944, Herz outlined the transformation in medical thinking that culminated in the understanding of dystonia as an organic brain symptom. This started with the belief that St. Vitus's dance, and subsequently many hyperkinetic disorders, were psychiatric in origin. Gradually, throughout the 17th and 18th centuries, chorea was separated out from this mélange of disorders and a variety of causes for chorea were identified. In the late 1800s, it was recognized that writhing movements superimposed on chorea indicated a different set of causes, and the concept of athetosis became established. Despite the identification of athetosis as a symptom of brain dysfunction, when sustained posturing (what we now call dystonia) was identified, it was felt to be psychiatric in origin. This was in part because of the unusual clinical features of dystonia described later in the chapter. In 1908, Schwalbe reported three children in one Ashkenazic Jewish family affected by dystonia and, although he felt they had "hysterical symptoms," he also suggested there might also be an organic component.[1] In 1911, when Oppenheim reported more cases of childhood-onset dystonia, he rejected the idea that the symptoms were in any way psychiatric, establishing childhood-onset dystonia as neurological condition.[2] The relationship between childhood-onset dystonia (which is usually not focal) and adult-onset dystonia (which is often

focal) was not clear until the 1960s, when Zeeman proposed that the focal dystonias were formes frustes of childhood-onset dystonia.[3] Even then, through the 1980s and 1990s, adults with focal dystonia and many children with dystonia were sent for psychiatric treatment. Widespread recognition of dystonia as an organic brain condition did not occur until botulinum toxin (BTX) injections provided the general neurological community with a relatively accessible treatment for the symptom.

Even after it became clear to some neurologists that dystonia was an organic condition, there was confusion about the distinction between dystonia as a neurologic condition and dystonia as a symptom of other conditions. In 1944, Herz clarified this by summarizing what was known about the symptom dystonia occurring in such conditions as Wilson's disease, Parkinson's disease, postencephalitic parkinsonism, and others. He concluded that, until the pathophysiology of dystonia was discovered, patients with dystonia should have the known causes of dystonia eliminated before being labeled as having the disease dystonia.[1] As brain imaging and other diagnostic tests became more sophisticated, attention was focused on familial dystonia in children with neither other neurological signs nor detectable neurological abnormalities. The search for genes for childhood-onset dystonia continued through the 1980s and 1990s, culminating in the discovery of the DYT1 gene in 1997.[4] There has been a continuing symbiosis between genetic and clinical classifications. Identification of distinct dystonia phenotypes stimulates the discovery of new genes for dystonia, and the discovery of new genes broadens the clinical phenotypes of identified syndromes.

Although treatment of dystonia with anticholinergics has a long history—going back to at least 1952,[5] the identification of high-dose anticholinergic treatment for childhood onset dystonia in the 1980s stimulated an effort to find other effective medications for all forms of dystonia, without marked success so far. By the late 1980s, it became clear that BTX was an effective treatment for focal symptoms of dystonia and it was approved for treatment of blepharospasm by the FDA in 1989. This supplanted the use of medications for adult-onset dystonia, which is so much more common than childhood-onset dystonia that further research into medication treatment became increasingly less common. The next major change in therapy appeared in the early 2000s. Thalamotomy for dystonia was shown to be effective by Cooper, who performed a large series of operations in the 1950s. However, almost all patients required bilateral operation, disturbance of speech and swallowing were frequent, and the benefits, while significant, did not clearly justify the risks. When deep brain stimulation (DBS) of the globus pallidus and subthalamic nucleus became common for Parkinson's disease, surgery for dystonia was revisited. Deep brain stimulation of the thalamus for dystonia was reported in the 1970s. In the early 2000s, pallidal DBS became increasingly frequent for generalized dystonia and began to be used to treat a variety of focal dystonias. Double-blind studies documenting the efficacy of DBS for primary generalized dystonia were published in 2005 and 2006.[6] The indications for DBS for various focal and secondary dystonias continue to be explored to the present.

There has been a search for the pathophysiology underlying dystonia starting with its recognition as a distinct neurological symptom/disease. Cocontraction of agonist and antagonist muscles was described in the 1940s, leading researchers to suggest a release of normally suppressed reflex activity[1] Abnormal blink reflex recovery times in patients with dystonia of the face and neck[6] identified in the 1980s suggested abnormalities of brainstem and spinal cord inhibitory neurons. Information about the physiology of dystonia expanded with the development of PET scanning and more sophisticated physiological techniques in the early 2000s. PET detected abnormal patterns of brain activation present in patients with dystonia and in asymptomatic gene mutation carriers.[6]

CLASSIFICATION

Dystonia is really a symptom, not a disease. The symptom dystonia has many causes (see Tables 3–3, 3–5, and 3–6) and a broad spectrum of age at onset, clinical course, and distribution of symptoms in the body. Dystonia is generally persistent once it starts, but there are rare conditions with paroxysmal dystonia, sometimes in combination with other hyperkinetic movements. Dystonia involves sustained involuntary muscle contractions, but there are sometimes neurological signs such as tremor, parkinsonism, or myoclonic jerks in patients who have no

Table 3–1 **Classification of Dystonia**

I.	Temporal pattern
	Sustained
	Paroxysmal
II.	Etiology
	Primary
	Dystonia-plus
	Secondary degenerative
	Secondary nondegenerative
III.	Distribution of signs throughout the body
	Focal
	Segmental
	Multifocal
	Generalized
	Hemidystonia
IV.	Age at onset
	Childhood onset
	Adolescent onset
	Adult onset
V.	Initial site in the body
	Leg onset
	Arm onset
	Neck onset
	Cranial onset
VI.	Genetic status
	Sporadic
	Autosomal dominant
	Autosomal recessive
	X-linked recessive
	Mitochondrial

Note: See text for explanations.

other identifiable neurological disease. In order to make sense of these variations, many different and parallel systems have been developed to classify dystonia. Most classification systems include the following domains: temporal pattern, etiology, distribution of signs throughout the body, age at onset, initial site in the body, and genetic status (see Table 3–1).

Temporal Pattern

Most people with dystonia have sustained muscle contractions. Rarely, people may have attacks of dystonia lasting seconds to days and may be normal or virtually normal in between attacks, a pattern called paroxysmal dystonia.

Etiology

There are so many potential causes for the symptom dystonia that it is impossible to determine the etiology by testing for all possible causes. Considerable attention was paid to the classification of dystonia to enable physicians to approach each case in a rational manner. Physicians must use the clinical characteristics of dystonia plus possibly a few diagnostic tests such as brain MRI and eye exam for Kayser-Fleischer (KF) rings to guide other diagnostic testing. Most people with dystonia have a normal MRI and normal results on all other currently available tests, with the possible exception of genetic testing. Most patients with pure dystonia have progressive symptoms (at least for months or years), but do not have evidence of dying nerve cells. Some patients with dystonia and neurological signs as myoclonus or parkinsonism are also found to lack dying nerve cells. It is tempting, therefore, to simply distinguish between patients with and without dead or dying neurons. Unfortunately, there are some well-defined causes of dystonia—such as motor tics, exposure to centrally acting dopamine receptor blocking agents, or anticonvulsants—that also lack evidence of dead or dying cells. Therefore, most physicians use a hybrid classification system:

Primary (idiopathic) dystonia: Patients have dystonia as the only sign or symptom (with the possible exception of tremor) and no other identifiable neurological disease.

Dystonia-plus: Patients have dystonia with either myoclonus or parkinsonism and no dead or dying nerve cells.

Secondary dystonia: Patients with dystonia who have another identifiable cause for their symptoms. This includes neurodegenerative diseases with progressive loss of nerve cells (usually including brain neurons and usually with other neurological signs and symptoms), diseases with dead nerve cells that are not progressive, and biochemical diseases with no evidence of dead or dying nerve cells. All secondary causes of dystonia may be sporadic or inherited.

Distribution of Signs Throughout the Body

The distribution of dystonic signs throughout the body provides a clue as to diagnosis and is important for planning treatment. In sustained dystonia it is usually obvious what parts of the body are involved, but it sometimes is

challenging to classify the distribution. Some patients may have severe dystonia in some parts of the body and only subtle involvement in other muscles (this is common in blepharospasm, dystonia of the orbicularis oculi, where at least 80% of patients will have some involvement of at least one other facial muscle innervated by the facial nerve).[7] In addition, because dystonia may be task-specific, it may be necessary to have patients perform specific activities, such as writing with their nondominant hand or playing a musical instrument, in order to activate the dystonia. While there is no universal standard for distribution, most physicians use some variant of the following system:

Focal: involvement of one of the following movable parts of the body: eyelids, tongue, jaw, vocal cords, neck, trunk, or a single upper or lower extremity. There may be only a single muscle involved, such as the orbicularis oculi or a finger extensor, or every muscle in the limb or body part might be involved. There are various approaches to the face: some consider the orbicularis oculi separately from other facial nerve innervated muscles, others consider all facial nerve innervated muscles as part of the same segment. If the muscles are considered separately, then Meige syndrome would be more than one facial muscle independent of the innervation. If all facial nerve innervated muscles are considered one segment, then Meige syndrome consists of facial muscles innervated by more than just the facial nerve, for example, some combination of eyelids, jaw, tongue, and neck.

Segmental: involvement of two or more contiguous body parts, such neck and face, both legs or trunk and one or both legs (crural), both arms, or both legs.

Multifocal: more than one focal part of the body, but not in a segmental distribution, such as one arm and the contralateral leg.

Generalized dystonia: One definition is involvement of trunk and four limbs. Another definition emphasizes the potential for interfering with walking: crural + at least one other limb.

Hemidystonia: dystonia of upper and lower extremity on one side, plus or minus the ipsilateral trunk and/or face. This is usually a sign of secondary dystonia with a contralateral brain lesion.

Age at Onset

As with so many other aspects of dystonia, there is general agreement on the broad outline but the details are not as clear. There is no question that the age at onset has profound implications for the etiology, prognosis, and treatment of dystonia. Most classification systems recognize two or three categories, with the boundaries somewhat vague:

Childhood onset: up to about 12 years of age.
Adolescent onset: from about 12 years to 20 or 26 years of age.
Adult onset: above 20 or 26 years of age.

Childhood-onset dystonia is usually genetic in origin, more likely to include some of the rare degenerative causes of dystonia, more likely to spread beyond the site at onset, and more responsive to oral medications. Adult-onset dystonia is less likely to improve with medications, usually sporadic, and much less likely to spread and when it does spread the symptoms usually cluster in one or two contiguous segments of the body. Adolescent-onset dystonia usually has the childhood pattern of dystonia but sometimes has the adult pattern. For the relationship between age at onset and distribution of dystonia, see Figure 3–1.

Initial Site in the Body

There is a peculiar relationship between the initial site of dystonia, the age at onset, and the course of the disease. Dystonia in the legs starts at the youngest ages in children, spreads the fastest, often reaches a plateau fairly quickly and rarely appears in adults with primary dystonia. Dystonia starting in the arms generally appears later than the legs, can be stable for years and then start to spread, and can start in adults. Dystonia starting in the neck generally appears in older people than that starting in the arms (although there is a small peak in adolescence), and primary dystonia in the face generally appears at an even older age.[7]

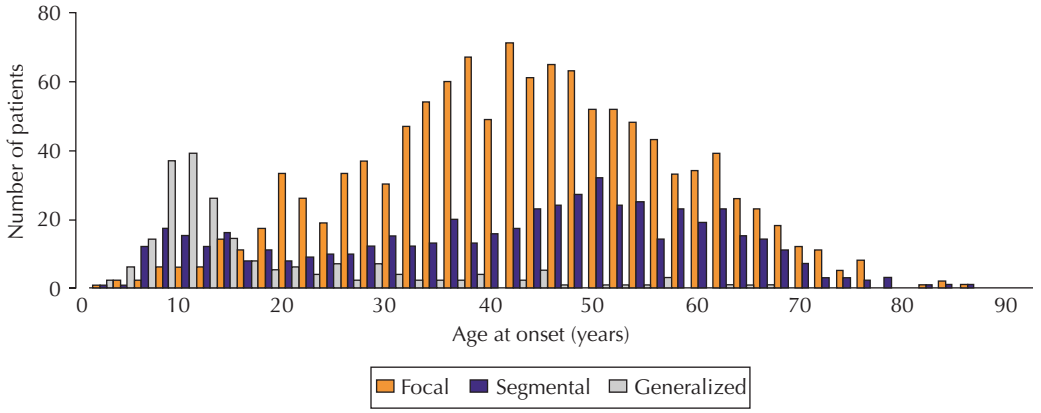

Figure 3–1. Relationship between age at onset and distribution of dystonia. Most cases of generalized dystonia started in chilhood (median age about 10 years). Focal and segmental dystonia tended to start later in life (the median age at onset of segmental dystonia was about a decade later than that of focal dystonia), but both had a small peak earlier in life, suggesting multiple etiologies. Data from Columbia Presbyterian Medical Center courtesy of Dr. Susan Bressman. (From: Carvalho Aguiar PM de C, Ozelius LJ. Classification and genetics of dystonia. Lancet Neurology 2002;1:316–325. Figure 1.)

Genetic Status

Genetic status is always of interest in all forms of dystonia. Given the large number of diseases that can cause the symptom dystonia, it is no surprise that virtually every known type of inheritance pattern can be found in some dystonic syndrome. The majority of genetic inheritance in primary dystonias is dominant with reduced penetrance, although recessive inheritance has been reported. Similarly, dystonia-plus syndromes may be either dominant or recessive, and the most common mutation causing dopa-responsive dystonia (in the gene for GTP cyclohydrolase 1) is dominant with sex-dependent, reduced penetrance. In one reported case, myoclonus-dystonia resulted from maternal uniparental disomy with maternal imprinting (the patient inherited both copies of the normal gene for epsilon sarcoglycan from his mother and both were turned off by methylation, producing loss of function). Inherited secondary dystonia broadens the possibilities dramatically, including mitochondrial inheritance and X-linked recessive inheritance (in Lubag disease). For specific examples, see Tables 3–3 and 3–6.

PHENOMENOLOGY

Dystonia is a complex neurological symptom that is difficult to define and for which there are no definitive diagnostic tests. Prior to 2013, the most commonly used definition of dystonia was proposed by a committee of the Dystonia Medical Research Foundation in 1984: "Dystonia is a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements, or abnormal postures."[8] This definition was updated in 2013 by a Consensus Committee established by the Dystonia Medical Research Foundation, the Dystonia Coalition, and the European Dystonia Cooperation in Science and Technology Action.[9] They proposed a more elaborate definition: "Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation." This definition, unlike the previous definition, does include people with dystonia who have muscle contractions that are not sustained but alternate with periods of normal or even reduced tone (thus the name dys-tonia). Unfortunately, this definition is not easy to apply and is not specific. The definition applies to all forms of tremor, and there are symptoms consisting of sustained contractions that are not considered dystonia. These are generally labeled pseudodystonia.[9] They include splinting to reduce pain (atlantoaxial subluxation, painful neck and back

tumors, back pain for other reasons), neuromuscular causes of muscle spasm, and others—see Table 3–2. One peculiar pseudodystonia is neck flexion to relieve symptoms of gastro-esophageal reflux or Sandifer's syndrome.[10] Most experts do not consider decorticate and decerebrate posturing as forms of dystonia. One particularly troublesome pseudodystonia is congenital muscular torticollis, as BTX injections are not an indicated treatment for this condition in adults. Congenital muscular torticollis is a condition in which there is fibrosis of the sternocleidomastoid causing head tilt in infants that worsens as long as the child grows—since the SCM cannot elongate, it tilts the head farther over time.[11] This is probably due to an abnormal anatomic problem in utero, as these infants usually also have facial hemiatrophy on the side of the head tilt.

There have often been suggestions that other nonmotor phenomena may accompany primary dystonia, but this has been difficult to document and probably varies with the cause of the dystonia. Some, but not all, studies have found that people carrying the mutation for myoclonus-dystonia may have more obsessive-compulsive disorder and alcohol dependence than controls.[12] Some studies have demonstrated subtle learning disturbances in patients with dystonia and with DYT1 dystonia in particular. Psychiatric disturbances such as depression and social phobia are common in people with dystonia but may represent reactions to their symptoms.[13]

Table 3–2 **List of Pseudodystonias (Imitators of Dystonia)**

Dystonic (tonic) tics
Head tilt (vestibulopathy, trochlear nerve palsy)
Bent spine, camptocormia, scoliosis
Atlanto axial and shoulder subluxation
Amold-Chiari malformation
Soft tissue neck mass
Congenital muscular torticollis
Congenital Klippel-Feil syndrome
Satoyoshi syndrome
Dupuytren's contractures
Trigger digits
Neuromuscular causes (Isaacs syndrome, etc.)
Spasms (hypocalcemia, hypomagnesemia, alkalosis)
Orthopedic and rheumatological causes
Sandifer syndrome
Deafferentiation (pseudoathetosis)

From: Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: a consensus update. Mov Disord 2013;863-873. Table 2.

Primary Dystonia

The first challenge in diagnosing primary dystonia is to distinguish the symptom dystonia from the other hyperkinetic symptoms. Even though no other hyperkinetic movements are usually sustained, this can sometimes be difficult. Many people with torticollis (cervical dystonia) and some people with limb dystonia have superimposed tremor. Sometimes, the tremor has a predominant direction: a fast phase in one direction followed by a slow phase in the opposite direction. This distinguishes it from tremor of essential tremor (ET) type. However, many people with dystonia will also have a regular, symmetric tremor. It is not known whether this is the coincidence of a common disease (ET) with an uncommon symptom (dystonia) or evidence of an etiologic or genetic relationship. Also, because the amplitude of ET depends in part on the mass of the shaking body part, some people with ET will tighten all the muscles of the arm while writing to increase the mass that is shaking and dampen the tremor. This sustained muscle tightening can resemble writer's cramp (brachial dystonia), and in some people with ET this trick is automatic and hard to voluntarily suppress. Tics are usually brief and paroxysmal, but some tics are more prolonged ("dystonic tics"). If these dystonic tics are frequent, it may be difficult to distinguish these tics from very mild dystonia (which may come and go or be task specific). As if this were not complicated enough, a minority of people with dystonia also have tics. As with ET, it is not clear whether this represents chance co-occurrence with a common disease or a specific relationship. The typical chorea of Huntington's disease or neuroacanthocytosis or the dyskinesia of tardive syndromes is easy to distinguish from dystonia, but it is important to keep in mind that dystonia may be a symptom in those diseases. In those cases, the dystonia is usually minor, although occasionally the dystonia can dominate the clinical picture.

The phenomenology of primary childhood-onset and adult-onset dystonia are generally different, although there is some overlap, especially in the teenage and young adult years. Adult- and childhood-onset dystonia often

Table 3–3 **Primary Dystonia and Dystonia-Plus**

	Gene or Locus	Phenotype	Transmission
Primary Dystonia			
DYT1	TOR1A	Generalized early-limb-onset dystonia	AD
DYT2	None	Early-onset generalized with prominent cranial-cervical dystonia	AR
DYT4	TUBB4a	Whispering dysphonia-plus	AD
DYT6	THAP1	Craniocervical and limb dystonia	AD
DYT7	18p (?)	Adult-onset cervical dystonia	AD
DYT13	1p36.13-p36.32	Craniocervical, laryngeal, and limb dystonia	AD
DYT17	20p11.22-q13.12	Segmental or generalized dystonia with severe dysphonia	AR
DYT21	2q14.3-q21.3	Adult-onset generalized or multifocal dystonia often starting as blepharospasm	AD
DYT23	CIZ1	Adult-onset cervical dystonia	AD
DYT24	ANO3	Adult-onset segmental brachial-cervical-cranial dystonia	AD
DYT25	GNAL	Cervical-plus dystonia, wide age at onset	AD
Dystonia-Plus			
DYT5a	GCH1	Dopa-responsive dystonia	AD
DYT5b	TH	Dopa-responsive dystonia	AR
DYT11	SGCE	Myoclonus-dystonia	AD
DYT12	ATP1A3	Rapid-onset dystonia parkinsonism	AD
DYT14 (now DYT5a)		Dopa-responsive dystonia	AD
DYT15	18p11	Myoclonus-dystonia	AD
DYT16	PRKRA	Early-onset dystonia parkinsonism	AR
Paroxysmal Dystonia/Dyskinesia			
DYT8	MR1	Paroxysmal dystonic choreoathetosis (nonkinesigenic)	AD
DYT9 (now DYT18)		Paroxysmal dyskinesias with episodic ataxia and spasticity	AD
DYT10	PRRT2	Paroxysmal kinesigenic choreoathetosis	AD
DYT18	SLC2A1	Paroxysmal exercise-induced dystonia 2	AD
DYT19	16q	Paroxysmal kinesigenic dyskinesia 2	AD
DYT20	2q	Paroxysmal nonkinesigenic dyskinesia 2	AD

AD = autosomal dominant. ANO3 = anoctamin 3. AR = autosomal recessive. ATP1A3 = ATPase, Na^+/K^+. CIZ1 = cip1-interacting zinc finger protein 1. GCH1 = guanosine triphosphate cyclohydrolase 1. GNAL = guanine nucleotide-binding protein G(olf) subunit alpha. MR1 = myofibrillogenesis regulator 1. PRKRA = double-stranded RNA-activated protein kinase. PRRT2 = proline-rich transmembrane protein. SGCE = ε-sarcoglycan. SLC2A1 = Solute carrier family 2 (facilitated glucose transporter), member 1. TH = tyrosine hydroxylase. THAP1 = thanatos associated protein. THD = tyrosine hydroxylase deficiency. TOR1A = torsin A.

Modified from: Phukan J, Albanese A, Gasser T, et al. Primary dystonia and dystonia-plus syndromes: clinical characteristics, diagnosis, and pathogenesis. Lancet Neurol 2011;10:1074–1085.

start as a task-specific dystonia. When it starts in the arms, common triggers are writing, typing, playing a specific instrument, or other forms of common activities performed with the arms, hands, or fingers. Because dystonia seems more common in people who perform the same activity repeatedly (such as musicians or stenographers), this pattern suggests that overuse may contribute to the development of dystonia. On the other hand, there are many other professions that involve persistent, repetitive upper-extremity use that do not seem to have increased prevalence of dystonia. Cervical dystonia is usually better with sitting and worsens with walking (although the opposite is true in occasional patients, a pattern sometimes called paradoxical dystonia). An occasional patient will only develop cervical

dystonia when driving a car or when alone (or, because dystonia is often unpredictable and confounding, only in the presence of others). There are similar patterns with dystonia of the face, tongue, or jaw: some will only have symptoms or have worse symptoms when not talking while others will have the opposite pattern.

One extraordinary observation about dystonia is the ability of some people to influence their symptoms by performing a particular movement, called a sensory trick. This is often present early in the course of the disease and disappears if the symptoms worsen. People with cervical dystonia lightly touch their cheek and their head straightens. When the cheek is on the side of the turning (a push would oppose the direction of turning), the French call this a geste antagoniste. Often, a touch on the opposite cheek works just as well (a geste agoniste). Other sensory tricks in cervical dystonia include touching the back of the head, resting the back of the head against a wall or head rest of a chair, putting the hands in the air, and others. There are similar sensory tricks for dystonia in other parts of the body. Lower-extremity dystonia in children is sometimes present when they walk forward but not if they run or walk backward. People with writer's cramp may avoid the involuntary spasms by holding the pen in novel ways (between two fingers or grabbing it with their fist). People with jaw-opening or -closing dystonia may hold a toothpick, pipe stem, pen, or other hard object in their mouth and improve functioning. Blepharospasm often improves with talking, but may also improve by looking down or pulling the lateral canthus sideways and it may worsen or be present only with talking. There are an astonishing variety of sensory tricks that have been recorded—see Table 3–4.[14] Although not usually recorded, some similar maneuvers may temporarily worsen dystonia, although it is hard to distinguish this phenomenon from the phenomenon of task-specificity. The underlying physiology of sensory tricks has fascinated observers ever since the phenomenon was first reported over a century ago. In some patients, simply imagining the movement improves the dystonia, and PET imaging of patients while they imagine the trick causes a decrease in activity in the supplementary motor area, which is usually hyperactive in dystonia.[14,15] For an example of a complex dystonia improving with a sensory trick, see Figure 3–2.

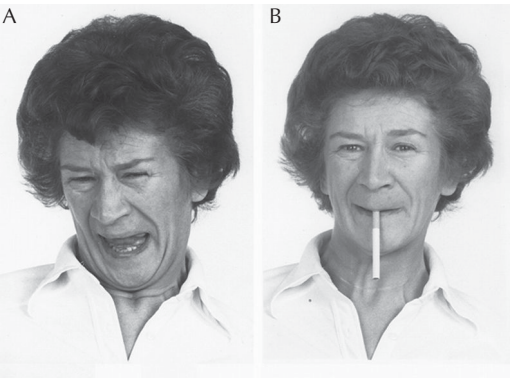

Figure 3–2. Sensory trick. Patient with blepharospasm, jaw-opening dystonia, and torticollis improves significantly in all areas with an object (cigarette) in her mouth. (From: Ivan Donaldson, C. David Marsden, Susanne Schneider, and Kailash Bhatia. Marsden's Book of Movement Disorders. Figure 37.6.)

CRANIAL DYSTONIA

A. Blepharospasm: Judging by patients' reports, blepharospasm often starts as increased blink rate. Even at this stage, some patients report dry itchy eyes and light sensitivity. This is the only focal dystonia that includes a sensory complaint other than pain. It is not clear whether these sensory symptoms are a result of the increased blinking or whether they are themselves early symptoms of dystonia. When blepharospasm worsens, people next develop abnormally forceful blinks and then episodes of forceful, sustained eye closure. At the Columbia University Movement Disorder Center, about 80% of patients with blepharospasm also developed dystonic contractions, usually minor, in some other muscle innervated by the facial nerve. Unlike cervical dystonia, it is not clear whether people with blepharospasm ever have spontaneous remissions, although at the Movement Disorder Center we saw a small number of patients who had blepharospasm disappear to be replaced by jaw or tongue dystonia. A small percentage of patients with primary blepharospasm have either respiratory dysrhythmia and/or inspiratory stridor. In all cases seen at the Movement Disorder Center, this stridor disappeared during sleep (unlike in tardive dystonia, where the stridor may persist during sleep). For an example of blepharospasm, see Figure 3–3.

Table 3–4 **List of Sensory Tricks According to Type of Dystonia**

Dystonia	Sensory Trick
Cervical dystonia	Touching specific part of the face, cheek, chin, occipital region, temple, forehead, nose, mastoid, occipital region, back of neck. Raising the arm and holding the finger near the target region without touching the face, or prior to touching the face. Visual fixation at a specific target focusing on stationary object while walking, looking at oneself in the mirror. Forcible tricks with counterpressure to the cheek, temple, chin, back of head, mastoid, forehead. Resting the back of the head or neck, bending the trunk forward, resting the back or shoulder, yawning, wearing a collar/scarf, leaning the elbows on the armrest. Imagining or merely thinking about performing a sensory trick.
Apraxia of eyelid opening, blepharospasm	Tight goggles or spectacles, Lundie Loops. Device inserted in glasses to mimic touch to lateral eyelid. Touching/pulling eyelids, tape on eyebrow. Touching specific parts of the face (forehead, nose, side of eyelids, chin). Pushing back of the head. Massaging cheek bones, eyelid, forehead. Closing the jaw, chewing gum. Touching bitemporal skin beside eyes. Covering the eye. Picking teeth. Wearing a cap or turban.
Meige syndrome	Sleeping/relaxing, talking, singing/humming, pulling on upper eyelid, pinching back of the neck, yawning, belching, sucking in or blowing out cheeks, drinking cold and/or alcoholic beverage.
Lower cranial dystonia, oromandibular dystonia	Toothpick in mouth, holding object clenched between the teeth, dental splint, touching lip, touching lower corner of face. "Mandibular sensory trick device" Touching tongue to palate, biting lips, swallowing, pulling face up, bending neck forward. Chewing gum, sucking. Kissing, whistling. Pen/cigarette/tongue depressor in mouth. Biting food/plastic between left upper and lower molars → dental prosthesis device 3 mm above molar. Smiling, singing, talking, thinking about talking. Biting piece of cotton or plastic. Dental splint. Playing with larger mouthpieces. 5 min ice massage of facial muscles.
Laryngeal dystonia	Grimacing, laughing, loud background noise.
Writer's cramp	5 min immersion in cold water. Shifting pen holding, holding pen between index finger and thumb vertically, writing with a closed fist. Use pens of different sizes and calibers, using chalk and blackboard or painting. Touching specific part of the contralateral normal hand to a specific part of the dystonic hand. Holding hands over head, run in a clockwise direction, mental imagery of running in a clockwise direction.
Runner's dystonia	Beach walking, applying pressure with hand at hip.
Camptocormia	Low-slung backpack, using wheeled walker, pressing back against hallway.
DYT1 dystonia	Piano playing.

From: Ramos VFML, Karp BI, Hallett M. J Neurol Neurosurg Psychiatry 2014. doi:10.1136/jnnp-2013-306971.

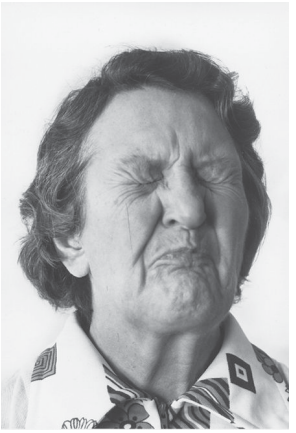

Figure 3–3. Patient with severe blepharospasm. Other facial nerve innervated muscles (frontalis, orbicularis oris, depressor anguli oris, platysma) are also involved, but jaw and tongue are probably spared. (From: Ivan Donaldson, C. David Marsden, Susanne Schneider, and Kailash Bhatia. Marsden's Book of Movement Disorders. Figure 37.4.)

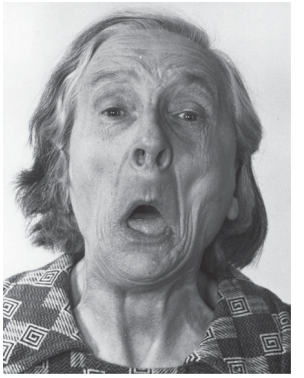

Figure 3–4. Patient with jaw-opening dystonia. There is mild involvement of the frontalis and platysma. (From: Ivan Donaldson, C. David Marsden, Susanne Schneider, and Kailash Bhatia. Marsden's Book of Movement Disorders. Figure 37.3.)

B. Jaw dystonia: Jaw-closing dystonia seems to be more common than jaw-opening dystonia. Most patients seem to have only opening or closing, but it is hard to diagnose both in the same patient because one form might overwhelm the other (most suspected cases arise when the opposite motion appears after treatment with BTX injections). Side-to-side jaw movements are even less common in primary dystonia, although more common in tardive syndromes. At least with jaw-closing dystonia, the initial symptoms may appear only with talking and eating and may disappear with activities such as singing. Putting a pencil or pipe stem between the cheek and the teeth may help the symptoms. For an example of jaw-opening dystonia, see Figure 3–4.
C. Vocal cord dystonia (spasmodic dysphonia): Adductor spasm is far more common than abductor spasm and produces a strained or strangled quality to speech. In adductor spasm, sounds that require vocal cord adduction are easier to say than sounds requiring vocal cord abduction (sustained "e" is easier than sustained "a"). Abductor spasm is essentially the opposite: speech has a breathy quality and you can hear air escaping through the open vocal cords; sounds requiring vocal cord abduction are easier to pronounce (sustained "a" is easier than sustained "e"). Whispering (speaking without using the vocal cords) is normal as long as dystonia does not involve pharyngeal muscles, lips, tongue, and other sound-producing muscles. As with jaw dystonia, co-contraction of agonist and antagonist (simultaneous ab- and ad- ductor dysphonia) seems to be extremely rare, but also hard to diagnose. Most people with primary spasmodic dysphonia have no trouble swallowing, are not at risk for aspiration, and do not have airway obstruction during sleep.

CERVICAL DYSTONIA

Not all patients with abnormal head deviation have dystonia. Patients with neck masses of any etiology or atlantoaxial dislocation may have abnormal tilt of the head. Fixed painful posture and increased pain when attempting to straighten the head are clues that this may be a pseudodystonia. In cervical dystonia (CD), the head can assume any position possible with voluntary motion. The most common single position is tilt to one side and rotation to the opposite side. This is the action of the sternocleidomastoid muscle, but that is virtually never the only muscle involved in CD. Pure flexion, extension rotation, tilt to one side, and shift of the head all occur as part of CD. For examples, see Figure 3–5. In primary adult-onset CD there is almost always a single dominant direction. In some cases of secondary CD (primarily associated with various forms of birth injury) and rarely

in primary CD, there can be right deviation alternating with left deviation. Combinations of various movements are the rule, although anterocollis, retrocollis, and shift seem to be relatively less common in primary CD. Since the muscle involvement in CD may vary with activity, it may be misleading to assess muscular involvement in CD only in the sitting position. One clue as to muscle involvement in CD is muscle hypertrophy, which develops in most patients with prolonged CD. In adult-onset CD, the head deviation can be tonic or, as described previously, there can be superimposed tremor.

As with dystonia in other areas, it may be hard to distinguish dystonic movements from compensatory maneuvers. For example, some patients with right rotational CD will keep their head turned slightly to the left. This also takes advantage of the muscle length-tension relationship, so that shortening or stretching the muscle reduces the maximum achievable force of contraction. For this reason, some patients will throw their heads past midline when attempting to turn their head in the direction opposite to the dystonic deviation. There is more contributing to disability in CD than just the magnitude

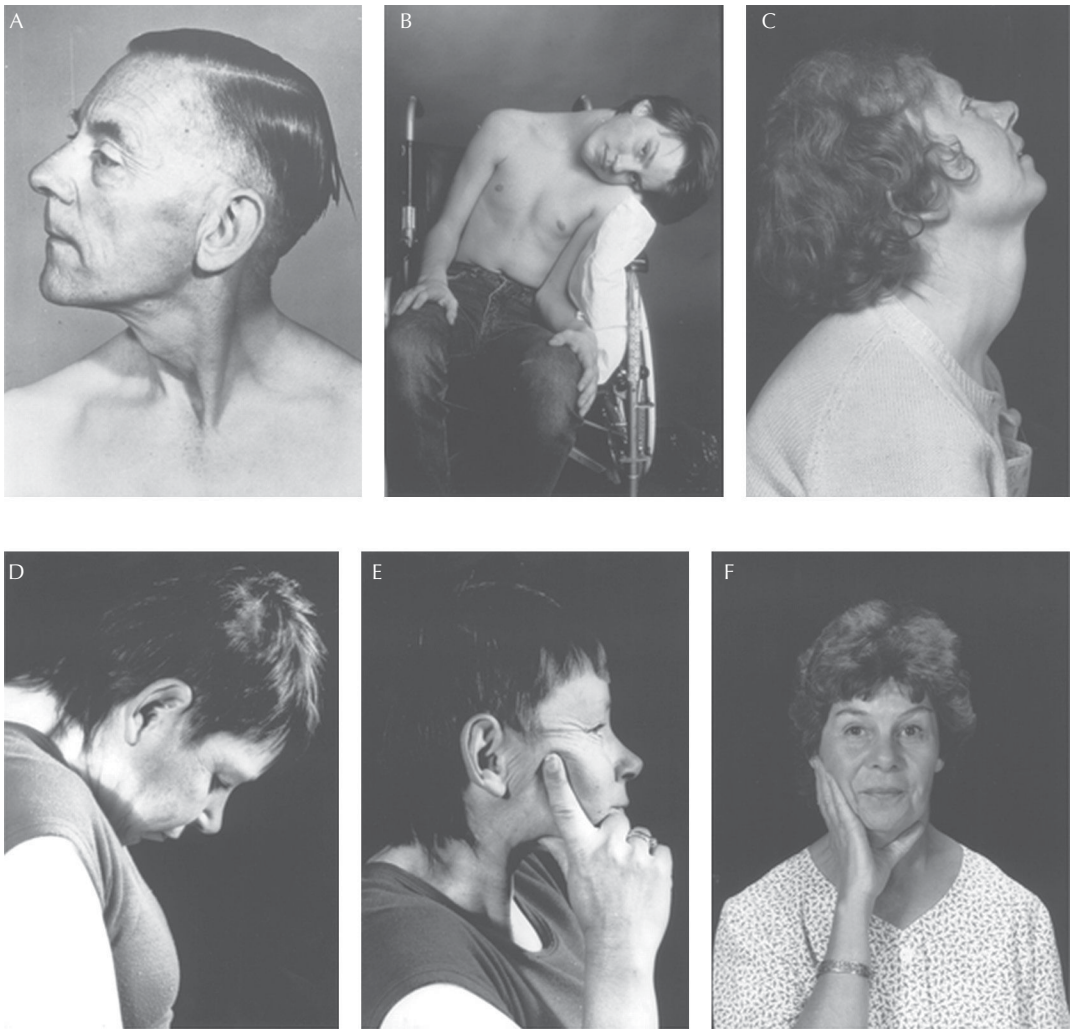

Figure 3–5. Different head positions in torticollis: Pure rotation (A), Pure laterocollis (with left brachial dystonia) (B), pure retrocollis (C), anterocollis before and after a sensory trick (touching cheek and chin) (D,E), and torticollis stabilized by a sensory trick (F). (From: Ivan Donaldson, C. David Marsden, Susanne Schneider, and Kailash Bhatia. Marsden's Book of Movement Disorders. Figure 38.5.)

of head deviation. Everything else being equal, rotation away from the dominant hand is more disabling than rotation toward the dominant side. A majority of patients with CD at movement disorder centers have chronic neck pain associated with their disease, often with muscle tenderness. This pain is usually associated with muscle contraction, as it often disappears with low doses of BTX. I find it mysterious that the pain in CD persists despite continued contraction of muscles during the waking hours. This is a form of muscle training, and that usually makes the pain associated with excessive exercise disappear. The pain is usually in the muscles producing the head deviation, but occasionally there is pain, sometimes the majority of the pain, in muscles that oppose the dominant direction. It is not clear whether this represents muscle contraction attempting to counteract the deviation or represents dystonia in the antagonist muscles, part of cocontraction of agonist and antagonist muscles, the presumed physiology of dystonia. Many patients complain of the constant pulling of neck muscles that interferes with concentration and makes common activities more difficult. People with CD sometimes have superimposed brief, painful spasms that are usually very disabling. Finally, embarrassment is disruptive for many people.

A peculiar feature of CD is that patients occasionally have spontaneous remissions! These usually occur within the first five years of disease and are often followed by relapses.[16] Some patients can have multiple remissions and relapses. Equally amazing is that some patients who remit may have a different head position if they relapse. Patients with severe chronic CD are at risk for radiculopathy and myelopathy. Patients with CD have a higher incidence of mild scoliosis predating the dystonia.[17] The significance of this is not known, but it suggests that mild scoliosis may be a manifestation of dystonia.

BRACHIAL DYSTONIA

Brachial dystonia often appears only with certain activities. The most common is probably writing, although upper-extremity dystonia seems to be proportionately more common among musicians. There is a rough correlation between the type of activity and the type of musician's dystonia.[18] Both proximal and distal muscles can be affected. As the symptoms worsen, more activities often trigger dystonic spasms and, in some cases, dystonia eventually becomes present at rest or constant dystonic postures are present. When elbow extension is part of the dystonia, patients may write with the elbow maximally flexed to put the extensor muscles at mechanical disadvantage and reduce the dystonic movement. For an example of writer's cramp, see Figure 3–6.

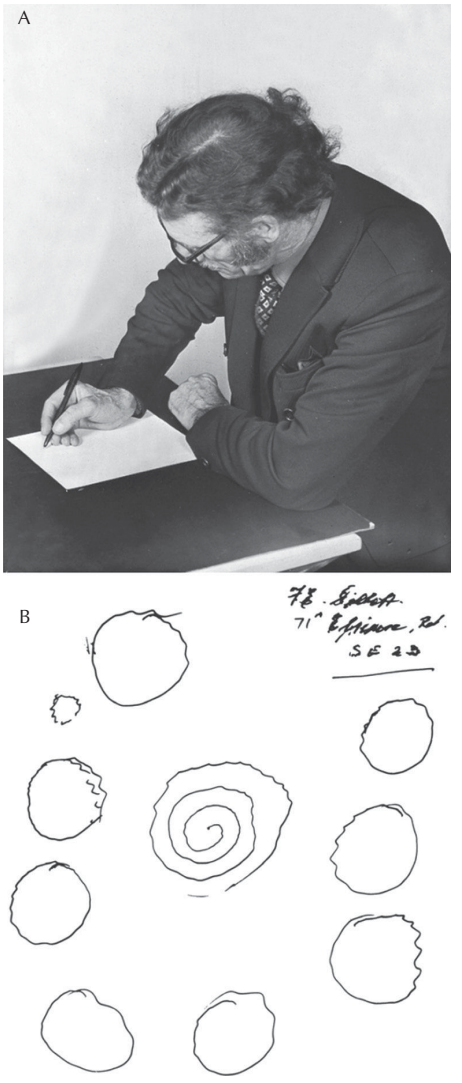

Figure 3–6. Patient with writer's cramp. When attempting to write, he has abduction at the shoulder, extension at the wrist (A). In the bottom panel, his writing is illegible (B) and he cannot copy an Archimedes spiral. (From: Oxford Textbook of Medicine (5th Edition). Edited by David A. Warrell, Timothy M. Cox, and John D. Firth. Figure 24.7.3.2.)

TRUNCAL DYSTONIA

Truncal dystonia may start as kyphosis (sometimes called dromedary gait), hyperextension, lordosis, scoliosis, or a combination of these. As with other locations of dystonia, the initial symptoms may appear only with some activities, commonly walking. Truncal involvement is relatively common in childhood-onset DYT1 dystonia (and probably childhood-onset dystonia not linked to DYT1) and is occasionally

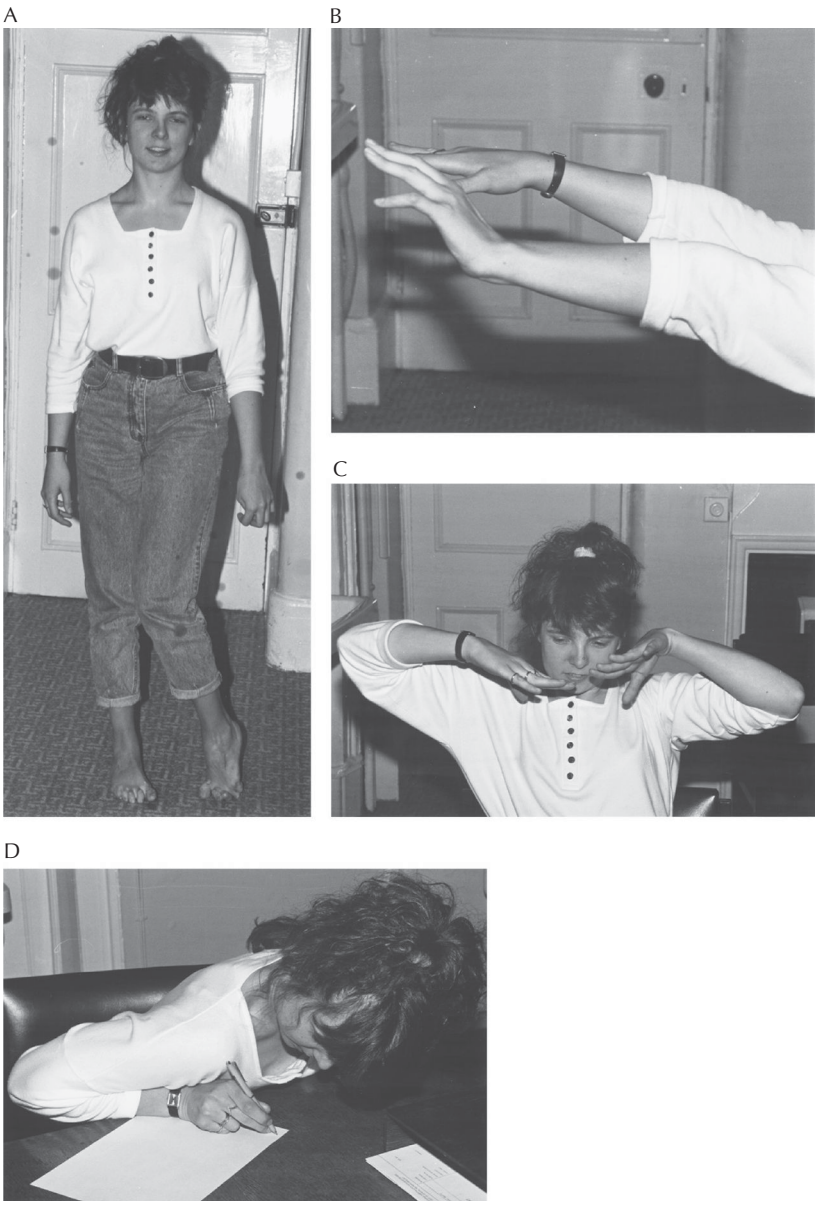

Figure 3–7. Patient with mild generalized dystonia. While standing (A), she has slight inward rotation of the left arm with flexion of the fingers. More dramatic is internal rotation and flexion of the left hip, flexion of the left knee, plantar flexion of the left foot, and curling of the left toes. The right foot is slightly turned in. In B and C, she has different abnormal postures of the left hand and fingers depending on her arm position. In D, she has an abnormal grip while writing with her right hand. She leans forward and maximally flexes her elbow, possibly to compensate for extensor dystonia in the arm. (From: Ivan Donaldson, C. David Marsden, Susanne Schneider, and Kailash Bhatia. Marsden's Book of Movement Disorders. Figure 35.3.)

the first sign of dystonia. Patients with severe chronic truncal involvement are at risk for radiculopathy and myelopathy. Isolated truncal dystonia is rare—jerky truncal arching suggests a possible tardive etiology at any age.

LOWER-EXTREMITY DYSTONIA

It is extremely rare for primary dystonia to involve the lower extremities in primary adult-onset dystonia. As described previously, the initial symptoms in lower-extremity dystonia may only be present with walking and not with running, skipping, or walking backward or sideways. The symptoms usually start on one side but often spread quickly to the other side. Distal or proximal muscles or both may be involved from the onset. Dystonia starting with inversion of one foot during walking suggests possible dopa-responsive dystonia. It is sometimes difficult to distinguish the dystonic contraction from the person's attempt to counteract the contraction (walking with locked knees may be a manifestation of knee extension or an attempt to compensate for knee flexion). Occasionally, especially if hip muscles are involved, the gait may be most unusual, and patients are sometimes mistakenly thought to have a psychogenic disorder.

GENERALIZED DYSTONIA

Primary generalized dystonia by definition involves the legs and so typically occurs in childhood-onset primary dystonia. Even within childhood-onset dystonia, it is usually the youngest children (and those that begin with dystonia in the legs) that become generalized.[7] Rarely, there is a dramatic sustained increase in symptoms that can cause muscle breakdown, myoglobinuria, respiratory compromise, and severe dysphagia. This is called dystonic storm or status dystonicus.[19] For an example of generalized dystonia, see Figure 3–7.

Dystonia-Plus Syndromes

DOPA-RESPONSIVE DYSTONIA

Childhood-onset dystonia with exquisite response to levodopa (dopa-responsive dystonia; DRD, DYT5, DYT14) was described by Segawa in 1976.[20] Initial patients were diagnosed because of their dramatic response to levodopa and the diurnal fluctuation in their symptoms: better to normal in the morning or after sleep and progressively worse in late afternoon and evening. The full spectrum of the disease was not appreciated until the discovery that most patients had a mutation in the gene for GTP cyclohydrolase 1 (GCH1), which is necessary for the synthesis of tetrahydrobiopterin, itself a necessary cofactor for tyrosine hydroxylase. Most patients with mutations in this gene have childhood onset of lower-extremity dystonia with sex-dependent parkinsonism (minimal in girls, more severe in boys), diurnal fluctuation, and excellent response to levodopa that is sustained for many decades without motor fluctuations. However, the range of presentations is large and continues to grow, encompassing lower-extremity hyperreflexia mistakenly diagnosed as cerebral palsy, generalized hypotonia, adult-onset pure parkinsonism, or adult-onset focal dystonia (oromandibular dystonia or cervical dystonia).[21] The biochemical nature of the disorder is evident from reduced levels of CSF biopterin and neopterin and the fluorodopa PET scan, which, unlike in juvenile-onset parkinsonism, is normal. Eventually, more severe forms of DRD were identified resulting from mutations in other genes producing enzymes necessary for the production of dopamine: tyrosine hydroxylase itself or two enzymes necessary for tetrahydrobiopterin synthesis, sepiapterin reductase, and 6-pyruvoyl tetrahydropterin synthase (6PTS). These mutations produce developmental delay, mental retardation, and other neurological signs and symptoms with relatively minor dystonia.[22] The parkinsonism in these mutations may not improve substantially with levodopa and motor fluctuations may develop, although patients with significant residual enzyme activity may resemble patients with GCH1 mutations.

MYOCLONUS-DYSTONIA

Patients with primary childhood-onset dystonia occasionally had rapid jerks in a dystonic limb that looked (and sometimes were) rapid enough to qualify as myoclonus (myoclonus-dystonia; M-D, DYT11, DYT15). Rarely, such patients had myoclonic jerks in limbs that did not have dystonic movements as well. The significance of this was not clear until the discovery of a

mutation in the gene for epsilon-sarcoglycan (SGCE). Epsilon-sarcoglycan was known to be a muscle protein, but it also occurs in the brain and the function there is unknown. The inheritance pattern is autosomal dominant with reduced penetrance, and the penetrance is a function of maternal imprinting: if the paternal gene has a pathogenic mutation and the maternal gene is turned off by methylation, there is complete penetrance.[12] The majority of cases of inherited M-D are linked to SGCE mutations, but other mutations and sporadic cases were described.[12] Typical SGCE-related M-D starts in childhood, usually with myoclonus sparing the legs. Dystonia may be mild to severe. However, in affected families, some individuals have pure dystonia or pure myoclonus. After the discovery of the SGCE mutations, review of the literature revealed that patients in families with pure myoclonus (essential myoclonus) sometimes were reported to have relatives with dystonia. At the time, this concurrence of two rare conditions did not raise suspicion that the conditions were related. Rare case reports described families with SGCE mutations and tremor, parkinsonism, or seizures, but it is not known whether these were manifestations of the mutations or coincidentally ran in those particular families. The brain MRI is normal in M-D patients. Alcohol dramatically reduces myoclonus in many but not all patients, and sometimes the dystonia also improves. Sodium oxybate, which mimics the effects of alcohol in the brain, has been reported to improve symptoms of M-D, but it can be highly sedating.[23] Clonazepam also sometimes produces significant improvement, but is not always well tolerated. Multiple other treatments, including DBS, have been reported to help M-D, but controlled studies are very difficult to perform due to the rarity of the condition.[12] A variety of nonmotor symptoms, including obsessive-compulsive disorders, alcohol abuse, depression, and anxiety, have been reported to be prevalent in M-D families, but because of the rarity it is hard to know whether this is an essential feature of the biochemical disturbance or coincidence, as these conditions are both common and familial. Given the improvement with alcohol, it is tempting to conclude that alcohol abuse results from self-medication with alcohol, but in some families alcohol abuse is prevalent in family members who had neither myoclonus nor dystonia.

RAPID-ONSET DYSTONIA PARKINSONISM

Of the many dystonia-parkinsonism syndromes, rapid-onset dystonia parkinsonism (RDP, DYT12) stands out clinically because there is no abnormal pathology on routine examination and the symptoms of dystonia and parkinsonism develop over minutes or weeks and then plateau. The condition can be sporadic or inherited. In 2004, mutations were discovered in the gene for ATPase, ATP1A3, which is involved in sodium and potassium membrane transport and is inherited in an autosomal dominant fashion with greatly reduced penetrance.[22,24] This mutation accounts for some of the familial and apparently sporadic cases. In some cases, dystonia may be present and relatively stable for years before the abrupt onset of parkinsonism and rapid worsening of dystonia. Other symptoms, including psychiatric symptoms and seizures, have been reported so rarely that it is not clear whether these are actually part of the syndrome. The age at onset is usually in adolescence or early adulthood, but the range is great. Onset of the disease is often precipitated by physical or emotional stress. The parkinsonism is not levodopa responsive. There may be progression in symptoms after onset, but it is usually subtle in most cases. Another clinical clue is the peculiar fixed smile, or risus sardonicus, that is sufficiently uncommon that it suggests Wilson's disease, brain iron accumulation diseases or other rare conditions. The risus is often accompanied by dysphagia and slurred speech.[24] Most recently, a surprising discovery was reported: mutations in ATP1A3 may also cause alternating hemiplegia of childhood (AHC), a paroxysmal disorder with a very different course and age at onset![25] As extraordinary as it may seem to clinicians, it now appears that RDP and AHC are different presentations along a single spectrum. Now that the genetic basis of the disorder is known, cases have been identified where RDP may start before age 18 months and have multiple discrete episodes such as oculogyria and recurrent dystonia (as in AHC) and AHC may start after 18 months. Once that was recognized, it became easier to focus on the many common features of the two conditions: rapid onset, primarily dystonia with features of parkinsonism, descent of involvement over time from face to arms to legs, severe bulbar involvement, and onset of disease triggered by stress.[26]

OTHER DYSTONIA PARKINSONISM SYNDROMES

There are two other dystonia-parkinson syndromes recently identified and with no known pathology, so that it is not clear whether they belong in the category of dystonia-plus or secondary dystonia. Since the biochemical basis is clear and the MRI is normal in both conditions, here they are categorized under dystonia-plus syndromes.

DYT16 is a childhood-onset, recessive disease presenting with pure dystonia or with dystonia followed by parkinsonism that is minimally responsive to levodopa. Cranial and axial symptoms are common, as is laryngeal dystonia. All reported cases had the peculiar fixed smile seen in Wilson's disease, the risus sardonicus. Developmental delay was common. Mutations were found in the gene for protein kinase interferon-inducible double-stranded RNA-dependent activator (PKRA) that is involved in stress-induced apoptosis and nervous system development in Drosophila.[27]

A small number of children were reported with a presumably recessive disease due to mutations in the gene for the dopamine transporter, SLC6A3. These children developed dystonia in infancy and often had dystonic storm. Parkinsonism that was poorly responsive to levodopa was present at the onset or eventually developed. The reported children were severely affected and often had other features, such as chorea, irritability, dysphagia, oculogyria, and developmental delay.[28] More recently, patients were identified with mutations in this gene but with normal development until age 11, onset as head tremor, and variable degrees of parkinsonism. Only one had dystonia in the form of anterocollis associated with parkinsonism.[29] Obviously, the full clinical spectrum of this disease (now labeled dopamine transporter deficiency syndrome or DTSS) has yet to be established.

Secondary Dystonia

Most forms of secondary dystonia can be identified by other neurological abnormalities. However, some causes of secondary dystonia consist exclusively of dystonia or have only subtle other abnormalities and may be challenging to identify clinically. With the exception of brain MRI, routine blood work, and perhaps a slit-lamp exam for K-F rings to rule out Wilson's disease, patients are first assessed clinically and receive more extensive testing if the clinical picture suggests secondary dystonia. There are a number of clinical features that either establish or suggest a secondary etiology. The following are not compatible with primary dystonia, although it is possible to have idiopathic dystonia and a coincidental neurological condition:

Relevant abnormal brain MRI or other laboratory test.
Any abnormal neurological sign except for tremor: most commonly ataxia, dementia, seizures, neuropathy, abnormal reflexes, weakness, or cranial nerve abnormalities. Myoclonus and parkinsonism as the only additional features suggest a dystonia-plus syndrome.
Nonphysiologic features on examination such as give-way weakness, nonphysiologic sensory loss, distractibility, or tremor with variable frequency or direction or that entrains to alternating movements with another limb suggest a psychogenic etiology.

Equally important in governing diagnostic evaluation are features that are uncommon, but not impossible, in primary dystonia and therefore require further evaluation:

Hemidystonia.
Sudden onset of dystonia.
Dystonia present at rest or fixed at onset.
Persistently painful dystonia (except for CD)
Site at onset atypical for age at onset (e.g., leg onset in adults, cranial onset in children).
Early onset of speech disturbance (not due to laryngeal dystonia).
History of exposure to a risk factor for secondary dystonia (e.g., birth injury, exposure to dopamine receptor blockers or other dystonogenic toxins, encephalitis, head trauma, etc.)

There are far too many causes of secondary dystonia to discuss them all in detail in this chapter. For an extensive list see Tables 3–5 and 3–6.[24,30,31] Secondary dystonia can be classified as secondary dystonia with no brain lesion, with a static brain lesion, and with progressive brain lesions.

SECONDARY DYSTONIA: NO BRAIN LESION

These diseases do not involve dead or dying nerve cells and generally lack a known pathology, at least by current pathological methods, although this may change as newer pathological techniques and methods become available. These include dopamine receptor blocking agent (DRBA)–induced dystonia (acute and chronic), psychogenic dystonia, dystonic tics, and a variety of rare dystonic syndromes caused or triggered by peripheral injury (dystonic painful legs-moving toes, dystonic jumping stump and mixed movement disorders in other parts of the body such as shoulders, dystonia associated with autonomic dysfunction called complex regional pain syndrome). Levodopa induces dystonia, but it is not clear whether this happens in the absence of identifiable cellular injury (perhaps worsening of tardive dystonia by levodopa might be considered in this category). Unlike most degenerative causes of dystonia, many of these causes may produce pure or almost pure dystonia, which sometimes makes it difficult to distinguish them from primary dystonia.

Acute and Tardive Dystonia

Acute dystonia appears very quickly after DRBA exposure, usually includes retrocollis and sometimes oculogyria, almost always disappears after the DRBA is stopped, and sometimes disappears even if the DRBA is continued. Tardive dystonia (TDyst) accounts for about 25% of the nonparkinsonian secondary dystonia at the Columbia University Movement Disorder Center. Tardive dystonia and other tardive syndromes such as tardive dyskinesias and tardive akathisia are persistent movement disorders starting after (or during) exposure to any centrally acting DRBA, whether for psychiatric reasons or gastrointestinal complaints. Although many patients with TDyst have dyskinesias or akathisia as well, some have pure dystonia that may be indistinguishable from primary dystonia. Nonetheless, there is a characteristic presentation of dystonia that strongly suggests a tardive etiology: jerky retrocollis, truncal arching, and jerky inturning of the arms. In addition, most patients with primary adult-onset dystonia of the neck and back worsen with walking and improve with lying while the opposite is true for many patients with TDyst: better walking than lying. Aside from these differences, there are no tests to distinguish TDyst from primary dystonia or other causes of pure dystonia. History of exposure to DRBA in a reasonable time frame establishes a presumptive diagnosis of TDyst, but such history may be difficult to obtain. Also, DRBA can be obtained without prescription in some other countries and may be used without patients' knowledge after surgery: for sundowning, for smoking cessation, as contaminants in recreational drugs, and so forth. The prevalence of TDyst is not well known: most studies record prevalence of 1% to 2%, but this depends in part on the age of exposure to DRBA: older patients are more likely to develop dyskinesias and younger ones are more likely to develop dystonia. One VA study of young patients by neurologists included patients with mild dystonia and recorded a prevalence of 21%, but this has not been replicated.[32] The distribution in the body is somewhat different between TDyst and primary dystonia: eyelids, jaw, trunk, and especially legs are more commonly involved in TDyst in adults than in primary dystonia. As with other tardive syndromes, dystonia may appear shortly after starting the DRBA, after chronic use at the same dose, or many months after the DRBA is stopped. For treatment of Tdyst, see section on treatment in the next chapter.

Psychogenic Dystonia

Psychogenic movements arise from a psychological disorder rather than from identifiable brain dysfunction. This leaves open the possibility that, in the future, we may identify a biochemical disorder underlying psychogenic movements just as we believe that depression, bipolar disorder, obsessive-compulsive disorder, and schizophrenia are biochemical disorders of the brain. The fact that psychogenic symptoms are rooted in people's life experiences is no less compatible with a biochemical disorder than is Tourette's syndrome. Psychogenic dystonia is treatable, and the approach to psychogenic dystonia should be identical to the approach to any other dystonia: make a differential diagnosis, perform whatever tests are necessary, and then treat the most likely cause. For details, see the chapter on psychogenic disorders.

SECONDARY DYSTONIA: STATIC BRAIN LESION

Virtually any type of brain insult can occasionally produce dystonia, usually when the damage includes the basal ganglia or their connections. For an extensive list see Table 3–5. Delayed-onset dystonia after birth injury requires some comment.

Children with static encephalopathy (cerebral palsy) may have dystonia starting in infancy, sometimes with chorea and sometimes the kinetic dystonia called athetosis. In the 1950s, it was recognized that chorea and athetosis after birth injury could progress for years, but it was not until 20 years later that it was recognized that some children with birth injury who have normal development and no abnormal neurological signs may also develop dystonia later in childhood: delayed-onset dystonia after birth injury.[33] This is one of the few secondary dystonic syndromes with pure dystonia, and dystonia in these children may be indistinguishable from genetic dystonia. There is no test for this syndrome, and the MRI is usually normal or shows mild generalized atrophy. The dystonia is usually static, but may progress into young adulthood. As

Table 3–5 **Secondary Dystonia With Fixed Lesion**

Focal Brain Lesions	
Vascular processes	Infarction, hemorrhage
Trauma	
Tumor	Astrocytoma, glioma, lymphoma, metastasis, cysts, vascular malformations
Encephalitis	Exogenous: viral, bacterial, and fungal infections Endogenous: encephalomyelitis disseminata, paraneoplastic encephalitis Postinfectious: poststreptococcal encephalitis
Diffuse Brain Damage	
Impairment of neuronal energy metabolism	
Ischemia	Cardiac arrest hypoxia
Hypoxia	Asphyxia
Mixed	Cerebral palsy
Glucose	Hypoglycemia
Impairment of systemic metabolism	
Bilirubin	Kernicterus
Calcium	Basal Ganglia calcifications, Fahr disease
Sodium	Hyponatremia, hypernatremia
Increased intracranial pressure	
Subdural hematoma	
Drugs	
Acute	
Dopamine receptor-blocking agents	
Benzamides	
Antihistamines	
Dopamine agonists in Parkinson's disease	
Chemical agents	
Manganese, copper, methanol, cyanide, carbon monoxide	
Ephedrone	
Physical interactions	
Electricity, radiation	
Indirect central nervous effects	
Peripheral trauma with causalgia with/without reflex sympathetic dystrophy	
Peripheral trauma without causalgia?	

From: Dressler D. Nonprimary dystonias. Handb Clin Neurol 2011;100:513–538.

far as we can tell, response to treatment of delayed-onset dystonia with medicines[34] and possibly DBS is similar to the response in primary dystonia.

SECONDARY DYSTONIA: PROGRESSIVE BRAIN LESIONS

There are a large number of progressive neurological diseases, both inherited and sporadic, that can cause dystonia, usually in conjunction with other neurological signs and symptoms (Table 3–6).

Idiopathic Parkinson's Disease, Parkinson-Plus Syndromes, and Other Forms of Parkinsonism

Dystonia can be present in all forms of dopamine deficiency disease. In parkinsonism, the prevalence of dystonia is higher in young patients no matter what the cause of the parkinsonism (Parkin gene, Wilson's disease, drug-induced parkinsonism, etc.)

A. Idiopathic PD: Patients with young-onset PD (with or without an identifiable gene) can present with hemidystonia at a time

Table 3–6 **Heredodegenerative Dystonia**

	Gene or Locus	Phenotype	Transmission
Aceruloplasminemia	CP	Dementia, ataxia, facial dystonia, +/– DM	AR
Ataxia-telangiectasia	ATM	Cerebellar ataxia and telangiectases	AR
Ataxia with ocular apraxia 1 (AOA1)	APTX	Ataxia, ocular apraxia neuropathy +/– mental retardation, hypoalbuminemia	AR
Ataxia with ocular apraxia 2 (AOA2)	Senataxin	Ataxia, ocular apraxia neuropathy +/– mental retardation	AR
Choreoacanthocytosis	VPS13A	Parkinsonian features and orofacial dyskinesias	AR
Ceroid-lipofuscinosis	CLN3	Cerebral atrophy and macular degeneration	AR
Deafness-dystonia syndrome	TIMM8A	Progressive deafness and dystonia	XR
Dentatorubralpallidoluysian atrophy	ATN1	Ataxia, chorea, and dementia	AD
DYT3	TAF1	Dystonia-parkinsonism	XR
Familial basal ganglia calcifications (Fahr disease)	SLC20A2, PDGFRB, PDGFB & others	Personality change, psychosis, multiple movement disorders, seizures, PKD	AD
Fucosidosis	FUCA1	Mental retardation, seizures, and neuropathy	AR
Glutaric acidaemia	GCDH	Infantile encephalopathy with dystonic choreoathetosis	AR
GM1 gangliosidosis	GLB1	Ataxia, short stature, vertebral deformities	AR
Hemachromatosis	HFE, others	Cirrhosis, joint pain, CHF	AR
Homocystinuria	CBS, others	Mental retardation, stroke, multiple movement disorders	AR
Huntington's disease	IT-15	Chorea, dystonia, parkinsonism and dementia	AD
Leber hereditary optic atrophy	Several genes	Optic atrophy, tremor, and dystonia	M
Lesch-Nyhan syndrome	HPRT	Mental retardation, motor delay, and spasticity	XR
Leigh syndrome	Several genes	Early onset, rapid progression, and clinical heterogeneity	M or AR

(continued)

Table 3–6 **(Continued)**

	Gene or Locus	Phenotype	Transmission
Megalencephalic leuko-encephalopathy with subcortical cysts	MLC1 & others	Megalencepaly, ataxia, spasticity, mental retardation, Sz, dystonia	AR
Metachromatic leukodystrophy	ARSA	Mental retardation, spasticity, and bulbar palsies	AR
Neuroferritinopathy	FTL	Neurodegeneration with brain iron accumulation type 2	AD
Neuronal intranuclear inclusion disease (NIID)	Unknown	Oculogyric crises, parkinsonism, ataxia, multiple central and peripheral nervous system symptoms	AR
MERRF/MELAS	Multiple	Encephalomyopathy, seizures, stroke, movement disorders	M
NPC1	NPC1	Mental retardation, motor delay, and spasticity	AR
NPC2	HE1	Mental retardation, motor delay, and spasticity	AR
PARK14	PLA2G6	Neurodegeneration with brain iron accumulation type 2	AR
PARK2	PRKN	Early-onset parkinsonism	AR
PARK7	DJ1	Early-onset parkinsonism	AR
PKAN	PANK2	Neurodegeneration with brain iron accumulation type 1	AR
Pelizaeus-Merzbacher disease	PLP1	Progressive pyramidal and cerebellar signs and rolling head tremor	XR
Propionic acidemia	PCCA/PCCB	Developmental delay, seizures, stroke-like episodes	AR
Rett syndrome	MECP2	Mental retardation, motor delay, autism, and epilepsy	XD
SCA17	TBP	Parkinsonism, chorea, and dementia	AD
SCA3	ATXN3	Ataxia, spasticity, and ocular movement abnormalities	AD
Tay-Sachs disease	HEXA	Infancy onset, paralysis, dementia, and blindness, fatal by age 2–3 years	AR
Wilson's disease	ATP7B	Tremor, dystonia, and parkinsonian features	AR

AD = autosomal dominant. AR = autosomal recessive. APTX = aprataxin. ARSA = arylsulfatase A. ATP1A3 = ATPase, Na^+/K^+. ATP7B = ATPase transporting Cu^{2+}-transporting beta polypeptide. ATM = ataxia-telangiectasia mutated gene. ATN1 = atrophin 1. ATXN3 = ataxin-3. CBS = cystathionine beta-synthase. CLN3 = ceroid-lipofuscinosis, neuronal 3. CP = ceruloplasmin. DJ1 = oncogene DJ1. DM = diabetes mellitus. FTL = ferritin light chain. FUCA1 = alpha-L-fucosidase 1. GCDH = glutaryl-CoA dehydrogenase. GCH1 = guanosine triphosphate cyclohydrolase 1. GLB1 = β galactosidase. HE1 = epididymal secretory protein. HEXA = hexosaminidase A alpha polypeptide. HFE = high Fe. HPRT = hypoxanthine guanine phosphoribosyl-transferase 1. IT-15 = important transcript 15 (Huntingtin). M = mitochondrial. MECP2 = methyl-CpG-binding protein 2. MR1 = myofibrillogenesis regulator 1. NPC1/2 = Niemann-Pick type C1/2. PANK2 = pantothenate kinase 2. PCCA/B = propionyl CoA carboxylase, α/β subunit. PDGFB = platelet-derived growth factor subunit B. PDGFRB = platelet-derived growth factor receptor, beta-type. PKAN = pantothenate kinase-associated neurodegeneration. PLA2G6 = phospholipase A2 group VI. PLP1 = proteolipid protein 1. PRKRA = double-stranded RNA-activated protein kinase. SCA = spinocerebellar ataxia. SGCE = ε-sarcoglycan. SLC20A2 = solute carrier family 20 phosphate transporter member 2. TAF1 = TBP associated factor. TBP = TATA box-binding protein. TH = tyrosine hydroxylase. THAP1 = thanatos associated protein. THD = tyrosine hydroxylase deficiency. TIMM8A = translocase of inner mitochondrial membrane 8. TOR1A = torsin A gene. VPS13A = vacuolar protein sorting 13. XD = X-linked dominant. XR = X-linked recessive.

Modified from: Phukan J, Albanese A, Gasser T et al. Primary dystonia and dystonia-plus syndromes: clinical characteristics, diagnosis, and pathogenesis. Lancet Neurol 2011;10:1074–85.

when the parkinsonism is extremely subtle and may be hard to detect. The dystonia is generally on the side that will eventually be more affected with parkinsonism. The dystonia in young-onset PD may improve with dopamine replacement, it may worsen, or it may not be affected by this treatment at all.[35] When dopamine replacement is ineffective, anticholinergics may be tolerated and effective. In older untreated patients, toe cramping is relatively common; it often occurs at night or in the morning but may appear anytime and is usually interpreted as dystonia. This usually disappears with treatment of the parkinsonism, unlike the dystonia in young patients, making it questionable whether this has the same physiology as other forms of dystonia in parkinsonism. Patients with PD may also develop dystonia as a side effect of treatment, usually with levodopa. This may occur as a peak-dose phenomenon (when medication levels peak in the brain), as withdrawal dystonia (when a dose of medication has worn off or in the morning, when dopamine brain levels are low) or in the dystonia-improved-dystonia or DID pattern, which is often painful. In DID dystonia, the dystonia appears twice after each dose, once as dopamine levels rise shortly after a dose and once as dopamine levels fall as the previous dose is wearing off.[36] When the dystonia prior to medication in idiopathic PD does not improve with anti-PD therapy, the options are similar to the treatment for other adult-onset focal dystonias: medications if tolerated, BTX for pain and focal symptoms, and DBS of the globus pallidus. When dystonia in PD is a side-effect of anti-PD medications, management is similar to the management of dyskinesias, is complex, and requires balancing symptomatic benefit with side effects (see chapter on drug-induced movement disorders).

B. All Parkinson plus syndromes and all forms of secondary parkinsonism can include dystonia. Multiple system atrophy (MSA), cortical-basal ganglionic degeneration (CBGD) and progressive supranuclear palsy (PSP) all can manifest dystonia.[35] This is strikingly the case with CBGD and occasional cases of PSP that mimic CBGD, where focal limb dystonia or hemidystonia is often a major presenting sign.

Wilson's Disease

Although Wilson's disease is a very rare cause of dystonia, diagnosing Wilson's disease is a priority for neurologists because the disease is treatable and fatal if not treated. Neurologic symptoms, usually a movement disorder, are a common presentation of Wilson's, depending on the age at onset. Wilson's is usually dominated by dystonia in adolescents and young adults and by tremor in older adults. Over 85% of patients with neurologic Wilson's will have cranial involvement, and all the cases at the Columbia University Movement Disorder Center had cranial parkinsonism with a risus sardonicus. Subtle imbalance is also very common (with a slightly abnormal pull test). Although only about 50% of reported cases have psychiatric symptoms preceding the neurologic symptoms, subtle personality change seems almost always to be present but can require focused questioning to elicit. Wilson's disease should be suspected in an adolescent with less than five years of dystonia, especially if they have features such as an abnormal MRI, a risus sardonicus, cranial parkinsonism or postural imbalance. Wilson's disease is extremely rare (about 17 per million), older-onset Wilson's is usually not dystonic but tremulous, and focal-onset primary dystonia, especially CD, is much more common in individuals in their 30s through 50s than is Wilson's disease. This poses a dilemma for clinicians. It is not clear whether every patient with new-onset CD should be tested for Wilson's disease. One strategy it to test new-onset CD for Wilson's disease only if there are atypical features as listed. For further details about diagnosis and treatment of Wilson's disease, see the chapter on Wilson's disease.

An even less common condition than Wilson's disease is dystonia with brain manganese accumulation (DBMA), which I mention here because, like Wilson's disease, it is potentially treatable. Dystonia with brain manganese accumulation is a form of heavy metal deposition causing a variety of basal ganglia syndromes including dystonia and parkinsonism. At least some cases are due to mutations in a gene for a manganese transporter, SLC30A10. It is similar in many ways to Wilson's disease, except that K-F rings are not present. When it starts in early life, it presents with dystonia, but it may cause parkinsonism when appearing

later in life. It has been documented to cause a spastic paraparesis, but it is rarely reported and it is reasonable to expect that other basal ganglia and cerebellar symptoms will eventually surface because there is hyperintense signal in the basal ganglia, subthalamic nucleus, and dentate nucleus. Other reported features include cirrhosis, polycythemia, hypermanganesemia, and iron depletion. As with Wilson's disease, chronic treatment with manganese chelators can prevent progression of the disease and reverse symptoms to some extent.[37]

Neurodegeneration With Brain Iron Accumulation

This is a family of diseases that all produce iron deposits in the brain, usually including the basal ganglia, and produce some combination of dystonia, parkinsonism and sometimes other neurological signs and symptoms (neurodegeneration with brain iron accumulation, or NBIA). These diseases are uncommon, but the brain iron can usually be detected by MRI, so the diagnosis is being made more commonly. With the increasing number of cases, the spectrum of signs and symptoms has expanded, as has the number of different genes that can cause this syndrome (for review, see reference 38). The prototype of these conditions is pantothenate kinase-associated neurodegeneration (PKAN, formerly known as Hallervorden-Spatz disease). Based on cases of PKAN with an identified mutation (about half of cases with the syndrome), the majority have increased iron in the globus pallidus and many, but not all, have a hyperdensity in the medial pallidum surrounded by an area of hypodensity ("eye of the tiger" sign). There are two presentations. When the disease presents in early childhood, the disease is more severe and pigmentary retinopathy, spasticity, cognitive impairment, developmental delay, and other neurological signs and symptoms are usually present in addition to dystonia and parkinsonism. There is a later onset, milder presentation in which retinopathy, optic atrophy, cognitive impairment, and spasticity are not present or mild and dystonia or parkinsonism dominate. Tics and behavioral abnormalities have been reported in the milder presentation but are not universal. There seems to be a predilection of both the dystonia and the parkinsonism to affect cranial structures, but this may not be true in all PKAN variants. The neurological details appear to vary with the particular gene and mutation causing the syndrome, and diagnostic patterns will probably emerge over time. For the time being, in patients with young-onset parkinsonism-dystonia with evidence of iron on MRI (or with "eye of the tiger"), testing for the known gene mutations is indicated.[38] In the older-onset presentations, some patients may improve with levodopa (for the parkinsonism) or anticholinergics (for parkinsonism and dystonia), but the disease continues to progress slowly. Deep brain stimulation has been reported to help the dystonia in a few cases.[38] Studies of iron chelators that cross the blood-brain barrier are underway, but it is not known whether iron deposition causes the disease or is a consequence of the disease.[38]

X-Linked Dystonia-Parkinsonism

X-linked dystonia-parkinsonism (XDP, Lubag, or DYT3) is almost exclusively present in male descendants of inhabitants of the island of Panay in the Philippines. Dystonia usually starts in the legs or face in early adult life and progresses over a few years to generalized dystonia in almost all people, although the range of age at onset and speed of progression is large. In most, parkinsonism eventually appears and also gradually worsens and in a few people (generally with older age at onset), parkinsonism can be the presenting symptom. In most patients, dystonia tends to recede as parkinsonism worsens. Cranial structures, speech, and swallowing are frequently affected. A handful of women have had symptoms of XDP.[39] Although the genetics of XDP are not fully understood, mutations have been identified in a gene on the X chromosome for the TATA box-binding protein-associated factor 1 (TAF1). This mutation causes dramatic change in expression of multiple genes, including genes involved in dopaminergic transmission and neurotransmitter release.[40] The pathology of XDP in patients with primary dystonia is severe loss of striatal output neurons to the substantia nigra pars compacta (striasomal neurons) and mild loss of output neurons to the globus pallidus and substantia nigra pars reticulate (matrix neurons).[41] In advanced cases with more parkinsonism, more severe loss of matrix neurons was found.[41] Treatment with dopamine replacement strategies and

antidystonic medications has generally been of minimal success. Botulinum toxin can be used for focal symptoms, and there have been a few reports of beneficial effects of DBS.[42]

PAROXYSMAL DYSTONIA

The paroxysmal dystonias are so rare that definition of different paroxysmal syndromes is still in flux. There are three main groupings of paroxysmal syndromes. In 1940 Mount and Reback described a large family with attacks of chorea and dystonia lasting hours that they called familial paroxysmal choreoathetosis.[43] This syndrome is now called paroxysmal nonkinesigenic dystonic choreoathetosis or paroxysmal nonkinesigenic dystonia (PNKD). In 1967, Kertesz reported cases of episodic involuntary movements lasting seconds to minutes and triggered by voluntary movements that he called paroxysmal kinesigenic choreoathetosis, now called paroxysmal kinesigenic dystonic choreoathetosis or paroxysmal kinesigenic dystonia (PKD).[44] A third syndrome, triggered by exercise and intermediate in duration between the other two was described by Lance in 1977.[45] This is now known as paroxysmal exercise-induced dystonia (PED). All three types may be inherited or sporadic and all have been produced by other known neurological disorders. The inherited disorders so far have had autosomal dominant transmission with varying degrees of reduced penetrance. There was a fourth subtype of paroxysmal dystonia arising from sleep (paroxysmal hypnogenic dystonia), but (so far), all known cases of that have turned out to be forms of epilepsy.[46] Subsequent advances in genetics and further clinical description will help classify intermediate and atypical cases of paroxysmal disorders that include dystonia in their phenomenology.

Paroxysmal Kinesigenic Dystonia

Typical cases of PKD start in childhood or adolescence, are more common in boys, last seconds to a few minutes, are generally triggered by sudden movement, and are easily abolished by anticonvulsants, usually in small doses. There have been reports of a similar syndrome in infants that may be related.[47] In some patients there seems to be a refractory period after an attack, but this is hard to document, as the same sudden movement may be repeated multiple times without triggering an attack. People may have multiple attacks per day, occasionally up to 100 per day, although there seems to be a tendency for the number of attacks to decrease over long periods of time. The movements may be dystonic, choreic, or a combination of the two. They may be unilateral, bilateral, or sometimes vary from side to side. Speech may be affected, but language has never been reported to be affected. Walking is affected if the lower extremities are involved. Many patients report an abnormal sensation preceding the movements, usually in a limb involved in the dystonia. Some patients can abort the movements during the aura phase. They have difficulty explaining exactly how they do this. Most maneuvers involve relaxing and stopping movement, but some patients either tighten relevant muscles or pay attention to the body part in some hard-to-describe way.[48] Treatment is easy in the majority of cases. Although older anticonvulsants such as carbamazepine are often used, many anticonvulsants seem to be effective. Movement disorder neurologists have long thought of PKD as a form of subcortical seizure. Patients with benign infantile seizures may have family members with PKD (or have PKD themselves). This resulted in the entity of infantile convulsions and paroxysmal choreoathetosis (ICCA). It has also been observed that patients with PKD (and PNKD) may have an increased incidence of migraine. These observations became united with the discovery that hemiplegic migraine (and rarely other forms of migraine), PKD, and ICCA may all be manifestations of mutations in the gene for proline-rich transmembrane protein (PRRT2), a protein of unknown function but known to interact with synaptosomal-associated protein 25 (SNAP25), which is necessary for calcium-mediated quantal release of neurotransmitter.[49] PKD is now identified as DYT10. There are patients with typical familial PKD in whom no PRRT2 mutation can be found, so it is likely there is at least one other gene for PKD.[50] There are also apparently sporadic and secondary cases of PKD. Diseases reported to cause PKD include multiple sclerosis, thalamic stroke, brain trauma, encephalitis, metabolic disturbances such as hypo- or hyperglycemia, and many others.[51] Most recently, PKD was reported to be associated with familial idiopathic basal ganglia calcification (Fahr's syndrome or IBGC) caused

by a mutation in the SLC20A2 gene, previously known to cause nonparoxysmal dystonia.[52]

Paroxysmal Nonkinesigenic Dystonia

Paroxysmal nonkinesigenic dystonia also generally starts in childhood, involves attacks usually lasting hours to days, and generally does not improve with anticonvulsants. The spectrum of phenomenology is much broader than that of PKD. Recently, mutations were discovered in some patients with PNKD in the myofibrillogenesis regulator gene (MR-1) causing autosomal dominant disease. The function of the MR-1 protein is unknown, but it may play a role in the stress response and, in particular, to detoxify a compound in coffee and alcohol related to oxidative stress.[48] The characteristics of patients with PNKD and the MR-1 gene have been carefully described. Symptoms usually start in early childhood, boys and girls are at comparable risk, attacks usually last a few hours (although occasionally are as short as 5 minutes and as long as 12 hours), attacks are frequently precipitated by caffeine, alcohol, or stress and may improve with benzodiazepines. Attacks are usually infrequent (but the frequency is affected by lifestyle).

Paroxysmal Exercise-Induced Dystonia

Paroxysmal exercise-induced dystonia is the least common of the recognized paroxysmal dystonias and it was not clear that it was a distinct entity until the discovery that some (but not all) patients with PED had low cerebrospinal fluid (CSF) glucose levels and had a mutation in a glucose transporter gene SLC2A1 (solute carrier family 2—facilitated glucose transporter—member 1) encoding the protein GLUT1.[53] Paroxysmal exercise-induced dystonia also usually starts in childhood or adolescence, lasts minutes to hours, and may involve hemidystonia or other distributions in the body. In patients with GLUT1 mutations, exercise precipitates the attack and the attacks usually cease shortly after exercise has stopped. There are too few cases to evaluate the efficacy of any single medication, but some patients with the GLUT1 mutation improved with a ketogenic diet.[53]

Alternating Hemiplegia of Childhood

Alternating hemiplegia of childhood is currently defined as attacks of weakness lasting minutes to days and starting in the first years of life. As noted previously, in 2012 it was discovered that at least some patients with this condition have mutations in the gene for the ATPase ATP1A3, so the spectrum of the disorder may change. As currently understood, symptoms include attacks of weakness and involuntary movements, usually dystonia and chorea. The weakness usually involves ipsilateral arm and leg, but odd combinations of limb weakness were observed. Many other phenomena can be present: swallowing or breathing abnormalities (when symptoms are bilateral), nystagmus and other ocular abnormalities, seizures, headaches, and autonomic phenomena such as tachy or bradycardia. Corticospinal tract signs are usually absent. As with the other paroxysmal disorders, an aura is often present. Developmental delay is common, and children usually gradually develop a variety of abnormalities, including dystonia and chorea, between attacks.[54] Treatment is difficult, but the calcium channel blocker flunarizine is usually given and seems to help a majority of patients. Other medications used with unclear success include seizure medications, benzodiazepines, melatonin, chloral hydrate, neuroleptics, beta blockers, L-dopa, antihistamines, selective serotonin reuptake inhibitors, and steroids.[54]

Others

There are a variety of rare paroxysmal dystonic disorders about which little is known.

Benign Paroxysmal Torticollis of Infancy. This rare condition starts in the first year of life, generally in the first 6 months. Affected infants have attacks of torticollis usually lasting days and occurring every month or two until about 3 years of age. Some infants also have pelvic twisting but rarely dystonia elsewhere. A significant minority have autonomic symptoms such as nausea, vomiting, irritability, and pallor and either have a family history of migraine or go on to develop migraine. The etiology is unknown, but some have suggested either a form of paroxysmal vertigo or a form of migraine.[55] There are rare cases of infants with paroxysmal dystonia in other parts of the body. A syndrome labeled transient idiopathic dystonia in infancy consists of multiple daily episodes of dystonic posturing (usually in the upper extremities) triggered by movement and lasting seconds to minutes. The condition

starts within about 6 months of birth and subsides before age 2. The phenomenology fits the general pattern of PKD, but I could find no evidence of genetic testing for that condition and I could not tell how many of these infants had a family history of a similar disorder (at least one infant had a father with the same condition).[47]

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Chapter 4

Dystonia: Part 2

Paul E. Greene

EPIDEMIOLOGY AND GENETICS

The prevalence of primary dystonia is difficult to determine because dystonia is uncommon and is probably underdiagnosed. It was estimated that at least one-half and possibly as many as two-thirds of cases may not be diagnosed.[1] Most studies start with doctor visits or records, with few population-based studies. Childhood-onset dystonia has been estimated to have a prevalence of 3 to 50 per million, with population-based studies at the high end of this range. Adult-onset dystonia is more common, but the range of estimates is extremely broad: from 30 to 7,320 per million (population-based studies were at both ends of this spectrum).[1] Data may be somewhat better for the two most common forms of adult-onset focal dystonia, cervical dystonia (CD), and blepharospasm. In the largest two of seven studies, the prevalence of CD was about 60 per million.[2] In the largest four of 10 studies, the prevalence of blepharospasm was between 30 to 40 per million.[2,3] A single large questionnaire-based study in the United States was an outlier, finding 3,900 per million people diagnosed with CD.[4] The prevalence of childhood-onset dystonia in Ashkenazic Jews is higher, although it is difficult to know exactly how much higher. A careful study (using many reasonable assumptions) estimated that the DYT1 gene is present in from 1/6,000 to 1/2,000 Eastern European Jews due to a founder effect from an ancestor probably in Lithuania

or Byelorussia about 350 years ago.[5] There are few incidence studies: In the diagnosed population, the incidence of childhood-onset dystonia was estimated as 2 per million and adult-onset dystonia as 24 per million in Rochester, Minnesota, and the incidence of CD as 11 per million in California.[1]

As discussed in Chapter 3, the recognition of dystonia as an organic brain symptom instead of a psychogenic symptom came with the identification of familial childhood-onset dystonia in Ashkenazic Jewish families. Because of markedly reduced penetrance, the small number of affected children in each family was misinterpreted as indicating autosomal recessive inheritance.[6] As physicians became more sophisticated, they realized that parent-child transmission in this rare condition could only happen in a dominant disease. This insight led investigators to pool data from multiple small families and eventually led to the identification of the first gene for dystonia, the DYT1 gene.[7] So far, 13 genes (22 loci) have been identified for diseases that produce dystonia as the primary symptom (although, as discussed in Chapter 3, tremor, parkinsonism, and myoclonus may be included)—see Table 3–1 in Chapter 3. Of the loci, 10 diseases would be classified as primary dystonia, six as dystonia-plus syndromes, and six as paroxysmal dystonia. Six genes have been identified as causing primary dystonia. Four of these have been identified so recently that the clinical characteristics of the diseases caused by mutations in those genes are poorly known. The identification of genes is helpful for diagnosis, but the hope is that as more genes are identified, the physiological pathway underlying dystonia can be identified. Once a gene is identified, the challenges are to: (1) identify all pathogenic mutations in the gene; (2) identify whether dystonia arises from gain or loss of function and, in the latter case, identify the function; (3) identify clinical features that are more common in dystonia associated with that gene; (4) identify any other clinical or subclinical features associated with mutations in the gene; and (5) identify genetic and nongenetic factors contributing to penetrance. This process in dystonia is in the earliest stages. I will discuss in some detail the genes for primary dystonia with the best-known clinical characteristics.

DYT1

The TOR1A gene associated with DYT1 dystonia makes a protein, torsin A, that is found in CNS neurons and is an ATPase. It is in a family of proteins that are chaperones causing conformational changes in target proteins involved in membrane trafficking, protein degradation, vesicle recycling, and so forth. The exact function mediating the expression of dystonia is not known, although overexpression of the mutant gene in animals causes membrane inclusions from endoplasmic reticulum and the nuclear envelope.[8] So far, only one mutation in the TOR1A gene, a GAG deletion, has clearly been associated with primary dystonia, although there are reports of two other mutations associated with atypical dystonia in two individuals.[8] The median clinical syndrome associated with this gene is onset just before adolescence starting in a limb and rarely involving the face, although uncommon variations have been reported.[8] Although characteristic of DYT1 dystonia, all of these can happen in dystonia not linked to DYT1. A variety of clinical and laboratory features, most notably an increased rate of major depression, are associated with the DYT1 mutation, but these occur in both symptomatic and asymptomatic carriers, so the relation to dystonia is not clear.[7] Only about one-third of gene mutation carriers ever develop symptoms of dystonia.[9] Residue 216 in the torsin A gene is aspartic acid in 88% of people and histidine in 12% of people. The histidine polymorphism protects against developing dystonia and accounts for some but not most of the reduced penetrance. It also protects against cytoplasmic inclusions in animal models.[10]

DYT6

DYT6 is associated with multiple mutations in the THAP1 gene. This gene codes for a protein containing a THAP (thanatos-associated protein) domain that binds DNA and plays a role in apoptotic cell death. The role of the THAP1 protein in the brain is not known, but it binds to the TOR1A promoter in cell and animal models, suggesting a common pathway for producing dystonia. Unlike DYT1 associated dystonia, the penetrance is about 60%, so there

are generally more affected members in each family. The mean age at onset is about 15 years, but the range is great (5 years to 38 years). There is a female predominance. Almost half the patients have initial symptoms in the arms and about one-quarter in the neck, and the disease rarely begins in the legs. As a group, this is very different from DYT1 dystonia, which frequently starts in the legs and rarely starts in the neck. Eventually over one-third become generalized, two-thirds have symptoms in the neck, and two-thirds have symptoms in a cranial structure (face, jaw, tongue, or vocal cords).[8,11]

DYT25

DYT25 is associated with mutations in the GNAL gene. Guanine nucleotide binding protein, alpha activating activity polypeptide is a member of the G-protein family and was first identified in the olfactory pathway. It also is the intermediary between dopamine D1 receptors (in the direct pathway of the basal ganglia, see below) and adenosine A2A receptors (indirect pathway) with adenylyl cyclase type 5 in medium spiny neurons.[12] The average age at onset is about 30 years but, as with DYT6, that range is very large (7 years to 54 years). Cervical dystonia was the initial symptom in over 80% of reported cases, and almost all had neck involvement eventually, but over 40% eventually had speech involvement, almost two-thirds had cranial involvement, and fewer than half remained with focal CD.[12] Only one-third eventually developed upper-extremity dystonia, which is considerably different from DYT6. Of course, the clinical spectrum may change as more cases are discovered.

DYT4

DYT4 is associated with mutations in the TUBB4A gene. Tubulin beta-4A chain protein is the main component of microtubules and is mainly expressed in the brain.[12] Although this was first reported as "whispering dysphonia," reexamination of living patients found adductor spasmodic dysphonia (SD) as the initial symptom in almost all patients.[13] Many patients with adductor SD will compensate by whispering, possibly leading to the confusion. Some patients remain mild (although dystonia usually spreads to the face at least) while many eventually develop generalized dystonia. The MRI is normal. However, many patients also have other features in addition to dystonia. Prior to dystonia, face and body become thin and the cheeks eventually become hollowed. Many develop speech and swallowing problems and require tube feeding. The tongue is sometimes slow, and sometimes tongue protrusions are present and patients have an open mouth.[13] Some patients had intermittent, alcohol-responsive SD.[13] Some developed a stiff-legged, skipping gait.[13] Most recently, mutations in the TUBB4A gene were also linked to a leukodystrophy causing spastic tetraplegia, ataxia, seizures, and a variety of basal ganglia symptoms, including dystonia, chorea, oculogyria, and parkinsonism.[12] These patients have a very abnormal MRI: hypomyelination, cerebellar atrophy, and atrophy of the putamen.[12] As of now, there is no known correlation between genotype and these two very different phenotypes.

DYT23, DYT24

Mutations associated with dystonia have been described in two genes in a very small number of individuals. Mutations in the ClZ1 gene (DYT23) were associated with primarily CD in a small number of unrelated individuals, but many variants of the gene have been identified in apparently normal controls, so the status of this gene is not clear. Cip1-interacting zinc finger (ClZ1) protein is involved in DNA synthesis and control of the cell cycle.[12] Mutations in the ANO3 gene (DYT24) were associated with CD, sometimes in combination with blepharospasm, SD, myoclonus, and brachial dystonia or upper-extremity tremor in several families.[12] Anoctamin 3 (ANO3) protein is known to be involved in calcium-mediated chloride channels but may have other as yet unknown functions.[12]

PATHOPHYSIOLOGY

There has long been a quest for the physiologic changes underlying dystonia. Observations of both primary and secondary dystonia have given important clues, but a convincing blueprint has yet to emerge outlining the steps

from an initial insult, biochemical or physical, leading to the complex symptom we recognize as dystonia. There is a link between disorders of dopamine and dystonia, but the relationship with dopamine is not simple. In addition to dystonia in the setting of reduced dopamine production or transmission (in untreated Parkinson's disease [PD] or dopa-responsive dystonia [DRD]), dystonia is also common as a result of dopamine stimulation (in treated PD). Diseases such as Wilson's disease that produce symptoms of dystonia (usually in addition to other neurological symptoms) involve the basal ganglia (perhaps in addition to other brain areas).

In most patients developing dystonia from a single brain lesion, the lesion is in the basal ganglia. In addition, there is considerable indirect evidence that the basal ganglia play a critical role in primary dystonia. Abnormalities of metabolism in the basal ganglia have been detected by fluorodeoxyglucose PET and functional MRI, and anatomic abnormalities have been detected by voxel-based morphometry and diffusion tensor imaging.[14] The growing use of deep brain stimulation (DBS) to treat both generalized and localized dystonia provided the opportunity to record electrical activity from the basal ganglia. Summed electrical fields from multiple neurons (local field potential, or LFP) show abnormal irregular 3- to 12-Hz oscillations in patients with dystonia, and these oscillations correlate with 3- to 10-Hz EMG activity in affected neck muscles in patients with CD.[15] One problem with such studies is that they cannot distinguish between causal physiological disturbances and compensatory physiological changes. Despite the links with the basal ganglia, some patients diagnosed with secondary dystonia have lesions outside the basal ganglia, usually in the thalamus, brainstem, and cerebellum but sometimes even in the cerebral cortex.[14] New evidence is gradually being interpreted as indicating that other brain systems besides the basal ganglia are abnormal in people with dystonia. One area that has been the focus of much attention is the cerebellum, as lesions of the cerebellum have been associated with dystonia and the cerebellum is involved in many of the areas of physiological abnormality in dystonia, as described below. Two subtle abnormalities in dystonia are felt to be moderated exclusively by the cerebellum. If a sensory input such as a sound is paired with elicitation of the blink reflex with a puff of air, eventually the sound alone will trigger a blink. This conditioning is weaker in patients with focal dystonia.[16] If someone is asked to make a saccade to a target and the target is moved before the target is reached, a corrective saccade is required. After repeated attempts, the initial saccade anticipates the movement and a second saccade is not necessary. This process is slowed in patients with myoclonus-dystonia.[16] On the other hand, patients with idiopathic dystonia do not have nystagmus or ataxia and do have a clear relationship with the dopamine system related to the basal ganglia. Prudente et al. make an argument that, despite the lack of obvious relationship between the cerebellum and dystonia, cerebellar circuits may still be associated with idiopathic dystonia.[16] However, it is not clear whether abnormalities in these other circuits play a role in generating dystonia, are a consequence of dystonia, or bear some other indirect relation to dystonia. It also is not clear that everyone we diagnose with idiopathic dystonia has the same pathophysiology. In any case, the main physiological abnormalities found in idiopathic dystonia can be divided into three general categories: deficiencies of inhibition, changes in cortical plasticity, and sensory changes.

Deficiency of Inhibition

Among other things, dystonia involves overflow of voluntary movement to muscles not necessary to the intended movement. Deficits of inhibition in dystonia have been identified at multiple levels of the nervous system, including the spinal cord, brainstem, and cerebral cortex. In dystonia, reduced inhibition can involve muscles that are antagonists of muscles that are voluntarily activated, but can also involve other nearby muscles not usually activated in the intended movement. There are multiple different inhibitory circuits in the nervous system, and several have been shown to be abnormal is some forms of dystonia. This includes abnormalities in cerebellar circuits—transcranial magnetic stimulation (TMS) of the cerebellum influences cortical excitability, and this is abnormal in patients with dystonia.[14] This was reviewed in detail by Hallett.[17] The problem is that many

of these same systems have been shown to be abnormal in psychogenic dystonia.[17] Of course, some patients with organic dystonia might have been misdiagnosed with psychogenic dystonia, but this still raises doubt as to the significance of these findings.

Plasticity

One physiological property receiving attention recently is what has been labeled cortical plasticity. When a peripheral nerve is stimulated prior to a cortical excitation (using TMS), the size of the evoked motor potential increases. This increase is larger and involves a larger area of the cortex in people with dystonia—labeled as cortical plasticity.[18] This abnormality is not present in people with psychogenic dystonia.[19] The cerebellum is also involved in modulating cortical plasticity: The effects of TMS of the cerebellum on cortical plasticity are also abnormal in dystonia.[14]

Sensory Abnormalities

Despite the fact that sensory symptoms are uncommon in dystonia, a variety of subtle sensory abnormalities have been identified in people with primary dystonia: decreased ability to distinguish two stimuli presented in rapid succession (abnormal temporal discrimination), decreased ability to detect the orientation of grooves placed on the skin, increased ability to detect the direction of small limb movements, and others.[17] Some have argued that temporal discrimination may be an obligatory phenotype in certain types of dystonia, because it is inherited and highly penetrant in unaffected relatives of patients with dystonia.[20]

Somewhat more interesting than the physiological studies have been metabolic studies by PET and other modalities.[14,21] The PET studies identified an abnormal metabolic pathway including the posterior putamen, globus pallidus, cerebellum, and supplementary motor area that was present in carriers of the DYT1 gene, whether symptomatic or not, and was present in symptomatic DYT1 carriers during sleep, when no dystonia was present.[21] Asymptomatic DYT6 carriers, however, had a different pattern, with decreased metabolism in the putamen and cerebellum, and there was increased metabolism in the parietal association areas and the presupplementary motor area in symptomatic carriers of either DYT1 or DYT6.[21] All this is difficult to integrate into a unified picture of the physiology of dystonia.

Given the link between dystonia and dopamine, there has been considerable effort to link known mutations causing primary dystonia with the dopamine system. There are few autopsies of people with primary dystonia, and no clear patterns have emerged.[22] One exception is a single report of four autopsies of patients with DYT1 dystonia and torsin-A/ubiquitin-positive inclusions in the brainstem and tau/ubiquitin-positive inclusions in the substantia nigra and locus ceruleus.[22] This has yet to be confirmed. In animal models of DYT1 dystonia, there are both pre- and postsynaptic dopamine abnormalities. Direct evidence for changes in the dopamine system in humans carrying the DYT1 gene have been equivocal, but D2 receptor binding measured by [11C]-raclopride PET seems to be lower in the putamen, caudate, and thalamus in people carrying the DYT1 and DYT6 genes, whether or not they are symptomatic.[21] The gene for DYT6 was identified more recently, and there is less data about its functions. There appears to be a potential, indirect connection between DYT6 and dopamine: One protein that binds the DYT6 gene product may play a regulatory role in the D2 receptor, and the DYT6 gene product may directly regulate the transcription of DYT1.[23]

TREATMENT

The treatment of dystonia currently consists of medications, botulinum toxin (BTX) injections, various surgeries for focal dystonias, DBS, and a small number of experimental treatments such as TMS. Various forms of physical therapy have been tried for dystonia with questionable success and little scientific study. In the last several decades, little attention has been paid to medication therapy, and no new proven medications have appeared. Documenting the efficacy of medications in dystonia is extremely challenging. Even when medications, such as anticholinergics, are proven to be effective, they

do not help all people with dystonia equally, possibly because dystonia is a syndrome. When only a subset of patients is expected to improve, a large number of patients need to be included in a study to detect even a clinically significant improvement. This is difficult to do in a rare disease. This problem could be circumvented by designing prospective, placebo-controlled studies only in patients who previously improve in open-label trials. However, when there are few alternative treatments, it is difficult to convince patients to participate in a blinded trial once they believe they have identified an effective medication. Nonetheless, all dystonia specialists are convinced that medications still have a role in the treatment of dystonia in certain settings.

Medications

WHO SHOULD RECEIVE MEDICATION

1. Dopa-responsive dystonia (DRD). All known patients with GTP cyclohydrolase deficiency, the most common cause for DRD, improve dramatically with low doses of levodopa, sustain this improvement for many decades if not a lifetime, and usually do not develop troublesome motor fluctuations. The improvement is so dramatic and sustained that no controlled trial has ever been performed! Children with DRD usually need minimal doses (50–150 mg) and improve substantially within days.[24] It is necessary to initiate therapy with very small doses of levodopa (usually 50 mg daily), because higher doses may produce unpleasant dyskinesias. Supplemental carbidopa may be necessary at these low doses to prevent nausea. People with DRD who are treated much later in the course of the disease may need somewhat higher doses (and take longer to improve) but do not seem to need the kind of doses required in primary PD. Although all anticholinergic medications and dopamine agonists also provide significant relief, they do not benefit patients as much as levodopa and there is no reason to use them in typical patients. Patients with tyrosine hydroxylase deficiency causing DRD may not improve as much, and DBS of the subthalamic nucleus may be an alternative for these patients.[25] Because of this, a trial of levodopa as initial therapy should be strongly considered for every child with dystonia even if the presentation is atypical for DRD. This is not necessary if an alternative diagnosis is certain (e.g., they possess a gene for an alternative form of dystonia in the family or there is a relevant MRI abnormality). Dopa-responsive dystonia presenting as an adult-onset focal dystonia is very rare, but a levodopa trial is reasonable in adult-onset dystonia when there is a relative with childhood-onset dystonia and no alternative genetic association.
2. Childhood-onset dystonia. Many children have disabling symptoms in multiple regions of the body, so that the use of BTX injections as sole therapy is impractical. Although there is a paucity of prospective controlled studies, there is extensive clinical experience suggesting that medications can provide significant benefit for a significant minority of children with dystonia. Despite the reassuring safety record of BTX to date, the consequences of chronic BTX injections over multiple decades are unknown. It is, therefore, preferable to treat children with medication when possible.
3. Tardive dystonia. Unlike other forms of adult-onset dystonia, tardive dystonia often responds to antidopaminergic strategies. Despite the apparent paradox, when typical dopamine receptor blocking agents (DRBAs) cause tardive dystonia, increasing the dose may improve the symptoms. The underlying disease, however, probably continues, as symptoms may return over time (and may be worse), and if the blocker is stopped or the dose lowered, the symptoms usually return. However, dopamine depletors (reserpine, tetrabenazine) and the tyrosine hydroxylase inhibitor alpha-methyl para-tyrosine (metyrosine or demser) also improve symptoms. Movement disorder neurologists make a distinction between a variety of tardive syndromes: oral-buccal-lingual dyskinesias sometimes with piano-playing fingers and toes (tardive dyskinesias), dystonia (tardive dystonia), and akathisia. Of these, tardive dyskinesia improves the most and at the lowest doses of tetrabenazine.
4. Patients with adult-onset focal or segmental dystonia who receive insufficient benefit from BTX injections or surgery. Most

patients with adult-onset dystonia have symptoms primarily in one region of the body (usually involving neck, upper face, vocal cords, upper extremities, or oromandibular muscles). Some, however, require treatment of muscles that are not limited to a single segment, and it may not be practical to inject BTX into a sufficient number of contracting muscles. These patients may be candidates for medication trials. Some patients with focal or segmental dystonia will fail to improve significantly after BTX treatment or develop resistance to the injections.[26] Until there is more data about the role of DBS in focal, adult-onset dystonia, these patients may benefit from medications.

WHAT MEDICATIONS

I will discuss the most common medications used to treat primary dystonia, considering the evidence for efficacy, indications, and adverse effects. In uncontrolled studies, small response rates may suggest placebo effect. However, it is well to keep in mind that even well-designed, prospective, placebo-controlled trials may fail to detect significant benefit that occurs in only a small percentage of patients.

Dopaminergic Agents

Dopaminergic agents have also been used to treat non-DRD patients. The results of controlled, oral studies of dopaminergic agents in non-DRD dystonia have been contradictory. Several small controlled studies found benefit from bromocriptine or lisuride. Other studies failed to find such benefit from bromocriptine, amantadine, or levodopa. An early review of studies up to 1985 concluded that improvement from dopaminergic agents was rarely dramatic and that these agents worsened symptoms in almost 20% of patients.[27] Despite these disappointing results, an occasional patient with non-DRD dystonia does seem to improve, suggesting more than a placebo response.

Most patients with dystonia tolerate dopaminergic agents well. Nausea, orthostatic hypotension, confusion or hallucinations, and dopa dyskinesias have been reported in patients with dystonia, but are uncommon. However, a substantial minority will experience worsening of symptoms or the development of superimposed levodopa dyskinesias.

Anticholinergics

A prospective, placebo-controlled study documented the efficacy of high-dose trihexyphenidyl in alleviating the symptoms of dystonia in children and young adults.[28] Thirty-one childhood-onset patients were studied, with a mean age at time of treatment of 18.6 years. Sixty-seven percent of patients treated with trihexyphenidyl improved, which was significantly better than those treated with placebo. Most continued to benefit from trihexyphenidyl after a mean 2.4 years at a mean dose of 40 mg daily. There has not been another prospective controlled study in children. Uncontrolled reports have found similar benefit in children.[29] Several case reports and small series have suggested that anticholinergics may be effective in young patients with some secondary dystonias, for example, after cerebral infarct,[30] delayed-onset dystonia after birth injury,[31,32] and others.

It has been more difficult to determine the effectiveness of oral anticholinergic agents in treating adults with focal dystonia. There were several small studies showing benefit in adult-onset dystonia[33–37] but also studies that failed to find benefit.[38] These older studies had varying degrees of control and blinding and rarely met modern criteria for well-designed studies.

In both children and adults, the dose of anticholinergic medications must be increased gradually if side effects are to be avoided. Benefit may not appear for many weeks on a constant dose, and so lengthy trials are more likely to be productive.[28] Most patients require high doses of anticholinergic agents before improvement is seen. The effective dose varies from patient to patient and from agent to agent. For example, the published effective doses vary from 5 mg to 120 mg per day of trihexyphenidyl,[28] and from 50 mg to 800 mg per day of ethopropazine.[39] Many anticholinergics have been used to treat dystonia, including trihexyphenidyl, benztropine, biperiden, ethopropazine, atropine, biperiden, procyclidine, orphenadrine, scopolamine, and transderm scopolamine. Side effects may vary from agent to agent, so that switching anticholinergic medications is sometimes helpful. Peripheral side effects such as blurred vision, constipation, dry mouth, and urinary retention can usually be treated with pilocarpine eye drops for

blurred vision and with pyridostigmine for the other side effects. Central nervous system side effects such as short-term memory loss, confusion, or psychosis are frequently dose limiting, especially in adults. Other central side effects occasionally occur, such as restlessness, chorea, or exacerbation of a preexisting tic disorder.[28] Abrupt withdrawal of anticholinergics may not only dramatically increase dystonia but may also precipitate cholinergic crisis.[40]

Baclofen

There have been no controlled studies of baclofen in the treatment of dystonia, but in retrospective studies the Columbia University Movement Disorder Group found baclofen to be of marked benefit in a significant minority of children and of some benefit in a small minority of adults with dystonia.[41] There have been reports of improvement in adults with focal dystonia from baclofen, but this has not been consistent.[29] Despite the lack of definitive evidence, we consider baclofen to be the medication most likely to be beneficial in most children and adults with dystonia after anticholinergics.

Side effects are a major limiting factor in treating adults with baclofen. Even with gradual increase in dosage, lethargy, upset stomach, dizziness, "floppiness," dry mouth, or urinary urgency or hesitation prevent treatment with high doses of baclofen in many patients. Confusion, hallucinosis, and paranoia have been reported, but are rare. Rapid decrease in the dose of baclofen may precipitate psychosis or seizures, so all patients should be warned not to discontinue baclofen abruptly. Baclofen is better tolerated in children, although the same kinds of side effects can be seen.

Benzodiazepines

Benzodiazepines are frequently used in the treatment of dystonia, but documentation of benefit in well-designed controlled studies is lacking. There have been many uncontrolled reports of benefit from benzodiazepines, including clonazepam, diazepam, and others. The Movement Disorder Group at Columbia found them of modest benefit in retrospective studies in children and adults with dystonia, including patients with hemidystonia.[39,42] Since symptoms of dystonia worsen with physical and emotional stress, it is difficult to know how much of the benefit from benzodiazepines comes from the antianxiety effect. Occasional patients, however, seem to improve markedly. Sedation and ataxia are the limiting side effects for most patients taking benzodiazepines. Patients with dystonia can sometimes tolerate very large doses of benzodiazepines if the doses are increased gradually. Some patients taking high doses of clonazepam become irritable. Nocturnal drooling and depression are possible side effects of benzodiazepines, but seem to be rare. There is always concern that patients taking benzodiazepines may develop withdrawal on stopping the medication or may develop tachyphylaxis. Patients with dystonia do get withdrawal symptoms if benzodiazepine doses are lowered rapidly, and it may be difficult to determine whether the resulting worsening of dystonia represents evidence that the medication produced unsuspected benefit. Tachyphylaxis is rarely seen in patients with dystonia.

Antidopaminergic Agents

Paradoxically, occasional patients with dystonia seem to improve with a variety of antidopaminergic agents. Some controlled studies found benefit,[43] while others did not.[33,44] Open label studies had similarly mixed results. Patients with severe dystonia, or acute exacerbation of dystonia ("dystonic storm"), sometimes improved with the combination of a dopamine receptor blocker, a dopamine depleter, and an anticholinergic agent.[45,46] In the case of tardive dystonia, dopamine depleters such as reserpine and tetrabenazine are especially useful.[47]

With the possible exception of reserpine, tetrabenazine, and the true atypical neuroleptic clozapine, dopamine receptor blockers can produce tardive symptoms (akathisia, dyskinesias, or even dystonia) in patients with dystonia, and these may become more disabling than the original symptoms. There are almost no convincing reports of clozapine producing tardive syndromes, and there are relatively few reports of tardive syndromes from the atypical neuroleptic quetiapine. Clozapine and quetiapine have been reported to help some patients with tardive dystonia.[48,49] In addition to the risk of tardive syndromes, patients with dystonia often tolerate antidopaminergic agents poorly. Sedation, apathy, nausea, orthostatic hypotension, insomnia, acute dystonic reactions, acute akathisia, worsening of dystonic symptoms, and confusion have

all been seen with these agents, but usually can be reversed with reduction in dose or discontinuation of the medication. Depression, especially with dopamine depleters, can be severe and can be life threatening if not recognized and treated, usually with reduction in dose. Drug-induced parkinsonism is often the limiting factor in treating patients who seem to benefit from dopamine depleters. The parkinsonism is reversible and dose dependent and can be controlled with reduction in dose. Unfortunately, dystonia does not improve in some patients until parkinsonism appears. In these patients, parkinsonian symptoms may be reduced by the addition of anticholinergic agents, amantadine, or levodopa. This is not always effective, however, and addition of dopaminergic agents may also reverse improvement in dystonic symptoms induced by the antidopaminergic treatment.

Carbamazepine

Carbamazepine occasionally produces dystonia as a toxic effect in patients treated for seizures.[50] Paradoxically, it has been reported to treat dystonia in some uncontrolled series.[39,51,52] Some carbamazepine successes may have been patients with DRD. However, some patients who improved with carbamazepine did not have DRD, as they did not improve with levodopa.[51,52]

Other Agents

Many other medications have been used to treat dystonia in isolated cases but the evidence is so poor for these agents that they are almost never used. The list includes tricyclic antidepressants, dantrolene, cyproheptidine, 5-HTP, propranolol, phenytoin, clonidine, MAO inhibitors, barbiturates, L-tryptophan, amphetamines, riluzole, mexilitine, lithium, salmon calcitonin, and cannibidiol. Tetrahydrobiopterin was reported to benefit some patients with dystonia, but these probably had DRD. Antihistamines have occasionally been reported to produce benefit, and it has been suggested that the effect may not be entirely due to their anticholinergic properties.[53,54] There was a single report that the muscle relaxant tizanadine, sometimes used as a substitute for baclofen, might also help dystonia.[55] There have been a handful of reports that the antiarrhythmic agent mexiletine may help generalized and focal dystonia.[56]

Botulinum Toxin

Medications are much less effective in adults, and many adults can benefit from BTX, which inhibits calcium-mediated quantal release of acetylcholine, producing muscle denervation ("chemical denervation"). Spinal cord and brain effects of BTX have been demonstrated, but there is no evidence that these effects play any role in the therapeutic effects of BTX. For reasons that are not clear, if you weaken a single dystonic muscle, the dystonic spasms improve before you lose normal function of the muscle. For example, forceful eyelid closure always improves after BTX injections of the orbicularis oculi with only modest slowing of normal blinking. When dystonia primarily affects one or two muscles, the therapeutic effects of BTX are substantial (for blepharospasm, adductor spasmodic dysphonia, simple extensor finger dystonias, etc). When multiple muscles are involved, there is usually improvement, although there may not be enough improvement to improve function.

Successful use of BTX involves first determining which symptoms bother the patient the most, then deciding on which muscles to inject and finally deciding on the dose per muscle. Even patients with complex dystonic movements may be bothered primarily by symptoms caused by a small number of muscles. For example, multiple facial muscles may be involved but only sustained eye closure produces disability, or multiple neck muscles may be involved but pain originating from one or two muscles is the major complaint. Once the major complaint is identified, it may be easy or hard to select a few appropriate muscles. This is usually easy in the face but may be difficult in the hand or neck. Some muscle contractions may be compensatory, and with chronic disease patients may not be conscious of trying to overcome the dystonia. Sometimes it is difficult to determine the full extent of muscle involvement, since dystonia may change or only be present during particular situations that are not easily accessible (such as driving a car). In chronic patients, the presence of muscle hypertrophy may be helpful. It is easy to determine the optimal dose for one or two muscles by starting with a small dose and gradually increasing the dose. It is impossible to scientifically determine the optimal doses for multiple muscles when the only outcome is overall improvement in the dystonia.

Deeper muscles can be identified by EMG, but it is very difficult to determine effective doses. This is especially difficult when the functions of the deep muscles are synergistic, as in posterior neck muscles or many extensor or flexor limb muscles.

The main side effects of BTX injections are excessive weakness in injected muscles or leakage to nearby muscles causing unintended weakness. For example, injection into the pretarsal component of the orbicularis oculi may leak to the levator palpebrae, causing ptosis; injection into the lower lid may cause entropion; and injection into the lower two-thirds of the sternocleidomastoid or into the scalenus medius may leak to pharyngeal muscles causing dysphagia. Allergic reactions, with the exception of hives, are very rare. A few cases have been reported of herpes zoster appearing several weeks after BTX injections in the same dermatome.[57] There are a small number of reports of patients developing generalized weakness after relatively small doses of BTX, as low as 6.25 units per kilogram.[58,59] Alan Scott determined the toxic dose of BTX by intramuscular injection to be about 40 units per kilogram in monkeys, but the toxic dose is not known in humans, and some people are more sensitive to the toxin than others.[60] It is also possible that inadvertent intravenous injection might cause botulism at lower doses. Some but not all reports of generalized weakness describe ptosis and weakness of other small muscles consistent with typical botulism. It is not clear how to interpret reports of generalized weakness after BTX injections that do not include such small muscle weakness. There is a single report of immune mediated encephalitis in three patients after BTX injection.[61]

Summary

Treating dystonia requires patience and persistence on the part of the patient, family, and physician. Medications are often successful in children and adolescents, and a large minority of these patients improve dramatically. Unless surgery becomes a first-line treatment for dystonia in children, medications will remain the mainstay of therapy. A levodopa trial is often the first maneuver. Anticholinergics remain the medication most likely to produce benefit in most children, but baclofen and benzodiazepines remain reasonable options. Treatment with the other medications listed above may be appropriate where surgery is inappropriate or ineffective. While dopamine receptor blocking agents may help a small percentage of patients, the risk of tardive syndromes makes the use of these agents undesirable except for the most severely affected patients. Although BTX is the mainstay of therapy for adult-onset focal dystonia, medications remain an option for selected adults as outlined above. With the exception of dopaminergic agents, which are much less likely to benefit adults, medication trials in adults proceed in the same order as trials in children.

Surgery

THALAMOTOMY AND PALLIDOTOMY

In 1969, Irving Cooper reported a series of patients with dystonia who were operated on starting in 1964.[62] Most of these were treated with large lesions in the posterior ventrolateral thalamus, although a few had lesions in the globus pallidus. Although many had significant benefit, especially for limb dystonia, bilateral thalamotomy entailed significant risk, including disturbance of speech and swallowing, and is rarely done today. In the early 1990s, the operation pioneered by Leksell using lesions in the ventroposterolateral pallidum was revived and replaced thalamotomy but, as with thalamotomy, bilateral pallidotomy entailed significant risk of dysarthria and dysphagia and has largely been replaced by DBS, although unilateral pallidotomy is still performed to treat a static unilateral dystonia without using hardware.[63]

DEEP BRAIN STIMULATION

Deep brain stimulation of the globus pallidus interna (GPi) was first reported for the treatment of CD by Mundinger in 1977 but was not reported for generalized dystonia until 1999, after DBS became a common treatment for PD.[7] Deep brain stimulation has now virtually replaced pallidotomy as the surgery of choice for generalized dystonia. One literature review concluded that patients with primary generalized dystonia had a mean improvement in dystonia rating scores of 60.7% across all studies and that shorter duration of symptoms, milder

disease, and possessing the DYT1 gene were all significantly associated with better outcome.[64] However, this was based primarily on open-label studies. The one double-blind study found a mean improvement in ratings of only 34.4% after adjustment for placebo effect.[65] Similarly, in open-label trials of DBS for CD there was a mean improvement in ratings of 52.3% but only 33.3% in a single-blinded trial.[64] In other small studies, 66% of patients with axial dystonia, 58% of patients with myoclonus-dystonia (both dystonia and myoclonus!), and 74.9% of patients with pantothenate kinase-associated neurodegeneration (PKAN) improved. One important lesson from these studies is that a blinded, placebo-controlled design is essential for evaluating the benefit from surgical therapy in dystonia. There is another lesson about the placebo effect in surgical therapy for dystonia. In the blinded placebo-controlled study of generalized dystonia, the placebo group improved by 4.9% over baseline in motor ratings. The mean improvement in open-label studies was 60.7%, whereas the active group in the blinded study only improved by 39.3%. One would expect this difference to be due to placebo effect, yet the placebo group in the blinded study only improved by 4.9%. This implies that patients with dystonia have markedly less placebo effect when they are told they may get placebo (in a placebo-controlled study) than they do in open-label trials, when they know they are not receiving placebo. The role for DBS in blepharospasm and Meige syndrome is not clear. One long-term study of 12 patients with blinded ratings found statistically significant improvement in cranial symptoms of 47% to 64% on the Burke-Fahn-Marsden Dystonia Rating Scale (but no statistically significant improvement in CD).[66] All studies of DBS for focal dystonia have been small, because only patients who do not respond to BTX and medication participate. For this reason, it may be some time before it becomes clear which patients with focal dystonia are likely to benefit from DBS.

There is controversy about whether microelectrode recording is necessary for adequate results of DBS, and hopefully this will be determined by prospective study in the near future.[67] Deep brain stimulation is usually considered relatively safe, but systematic recording of side effects is not often done. In one careful study of DBS (that included only 26 patients with dystonia out of 198 patients total), there were 92 serious adverse events and 45 persistent adverse events, including 17 (8.6%) with severe intracranial hemorrhage or other bleeding, 5 (2.5%) with persistent change in mental status, 4 with persistent seizures, and 12 with severe infection.[68] There have been reports of bradykinesia induced by GPi stimulation. Stimulation to the subthalamic nucleus may provide an alternative to the GPi,[69] but no short- or long-term comparison of the two targets is yet available.

DENERVATION SURGERIES

Blepharospasm

Two general types of peripheral surgery have been used for blepharospasm: partial myectomy of the orbicularis oculi and neurectomy of branches of the facial nerve. Most comparative studies found myectomy to be significantly more successful that neurectomy.[70,71] Most studies of myectomy have been retrospective reviews or questionnaire based, often by proponents of the surgery.[72] These studies show very high rates of success, equal in some cases to the results from BTX.[72] There have been some anomalies in the data, however. For example, one early comparative study found that only 18% of patients had significant recurrence of blepharospasm after myectomy, but 32% required subsequent procedures, including BTX.[70] Very few patients at the Movement Disorder Group at Columbia University had myectomy and they did not have good outcomes, but this may reflect ascertainment bias. Another potential problem is that BTX injections can be difficult after the surgery if there is not enough subcutaneous tissue to receive the volume of injection, causing the injections to be very painful.

Cervical Dystonia

Microvascular decompression of the spinal accessory nerve was never widely used, probably because most movement disorder neurologists did not believe that overactivity of the spinal accessory nerve accounted for CD in the vast majority of patients.[73] There are two other decompression surgeries targeting the muscles that are known to be involved in CD, using intradural or extradural approaches. Neither procedure was studied extensively, but

the intradural approach seemed to have more adverse consequences and the extradural approach, sectioning the motor roots or posterior ramisectomy, was more widely used.[29] There were two direct comparisons between DBS and ramisectomy.[74,75] In a small, retrospective, open-label study, 16 patients who received peripheral denervation improved 59% in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) ratings while eight who received GPi-DBS improved 66% in TWSTRS ratings. The difference was not statistically significant.[74] In a slightly larger retrospective study, 20 patients with selective peripheral denervation were compared with 15 patients with GPi-DBS. Patients with DBS were statistically more likely to have a good outcome and less likely to have a bad outcome.[75] Side effects were more common in the selective denervation group, and 7 of the 30 denervation patients ultimately underwent DBS. There are no prospective or randomized studies, but there are few neurosurgeons currently performing these procedures in the United States.

Intrathecal Baclofen

As noted above, side effects of oral baclofen often limit benefit, especially in adults. This can be circumvented by infusing baclofen directly into the thecal sac. The mechanism whereby baclofen influences dystonia is not known. Since dystonia is felt to be generated in the brain, it would make sense that the relevant action of baclofen would be in the brain, not in the spinal cord. Nonetheless, intrathecal baclofen (ITB) does seem to affect dystonia at least as much as oral baclofen without producing as many central side effects. It is not clear how much and for whom ITB is superior to oral baclofen. A retrospective review of patients at the Columbia University Movement Disorder Group did not document significant benefit.[76] Although there are many reports of benefit in dystonia, especially for dystonia and cerebral palsy, there have been no controlled studies.[77] Intrathecal baclofen has been reported to be useful for treating dystonic storm.[78] In addition to the usual problems with any infusion system, there is an additional problem with ITB and dystonia.[79] Dystonia requires higher ITB doses than spasticity. When the reservoir is low in the pump, the rate of delivery may drop, requiring increased infusion rates. When the pump is refilled, the patient may be overdosed, which can result in respiratory arrest.

TRANSCRANIAL MAGNETIC STIMULATION

Physiologic experiments indicate that the cortex, and in particular the anterior cingulate gyrus, is involved in the generation of dystonia.[80] Based on this, there have been attempts to treat focal dystonia with TMS. One blinded controlled study found benefit from TMS in blepharospasm and another from the same group found no benefit from TMS in brachial dystonia.[80,81] The value of TMS for dystonia awaits further study.

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Chapter 5

Chorea, Athetosis, and Ballism

Kevin M. Biglan

INTRODUCTION

The terms "chorea," "athetosis," and "ballism" are all derived from Greek words meaning "to dance," "not fixed," and "to throw" respectively. Consistent with this shared etymology, chorea, athetosis, and ballism represent a spectrum of phenomenologically related movement disorders with shared pathophysiology and overlapping etiologies. Descriptions of chorea date back to the middle ages associated with community outbreaks of "dancing mania" and Sydenham's description of St. Vitus's dance or acute chorea of childhood in the 17th century was the first clear description of chorea.[1] However, it was not until the latter half of the 19th century that chorea began to represent a distinct phenomenological entity.[2] The association of hemiballism and the contralateral subthalamic nucleus (STN) was first described by Purdon Martin in 1927[3] and subsequently confirmed by Whittier and Mettler through lesioning of the STN in monkeys.[4] "Athetosis" was coined by the US neurologist William Alexander Hammond from the Greek for "not fixed, without position or place" in 1871, alluding to the continuous movement associated with this condition.[5]

Chorea, athetosis, and ballism are often seen simultaneously in the same patient and the term chorea-athetosis is commonly used in the clinical setting. The distinction between chorea and ballism can be even more challenging, as not only do they often coexist but also ballism frequently evolves into chorea and animal models of chorea can also produce ballism. Therefore it is commonly held that ballism is simply a more extreme manifestation of

the same pathophysiologic process that invokes chorea. Taken as a whole these disorders are relatively common and indicative of a wide variety of structural, pharmacological, and metabolic abnormalities involving the basal ganglia and specifically the corpus striatum.

PHENOMENOLOGY

Chorea, athetosis, and ballism lie on a spectrum of choreic phenomenon with ballism on one end associated with proximal rapid large-amplitude flinging movements, chorea in the middle with lower amplitude random flowing movements, and athetosis with its slower more distal writhing movements on the other.

Chorea is characterized by brief, irregular, random, nonrhythmic movements that flow from one body part to another. The movements are generally low amplitude, and unpredictable and can involve all muscle groups including the face and trunk. Ballism is more rapid, described as flinging or violent movements, involving proximal muscle groups of the limbs. Athetosis is slower, near continuous, writhing movements of the distal extremities. These movements frequently coexist with more classical choreic movements and even dystonia.

Chorea is often associated with a variety of secondary features (Table 5–1). Parakinesis, the incorporation of an involuntary movement into a seemingly voluntary movement, is manifest by the crossing and uncrossing of the legs, the rubbing of the chin or the adjustment of one's glasses. In fact, when subtle, chorea is often mistaken for voluntary movements and the person described as fidgety or restless. Motor impersistence is seen in the inability to maintain eye closure or tongue protrusion or the classic "milk maid's grip" upon shaking hands. Chorea may be partially suppressible though not to the extent seen with tics. Finally, abnormalities of reflexes have been described with reflexes being "hung up" or "pendular" in individuals with chorea.

DIFFERENTIAL DIAGNOSIS AND EVALUATION

The etiologic causes of choreiform disorders are broad and can reflect a wide variety of processes affecting the basal ganglia. Generally, chorea either represents the primary manifestation of an inherited disorder or is acquired secondary to basal ganglia insults due to various comorbid medical conditions, medications or toxins, or structural abnormalities. Table 5–2 outlines the extensive differential diagnosis of chorea.

It deserves mentioning that athetosis and ballism, while being commonly associated with chorea and lying on the spectrum of choreiform disorders, often suggest specific localization and etiology. Athetosis is a common feature of cerebral palsy and can be the distinguishing characteristic and when present in the setting of a congenital movement disorder with dystonia, spasticity, and possibly mental retardation is nearly diagnostic. Unilateral or hemi-ballism is a relatively rare condition that is usually associated with a structural lesion, often a stroke, involving the contralateral subthalamic nucleus. Acute-onset hemiballism is presumed vascular in origin, though it has been reported in metabolic disorders.[6] Ballism from any cause tends to be self-limited, gradually evolving into chorea.

Given the broad and extensive potential etiologies of chorea, a systematic approach to the evaluation of the patient with chorea is critical. Figure 5–1 represents an initial approach in the evaluation of new-onset chorea, athetosis, or ballism. As with most neurological disease, the acuity of onset matters. Acute-onset hemiballism is almost always the

Table 5–1 **Features Associated With Chorea**

Athetosis	Slow, writhing movements of distal limbs
Ballism	Rapid, flinging movements of proximal limbs
Parakinesis	Incorporation of an involuntary movement into a voluntary movement, e.g., crossing and uncrossing of legs, adjusting glasses, rubbing chin
Motor impersistence	Inability to maintain tongue protrusion, "milk maid's grip"
Partial suppressibility	Brief ability to voluntary reduce the severity of movements
Deep tendon reflex	"hung up" or "pendular" reflexes
Gait	Irregular or dance-like gait

Table 5–2 Differential Diagnosis of Disorders Associated With Chorea

INHERITED CHOREAS

Autosomal Dominant
- Huntington's disease
- Spinocerebellar ataxia 17
- Spinocerebellar ataxia 1-3
- Huntington's disease-like 1, 2
- Dentatorubropallidoluysian atrophy
- Neuroferritinopathy
- Benign hereditary chorea
- GLUT1 deficiency

Autosomal Recessive
- Neuroacanthocytosis
- Wilson's disease
- Huntington's disease-like 3
- Friedreich's ataxia
- Ataxia-telangiectasia
- Ataxia with oculomotor apraxia
- Neurodegenerative disorders associated with brain iron accumulation
  - *Pantothenate-kinase-associated neurodegeneration (PKAN)*
  - *Phospholipase A2G6-associated neurodegeneration (PLAN)*
- *Aceruloplasmenia*
- Other pediatric metabolic disorders
- *Glutaric aciduria*
- *Propionic academia*

X-linked
- McLeod syndrome
- Lesch-Nyan syndrome
- Lubag

Mitochondrial
- Leigh's syndrome
- MELAS

ACQUIRED/SPORADIC CONDITIONS

*Drug-induced**
- Tardive dyskinesia
- Side effect of concomitant medication

Immune-mediated
- Sydenham's chorea (poststreptococcal)
- Autoimmune
- *Systemic lupus erythematosus*
- *Antiphospholipid antibody syndrome*
- *Other systemic collagen vascular disorders/CNS vasculitides*
- Paraneoplastic

Infectious
- HIV/AIDS associated
- *HIV encephalopathy*
- *Toxoplasmosis*
- *Lymphoma*
- Variant Creutzfeldt-Jakob disease
- Neurosyphilis
- Miscellaneous infections
- *Viral enchephalitides*
- *Mycoplasma encephalitis*
- *Cysticercosis*

Neoplastic
- Primary or metastatic brain tumor
- CNS lymphoma
- Paraneoplastic

Endocrine
- Hyperthyroidism
- Hypo/Hyperparathyroidism
- Chorea gravidarum

Metabolic
- Hyper/hypoglycemia
- Electrolyte disturbances
- Acquired hepatocerebral degeneration
- B_{12} deficiency

Vascular
- Subcortical/Basal ganglia infarcts or hemorrhage
- Vascular malformations
- Moya-Moya

Miscellaneous
- Polycythemia Vera
- Postpump chorea
- Multiple sclerosis
- Toxins
- Hypoxic-Ischemic encephalopathy
- Sporadic neurodegenerative disorders
- *Alzheimer's disease*
- *Cortical-basal degeneration*

*Table 5–2 summarizes medications associated with chorea.

MELAS = Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes.

result of a subcortical stroke and rarely an acute metabolic disturbance, while chorea in Huntington's disease (HD) is invariably chronic and insidious. Whether the choreiform disorder is focal, hemi, or generalized seems to be less useful in the differential diagnosis, as systemic conditions can often cause a focal-onset chorea.[6]

Choreiform disorders can be broadly categorized as being either inherited or acquired. This classification scheme must be approached with caution, as even seemingly sporadic choreiform disorders may have a genetic underpinning even in the absence of a family history. The following sections discuss the more common and important choreiform disorders classified as inherited or acquired.

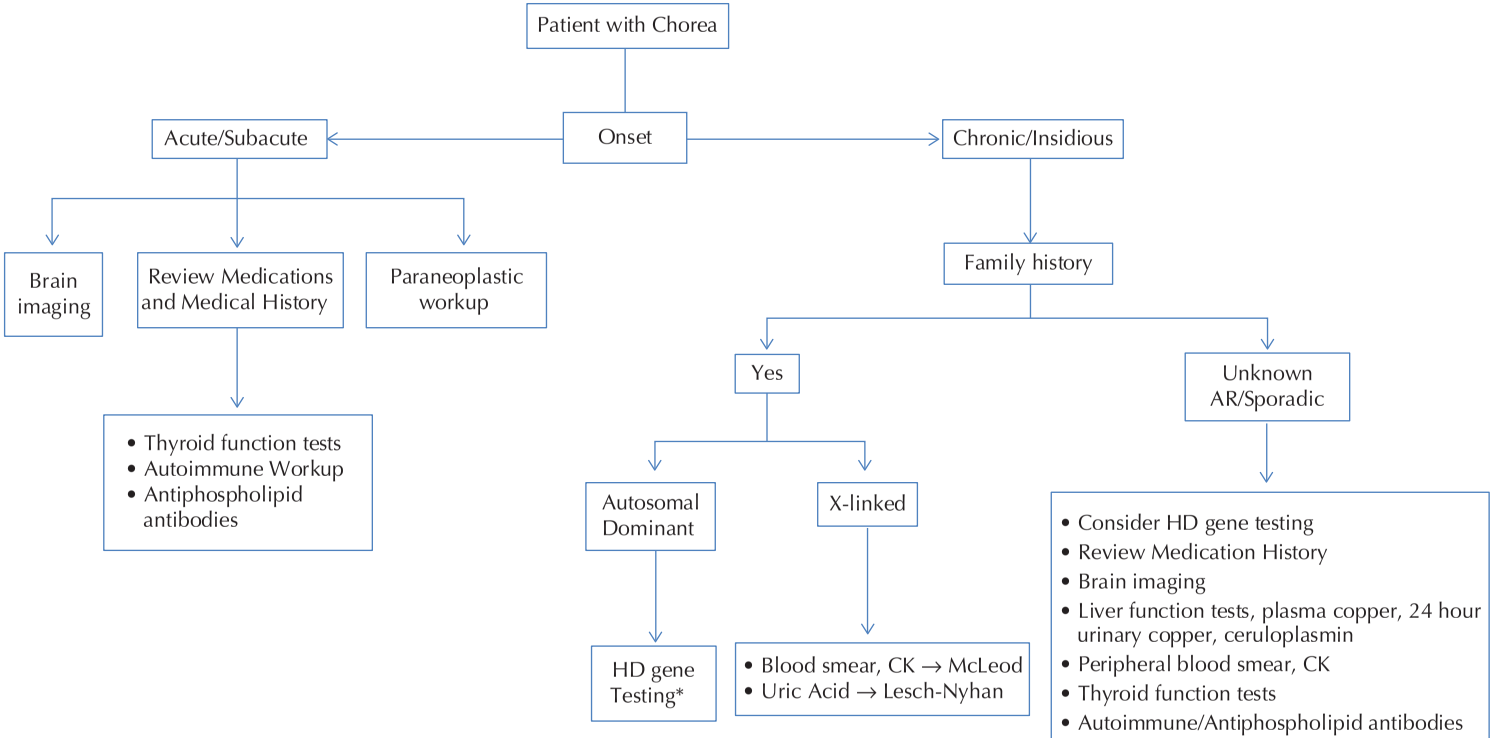
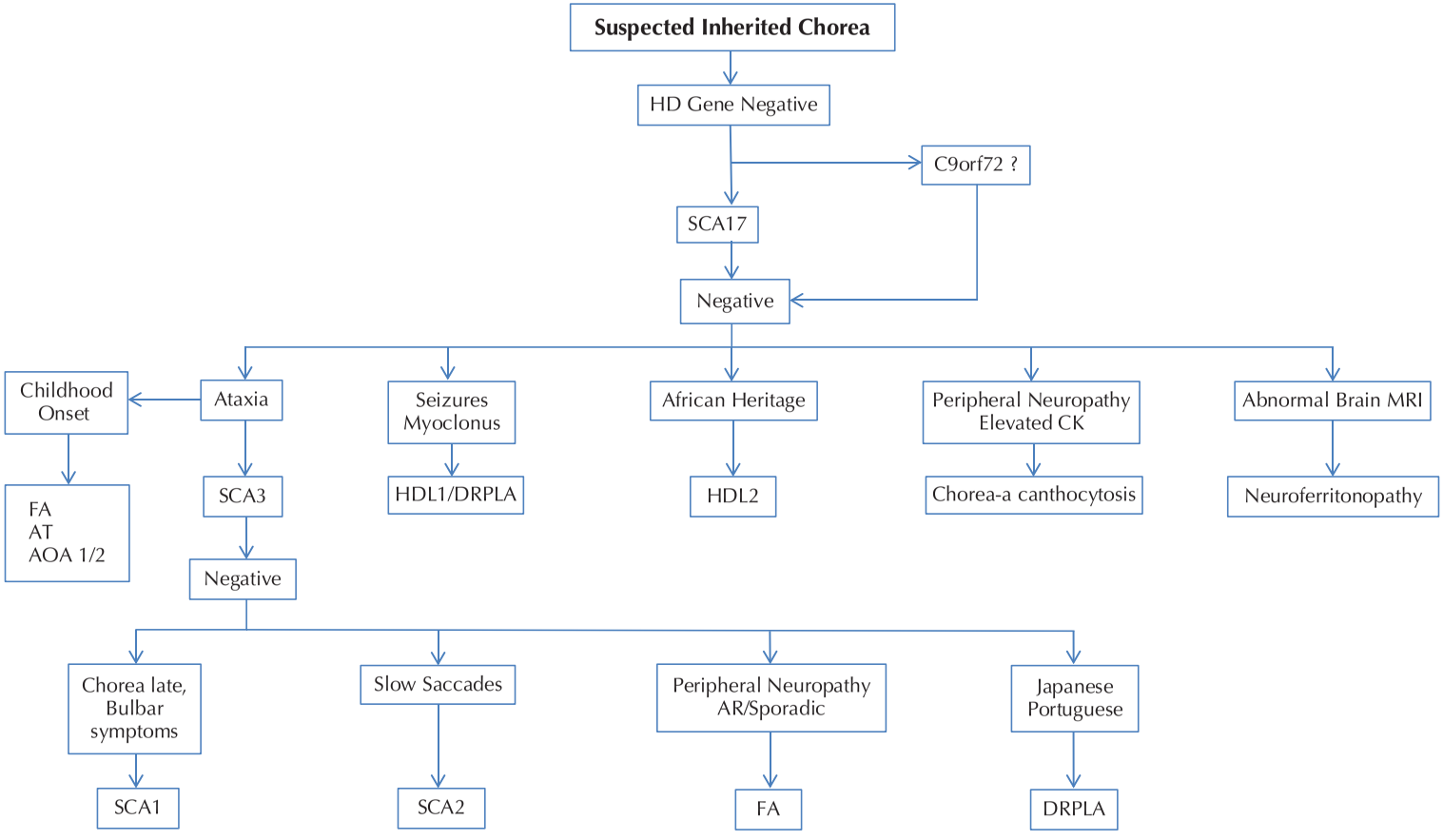


Figure 5–1. Evaluation of the patient with chorea.



HD = Huntington's disease
SCA = spinocerebellar ataxia
AR = autosomal recessive
DRPLA = Dentatorubropallidoluysian atrophy

FA = Friedreich's ataxia
AT = Ataxia-telangiectasia
AOA = Ataxia with oculomotor apraxia

HDL = Huntington's disease-like
CK = Creatinine phosphokinase

Figure 5–2. Approach to genetic workup of inherited chorea.

Inherited Choreas

Huntington's disease is the most common cause of inherited chorea worldwide. It is also a common cause of sporadic chorea, with up to 50% of patients in one series of sporadic adult-onset chorea carrying the mutation for HD.[7] In fact, it is not unreasonable to consider genetic testing for HD in both sporadic and presumed familial causes of adult-onset chorea. Huntington's disease phenocopies, that is, adult-onset chorea with HD features, are relatively uncommon, making up approximately 1% of individuals in genetic testing centers. Among these HD phenocopies genetic diagnoses are uncommon. Wild and Tabrizi[8] demonstrated, in 285 individuals with HD phenocopies, that only 3% had an identifiable genetic diagnosis. In pooling this data with data from other centers, they identified spinocerebellar ataxia 17 as the most common genetic HD phenocopy, followed by HD-like 2, Friedreich's ataxia, and familial prion disease. Dentatorubropallidalluysian atrophy (DRPLA), which is classically reported as an HD phenocopy, was surprisingly not seen. This may reflect that DRPLA is common in Japanese but rare in European populations. More recently, in a larger cohort, this same group identified an expanded hexanucleotide repeat in the C9orf72 gene in otherwise genetically unidentified HD phenocopies and suggested it may be a more common cause of this phenotype; however these findings need to be confirmed in other cohorts.[9] Figure 5–2 outlines a proposed genetic workup of HD gene–negative choreiform disorders based on the work of Tabrizi's group and known genotype-phenotype relationships.[9] Importantly, while this approach is valuable, the vast majority of HD phenocopies will not be genetically identifiable.

HUNTINGTON'S DISEASE

Huntington's disease is an autosomal dominant fatal and progressively disabling neurodegenerative disease and the most common cause of inherited adult-onset chorea. While hereditary choreiform disorders had been described previously, it was George Huntington's description, "On Chorea" published in the *Medical and Surgical Reporter* on April 13, 1872, that succinctly and accurately captured the cardinal features of the disease and led to the eponymic designation[10] (Figure 5–3). However, it was not until 1993 that the HD Collaborative Research Group identified an expansion of an unstable cytosine-adenine-guanine (CAG) trinucleotide repeat of the IT-15 gene on the short arm of chromosome 4 as the causative mutation.[11]

Huntington's disease is a relentlessly progressive and lethal disorder. Illness may emerge at any time of life, with the peak incidence between 35 to 40 years of age.[12] The average age of death for HD patients in the United States is approximately 60 years[13] but is lower in less developed countries.[14] Age of onset and progression of underlying disease are inversely associated with CAG repeat length, with the longest repeats associated with juvenile-onset disease and a more rapid disease[11,15,16] (Figure 5–4). The association of CAG repeat length with age of onset combined with the instability of the CAG expansion during meiosis accounts for the phenomenon of anticipation, where subsequent generations develop disease at an earlier age.

Huntington's disease is characterized clinically by the triad of an extrapyramidal movement disorder, progressive cognitive decline (dementia), and an array of behavioral disturbances. Chorea is the prototypical motor manifestation of HD, occurring in 90% of patients, though a wide range of other motor abnormalities have been described.[17–23] The chorea begins subtly with slight movements of the fingers and toes, and in at-risk individuals prior to diagnosis these subtle movements predict mutation status[24] and

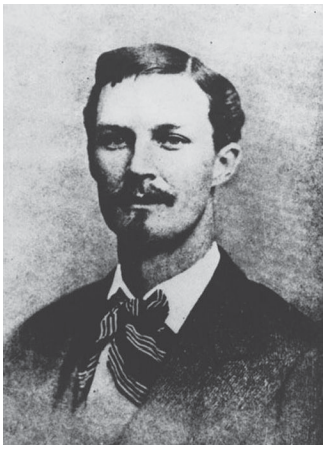


Figure 5–3. George Huntington in 1872, at about the time of the presentation of his classic thesis titled "On a Form of Chorea Vulgarly Called 'Magrums'" (With kind permission of the National Library of Medicine.)

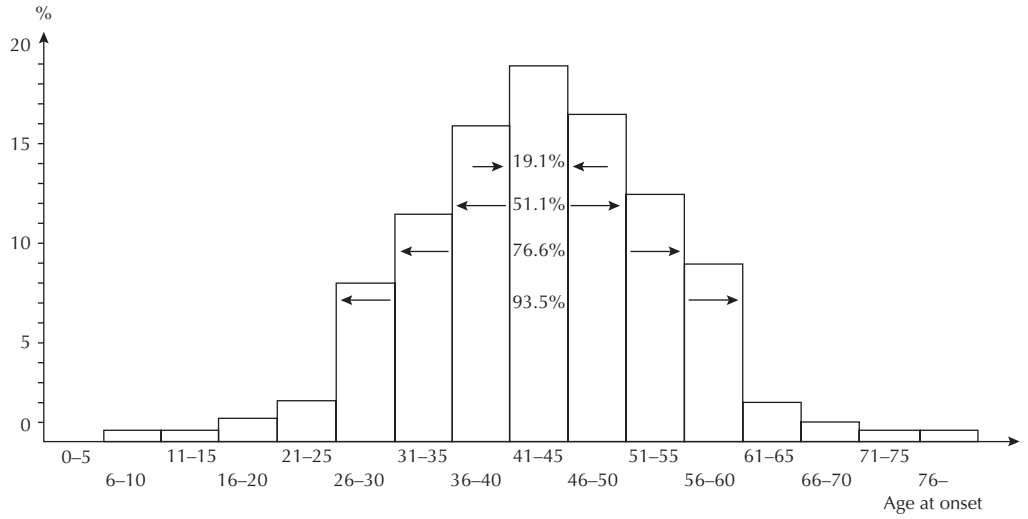


Figure 5–4. The distribution of ages of onset in 802 patients with Huntington's disease from the data of Wendt and Drohm's (1972) survey. (Reproduced from Vogel F, Motulsky AG. Human Genetics: Problems and Approaches. Springer Verlag, 1979. © Springer.)

distinguish carriers of the CAG expansion from noncarrier controls.[25] Chorea has been shown to be the most specific feature of mutation status in at-risk individuals.[25] Cognitive impairment is ubiquitous in HD and typically progresses from selective deficits in psychomotor, executive, and visuospatial abilities to more global impairment,[26–30] with higher cortical functions usually spared. Similar to motor features, subtle cognitive features are often seen early, even decades prior to motor onset, and are predictive of mutation status.[31] Psychiatric illness has been recognized as an important feature of HD since George Huntington reported on the "tendency to insanity and suicide." A wide range of psychiatric and behavioral disturbances are currently recognized.[32] Mood disorders, psychosis, anxiety, obsessions, compulsions, aggression, irritability, and apathy may be prominent and disabling features of HD. Depression is the most common behavioral feature of HD, occurring in as many as half of HD patients,[32,33] and a suicide rate five times more frequent than in the general population accounts for 2%–5% of HD mortality.[34]

The juvenile variant of HD, where onset occurs before age 20, is typically manifested by an akinetic-rigid phenotype and paternal inheritance and only rarely chorea.[16,35] Cognitive and behavioral symptoms presenting as a decline in school performance are more severe than in adult-onset disease and often predate the onset of motor abnormalities.[16,35–48] Paternal inheritance of the HD gene is the rule for onset before the age of 10 and still predominates (about 3:1 paternal:maternal) for onset before the age of 20.[38] This reflects the greater likelihood of large expansions arising during spermatogenesis compared with oogenesis.

Huntington's disease has a worldwide distribution reflecting multiple introductions of the gene from European migrations.[49] New mutations are rare and likely represent expansion of the unstable trinucleotide repeat from an intermediated range (30–35 repeats) in the parent to the pathologic range (≥ 36 repeats) in the offspring.[11] It has the highest prevalence rates around Lake Maracaibo in Venezuela and the Moray Firth region of Scotland and is relatively rare in Asian countries and among African blacks.[50,51] Approximately 30,000 people in the United States have clinical manifestations of HD, and an additional 150,000 healthy people are at risk of developing HD.[52,53] Among individuals of European descent, HD has a relatively uniform prevalence ranging from 2 to 8 per 100,000.[50]

The neuropathology of HD is characterized by selective neuronal vulnerability, particularly involving the caudate and putamen of the corpus striatum.[54] Over time, all brain regions are prominently affected, resulting in global brain atrophy.[54,55] Figure 5–5 illustrates

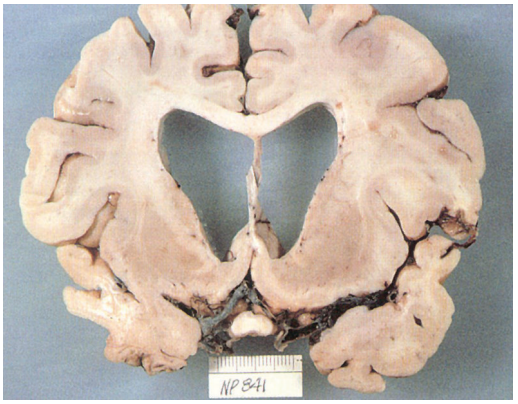


Figure 5–5. Gross pathology of Huntington's disease brain showing caudate atrophy.

the striking caudate atrophy characteristic of the HD brain. Microscopically, the pathological hallmark of the disease is the preferential loss of medium-sized spiny neurons projecting from the striatum to the external pallidum.[56]

While HD is associated with a variety of motoric phenotypes, it remains the prototypical choreiform disorder and the most common cause of inherited adult-onset chorea. Our understanding of the pathophysiology and the effectiveness of therapeutics for chorea have largely arisen from studies in HD. In addition, HD represents one of the most important genetic disorders of adulthood. Huntington's disease was the first disease recognized to arise from a trinucleotide expansion that can be detected by DNA testing and serves as a model for the experimental therapeutics of adult-onset neurodegenerative diseases.

C9ORF72 EXPANSIONS

C9orf72 is a recently described hexanucleotide repeat in a noncoding region associated with frontotemporal lobar degeneration and amyotrophic lateral sclerosis.[57,58] More recently this mutation was identified in 10 of 514 HD phenocopies, possibly making this the most common genetic cause of an HD-like disorder.[9] Mean age of onset was about 43 years, with childhood onset reported. Behavioral symptoms were common initial features. A heterogeneous extrapyramidal movement disorder with parkinsonism, chorea, dystonia, myoclonus, and tremor was reported. Mild cognitive features with executive dysfunction were common. This preliminary report will need to be confirmed in additional studies, however, C9orf72 expansions should be considered as a relatively common genetic cause in HD phenocopies.

CEREBELLAR ATAXIAS

Autosomal dominant spinocerebellar ataxias (SCAs) represent some of the more common disorders with adult-onset chorea mimicking HD. SCA-17 is often the most common disorder identified among HD mutation negative individuals with the HD phenotype and chorea.[8] Chorea has variably been reported in SCAs 1-3.[59–61] Dentatorubropallidoluysian atrophy (DRPLA) is a rare autosomal dominant ataxic disorder with epilepsy and extrapyramidal features mimicking HD.[62] Among the autosomal recessive ataxias, Freidreich's ataxia, ataxia-telangiectasia, and ataxia with oculomotor apraxia have been associated with chorea.

Similar to HD, SCA-17 is an adult-onset autosomal dominant trinucleotide repeat disorder. Genetically it is associated with an expansion of a repeating CAA-CAG sequence on a gene encoding for a TATA box-binding protein on chromosome 6.[63] An inverse relationship to age of onset and repeat length exists for SCA-17. Cerebellar ataxia is the overwhelming clinical feature, though a classical HD phenotype has been described.[64,65] In addition, other extrapyramidal motor features, pyramidal signs, epilepsy, dementia, and behavioral disturbances have been variably seen.[66]

Spinocerebellar ataxia-3, or Machado-Joseph disease, is the most common SCA worldwide.[67] It results from an unstable trinucleotide CAG repeat expansion in the ataxin-3 gene.[68] It is a clinically heterogeneous disorder. Progressive cerebellar ataxia is the most common feature but is always associated with a variety of pyramidal, extrapyramidal, and lower motor neuron manifestations. More than other ataxias, extrapyramidal manifestations predominate, with parkinsonism and dystonia being most common and chorea occurring rarely.[61] In SCA-1, chorea may be a late manifestation of the illness and tends to occur in the setting of progressive cerebellar and bulbar dysfunction.[59] SCA-2, similar to SCA-3, has a more heterogeneous phenotype. Classically saccadic eye movements are slow early and areflexia and polyneuropathy are prominent. Chorea is occasionally reported.[60] A single report identified

a Greek individual with the SCA-8 mutation presenting with an HD phenotype including chorea,[69] though confirmation in this rare condition is needed (Figure 5–6).

Dentatorubropallidoluysian atrophy is an autosomal dominant trinucleotide repeat disorder resulting from a CAG expansion on chromosome 12. Clinically it is characterized by progressive cerebellar ataxia, chorea, myoclonic epilepsy, dementia, and behavioral disturbances.[70] It is almost exclusively seen in Japanese populations, where it is more common than HD, and is rarely seen in European populations with the exception of pockets in Portugal.[67,70,71] Another notable exception to the Japanese heritage is the Haw River syndrome. The Haw River syndrome affects multiple generations of an African American family in North Carolina and is caused by the same CAG expansion as DRPLA.[72] There is an inverse relationship between age of onset and CAG length, with ataxia being the earliest feature and chorea being a generally late manifestation.[73]

Friedreich's ataxia is the most common inherited ataxia and is caused by an autosomal recessively inherited GAA trinucleotide repeat expansion in the frataxin gene on chromosome 9.[74] Classically it is a childhood-onset disorder presenting with gait ataxia and clumsiness associated with cerebellar degeneration, peripheral sensory loss, and areflexia, with pyramidal tract weakness occurring late.[75] It has occasionally been associated with chorea.[76] Nonneurological manifestations include cardiomyopathy, diabetes mellitus, and skeletal deformities (scoliosis).

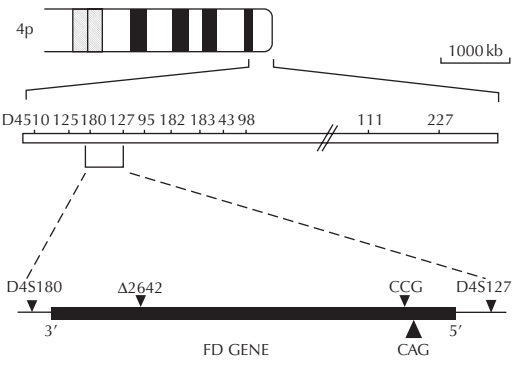


Figure 5–6. Schematic map showing the position of the Huntington's disease gene and the CAG repeat associated with the disease on 4p16.3. (Reproduced from Andrew SE, Hayden MR. Origins and evolution of Huntington disease chromosomes. Neurodegeneration 1995;4:239–244.)

Ataxia-telangiectasia (AT) is a rare early-onset ataxic disorder associated with oculocutaneous telangiectasia.[77] It is an autosomal recessive disorder due to an A-T mutated gene on chromosome 11 that encodes for the ATM protein that plays an important role in DNA repair.[78] Onset of ataxia begins around the age of 2 or 3, with affected individuals being wheelchair bound by 10 years of age. Telangiectasia occurs years after the onset of ataxia making clinical diagnosis challenging. Other features include immunodeficiency, increased risk of malignancy, radiosensitivity, and increased serum alpha-fetoprotein levels, the latter being useful diagnostically. Chorea-athetosis is seen in the majority of affected children.[77,79] Since the identification of the gene and more accurate diagnosis, variants of AT with later onset illness have been identified, many of these presenting with extrapyramidal motor features. In a series of 13 individuals with late-onset, variant AT, greater than 50% presented with chorea-athetosis of unknown cause.[79] Therefore, AT must be considered in sporadic adult-onset chorea of unknown cause. Serum alpha-fetoprotein levels are invariably increased.

Ataxia with oculomotor apraxia (AOA) consists of two types (types 1 and 2). Both are rare autosomal recessive diseases associated with progressive cerebellar ataxia and oculomotor apraxia (inability to initiate horizontal saccades without head movements).[80,81] Initially described in Japanese families, AOA1 is characterized by early-onset ataxia, oculomotor apraxia, neuropathy, and mental retardation. This is a slightly later onset disease compared with AT with mean age of onset of 7. Chorea occurs frequently at onset, affecting nearly 80% of patients but disappearing with disease progression.[80] Hypoalbuminemia and hypercholesterolemia are associated laboratory features that may help diagnostically. Similarly, AOA2 is characterized by progressive ataxia and polyneuropathy however oculomotor apraxia occurs in only 50% of patients. It is distinguished from AOA1 by its later onset (mean age of 15 years with a range from 2 to 72 years of age), slower progression, lack of cognitive impairment, and lower frequency of extrapyramidal complications.[81] In a large series, chorea was seen in only 10% of patients.[81] As with AT, alpha-fetoprotein is often elevated in AOA2.

HUNTINGTON'S DISEASE–LIKE DISORDERS

Huntington's disease–like (HDL) disorders are a group of neurodegenerative diseases that are phenotypically similar to HD. In general these disorders are inherited diseases associated with an extrapyramidal movement disorder, cognitive decline and psychiatric disturbances.

An autosomal dominant neurodegenerative disorder, HDL1 is caused by a mutation in the prion protein on chromosome 20.[82,83] In addition to characteristic motor features with prominent chorea-athetosis, cognitive decline, and psychiatric features, families with HDL1 frequently have ataxia and epilepsy. Age of onset is in young to mid-adulthood, and the disease is universally fatal.

An autosomal dominant disorder, HDL2 results from a CTG-CAG trinucleotide repeat expansion in the junctophilin 3 gene on chromosome 16.[84] Of the HDL disorders, HDL2 is most phenotypically similar to HD and is characterized by onset in midadulthood, chorea, behavioral symptoms, weight loss, and dementia, with death occurring approximately 20 years after disease onset.[85] As in HD, there is marked striatal atrophy. It occurs almost exclusively in individuals of African heritage and is an important cause of HD phenocopies in this population.[86] Acanthocytosis is seen in up to 10% of patients, but the inheritance pattern and normal creatine phosphokinase (CK) levels distinguish it from neuroacanthacytosis.[87]

Because it is a poorly characterized disorder, the inclusion of HDL3 among the HDL disorders is somewhat misleading, as it is an autosomal recessive disorder. It was initially described in a single Saudi family, and some controversy exists over the genetic localization.[88,89] Clinically the disease is of early onset, in the first decade of life, associated with pyramidal and extrapyramidal dysfunction (including chorea), seizures, and cognitive impairment.

The disorder SCA17 is often referred to as HDL4, given the clinical overlap with HD in some families and some individuals, and is discussed with the cerebellar ataxias.

BRAIN IRON ACCUMULATION DISORDERS

Disorders of brain iron accumulation consist of a group of heterogeneous inherited disorders associated with a progressive extrapyramidal movement disorder and excessive iron accumulation in the brain.[90] These disorders share characteristic MRI findings with low T2 signal intensity in the basal ganglia reflecting iron accumulation.[91] The globus pallidus is most commonly involved with variable involvement of the striatum, substantia nigra, and cerebellum. A central T2 hyperintensity may be seen within the area of low attenuation giving the classic "eye of the tiger sign." Figure 5–7 shows the characteristic imaging in patients with neuroferritonopathy.[92] Newer MRI techniques, namely, susceptibility weighted imaging, may be a more sensitive tool for detecting iron deposition in these patients.[92] These disorders

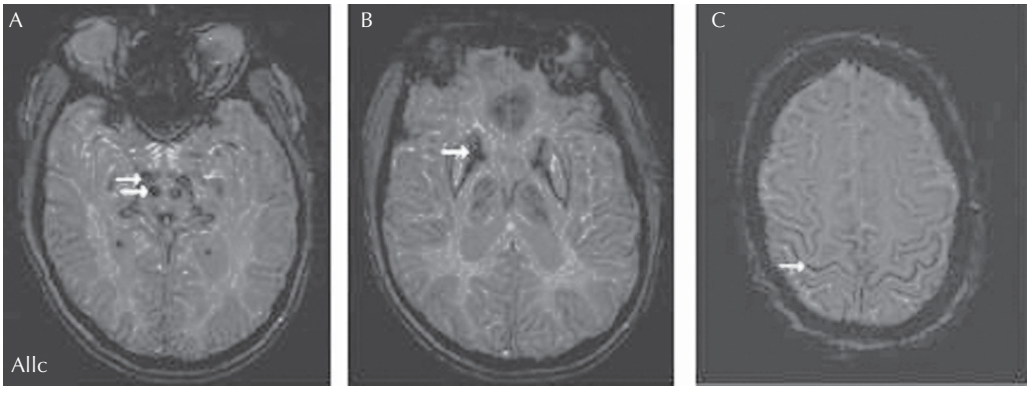


Figure 5–7. Characteristic imaging findings in disorders of brain iron accumulation. Susceptibility weighted MRI imaging showing iron in (A) red nucleus and substantia nigra, (B) globus pallidus, (C) motor cortex. (From Lehn A, Boyle R, Brown H, Airey C, Mellick G. Neuroferritonopathy. Parkinsonism Rel Disord 2012;18:909–915.)

are rare and present with a variety of extrapyramidal and cerebellar symptoms. These disorders include the autosomal dominant neuroferritonopathy, and the autosomal recessive pantothenate-kinase-associated neurodegeneration (PKAN), phospholipase A2G6-associated neurodegeneration (PLAN), aceruloplasminemia, fatty acid 2-hydroxylase associated neurodegeneration (FAHN), and Kufor-Rakeb disease (PARK 9). The latter two diseases have not been associated with chorea and are not discussed.

Neuroferritonopathy is an adult-onset autosomal dominant disorder caused by various mutations in the ferritin light chain polypeptide gene resulting in abnormal ferritin function.[92] Chorea is the most common manifestation, but other extrapyramidal signs may predominate including dystonia and Parkinsonism.[93] Cognition is usually preserved. While routine blood work including blood counts and hemoglobin levels are normal, ferritin levels are often, but not invariably, low. Brain imaging with MRI is the most useful diagnostic tool and shows the characteristic T2 signal hypointensities in the cerebellum, substantia nigra, globus pallidus, striatum, and motor cortex.[94] These abnormalities may even be seen in the premanifest phase of asymptomatic carriers.[93]

Pantothenate-kinase-associated neurodegeneration, neurodegeneration with brain iron accumulation (NBIA) type 1, is a genetically heterogeneous autosomal recessive disorder, with mutations in the pantothenate kinase 2 gene responsible for half of the cases.[95] Classically this is an early-onset disorder presenting around the age of 3 with profound dystonia often affecting the oromandibular region.[91] Chorea, parkinsonism, dementia, and behavioral changes are also seen. Pigmentary retinopathy, as opposed to optic atrophy, is frequently seen.[96] Rarely late-onset cases have been reported. An MRI scan shows the classic "eye of the tiger sign" involving the globus pallidus. Acanthocytosis is seen in approximately 8%–10% of subjects, however, the young onset and characteristic MRI findings distinguish it from neuroacanthocytosis.[97]

Phospholipase A2G6-associated neurodegeneration, NBIA type 2, is an autosomal recessive disorder due to mutations in the PLA2G6 gene. Early-onset cases have infantile neuroaxonal dystrophy (INAD) that is characterized clinically by cerebellar ataxia, truncal hypotonia, progressive pyramidal and extrapyramidal motor dysfunction, and mental retardation.[91] While dystonia and parkinsonism are characteristic, chorea has occasionally been reported in INAD.[98] Late-onset cases are less common and have not been associated with chorea.

Aceruloplasminemia is an autosomal recessive disorder caused by mutations in the ceruloplasmin gene on chromosome 3.[99] Neurological signs present in adulthood with initial cognitive impairment associated with craniofacial dyskinesia and ataxia.[100] Chorea is occasionally seen. Retinal degeneration and diabetes mellitus predate neurological signs by a decade and are a useful clue to the diagnosis. Serum ceruloplasmin is undetectable and copper and iron levels are low. In contrast to neuroferritinopathy, ferritin levels are elevated.

NEUROACANTHOCYTOSIS

Neuroacanthocytosis (NA) is a heterogeneous group of rare disorders where progressive neurological dysfunction is associated with acanthocytosis. Acanthocytosis refers to the spiky deformity of the red blood cells seen on a peripheral smear (see Figure 5–8). The classic NA syndromes include chorea-acanthocytosis and McLeod syndrome and are adult-onset disorders with basal ganglia degeneration, movement disorders usually manifest as chorea, cognitive impairment, and behavioral

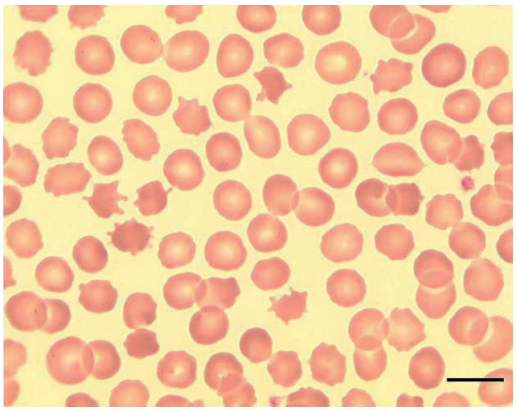


Figure 5–8. Acanthocytosis on peripheral blood smear of individual with McLeod syndrome. May Gruenwald-Giemsa; x100; scale bar = 10 µm. (From: Jung HH, Danek A, Walker RH. Neuroacanthocytosis syndromes. Orphanet J Rare Dis 2011;6:68.)

features.[101] With the exception of the hereditary pattern, these disorders are clinically HD phenocopies. Chorea-acanthocytosis is autosomal recessive, and McLeod is X-linked recessive. Both HDL2 and PKAN are occasionally associated with acanthocytosis and are sometimes included with this group of disorders.

Chorea-acanthocytosis is a rare disorder most commonly seen in Japan, with other pockets in isolated groups.[102,103] It is an autosomal recessive disorder due to various mutations in the VPS13A gene encoding for the chorein protein on chromosome 9.[102] Onset is in the 20s, with cognitive and psychiatric manifestations predominating early. The movement disorder is characterized by generalized chorea, though limb and feeding dystonias are often seen. Seizures occur in one-third of patients and may be the initial manifestation of illness. Peripheral nerve involvement with myopathy and axonal polyneuropathy are common but mild. Creatine kinase (CK) levels are elevated in most patients. Traditionally the identification of acanthocytes in the peripheral blood smear in the appropriate clinical setting was used for the diagnosis, however, acanthocytes are notoriously difficult to identify using standard techniques and may be negative early in the course of the disease.[104,105] Genetic testing is not feasible, given the diversity of mutations identified. The absence of chorein protein expression in erythrocytes may be a useful marker of disease but is not widely available.[106] Practically, an adult-onset sporadic or autosomal recessive disorder with chorea, peripheral neuropathy, and elevations in CK is sufficient for diagnosis of neuroacanthocytosis (both chorea-acanthocytosis and McLeod syndrome).

The McLeod phenotype was initially identified as a rare blood group phenotype defined by the absence of the Kx antigen and by weak expression of Kell antigens.[107] It was not until later that this blood group phenotype was noted to be associated with the insidious choreiform disorder known as the McLeod syndrome.[108,109] It is even rarer than chorea-acanthocytosis, with only a few hundred cases identified worldwide. Clinically it presents in males from 25 to 60 years of age, generally of later onset and more slowly progressive than chorea-acanthocytosis.[110] Chorea may be the presenting feature in one-third of patients and is seen at some point in the disease course in most patients.[111] Psychiatric manifestations may be prominent and predate the movement disorder.[101] Cognitive dysfunction occurs only after disease of long duration. Creatine kinase levels are usually elevated. Peripheral neuropathy and myopathy are seen and may be more severe than in chorea-acanthocytosis.[112] Rhabdomyolysis has been reported in McLeod syndrome associated with neuroleptic use.[113] Cardiomyopathy is seen in greater than half of patients and is a frequent cause of mortality.[114] Diagnostic evaluation is similar to that for chorea-acanthocytosis, though the identification of the McLeod blood group phenotype is diagnostic.

BENIGN HEREDITARY CHOREA

Benign hereditary chorea (BHC) is an autosomal dominant childhood-onset disorder associated with nonprogressive chorea and no other associated neurological features.[115] It may be associated with hypothyroidism and pulmonary disease. Many cases are the result of variable mutations on the thyroid transcription factor 1 (TTF1) gene on chromosome 14,[116,117] though a few families with BHC are not linked to this locus.[118] Some cases, paradoxically, are levodopa responsive.[116] Diagnosis is based on a childhood-onset disorder with isolated nonprogressive chorea and the elimination of other causes.

WILSON'S DISEASE

Wilson's disease is an autosomal recessive disorder of impaired copper metabolism resulting in an extrapyramidal movement disorder and liver dysfunction. Dystonia, tremor, and parkinsonism predominate, with chorea occurring occasionally. Wilson's disease is discussed in greater detail in Chapter 11.

Acquired/Sporadic Choreas

In the absence of a genetic cause for chorea, sporadic or acquired causes should be considered. As many of the acquired causes are potentially treatable, diagnostic evaluation for acquired causes should be considered in parallel with genetic evaluation. In a series of consecutive cases of sporadic chorea[119] the underlying etiology was identified in 94% of

cases. Vascular causes were the most common (41%) followed by drug-induced (12%), AIDS (10%), and metabolic causes (8%). Huntington's disease was also identified in 10% of patients, reinforcing the need to consider HD in any adult-onset choreiform disorder independent of the family history.

DRUG-INDUCED CHOREA

Chorea may be caused by a wide variety of medications. Chorea may be the direct result of medications, a reactivation of latent Sydenham's or delayed (tardive) effect of dopamine receptor blocking agents. Table 5–3 summarizes medications associated with chorea. In most cases, drug-induced chorea is reversible with removal of the offending agent.[119] The exception is in cases of chorea as a result of tardive dyskinesia, where the chorea may be permanent and persist despite the removal of the dopamine receptor blocking agent.[120]

A variety of medications may cause chorea as a direct side effect. Levodopa-induced dyskinesias in Parkinson's disease patients is likely the most common example of drug-induced chorea encountered clinically. Anticonvulsants have been commonly reported to cause chorea, with phenytoin most frequently implicated, and importantly the chorea may be focal.[121–125] Amphetamines facilitate presynaptic release of monoamines including dopamine and may cause a variety of hyperkinetic movements, including chorea.[126,127] Movements usually, but not invariably, resolve. Similarly, cocaine enhances monoamine neurotransmission but, unlike amphetamines, it does so through blocking presynaptic reuptake and has been associated with a variety of movement disorders including chorea.[128,129] Lithium intoxication has been proposed as a cause of chorea, though concomitant antipsychotic use and metabolic abnormalities in many cases make ascertaining causality challenging.[130] Oral contraceptives are a well-recognized cause of chorea[131,132] and it may also occur with estrogen-containing hormone replacement therapy.[133,134] Many cases of estrogen-related chorea occur in the setting of a history of autoimmune chorea, suggesting that immune-mediated mechanisms may play a role.[132,135,136] Chronic alcohol use is associated with dopamine receptor hypersensitivity, and orolingual choreiform movements are seen after one to two weeks of abstinence.[137,138]

Dopamine receptor blocking agents (DRBA) are notoriously associated with hyperkinetic movement disorders as a component of a tardive syndrome. Neuroleptic antipsychotics are most commonly implicated; however, other dopamine receptor antagonists (metoclopramide, prochlorperazine) may be underrecognized causes of these syndromes. By the strictest definition, tardive syndromes require at least 3 months' exposure to a DRBA, moderate abnormal movements in one or more areas, and at least mild movements in two or more areas, and the absence of another cause for the movements.[139] The phenomenology can be mixed with classic forms causing repetitive bucco-oral-lingual movements.[140] Dystonia is also common. A withdrawal emergent syndrome, where an emergence or exacerbation of hyperkinetic movements occurs with withdrawal of DRBA, can occur and may portend a more persistent tardive syndrome. Tardive syndromes are notoriously difficult to treat; therefore prevention of tardive syndromes is the best treatment and DRBAs should be avoided whenever possible. Evidence supports that the rapid discontinuation of the offending agent increases the likelihood that the condition will eventually resolve. The usual course is for gradual recovery.[141] If antipsychotics are

Table 5–3 Drugs Associated With Chorea

Levodopa/Dopamine Agonists in Parkinson's Disease
Anticonvulsants
• Phenytoin
• Carbamazepine
• Gabapentin
• Valproate
• Lamotrogine
Psychostimulants (e.g., amphetamines)
Hormonal therapy containing estrogen (e.g., oral contraceptives)
Lithium
Neuroleptic antipsychotics
Miscellaneous dopamine blocking agents
• Metoclopramide
• Prochlorperazine
Drugs of abuse
• Ethanol withdrawal
• Amphetamine
• Cocaine
Methadone

necessary then clozapine or quetiapine are the antipsychotics of choice, though even atypical antipsychotics may cause or exacerbate tardive syndromes.[142] Increasing the dose or use of more potent antipsychotics will often temporarily reduce the severity of the movements; however this should be avoided as it leads to an increased likelihood of a persistent and more severe movement disorder. Presynaptic dopamine-depleting drugs like tetrabenazine may be effective.[143] High-dose vitamin B6 supplementation has shown some benefit,[144] and benzodiazepines show preliminary evidence of being useful.[145] Ultimately combination therapy, including removal of the offending agent, tetrabenazine, vitamin B6 supplementation, benzodiazepines, and botulinum toxin injections may be necessary to provide some symptomatic relief to affected individuals.

IMMUNE-MEDIATED CHOREA

Immune-mediated chorea is a common consideration in sporadic choreas. Chorea is presumed secondary to neuronal antibodies. Sydenham's chorea (SC) is the primary consideration in children, with the acute-onset chorea occurring in 96% of patients with this presentation in once series from western Pennsylvania.[146] In adults the causes are more diverse and include systemic lupus erythematosus (SLE), antiphospholipid antibody syndrome (APS), and paraneoplastic etiologies and are a relatively common cause of chorea after HD.[147,148]

Sydenham's Chorea

Sydenham's chorea is a major cause of childhood-onset chorea and is a delayed manifestation of group A beta-hemolytic streptococcal infection and a major manifestation of rheumatic fever.[149] The eponymic designation of SC arises from Thomas Sydenham's seminal description of a childhood-onset chorea, though he made no mention of its relationship to rheumatic fever.[1] In the 19th century multiple reports confirmed the association of rheumatic fever and SC and solidified the importance of this postinfectious movement disorder.[2] However, it was not until recently that the mechanism was recognized to be secondary to immunogenic mimicry with antistreptococcal antibodies cross-reacting with basal ganglia neurons.[150] In addition, anti-dopamine D1 receptor (D1R) and D2 receptor (D2R) antibodies have been identified in SC and the ratio of anti-D2R/D1R correlated with SC severity, suggesting an immune-mediated imbalance in dopamine signaling may be responsible.[151]

While currently viewed as a disease of developing countries, outbreaks continue to be seen in the United States.[147,152,153] Recognition of the disorder is important largely to prevent long-term complications associated with rheumatic fever. Chorea may be the presenting manifestation of rheumatic fever and occurs in 26% of individuals with the condition.[153] In children with acute-onset chorea, SC is the overwhelming diagnosis in the vast majority.[146] The average age of onset is 9–10 years. Hemichorea is common, occurring in up to 30% of patients suggesting that markedly asymmetric or even hemichorea does not always arise from structural lesions. As in other autoimmune disorders, females tend to predominate. Cardiac involvement is the most common concurrent major criteria in patients with SC, and all patients with SC need a cardiac evaluation.

The diagnosis of SC is based on congruent history, physical examination, and serological evidence of a streptococcal infection. Imaging should be reserved for those with atypical presentations or hemichorea. The disease is usually self-limited, with most resolving within 6 months, though some reports suggest that up to one-half of individuals may have persistent chorea up to 2 years.[154] Treatment consists of treating the underlying infection with penicillin and considering prophylactic penicillin use to prevent future infections.[155] Immunomodulatory therapies with plasma exchange or intravenous immune globulin (IVIG) may be beneficial in resistant cases.[156]

Autoimmune Disorders

Chorea may be a manifestation of autoimmune disorders. It is widely recognized as a manifestation of SLE and APS and is the only movement disorder recognized as a complication of neuropsychiatric SLE.[157] Consistent with this, autoimmune chorea is most commonly seen in SLE and APS, affecting 1%–2% of adults with these conditions and even greater numbers of pediatric cases.[158,159] The presence of chorea in SLE is associated with the presence of antiphospholipid antibodies in greater than 90% of patients,[148,160] while in a series

of patients with chorea and antiphospholipid antibodies only 27% had SLE or lupus-like disorders,[161] suggesting a meaningful role of antiphospholipid antibodies on the development of chorea. While individuals with APS and chorea may demonstrate cerebrovascular disease, the subacute onset of chorea and the absence of basal ganglia imaging abnormalities and response to immunomodulatory treatment speak against a vascular cause.[148]

Chorea has also been reported in a variety of other autoimmune conditions, including Sjoegren's syndrome, rheumatoid arthritis, autoimmune-mediated thrombocytopenia purpura, autoimmune thyroid disease, and diabetes mellitus.[147] Unlike degenerative causes of adult-onset chorea, autoimmune chorea is far more likely to occur in women, be of subacute onset, and have a fluctuating course with spontaneous remissions and may present focally.[147,148] Finally, the presence of serologic evidence of autoimmunity and response to immunomodulatory therapy is supportive of the diagnosis.

Paraneoplastic

Chorea is a rare paraneoplastic phenomenon, representing approximately 1% of all individuals with neurological paraneoplastic syndromes in a European registry,[162] but as it may be the initial manifestation of an occult cancer it is an important clinical entity. Onset of chorea is subacute and may be focal or generalized.[147,162] It is associated with a wide variety of cancer types but most commonly lung cancer. The movement disorder often precedes the identification of the cancer. Paraneoplastic chorea is seen with CV2/CRMP-5 and Hu/ANNA-1 antibodies almost exclusively. In contrast to other immune-mediated choreas, individuals with paraneoplastic chorea are older (mean age of onset 72–75), are more likely to be male, have associated weight loss, and have evidence of peripheral nerve involvement.[147] Treatment of the underlying cancer may be effective in improving the chorea.

INFECTIOUS CHOREA

A variety of infectious and postinfectious etiologies have been proposed as being associated with chorea. Sydenham's chorea is the most common disorder associated with infection (group A beta-hemolytic streptococcus). It is a delayed response to infection in children and is presumably mediated by antibodies to strep cross-reacting with basal ganglia neuronal elements and for this reason it is discussed under immune-mediated choreas.

A common cause of acquired chorea is HIV and AIDS.[119] Chorea may be the result of direct infection from HIV, namely, HIV encephalopathy, or of secondary infections.[119,163] Toxoplasmosis, with its predilection for the basal ganglia, is commonly implicated.[164]

Chorea has also been reported with neurosyphilis, mycoplasma encephalitis, cysticercosis, borreliosis, and various viral encephalitides.[119,165–171] Chorea may result from direct infection, from mass lesions (as in cysticercosis), or due to immunogenic mimicry.[167,169,170,172]

Variant Creutzfeldt-Jakob (vCJD) disease rarely presents with chorea,[173,174] though chorea is a common manifestation at some time during the course of illness, affecting 20 of 35 pathologically proven cases in one series.[175] Classically this condition presents with early psychiatric disturbances, persistent painful sensory symptoms, ataxia, and dementia with progression to mutism and death. An EEG does not show the typical pattern seen in sporadic CJD, and MRI often shows high intensity T2 signal in the pulvinar regions.

ENDOCRINE RELATED CHOREA

Endocrinologic disturbances have been observed in patients with chorea. Classically hyperthyroidism is the most common endocrinologic cause of chorea, and thyroids should be checked in all cases of sporadic chorea.[176] As previously noted, exogenous estrogens in the form of oral contraceptives or hormone replacement therapy are associated with the development of chorea, but endogenous changes in estrogen during pregnancy is a well-recognized cause of chorea, namely, chorea gravidarum.[177] Finally, hypoparathyroidism may rarely be associated with paroxysmal chorea, presumably related to a combination of calcium deposition in the brain and fluctuations in serum calcium levels.[178]

Chorea and thyroid disease are well associated. Some debate exists about whether chorea is secondary to hyperthyroidism or is a result of autoantibodies seen in Grave's disease and Hashimoto's thyroiditis. Chorea has been reported in a case of Hashimoto's encephalopathy associated with normal thyroid levels.[179] In addition, a case of chorea in

a patient with hypothyroidism did not respond to thyroid replacement, subsequently, antithyroid antibodies were identified and the chorea responded to steroids.[176] In contrast, treatment of hyperthyroidism has resulted in resolution of chorea independent of thyrotropin receptor antibody levels in Grave's disease.[180] Regardless, in chorea associated with thyroid dysfunction, thyroid levels should be normalized and autoantibodies evaluated.

Chorea gravidarum is a characterized by chorea with onset during the first trimester that usually persists throughout the pregnancy until delivery.[177] It occurs most commonly in individuals with a previous history of rheumatic fever and Sydenham's chorea and is thought to be secondary to changing estrogen levels in the setting of a predisposed brain.[181] Chorea from other causes, including SLE and APS, can also be triggered by pregnancy and these conditions should be sought.[182] Treatment is largely symptomatic with delivery resulting in resolution of the chorea.

METABOLIC CAUSES OF CHOREA

Chorea may rarely be a manifestation of a variety of metabolic abnormalities, including electrolyte disturbances,[183] hyperglycemia,[6] B12 deficiency,[184] and chronic liver disease in the setting of acquired hepatocerebral degeneration.[185] In most cases of metabolic causes, chorea onset is acute to subacute and resolves with resolution of the underlying metabolic derangement. Chorea may be generalized, focal, or unilateral, and ballism has been reported.[6,186] Rarely persistent chorea after hyperglycemia has been reported.[186]

Acquired hepatocerebral degeneration (AHD) was first recognized by van Woerkem in 1914[187] and is characterized by a combination of cognitive and motor impairment in the setting of chronic liver disease not secondary to Wilson's disease.[185] It affects approximately 1% of cirrhosis patients and classically is associated with parkinsonism and cerebellar signs, though a wide variety of motor system disorders are reported including chorea.[185,188] T1 hyperintensities in the globus pallidus on MRI are universal, with abnormalities in other basal ganglia, cerebellar, and brainstem regions also being common.[185] Unfortunately, normalization of liver function with liver transplantation does not improve neurological outcomes.

VASCULAR CAUSES OF CHOREA

Stroke and intracerebral hemorrhages may be the most common cause of acquired chorea.[119] Chorea and ballism may develop acutely or as the motor deficit improves.[189] It is invariably focal or unilateral. Hemiballism is the prototypical acute stroke manifestation, and while it is classically believed to be due to involvement of the subthalamic nucleus, numerous other localizations have been identified including the cortex.[190,191] Chorea most commonly reflects vascular insults to the striatum, globus pallidus, or thalamus.[189] Both chorea and ballism from vascular insults are usually self-limited and slowly improve over time.

POLYCYTHEMIA VERA

Polycythemia vera is a myeloproliferative disorder associated with excessive erythrocyte production and complications associated with reduced peripheral oxygenation and hyperviscosity. It affects men slightly more than women, with onset usually after the age of 50. Chorea may be the presenting manifestation of illness in some patients. The underlying disease is more common in women.[192] Chorea may be focal or generalized and tends to fluctuate in severity and is responsive to treatment (e.g., phlebotomy) aimed at reducing erythrocyte levels.[193] How polycythemia results in chorea is unclear, though recent PET and SPECT imaging studies suggest reversible alterations in basal ganglia metabolism and dopaminergic function.[194]

POSTPUMP CHOREA

Postpump chorea refers to the development of chorea-athetosis or ballism within 2 weeks of cardiopulmonary bypass.[195] Chorea invariably evolves after a delay ranging from 3 to 12 days post surgery.[196] It is most commonly reported in children, affecting approximately 1% of children undergoing cardiac bypass.[196] Chorea may resolve or be persistent. Risk factors include longer bypass time, cooling to lower temperatures, and presence and duration of circulatory arrest. It has only rarely been reported in adults undergoing cardiopulmonary bypass.[197]

OTHER MISCELLANEOUS CAUSES OF CHOREA

Various other disorders affecting the central nervous system and the basal ganglia have been

associated with chorea. Rarely chorea and ballism have been reported in multiple sclerosis[198] and may follow a relapsing-remitting course with 50% of cases spontaneously resolving. Carbon-monoxide poisoning is most commonly associated with parkinsonism and dystonia but only rarely chorea.[199] Organic mercury poisoning causes parkinsonism, ataxia, visual loss, paresthesias, and chorea.[193] Perinatal hypoxic-ischemic injury may result in cerebral palsy manifest by chorea-athetosis, dystonia, and pyramidal tract dysfunction. Postnatal hypoxic-ischemic injury more commonly causes dystonia and parkinsonism.[200] Chorea may be seen in other sporadic neurodegenerative diseases but is generally not an overwhelming feature of these other diseases.

THERAPY

When possible, treatment of the underlying disorder that is responsible for the chorea is often beneficial in improving the hyperkinetic movements (e.g., correcting hyperglycemia or treating an underlying cancer in cases of paraneoplastic chorea). A decision to treat chorea should be based on a thorough understanding of the physical and social impact of the chorea on the individual patient and should be reserved for the patient where chorea is having a significant functional impact. The mainstay of pharmacological treatments for chorea is medication that modulates dopamine, either through postsynaptic dopamine blockade (haloperidol) or presynaptic dopamine depletion (tetrabenazine). Antiglutamatergic agents have also shown promise.[201]

While dopamine receptor blocking agents are widely believed to be effective in improving chorea in a variety of settings,[202–204] there are few rigorous studies evaluating this approach. Fahn conducted a crossover placebo-controlled study of the antipsychotic perphenazine in 17 patients with HD and found an appreciable improvement in chorea.[205] Despite mixed results in HD associated chorea,[204,206] antipsychotics are still widely used in the treatment of chorea.[207] Caution needs to be considered with the use of these drugs, given their propensity for causing tardive dyskinesia.

Tetrabenazine, a selective presynaptic depleter of vesicular-stored catecholamines, has shown efficacy in chorea. In double-blind randomized placebo-controlled trial in 84 subjects with HD and prominent chorea, chorea was significantly improved and the clinical global impression improved by about 25% in tetrabenazine treated patients.[208] However, tetrabenazine treatment was associated with a higher occurrence of parkinsonian features and depression, both predictable and recognizable consequences of catecholamine depletion. Such adverse effects can be managed by reduction in dosage or discontinuation of tetrabenazine, and recent analyses suggest that tetrabenazine can be used safely in this population.[209]

Amantadine, an antiviral agent and partial N-methyl-D-aspartate (NMDA) antagonist, has shown mixed results in treating chorea in randomized controlled trials,[210,211] but given its relatively benign safety profile, it may be considered in mild cases. Riluzole, a drug approved for use in amyotrophic lateral sclerosis that retards presynaptic glutamate release, was shown to have a mild beneficial effect on chorea at dosages of 200 mg/day; however, its costs and potential to cause liver function test abnormalities has limited its use.[201] A number of studies have suggested a beneficial effect of atypical antipsychotics on chorea; however, only clozapine has been subjected to rigorous assessment but with mixed results.[212] Levetiracetam showed benefit on chorea in open-label studies but has yet to be subjected to a randomized double-blind placebo-controlled study.[213,214]

Deep brain stimulation of the globus pallidus interna (GPi) is an effective approach for addressing levodopa-induced dyskinesias in Parkinson's disease,[215] and increasing evidence is suggesting its role in choreiform disorders. Various case reports and case series suggest a benefit on chorea from disease states as varied as HD,[216] chorea-acanthocytosis,[217] and cerebral palsy with chorea-athetosis.[218] Currently, this approach remains experimental yet promising and should be reserved for severe drug-resistant cases.

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Chapter 6

Tourette's Syndrome and Other Tic Disorders

Roger M. Kurlan

INTRODUCTION

Tourette's syndrome (TS) is a childhood-onset condition characterized by chronic motor and vocal tics. Tics are a heterogeneous phenomenon, taking on a variety of forms. Tics should be differentiated from other movement disorders, particularly myoclonus, dystonia, and stereotypies, as well as compulsive actions. Tourette's syndrome is the main member of a small group of primary tic disorders, but there are a variety of other conditions that can cause tics. Tourette's syndrome is now viewed as a neuropsychiatric spectrum disorder that includes attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD) and perhaps other behavioral problems in association with tics. Most patients with TS experience a lessening of tic severity as they grow into adulthood, and some patients have a

complete remission of their symptoms. Current evidence points to heightened striatal dopamine neurotransmission associated with loss of cortical inhibition of basal ganglia output as underlying TS. There is a strong genetic influence. A form of behavioral therapy, habit reversal, can help reduce tics. Most patients with tics that impair function will require pharmacotherapy. Guanfacine, tetrabenazine, and atypical and classical antipsychotics are the most commonly used drugs. Local intramuscular injections of botulinum toxin can be very effective when there are a few particularly bothersome tics. Deep brain stimulation surgery has been used for cases with severe, disabling, medication-refractory TS, but results have been mixed. A key aspect of managing TS is recognizing and appropriately treating comorbid psychiatric and behavioral conditions.

CLINICAL PHENOMENOLOGY

The Clinical Spectrum of Tics

Typical tics are considered one of the quickest of the hyperkinetic movement disorders, although tics can take on a variety of forms (Table 6–1). There are two main divisions of tic phenomenology, motor and phonic (vocal) types. A motor tic is an abrupt, usually jerky repetitive movement. A simple motor tic is an abrupt jerk or twitch, such as an eyeblink, a facial grimace, or a head jerk. There are also some variants of simple motor tics that include dystonic tics, which are slow twisting movements resembling dystonia, such as a torticollis-like neck twisting or blepharospasm, and tonic tics, which consist of isometric contractions, such as tensing abdominal, neck, or buttocks muscles. Complex motor tics are more complicated, often purposeful-looking movements like touching or tapping. Some complex motor tics are so bizarre (e.g., pulling down pants, punching walls) that they are often mistaken for a behavioral disorder.

Table 6–1 **Tic Types**

Motor Tics
Simple Motor Tics
Dystonic Tics
Tonic Tics
Complex Motor Tics
Copropraxia
Echopraxia
Phonic (Vocal) Tics
Simple Phonic Tics
Complex Phonic Tics
Coprolalia
Echolalia
Pallilalia
Sensory Tics (Premonitory Sensations)
Mental Tics
Mental Coprolalia

The second main category of tics is phonic tics (also called vocal tics). Phonic tics are noises or sounds produced by the movement of air through the mouth, nose, or throat. Under this definition then, for example, a sound produced by a tic consisting of clicking the teeth together or the snapping of fingers, would not be considered a phonic tic. Simple phonic tics include inarticulate noises and sounds such as throat clearing, sniffing, or coughing. Complex phonic tics have linguistic meaning and consist of words or partial words. An example of a complex phonic tic is coprolalia, obscene or socially inappropriate utterances, probably the most notorious feature of TS. Coprolalia occurs in only a minority of cases in reported series.[1] Some patients experience only obscene or socially inappropriate thoughts or images without any verbal expression, a phenomenon termed "mental coprolalia." This might be considered a type of mental tic. Other types of complex phonic tics are echolalia (verbal repetition of the speech of others) and pallilalia (repetition of the person's own words). There are motor tic equivalents of some of these, including copropraxia (obscene gesturing) and echopraxia (copying the actions of others). Because of the nature of some of the most common tics (eyeblinking, sniffing, snorting, coughing, throat clearing), children are often referred to ophthalmologists or allergists before properly being diagnosed with tics.

Tics are often preceded by urges or uncomfortable sensations, called sensory tics[2] or premonitory sensations,[3] usually localized at the site of the tic, and patients frequently report performing their tics in order to relieve the sensations. Related to this phenomenon, tics have been described as "unvoluntary" rather than truly involuntary, meaning there is some ability initially to voluntarily suppress their expression but the urges and sensations build until there is an irresistible impulse to release

the tics. Patients with TS tend to suppress their tics (sometimes subconsciously) in socially sensitive places like school or church, often leading to a sense of mental fatigue.

From a perspective of hyperkinetic movement disorders phenomenology, characteristics of tics are that they mimic normal coordinated movement; vary in type, intensity, time, and location; occur out of a background of normal motor activity; are not constantly present (unless extremely severe); lack rhythmicity; and are usually voluntarily suppressible at least temporarily.

Differential Diagnosis of Tics

As discussed above, tics encompass a complicated and heterogeneous clinical phenomenology, including motor and phonic types, simple and complex forms, and subtypes such as dystonic, tonic, and mental tics. It is safe to say that virtually any movement or sound the human body is capable of making can be a manifestation of a tic. This clinical complexity, on the one hand, may contribute to challenges in properly diagnosing tics, but on the other hand it may assist with properly distinguishing tics from other hyperkinetic movement disorders. For example, myoclonus or chorea can resemble the quick jerks of simple motor tics, but because simple motor tics are often accompanied by complex motor tics or phonic tics, they can be appropriately diagnosed by "the company they keep." Thus, the presence of phonic tics can allow the proper identification of body jerks as motor tics and vice versa. Thus, while diaphragmatic or respiratory muscle myoclonus or chorea can produce hiccup, cough, sigh, or other noises reminiscent of simple phonic tics, the establishment of a tic disorder diagnosis can be made by the observation of other types (e.g., complex motor, dystonic) of tics. In addition, myoclonus and chorea tend not to be repetitive in the same location, as tics are. The presence of premonitory sensations appears to be a feature of tics and not other neurological hyperkinetic movement disorders. Although voluntary suppressibility is a characteristic feature of tics, patients can sometimes suppress other types of hyperkinetic movement disorders temporarily.

While dystonic tics are slow, twisting movements resembling dystonia, compared to dystonia, dystonic tics usually occur in brief bursts of movement, are not continuous, tend to produce abnormal postures that are not as sustained, and are often associated with premonitory sensations.[4] Dystonic tics are usually accompanied by other more typical motor tics or phonic tics, thus revealing their nature. It should be noted that tics and dystonia can occur together,[4] sometimes in a familial pattern.[5]

Motor and vocal tics should be distinguished from movement abnormalities typically associated with psychiatric, cognitive, and sensory disorders (see Chapter 7). Stereotypies, which occur in patients with congenital deafness and blindness, mental retardation, autism, Rett syndrome, dementia, encephalopathies, and psychosis, are coordinated, rhythmic, repetitive, and patterned movements, postures, or vocalizations that are carried out virtually the same way over and over again. Stereotypies can be quite complex, such as walking in circles, standing-sitting, and repeating words or phrases, and some can be self-harming (e.g., skin scratching or picking, eye poking, hand biting). Compared to tics, stereotypies are characteristically more stereotyped, with the same movement (e.g., hand flapping, body or head rocking, head banging) or vocalization (e.g., yelling, moaning, hissing) occurring repeatedly for long periods of time. Patients with stereotypies will usually have signs of severe auditory or visual sensory loss, global cognitive dysfunction, or psychosis. Stereotypies are not known to have premonitory sensations and may be more difficult to suppress than tics.

Mannerisms are peculiar or unusual characteristic ways of performing a normal activity. These include things like an odd gait or a peculiar speech. Mannerisms serve to attract attention to an individual and are usually associated with schizophrenia but can be seen in normal people. Habits are repetitive, coordinated movements or sounds seen in normal individuals particularly during times of boredom, fatigue, self-consciousness, or anxiety. Common habits include foot tapping, abduction-adduction of thighs, finger drumming, thumb twiddling, popping finger joints, chewing finger nails, humming, pushing up glasses, and hair twirling. Some habits are developmental (e.g., thumb sucking) and some are socially inappropriate (e.g., nose picking, smoking). Like tics, habits are associated with stress and heightened anxiety and sometimes with fatigue. Habits are

easier to suppress, at least temporarily, than tics. Complex motor tics may be difficult to distinguish from compulsions.

Primary Tic Disorders

Primary tic disorders are considered to have a largely genetic or idiopathic etiology. The best known is TS (sometimes called Tourette's disorder), a childhood-onset condition characterized by chronic (more than 1 year) motor and vocal tics. Standard diagnostic criteria for Tourette's disorder are listed in Table 6–2.[6] Most patients with TS will have multiple types of tics that vary in type over time, coming in "waves" of different groups of tics, and varying in frequency and intensity from week to week or month to month. While tics tend to worsen during times of stress, the waxing and waning of tic severity is a characteristic of the natural history of TS, and exacerbations are not necessarily linked to any kind of emotional problems.

Some patients have only motor tics (chronic motor tic disorder), and some have only vocal tics (chronic vocal tic disorder), but because vocal tics are produced by muscle activity in the mouth, pharynx, and respiratory system, there is no real neurobiological justification for distinguishing motor and vocal tic types, which has occurred largely on a historical basis. Therefore, most clinicians consider these two conditions to represent variants of TS.

It appears that a large number of children experience tics with a short duration (less than 1 year) during the course of development. This has been categorized as transient tic disorder, and because this manifestation of tics has been hypothesized to represent normal basal ganglia synaptogenesis during brain development, the term "physiological tics" has also been used.[7] This is analogous to reported observations that infants commonly show distal chorea and that young children often have transient dystonic features as part of normal development. The 1-year time limit for transient tic disorder has been used because once tic duration exceeds this time period, children are likely to experience chronic tics (i.e., TS). If a clinician first evaluates a patient with a tic duration of less than 1 year, it is appropriate to defer the diagnosis (tic disorder, diagnosis deferred) until the transient or chronic nature of the tics can be established with a full year of observation.

The Neuropsychiatric Spectrum of Tourette's Syndrome

While TS is characterized and diagnosed by the presence of tics, the condition is now viewed as a neuropsychiatric spectrum disorder in which tics are commonly associated with features of OCD and of ADHD.[8] The combination of tics, OCD, and ADHD is often referred to as "the TS triad."[9] Family-genetic studies have suggested a familial aggregation and hereditary relationship between these three conditions.[10,11] Evidence suggests males are prone to experience tics and ADHD while females are more likely to express OCD.[10] Other psychiatric conditions that are reported to occur more frequently in children with TS compared with the general population include rage attacks, depression, bipolar disorder, impulse control problems, and anxiety, although their prevalence and the exact nature of their relationship to TS remain unclear. It is possible, for example, that some behavioral problems arise from difficulties living and coping with TS.

While OCD is one of the most common psychiatric comorbidities of TS, compulsions and complex motor tics are sometimes difficult to distinguish, particularly when the two

Table 6–2 **Diagnostic Criteria for Tourette's Disorder**

1. Both multiple motor and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently.
2. The tics occur many time a day (usually in bouts) nearly every day or intermittently throughout a period of more than 3 consecutive months.
3. The onset is before age 18 years.
4. The disturbance is not due to the direct physiological effects of a substance (e.g., stimulants) or a general medical condition (e.g., Huntington's disease or postviral encephalitis)

phenomena often coexist. In contrast to tics, compulsions are carried out in response to an obsession (e.g., repeated hand washing to prevent contamination), to ward off future harm (e.g., repeated checking of stoves and other appliances to avoid danger), to decrease anxiety, or according to certain rules. This rule-based (ritualistic) quality is characteristic of compulsions, and clinicians should ask patients about the presence or absence of such rules. Typical rules relate to order, symmetry, number of repetitions, or time of day (e.g., morning or bedtime rituals). It is quite unusual for complex motor tics to occur in the absence of simple motor tics, thus helping to identify them. The author has found that some individual actions, such as repetitive tapping or touching, may be difficult to classify as a tic or a compulsion and may have features of both. The author refers to these as "compulsive tics" or "compultics."[12]

Probably the most common behavioral comorbidity of TS is ADHD. Some tics possess qualities of impulsiveness, aggressiveness, or social inappropriateness often linked to ADHD. The author calls these "impulsive tics" or "impultics."[12] Examples include yelling out insults, punching self or others, or touching a hot stove. Reflecting the complex interrelationships between TS and its psychiatric comorbidities, there are actions that simultaneously have qualities of tics, compulsions, and impulsiveness (e.g., pushing someone after they have sneezed to prevent contamination), which can be considered "compulsive/impulsive tics."[12]

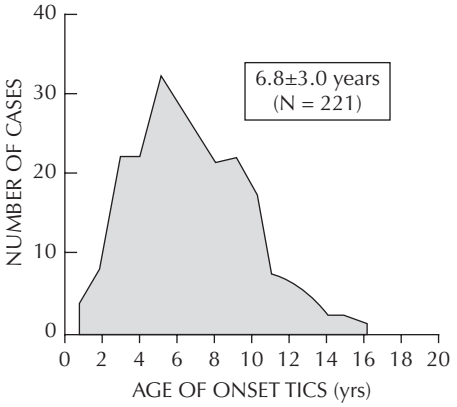

Figure 6–1. Identified ages at onset of tics in Tourette's syndrome.

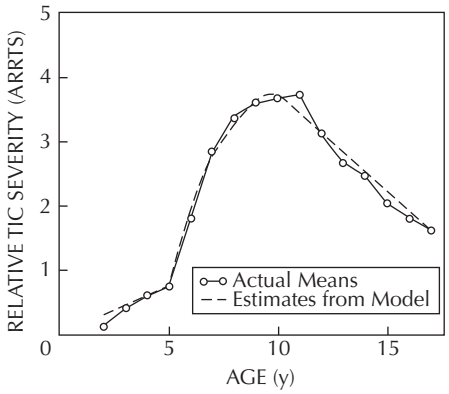

Figure 6–2. Age and relative tic severity.

Epidemiology and Natural History of Tourette's Syndrome

The prevalence of TS in children is estimated to be about 1%.[13] It appears to occur in all racial and ethnic groups. Risk factors include a positive family history (of tics, OCD, and possibly ADHD) and male gender.

Tics in TS typically have their onset in childhood, with the vast majority appearing before the age of 10. A graph of identified ages at onset in one TS center is shown in Figure 6–1. Most longitudinal and retrospective studies suggest that as children with TS grow into adolescence and adulthood, tics resolve in about one-third of cases and substantially lessen in severity in another third.[14,15] In the remainder, TS continues lifelong with no substantial reduction of symptoms. There are no known reliable predictors of the ultimate outcome. For those who do improve, tics typically begin to lessen in severity around age 12–14 (Figure 6–2) but may take until the late 20s to resolve. Careful longitudinal studies of TS are lacking, and thus information on the natural course is limited.

Secondary Tic Disorders

Aside from the primary tic disorders, a variety of other conditions can cause tics (Table 6–3). In order to achieve more homogeneity and clarity of diagnosis, the author prefers to avoid using primary tic disorder diagnoses (e.g., TS) in these settings, instead indicating that the tics are secondary to another condition. Secondary tic disorders are often evident by the presence of other

Table 6–3 **Differential Diagnosis of Tics**

Physiological Tics
Primary Tic Disorders
Tourette's Syndrome
Chronic Motor Tic Disorder
Chronic Vocal Tic Disorder
Transient Tic Disorder (physiological tics)
Secondary Tic Disorders
Brain Developmental Disorders: mental retardation, autism, Asperger's syndrome, Rett syndrome, genetic and chromosomal abnormalities, developmental stuttering
Brain Insults: head trauma, stroke, infections
Postinfectious: postencephalitis, Sydenham's chorea, PANDAS (?)
Neurodegenerative Diseases: Huntington's disease, neurodegeneration with brain iron accumulation
Systemic Illnesses: neuroacanthocytosis, Behcet's disease
Childhood Narcolepsy/Cataplexy
Peripheral Trauma
Medications: tardive tics, stimulants, antiepileptics, levodopa, antidepressants
Toxins: carbon monoxide, mercury, wasp venom
Psychogenic

N.B. PANDAS = Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infection, (?) = unsure, controversial.

neurological dysfunction in addition to tics. Since they are much less common than primary tic disorders, diagnostic assessments for secondary causes of tics in the form of blood testing or neuroimaging are generally not necessary when confronted with a child who has tics in the absence of any other significant neurological deficits.

Just like other neurological movement disorders, tics can occur following generalized or more focal (usually the basal ganglia-frontal lobe pathways) brain insults. Probably most common are the brain developmental disorders, such as mental retardation, autism, Rett syndrome, and Asperger's syndrome.[16–18] Many other genetic and chromosomal developmental disorders involving the brain have also been reported to be associated with tics.[19] In these brain developmental disorders, tics are often accompanied by stereotypies. Tics have been observed in patients with developmental stuttering.[20]

A small number of cases have been reported in which tics have been observed as a sequela of other brain disorders.[21] Head trauma, viral encephalitis, and other brain infections (*Mycoplasma pneumoniae*, Lyme disease) have been described as causes of tics. Stroke is another reported cause, particularly when localized to the basal ganglia. It has been recognized that tics often occur as part of the movement disorder of Sydenham's chorea, the presumed autoimmune manifestation of acute rheumatic fever, particularly appearing after the chorea dissipates.[22] Based on this observation, a nonrheumatic form of poststreptococcal autoimmune encephalopathy has been hypothesized and termed pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS).[23] Tics were originally proposed to be one of the key manifestations of PANDAS, although more recently this association has been downplayed because of a variety of inconsistencies and negative research studies.[24,25] At this time, the treatment of children with tic disorders with antibiotics or immune-modifying therapies based on the PANDAS hypothesis is not recommended.

Tics may accompany other neurological signs in certain neurological illnesses, many of which are discussed in this book, including Huntington's disease,[26] neurodegeneration with brain iron accumulation (formerly Hallervorden-Spatz disease),[27,28] neuroacanthocytosis,[29,30] and Behcet's disease, a chronic relapsing and remitting vasculitic disorder that is characterized by oral and genital ulcers, skin lesions, and uveitis.[31] Two patients who developed tics after peripheral trauma have been described.[32] The first experienced facial trauma followed by facial and sniffing tics, and the second suffered a neck injury followed by

neck/head turning tics. Recently, tics (facial grimaces, eyebrow raising, perioral and tongue movements) have been described as a component of a complex movement disorder associated with onset of narcolepsy and cataplexy in childhood.[33]

Like other hyperkinetic movement disorders, tics can be the long-lasting and primary manifestation of tardive dyskinesia (tardive tics), which occurs following exposure to dopamine receptor antagonist drugs such as antipsychotics and antiemetics.[34] Several medications have been reported to temporarily induce tics, including psychostimulants (amphetamines, methylphenidate, pemoline, cocaine, heroin), antiepileptics (carbamazepine, phenytoin, phenobarbital, lamotrigine), levodopa, and antidepressants. Exposure to certain environmental toxins, including carbon monoxide, mercury, and wasp venom, has been reported as a rare cause of tics.

Tics can be a manifestation of a psychogenic movement disorder, a type of conversion disorder in which intense and often subconscious psychodynamic conflicts are transformed into neurological symptoms. These have been referred to as pseudotics or psychogenic tics.[35] Like pseudoseizures, which often occur in patients with epilepsy, probably the most common group to experience psychogenic tics is patients with true tic disorders like TS. Patients embellish their TS symptoms by having pseudotics in addition to their actual tics. In the first description of psychogenic tics, patients were observed to have highly dramatic manifestations, such as falling to the floor or yelling very loudly.[35] Other potentially helpful clinical features in establishing a psychogenic etiology include being incongruent with the typical appearance of classical tics, marked accentuation with suggestion (although true tics can be suggestible) and reduction with distraction, absence of premonitory sensations, presence of other conversion symptoms or signs, associated histrionic or indifferent personality features, and evident psychodynamic problems or secondary gain (see Chapter 13).

ETIOPATHOGENESIS

While evidence suggests that a state of excessive central dopamine neurotransmission exists in TS, the fundamental cause of the illness and its neurobiological mechanisms remain poorly understood. Neuroimaging studies have reported volumetric changes in the basal ganglia and other brain regions, but the results have not been consistent. Neuroimaging has not identified increases in striatal presynaptic monoaminergic vesicles[36] or striatal dopaminergic innervation in TS patients compared with controls.[37] Family studies suggest a complex inheritance pattern in TS[38] that often includes bilineal (maternal and paternal) transmission.[39] Associations have been reported between TS and some genetic loci,[40,41] but they appear to account for only a small portion of cases. Tourette's syndrome has also been associated with recurrent exonic copy number variants (DNA deletions and duplications),[42] which appears to be involved in a variety of neurodevelopmental disorders. A popular pathophysiologic model of TS proposes that the primary functional problem in TS is failure of the cerebral cortex to appropriately suppress spontaneous, aberrant activity in the basal ganglia that generates tics[43] and is depicted graphically in Figure 6–3.

The observation that TS resolves or lessens for a substantial number of patients as they grow into adulthood suggests that the underlying mechanisms involve processes that may correct themselves as the brain matures.

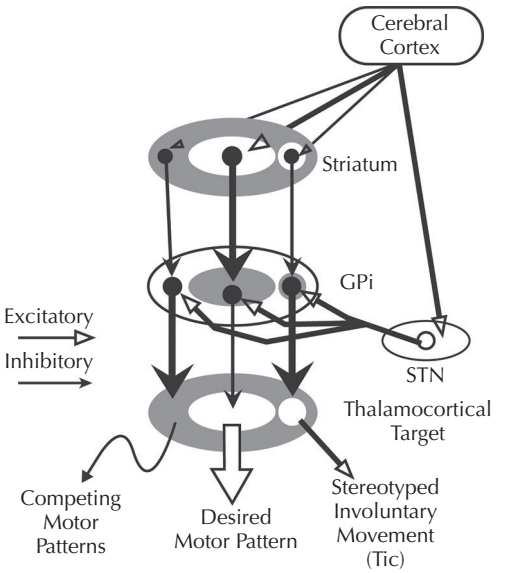

Figure 6–3. Pathophysiologic model of Tourette's syndrome.

DIAGNOSIS

For most patients presenting with tics, the diagnosis of a primary tic disorder is made clinically; neuroimaging or other laboratory testing is not necessary to make the diagnosis. Tic suppression is common in physicians' offices, and the best time to look for tics is when the patient is walking into or out of the examination room. For individuals with TS, it is important to have a high index of suspicion for the common comorbid psychiatric conditions, OCD and ADHD. Clinical rating scales, such as the Yale Brown Obsessive Compulsive Scale or the Conners Parent or Teacher ADHD Rating Scales, can be used for this purpose.

The presence of neurological abnormalities on examination in addition to tics or the onset of tics in adulthood should prompt consideration of a secondary etiology. In these cases, more extensive diagnostic evaluations may be needed.

THERAPY

For many people with TS, the tics are mild and not disabling and education about the condition and some supportive counseling are sufficient. For children, a key focus is on maintaining and strengthening self-confidence and self-esteem in the face of TS. Supportive counseling may be helpful for these purposes. Tics can be disabling by causing social embarrassment, isolation, and sometimes conflict (e.g., with verbal insults). Some tics are painful (e.g., neck jerks) and some can be self-injurious (e.g., scratching, poking). When tics are disabling, tic-suppressing therapy is indicated. General approaches to treating TS and its common comorbidities are summarized in Table 6–4.

Behavioral Therapy

Clinical trials have demonstrated tic-suppressing efficacy of a form of cognitive behavioral therapy termed habit reversal treatment, which involves training patients to self-monitor their tics and premonitory sensations and to respond to these by performing a voluntary behavior that is physically incompatible with the tic.[44] Potential shortcomings of habit reversal therapy are that it is not widely available, it is time-consuming, and its long-term benefits have not been examined. Its clinical value remains controversial, but some experts advocate trying this therapy prior to initiating medication in nonsevere cases.

Pharmacotherapy

The only FDA-approved medications for TS are the classical neuroleptic antipsychotics haloperidol and pimozide, which block D2 dopamine receptors. Their efficacy is supported by past controlled clinical trials, although these early trials utilized outcome measures that were often not standardized. Long-term tic control often requires chronic therapy (Table 6–5). In a controlled trial of patients whose tics were controlled after 1 to 3 months of pimozide therapy, those in whom therapy was withdrawn (placebo group) relapsed (required an increase in drug dosage) after a mean of 37 days compared to 231 days in patients staying on the drug.[45]

Randomized controlled trials have also supported the efficacy of the newer atypical antipsychotic risperidone for suppressing tics with similar magnitudes of benefit as the classical neuroleptics.[46,47] Observational data suggest that some of the other members of this drug class, particularly such as aripiprazole, may

Table 6–4 **Treatment Options for the TS Triad**

Tics	OCD	ADHD
Habit Reversal	Cognitive-Behavioral Therapy	Behavior Therapy
Alpha Agonists, Tetrabenazine	Selective Serotonin Reuptake Inhibitors	Alpha Agonists
Atypical Antipsychotics	Atypical Antipsychotics	Atomoxetine
Classical Neuroleptics	Deep Brain Stimulation	Methylphenidate
Botulinum Toxin		
Deep Brain Stimulation		

N.B. OCD = obsessive-compulsive disorder, ADHD = attention deficit hyperactivity disorder.

Table 6–5 **Tic-Suppressing Medications**

Medication	Daily Dose (mg)	Common Side Effects	Comments
Alpha Agonists			
Clonidine	0.05–0.5	Sedation, dizziness, headache, irritability	Oral, transdermal forms
Guanfacine	0.5–4	Sedation, dizziness, headache, irritability	Less sedation, fewer doses
Antipsychotics			
Haloperidol*	0.5–20	Sedation, depression, increased appetite, parkinsonism	
Fluphenazine	0.5–20	Sedation, depression, increased appetite, parkinsonism	
Pimozide*	0.5–10	Sedation, depression, increased appetite, parkinsonism	ECG monitoring of Q-T interval needed
Risperidone	0.5–16	Sedation, weight gain, glucose intolerance, parkinsonism	
Aripiprazole	2–30	Sedation, weight gain, glucose intolerance, parkinsonism	
Dopamine Depletor			
Tetrabenazine	12.5–100	Sedation, insomnia, depression, restlessness	Expensive, dose influenced by CYP2D6

*FDA approved for this indication.

N.B. This list is not comprehensive.

likewise lessen tics. The most frequent side effects of all of antipsychotic agents include sedation, depression, increased appetite, and parkinsonism. Fortunately, patients with TS treated with antipsychotics rarely develop tardive dyskinesia, possibly due to the underlying state of their dopamine receptors.[48] While the atypical antipsychotics have fewer motor complications, such as parkinsonism, they commonly induce weight gain and glucose intolerance (metabolic syndrome), and these risks must be taken into account when selecting therapy for patients with TS.

Although antipsychotics have documented efficacy for suppressing tics, because of their frequent side effects, other medications are often used first. Several trials have supported efficacy of the alpha-2 adrenergic drugs clonidine and guanfacine.[49,50] The magnitudes of benefit reported are generally lower than for the antipsychotics, although no head-to-head comparisons have been published. Because they also have efficacy for ADHD, the alpha agonists may be a good first-line choice for patients with both tics and ADHD. Common side effects of the alpha agonists are sedation, dizziness, headache, and irritability. Hypotension is generally not a problem, although syncope is a rare side effect. Guanfacine is usually preferred because it tends to cause less sedation and can be given once (bedtime) or twice daily compared with 3 to 4 daily doses for clonidine. A transdermal form of clonidine is available and useful for children who cannot swallow pills.

Tetrabenazine is a drug that depletes presynaptic dopamine and in case series has been reported to reduce tics.[51] Some clinicians recommend tetrabenazine as a first-line treatment for tics. No comparison trials have been performed to determine the best initial medication. The most common side effects of tetrabenazine are sedation, insomnia, restlessness, and depression. A recent small clinical trial indicated that topiramate is effective for tics.[52] There is inadequate evidence to recommend other medications suggested to lessen tics, including clonazepam, leviteracetam, dopamine agonists, and baclofen.

Although it is common practice to combine drug classes, such as an antipsychotic and an alpha agonist, in the treatment of tics, this approach has not been studied systematically.

Botulinum Toxin

Although controlled trial data are lacking, local intramuscular injections of botulinum toxin

is a therapeutic option when there are a few particularly bothersome tics. Case series indicate that botulinum toxin can reduce tics as well as associated premonitory sensations and pain.[53,54] Eye blinking, neck, and shoulder tics are the most common tics treated this way. The benefits are temporary, lasting 3 to 6 months.

Deep Brain Stimulation

Deep brain stimulation (DBS) surgical treatment has recently been used for TS patients with disabling and medication-refractory tics. The results of double-blind, crossover (with stimulation on or off) trials involving thalamic stimulation indicate that some patients can have substantial benefit.[55,56] However, the best patient selection criteria and the optimal location for the electrodes (thalamus, globus pallidus, putamen, subthalamic nucleus, and other areas have been used) in TS have not been established. Deep brain stimulation can be complicated by stroke, infection, and side effects during stimulation, such as paresthesias, visual symptoms, and dysarthria. Some patients with TS and self-harming tics/compulsions damaged the DBS equipment or caused infections by picking, scratching, or digging at it.

Treatment of Comorbidities

An important part of managing patients with TS is to treat psychiatric comorbidities appropriately. Cognitive-behavioral therapy, selective serotonin reuptake inhibitors (SSRIs; Table 6–6) and atypical antipsychotics are established therapies for OCD; DBS surgery has been shown to be effective for severe cases.

Table 6–6 **Selective Serotonin Reuptake Inhibitors**

Drug	Daily Dose (mg)
clomipramine	25–250
citalopram	10–40
escitalopram	10–20
fluoxetine	10–60
fluvoxamine	25–300
paroxetine	10–60
sertraline	25–200

N.B. The list is not comprehensive.

Because stimulants can induce tics, it had been recommended that these drugs should be avoided in children with ADHD who have tics or even a family history of tics. Randomized, blinded, and placebo-controlled trials have shown, however, that at least the stimulant methylphenidate does not exacerbate tics in children with TS and is effective in treating coexisting ADHD.[57,58] Other stimulants, such as dexedrine and mixed amphetamine salts, have not been studied similarly in patients with TS. The selective norepinephrine reuptake inhibitor atomoxetine has been shown to improve ADHD symptoms without worsening of tics in children with both conditions.[59] Medications used to treat ADHD are summarized in Table 6–7.

Table 6–7 **Medications for ADHD**

Drug (Brand Name)	Daily Dose (mg)	Doses/day
Nonstimulant		
atomoxetine (Strattera)	10–120	1
Stimulants		
methylphenidate (Ritalin)	2.5–60	2–4
methylphenidate ER (Concerta)	18–90	1
methylphenidate ER (Metadate CD)	10–60	1
D-methylphenidate (Focalin)	2.5–20	2–3
D-methylphenidate ER (Focalin XR)	5–40	1
methylphenidate transdermal (Daytrana)	10–30	1
D-,L-amphetamine (Adderall)	2.5–60	1–2
D-,L-amphetamine (Adderall XR)	5–30	1
lisdexamfetamine (Vyvanse)	30–70	1

N.B. The list is not comprehensive. ER = extended release.

Given the fact that many TS patients require treatment for both tics and comorbidities, combination therapy with tic-suppressing, anti-OCD and anti-ADHD medications is commonly employed. No formal assessments of such combination therapy have been reported.

SUMMARY

Tourette's syndrome is a common childhood-onset disorder characterized by chronic motor and vocal tics. The clinical presentation of tics can be quite heterogeneous, with a variety of tic types described. Tics must be distinguished from other hyperkinetic movement disorders, particularly myoclonus, dystonia, and stereotypies. Complex motor tics and compulsions can appear quite similar and may be difficult to distinguish. There are a number of neurological disorders in which tics occur as a secondary feature, and these should be considered in the differential diagnosis of TS. Tourette's syndrome is viewed as a neuropsychiatric spectrum disorder in which tics are often associated with ADHD, OCD, and other behavioral disturbances. The natural course of TS is such that for many patients tics improve or resolve as they grow into adulthood. Genetic factors are important in the pathogenesis of TS. Basal ganglia dysfunction with abnormalities of dopamine neurotransmission has been implicated. There appears to be a reduction in cortical inhibition and control of motor output from the basal ganglia. Habit reversal behavioral therapy can be used to suppress tics. For disabling tics, established pharmacotherapy includes guanfacine, tetrabenazine, and antipsychotic drugs. Botulinum toxin injections can be used when there are a small number of particularly problematic tics. Deep brain stimulation has been tried for very severe cases, but the results have not been consistently good. A key part of optimally managing patients with TS is to recognize and treat associated behavioral problems such as ADHD and OCD.

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Chapter 7

Habits, Mannerisms, Compulsions, and Stereotypies

Roger M. Kurlan

INTRODUCTION

There is a group of peculiar and repetitive movements that are characteristically seen in normal individuals, those with psychiatric conditions, or people with impaired mentation or sensory processing. These must be distinguished from the usual neurological hyperkinetic movement disorders. *Habits* are repetitive movements (e.g., finger drumming or leg tapping) performed by normal people when they are bored, anxious, self-conscious, or tired. Certain habits, such as thumb sucking, occur as part of normal development, and some, like smoking or nose picking, are considered dangerous or socially inappropriate. Some people carry out normal actions in a peculiar fashion (e.g., a wiggling gait, a gesture while eating, an odd word pronunciation), usually in an attempt to call attention to themselves. These are referred to as *mannerisms*. Mannerisms are particularly common in patients with schizophrenia. *Compulsions* are repetitive, often ritualistic actions carried out in response to an obsession (e.g., hand washing to avoid contamination), to reduce anxiety or to avoid a future dreaded outcome. Compulsions are part of obsessive-compulsive disorder (OCD) but can also be associated with other psychiatric and neurological conditions, particularly those linked to basal ganglia dysfunction such as Tourette's syndrome (TS). Cognitive-behavioral therapy, selective serotonin reuptake inhibitors, atypical antipsychotics, and deep brain stimulation surgery (in very severe cases) are useful therapies for compulsions. *Stereotypies*

are repetitive movements (e.g., rocking, finger wiggling) or sounds (e.g., moaning, humming) carried out by individuals with cognitive dysfunction (dementia, autism, mental retardation) or severely impaired sensory function (congenital blindness, deafness). The cause of stereotypies is unknown, but self-stimulation has been suggested and the condition has been linked to impaired dopamine neurotransmission in the brain.

The topic of this chapter is the repetitive, excessive, or peculiar movements that occur in normal individuals (habits, mannerisms) or in the setting of psychiatric (mannerisms, compulsions, stereotypies) or cognitive and higher sensory disorders (stereotypies).[1]

HABITS

Habits can be defined as repetitive, coordinated movements that are seen in otherwise normal individuals, particularly during times of boredom, fatigue, anxiety, or self-consciousness. Common examples of habits are shown in Table 7–1. It is important to recognize that some actions listed as habits might be categorized as a different type of movement disorder if they appear in a different clinical context. For example, repetitive foot tapping might represent a habit in a healthy person, a compulsion when performed in response to an obsession in a patient with OCD, a complex motor tic in a patient with TS, or a stereotypy in an autistic individual. Thus, the clinical setting is very important for the accurate interpretation of these kinds of movements that can look essentially identical.

Some habits are quite common in the course of normal development ("physiological habits"). They tend to disappear over time as the child learns that they are socially inappropriate at older ages. Finger (usually thumb) sucking, or a substituted sucking of a pacifier, blanket, or other object, has been estimated to occur in 80% of all infants and typically disappears by the age of 3 or 4 years. Occasional finger sucking, however, persists in up to 30% of 12-year-olds. If finger sucking persists in prominent form beyond the age of 9 years, it is often associated with general emotional and social immaturity. The reasons for finger sucking are unknown, but incompleteness of the sucking phase of feeding is a hypothesis supported by the observation that if feeding is interrupted before satiety in some domestic animals, sucking or licking behaviors may occur.

Nail biting is a habit that usually appears between the ages of 4 and 6 years. It is seen in 40%–55% of adolescents and declines in frequency after puberty so that only about 20% of young adults bite their nails. Pencil or pen biting or chewing gum might be substituted habits for nail biting. While finger sucking usually takes place when the child is tired or unoccupied, nail biting tends to occur during times of anxiety and stress.

Some habits are considered socially inappropriate or dangerous, such as cigarette smoking, tobacco chewing, or overeating, and may be appropriate targets for therapy.

Table 7–1 **Common Habits**

Eye rubbing
Ear rubbing, picking, pulling
Nose rubbing, scratching, picking
Thumb/finger sucking, nail biting, picking teeth
Hair, moustache, or beard rubbing, pulling, twirling
Head or chin rubbing, scratching
Fist clenching, popping finger joints, twiddling thumbs, tapping or drumming fingers, manipulating clothing, jewelry, eyeglasses
Foot tapping, abduction-adduction of legs

MANNERISMS

A mannerism is an unusual or peculiar way of performing a normal activity, such as eating, walking, or talking. Mannerisms often include odd gestures, commonly unique to an individual. The term refers to odd, idiosyncratic, or bizarre variations of normal human actions. Many normal people display a mannerism or two that can be regarded as no more than a slight eccentricity. Examples include peculiar word pronunciations, a flip of the head/hair, a wiggling gait. Mannerisms are often used to attract attention, especially in individuals who are insecure and wish to appear more confident than they are.

Patients with schizophrenia often display a variety of odd, senseless variations of normal behavior that would be considered to be mannerisms. Some examples include imitating a famous person's speech or behavior, distorted expressive gestures, and bizarre gaits, such as

lifting the legs like a stork. Schizophrenic speech may have mannerism qualities, such as telegrammatic jargon or speaking in rhyme. Mannerisms may remain constant for years or they may be changed frequently. They may be so extreme that they interfere with the underlying action.

COMPULSIONS

Compulsions are repetitive and seemingly purposeful behaviors that are typically carried out (1) to avoid future problems or a dreaded event (e.g., superstitiously checking that doors are locked to prevent death to a loved one); (2) according to specific rules (i.e., ritualistically), such as a certain number of times, in a certain order, at a certain time of day (e.g., bed time rituals), or evenly on the two sides of the body ("evening up"); or (3) in response to an obsessive thought pattern (e.g., hand washing in response to fears of contamination). Some common compulsions are listed in Table 7–2.

Obsessions are recurrent ideas, thoughts, images, or impulses that invade consciousness and are experienced as senseless or repugnant. Obsessions are generally unpleasant and may be frightening or violent. Attempts are made to ignore, resist, or suppress obsessions and compulsions. Common obsessions are listed in Table 7–3.

For individuals in whom obsessions and compulsions are the primary feature and interfere with normal functioning, the diagnosis of primary OCD is made. This is considered an anxiety disorder because obsessions lead to anxiety, which may in turn be relieved temporarily by the performance of the compulsions. The cycle then repeats itself. First symptoms of OCD can occur in childhood and usually by the early 20s. Onset of OCD may be sudden or gradual, and the condition often has an episodic course. Obsessive-compulsive features can also occur secondarily to other psychiatric conditions, such as major depression and schizophrenia.

Table 7–2 **Common Compulsions**

Checking (doors, locks, appliances)
Ordering, arranging, counting
Evening up
Hoarding, collecting
Excessive hand washing, showering, bathing, grooming
Excessive cleaning
Measures to remove contact with contaminants
Measures to prevent harm to self or others
Rituals (in/out door, up/down from chair, etc.)
Repeated touching

Table 7–3 **Common Obsessions**

Symmetry, order, exactness
Concern with dirt, germs
Disgust for urine, stool, saliva
Religious scrupulosity
Thoughts or images of something terrible happening to self/others (death/illness, fire, accident, etc.)
Lucky or unlucky numbers
Fear of harming self or others
Forbidden, aggressive, or perverse sexual thoughts, images, or impulses

As mentioned in Chapter 6, there is a clear interrelationship between OCD and tics. It has been estimated that 17% of adults with OCD have tics, and an increased rates of tics is found in their relatives.[2] About half of individuals with TS experience obsessive-compulsive features,[3] and an increased prevalence of OCD has been identified in first-degree relatives of TS patients, independent of concurrent OCD in the TS probands.[4] It has been suggested that there are different subtypes of OCD, with one form that is tic related.[5,6] Studies suggest that the specific types of obsessions and compulsions differ when associated with TS compared to primary OCD. Mental play (e.g., counting ceiling tiles), echophenomena, symmetry, touching, self-injurious aggressive, and violent symptoms are more common in individuals with tics, while contamination obsessions, washing behaviors, ordering, and hoarding are seen more often in patients with primary OCD.

Compulsions are sometimes difficult to distinguish from complex motor tics, especially because the two conditions commonly coexist. The following characteristics of compulsions can be helpful in making the distinction. Compulsions tend to occur in association with obsessions and are often performed in response to obsessive thoughts. Compulsions are often carried out in a ritualistic fashion, being linked to certain rules (e.g., number of times, order, symmetry), while tics are not. Also, compulsions are often done to ward off future harm while tics are not. Finally, tics generally

Table 7–4 **SSRI Medications for OCD**

Generic Name	Brand Name	Usual Daily Dose (mg)
Clomipramine	Anafranil	25–250
Citalopram	Celexa	10–40
Escitalopram	Lexapro	10–20
Fluoxetine	Prozac	10–60
Fluvoxamine	Luvox	25–300
Paroxetine	Paxil	10–60
Sertraline	Zoloft	25–200

N.B. SSRI = selective serotonin reuptake inhibitor.

respond to dopamine antagonist medications, while compulsions characteristically improve following selective serotonin reuptake inhibitor (SSRI) therapy.

In addition to tics, obsessive-compulsive symptoms occur in association with other movement disorders, including Sydenham's chorea, pediatric neuropsychiatric disorders associated with streptococcal infection (PANDAS), Huntington's disease, dystonia, and Parkinson's disease, suggesting that basal ganglia dysfunction can cause OCD. Psychosurgical procedures (including anterior capsulotomy and cingulotomy and deep brain stimulation involving the nucleus accumbens) that alter basal ganglia-frontal lobe connections have been used successfully to treat severe, disabling OCD, further evidence of this anatomic localization.

Disturbances of central serotonergic systems are thought to occur in OCD and SSRIs are the most predictably effective medications (Table 7–4). Atypical antipsychotic drugs (e.g., risperidone, aripiprazole) can be added for resistant cases. Cognitive-behavioral therapy is often effective for OCD and should be considered as first-line therapy, prior to the initiation of drug treatment.

STEREOTYPIES

A recent review of this topic presented the following definition of stereotypy: a non-goal-directed movement pattern that is repeated continuously for a period of time in the same form and on multiple occasions and which is typically distractible.[7] This definition is incomplete, because stereotypies may be expressed as repetitive vocalizations as well as movements. Moreover, stereotypies tend to occur in individuals with defective mentation or deprived of visual or auditory sensory input. Similar to tics, stereotypies can consist of simple (e.g., grinning, staring) and complex (e.g., rocking, head shaking, walking in circles) movements and simple (e.g., moaning, humming) and complex (e.g., words, phrases, sentences) vocalizations. Also like tics, stereotypies can be obscene (e.g., lewd words or phrases) or self-injurious (e.g., head banging, biting, scratching). Compared to tics, stereotypies are longer lasting, tend to be the same type over and over again, and occur in the specific settings of cognitive/mental impairment or sensory deprivation. Stereotypies are generally considered to be involuntary and non-goal-directed. However, because these behaviors are often seen in individuals with severe cognitive dysfunction, the true intentional quality of stereotypies cannot be accurately assessed. Indeed, it has been suggested that stereotypies might be voluntary, serving as a form of self-stimulation. In individuals without severe mental impairment, stereotypies can be temporarily suppressed at will. Stereotypies often decrease in these individuals when they are engaged in activities such as drawing or counting. Common stereotypies are listed in Table 7–5 and conditions in which stereotypies occur are listed in Table 7–6.

Stereotypies often occur in patients with mental retardation. One study involving 102 institutionalized mentally retarded adults found that 34% demonstrated at least one type of stereotypy, including rhythmic movements (26%), bizarre posturing (13%), and object manipulation (7%).[8] There is an inverse correlation between stereotypies and IQ, but stereotypies do occur in individuals with mild mental retardation.[9]

Table 7–5 **Common Stereotypies**

Staring at flickering light, smelling objects
Bruxism, lip movements, biting, grimacing, smiling
Vocalizations (e.g., moaning, hissing, humming, blowing, snorting, yelling, singing)
Head banging, nodding, shaking, posturing
Finger waving, waving objects, arm flapping, finger flicking, drumming, hand rubbing, stroking, fist pounding, feeling objects
Body rocking, twirling, circling, sitting/arising
Jumping, hopping, walking back and forth or in circles
Lip or hand biting, eye poking or gouging, self-scratching or -hitting

Table 7–6 **Conditions Associated With Stereotypies**

Mental retardation
Autism, pervasive developmental disorder, Rett syndrome
Dementia
Neuroacanthocytosis
Childhood encephalopathies (e.g., viral, ceroid lipofuscinosis, phenylketonuria, Lesch-Nyhan syndrome)
Schizophrenia
Severe agitated depression
Akathisia (drug-induced)
Tardive dyskinesia
Congenital blindness and deafness
Developmental (physiologic)

Stereotypies may be the most recognizable feature of children and adults with autism.[10] These often include what has been interpreted as self-stimulatory behaviors such as body rocking, finger wiggling, and humming. Rett syndrome is a form of autism appearing in girls and is due to a mutation in the MECP2 gene at Xq28. It is characterized by the presence of hand-wringing stereotypies, although other types can occur as well.[11] Stereotypic self-injurious behavior, such as self-hitting or scratching, can be seen in mental retardation or autism. While head banging and some other self-injurious behaviors can occur in normal children, this type of behavior is usually abnormal. Stereotypies can also be seen in children with pervasive developmental disorder (Asperger's syndrome), often considered a milder form of autism.

Encephalopathy caused by phenylketonuria, infantile ceroid lipofuscinosis (hand "knitting" stereotypies), Lesch-Nyhan syndrome (self-injurious stereotypies), or prenatal viral encephalitis can lead to an autistic syndrome with stereotypies in childhood. In adults, stereotypies are seen in patients with dementia, including Alzheimer's disease and frontotemporal dementia.[12]

Schizophrenia is another condition in which stereotypies can occur. Stereotypies are particul arly characteristic of the catatonic form of the illness. Stereotypic maintenance of unusual postures, shifting position, tapping and touching objects, and repetitive verbalizations are typical features of the catatonic state. The particularly strange stereotypic behavior seen in catatonic and other severe psychiatric disorders have been described under a variety of terms, such as "bizarrery," "grotesquery," and "parakinesia." Some patients with severe, agitated depression demonstrate stereotypic behaviors such as moaning or walking back and forth or in circles. The same behavior can be seen as part of drug-induced akathisia (motor restlessness).

Individuals with congenital deafness and blindness may exhibit stereotypies. Compared with patients with autism, these stereotypies are generally less bizarre and less repetitive, although they may appear similar. Common examples in individuals with congenital visual or hearing loss are body or head rocking/rolling. The stereotypies of deaf children are usually accompanied by noises, while those of blind children are not.

At least some stereotyped behavior, such as sucking and clasping, are part of normal neonatal development and function to maintain close contact with the mother. These stereotyped behaviors associated with normal infant development are typically present from birth and appear to peak around 24 months of age, eventually disappearing.[13–16] With development beyond infancy, other stereotyped activities often occur, such as bruxism, body rocking, and head banging (seen in up to 15% of normal children). It has been reported that these repetitive movements are typically replaced in normally developing children by more complex repetitive behaviors linked to an insistence on sameness and ritual with regard to daily activities as well as to ordering objects.[16] Thus, they may represent precursors of obsessive-compulsiveness.[17] Stereotypies (e.g., hand flapping) can also be observed in otherwise normal children, often during times of emotional excitement.[18] All of these stereotypies associated with normal human development might be considered forms of "physiological" or "developmental" stereotypy.

Some clinicians have classified the typical orolingual-masticatory movements of tardive dyskinesia as a form of stereotypy (tardive stereotypies) because they are more patterned and more predictable than alternative nosologies such as chorea. Since antipsychotic drugs are known to produce all known types of involuntary movement disorders as part of tardive dyskinesia, it is not surprising that stereotypies might result as well. Patients with neuroacanthocytosis may develop orolingual stereotypic

movements similar to tardive dyskinesia and sometimes including self-injurious actions such as biting lips or tongue. In this situation, patients may be unable to keep food in their mouth.

Developmental and behavioral theories have been presented to explain the development of stereotypies in man. It has been proposed that social isolation might be a key factor in converting normal developmental stereotypic behavior into chronic stereotypies. In this view, autism, mental retardation, dementia, encephalopathy, and congenital deafness and blindness lead to stereotypies because they are each a form of mental or sensory deprivation and isolation. This process has been demonstrated in nonhuman primates and other animals that are isolated during development.[19,20] An extension of this theory is that when an individual is isolated, stereotypies represent attempts by the person to increase self-stimulation, perhaps to a predetermined level. Alternatively, others have argued that stereotypies occur as attempts to block out or decrease what is interpreted as an overstimulating environment, being a motor expression of underlying tension and anxiety. A behavioral theory suggests that stereotypies begin as normal behaviors that are later reinforced and shaped by operant conditioning.

Most studies of stereotypic behavior in animals have focused on the importance of dopamine pathways in the basal ganglia and limbic system. In rats, intrastriatal administration of dopamine and systemic delivery of dopaminergic medications, such as apomorphine or amphetamine, both produce dose-related stereotypic behaviors that can be prevented by pretreatment with dopamine receptor antagonist drugs. In vivo microdialysis in rats has shown a close correlation between striatal extracellular release of dopamine and serotonin and amphetamine-induced stereotypic behavior. Studies examining dopamine receptor subtypes indicate that D2 receptors mediate stereotypic behavior in animals and that activation of D1 receptors potentiates these effects. Brain neuropeptides, such as neurotensin, cholecystokinin, and opioids, particularly in limbic sites, have been implicated as well. It is important to keep in mind that the direct relevance of animal behavior to human stereotypies remains unknown. Furthermore, the term "stereotypy" is sometimes used in the animal research literature to describe behaviors that are not clearly stereotypic as seen in humans.

Some studies have suggested that stereotypies may interfere with learning in children with autism. This raises the possibility that suppressing sterotypies medically might facilitate learning. Antipsychotic dopamine and serotonin blocking medications, such as risperidone, have been used to decrease stereotypic behavior in children with autism, particularly when self-injurious.[21] The potential benefits of treatment, however, must be weighed against the common side effects of such medications, such as sedation, depression, and weight gain.

SUMMARY

This chapter reviewed abnormalities and peculiarities of movement that are not typically viewed as classical neurological hyperkinetic movement disorders. Habits are seen in normal individuals as part of the process of development or at times of anxiety or boredom. Mannerisms are strange or bizarre ways of carrying out normal activities and are seen in normal individuals as a form of attention seeking or in patients with schizophrenia. Compulsions are repetitive actions that are linked to obsessions and are commonly rule-bound (ritualistic). Compulsions are associated with disorders of the basal ganglia and are often responsive to treatment with cognitive-behavioral therapy or SSRIs. Stereotypies are highly repetitive, prolonged movements and noises that have many similarities to tics and occur in individuals with impaired cognitive or sensory processing. The underlying mechanisms of stereotypies remain unclear, but basal ganglia dysfunction and abnormalities of dopamine neurotransmission have been implicated.

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Chapter 8

Myoclonus and Asterixis

Paul E. Greene

HISTORY AND CLASSIFICATION

Myoclonus is usually defined as brief shocklike muscle contractions. A patient with multifocal myoclonus was described in 1881 by Nikolaus Friedreich, who coined the term "paramyoclonus multiplex" in the same year to distinguish it from seizures.[1] Negative myoclonus was not recognized until much later: in 1949 Raymond Adams and Joseph Foley described "almost rhythmical" tremor in patients with hepatic encephalopathy and in 1953 identified the cause as sudden pauses in muscle activity causing loss of tone or asterixis.[1] The term "negative myoclonus" was introduced in 1976 by Shahani and Young in describing the interruptions in voluntary muscle activity in posthypoxic intention myoclonus.[2] Myoclonus is extremely varied in its etiology and clinical features and the classification of myoclonus reflects this (Table 8–1). The categories of myoclonus sometimes overlap, as described below. For example, focal myoclonus may result from epileptic-associated or nonepileptic processes, and segmental myoclonus can originate either in the spinal cord or brainstem.

PHENOMENOLOGY AND ETIOLOGY

Although myoclonus syndromes can be extremely complicated, the pattern of myoclonus often gives a clue as to the etiology, so it is

Table 8–1 **Classification of Myoclonus**

Positive or negative
Etiology
- Physiologic—part of normal physiology
- Essential—not associated with a known disease
- Pathological
  - Associated with epilepsy
  - Nonepileptic

Site of origin in the central nervous system
- Cerebral cortex
- Basal ganglia
- Brainstem
  - Reticular reflex myoclonus
  - Rhythmic brainstem myoclonus
- Spinal cord
  - Segmental
  - Propriospinal
- Peripheral nerves

Distribution in the body
- Focal
- Multifocal
- Segmental
- Generalized

Eliciting stimulus
- Spontaneous
- Postural
- Action

Intention
- Reflex evoked

Pattern
- Rhythmic
- Nonrhythmic

reasonable to segregate the various etiologies of myoclonus with their most typical patterns.

Negative myoclonus or asterixis is generally defined as sudden onset of a brief cessation of muscle contraction. This can occur in the setting of positive myoclonus of most etiologies, although it seems especially common in posthypoxic myoclonus and metabolic encephalopathies. Negative myoclonus of cortical origin in the setting of seizures is usually time-locked to epileptiform discharges, lasts from 100 msec to 400 msec and is not preceded by positive myoclonus (Figure 8–1). Cortical negative myoclonus not associated with seizures is often preceded by a positive myoclonic jerk. Negative myoclonus has been reported from thalamic (most commonly ventral lateral and posterior) and parietal lesions, but also rarely from lesions in multiple other parts of the brain: internal capsule, frontal cortex, cerebellum, and midbrain.[2] This is usually focal or unilateral but can be bilateral. Negative myoclonus can consist of single episodes or semirhythmic events or can occur so frequently it resembles tremor. Almost every form of pathology has been associated with asterixis: vascular, trauma, tumor, and inflammation. The symptoms associated with negative myoclonus stem from the loss of muscle tone: dropping objects, breaks in vocalizations, and falling.

There has been speculation that negative myoclonus arises from sudden brief excitation of inhibitory neurons, but there is no direct evidence for that. Stimulation of the cortex by transcortical magnetic stimulation is unable to elicit a muscle contraction during an episode of negative myoclonus, but this could come either from inhibitory activity in the cortex or excitatory activity that activates inhibitory neurons at a lower level.[2]

Positive myoclonus is generally defined clinically as an extremely brief muscle contraction. It can originate in multiple levels of the nervous system: cerebral cortex, subcortical nuclei, brainstem, spinal cord, and peripheral nerves. The rapid contraction can often be detected clinically, but myoclonus is a movement disorder sign for which electrophysiologic testing usually provides the definitive diagnosis. Most myoclonic contractions last 50–70 msec, which is too brief for most people to imitate,

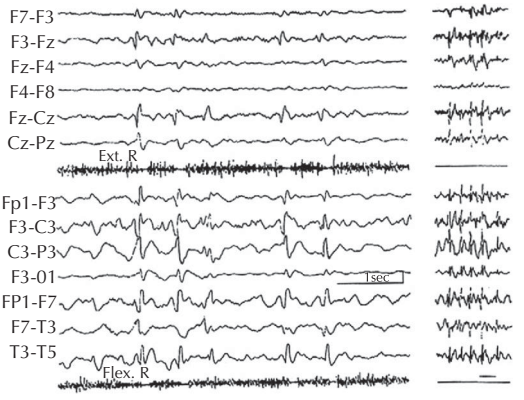

Figure 8–1. Epileptic negative myoclonus. EEG/EMG in a patient with epileptic negative myoclonus. On the left, cortical spikes are followed by brief interruptions in ongoing muscle activity in the right wrist extensor (Ext R) and right wrist flexor (Flex R). On the right, with the muscle at rest, there is no muscle correlate with cortical spikes. (From: Rubboli G, Tassinari CA. Negative myoclonus: an overview of its clinical features, pathophysiological mechanisms, and management. Neurophysiol Clin 2006;36:337–343. Figure 2.)

although in small muscles there are some individuals that can voluntarily produce such contractions. There are also muscle jerks generally considered myoclonus that last longer than 100 msec. It may be more useful clinically to think of myoclonus as a muscle contraction where the time to peak contraction is extremely fast even if the duration of contraction is 100 msec or longer.

Physiologic Myoclonus

Startle, hiccup, benign sleep myoclonus of infancy, and hypnic jerks are examples of physiologic myoclonus. Physiologic myoclonus usually does not need treatment, but exaggerated or prolonged forms may (see "Exaggerated Startle" and "Chronic Hiccup" below). Sleep myoclonus is unusual in that there is evidence it originates in the cervical spinal cord, at least in some cases, see Figure 8–2.[3] All other forms of myoclonus may be considered pathological.

Cortical Myoclonus

Almost any condition that can produce seizures may produce cortical myoclonus, and vice versa. For diseases causing progressive cortical myoclonus, there is sometimes a combination of myoclonus, seizures, dementia, and ataxia in various combinations. The traditional classification for such conditions has evolved gradually after much debate, since diseases can sometimes present with severe myoclonus and sometimes with severe epilepsy. Current classification divides these syndromes according to whether seizures or myoclonus are the main feature: progressive myoclonus ataxia (PMA), where myoclonus (and ataxia) predominate, and progressive myoclonus epilepsy (PME), where seizures predominate.

CORTICAL MYOCLONUS ASSOCIATED WITH EPILEPSY

Occasional myoclonic jerks are common in the setting of epilepsy, both myoclonic and nonmyoclonic. These are conditions in which seizures usually (although not always) predominate. There are many PME syndromes, but I will focus on conditions where the predominant feature is myoclonus and not epilepsy. There are many causes of PME, including potentially treatable celiac disease and other autoimmune diseases.[4,5] However, the main ones are Unverricht-Lundborg's disease (EPM1), Lafora body disease (EPM2), neuronal ceroid lipofuscinosis, sialidosis and other storage diseases, DRPLA (dentatorubropallidoluysian atrophy), and mitochondrial diseases such as MERRF (myoclonic epilepsy with ragged red fibers). For details about the common causes, see references 6–8. There are two conditions in this category with special relevance to movement disorders: epilepsia partialis continua (EPC), which may be mistaken for segmental myoclonus, and familial cortical myoclonic tremor with

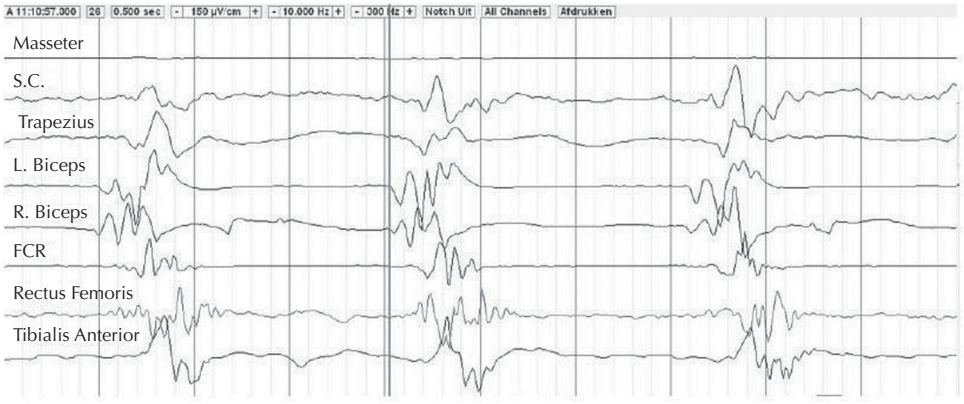

Figure 8–2. Benign sleep myoclonus. EMG recording in an infant with benign sleep myoclonus showing initial contraction in the left and right biceps, spreading caudally to the flexor carpi radialis (FCR), the rectus femoris, and the tibialis anterior and rostrally to the trapezius, the sternocleidomastoid (SC), and the masseter. (From: Fokke C, Fock JM, Brouwer OF, Elting JWJ. Benign neonatal sleep myoclonus: a case with a spinal generator? Neurology 2011;77;1308–1309.)

epilepsy (FCMTE), which often starts with myoclonus that looks like tremor.

Epilepsia Partialis Continua

This is a form of persistent focal motor epilepsy with different causes in children and adults. The most common causes in adults are hyperglycemia and stroke, and the condition either improves spontaneously or often can be treated with anticonvulsants.[9] In children, it is more malignant, often resulting from inflammatory disease or Rasmussen's encephalitis—which may be an inflammatory disease.[10] When immunosuppression is not effective, treatment is difficult to impossible and hemispherectomy has been used with variable results.[11] When limited to the face, the phenomenology of EPC is indistinguishable from that of hemifacial spasm (HFS) except that the masseters are never involved in HFS and frequently involved in EPC.

Familial Cortical Myoclonic Tremor With Epilepsy

This is a hereditary condition that combines myoclonus resembling essential tremor (ET) and seizures. This syndrome has multiple names in the literature (benign adult familial myoclonic epilepsy, BAFME; familial adult myoclonic epilepsy, FAME) and may present either with seizures or with a myoclonic "tremor."[12] Although there is some variation, patients usually develop a fine 7- to 15-Hz postural and action tremor in their 20s (but the age at onset ranges from 10 years to 60 years) and then later develop seizures. The seizures are usually generalized but may be partial complex or myoclonic seizures. The myoclonus mimicking tremor may involve other body parts including neck and lower limbs, and there may be occasional obvious myoclonic jerks. Cognitive impairment can occur but is not universal. Most cases have had autosomal dominant inheritance, and linkage has been found to loci on chromosomes 2p (FCMTE2), 5p (FCMTE3), and 8q (FCMTE1), but no gene has yet been identified.[12,13] A family was identified with autosomal recessive FCMTE probably due to a mutation in the CNTN2 gene producing contactin 2 necessary for voltage-gated potassium channels.[14] Because the features of this syndrome are complex and few families have been identified, there was some question as to whether this autosomal recessive family did have the FCMTE syndrome.[15,16] In patients in one family, there were cerebellar abnormalities (without cerebellar symptoms), and a few patients in multiple families developed dementia and parkinsonian gait in old age with evidence of dopaminergic deficit.[17–19] The significance of these observations is not known.

CORTICAL MYOCLONUS NOT ASSOCIATED WITH EPILEPSY

These are syndromes where seizures usually do not occur or are not usually the major clinical problem. The pattern of myoclonus is usually focal or multifocal, although generalized myoclonus is possible (but probably rare) if there is spread of signal across the corpus callosum.[20] When multifocal, the contractions are not synchronous. Other cortical deficits are common but not inevitable. The myoclonus is often stimulus sensitive, triggered by rapid movement of a limb or by eliciting deep tendon reflexes. The muscle contractions are very brief, usually under 50 msec. The etiology of cortical, nonepileptic myoclonus involves virtually every class of brain insult: vascular disease, tumors, toxins, trauma, and neurodegenerative diseases.[21] A partial list is in Table 8–2. I will discuss a few of these in detail.

Progressive Dementia/Encephalitis With Myoclonus

Dementia and encephalitis of every sort are commonly associated with myoclonus and potential seizures—see Table 8–2. In most cases, the co-occurrence of cognitive impairment and myoclonus is of little diagnostic or therapeutic implication. There are some exceptions:

Creutzfeldt-Jakob Disease

Virtually any pattern of cortical myoclonus may occur in CJD: rhythmic or nonrhythmic, generalized or focal, spontaneous or stimulus evoked.[21] The disease is generally divided into three broad categories: inherited, sporadic, and acquired, although symptoms and pathology may overlap. The clinical features depend on multiple factors: (1) whether there is a methionine or valine at codon 129 of PRNP, the gene for the prion protein; (2)

Table 8–2 Etiology of Myoclonus

I. Epileptic myoclonus (seizures dominate)
A. Fragments of epilepsy
- Isolated epileptic myoclonic jerks
- Epilepsia partialis continua
- Idiopathic stimulus-sensitive myoclonus
- Photosensitive myoclonus
- Myoclonic absences in petit mal epilepsy

B. Childhood myoclonic epilepsy
- Infantile spasms
- Myoclonic astatic epilepsy (Lennox-Gastaut)
- Cryptogenic myoclonus epilepsy (Aicardi)
- Awakening myoclonus epilepsy of Janz (juvenile myoclonic epilepsy)

C. Benign familial myoclonic epilepsy (Rabot)
D. Progressive myoclonus epilepsy

II. Nonepileptic myoclonus (progressive or static)
A. Storage disease
- Lafora body disease
- GM2 gangliosidosis (late infantile, juvenile)
- Tay-Sachs disease
- Gaucher's disease (noninfantile neuronopathic form)
- Krabbe's leukodystrophy
- Ceroid-lipofuscinosis (Batten)
- Sialidosis (cherry-red spot) (types 1 and 2)

B. Spinocerebellar degenerations
- Ramsay-Hunt syndrome
- Friedreich's ataxia
- Ataxia-telangiectasia

C. Other spinocerebellar degenerations
- Basal ganglia degenerations
- Wilson's disease
- Torsion dystonia
- Neuronal degeneration with iron accumulation syndromes
- Progressive supranuclear palsy
- Huntington's disease
- Parkinson's disease
- Multisystem atrophy
- Corticobasal degeneration
- Dentatorubropallidoluysian atrophy

D. Dementias
- Creutzfeldt-Jakob disease
- Alzheimer's disease
- Dementia with Lewy bodies
- Frontotemporal dementia
- Rett syndrome

E. Infectious or postinfectious
- Subacute sclerosing panencephalitis
- Encephalitis lethargica
- Arbovirus encephalitis
- Herpes simplex encephalitis
- Human T-lymphotropic virus I
- HIV
- Postinfectious encephalitis
- Miscellaneous bacteria (streptococcus, clostridium, other)
- Malaria
- Syphilis
- Cryptococcus
- Lyme disease
- Progressive multifocal leukoencephalopathy

F. Metabolic
- Hyperthyroidism
- Hepatic failure
- Renal failure
- Dialysis syndrome
- Hyponatremia
- Hypoglycemia
- Nonketotic hyperglycemia
- Multiple carboxylase deficiency
- Biotin deficiency
- Mitochondrial dysfunction
- Hypoxia
- Metabolic alkalosis
- Vitamin E deficiency

G. Toxic and drug-induced syndromes
H. Physical encephalopathies
- Post hypoxia (Lance-Adams)
- Posttraumatic
- Heat stroke
- Electric shock
- Decompression injury

I. Focal nervous system damage
- CNS
  - Post stroke
  - Post thalamotomy
  - Tumor
  - Trauma
  - Inflammation (e.g., multiple sclerosis)
  - Moebius syndrome
  - Developmental
  - Idiopathic
- Peripheral nervous system
  - Trauma
  - Hematoma

J. Malabsorption
- Celiac disease
- Whipple's disease

K. Eosinophilia-myalgia syndrome
L. Paraneoplastic encephalopathies
M. Opsoclonus-myoclonus syndrome
- Idiopathic
- Paraneoplastic
- Infectious
- Other

N. Exaggerated startle syndrome
- Hereditary
- Sporadic

O. Hashimoto's encephalopathy
P. Multiple system degenerations
- Allgrove syndrome
- DiGeorge syndrome
- Membranous lipodystrophy

Q. Unknown
- Familial
- Sporadic

Modified from: Caviness JN, Brown P. Myoclonus: current concepts and recent advances. Lancet Neurol 2004;3:598–607.

whether there is variant 1, 2 or variants that are sensitive to protease in the prior protein; (3) the particular mutations causing the genetic forms of CJD.[22] The inherited form usually progresses over years; may begin with ataxia, spasticity, dementia, insomnia, or even parkinsonism; and is less likely to have myoclonus. The acquired forms, especially the variant CJD associated with bovine spongiform encephalopathy, usually begin with psychiatric disturbance and progress more slowly than sporadic CJD, although not as slowly as most inherited variants. The most common form of sporadic CJD begins with dementia, includes myoclonus at some stage, and progresses to severe dementia and death over a few months to about 1 year (see Table 8–3). In any category, when the dementia progresses slowly, myoclonus may be present later in the course or not at all.[23] When present, periodic generalized myoclonic jerks 1–2 per second and an EEG pattern of periodic generalized sharp waves strongly suggests this diagnosis. Even without periodic myoclonic jerks, any dementia with myoclonus that progresses to loss of independence in months deserves consideration of CJD. Some of the myoclonus in CJD is probably of subcortical origin.[21]

Cortical-Basal Ganglionic Degeneration, Other Parkinson-Plus Syndromes, and Parkinson's Disease

Cortical-basal ganglionic degeneration (CBGD) combines parkinsonism with focal cortical deficits, such as apraxia, agnosia, expressive aphasia, myoclonus, and rarely hemiparesis. In the original presentation, patients had levodopa-unresponsive parkinsonism with severe, fixed unilateral dystonia and effortful speech, but it became clear that clinical presentations are varied, including dementia with minimal parkinsonism and no dystonia. Patients with CBGD may develop spontaneous, rhythmic, focal cortical myoclonus, usually of an arm or a leg—see Figure 8–3.[24] This is usually on the more affected side of the body (which may also be dystonic) and can improve with clonazepam. When this kind of myoclonus is combined with parkinsonism, CBGD is the likely diagnosis. A syndrome similar to CBGD can result from progressive supranuclear palsy (PSP), Alzheimer's disease, frontotemporal dementia, and other conditions, and some now use a category of cortical-basal syndrome (CBS) to encompass all these diseases when they produce asymmetric, levodopa-unresponsive, hemidystonic parkinsonism. It is not clear whether myoclonus at rest can be present in CBS from these other conditions. Most forms of parkinsonism can include postural and action myoclonus of cortical origin (even in the absence of seizures), including diffuse Lewy body disease, Parkinson's disease dementia, multiple system atrophy, CBGD, most of the conditions that produce CBS, and even Parkinson's disease itself.[24,25] Usually, this produces an irregular, high-frequency, small-amplitude myoclonus that is easily confused with tremor, although occasional clear myoclonus jerks may be superimposed. This myoclonus is usually positive, but cases of negative myoclonus masquerading as tremor have also been documented—see Figure 8–4. In addition to the underlying disease, action myoclonus can be a side effect of amantadine and most other anti-Parkinson medications, including levodopa.[24]

Progressive Myoclonus Ataxia

As noted above, PMA is a syndrome that combines myoclonus, ataxia, rare seizures, and a variety of other signs and symptoms, including progressive cognitive impairment and dystonia, in which myoclonus is often the most obvious sign. Myoclonus and ataxia are the usual presenting symptoms. The myoclonus may have almost any distribution, multifocal, segmental, or generalized. It can be present at rest, is usually increased with action and intention (mimicking dysmetria), and can be triggered by sensory stimuli. In a majority of cases the myoclonus is cortical in origin.[21] There is some evidence that the focal reflex myoclonus may be subcortical in origin in some cases.[26] The syndrome may be inherited or sporadic. In about 40% of sporadic cases no diagnosis can be made even with extensive testing.[21] The more common identified causes for PMA include sialidosis, Unverricht-Lundborg disease (Baltic myoclonus), mitochondrial disorders, neuronal ceroid lipofuscinosis, CJD, progressive multifocal leukoencephalopathy, Friedreich's ataxia, DRPLA, and some spinocerebellar ataxias (SCAs, most prominently SCA14).[21,27] Rare causes continue to emerge. A mutation was identified in the gene for Golgi

Table 8–3 **Signs and Symptoms in Sporadic Creutzfeldt-Jakob Disease**

	sCJD Cognitive Type			sCJD Ataxic Type		sCJD (All Subtypes)
	MM1/MV1	MM2	VV1*	VV2† (n = 103)	MV2 (n = 85)	(n = 515)
Age at onset (years)	66 (42–91)	66 (49–82)	43 (19–71)	64 (41–83)	62 (40–81)	64 (19–91)
Duration (months)‡	4 (1–24)	14 (3–24)	19 (4–72)	6 (3–18)	17 (4–43)	8 (1–72)
Presentation						
Cognitive decline	192/273 (70%)	23/23 (100%)	26/27 (96%)	28/96 (29%)	20/27 (74%)	289/446 (65%)
Ataxia	106/273 (39%)	3/23 (13%)	0/27	94/96 (98%)	22/27 (81%)	225/446 (50%)
Psychiatric	63/273 (23%)	2/23 (9%)	9/27 (33%)	10/96 (10%)	9/27 (33%)	93/446 (20%)
Visual signs	74/273 (27%)	0/23	0/27	3/96 (3%)	0/27	77/446 (17%)
Aphasia	63/273 (23%)	7/22 (32%)	1/27 (4%)	2/96 (2%)	3/27 (11%)	76/445 (17%)
Advanced stage						
Cognitive decline	257/277 (93%)	18/18 (100%)	27/27 (100%)	47/47 (100%)	53/53 (100%)	402/422 (95%)
Ataxia	147/277 (53%)	8/18 (44%)	6/12 (50%)	47/47 (100%)	53/53 (100%)	261/407 (64%)
Psychiatric	91/277 (33%)	12/18 (67%)	20/27 (74%)	10/47 (21%)	31/53 (58%)	164/422 (39%)
Visual signs	113/277 (41%)	4/18 (22%)	0/12	0/47	13/53 (25%)	130/407 (32%)
Aphasia	97/277 (35%)	13/18 (72%)	4/12 (33%)	0/47	19/53 (36%)	133/407 (33%)
Parkinsonism	69/277 (25%)	13/18 (72%)	6/12 (50%)	3/4 (75%)	40/53 (75%)	131/407 (32%)
Pyramidal	166/277 (60%)	15/18 (83%)	7/2 (58%)	23/47 (50%)	18/53 (34%)	229/407 (56%)
Myoclonus¶	205/211 (97%)	15/18 (83%)	11/27 (41%)	39/59 (66%)	39/53 (74%)	309/368 (84%)
EEG sensitivity‖	73% (189)	24–44% (21)**	0–42% (27)**	13% (59)	8% (52)	44% (348)
CSF sensitivity‖						
14.33 Protein	100% (108)	40% (5)	100% (4)	100% (23)	100% (2)	95% (142)
Tau	97% (115)	53% (15)	100% (4)	100% (23)	100% (6)	88% (163)
MRI sensitivity‖	80% (49)†‡	93% (15)	100% (2)	60% (15)	100% (8)	81% (89)

Data are mean (range), n/N (%), or % (N). sCJD = sporadic Creutzfeldt-Jakob disease. M = methionine. V = valine. Prp^{Sc} = scrapie prion protein. EEG = electroencephalogram.

*Cali I, Gambetti P, unpublished (15 cases); †Cali I, Gambetti P, unpublished data (17 cases). ‡Duration is time from first symptom to death. §Including other types of dyskinesia.

¶ Rare at presentation. ‖95%CIs not available; data should be interpreted with reference to sample size. **Ranges are the variations reported.

†† sCJDMV1 alone has a sensitivity of 100% on the basis of six cases.

Modified from: Puoti G, Bizzi A, Gianluigi Forloni G et al. Sporadic human prion diseases: molecular insights and diagnosis. Lancet Neurol 2012;11: 618–628. Table 2.

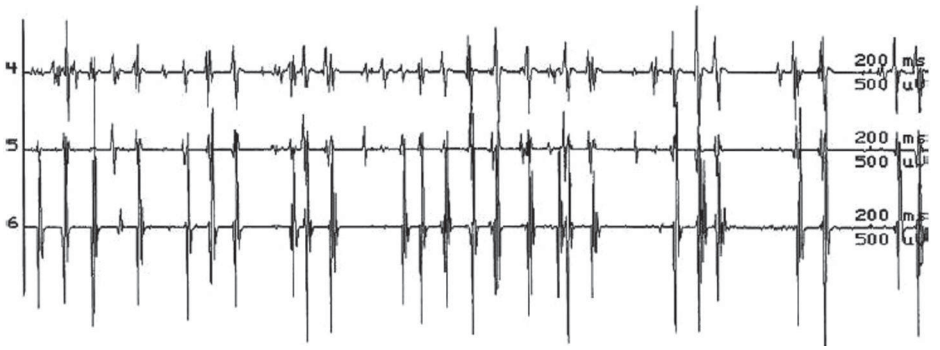

Figure 8–3. Rhythmic cortical myoclonus in CBGD. Surface EMG in a patient with CBGD with myoclonus at rest synchronous in wrist extensors (line 4), wrist flexors (line 5) and abductor pollicis brevis (line 6) in one limb. (From: Defebvre L. Myoclonus and extrapyramidal diseases. Neurophysiol Clin 2006;36:319–325. Figure 3.)

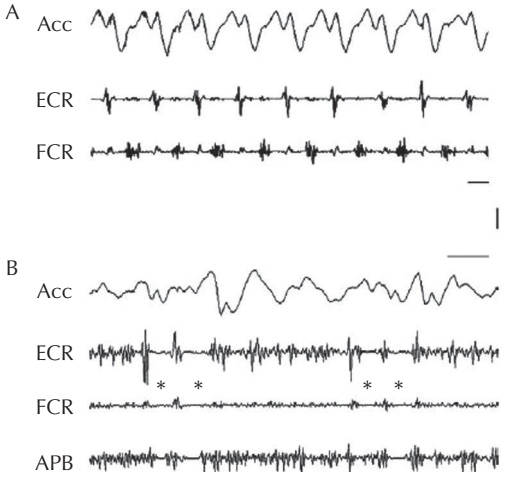

Figure 8–4. Negative myoclonus masquerading as tremor in parkinsonism. EMG and accelerometry (Acc) in parkinsonian rest tremor (A). There are alternating contractions in extensor carpi radialis (ECR) and flexor carpi radialis (FCR). In panel B, negative myoclonus interrupts ongoing EMG activity in ECR and abductor pollicis brevis (APB) simulating tremor. "*" indicated episodes of negative myoclonus. Horizontal lines represent 100 msec, and vertical line is 500 μV. (From: Defebvre L. Myoclonus and extrapyramidal diseases. Neurophysiol Clin 2006;36:319–325. Figure 1.)

Qb-SNARE protein (GOSR2) causing ataxia, myoclonus, seizures, sensory neuronopathy causing areflexia, and chronic anterior horn cell degeneration.[28,29] The GOSR2 protein is involved in protein transport from the endoplasmic reticulum into the Golgi apparatus. Patients with this syndrome may have severe seizures, but ataxia and myoclonus may precede significant seizures by years, so that PMA will be the diagnosis in some cases. Most recently, a patient with PMA was found to have a mutation in MRE11, a gene previously associated with ataxia-telangiectasia-like disorders.[30] One rare treatable cause for PMA is celiac disease. The link between celiac disease and neurological syndromes is controversial. The antibodies used to diagnose the condition are frequently present in genetically diagnosed cerebellar degenerations and may not be specific for celiac disease.[31] However, there are reports of neurological symptoms improving in patients after gluten-free diet, so it is worth testing patients with otherwise undiagnosed PMA for antigliadin antibodies and antitissue transglutaminase.[31]

Action Myoclonus-Renal Failure Syndrome

A rare disorder first reported by Andermann et al in 1986,[21] action myoclonus-renal failure syndrome (AMRF) usually starts as kidney dysfunction or upper-extremity postural and action tremor and progresses to multifocal myoclonus, probably of cortical origin, cerebellar dysfunction including ataxia and dysarthria and sometimes seizures, deafness, demyelinating neuropathy, or dilated cardiomyopathy.[32,33] The kidney dysfunction is progressive and leads to kidney failure in some but not all patients. No treatment is currently available except that dialysis and kidney transplant may be lifesaving. The disorder was inherited in a recessive fashion in reported cases and was shown to be associated with mutations in the lysosomal protein SCARB2. However, identical mutations have been found in some patients with PME

who did not develop renal failure and would be diagnosed with PMA.[33]

Basal Ganglia

It is difficult to document myoclonus originating from the basal ganglia. However, there are multiple indirect studies indicating that myoclonus may originate from the basal ganglia. Negative myoclonus has been reported with lesions of the thalamus, and there was indirect evidence supporting a left thalamic origin of right upper-extremity 1–2 Hz myoclonus in a girl with antiglutamate receptor antibodies.[2,34]

Brainstem Myoclonus

The hallmark of brainstem myoclonus is bilateral symmetric myoclonic contraction of muscles. Although this pattern of contraction can be seen with a cortical origin, that appears to be rare. Electrophysiological testing shows a time-locked relationship between muscles at different levels of the nervous system. If the origin of the myoclonus is high in the brainstem, the pattern of muscle contraction indicates downward spread of signal that might originate in the brainstem or in higher centers. Often, however, the pattern of muscle contraction can be tracked both upward and downward from a focus in the brainstem, definitively eliminating the spinal cord or higher centers as origins for the syndrome. There are three forms of brainstem myoclonus: segmental branchial myoclonus, exaggerated startle, and reflex reticular myoclonus.

RHYTHMIC SEGMENTAL BRANCHIAL MYOCLONUS

Palatal Myoclonus

In palatal myoclonus (PM), there are rhythmic or somewhat rhythmic palate elevations sometimes accompanied by other movements synchronous with the palate movements, including ocular myoclonus, ocular bobbing, rhythmic movements in other brainstem-innervated muscles, and sometimes even limb jerks or tremor.[35] The palate movements in PM were considered myoclonus because spinal myoclonus is rhythmic, the movements are sometimes fast enough to be myoclonus, and the movements may be accompanied by ocular myoclonus. However, the movements are often much slower than typical myoclonus (and sometimes sustained, suggesting dystonia), and some have suggested that this is not a myoclonus syndrome at all and that the name be changed to palatal tremor. It can be primary (essential) or secondary (symptomatic).

Primary PM: Patients with primary PM usually present with clicking of the ears that keeps them from sleeping. Sometimes they are unaware of the palate movements. The concept of primary PM excluded other movements possibly except for eye movements synchronous with the palate movements. In fact, the situation is far more complicated. Based on review of the literature, almost one-third of patients otherwise classified as primary had synchronous movements in other facial muscles (orbicularis oculi and oris, masseter, and temporalis).[36] Many of the reported cases were felt to represent a central generator, but some patients could voluntarily produce repetitive palate movements and others started with involuntary rhythmic palatal movements but eventually could start and stop rhythmic palatal movements at will.[36] This led to a suggestion that in many patients primary PM is psychogenic.[37,38] In these patients, movements were distractible, disappeared during sleep, were triggered by stress, and had other features felt to be inconsistent with organic disease.[38] It is certainly possible that some patients have psychogenic PM, but the concept that most patients with primary PM are psychogenic is highly controversial. The clicking is usually due to the eustachian tube snapping open or closed, implying involvement of the tensor veli palatini.

Secondary PM: The majority of reported cases with secondary PM are associated with a brainstem lesion in the pathway from the dentate nucleus via the brachium conjunctivum to the central tegmental tract to the inferior olive (called the triangle of Guillain-Mollaret), although PM after thalamic infarct has been reported.[35,39] Virtually every kind of lesion has been associated with secondary PM, most commonly vascular lesions but also trauma, tumors, multiple sclerosis, vasculitis, encephalitis, and degenerative diseases such as PSP and Krabbe disease. In some of these cases, there is hypertrophy of the cells of the inferior olive,

suggesting that these cells are the pacemaker for the movement.[35] Although there is some overlap between the clinical features of primary and secondary PM, patients with secondary PM are older, more likely to be male, more likely to have no spontaneous remissions, more likely to have symptoms during sleep, much less likely to have ear clicking, more likely to have PM involving the levator veli palatini (as opposed to primary PM, which is more likely to involve the tensor veli palatini), more likely to have higher frequency movements of the rhythmic palate movements, and more likely to have monosynaptic and oligosynaptic brainstem reflexes in addition to polysynaptic brainstem reflexes.[35,40] Other brainstem-innervated muscles, such as tongue, jaw, and sternocleidomastoid muscles, may be involved. Palatal myoclonus with progressive ataxia is a recognized syndrome and some familial cases are due to adult-onset Alexander disease.[40] Symptoms in secondary PM vary according to the neurological systems involved. When eye movements are involved, patients may have oscillopsia. On occasion, patients may have rhythmic movements of other branchial muscles similar to the movements in palatal myoclonus but sparing the palate.

Treatment of primary PM is difficult. The movements rarely improve with clonazepam or anticonvulsants. The easiest maneuver is providing white noise at bedtime to allow the patient to fall asleep (tuning a radio between channels works). Pharyngeal injections of botulinum toxin have also been used to suppress the clicking.[41] Treatment of secondary PM is even more difficult unless the underlying disease can be treated.

Middle Ear Myoclonus

A rare cause of tinnitus is middle ear myoclonus (MEM, myoclonus in the absence of PM or HFS). At the Mayo Clinic, the incidence of MEM was 1.3 cases per 100,000 person-years.[42] Although it is usually difficult to distinguish which muscles are involved, it is felt to be either the stapedius muscle (innervated by the facial nerve and displacing the tympanic membrane posteriorly) and/or the tensor tympani (innervated by the trigeminal nerve and displacing the tympanic membrane inward).[42,43] It is said that stapedius contraction produces a buzzing sound and tensor tympani contraction produces a clicking sound, but it is not clear whether that is always the case.[42] Multiple medications have been reported to partially help in individual cases and small series, including benzodiazepines, orphenadrine, carbamazepine, and piracetam.[42] Surgical section of the muscle tendon has been reported for both muscles and felt to be successful in multiple cases, but the total number reported is small.[42] One form of MEM that is extremely rare is MEM synchronous with forced eye closure.[44] It is felt this involves the tensor tympani as well as the stapedius muscles via a reflex arc between cranial nerve nuclei VII and V.[44]

Whipple's Disease

Whipple's disease is caused by an infection by the bacterium *Tropheryma whipplei*, characterized by widespread disease with predominately gastrointestinal and neurological symptoms. The most common neurological symptoms are dementia, opthalmoplegia, and myoclonus, although acute encephalopathy and seizures may occur.[45] Hypersomnia is not rare. The myoclonus can be focal or segmental and is often rhythmic. One myoclonic syndrome that strongly suggests Whipple's disease is very slow (less than 3 Hz), rhythmic myoclonus that is synchronous in the eyes, jaw, and sometimes facial and limb muscles called myorhythmia (although this term has also been applied to other forms of very slow rhythmic myoclonus). Unfortunately, diagnosing the disease may be very difficult because in occasional cases, there is no cerebrospinal fluid (CSF) pleiocytosis and duodenal biopsy may be negative.[45] Identification of *T. whipplei* DNA in CSF is more sensitive, but even that may be negative on occasion.[45] The disease is treatable with antibiotics, and the myoclonus may respond to clonazepam, possibly to other medications for myoclonus, and possibly to immunomodulatory treatments.[21,46,47]

RETICULAR REFLEX MYOCLONUS

Reticular reflex myoclonus consists of bilateral synchronous myoclonic jerks originating in the brainstem and elicited by sensory stimuli. Proximal muscles are preferentially involved, and flexor muscles are involved preferentially over extensor muscles. The distinction between

exaggerated startle and reticular reflex myoclonus is not clear, but most investigators find several distinguishing features: in reticular reflex myoclonus, the muscle burst duration is much shorter, the sternocleidomastoid is involved earlier than the orbicularis oculi, and there is no delay in involvement of the intrinsic hand and foot muscles, unlike the situation in exaggerated startle (see "Exaggerated Startle" and references 48, 49). There are multiple causes for reticular reflex myoclonus, including hypoxia, renal or hepatic failure, stiff person syndrome, hyper- or hypoglycemia, toxins (methyl bromide or bismuth intoxication), and others.[21,50]

EXAGGERATED STARTLE

Normal startle is a reflex probably originating in the reticularis pontis caudalis nucleus, which integrates auditory and sensory input from the body and especially from the face. Multiple stimuli, primarily loud noise but also unexpected taps to the forehead or other unexpected stimuli, produce, after a delay of about 40 msec, contractions in the orbicularis oculi followed by activation of muscles up and down the brainstem and down through the spinal cord, primarily in proximal and flexor muscles symmetrically. The normal reflex has two phases. The first phase lasts several hundred milliseconds, begins with orbicularis oculi contraction, and is relatively stereotyped.[48] The orbicularis oculi actually undergoes at least two separate contractions during the first phase, suggesting the involvement of two separate reflexes see Figure 8–5.[48] After the first phase, there is a delay of several hundred milliseconds and then the second phase begins. The second phase lasts several seconds, varies according to the situation, and has emotional and voluntary components.[48] The normal startle reflex fatigues rapidly and usually disappears after 3–6 successive stimuli.[48,50] There are two ways in which normal startle may be "exaggerated":

Type I. The trigger for startle is much milder than the typical stimulus, the startle itself of larger amplitude and involving more muscles, and (often) the reflex does not fatigue as rapidly as normal or does not fatigue at all. After a brief delay, the reflex is succeeded by generalized muscle stiffness lasting seconds, during which voluntary movement is not possible.

Type II. The trigger and startle are typical, but after the startle a variety of movements (epileptic or nonepileptic complex movements) ensue.

The paradigmatic Type I startle condition is the hyperekplexia syndrome.

Type I Startle: Hyperekplexia Syndrome

The hyperekplexia syndrome is an inherited or sporadic condition starting in infancy with an extraordinary response to minimal stimuli (gentle touch or normal background noise). Infants with hyperkplexia stiffen all over in response to stimuli, their fists clench, their limbs may tremble, and respiration ceases, possibly because of chest wall stiffness. These children are at high risk for death by cardiorespiratory failure or brain damage due to prolonged hypoxia. As they grow, this dramatic response subsides, but they then develop a more typical exaggerated startle response, triggered by taps to the face or loud noises. This may prove dangerous as well as disruptive, as children may fall during a startle. Many have abnormal gait and mild developmental delay, but it is not clear whether this is part of the disease or because of mild hypoxic brain damage. Over long periods of time, the startle becomes less exaggerated (and falling often stops), but some degree of exaggerated startle persists. The most common known gene associated with hereditary hyperekplexia and some sporadic infants is the alpha1 subunit of the glycine receptor, which provides a potential physiological explanation for the presumed loss of inhibition of a normal startle reflex.[50] There are known mutations in other genes involved in glycine function: the sodium/chloride dependent glycine transporter, the beta1 subunit of the glycine receptor, and two genes involved with assembling glycine and GABA receptors gephyrin and collybistin.[51] There is a significant minority of patients with inherited hyperekplexia in whom the genes have not been identified.

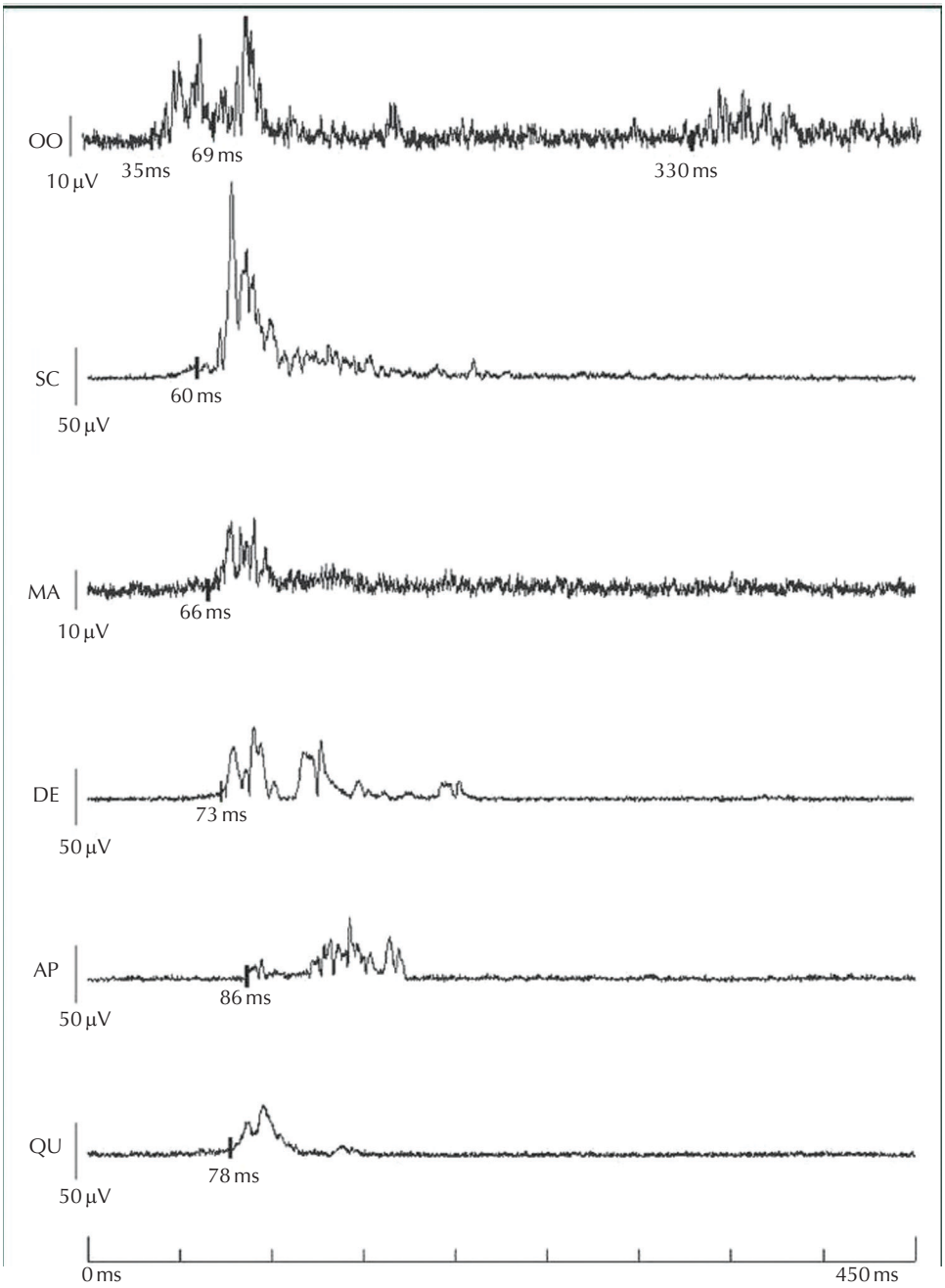

Figure 8–5. Exaggerated startle response. Rectified EMG averaged over eight stimuli after a 107 decibel tone in 15-year-old girl with exaggerated startle. There are three responses in the orbicularis oculi (OO) at latencies of 35, 69, and 330 msec. If you ignore the 35-msec response, the first response to auditory startle is now in the sternocleidomastoid (SC) at latency 60 msec, followed by the masseter (MA) at latency 66 msec, the OO at latency 69 msec, the deltoid (DE) at latency 73 msec, the quadriceps (QU) at latency 78 msec, and finally the abductor pollis brevis (AP) at latency 86 msec. The AP latency is unexpectedly long. (From: Bakker MJ, van Dijk JG, van den Maagdenberg AM, Tijssen MAJ. Startle syndromes. Lancet Neurol 2006;5:513–524. Figure 1.)

Type II Startle

The most common type II exaggerated startle syndrome is startle evolving into seizures, and a variety of seizure types may become startle epilepsy.[50] The most unusual variant of this type of exaggerated startle are the family of conditions typified on this continent by the Jumping Frenchmen and the Ragin' Cajuns of related ancestry (French Canadians and Acadians).[52] This type of syndrome seems to occur in many disparate cultures (Latah in southeast Asia; Imu in Hokkaido, Japan; Mali in the Philippines; Myriachit in Siberia; and others).[53] After startle, people with these conditions engage in a wide variety of behaviors, including complex jumps, vocalizations as in Tourette's syndrome, echopraxia, echolalia, and forced obedience (following commands to perform normally taboo actions). The content of the startle-triggered rituals varies from culture to culture. For example, people with Latah were predominately women and they tended to have vivid, frightening dreams before the onset, whereas Jumping Frenchmen were predominately men who were shy and ticklish and the behaviors decreased or disappeared when they left logging camps.[52,53] Some have treated this as a psychologically determined elaboration of a common phenomenon (startle). The concept of a physiological disorder whose manifestations are culture dependent, however, is well established for tics and may eventually be established for these disorders. For a list of causes of exaggerated startle syndromes and startle-initiated disorders, see Table 8–4.

Spinal Myoclonus

SPINAL SEGMENTAL MYOCLONUS

Spinal segmental myoclonus originates from a focus in the spinal cord and spreads to involve muscles at a few segmental levels above and below the focus (Figure 8–6). The jerking is often present at rest, persists or worsens with posture and action, and may change with body position. The individual muscle contractions are much longer than those of cortical or brainstem myoclonus, lasting up to 1,000 msec. The myoclonus is more likely to be rhythmic and less likely to be stimulus evoked than myoclonus originating

Table 8–4 **Exaggerated Startle Syndromes**

Hyperekplexia	Stimulus-Induced Disorders	Neuropsychiatric Disorders
Neonatal stiffness, startle, and stiffness with startle	Nonepileptic	Startle-induced tics
Excessive startling	Without rigidity	Culture-specific syndromes
Cerebral	Paroxysmal kinesigenic dyskinesias	Latah
Cerebral palsy	Episodic ataxia	Jumping Frenchmen of Maine
Postanoxic encephalopathy	Cataplexy (narcolepsy)	Myriachit
Occlusion of posterior thalamic arteries	Reflex myoclonus	Functional startle syndromes
Posttraumatic	With rigidity	Anxiety disorders
Paraneoplastic	Stiff-person syndrome	Posttraumatic stress syndrome
Multiple sclerosis and lateral sclerosis	Progressive encephalomyelitis with rigidity	
Cerebral abscess with encephalitis Brainstem	Strychnine poisoning	
Brainstem	Tetanus	
Brainstem infarction	Epileptic	
Brainstem hemorrhage	Reflex epilepsy	
Brainstem encephalopathy	Progressive myoclonus epilepsy	
Pontocerebellar hypoplasia	Pyridoxine-dependent epilepsy	
Posterior fossa malformations		
Medulla compression		
Multiple system atrophy		

From: Dreissen YEM, Tijssen MAJ. The startle syndromes: physiology and treatment. Epilepsia 2012;53(S7):3–11. Table 1.

in other parts of the nervous system. The signal spreads up and down the spinal cord along the corticospinal tracts. Because this form of myoclonus does not go through the thalamus or other parts of the reticular activating system, it usually persists in sleep. A spinal cord lesion often cannot be identified, and other spinal cord deficits, such as weakness and sensory loss, are usually not present. Conditions associated with spinal segmental myoclonus include infections such as herpes zoster, tumors, myelitis, vascular disease, and inflammation.[40,54] There are rare reports of spinal myoclonus due to anesthesia by intrathecal opioid infusion. Many of these patients had other potential causes of myoclonus, and the origin of the myoclonus is usually not identified, but this does seem like a possible cause for spinal segmental myoclonus in at least some cases.[55] Clonazepam is probably the most successful treatment for spinal segmental myoclonus but only helps a minority of patients. Levetiracetam, tetrabenazine, trihexyphenidyl, baclofen, carbidopa/levodopa, valproate, and 5-hyrdoxytryptophan (5-HTP) have all been reported to be of benefit in small numbers of patients. As with most other focal hyperkinetic movements, botulinum toxin injections may help if localized contractions are troublesome or painful.[40,56]

PROPRIOSPINAL MYOCLONUS

Propriospinal myoclonus originates from a focus in the spinal cord; spreads for multiple segments at a much lower speed than spinal segmental myoclonus, about 5–6 m/sec; and the contractions may last from 50 msec up to 4

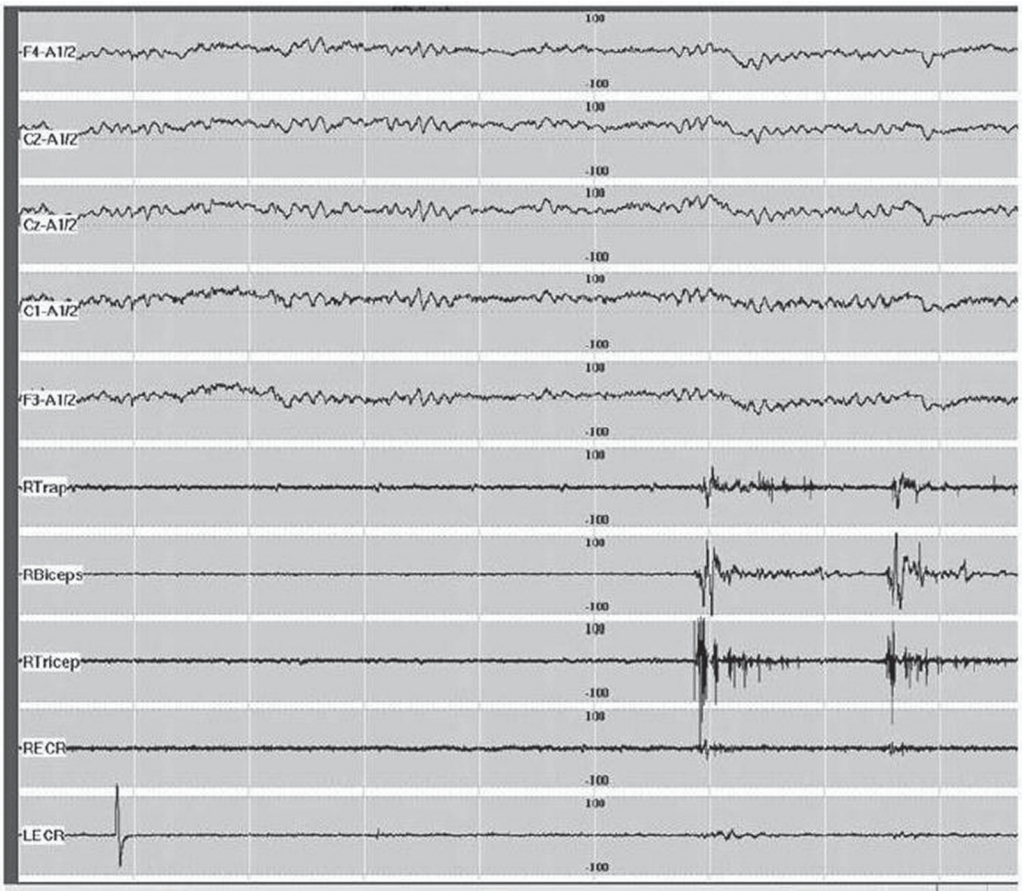

Figure 8–6. Spinal segmental myoclonus. Patient with spinal segmental myoclonus has myoclonic bursts in the right triceps without an EEG correlate. There is synchronous activity with decreasing ampliture in the right biceps and right trapezius and minimal activity in the left greater than right extensor carpi radialis (ECR). (From: Kojovic M, Cordivari C, Bhatia K. Myoclonic disorders: a practical approach for diagnosis and treatment. Ther Adv Neurol Disord 2011;4:47–62. Figure 5.)

sec.[54,57,58] Axial muscles are usually involved, and the myoclonus is usually not rhythmic, is more often stimulus evoked than spinal segmental myoclonus, and is often worse lying down (see Figure 8–7).[57] In some cases, there is a premonitory sensation and symptoms may be worse in the transition between sleep and wakefulness.[57]

The rate of spread of propriospinal myoclonus in some patients is so slow that you can actually see the spread. In two studies from the same center, it was felt that most patients with spinal segmental or propriospinal myoclonus had a psychogenic etiology.[59,60] This was based on the presence of Bereitschaftspotentials before some contractions, muscle contraction burst length greater than 1000 msec, variable spinal cord conduction velocity, asynchronous activation of agonist and antagonist muscles, and involvement of facial muscles (not conforming to the criteria originally proposed by Brown et al.[54,59,60] Bereitschaftspotentials are electrical potentials in the supplementary motor area that precede voluntary movements. Another review found Bereitschaftspotentials in none of 10 patients with propriospinal myoclonus, myoclonus during sleep in three, and fiber tract abnormalities in all by diffusion tensor imaging and concluded they had organic disease.[57] Although everyone agrees that some patients with spinal myoclonus are psychogenic, it is not known how common this is. The condition is hard to treat, with clonazepam most reported to help, although there are occasional reports of benefit from zonisamide and possible benefit from valproate, levetiracetam, oxcarbazepine, and others.[57]

Mixed Cortical/Subcortical or Unclear Origin

There are several etiologies of myoclonus not mentioned above that typically cause syndromes of mixed cortical/subcortical or unclear origin.

ESSENTIAL MYOCLONUS (MYOCLONUS-DYSTONIA SYNDROME)

For historical reasons, there is a category of essential myoclonus, indicating that no other neurological disease can be identified. This was used for individuals and families that developed myoclonus (usually very early in life) and developed no other symptoms over very long periods of time. As described in the section on dystonia, the families with this essential myoclonus occasionally had members who had dystonia (exclusively or in combination with myoclonus), and essential myoclonus is now

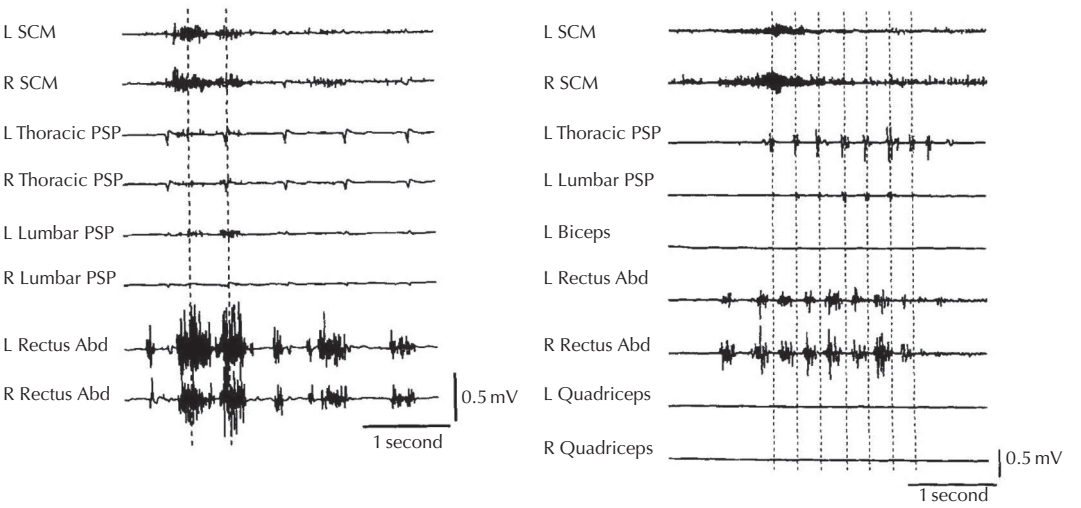

Figure 8–7. Propriospinal myoclonus. EMG activity in two patients with propriospinal myoclonus during axial flexion jerks. On the left, there is cocontraction of right and left rectus abdominus (Abd) and right and left sternocleidomastoid (SCM) with lesser degrees of activity in the lumbar and thoracic paraspinal (PSP) muscles. On the right, there is rhythmic contraction of the left and right rectus abdominus muscles alternating with cocontraction of the right greater than left SCM and left thoracic greater than lumbar PSP. (From: Brown P, Rothwell JC, Thompson PD, et al. Propriospinal myoclonus: evidence for spinal "pattern" generators in humans. Mov Disord 1994;9:571–576. Figures 1 and 2.)

known to be the myoclonus-dystonia syndrome. Many of these have mutations in the gene for epsilon-sarcoglycan (SGCE), but other genes have been implicated, and apparently sporadic cases have also been reported.[61] The myoclonus can be at rest, with action, or stimulus evoked and with a large range of durations (except not short enough to be cortical). Negative myoclonus has also been reported.[61] Physiologic evidence so far implicates subcortical structures as being the site of origin, but the exact location is not known and the cortex has not been eliminated as a potential site for some of the myoclonus.[61] We do not currently know the cause for myoclonus in those individuals or families with this type of pure myoclonus and no identified gene.

POSTHYPOXIC MYOCLONUS (CHRONIC POSTHYPOXIC MYOCLONUS OR LANCE-ADAMS SYNDROME)

This syndrome stands out because cognitive impairment is not progressive and may be modest compared with the impact of the myoclonus. The myoclonus appears after severe hypoxic episodes (such as cardiac arrest), and the appearance is often delayed: usually by days but up to months after the hypoxic event. This is usually distinguished from myoclonus that appears within 24 hours of the event. The acute myoclonus appears while the patient is comatose and is usually generalized, spontaneous, and in response to tactile stimuli. Most of these patients die. The chronic myoclonus may be present at rest, but is worse with posture and action and usually worst with intention. Cortical and subcortical, positive and negative myoclonus are usually present, including exaggerated startle. Ataxia and other cerebellar signs and symptoms such as scanning speech and dysmetria are usually present but may be difficult to demonstrate due to the myoclonus. Negative myoclonus often is severe and may make walking impossible due to loss of tone at the hips and knees. Symptoms do seem to improve modestly over long periods of time, but many patients remain severely disabled. Efforts to treat the myoclonus with benzodiazepines, anticonvulsants, and other medications have so far produced modest results at best. Clonazepam and valproate often produce some benefit but usually not enough to restore reasonable functioning.[62] Levetiracetam, baclofen and intrathecal baclofen, diazepam, ethanol, 5-HTP, methysergide, and pallidal DBS have been reported to help in scattered cases, unlike phenytoin, primidone, phenobarbitol, and tetrabenazine, which were tried without success in published reports.[62–64] Based on the improvement in some cases with alcohol, the alcohol analogue gamma hydroxybutyrate was tried and reported to produce significant benefit in a small number of patients.[62]

ORTHOSTATIC MYOCLONUS

There have been several reports of arrhythmic myoclonus that appeared primarily when standing, with a feeling of unsteadiness resembling the symptom in orthostatic tremor (OT).[65] In most patients, the myoclonus continued during walking, but in a few, symptoms improved with walking. The average frequency of myoclonic bursts was sometimes in the range of OT, but myoclonus in the left and right legs was not coherent, unlike the tremor in OT.[66] Most of these patients had diseases known to cause myoclonus (including Parkinson's disease and parkinsonism), but a large minority had no identifiable cause. Most had postural but not rest myoclonus in several limbs, so it is not clear whether this is an independent syndrome or a previously unrecognized pattern of myoclonus in known conditions—see Figure 8–8. The origin of the myoclonus in the nervous system is not known, but the physiology of 28 patients was described in abstract form.[67] Most had subcortical myoclonus (all with Parkinson's disease) and the rest had cortical myoclonus, most with cerebellar syndromes, including Multiple System Atrophy (MSA).

PSYCHOGENIC MYOCLONUS

Any form of myoclonus may be psychogenic in origin. As noted above, some have suggested that many patients with propriospinal myoclonus may be psychogenic. Exaggerated startle is a common psychogenic symptom. As with other psychogenic symptoms, the clues to the diagnosis are distractibility, sudden onset, paroxysmal appearance of symptoms, slow speed of at least some movements, and inconsistent electrophysiology. In psychogenic myoclonus, symptomatic treatment is contraindicated and treatment should be directed at the underlying condition. For details, see the chapter on psychogenic movements.

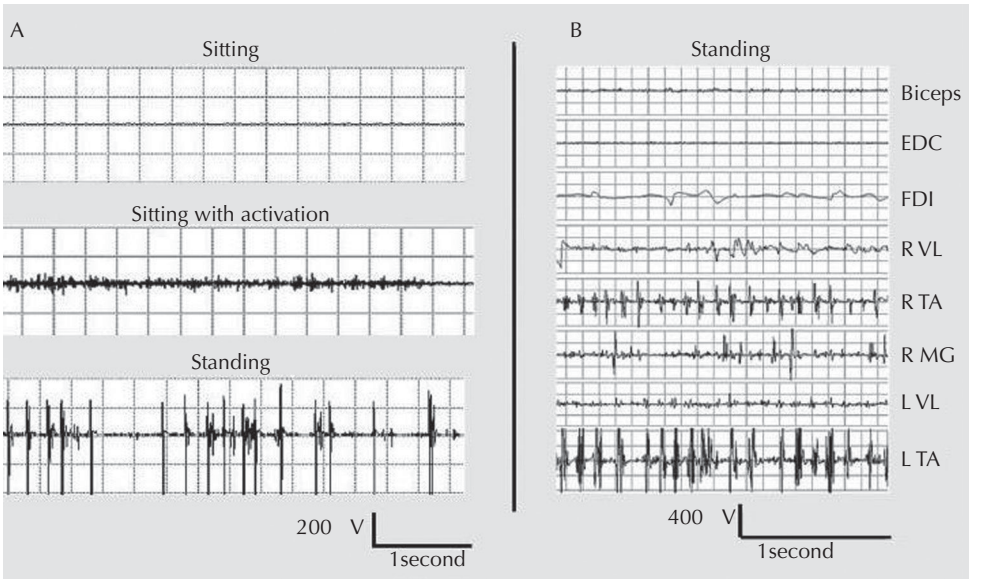

Figure 8–8. Orthostatic myoclonus. A. Surface EMG recorded from the medial gastrocnemius of a patient with orthostatic myoclonus. There is no myoclonus while sitting, clear myoclonus while standing, and possible slight myoclonus with the legs outstretched (activation). B. EMG recording of a patient standing, demonstrating orthostatic myoclonus in the left greater than right tibialis anterior (TA), less myoclonus in the right medial gastrocnemius (MG), and right greater than left vastus lateralis (VL). There was minimal if any myoclonic activity in the biceps, extensor digitorum communis, and first dorsal interosseus. (From: Glass GA, Ahlskog JE, Matsumoto JY, Orthostatic myoclonus: a contributor to gait decline in selected elderly. Neurology 2007;68:1826–1830).

OPSOCLONUS-MYOCLONUS

There are a growing number of autoimmune syndromes associated with mixed cortical/subcortical myoclonus. Some, but not all, are associated with cancer. It is not clear at this time whether there are patterns of myoclonus that are unique to any of these syndromes.

Opsoclonus-myoclonus is generally an autoimmune syndrome, although other causes have rarely been identified.[21] The defining feature is opsoclonus, an eye movement disorder in which there are back-to-back saccades in all directions without intersaccadic intervals. The myoclonus that accompanies this is unusual, usually consisting of multifocal myoclonus so frequent and severe that it appears to be tremor of trunk and all extremities (one of the few situations in which total body tremor is not a psychogenic symptom). This has been called polyminimyoclonus (a term that was originally applied to the tremulous-looking finger myoclonus sometimes seen in Alzheimer's disease and other dementias). Although not mentioned in the name, ataxia is virtually always present. Based on clinical criteria alone, there occasionally appear to be autoimmune syndromes of pure opsoclonus (opsoclonus sans myoclonus) and of pure polyminimyoclonus, as well as asymmetric variants (hemiopsoclonus myoclonus).[68] In children, about half the reported cases follow a mild infection and about half are associated with tumors, usually neuroblastoma. In adults only about 20% of cases are associated with tumors, including cancer of breast, ovaries, uterus, and lung.[68,69] Although tumor markers are occasionally found, no specific marker has yet been identified. There was a report that $CD18_{\beta}$ B cells may be expanded in the CSF in about half the children with opsoclonus-myoclonus.[68] About one-fifth of children make a rapid and complete recovery, but the rest have a relapsing remitting course or have permanent neurologic deficits. Many treatments for the disease have been tried with limited success, including high-dose steroids, intravenous immunoglobulin (IVIg), adrenocorticotropic hormone (ACTH), and immunosuppressants.[68] There is some preliminary data that combining corticotropin with IVIg and possibly immunosuppressants may be more effective.[70] Symptomatic treatment for myoclonus has generally been of little benefit.

OTHER FORMS OF AUTOIMMUNE MYOCLONUS

There has been an explosion in the identification of separate antigens associated with autoimmune encephalitis. There is a suggestion that syndromes involving antibodies against extracellular antigens may be successfully treated with immune suppression while those involving antibodies against intracellular antigens are harder to treat. This may not be the case, as many patients with autoimmune disease may have multiple autoantibodies and it is often not clear which antibodies are pathogenic and some of the damage in these conditions may be T cell mediated.[31] Many of these conditions cause myoclonus in addition to a variety of other movements. For a recent review, see Baizabal-Carvallo and Jankovic[31] and Table 8–5.

Table 8–5 **Myoclonus Associated With Autoantibodies**

Antibodies (Main Antigen)	Tumors	Main Features
Intracellular antigens (commonly paraneoplastic)		
Anti-Hu (ANNA1)	SCLC, other	Encephalomyelitis, sensory neuropathy, LE, brainstem encephalitis. MDs: ataxia, pseudoathetosis (with sensory neuropathy), cerebellar syndrome, opsoclonus-myoclonus-ataxia
Antiamphiphysin	Breast, SCLC	Encephalomyelitis with rigidity, sensory neuropathy, myoclonus, SPS
Anti-Ri (ANNA2)	Breast, SCLC	Brainstem encephalitis, rigidity, opsoclonus-myoclonus-ataxia, cerebellar syndrome
Membrane antigens (less commonly paraneoplastic)		
Anti-VGKC	SCLC, thymoma	Encephalitis, hyponatremia, REM-sleep disorders, myoclonus, Creutzfeldt-Jakob-like syndrome, chorea, tremor, SPS, ataxia, Morvan's syndrome
Anti-LGl1	SCLC, thymoma, ovarian teratoma	Encephalitis, hyponatremia, REM-sleep disorders, myoclonus, neuromyotonia, stereotypies, or tonic seizures
Anti-mGluR5	Hodgkin disease	"Ophelia syndrome," memory loss, hallucinations, behavioral change, seizures, myoclonus
Other antigens (rarely or non-paraneoplastic)		
Antiglycine (α1 subunit) receptor	Rarely lung, thymoma	Encephalomyelitis with rigidity and myoclonus (PERM), cranial nerve involvement, autonomic dysfunction, dysphagia, psychiatric symptoms, pruritus, hypersomnia, SPS, hyperekplexia, ataxia, tetanus-like syndrome
Anti-AMPAR (GluR3); anti-Munc18-1 in 20%	Rare	Rasmussen's encephalitis, myoclonus, chorea, athetosis, hemidystonia
Anti-GAD65 and GAD67; Anti-GABAR-AP	Rarely thymoma	Limbic/brainstem encephalitis, DM type 1, palatal myoclonus, cerebellar syndrome, opsoclonus-myoclonus-ataxia
Anti-TPO and anti-NAE	None	Encephalitis, seizures, strokelike episodes (SREAT), myoclonus, tremor, chorea, myorhythmia, palatal myoclonus

ANNA1 = antineuronal nuclear antibody type 1. SCLC = small-cell lung cancer. LE = limbic encephalitis. SPS = stiff-person syndrome. VGKC = voltage-gated potassium channel. REM = rapid eye movement. LGI1 = leucine-rich glioma-inactivated 1. AMPAR = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor. GABA = gamma-aminobutyric acid. GAD = glutamic acid decarboxylase. PERM: progressive encephalomyelitis, rigidity, and myoclonus. TPO = thyroid peroxidase. GABAR-AP = gamma-aminobutyric acid receptor associated protein. NAE = N-terminal alpha enolase. mGluR5 = metabotropic glutamate receptor 5. Munc18 = mammalian uncoordinated-18 protein. DM = diabetes mellitus.

Modified from: Baizabal-Carvallo JF, Jankovic J. Movement disorders in autoimmune diseases. Mov Disord 2012;27:935–946.

CHRONIC HICCUP

There is a long list of reported causes of chronic hiccup, including anti-Parkinson medications, seizures, virtually any kind of brainstem lesion, phrenic nerve irritation, angina or silent myocardial infarction, cancer (in as many as 9% of advanced patients), alcoholism, and many others.[66,71–73] Many cases have no detectable etiology. The Cochrane Database in 2013 found no controlled studies of treatments for chronic hiccup except for acupuncture and found those studies unconvincing due to possible bias.[74] Many of the maneuvers used for acute hiccups have also been advocated for chronic hiccups, including the Valsalva maneuver, traction on the tongue, startle, breath holding, and many, many others.[73] I have experience with very few of these, but I have seen temporary improvement in chronic hiccups in multiple patients after evoking a gag reflex. For most chronic patients seeing a doctor, these maneuvers do not provide sufficient relief. Dopamine receptor blockers have long been used to treat chronic hiccups but entail a risk of producing tardive syndromes. Patients referred to specialty clinics have usually failed to improve with dopamine receptor blocking agents (DRBAs) or had only temporary relief. There have been case series and a single double-blind, placebo-controlled randomized trial reporting benefit with baclofen, and baclofen has to be considered the drug of first choice.[73] There have been case series of patients reportedly improving with gabapentin.[73] Other medications tried for chronic hiccups include amitriptyline, valproic acid, methylphenidate, amantadine, nifedipine, nimodipine, and marijuana.[56,71,73] If the symptoms are severe and intractable, nerve block, section, or stimulation of the phrenic nerve have been used.[71]

BENIGN SLEEP MYOCLONUS

Although this is a form of physiological myoclonus, not pathologic myoclonus, I mention it here because it can be mistaken for seizures and some infants with this condition have been mistakenly treated with antiepileptics.[75] The condition starts shortly after birth up to a few years after birth and causes rhythmic myoclonus during sleep or drowsiness. The EEG is negative; the condition resolves spontaneously in days, weeks, or occasionally years; and these infants are not at risk for epilepsy.[75]

ELECTROPHYSIOLOGIC TESTING

Cortical myoclonus usually consists of muscle contractions lasting under 50 msec. By recording from muscles innervated at different levels in the brainstem and spinal cord, it is usually obvious that the signal for muscle contraction is spreading down from above the brainstem. There are also several cortical abnormalities that may be detected in some patients with cortical myoclonus. With averaging of multiple sensory stimuli, positive and negative waves on the EEG occur between 20 and 40 msec after the stimulus and the difference between consecutive positive and negative peaks may be increased in cortical myoclonus. These giant somatosensory evoked potentials (SEPs) may not be present, however, and may occur in other conditions besides cortical myoclonus.[20] There are several sensory evoked muscle contractions that happen after an H reflex (long latency reflexes or LLRs) with the latency depending on the limb that is stimulated. These can be detected by averaging multiple stimuli and may occur at rest and with gentle muscle contractions. The shortest LLR (called the C reflex) and the longest LLR are present in about 10% of normals with gentle contraction but never present in normal people at rest.[20] Because these LLRs involve a pathway including the cortex, an enhanced LLR indicates cortical excitability consistent with cortical myoclonus (Figure 8–9). Some but not all of the LLRs recorded during voluntary contraction may also indicate a hyperexcitable cortex. There are high-frequency oscillations in the EEG correlated with gentle muscle contractions, and the correlation may be abnormally increased during myoclonic jerks.[20] Finally, using paired pulse stimulation by transcranial magnetic stimulation (TMS), there may be abnormal cortical excitability in cortical myoclonus (lower threshold for evoking a motor response) or decreased intracortical inhibition (less inhibition of response to a TMS pulse delivered 3 msec after a conditioning pulse). Unfortunately, these tests are helpful only if positive and may not be detectible in all cases of cortical myoclonus.[20]

The hallmark of brainstem and spinal myoclonus is simultaneous spread of contractions to muscles at segmental levels both above and below the site of origin.[20] However, there is a small amount of jitter, so the distinction between organic and psychogenic

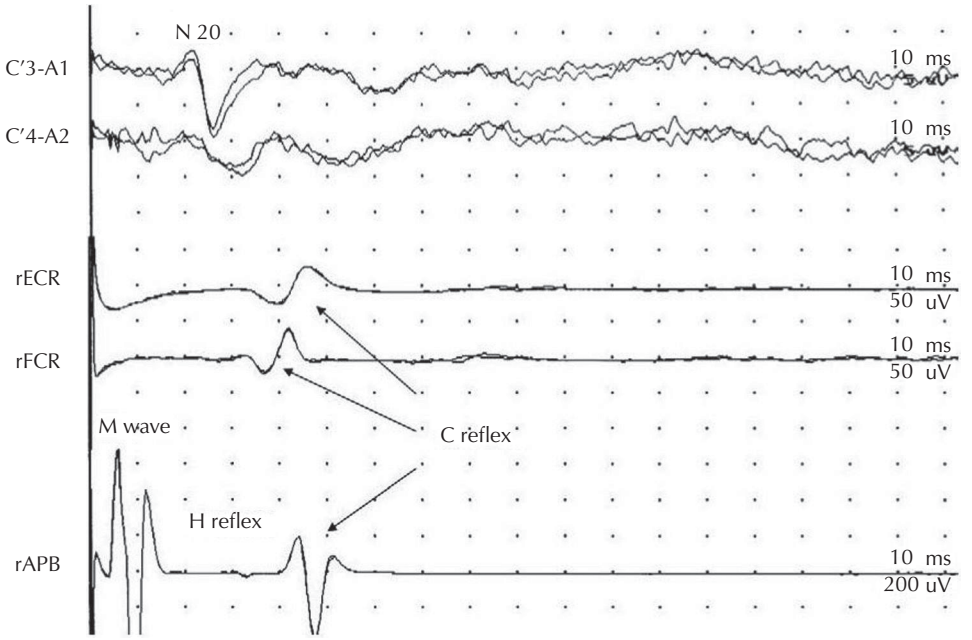

Figure 8–9. Abnormal long latency reflex at rest. Type I Long Latency Reflex or C reflex in the right extensor carpi radialis (ECR), flexor carpi radialis (FCR), and abductor pollicis brevis (APB) about 40 msec after two superimposed series of repetitive stimulations of the right median nerve at the wrist. A very small H reflex can be seen in the APB at about 30 msec. (From: Cassim F, Houdayer E. Neurophysiology of myoclonus. Neurophys Clin 2006;36:281–291. Figure 7.)

myoclonus may not be as definite as we would wish. Contractions in brainstem myoclonus are usually intermediate in duration between cortical and spinal myoclonus (75 msec to 300 msec).[69] Contractions in spinal myoclonus are the longest of any myoclonus, lasting up to hundreds of milliseconds.[20] The contractions in propriospinal myoclonus spread more slowly than those in spinal segmental myoclonus, may involve axial muscles at all levels of the spinal cord, may be spontaneous or evoked by sensory input such as touch, and can vary in duration from 50 msec to hundreds of milliseconds.[54,57,58]

The pause in contractions in negative myoclonus may or may not be preceded by a positive contraction and lasts less than 500 msec.[2]

TREATMENT

Myoclonus may be treatable even when the underlying disease cannot be treated. The underlying disease does not usually determine which treatments for myoclonus are likely to be successful, although in some cases, the site of origin may dictate what drugs are most likely to succeed. All medications are increased gradually to tolerance. When benefit from one medication is inadequate it is reasonable to add a medication with a different mode of action, so that polypharmacy is common in patients with difficult-to-treat symptoms.[49]

Ethosuxamide and levetiracetam have been reported to treat epileptic-related negative myoclonus, but a variety of anticonvulsants have been reported to worsen it, including valproate, phenytoin, lamotrigine, carbamazepine, and oxcarbazepine.[2] It is not clear whether there is a generally effective treatment for non-epileptic-related negative myoclonus.

Clonazepam can be effective for myoclonus of cortical origin and seems to be more effective than other benzodiazepines, although that has rarely been demonstrated by controlled trials. Sedation from clonazepam at low doses often disappears over time. Impotence in men and, at high doses, irritability and ataxia may be dose limiting. Levetiracetam is effective for cortical myoclonus and, because it has fewer side effects than clonazepam, is a reasonable second choice for patients who improve with clonazepam but develop intolerable side effects. Some patients with post-hypoxic myoclonus were reported to improve with levetiracetam, which probably makes it

the drug of first choice for that difficult-to-treat syndrome. Valproic acid has been used to treat all forms of myoclonus, but is used less than other agents because of the potential for hepatic failure, thrombocytopenia, and pancreatitis. Drug-induced parkinsonism from valproic acid is not rare but is easily managed by dose reduction or addition of anti-Parkinson medications. When everything else fails, a variety of medications have been tried to treat myoclonus, including primidone, baclofen, 5-HTP, trihexyphenidyl, carbidopa/levodopa, and tetrabenazine, without spectacular results but possibly with some benefit. For a summary of medications used to treat various forms of myoclonus, see Table 8–6. Botulinum toxin injections have been used for focal jerks or for pain.[49] Deep brain stimulation has been reported once to help posthypoxic myoclonus.[64]

Table 8–6 **Treatment of Myoclonus Based on Small Clinical Studies**

	First Choice	Second Choice	If necessary
Cortical			
In general	levetiracetam (to 3,000 mg/day)	valproate (1,200–2,000 mg/day) clonazepam (to 15 mg/day)	primidone, carbamazepine, phenytoin, vigabatrin, sodium oxybate, 5-HTP, phenobarbital
Posthypoxic cortical reflex myoclonus	clonazepam (to 6 mg/day) valproate (1,200–2,000 mg/day)	sodium oxybate	
Subcortical			
Myoclonus-dystonia	clonazepam (to 6 mg/day), trihexyphenidyl (to 80 mg/day)		levodopa, sodium oxybate, valproate, levetiracetam, 5-HTP, Zolpidem, DBS
Opsoclonus-Myoclonus syndrome	rituximab, ACTH, IVIg, clonazepam		
Hyperekplexia	clonazepam (to 6 mg/day)		
Reticular reflex Myoclonus	5-HTP (to 15 mg/day)		
Palatal myoclonus	clonazepam, carbamazepine, valproate, phenytoin, barbiturates, baclofen, anticholinergics, tetrabenazine, lamotrigine, sumatriptan, tinnitus-masking device, BTX		
Orthostatic myoclonus	clonazepam (optimum dose unknown)		
Spinal			
Segmental	clonazepam (to 6 mg/day)		
Propriospinal	clonazepam (to 6 mg/day)		
Peripheral			
Hemifacial spasm	BTX		Microvascular decompression, anticonvulsants, baclofen
Others	BTX		

BTX = botulinum toxin. 5-HTP = 5-hydroxytryptophan. ACTH = adrenocorticotropic hormone.

Modified from: Dijk JM, Tijssen MAJ. Management of patients with myoclonus: available therapies and the need for an evidence-based approach. Lancet Neurol 2010;9:1028–1036.

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Chapter 9

Restless Legs Syndrome

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CLINICAL PHENOMENOLOGY

Restless legs syndrome (RLS) is characterized by uncomfortable sensations in the legs resulting in a feeling of restlessness and an urge to move the legs.[1–3] It occurs usually 20–60 minutes after lying down to go to sleep for the night when the person becomes drowsy. The symptoms can appear during the day, particularly during periods of inactivity, such as sitting in a theater or sitting during long car or airplane trips. A small number of cases of restless arms have been described. The sensations are variably and often vaguely described with terms like "pulling," "drawing," "crawling," "tingling," "pain," and others.[4] The sensations are usually bilateral and tend to be localized deep within the muscles or bones of the legs. The restlessness can cause sufferers to constantly shift leg positions, arise from bed, walk about (particularly on cold surfaces), run water over their legs, stretch their legs, or exercise in attempts to relieve the restless feeling. The primary disability of RLS is loss of sleep.[4] Sleep studies have shown that individuals with RLS experience prolonged sleep onset latency, shorter total sleep time, and longer REM sleep latency. Interestingly, despite decreased, fragmented, and disrupted sleep, most RLS sufferers do not complain of excessive daytime sleepiness. Chronic sleep deprivation, which occurs in RLS, has been linked to a number of medical problems, including increased cardiovascular morbidity, increased insulin resistance, impaired glucose tolerance, and obesity. Decreased concentration, depression, and impaired learning are also associated with sleep deprivation. Diagnostic criteria for RLS have been presented by the International Restless Legs Syndrome Study Group[5] (Table 9–1).

Restless legs syndrome is a sensory or mental condition with similarities to drug-induced akathisia (a general feeling of motor

Table 9–1 **Diagnostic Criteria for RLS**

1. An urge to move the legs, usually accompanied by or caused by uncomfortable and unpleasant sensations in the legs. (Sometimes the urge to move is present with the uncomfortable sensations, and sometimes the arms or other body parts are involved in addition to the legs.)
2. The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity, such as lying or sitting.
3. The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
4. The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night. (When symptoms are very severe, the worsening at night may not be noticeable but must have been previously present.)

Supportive Clinical Features:
1. Positive family history of RLS
2. Response to dopaminergic therapy
3. Presence of periodic limb movements of sleep

restlessness not directed specifically to the legs). In both cases, the key symptom needed for diagnosis is that the patient describes a feeling of restlessness. Restless legs syndrome itself does not consist of involuntary movements per se (the patient purposely moves in trying to relieve the discomfort), but it is frequently associated with involuntary movements termed "periodic limb movements of sleep" (PLMS).[1,6] These typically consist of 1- to 2-second flexion jerks of one or both legs that occur during sleep. The jerks are followed by a sustained tonic spasm. The movements can just be dorsiflexion of the great toe and foot, but more parts of or the whole the leg can be involved, resembling a flexion reflex. Usually PLMS occur in runs every 20 seconds or so for several minutes or hours. The patients themselves are often not aware of PLMS but can be awakened by them. Often, PLMS are more noticeable by and sometimes bothersome to the bed partners. Generally PLMS appear during periods of arousal in sleep in stages I and II and decrease during stages III and IV. They rarely occur during REM sleep. Occasionally, PLMS can occur in a wakeful patient when drowsy. Sleep studies suggest that about 85% of patients with RLS have PLMS but some people have PLMS without RLS.[5,7]

A recent study indicated that nocturnal eating is a common feature of RLS, with 61% of patients reporting this feature. It was further suggested that treatment with dopaminergic medications can reduce this problem.[8]

Restless legs syndrome is now considered one of the most common movement disorders. A large population study found that 7.2% of adults reported symptoms of nighttime restlessness, with 2.7% describing moderately or severely distressing symptoms.[9] Other studies have reported prevalence rates of between 3% and 10%. Restless legs syndrome can begin at any age, with about one-third of cases having onset before the age of 20 years. Thus, RLS should be considered in the differential diagnosis of sleep problems in children.[10] The symptoms tend to worsen over the years, and most patients seek medical attention in middle life. The incidence of RLS appears to increase with age. The severity of symptoms can vary over time, with about 15% of patients reporting prolonged periods of or permanent remission.[5] Probably for many individuals with RLS, the condition is not disabling.

ETIOPATHOGENESIS

Most cases of RLS appear to occur on a hereditary basis, usually with autosomal dominant inheritance.[2,3] To date, linkage has been identified to genes on chromosomes 12q (RLS1), 14q (RLS2), and 9p24-22 (RLS3), but the nature of the abnormal genes has yet to be elucidated.[11] Primarily based on pharmacological responses, some neurochemical brain disturbances have been implicated. Abnormal dopaminergic neurotransmission has been suggested, given clinical response to dopaminergic medications. One neuroimaging study identified low D2 receptor binding in the striatum,[12] but that finding has not been consistently observed. A disturbance of the endogenous opioid system has been suggested by the response to opiate analgesic medications, but a PET study of opioid receptor availability showed no difference from controls.[13] Low levels of ferritin and high levels of transferrin in cerebrospinal fluid have been identified in certain stages of RLS,[14]

and one neuropathologic examination reported decreased H-ferritin, but not iron, in the substantia nigra of patients with RLS.[15] Thus, a disturbance of brain iron metabolism has been suggested in RLS.

There appear to be secondary forms of RLS, occurring due to or accentuated by other medical conditions. Consistent with a possible role of iron, both anemia and iron deficiency may lead to symptoms of RLS. This may explain the common occurrence of RLS in patients with chronic renal failure treated with hemodialysis. A recent study found that 12% of pregnant women experience symptoms of RLS.[16] Although this is expected to be related to the common anemia of pregnancy, only 20% of affected women had low hemoglobin levels. Smoking and positive family history of RLS, but not anemia or ferritin or estrogen levels, appeared to be closely tied to the occurrence of RLS in pregnancy. Serum iron and ferritin levels should be checked in all patients presenting with RLS or those experiencing a prominent exacerbation of symptoms. Patients with Parkinson's disease (PD) often report RLS,[17,18] another observation compatible with a disturbance of central dopamine neurotransmission. Pallidotomy or pallidal deep brain stimulation has relieved RLS in some patients with PD, pointing to a localization of dysfunction in RLS to the basal ganglia. Perhaps the most common aggravating condition for RLS is lumbar spinal osteoarthritis and stenosis, and these should be considered in patients who experience a worsening of their symptoms.

There are certain medications, particularly antidepressants, antihistamines, and antinausea drugs, that can precipitate or worsen RLS. Dose reductions or changes in these drugs should be considered.

THERAPY

Evidence-based, generally used and effective medications for the treatment of RLS are summarized in Table 9–2.[4,7,19,20] An evidence-based practice parameter for the treatment of RLS was published by the American Academy of Sleep Medicine in 2004[21] and updated in 2012.[22] Therapy is aimed at the uncomfortable sensations in the legs and the feelings of restlessness that interfere with sleep. A recent study found that when accompanying RLS, PLMS are not associated with nighttime arousals and should not be a specific target for treatment.[23]

Table 9–2 **Medications for RLS**

Drug Class/ Medication	Bed Time Dose Range (mg)
Antiepileptics	
Gabapentin	100–2400
Pregabalin	25–900
Benzodiazepines	
Clonazepam	0.25–30
Dopaminergics	
Pramipexole	0.125–4.5
Pramipexole extended release	0.375–4.5
Ropinerole	0.25–5
Ropinerole extended length	2–10
Opiate Analgesics	
Codeine	30–360
Tramadol	50–200
Oxycodone	2.5–5

Single bedtime doses of medications for RLS are usually prescribed. Many clinicians start with the benzodiazepine clonazepam, because it tends to be well tolerated. Opiates such as tramadol, oxycodone, and codeine can be quite useful.[24]

Probably the most predictably beneficial medications are the dopaminergic drugs, usually one of the dopamine receptor agonists.[25] Several randomized double-blind, placebo-controlled trials identified efficacy for the dopamine agonists pramipexole[26–28] and ropinerole.[29–31] This drug class, however, is associated with problems during long-term use and may be falling out of favor. The antiepileptic drugs gabapentin and pregabalin are other potential options.[32–35] Some other medications with reported benefits for RLS, although not commonly used, are baclofen, carbamazepine, and clonidine.

It is important to know that appropriate therapy for RLS is not simple and the treating physician has to constantly monitor the patient's symptoms and response to their current medications.[36] Patients should be seen at least twice

each year for RLS. One cannot simply prescribe a medication and leave the patient without careful attention for long periods of time. The reason relates to three common complications of therapy for RLS: tolerance, rebound, and augmentation.

Tolerance refers to the tendency for the benefits of medications for RLS to gradually wear off over time, resulting in the need for steadily increasing doses. Eventually, with higher doses, medication side effects may outweigh any benefits. Tolerance can occur with any of the medications for RLS.

Rebound is a phenomenon linked to tolerance, in which an end-of-dose loss of benefit occurs, especially for short-acting dopaminergic medications such as levodopa. Rebound can contribute to nighttime awakenings. Tolerance may be related to a downregulation (desensitization) of dopamine receptors over time when dopaminergic therapy is used, but the exact mechanisms are unknown.

Augmentation is a phenomenon in which the medications not only lose benefit over time but also result in a worsening of symptom severity above and beyond the level at the time the medication was started.[37,38] It has been estimated that nearly half of patients treated with dopaminergic drugs will develop augmentation.[39] Signs of augmentation include an increased sensation of restlessness, onset of symptoms before lying down for bed or in the daytime, involvement of the arms, and reduced duration of benefit from prescribed medications. Published diagnostic criteria for augmentation are presented in Table 9–3.[40] A rating scale for the severity of augmentation has been developed.[41] It has been suggested that augmentation may result from heightened dopamine neurotransmission caused by overstimulation of D1 receptors compared with D2 receptors.[42] Dopamine receptor supersensitivity is another proposed mechanism.

Augmentation is largely a feature of dopaminergic medications, particularly levodopa (therefore it is not often used), but also commonly with dopamine agonists. A few cases have been described in association with tramadol therapy. The newer longer acting oral or skin patch formulations of dopamine agonists may be less likely to cause augmentation, but long-term prospective treatment studies are needed.

Because of tolerance, rebound, and augmentation, current optimal therapy for RLS involves a drug class rotation strategy.[38] The four drug classes involved include benzodiazepines, opiate analgesics, dopamine agonists, and antiepileptics. The treating physician should select one drug to start with (e.g., clonazepam from the benzodiazepine class) and identify the effective and well-tolerated dose. The patients should be carefully followed, and when tolerance appears, a few dose increases can be used. However, once tolerance is clearly a problem, clonazepam should be tapered and discontinued and there should be a switch to a medication from one of the other classes (e.g., codeine from the opiate analgesia class). This process can be continued in a similar fashion over time.

Once augmentation appears it is important not to keep raising the medication (usually a dopamine agonist) dosage[43] but rather to get the patient off this drug class and to switch to a medication from another class. Unfortunately, it is common to encounter patients with marked tolerance and augmentation who have been kept on their dopamine agonist for years, often on steadily increasing dosages. For these patients, it is often very difficult to switch them to an alternative therapy. These patients, despite coming off the dopamine agonist and starting medications from other classes, even in high doses, commonly go through a "withdrawal" period of severe RLS symptoms and poor sleep that can last for months. The optimal approach to dealing with such patients remains unknown. This is one of the reasons that it is important to get patients off dopaminergic therapy at the time augmentation first becomes apparent. Iron deficiency is known to precipitate augmentation, and this condition should be investigated and treated if present.

Table 9–3 Diagnostic Criteria for Augmentation

A.	Prior response to dopaminergic medication; an increase in symptom severity on 5 of 7 days for which no other cause is identified.
B.	A paradoxical response to medication.
C.	An earlier onset of symptoms by at least 4 hours or an earlier onset of 2–4 hours plus at least one of the following: shorter latency to symptoms when at rest, extension of symptoms to other body parts, greater intensity of symptoms, decreased duration of medication benefit.

Augmentation is diagnosed with A+B, A+C, or A+B+C.

Table 9–4 **Considerations in Dealing With Worsening RLS**

1. Consider tolerance or rebound to current medication(s)
2. Consider medication-induced augmentation
3. Consider exacerbating drugs (antidepressants, antihistamines, antiemetics)
4. Exclude iron deficiency, anemia
5. Consider lumbar spine arthritis or stenosis

All patients presenting with RLS or experiencing a new exacerbation should have hematocrit, serum iron, and ferritin levels checked and anemia or iron deficiency corrected if present. Vitamin C is often prescribed along with oral iron supplementation to promote absorption. Some clinicians have suggested routine treatment with iron supplements even if blood testing reveals no deficiency. Physical therapy or other treatments should be considered for patients with back pain related to lumbar spinal osteoarthritis or stenosis. The use of opiate analgesics could help these conditions and RLS at the same time. The concurrent use of a medication that can worsen RLS (antidepressants, antihistamines, antinausea drugs) should be considered in patients experiencing an exacerbation. Appropriate clinical considerations when facing a patient with worsening RLS are summarized in Table 9–4.

SUMMARY

Restless legs syndrome is a common condition that affects children and adults by interfering with sleep due to uncomfortable sensations in the legs that come on soon after lying down in bed. Sufferers must move their legs or arise from bed and walk about to obtain relief. It is often associated with involuntary flexion and spasm movements of the legs termed PLMS. Most patients with RLS have a positive family history, and genetic factors appear to be important. There are also secondary causes of RLS that should be considered. Dysfunction of the basal ganglia and limbic system and abnormalities of dopamine neurotransmission and iron metabolism have been implicated. Dopaminergics, narcotic analgesics, clonazepam, gabapentin, and pregabalin are the most commonly used medications. Tolerance, rebound, and augmentation are major problems associated with long-term therapy. Drug class rotation should be considered to combat these potential complications of RLS therapy.

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Chapter 10

Drug-Induced Movement Disorders

Paul E. Greene

INTRODUCTION

Virtually every movement type can be induced by some drugs or toxins. This includes tremor, dystonia, tics, myoclonus, chorea, and less clearly defined movement types such as dyskinesias.[1] Most of these disorders have no specific diagnostic or gold standard test and are diagnosed as drug induced because of the proximity of the drug exposure to the onset of the movement disorder. It is important to remember that proximity, while suspicious, does not establish causation. Without comparing large numbers of exposed and unexposed individuals taking the drug, it is difficult to be certain that the drug exposure was the cause or even contributed to development of the symptom. If the movements subside when the drug is stopped, that strengthens the possibility of causation, but even then some doubt remains. If the movements do not subside when the agent is stopped (or if the agent cannot be stopped), treatment is usually determined more by the nature of the movements than by the etiology. Some of the drug causes for the main movements are listed in Table 10–1. In the cases of dopamine receptor blocking agents (DRBAs) and levodopa, the phenomenology and treatment of the drug-induced movements are sufficiently different to warrant separate detailed discussion.

Table 10–1 **Drug-Induced Movements as of 2011**

Chorea	
Analgesics	
Methadone	2 case reports
Antiarrhythmics	
Cibenzoline	1 case report
Digoxin	1 case report
Anticholinergics	
Trihexyphenidyl	Review and case series
Anticonvulsants	
Carbamazepine	1 case report
Ethosuximide	1 case report
Gabapentin	4 case reports
Lamotrigine	2 case reports
Phenobarbital	1 case report
Phenytoin	9 case reports
Valproic acid	3 case reports
Zonisamide	1 case report
Antidepressants	
Fluoxetine	5 case reports
Fluvoxamine	1 case report
Paroxetine	1 case report
Antihistamines	
Cyclizine	1 case report
Cyproheptadine	1 case report
Diphenhydramine	1 case report
CNS stimulants	
D-amphetamine	7 case reports
H_2 receptor blockers	
Cimetidine	2 case reports
Oral contraceptives	3 case reports
Dystonia	
Analgesics	
Fentanyl	1 case report
Anticonvulsants	
Carbamazepine	3 case reports
Felbamate	1 case report
Phenobarbital	3 case reports (overdose)
Tiagabine	3 case reports
Antidepressants	
Amitriptyline	1 case report
Buproprion	1 case report
Doxepine	1 case report
Escitalopram	1 case report
Fluoxetine	7 case reports
Fluvoxamine	>3 case reports
Mirtazapine	2 case reports
Paroxetine	2 case reports
Sertraline	2 case reports
Tranylcypromine	1 case report
Trazodone	1 case report
Antihistamines	
Benztropine	1 case report
Diphenhydramine	4 case reports
Anti-inflammatories	
Azapropazone	1 case report
Mefenamic acid	1 case report
Benzodiazepines	
Diazepam	3 case reports
Calcium channel blockers	
Nifedipine	1 case report
Verapamil	1 case report
Chemotherapies	
5-FU	1 case report
H_2 receptor blockers	
Ranitidine	5 case reports
Myoclonus	
Analgesics	
Fentanyl	1 case report
Meperidine	1 case report
Morphine	2 case reports
Anticonvulsants	
Carbamazepine	2 case reports
Primidone	1 case report (negative myoclonus)
Tics	
Anticonvulsants	
Carbamazepine	5 case reports
Gabapentin	1 case report
Lamotrigine	1 case report
Phenobarbital	1 case report
Phenytoin	1 case report
Tremor	
Antiarrhythmics	
Amiodarone	Several studies
Melixitene, Procainamide	
Anticonvulsants	
Valproic acid	Common
Lamotrigine	2%–5%
Antidepressants	
Citalopram	1 case report
Sertraline + oxycodone	1 case report
SSRIs	Randomized clinical trial
Amitriptyline	
Beta-adrenergic agents	
Terbutaline, metaproterenol, isoethanine, epinephrine, adrenaline, salbutemol, salmeterol	Multiple reports

(continued)

Table 10–1 (**Continued**)

Calcium channel blockers	
Nifedipine	1 pilot study
H_2 receptor blockers	
Cimetidine	3 case reports
Immunosuppressants	
Cyclosporine	2 reviews
Tamoxifen, cytarabine, Ifosfamide, tacrolimus	
Mood stabilizers	
Lithium	Review of drug database
Methylxanthines	
Theophylline	
All neuroleptics and dopamine depletors	
Sodium calcitonin	1 case report

Adapted from: Zesiewicz TA, Sullivan KL. Drug-induced hyperkinetic movement disorders by non-neuroleptic agents. Handb Clin Neurol 2011;100:347–363; and Arbaizar B, Gómez-Acebo I, Llorca J. Postural induced-tremor in psychiatry. Psychiatr Clin Neurosci 2008;62:638–645.

MOVEMENT DISORDERS INDUCED BY DRUGS EXCLUDING LEVODOPA AND DOPAMINE RECEPTOR BLOCKING AGENTS

Chorea can be caused by multiple drugs and, except for DRBA-induced movements, usually resolves when the drug is discontinued. Estrogens can cause self-limited chorea especially in women with prior Sydenham's chorea.[1] Anticholinergic medications can cause chorea indistinguishable from the chorea of Huntington's disease.[2,3] When used in high doses to treat dystonia, the anticholinergic-induced memory loss may further mimic Huntington's disease. Antihistamines occasionally cause chorea, perhaps because of an anticholinergic effect. Many antidepressants, including anticholinergic medications such as tricyclic antidepressants and serotonin reuptake inhibitors occasionally have been reported to cause chorea. All prodopaminergic medications, including stimulants such as methylphenidate and amphetamines, can occasionally cause chorea, usually in patients with preexisting brain lesions. Most anticonvulsants have been reported, but only rarely, to cause chorea, usually in patients with identified brain lesions.[1] In at least some of these, the movements resemble the dyskinesias of tardive dyskinesias more than the chorea of Huntington's disease. For an extensive list, see Table 10–1.

Tics are sometimes worsened by stimulants used to treat attention deficit disorder, but it is not clear this happens with therapeutic doses, and stimulants do not seem to cause tics in patients not otherwise predisposed to get them.[4] Tics are not commonly reported as a drug-induced phenomenon, although a small number of patients seem to develop tics after exposure to DRBAs despite the fact that DRBAs can be an effective treatment for tics![4,5] There is no generally accepted explanation for this. The explanation most commonly used for the appearance of hyperdopaminergic symptoms after exposure to drugs that block the dopamine receptor is that such exposure sometimes causes the dopamine receptor to become "supersensitive." Stimulation of supersensitive receptors by dopaminergic agents would then be responsible for the excess movements (see "Tardive Syndromes"). Sometimes the tics disappear if the DRBAs are stopped. If tics persist, the options are to treat as for idiopathic tics (see Chapter 6 in this volume) or treat as for other tardive syndromes (see "Tardive Syndromes").

Dystonia is rarely reported as a drug side effect, except after DRBA or levodopa exposure. Some of the reports are in a psychiatric setting, raising suspicion about possible unsuspected exposure to DRBAs. One exception is the antidepressant amoxapine, which has sufficient affinity for the D2 dopamine receptor to cause tardive syndromes and tardive dystonia.[1]

Rest tremor is a common side effect of all DRBAs. Action tremor is also a common drug-induced symptom, and it has been difficult to tell whether these tremors are exaggerated physiological tremor or unique to the provoking agent. Antidepressants and mood stabilizers such as lithium, valproic acid, and lamotrigine are a common cause of postural and action tremor, as are sympathomimetics and asthma medications. Probably the medications most likely to cause tremor are lithium, valproic acid, and selective serotonin reuptake inhibitors (SSRIs). While there is a wide range of prevalence of tremor in patients treated with lithium, 27% of patients across multiple studies had postural and/or action tremor, and perhaps one-third of patients found the tremor significantly intrusive.[6] Beta blockers were shown to be effective in treating lithium-induced tremor in blinded controlled studies, but noncontrolled studies suggested treatment with the same

medications used to treat essential tremor may also be effective.[6] About 25% of patients treated with valproic acid had postural/action tremor that appeared to be exaggerated physiological tremor and seemed to improve with long-acting valproic acid preparations.[7,8] Lithium and valproic acid can also produce parkinsonism and rest tremor.[9] An estimated 20% of patients taking SSRIs develop tremor.[7] The tremor can develop during treatment, as a withdrawal phenomenon, or as part of the serotonin syndrome (tremor, confusion, myoclonus, and other symptoms).[7] Drug-induced postural/action tremors are treated in the same manner as essential tremor when the medication cannot be stopped.

Myoclonus can be caused by any medication that can cause seizures as a side effect. Opioids, dopaminergic drugs, and most antipsychotics (including the atypical antipsychotic clozapine) are probably the most common drugs causing myoclonus. Even some antibiotics have been reported to rarely cause myoclonus, probably as a toxic effect.[9] Most anticonvulsants can cause negative myoclonus and, paradoxically, positive myoclonus when given in high doses despite being used to treat positive myoclonus.[1]

MOVEMENT DISORDERS INDUCED BY DOPAMINE RECEPTOR BLOCKING AGENTS

History

The introduction of DRBAs to treat schizophrenia in the early 1950s and the introduction of levodopa to treat Parkinson's disease (PD) in the early 1960s were both followed by the recognition that drug-induced movement disorders were a major limiting factor in treatment. Acute reactions from chlorpromazine treatment of schizophrenia were reported in 1952 in German, shortly after the drug was introduced.[10] Initially, there was confusion about the boundaries between the various types of neurological side effects: parkinsonism, immediate and delayed reactions, involuntary movements such as dyskinesias and dystonia, and restlessness. The first reports of persistent dyskinetic and dystonic movements appeared in 1956, but it was not until 1962 that a persistent DRBA-induced syndrome was clearly distinguished from the acute syndromes.[11] The relationship of long-lived movement disorders to prolonged exposure to DRBAs remained controversial for years after it was first described.[12] Once the link between DRBAs and long-lived or permanent movement disorders was established, there was pressure to develop DRBAs that did not entail such risk. This search has been only partially successful.

ACUTE DYSTONIC REACTIONS AND ACUTE AKATHISIA

The typical acute dystonic reaction begins hours to a few days after DRBA exposure, disappears quickly if the DRBA is stopped, may disappear even if the DRBA is not stopped, and responds well to anticholinergics or antihistamines. About 50% of the reactions occur within the first day of exposure, and 90% occur within the first 5 days.[13] The prevalence of tardive syndromes is difficult to estimate, because there may be a delay of months to years before symptoms are seen and symptoms may be masked by the same agent that causes the syndrome (see "Tardive Syndromes"). The prevalence of acute reactions should be easier to estimate because neither of those problems is present, yet the prevalence varies considerably from study to study. The prevalence of acute dystonic reactions ranges from 2% to 60% in patients treated with first-generation antipsychotics but is considerably lower (2%–3%) in patients treated with later generation medications.[13] Although there is some variation, in a full-blown acute dystonic reaction, the arms are usually extended at the elbows and retracted backward, the neck is hyperextended, and there are forced eye deviations (oculogyria), usually upward. Laryngospasm, tongue protrusion, and jaw clenching may occur.[13,14] When laryngospasm is present, the patient may have stridor, respiratory compromise, and even respiratory arrest.[13] Most patients are very distressed by this reaction, even in the absence of pain and even if they have had previous episodes. Virtually all these reactions respond quickly to anticholinergics or antihistaminics (especially via IV administration). Prophylactic treatment with these agents eliminates these episodes, although it is not clear whether this is wise (anticholinergics can produce side effects in many patients who would never have acute dystonic reactions). Occasionally, patients have

recurrent attacks of oculogyria after a single exposure to a DRBA.[13]

The phenomenology of acute akathisia is identical to tardive (chronic) akathisia (see "Tardive Syndromes") except that it appears within hours to days of starting a DRBA and resolves quickly when the DRBA is stopped. It appears to be more common than acute dystonia, perhaps because it occurs more frequently in older patients, from about 20% to 75% of patients.[13] It also appears to be less common with later generation neuroleptics than with first-generation neuroleptics.[13] Acute akathisia is frequently treated with beta blockers, anticholinergics, and other medications, but it is not clear how well these work.[13,14]

WITHDRAWAL EMERGENT SYNDROME

Although the term "withdrawal emergent syndrome" is sometimes used by psychiatrists to describe tardive symptoms that emerge when the dose of DRBA is lowered, the term was originally used to describe a short-lived, mixed movement disorder that appeared in children with schizophrenia when a DRBA was stopped.[15] The children developed a short-lived, spontaneously resolving condition with chorea of the Huntington's type (usually sparing the tongue, lips, and jaw), ataxia, and multiple other movements including myoclonus, tremor, and ballistic movements.[15,16] Children without schizophrenia can also develop this syndrome. The etiology is not known. Although this syndrome is not tardive in the sense of long-lasting, it may appear after prolonged exposure to a DRBA (which is then stopped), and it is important not to confuse this with the tardive syndromes, because it resolves spontaneously and usually does not require treatment even when severe.

TARDIVE SYNDROMES

Phenomenology

Tardive syndromes appear after exposure to centrally acting DRBAs. Patients may develop these syndromes after brief exposures (a few days of oral exposure or a single depot injection), after years of exposure, if the dose of a DRBA is lowered, or long after the DRBA is stopped (at least many months later). Unlike the acute reactions, which appear soon after exposure and usually disappear in hours or days, the other syndromes persist for months or years or last for the life of the individual. The adjective "tardive" originally signified that the syndrome only appeared after prolonged exposure, but it turned out that occasional patients developed tardive symptoms after brief exposures.[17,18] The name "tardive" was kept, but the meaning shifted from "onset after prolonged exposure" to "duration of months or years." Because there are currently no laboratory tests for either of these categories, it is not clear whether there may be intermediate syndromes (very short lasting tardive syndromes or very long lasting acute reactions). This may be more than an academic consideration, since oculogyric crises, the first recognized acute reaction, occasionally persist as recurrent oculogyric attacks that can be called tardive oculogyria.[13] The major tardive syndromes consist of dystonia, dyskinesias, and akathisia. A variety of other movement types have less often reported after exposure to DRBAs, including tardive tics,[19] tremor,[20] myoclonus,[21] and pain.[22] Persistent parkinsonism has been observed after exposure to DRBAs, but it is not known if the DRBAs caused the symptoms or were given to someone who would have developed exactly the same symptoms eventually without DRBA exposure (that is, unmasked subclinical parkinsonism).[23] Although some people develop a single tardive symptom, many patients have a mixture of two or more of these symptoms. Grunting and respiratory dysrhythmia can occur with both dyskinesias and akathisia, and it is not clear whether they belong in one or both of those categories or are have a separate pathophysiology.

Tardive dyskinesia (TD): Tardive dyskinesias usually affect cranial structures and can include any or all of the following: chewing movements, lip smacking, lip puckering, grimacing or vacuous smiling, and tongue protrusion ("tongue popping"). Torsional tongue movements are not only common in TD, but also may occur in other types of tardive syndromes that would otherwise not include dyskinesias. Tardive dyskinesia may also include movements of the neck (repetitive head movements in any direction), trunk (truncal rocking), and/or the distal extremities, including flexion/extension of the fingers ("piano-playing fingers,"

flapping at the wrists, flexion/extension of the toes, and flapping at the ankles. More proximal limb movements are uncommon but occasionally happen. Unlike the chorea of Huntington's disease, which is random and unpredictable, these movements are repetitive and relatively predictable and rarely involve the forehead. Motor impersistence (milkmaid's grip or inability to sustain tongue protrusion) is common in most forms of chorea and not present in TD even when the movements are severe. Unlike with tics, patients have no warning or urge before the movements, but many people can suppress the movements briefly. Some patients have respiratory dysrhythmia or grunting. When TD alone is present, these movements usually do not affect function (speaking, chewing, swallowing, and manual dexterity are not usually affected) and patients are often asymptomatic, although patients are aware that the movements are present. The movements may look different in children with developmental delay who develop TD after DRBA exposure. One peculiar clinical observation is that the oral/buccal movements of TD almost always improve dramatically when patients gently put one finger vertically across their lips. The movements often improve with speaking.

Tardive dystonia (TDyst): Tardive dystonia is described in the chapter on dystonia.

Tardive akathisia (TA): Akathisia means "inability to sit," and when severe, patients with TA cannot sit through a meal and may be unable to sit quietly in a chair, crossing and uncrossing their legs or popping out of the chair to pace. Tardive akathisia has both a motor component and a subjective component. Both are necessary to diagnose the condition with certainty, which presents difficulty in patients who cannot communicate (due to young age, aphasia, mental retardation, or dementia). Patients have an inner sense of discomfort, variably described as inner restlessness, jitteriness, jumpiness, or nervousness, anxiety, or distress. They feel compelled to move to reduce these feelings. There is usually a limbic quality to the movements: patients caress their face, hair, trunk, or arms and sometimes their genitals and wring their hands. When sitting, they cross and uncross their legs and fidget in other ways. When standing, they rock from foot to foot or march in place. Truncal rocking may be part of TA (but also occurs in TD) and, as mentioned previously, respiratory dysrhythmia and grunting may be present. Tardive akathisia may prevent patients from falling asleep, although most patients feel more comfortable lying down then being upright (and more comfortable pacing than standing or sitting).

Despite the fact that TD, TA, and TDyst often occur in combinations, neurologists feel strongly that the symptoms should be identified separately. Besides the occurrence of pure TD, TA, or TDyst, there are other pieces of indirect evidence supporting the concept of separate syndromes: the natural history is different (there is a higher remission rate with TD than with TA or with TDyst) and the pharmacology is different (TD responds to lower doses of dopamine depletors than TA or TDyst).

Differential Diagnosis

The movements of TDyst may be indistinguishable from the movements of idiopathic dystonia, although the syndrome of jerky retrocollis, truncal arching, and jerky inturning of the arms is almost always tardive. When mild, the movements of TD may be hard to distinguish from chorea of the Huntington's type, but when moderate to severe the predictability, absence of motor impersistence, and absence of forehead movements usually distinguish TD from chorea. Levodopa dyskinesias, however, may be indistinguishable from the movements of TD. This may provide a clue as to the etiology of both. If there is a question and it is possible to lower the dose of levodopa temporarily, this should help determine whether a patient has TD, levodopa dyskinesias, or both. There are some rare movements, such as edentulous dyskinesias and anticonvulsant induced dyskinesias that also resemble the movements of TD, but these are usually obvious by context. Idiopathic akathisia seems to be extremely rare. There are many other causes of agitation, inability to sit still, and proclivity to pace (including primary anxiety disorders, agitated depression/psychosis, serotonin-induced encephalopathy, and narcotic withdrawal), but most of these do not produce the characteristic movements of akathisia and it is not clear whether they share the same pathophysiology

as TA. Akathisia similar to TA occurs in postencephalitic and idiopathic parkinsonism and was reported in one patient with thalamic stroke.[24,25] Rare patients with acute bifrontal damage may temporarily exhibit signs compatible with akathisia (unpublished observations). Otherwise, the movements of TA are so characteristic that, when present, TA has to be suspected even when the patient does not or cannot describe inner restlessness or an exposure to DRBAs cannot be documented. When multiple movement types are present (a combination of movements of TA, TD, and TDyst), the diagnosis of a tardive syndrome is virtually certain, even though it may be hard to discover the causative agent (especially since the movements may appear many months after exposure has ceased). This rule of thumb does not apply when someone with dystonia or chorea is treated with DRBA and develops a superimposed tardive syndrome.

Pathophysiology

The pathophysiology of tardive syndromes is unknown. Any proposed mechanism must explain the following peculiar features of TS. Symptoms may appear after long exposure and even long after the exposure has ceased. Symptoms may disappear if the doses of DRBAs are increased, but may eventually return at the higher dose (and may be more severe). When DRBAs are stopped, symptoms often worsen transiently but may then improve gradually or they may last years or decades. If DRBAs are stopped and symptoms resolve but DRBAs are restarted, symptoms may return more quickly and be more severe and new symptoms may appear that were not originally present. There is no evidence of cell death on routine pathology. This suggests that symptoms and the disease may be discordant: the disease may be triggered by dopamine receptor blockade but symptoms may be suppressed by the same agent even as the disease continues and possibly worsens.

The dopamine supersensitivity hypothesis of tardive syndromes was originally proposed by Harold Klawans.[26] He suggested that chronic exposure to DRBAs eventually caused a permanent conformational change in dopamine receptors, making them "supersensitive" such that further stimulation by dopamine produced dyskinesia. That is probably not entirely correct but does explain some of the more puzzling observations. This hypothesis explains the peculiarities noted as well as the improvement of tardive symptoms with dopamine depleting agents (there is insufficient dopamine to excite the supersensitive receptors), worsening with levodopa and high-dose dopamine agonists, similarity to levodopa-induced dyskinesias, and lack of significant TD from clozapine (which does not induce supersensitivity in rats and is loosely attached to the D2 dopamine receptor).

The hypothesis fails to explain:

1. Delay in appearance of TD: supersensitivity happens quickly (in rats).
2. Why many patients do not get TD: most or all rats show supersensitivity after DRBA exposure.
3. Why TD persists after DRBAs are stopped: supersensitivity disappears quickly in rats after DRBA are stopped.

Autopsy and PET studies in patients have not so far provided conclusive evidence for any hypothesis. Some studies found a difference in D2 receptor density or binding in patients with TD,[27–29] but the studies were small and not all differences were statistically significant. Other studies did not find a difference.[12,30,31] This is not surprising, because it is not known exactly how to detect supersensitivity nor whether D2 is the only critical receptor. Other studies have focused on possible neuronal loss in the setting of tardive syndromes. A recent morphological study of schizophrenic patients with and without TD matched for duration of illness and duration of neuroleptic treatment using MRI voxel-based morphometry found reduction in gray matter volume primarily in the basal ganglia, especially in the caudate nuclei.[32] However, prior CT and MRI studies were contradictory about whether there were reductions in volume in gray or white matter in patients with TD.[32]

There have been other hypotheses to explain tardive syndromes, but these have even less evidence than the supersensitivity hypothesis: that DRBAs induce a deficiency of GABA in the striatum;[33] that DRBAs produce free radicals and the resulting oxidative stress produces neuronal damage;[34] that DRBAs induce glutamatergic overdrive;[35] and that DRBAs induce an imbalance between dopamine D1, D2 and D3 receptors.[36] Most recently, a hypothesis was

proposed that DRBA exposure changes synaptic plasticity (phenomena such as long-term potentiation and long-term depression) in the striatum (favoring the movement-enhancing direct pathway over the movement-inhibiting indirect pathway) and in the cortex (causing persistence of abnormal motor programs).[37] There has also been a search for genetic risk factors (including genome-wide association studies or GWAS) for the development of tardive syndromes with the inevitable discovery of multiple potential polymorphisms that might influence risk.[38] Some of these have been consistent with known hypotheses, but none so far have proven definitive in predicting features of tardive syndromes or in developing novel treatments.

There have been steady efforts to develop DRBAs that would not produce tardive syndromes, but so far only clozapine seems to be virtually free of risk (the antipsychotic quetiapine can produce tardive syndromes, but the risk seems lower than with other DRBAs except for clozapine). Dopamine receptor blocking agents were initially divided into typical and atypical antipsychotics, in the hope that atypical drugs would be substantially free of the risk of producing tardive syndromes. It soon became apparent that all currently available "atypical" antipsychotics except clozapine were quite capable of producing these syndromes. Currently, DRBAs are divided (somewhat arbitrarily) into first-generation antipsychotics (FGAs) with higher affinity for the D2 dopamine receptor and higher risk of producing tardive syndromes, second-generation antipsychotics (SGAs), and third-generation antipsychotics with lower affinity and presumably lower risk. Initial studies seemed to indicate significantly lower risk with SGAs, but more recent studies have concluded that the risk is modestly reduced, if at all.[39] Part of the difficulty is that a definitive study comparing two drugs would have to randomize a large group of patients and treat each group to exactly the same degree of improvement over a period of time lasting at least several years, a very tall order for psychiatric patients. It is not known why clozapine should have such a substantially lower risk of producing tardive syndromes than other agents (it has many unusual features, but none of them are unique to clozapine). Affinity for the D2 dopamine receptor does not accurately predict the likelihood of a drug producing tardive syndromes.[40] One interesting suggestion is that the determining factor in the proclivity of DRBAs to produce tardive syndromes is the dissociation rate, so that clozapine, unlike more typical antipsychotics, is easily displaced from the D2 dopamine receptor by dopamine.[40] A new purely antiserotonergic medication, pimavanserin, was shown to improve psychosis in PD without worsening parkinsonian symptoms and so might prove to be an antipsychotic without risk of producing tardive syndromes, but this remains to be demonstrated.[41]

Epidemiology

The prevalence and incidence of tardive syndromes are very difficult to establish for some of the reasons previously discussed (symptoms are suppressed by the causative agents and most patients cannot easily stop DRBAs for prolonged periods of time). For this reason, incidence rates may be more useful than prevalence rates, and these seem to be about 4% per year for second-generation DRBAs and somewhat over 5% per year for first-generation DRBAs, but this can vary considerably with agent used, diagnosis, and many other factors.[42,43] It is important to remember that there is a background prevalence of undiagnosed dyskinesias, at least in the elderly and in patients with schizophrenia.[42,44] It is equally difficult to identify factors that influence prevalence. It is almost certain that the prevalence of TD increases with age of the patient and duration of therapy. The relationship with age is just the opposite for TDyst, which is more common in young patients than in older patients. In some studies, it appears that tardive syndromes are more common in patients diagnosed with affective disorders rather than schizophrenia, but it is difficult to establish when equivalent doses are being used. Most studies that looked at this issue concluded that multiple separate exposures to DRBAs correlate with higher rates of tardive syndromes and more severe symptoms.[45] There was a suggestion that concurrent treatment with lithium reduces the risk of TD, but there were many confounding factors. It is very difficult to determine how often TD resolves and in what period of time, again because so many patients continue to require DRBAs. Movement disorder centers regularly see patients who have stopped DRBAs, but this is a highly selected group and

may not be representative of all patients exposed to DRBAs. It may be more useful to examine what happens with patients chronically treated with DRBAs. Although studies vary, most studies find that in a large percentage of patients with TD, symptoms resolve over long periods of time with relatively stable doses of DRBAs, although parkinsonism may worsen. One study by neurologists of patients with average age in the 60s and relatively stable doses over 14 years found that 62% had no TD at the end of the study and only 19% worsened, although 81% had worsened parkinsonism.[46]

Treatment

There are many medications reported to help tardive syndromes, usually in uncontrolled studies and case reports and occasionally in controlled studies, including valproic acid, steroids, lecithin, L-dopa, buspirone, and others.[39,47] Benzodiazepines, ceruletide, cholinergics, lithium, and estrogen were all found not to be beneficial (but remember that medications dramatically helping a few patients may not be detected in parallel design studies). Insulin produced benefit in one small study. There have been double blind studies of Vitamin E: some found benefit, others did not,[39] and it was not terribly helpful in patients with tardive syndromes at the Columbia University Movement Disorder Center. Baclofen and anticholinergic medications probably help TDyst but probably do not help TD, and anticholinergics can actually worsen TD. Any medication that can produce parkinsonism as a side effect will help some patients with tardive syndromes, but the percentage of patients improving may be so small that it does not show up in placebo-controlled, double-blind studies (e.g., valproic acid).[48] Medications that have shown benefit in controlled studies include amantadine, naloxone, clonazepam, levetiracetam, propranolol, ginkgo biloba, and clonidine[48,49] (see Tables 10–2 and 10–3).

At the Columbia University Movement Disorder Center, the most effective medications for tardive syndromes were antidopaminergic medications, including dopamine receptor blockers, dopamine depletors, and the competitive tyrosine hydroxylase inhibitor alpha-methyl–para-tyrosine (demser), all of which were shown to be effective in controlled studies.[49,50] First-generation DRBAs should be used to treat tardive syndromes only when nothing else helps. Although it has not been demonstrated directly, it is known that tardive syndromes may appear only after many years of exposure to neuroleptics, so there is the risk that these medications may help symptoms initially but worsen the disease in the long run and symptoms may reemerge.[17,18] Clozapine

Table 10–2 **Some Drugs That Have Been Used in the Treatment of Tardive Dyskinesia**

1. Catacholamine store depletors
   - Tetrabenazine
   - Reserpine
2. Dopamine receptor blockers
   - Phenothiazines
   - Butyrophenones
   - Atypical neuroleptics
3. Cholinergic agents
   - Denol
   - Choline
   - Lecithin
4. GABAergic drugs
   - Benzodiazepines
   - Diazepam
   - Clonazepam
   - Valproate
   - Baclofen
   - Progabide
5. Dopamine receptor agonists
   - Bromocriptine (low dose)
6. Catecholamine release blocker
   - Methyldopa
   - Alpha-methyltyrosine
7. Alpha adrenergic agonists
   - Clonidine
8. Beta adrenergic blockers
   - Propranolol
9. Calcium channel blockers
   - Verapamil
   - Diltiazem
10. Serotonin antagonists and partial agonists
    - Dyproheptadine
    - Ondansetron
    - Buspirone
11. Antiserotonin agents
    - Amantadine
12. MAO inhibitors
    - Selegiline
13. Opioid antagonists
    - Naloxone
14. Branched chain amino acids
15. Miscellaneous
    - Lithium
    - Vitamin E

Modified from Howland, references 48, 49.

Table 10–3 **Summary of Selected Published Results of Drug Therapy of Tardive Dyskinesia**

Treatment	Number of Cases	Total Improved (%)
Neuroleptic withdrawal	1,047	37
Neuroleptics	535	66
Noradrenergic antagonists	139	63
Other catecholamine antagonists	379	42
Catecholaminergic drugs	189	25
GABAergic drugs	293	48
Cholinergic drugs	424	38
Anticholinergic drugs	187	7
Anticholinergic withdrawal	15	60
Miscellaneous	399	37
TOTAL	3,614	43

From: Jeste DV, Lohr JB, Clark K, Wyatt RJ. Pharmacological treatments of tardive dyskinesia in the 1980s. J Clin Psychopharmacol 1988;8:38S–48S. © Lippincott Williams & Wilkins.

has very little if any risk of worsening the disease and helps on occasion (in part because it allows the disease itself to recover), but the requirement for weekly blood tests and the risk of agranulocytosis make it less attractive. Electroconvulsive therapy (ECT) can help TA and possibly the other tardive syndromes: the improvement is temporary but long-lasting in some.[51] The Columbia University Movement Disorder Group uses primarily reserpine and tetrabenazine, and published retrospective, open-label results. Reserpine and tetrabenazine helped symptoms of TD in over 75% of patients, but only about 64% achieved long-term benefit because of side effects from medications. The results were not quite as good with TA (52% improved) and TDyst (52% improved with a combination of anticholinergics and reserpine or tetrabenazine).[24,52,53] There have been several observations that tardive symptoms may disappear during periods of mania, but no one has yet been able to turn this into a usable treatment.[54] Two other modalities are increasingly used to treat tardive syndromes, although controlled studies have not been performed. Botulinum toxin is useful for treating focal symptoms (such as blepharospasm or troublesome dyskinesias in a few muscles). Deep brain stimulation (DBS) of the globus pallidus has been used with apparent success in treating TDyst and TD.[55] A list of the pros and cons and doses of medications used to treat tardive syndromes is in Table 10–4.

MOVEMENT DISORDERS INDUCED BY LEVODOPA

Phenomenology

Shortly after the introduction of levodopa for the treatment of PD, it became obvious that, in addition to marked improvement in many aspects of motor function, levodopa eventually also produced involuntary movements in many patients.[56] These levodopa-induced dyskinesias are similar in appearance to tardive dyskinesias and, as with TD, many patients with PD are barely aware of the movements and are not disabled by them. When severe, however, they can be disabling and dose-limiting for anti-Parkinson medications. The clinical nature of these movements has been described in great detail.[56] A recent classification scheme for levodopa-induced movements is summarized in Table 10–5. Most commonly, dyskinesias appear about halfway between doses of levodopa (peak-dose dyskinesias). A less common but still commonly observed pattern of dyskinesias (often in combination with dystonia or consisting of dystonia exclusively) is to appear as the levodopa effect begins to appear and again as the effects are wearing off (diphasic dyskinesias or DID dyskinesia = dyskinesia/improved/dyskinesia), causing two episodes of dyskinesia per each dose of levodopa. Diphasic dyskinesias may be triggered by the change in dopamine levels (rising or falling) rather than low doses of dopamine, since the movements disappear as the dose of medication is lowered. Dyskinesias are rare when other medication effects are worn off, but painful dystonia may happen at that time ("off" dystonia). Less commonly, dyskinesias may last as long as the benefit from the dose of levodopa ("square-wave" dyskinesias). There are some rare patterns of dyskinesia. Patients may have dyskinesias in one part of the body and Parkinson tremor or other signs in another part of the body (often with diphasic dyskinesias)

Table 10–4 **Treatment of Tardive Syndromes**

Therapeutic Option	Daily Dose Range	Clinical Syndrome	Comments
Oral agents			
Amantadine	From 100 to 300 mg/day	Classical tardive dyskinesia, tardive dystonia, tardive akathisia, tardive tremor	Risk of hallucinations and cognitive dysfunction in higher doses, especially in elderly.
Anticolinergics, e.g., trihexyphenidyl	From 1 to 40 mg/day or higher according to tolerability	Tardive dystonia	May worsen cognition and psychosis. May worsen oral-buccal-lingual (OBL) dyskinesia.
Baclofen	From 10 to 80 mg/day	Tardive dystonia	Usually tried after failure with anticholinergics or tetrabenazine. May be used in conjunction with anticholinergics.
Benzodiazepines, e.g., clonazepam	From 0.25 to 6 mg/day	Tardive dyskinesia, tardive dystonia, tardive myoclonus	Drowsiness may be dose limiting.
Ginkgo biloba	80 to 240 mg/day	Tardive dyskinesia, tardive dystonia	Clinical trials for TD used 240 mg/day. Caution in patients with antiplatelet agent anticoagulants.
Propranolol	From 20 to 160 mg/day	Classical tardive dyskinesia, tardive akathisia	Blood pressure and heart rate monitoring required.
Tetrabenazine	12.5 to 200 mg/day	Tardive dyskinesia, tardive dystonia, tardive akathisia, tardive tourettism, tardive tremor	Drowsiness, parkinsonism, depression, and acute akathisia may be dose limiting.
Botulinum toxin injections	Varies with product injected and selected muscle.	Tardive dystonia: blepharospasm, cervical dystonia, oromandibular dystonia	
Surgical procedures			
Deep brain stimulation		Severe and refractory tardive dyskinesia, tardive dystonia, and tardive tourettism	Globus pallidus has been the preferred target.

From: Aquino CCH, Lang AE. Tardive dyskinesia syndromes: current concepts. Parkinsonism Rel Disord 2014;20S1:S113–S117. Table 2.

Table 10–5 **Classification of Levodopa-Induced Hyperkinetic Movements**

1. Typical forms of dyskinesia
   a. "OFF" period dystonia
   b. Peak-dose dystonia
   c. Peak-dose dyskinesia
   d. Diphasic (DID) dyskinesia/dystonia
   e. Dyskinesia-parkinsonism
2. Less usual forms of dyskinesia
   a. Square-wave dyskinesia
   b. Respiratory dyskinesia
   c. Ocular dyskinesia
3. Other hyperkinetic movements related to levodopa
   a. Akathisia
   b. Enhanced tremor

Modified from: Prashanth LK, Fox S, Meissner WG. L-dopa-induced dyskinesia-clinical presentation, genetics, and treatment. Int Rev Neurobiol 2011;98:31–54. Table II; and Ha AD, Jankovic J. An introduction to dyskinesia—the clinical spectrum. Int Rev Neurobiol 2011;98;1–29.

sometimes called dyskinesia-parkinsonism. Rapid eye deviations may be present during periods of dyskinesia (ocular dyskinesias), or irregular breathing patterns (respiratory dyskinesias) may be present, sometimes accompanied by shortness of breath (but not by reduced levels of oxygen in arterial blood).

The levodopa-induced movements appear after years of treatment in patients treated early in the course of disease but can appear more quickly in patients first treated after the disease becomes moderate to severe. They often appear at about the same time as patients develop shortening of the duration of benefit from levodopa (motor fluctuations). As the disease progresses, the amount of medication required to treat symptoms increases, but the amount of medication required to produce dyskinesias decreases, so that many patients seem to be on a see-saw: low doses of medication produce fewer dyskinesias but inadequate benefit, whereas higher dose of medication produce adequate benefit but increased, and sometimes intolerable, dyskinesias. It has been estimated that the vast majority of patients treated with levodopa eventually develop dyskinesias (over 90% by 15 years[56]), but the prevalence varies with duration of disease, severity of disease, amount of medication, and possibly cause for the PD—many young-onset patients, especially with familial PD, seem to be particularly prone to severe dyskinesias.[56]

Pathophysiology

Dopamine release produces dyskinesias at therapeutic doses in moderate to advanced patients but not generally in mild patients. Understanding why this happens might produce significant understanding of the processes that create PD. The process whereby the brain becomes susceptible to dyskinesias is usually divided into a priming stage (before dyskinesias appear) and a maintenance stage, although there is not much data supporting this distinction. All proposed mechanisms for priming, such as episodic dopamine stimulation as opposed to continuous stimulation, derive from animal models and have not been documented in humans. The original explanation for the maintenance phase was that dopamine receptors became supersensitive over time in patients with PD treated with levodopa (similar to the development of TD after exposure to DRBAs), but experimental evidence for this is lacking in both animals and humans.[57] Studies using PET show that patients with dyskinesias have reduced dopamine terminals in the putamen by dopamine transporter (DAT) scan and have shorter duration of elevated dopamine levels in the putamen after a dose of levodopa than patients with PD who do not have dyskinesias, but this may simply mean that their disease is worse and they have more wearing off.[58] Dopamine receptor subtypes D1, D2, and D3 seem to be associated in some way with dyskinesias, but most of the evidence comes from animal models.[57] Overactivity of glutamate receptors (including NMDA, AMPA, and mGLU5), abnormalities of opioid precursors and opioid receptors, increased activity in adenosine A_{2A} receptors, abnormal activity in the cannabinoid CB_1 receptor (but unclear if decreased or increased activity), overactivity in the α_2 adrenergic receptor, abnormal nicotinic cholinergic activity (but unclear if decreased or increased), and other biochemical disturbances all are associated with levodopa dyskinesias, primarily in animal models.[57] In the past, it was accepted without question that levodopa-induced dyskinesias were caused by hyperactive dopaminergic neurons or receptors. There has now been a suggestion that these dyskinesias are actually mediated, at least in part, by serotonergic nerve terminals that take up levodopa and release dopamine as a "false" neurotransmitter.[59] In any case, dopamine D3 receptor antagonists, antagonists of the

glutamate NMDA and AMPA receptors, antagonists of the metabotropic glutamate receptor mGluR5, adenosine A2 receptor antagonists, cannabinoid receptor CB1 agonists, serotonin 5-HT_{1A} and 5-HT_{1B} agonists, and other agents ameliorate dyskinesias in animal models and are being or will be tested in humans.[56,60,61]

Treatment

Currently, strategies for ameliorating levodopa dyskinesias with medications include replacing all or some levodopa with dopamine agonists, reducing levodopa and adding catechol-O-methyltransferase (COMT) inhibitors, or addition of amantadine. Studies showed that early treatment with agonists before the introduction of levodopa produces fewer dyskinesias in the medium term in patients with mild PD, but also provide less benefit, and levodopa is eventually required in most patients. When levodopa is started, the ultimate amount of fluctuations and dyskinesias appear to be about the same with early agonist treatment as with early levodopa treatment.[60] Dopamine agonists have a longer-lasting effect than levodopa in many moderate to severe patients and may allow a longer interdose interval, a lower total daily dose of levodopa, and thus fewer dyskinesias with the same benefit. Currently available agonists are not always potent enough to accomplish this. Adding the COMT inhibitors entacapone or tolcapone may allow reduction of levodopa dose with the same benefit. If this can be done with lower peak dose levels, dyskinesias may improve. However, many patients will not receive sufficient benefit from these agents to allow sufficient improvement in dyskinesias while maintaining adequate benefit. Amantadine was shown to reduce dyskinesias without worsening symptoms in most patients.[60] Unfortunately, amantadine is an anticholinergic as well as a dopamine releaser and can produce hallucinosis and psychosis in patients with mild dementia. Clozapine also reduces dyskinesias, but not to the same extent as amantadine and requires frequent white blood cell count due to the risk of agranulocytosis, which is not practical for many patients.

When medication adjustments are not successful, DBS of the globus pallidus or subthalamic nucleus usually significantly reduces dyskinesias.[62] It is so effective for this that some have suggested using DBS before dyskinesias become severe.[63] Deep brain stimulation may not be as effective for dystonia, but more important, it sometimes permanently worsens dementia in patients with preexisting cognitive impairment and has a small (1–2 per hundred) risk of intracranial hemorrhage and other potential adverse effects, including infection, stroke, lead erosion or fracture, and, of course, death.[64] Another strategy for ameliorating dyskinesias and other fluctuations from levodopa is to provide a continuous supply of dopaminergic stimulation.[65] This is currently difficult to do, requiring a pump to deliver a dopamine agonist such as apomorphine into the bloodstream or levodopa into the intestines. A small steady supply of medicine in patients with levodopa dyskinesias reduces off-time, which is not surprising. It is surprising that a continuous supply also produces fewer dyskinesias at the same amount of benefit, since the threshold for improvement and dyskinesias is almost the same in patients with motor fluctuations. Diphasic dyskinesias are harder to deal with than peak-dose dyskinesias. If medication is increased (sometimes dramatically), the DID pattern shifts to the peak-dose pattern, but this may not be beneficial to the patient. Diphasic dystonia is often painful, and that can be improved with botulinum toxin injections in low doses if a small number of muscles is involved.

Thus, the search continues for more effective strategies to deal with dyskinesias. There is no question that continuous supply of dopamine is beneficial in patients with motor fluctuations, but no one has yet demonstrated that continuous supply of medication in untreated patients would prevent the development of dyskinesias.[60] There are multiple animal models for levodopa dyskinesias, but therapies successful in ameliorating or preventing dyskinesias in animals have not so far generated breakthroughs in treating dyskinesias in humans, suggesting that the current models do not reflect the pathophysiology of human PD.

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Chapter 11

Wilson's Disease

Roger M. Kurlan

CLINICAL PHENOMENOLOGY

Wilson's disease (WD) is a hereditary disorder of copper metabolism. It affects between one in 30,000 and one in 100,000 people worldwide and was first described by Kinnier Wilson in 1912.[1] Symptoms of the illness usually first appear in the second and third decades of life, but they can start in childhood or sometimes after age 50. Table 11–1 summarizes the clinical features of WD, which can be heterogeneous. About 40% of patients present with neurological features.[2,3] Dysarthria (rapid speech, slurring, or hypophonia) and drooling are common symptoms. While a hypokinetic parkinsonian (akinetic-rigid) movement disorder can be the primary manifestation of the illness, hyperkinetic features may occur, particularly generalized dystonia and tremor. A Wilsonian tremor is classically a slow, high-amplitude and proximal tremor that has been described as "wing beating" when the arms are elevated, the arms are flexed at the elbows, and the hands are placed by the nose. The tremor may have intention qualities, and there may be other cerebellar signs including titubation, clumsiness of the hands, and gait ataxia. Dystonia often involves the face, causing grimacing and an open mouth.[4] Chorea may be seen with or without dystonia. Because of the parkinsonism and dystonia, handwriting is often affected. Saccadic ocular movements are often slow, and there may be pseudobulbar features. Seizures occur rarely in the condition.[5] About 15% of patients present with psychiatric manifestations, including cognitive impairment (often impaired abstract thinking), frank dementia, and personality changes (impulsivity, disinhibition, antisocial behavior, emotional lability, mood changes, anxiety, insomnia), sometimes causing problems at school or work and psychosis.[6,7]

Table 11–1 **Clinical Features of Wilson's Disease**

Neurological: Tremor, dystonia, chorea, parkinsonism, dysarthria, dysgraphia, pseudobulbar signs, slow saccades, seizures
Psychiatric: cognitive impairment, dementia, impaired abstract thinking, personality changes, impulsivity, disinhibition, antisocial behavior, emotional lability, mood changes, anxiety, insomnia
Hepatic: acute or chronic hepatitis, cirrhosis, portal hypertension, hepatosplenomegaly
Hematalogic: hemolytic anemia
Renal: renal failure, amino aciduria (proteinuria), renal tubular acidosis, hematuria, stones
Skeletal: osteoporosis, osteomalacia, osteoarthritis, fractures, chondrocalcinosis, osteochondritis dessicans
Ocular: Kayser-Fleischer rings, sunflower cataracts, night blindness, optic neuritis, strabismus, optic disc pallor

Wilson's disease is known for its systemic effects. About 40% of patients present with manifestations of liver disease, including acute or chronic hepatitis, cirrhosis, portal hypertension, or hepatosplenomegaly.[8,9] Those with a hepatic presentation tend to be younger, with 95% being under the age of 20 years (usually between 7 and 15 years of age). The final 5% of patients present with other systemic manifestations, including hemolytic anemia, renal dysfunction (renal failure, hematuria, amino aciduria, renal tubular acidosis, kidney stones),[10] skeletal disturbances most often affecting the knees and spine (osteoporosis, osteomalacia, osteoarthritis, spontaneous fractures, chondrocalcinosis, osteochondritis dessicans), or ophthalmologic abnormalities.[8] Often helpful in diagnosis, golden brown copper deposits, termed Kayser-Fleischer (KF) rings, can be seen in Descemet's membrane of the cornea at the outer circumference of the iris. A slit-lamp examination may be needed to visualize them. The upper pole is typically involved first. While the absence of KF rings is very rare in the presence of neurological manifestations, they may be absent in those without neurological involvement.[11] The KF rings can also be seen in other conditions besides WD, including primary biliary cirrhosis, chronic active hepatitis, hepatic cirrhosis, chronic intrahepatic cholestasis, topical copper solution treatment of the eye, and an intraocular copper foreign body. There are also some medical disorders that can cause non-KF pigmented corneal rings, including multiple myeloma, carotenemia-arcus senilis, and chronic jaundice.[11] Other eye features of WD can include sunflower cataracts, night blindness, optic neuritis, strabismus, and optic disc pallor.[12,13]

Wilson's disease can now be diagnosed by genetic testing, although this is expensive and not yet widely available.[14–16] Other supportive tests include the presence of KF rings, a low level of the blood-copper-transporting protein ceruloplasmin (<20 mg/dL),[17] high 24-hour urine copper excretion (>100 micrograms), and increased copper concentration (>250 micrograms/gram dry weight) in the liver as measured following a biopsy.[2,18] Decreased serum ceruloplasmin can be seen in some other medical conditions as well as WD, including sometimes in normal neonates, severe copper deficiency, hepatic failure, tropical and nontropical sprue, protein-losing enteropathy, nephrotic syndrome, Menke's disease, and Kwashiorkor. Hereditary deficiency of ceruloplasmin (aceruloplasminemia) is an autosomal recessive disorder due to mutations in the gene for ceruloplasmin and can cause reduced serum ceruloplasmin levels. This disorder characteristically presents with diabetes, retinal degeneration, and dementia, but it can also cause a movement disorder, typically blepharospasm and oral or cervical dystonia. Magnetic resonance imaging of the brain in WD is usually abnormal and typically shows increased T2 signal in the striatum and sometimes other basal ganglia structures.[19,20] There may be a striking bilateral concentric laminar T2 hyperinstensity in the putamen. Hyperintensity in the midbrain with sparing of the red nuclei and the lateral substantia nigra has been described as creating a "giant panda" or "double panda" sign.[21–23] Positron emission tomography, transcranial brain sonography, and MR spectroscopy all may show evidence of copper accumulation or neuronal loss.[24–26] The laboratory diagnosis of WD is summarized in Table 11–2.

Table 11–2 **Laboratory Diagnosis of Wilson's Disease**

ATP7B gene mutation
Kayser-Fleischer rings on slit-lamp examination
Low serum ceruloplasmin (<20 mg/dL)
High urinary excretion of copper (>100 micrograms/24 hours)
High liver copper concentration (>250 micrograms/g dry weight)
Increased T2 signal intensity in the striatum on magnetic resonance imaging

ETIOPATHOGENESIS

Wilson's disease is an autosomal recessive disorder of copper metabolism that is caused by a mutation in the gene *ATP7B* which resides on chromosome 13. The *ATP7B* gene codes for a metal-transporting P-type adenosine triphosphatase (ATPase) that functions in moving copper across intracellular membranes, particularly in hepatic cells. About 500 mutations in this gene have been identified, and those that severely interfere with the function of the ATPase are associated with earlier disease onset and more severe manifestations. Most patients are compound heterozygotes, having two different mutations of the gene. Generally, a few mutations predominate in different populations. Because the illness is autosomal recessive there is a 25% chance that a sibling of an affected patient has WD. First-degree relatives of a diagnosed case should be screened for WD. Asymptomatic carriers can be treated early, prior to the appearance of any clinical manifestations.

The affected gene in WD functions to incorporate copper into the blood transport protein ceruloplasmin and to facilitate biliary excretion of copper. When defective, the ceruloplasmin level becomes reduced. Copper is not properly excreted from the liver in bile and accumulates in hepatocytes. Free copper is liberated into blood resulting in increased urinary excretion and deposition in a variety of organs, particularly brain, corneas, bones, and kidneys. In the brain, accumulation of copper leads to neuronal loss, axonal degeneration, astrocytosis, and cavitary necrosis with a focus in the basal ganglia, particularly the caudate and putamen. There may be cortical atrophy as well. Nodular cirrhosis develops in the liver.

TREATMENT

Wilson's disease is a curable condition and progression can be completely prevented, so there should be a high index of suspicion for its diagnosis in patients, particularly younger than age 50, who present with the potential neurological, psychiatric, hepatic, hematologic, or bone manifestations of the illness. It has been said that WD should be tested for in any child, adolescent, or young adult presenting with an otherwise unexplained movement disorder. Treatment for WD is life-long, and most patients do well on effective treatment. The greatest risk for a poor outcome is patient noncompliance with the prescribed therapies. Available treatments for WD are summarized in Table 11–3.

Table 11–3 **Available Treatments for Wilson's Disease**

Low copper diet
Copper Chelators
D-Penicillamine
Trientine
Tetrathiomolybdate
Dimercaprol
Zinc
Liver transplantation
Symptomatic medications for dystonia, parkinsonism, seizures

Diet. Patients should meet with a dietician to be instructed in how to avoid the major dietary sources of copper. High copper-containing foods include nuts, liver, mushrooms, chocolate, coffee, and shellfish. They should abstain from alcohol intake.

D-penicillamine. Historically this has been the drug of choice for treating WD and its benefits are well documented. It acts as a copper chelator, enhancing urinary excretion of the metal. In addition, the drug can induce metallothionein, an endogenous chelator of metals. Thus, the drug reduces the body burden of copper while also leading to the sequestration of free intracellular copper. The dose of penicillamine is gradually increased to 1000–1500 mg/day in 2–4 divided doses, usually given 1 hour prior to or 2 hours after food. The presence of food substantially impairs absorption of the drug.

Penicillamine is associated with a number of potential adverse effects, some of which may require withdrawal of the medication. Early on, patients may experience a sensitivity reaction with fever, rash, lymphadenopathy, neutropenia, thrombocytopenia, and proteinuria. If this occurs, the drug may have to be stopped and then reintroduced with steroid cover. Regular monitoring of blood counts and urinary protein is recommended. Late side effects typically appear after a year or so and can include a protein-losing nephropathy, bone marrow suppression (thrombocytopenia, aplastic anemia), a lupus-like systemic inflammatory

disorder, myasthenia gravis, and skin changes. Penicillamine can affect pyridoxine (vitamin B6) metabolism, so supplementation with this vitamin (25 mg/day) is usually done. For severe adverse effects, penicillamine should be stopped and replaced with an alternative therapy. This occurs in about one-third of treated patients. For any chelator, excessive treatment can lead to copper deficiency, which can manifest as sideroblastic anemia and hepatic siderosis.

Trientine. This drug is generally viewed as a weaker chelator than penicillamine and it is also more poorly absorbed and more expensive. However, it tends to be better tolerated. It can be considered as an option for first-line therapy. Trientine is started at 1200–1800mg/day in 2–3 divided doses, also given at least 1 hour before or 2 hours after food. The maintenance dose is 900–1200 mg/day. Pancytopenia can occur rarely with this drug, but hypersensitivity reactions and renal toxicity have not been described.

Ammonium Tetrathiomolybdate. Taken with meals, this drug forms a complex with copper in the food, thus preventing absorption. When taken between meals it is absorbed and complexes with copper in the blood, leading to hepatic metabolism and excretion in the bile. It has similar efficacy to trientine. Potential side effects include anemia, leukopenia, and elevation of liver enzymes. Unfortunately, this drug is not widely available.

Zinc. Zinc induces intestinal metallothionein, which binds to copper and reduces absorption. Hepatic metallothionein is also induced, thereby reducing the toxic effects of free copper. In adults, elemental zinc is prescribed at 150 mg/day given in 3 doses. Food should be avoided around the time of dosing if possible, but many patients cannot tolerate taking zinc on an empty stomach due to dyspepsia and gastritis. Using other formulations of zinc (acetate, sulfate, gluconate) may improve gastrointestinal tolerability. One study found that zinc produced equivalent efficacy to penicillamine in WD patients with predominantly neurological features.

The optimal treatment approach for WD has not been established. For symptomatic patients, initial treatment with dietary restriction and a chelator (penicillamine or trientine) appears to be appropriate. When selecting trientine, many clinicians combine it with zinc. Clinical improvement usually becomes evident about 3 months after starting chelation therapy, but it may be delayed for up to a year. Once the patient has responded and becomes asymptomatic, many clinicians switch to zinc for maintenance therapy. Zinc is also considered as initial therapy for mild cases and for prevention in those with the genetic mutation. Zinc also appears to be the safest agent in pregnancy. Clinical follow-up with routine, long-term monitoring of copper concentrations and excretion is essential. Successful decoppering therapy is marked by an initial increase in copper excretion that later falls. During chelation therapy, 24-hour urinary excretion of copper should be in the range of 200–500 micrograms. During zinc therapy the target is less than 125 micrograms. The non-ceruloplasmin-bound (free) serum copper typically falls during decoppering therapy and the target is 50–250 micrograms/L. Kayser-Fleischer rings can also be seen to fade over time with effective treatment.

About 10%–20% of patients with neurological manifestations of WD experience a clinical deterioration upon initiation of penicillamine therapy. The frequency of neurological deterioration upon starting therapy appears to be lower for trientine than for penicillamine. This problem has been ascribed to excessive release of copper into the circulation with additional accumulation in the brain. To avoid this potential complication, it has been suggested that penicillamine dosage should be adjusted in order to maintain a high urinary excretion of copper while at the same time keeping the serum copper steady (i.e., not allowing it to drop). One can also consider switching from one chelator to the other or using ammonium tetrathiomolybdate. Injections of dimercaprol can be considered in desperate cases but cannot be used chronically because the injections are painful.

For patients who deteriorate, liver transplantation is an option when the hepatic manifestations predominate. It has been reported that liver transplantation can reverse neurological deficits even when there is stable liver disease, but the value of liver transplantation for severe neurological WD remains unsettled.

For disabling dystonia, anticholinergic drugs or botulinum toxin injections can be considered for symptomatic benefits. Parkinsonism in WD may respond to antiparkinsonian drugs.

SUMMARY

Wilson's disease is perhaps the one condition that clinicians should always think about when dealing with a child, adolescent, or young adult patient presenting with a hyperkinetic or hypokinetic movement disorder. The reason is that the condition is completely curable with proper therapy. Probably the best screening test is to measure serum ceruloplasmin concentration or a slit-lamp eye examination. In addition, clinical expression can be prevented in relatives found to have the illness.

Dystonia and tremor are the most common hyperkinetic movement disorders in WD, although chorea may occur. Once diagnosed, institution of a low copper diet and chelation therapy (penicillamine or trientine with or without zinc) is recommended. The dose of the chelator should be titrated gradually to improve tolerability. Initial decoppering should probably also proceed gradually to reduce the risk of acute neurological deterioration that can occur upon initiation of therapy. Once the condition is stabilized, zinc appears to be the best option for maintenance therapy. Careful and long-term clinical and laboratory monitoring is essential to ensure proper treatment. If needed, standard symptomatic medications for dystonia or other neurological features can be used.

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Chapter 12

Peripherally Induced Movement Disorders

Paul E. Greene

INTRODUCTION

There is a variety of rare movement disorders associated with peripheral trauma and other forms of peripheral injury. For most of these disorders, there is ongoing controversy about whether the movement disorder originates in the peripheral nervous system or whether peripheral injury is the trigger for a centrally generated disorder. In some cases, the involuntary movements fit easily within traditional movement categories such as dystonia, tremor, and myoclonus. There are other disorders, such as rare isolated dyskinesias, where the movements are not easily categorized and so do not comfortably fit in any of the other hyperkinetic movement categories. Since there are few common principles in these conditions, I will discuss them each separately.

HEMIFACIAL SPASM

Hemifacial spasm (HFS) is a disorder in which there are involuntary contractions on one side of the face in muscles innervated by the facial

nerve (cranial nerve VII). According to Digre and Corbett, the condition was first described in 1875 by Schultze, but was first separated from other forms of facial twitching by Gowers in 1888.[1–3] According to Ehni and Woltman, the clue to the peripheral etiology of the condition came with the observation by Habel in 1898 of a woman whose HFS persisted after she developed an ipsilateral hemiparesis from a stroke, whereupon Babinski hypothesized that the spasms originated in the facial nucleus or facial nerve.[4–6] Hemifacial spasm is rare in the United States. The age-adjusted incidence was 0.78 per 100,000 per year in Olmsted County, Minnesota, between 1960 and 1984, which was 3% of the incidence of Bell's palsy (25.2 per 100,000).[7] The average prevalence was 7.4 per 100,000 for men and 14.5 per 100,000 for women, but the prevalence in women over the age of 60 was considerably higher (almost 30 per 100,000).[7] The only published prevalence outside the United States is from Norway, where the average prevalence was 9.8 per 100,000 and the prevalence in older individuals (age > 70) was 39.7 per 100,000.[8] These estimates are probably underestimates, because they were based on referrals to medical centers and because there appears to be substantial underdiagnosis of HFS in primary care settings.[8,9] The majority of cases of HFS are sporadic, although there are occasional reports of familial cases.[10–12] Hemifacial spasm appears to be more common in people of Chinese descent, but there is no estimate of actual prevalence in any Asian country. There is an overrepresentation of people of Asian background in movement disorder clinics in the United States with HFS compared to dystonia.[13] The generally accepted explanation for this increased prevalence is a genetically based variation in vascular anatomy that predisposes vessels to contact the facial nerve.[14]

The contractions in HFS usually start as individual muscle twitches, usually in the eyelids, causing extra blinks. As the disease progresses, other muscles innervated by the facial nerve become involved, and by the time most patients request treatment, most or all facial nerve innervated muscles are involved. The typical appearance of the face when all muscles are involved is shown in Figure 12–1. Trains of twitches develop, and when the disease is severe there are episodes of sustained muscle contraction produced by fusion of individual twitches. Patients may have periods where the eye is completely closed. Pain is rare (except in the rare patients with tic convulsif, a combination of HFS with trigeminal neuralgia) and may be more common in cases with involvement of the posterior auricular muscles. The contractions of HFS diminish, but do not disappear, during sleep.[4] Once multiple facial nerve muscles are involved, HFS progresses slowly, if at all. Although facial asymmetry is common, somewhat less than 15% of patients develop marked facial weakness and most patients with an asymmetric face will have a symmetric smile.[4] In the largest epidemiological study to date, including 1,003 clinically diagnosed patients (about one-quarter severely affected), 75.2% of cases started in the orbicularis oculi, 18.4% had clicking in the ear (at least in some cases from involvement of the stapedius muscle), 7.8% involved the auricular muscles, 0.6% involved occipital muscles, 1% were bilateral, and 2.3% had a family history of HFS.[10,15] Patients in the large Chinese cohort reported exacerbation of contractions with stress/anxiety, talking, cold, wind, and light stimulation, while relaxation and facial massage were alleviating factors—see Table 12–1. It is surprising that so many central nervous

Figure 12–1. Facial appearance in HFS. Facial appearance during a spasm. The left palpebral fissure is narrowed, the corner of the mouth is pulled to the left, the left corner of the mouth is elevated, there is deepening of the left nasolabial fold and contraction of the left platysma. (From: Marsden's Book of Movement Disorders. Ivan Donaldson, C. David Marsden, Susanne Schneider, and Kailash Bhatia. Chapter 52: Miscellaneous movement disorders. Figure 52.4.)

Table 12–1 **Factors Affecting Symptoms in 1003 patients with HFS**

Factors	Aggravate	Alleviate	Irrelevant
Stress/anxiety	838	3	162
Relaxation	18	759	226
Talking	498	58	447
Reading or watching	318	61	624
Facial massage	30	478	495
Exercise	93	107	803
Chewing	157	39	807
Alcohol	95	49	859
Cold, wind and light stimulation	477	7	519
Others	96	IS	894

From: Wang L, Hu X, Dong H, et al. Clinical features and treatment status of hemifacial spasm in China. Chin Med J 2014;127:845–849. Table 1.

system changes affect a condition generally felt to originate in the peripheral nervous system. Consequences of HFS included embarrassment (56%), interference with vision (52.7%), facial discomfort (41.3%), and sleep disorder (35.2%). Hypertension was present in 28.4%, but there was no control population.[10]

There are few other diseases that produce this picture. Facial dystonia is usually bilateral and usually does not produce muscle contractions that are synchronous in all involved muscles on one side of the face. Even in the rare patient with bilateral hemifacial spasm, the spasms are asynchronous from side to side, so that abnormal lid closure would not resemble the eye closure of blepharospasm, which is synchronous. The rippling movements of facial myokymia are often unilateral, but do not involve multiple muscles synchronously and are much slower than the twitching seen in HFS. Motor tics in the face may produce rapid twitching, but are usually preceded by a warning and are suppressible. Synkinesis after Bell's palsy does produce synchronous contractions in the upper and lower face but does not produce spontaneous contractions except in patients developing HFS in addition to the synkinesis. Epilepsia partialis continua does mimic the movements of HFS but usually involves the masseters (cranial nerve V) and is rarely limited to the face. There have been patients identified with psychogenic HFS, but these patients rarely have synchronous brief contractions in multiple facial-nerve-innervated muscles.[16] Although it is rarely necessary for diagnosis, there is a clinical sign that may be unique to HFS: the so-called "second Babinski sign" or "Babinski-2" sign, in which the eyebrow raises when the lid blinks closed (as opposed to blepharospasm in which the eyebrow usually pulls down as the eyes close (Figure 12–2).[17] All patients with HFS should have an MRI with attention to the posterior fossa, to identify the uncommon surgically accessible causes of HFS.

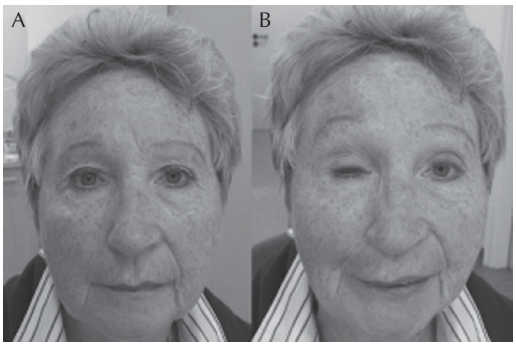

Figure 12–2. The other Babinski sign in HFS. Patient with right hemifacial spasm. Frame A, between spasms with right eyebrow slightly elevated. In Frame B, during a spasm, the right eyebrow is clearly elevated. (From: Pawlowski M, Gess B, Evers S. The Babinski-2 sign in hemifacial spasm. Mov Disord 2013;28:1298–1300. Figure 1.)

The etiology of HFS is thought to be compression of the facial nerve where it exits the brainstem, usually by an aberrant artery, such as the anterior inferior cerebellar artery, posterior inferior cerebellar artery, or internal auditory artery, but sometimes by a vein.[1,18] Irritation of the nerve at this site is felt to generate spontaneous electrical activity, causing muscle contractions, and an ephapsis leading

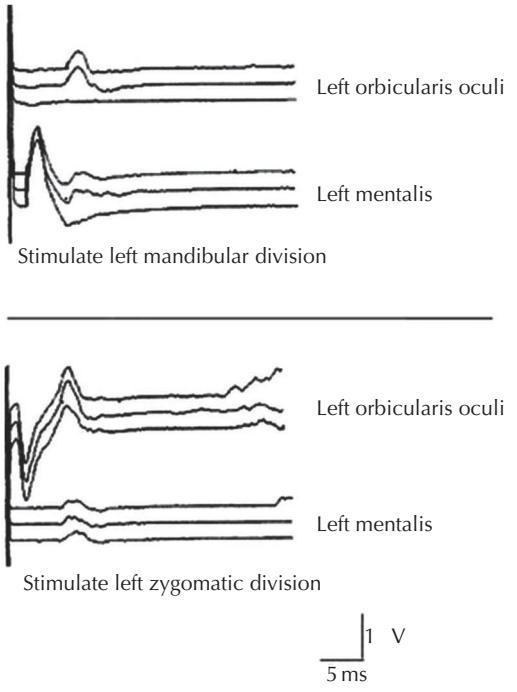

Figure 12–3. Abnormal cocontraction of muscles in hemifacial spasm. Abnormal spread of response in a patient with hemifacial spasm (so-called lateral spread response). With stimulation of the mandibular branch of the facial nerve (*top*), a delayed response is recorded from the ipsilateral orbicularis oculi. With stimulation of the zygomatic branch of the facial nerve (*bottom*), a delayed response is recorded from the ipsilateral mentalis. Unlike a synkinesis after a Bell's palsy, the spread of response in hemifacial spasm is due to "crosstalk" or spread of electrical signal across nerve fibers, and the abnormal response may not occur with all stimulations. (From: Clinical Neurophysiology (3rd ed.) Daube J, Rubin DI. Chapter 31: Cranial reflexes and related techniques. Figure 31-11.)

to "crosstalk" or simultaneous activation of axons going to different parts of the face[19] (see Figure 12–3). However, other causes of compression besides normal arteries rarely occur, including draining veins of arterio-venous malformations (AVMs), aneurysms, and tumors (usually benign). Plaques of multiple sclerosis in the central myelin at the root exit zone of the facial nerve have also been associated with HFS (Table 12–2).[20] If compression by aberrant arteries is the most common cause for HFS, it would be reasonable that arterial hypertension causing ectatic vessels might be a risk factor for HFS. Older reviews found the data equivocal.[4] More recent carefully controlled studies

Table 12–2 **Conditions Associated With HFS**

Vascular Abnormality
1. AV malformation
2. AV fistula
3. Fusiform aneurysm
4. Venous angioma
5. External carotid artery compression
6. Vertebrobasilar dolichoectasia
7. Compression of contralateral vertebral artery

Mass Lesion
1. Parotid tumor
2. CP angle lipoma
3. Acoustic neuroma
4. Arachnoid cyst
5. Meningioma
6. Schwannoma
7. Hemangioma
8. Glomus jugulare tumor
9. Astrocytoma
10. Ependymal cyst
11. Pontine glioma
12. Epidermoid cyst
13. Cerebellar gangliocytoma

Bony Lesion or Structural Abnormality
1. Paget's disease
2. Marfan's syndrome
3. Chiari malformation
4. Focal bone hyperostosis

Demyelinating

Stroke

Infection
1. Otitis media
2. Neurocysticercosis
3. Tuberculosis meningitis

Peripheral facial nerve injury

Bell's palsy

Modified From: Yaltho TC, Jankovic J. The many faces of hemifacial spasm: differential diagnosis of unilateral facial spasms. Mov Disord 2011;26:1582–1592. Table 2.

failed to find such an association.[21] Because HFS starts in the orbicularis oculi, you would also expect that the fibers of the facial nerve that innervate the orbicularis oculi would be the most vulnerable to compression and reside on the outside of the nerve, where they would be the first fibers to be compressed. The orientation of fibers at the root exit zone is not known, but the orbicularis oculi fibers are not

superficial in more peripheral regions of the nerve.[22]

Despite this, there has long been a minority view that compression of the facial nerve as it leaves the brainstem may not always be the proximate cause for HFS. Occasionally, HFS involving most facial nerve muscles is seen after a peripheral lesion of a branch of the facial nerve.[23] There is no obvious physiological mechanism whereby aberrant regeneration or formation of an ephapsis at the injury site could cause this. This suggests that the peripheral injury triggered a change in the facial nerve nucleus.[23–25] HFS rarely develops after Bell's palsy, but despite the rarity, the risk of developing HFS after Bell's palsy seems greater than the risk in the population at large. In a large referral center, 10.7% of patients referred with HFS had a preexisting Bell's palsy and Bell's palsy was the most common cause for secondary HFS.[20] Others propose that either a predisposition to nerve damage increases the risk of both HFS and Bell's palsy or that a presumed viral infection causing Bell's palsy also causes adhesions in the posterior fossa increasing the risk of microvascular compression of the facial nerve.[26] If there is a central origin for HFS, the likelihood of a facial nucleus change would increase as the site of compression is closer to the nucleus. In addition, there is a small amount of physiological data suggesting excitability of the facial nerve nucleus in HFS: enhanced F waves, increased recovery of the R2 component of the blink reflex, impairment of the inhibitory trigeminofacial reflexes, low threshold and enhanced amplitude of the R1 component of the blink reflex, evidence that crosstalk in idiopathic HFS may occur in the facial nerve nucleus, and other indirect findings.[23,27,28] In one survey, it was found that an unexpected percentage of patients with HFS also had dystonic blepharospasm, suggesting to the authors that a central reduction in inhibition might have caused both conditions.[24] This alternative hypothesis is strengthened by the small number of cases of HFS associated with central lesions at the site of the facial nerve nucleus.[29] However, central nervous system tumors in the vicinity of the facial nerve nucleus may extend along the nerve to the root exit zone (unpublished observation).

Hemifacial spasm can be treated with medications, botulinum toxin (BTX) injections, or by craniectomy and separation of offending vessels from the point of compression where the facial nerve leaves the brainstem (microvascular decompression). Medications are generally the least successful treatment. There is a single controlled study suggesting benefit from orphenadrine and dimethylaminoethanol,[30] but this treatment is rarely used today. Successful treatment of HFS in small numbers of patients has been reported with carbamazepine,[31,32,33] clonazepam,[34] baclofen,[35] gabapentin,[36,37] and felbamate.[38] The success rate of these medications is low: improvement was "rare" in 218 patients treated with carbamazepine and 148 patients treated with phenytoin in one large series.[39] At the Columbia University Movement Disorder Center, patients reported moderate to marked benefit in 19 of 87 trials with carbamazepine, clonazepam, or baclofen, but benefit was not sustained in any of these cases (unpublished data). However, these series consisted of patients referred for BTX or surgery, presumably biased toward patients failing medical therapy.

Botulinum toxin has proved extremely useful in treating HFS, especially for orbicularis oculi contractions, for which most series report an almost 100% success rate.[40] The success rate is much lower for lower facial muscles (although this is rarely reported) due to the development of facial weakness before resolution of the spasms. Excess weakness of the orbicularis oculi rarely occurs, although leakage to the levator palpebrae causing ptosis is common (perhaps more common than in dystonic blepharospasm). Diplopia is an uncommon side effect, usually due to leakage to one or another lateral rectus muscle, but the incidence depends on technique: use of small-bore needles in the region of the lateral canthus may predispose a patient to diplopia because greater pressure is required to expel the toxin, which then squirts out and affects the lateral rectus. Other side effects include ecchymoses at the injection site, dry eye, excess tearing, and bagginess under the eye. Lower lid entropion is very rare (paradoxically, BTX is a treatment for idiopathic lower lid entropion). All side effects from BTX injections are transient and depend on the injection technique. For instance, risk of ptosis depends on the volume of injection (greater the volume, higher the risk) and site of injections (closer to the midline of the upper lid, the greater the risk). For a list of side effects and durations

Table 12–3 **Side Effects of Botulinum Toxin Injections for HFS**

Side Effects	*n (%)*	Mean Onset Time (days)	Mean Duration Time (days)
Droopy mouth	146 (22.0)	5.6	31.1
Lid weakness	101 (15.2)	4.3	20.7
Teary	48 (7.2)	3.5	9.1
Ptosis	30 (4.5)	4.7	27.3
Edema	24 (3.6)	2.1	8.3
Frontalis weakness	22 (3.3)	4.1	26.8
Blurred vision and diplopia	16 (2.4)	5.8	20.1
Frown weakness	11 (1.7)	8.8	33.6
Dry eye	3 (0.5)	2.3	13.7
General reaction	1 (0.2)	2.0	6.0
Other	14 (2.1)	8.1	24.2

From: Wang L, Hu X, Dong H, et al. Clinical features and treatment status of hemifacial spasm in China. Chin Med J 2014;127:845–849. Table 3.

in a large center, see Table 12–3. There is no evidence that chronic BTX injections induce any permanent change, and patients injected for HFS do not develop antibodies to BTX, presumably because of the low doses involved. Benefit from BTX injections for HFS lasts 3–6 months, after which symptoms return and repeat injections are required.

Microvascular decompression, first popularized by Janetta in the 1970s, appears to be the definitive treatment for HFS.[41] When a vessel is compressing the facial nerve, a sponge is placed between the nerve and the vessel. In the largest series published to date, 1,342 patients were followed for up to 3 years and 90.5% were felt to have an excellent outcome after the first surgery;[42] 2.3% of patients did not improve and had a second surgery (in the opinion of the surgeons the wrong vessel had been decompressed) and 90% of these were felt to have an excellent response.[42] This is typical of most reports, although the results can vary widely (presumably depending on technique, type of patient, and type of assessment). In a review of over 5,000 patients operated between 2000 and 2011, improvement was rated as 75% to 100%.[43] There are some skeptics, however, who acknowledge benefit from surgery but question the rationale. In addition to questioning whether compression is the only cause for HFS (there are cases where no compressing vessel is found at the time of surgery), they also point out that placing a sponge on the root exit zone of the nerve may stop spasms even when there is no compressing vessel.[44]

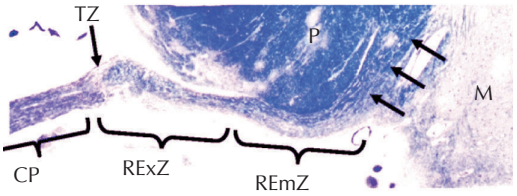

Figure 12–4. Emergence of the facial nerve from the brainstem. Photomicrograph of the facial nerve as it leaves the brainstem showing the root emerging zone (REmZ), the root exit zone (RExZ), the transition zone (TZ), and the cisternal portion (CP) of the nerve. P = pons, M = medulla. (From: Iijima K, Horiguchi K, Yoshimoto Y. Microvascular decompression of the root emerging zone for hemifacial spasm: evaluation by fusion magnetic resonance imaging and technical considerations. Acta Neurochir 2013;155:855–862. Figure 1.)

The site of vascular compression in HFS is usually identified as the root exit zone, but vascular compression of the root exit zone of the facial nerve is not found in all cases, and current MRI techniques are not yet sufficient to guarantee that an offending vessel will be found. The surgical anatomy of the facial nerve is complicated. The facial nerve emerges from the brainstem at the pontomedullary junction and is adherent to the pons for about 10 mm (the root emerging zone) before it separates from the brainstem at the root exit zone (Figure 12–4). This root emerging zone is difficult to see during the usual surgical approach and may account for some failures of microvascular decompression.[45] In other cases, the compressing vessel deeply indents

the facial nerve into the brainstem and this may not be detected during the usual surgical approach, resulting in lack of improvement.[46] This brainstem compression can sometimes be detected by heavily T2-weighted MR cisternography.[46] Rarely, as mentioned previously, a posterior fossa vein may be the cause of HFS and may be overlooked during a microvascular decompression, resulting in surgical failure.[18] Even when a compressing vessel is identified, it may not be the only culprit, so most surgeons monitor spread of signal between different branches of the facial nerve. If spread is not abolished when a vessel is decompressed, another cause for HFS must be found.[18] It is surprising that ephaptic transmission across fibers ceases immediately when the vessel is removed from the nerve (Figure 12–5).

However, at least 1%–3% of patients experience return of spasms and require repeat operation, possibly when the sponge is dislodged.[10,42] Serious complications (death, stroke, or cerebellar hematoma) are rare in most series. In two large reviews, permanent hearing loss occurred in up to 2.7%, permanent facial weakness in up to 1.2%, and cerebrospinal fluid leak in up to 13%.[43,47] Stroke occurred in up to 5.6% and death in up to 2.6%.[43,47] Other rare surgical complications, including wound infection or hematoma, bacterial meningitis, pulmonary embolism, cerebellar edema, hydrocephalus, and pseudomeningocele are also possible.[43,47] For all these reasons, many patients prefer to avoid surgery if possible, and BTX injections are the treatment of first choice for most patients.

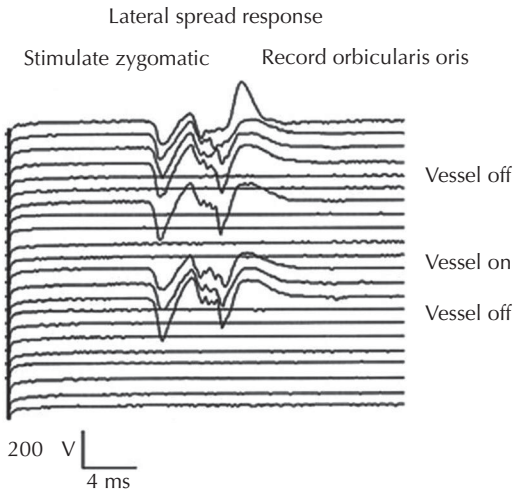

Figure 12–5. Abnormal spread of signal in HFS ceases immediately after microvascular decompression. During the microvascular decompression surgery, abnormal spread of electrical signal from the zygomatic branch of the facial nerve to the orbicularis oris disappears when the blood vessel is lifted off the facial nerve and returns when the vessel is in contact with the facial nerve. (From: Clinical Neurophysiology (3rd ed.) Daube J, Rubin DI. Chapter 43: Brain stem and cranial nerve monitoring. Figure 43-8.)

SPASTIC PARETIC HEMIFACIAL CONTRACTURE

This exceedingly rare condition may not truly belong with hyperkinetic disorders, as only tonic spasms are present, but it is sometimes mistaken for HFS and so I mention it here. Patients with intramedullary lesions in the vicinity of the facial nerve nucleus develop tonic contractions of muscles innervated by the facial nerve.[48,49] This is usually accompanied by myokymia, but the myokymia may disappear over time. Tumors are a common cause for this, so many patients will have slight facial weakness. If the facial weakness becomes severe, the spasms abate. Because multiple sclerosis is another cause, some patients (but not all) will be spastic, accounting for part of the name. An example of a patient with multiple sclerosis and spastic paretic hemifacial contracture is shown in Figure 12–6. Other causes for brainstem damage can also cause this, including autoimmune disease and radiation damage. At the Columbia University Movement Disorder Center, we saw one case associated with brainstem radiation with spasms triggered by voluntary movement (unpublished observation).

PAINFUL LEGS-MOVING TOES

The syndrome of painful legs accompanied by toe or foot movements (painful legs-moving toes, or PLMT) was first described by Spillane et al in 1971.[50] All subsequent elaborations on the syndrome are based on clinical observation, as there are no pathognomonic physiological, imaging, or pathological findings. One helpful

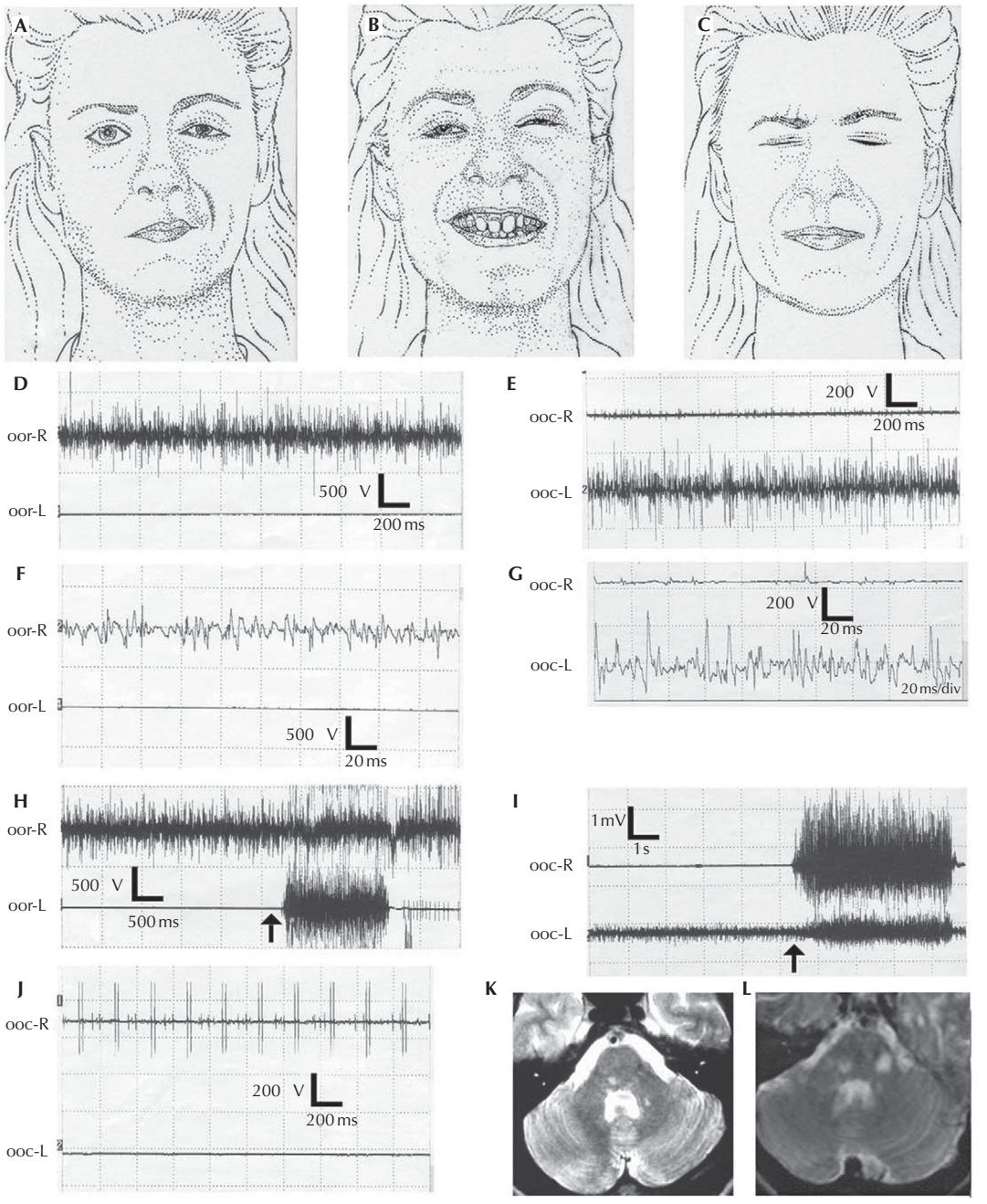

Figure 12–6. Spastic paretic hemifacial contracture in multiple sclerosis. A (line drawing): Patient with multiple sclerosis and spastic paretic hemifacial contracture (SPHC) at rest with sustained narrowing of the palpebral fissure, elevation of the angle of the mouth and the brow, and deep nasolabial fold. B, C (line drawings): Same patient with voluntary smile and squeezing eyes closed showing mild ipsilateral facial paresis. D–G: EMG recordings from OOr and OOc in patients with SPHC on the right (patient 1–D,F) and left (patient 2–E,G). Continuous contraction on the affected side is compared with EMG silence on the normal side. . H, I: recordings from OOr and OOc in the same two patients before and during voluntary contraction (starting at the arrow), showing greater activity during voluntary contraction of the normal muscle than activity in the abnormal muscle.. J: Myokymic discharges (doublets) in the affected OOc. K, L: MRI T2-weighted axial images during the episode of SPHC with lesion of the dorsal midpontine tegmentum near the facial colliculus, ipsilateral to SPHC in patient 1 (K) and bilateral lesions in the same region with the larger lesion ipsilateral to SPHC in patient 2 (L). (OOr, orbicularis oris; OOc, orbicularis oculi; R, right; L, left). (From: Koutsis G, Kokotis P, Sarrigiannis P et al. Spastic paretic hemifacial contracture in multiple sclerosis: a neglected clinical and EMG entity. Mult Sclerosis 2008;14:927-932 Figure 1.)

feature is the observation that, unlike most movement disorders, the movements continue during sleep in many patients with this syndrome. The pain is described in various ways, with aching, pulling, cramping, throbbing, and burning being common descriptors (numbness is rare except in patients with preexisting numbness from neuropathy).[51] The pain is rarely in an identifiable distribution, includes the toes and foot, but often extends up the leg. For most patients, the pain is unremitting and unchanging, although some report a change with activity (for better or worse). The toe movements may involve individual slow toe flexion and extension (often in the 0.5–2 Hz range) or simultaneous movements of all toes[52] (see Figure 12–7). Repetitive sideways toe movements of individual toes or fanning of all toes are characteristic of PLMT and are rarely seen in other dyskinetic disorders. Other complex movements may be present, including myoclonic and dystonic movements.[51,53] When dystonic movements dominate the clinical picture, this has been called "dystonic painful legs-moving toes." The movements may involve one or both feet. The movements are too regular and predictable to be confused with chorea, but sometimes may be similar to tardive or levodopa dyskinesias. For most patients, pain is the most disabling feature, although the movements are bothersome at times.

Starting with the original report, it was recognized that finger movements similar to the toe movements might accompany pain in the arms (the painful arms-moving fingers syndrome).[50] This syndrome, as is the case with PLMT, can involve one or both arms and one or more fingers. It was also noted in the original report that identical movements could be present without limb pain (painless legs-moving toes; painless arms-moving fingers). Patients usually develop pain in the limb before the movements, but an occasional patient with painless limb-moving digits will eventually develop pain.

Because of the characteristic slow finger or toe movements, clinical diagnosis is usually easy. It may be difficult to distinguish PLMT from tardive and levodopa dyskinesias, especially if there is no pain (in the case of possible painless limb-moving digits). Even when pain is present, there is a possibility of drug-induced dyskinesias superimposed on another cause for pain. If there is a serious diagnostic issue about possible levodopa-induced dyskinesias, levodopa can be temporarily lowered or discontinued, so it is always possible, at least theoretically, to distinguish PLMT from levodopa dyskinesias (it is not always easy to lower levodopa in Parkinson's disease). It can be more troublesome to distinguish tardive dyskinesias from PLMT. Even though the treatments for PLMT and tardive dyskinesias

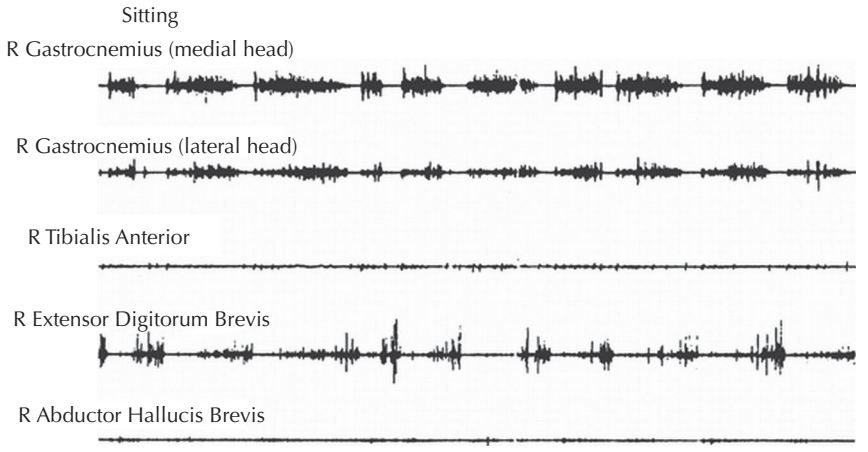

Figure 12–7. EMG in painful legs-moving toes. EMG of a patient with painful legs, moving toes showing alternating activity in the right gastrocnemius (flexion) and right extensor digitorum brevis (extension). Alternating abduction and adduction of the toes is also common. (From: Marsden's Book of Movement Disorders. Ivan Donaldson, C. David Marsden, Susanne Schneider, and Kailash Bhatia. Chapter 48: Painful legs and moving toes. Figure 48.2.)

are different, each one is difficult to treat, and so using response to therapy as a diagnostic tool is useful only if positive. One maneuver that is sometimes helpful is a sleep study, as the movements in drug-induced dyskinesias disappear in sleep while PLMT often does not. As far as I can tell, no psychogenic movements resembling PLMT have been reported, but that etiology is possible.[52] Unlike tardive or levodopa dyskinesias, if psychogenic etiology is suspected, a sleep study would not help, because psychogenic movements can occur during sleep.

Multiple different EMG patterns have been described in PLMT, including some muscle activity fast enough to qualify as myoclonus. It is not clear whether this reflects variation in the syndrome of PLMT or whether the EMG patterns are contaminated by the underlying peripheral diseases that are often present in PLMT.[51] The overwhelming majority of patients in large series have had historical, clinical, or electrophysiological evidence of radiculopathy or neuropathy. Some patients develop PLMT in the setting of spinal cord or brain conditions (such as Hashimoto's thyroiditis and Wilson's disease). Even when a peripheral disease such as radiculopathy is present, removing the irritation (e.g., removing a protruding disc) may relieve the symptoms, may not relieve the symptoms, or, most telling, may have the symptoms temporarily disappear only to later return.[52] All this has suggested to some that PLMT is a central disease with a peripheral trigger. Because of the extreme rarity of PLMT, it is difficult to systematically evaluate any particular hypothesis, thus ensuring that hypothesizing will continue for the foreseeable future.

Treatment of PLMT is difficult. Because of the rarity of the disease, there are few prospective or controlled studies. Reich lists some of the treatments that have been used, including sympathetic blockade, spinal cord stimulation, antidepressants, analgesics, baclofen, neuroleptics, and many others (Table 12–4). Botulinum toxin may reduce the movements (although toe movements require injection through the sole of the foot, which is unpleasant to say the least), but pain, not movements, is usually the major problem, and BTX only rarely helps pain.[54] In a large series of 55 patients, only 13% had a good outcome after multiple attempts at treatment.[51] There is occasional dramatic improvement with clonazepam.[52]

Table 12–4 **Treatments for Painful Legs–Moving Toes Syndrome**

Treatments reported to be effective for painful legs and moving toes
Sympathetic blockade
Epidural blockade
Transcutaneous electrical nerve stimulation
Application of local cold, heat, or tactile stimulation
Vibratory stimulation
Spinal cord stimulation
Botulinum toxin injections
Antiepileptic agents (gabapentin, carbamazepine, pregabalin)
Benzodiazepines
Tricyclic antidepressants
Adenosine triphosphate
Calcitonin
Cannabis
Antispasticity agents (baclofen)
Progabide
Quetiapine

From: Reich SG. Painful legs and moving toes. In: WJ Weiner, E Tolosa, eds. Handbook of Clinical Neurology, Vol. 100 (3rd series: Hyperkinetic Movement Disorders. Amsterdam: Elsevier; 2011:376–383. Table 29.3.

JUMPING STUMP, JUMPING SHOULDER

There are a large number of descriptions of focal movement disorders in the literature, some associated with peripheral trauma and some without any clear preceding stimulus. Some are painless and some painful, similar to the situation in PLMT. Most of these were characterized clinically and lacked sufficient physiological study to confidently place them in meaningful groups. I choose to start the discussion with the jumping stump syndrome, since this is one of the most dramatic examples. Amputees who develop involuntary movements of the remaining stump were reported at least as early as the American Civil War.[55] These movements have variously been described as jerky, semirhythmic,

dystonic and myoclonic. To my eye, what is striking about the Jumping Stump syndrome is that the movements are usually a mixed movement disorder consisting of both fast and slow, sustained movements. One option is to group together mixed movement disorders triggered by peripheral trauma or in the setting of potential abnormal sensory input (as in peripheral neuropathy or radiculopathy). In that case, jumping stump, jumping shoulder (after shoulder surgery, mastectomy or thoracotomy), abdominal movements after abdominal surgery, back movements after surgery for scoliosis, scapula movements after thoracic surgery, quadriceps movements after surgery for a femoral nerve sarcoma, and many others could be grouped together.[52] Just as in PLMT with and without pain and with and without an identified peripheral lesion, the cases of mixed movement disorders in various focal parts of the body without an obvious lesion could be categorized together (belly dancer's dyskinesia, for example).

COMPLEX REGIONAL PAIN SYNDROME

Complex regional pain syndrome (CRPS, or reflex sympathetic dystrophy = RSD) is a posttraumatic syndrome characterized by autonomic features such as edema, change in skin color or temperature, pain, allodynia or hyperalgesia, and limited range of motion that persist long after the effects of the initial injury are gone.[56] Once the syndrome was extended to patients with similar symptoms and signs but in the absence of a precipitating event, the diagnosis became extremely problematic.[57] Some patients have evidence of nerve damage (type II), while others have no such evidence (type I). Patients diagnosed with CRPS may worsen and develop other signs and symptoms, including neurological signs such as weakness, incoordination, and movement disorders such as dystonia, tremor, and myoclonus. Fixed, painful dystonia is the most common movement disorder. Even though this is more a persistent muscle contraction rather than a hyperkinetic disorder, 20% to 30% will have tremor or myoclonus and over 60% will have superimposed spasms in addition.[58] All three of the hyperkinetic movements are atypical in many ways, and this has generated an ongoing debate about how many of these patients have a psychogenic movement disorder. The debate is epitomized by an exchange of letters about CRPS associated dystonia and myoclonus. Lang and coauthors argued for a psychogenic etiology in many patients because of atypical features such as synchronous tremor in unaffected limbs, dramatic response to intrathecal baclofen suggesting placebo response, dystonic postures sparing pincer grasp, atypical spread (from one limb to the contralateral diagonal limb), and other atypical features not mentioned in this letter.[59,60] Munts, van Hilten, et al argued that CRPS rarely responded to psychiatric therapy, that dystonia was considered psychogenic in the 19th century by some of the founders of modern neurology, and that unusual does not necessarily mean nonphysiological.[61] Some have questioned the existence of RSD/CRPS with or without movement disorder.[62] Potential physiologic mechanisms and potential psychological predispositions have been found in various studies.[57] Long-term follow-up is similarly unhelpful: some studies find the majority of patients recovered in less than 1 year while other studies find symptoms persist and few people recover.[63] Although I think it is fair to say that while some patients with CRPS have movement disorders of a psychogenic etiology and can be cured by psychotherapy alone, it is not clear whether many, most, or all of the patients with movement disorders have a psychogenic etiology.[57] The therapeutic approach to this condition would seem obvious: just as in any other rare disorder without a gold standard diagnostic test, treat symptoms according to your best diagnosis while you continue to look for a definitive diagnosis. The symptomatic treatment depends on the phenomenology: tremor, dystonia, myoclonus, or a combination.

TRAUMA-INDUCED MOVEMENTS

There are a large variety of hyperkinetic movement disorders that arise shortly after peripheral trauma (trauma that does not cause identifiable brain injury). In most cases, it is

very difficult to determine what role, if any, the trauma had in causing the movement disorder. Many psychogenic movement disorders are triggered by emotional or physical trauma, but the criteria for diagnosing psychogenic movement disorders are imperfect at best, except in cases where psychotherapy alone cures the disorder (and even in that case it is possible that some self-limited disorders are mistakenly diagnosed as psychogenic). The potential connection to trauma is particularly difficult to establish when the symptoms of the disorder are atypical. A review of published cases of trauma-induced movement disorders in 713 patients found that 72% had dystonia, 25% had tremor, 13% had myoclonus, and the rest had a variety of disorders including painful legs-moving toes, chorea, and tics.[64] Psychogenic disorder was diagnosed in 14% (but no criteria were described for 41% of these) and CRPS was diagnosed in 36% (mostly without documented nerve injury). Similarly, psychogenic etiology may not have been considered in many of the patients not diagnosed with psychogenic disease. Of the 513 patients with dystonia, 62% were unusual in that they had fixed dystonia. It is hard to know what percentage of these patients truly had an unusual phenotype because of the precipitating injury and what percentage had psychogenic disease.

ISOLATED DYSKINESIAS

As noted in the section on jumping stump, there are a large number of case reports of involuntary movements involving isolated parts of the body (but usually multiple muscles). Most of these are repetitive and semirhythmic. They range in duration from extremely brief (usually categorized as myoclonic) to prolonged and sustained (usually categorized as dystonic), but many are a mixture of slow and fast movements. These may involve the ear, lips, jaw, tongue, diaphragm, abdominal wall, shoulders, trunk, and limbs. Some, but probably not all, may be unusual variants of primary dystonia or be due to unsuspected exposure to dopamine receptor blocking agents. Some of these are common enough to attract particular attention. Dyskinetic movements of varying duration causing irregular movements of the bellybutton have been called belly dancer's dyskinesias. Semirhythmic movements of the diaphragm, called diaphragmatic flutter and many other names, may cause shortness of breath, pain, abdominal gurgling, and abdominal movements. Abdominal protrusions can only be caused by diaphragmatic movements and should always trigger an evaluation of the diaphragm (usually by fluoroscopy). Diaphragmatic flutter and belly dancer's dyskinesias are rarely associated with known causes of dyskinesias, such as exposure to dopamine receptor blocking agents, but usually no obvious cause can be found (see Figure 12–8). Hemimasticatory spasm is action induced spasms of the masseters, temporalis, and sometimes external pterygoids causing forceful jaw closure.[55] This has been associated with linear scleroderma and hemifacial atrophy (Parry-Romberg syndrome). There is some evidence this may also be associated with central brainstem lesions from stroke or multiple sclerosis.[55]

BLINDISMS

Stereotyped behaviors have been noticed in blind or deaf people, some of whom also had developmental delay.[65] It would seem reasonable to categorize these with other stereotypies, but I am not convinced that all of them are purposeless and therefore should be categorized that way. Some of the swaying head movements in partially blind people may serve to keep a visual image moving on the retina. In any case, it is helpful to be aware that some involuntary movements are related to blindness and/or deafness.

SYNKINESES

Most synkineses appear after nerve injury, due to aberrant regeneration. However, there are a large number of unusual synkineses that are either congenital or occur in the setting of diseases like Parkinson's disease or Creutzfeldt-Jakob disease. The Marcus-Gunn jaw-winking phenomenon is an example. People with this have unilateral or bilateral ptosis that improves with jaw opening (presumably

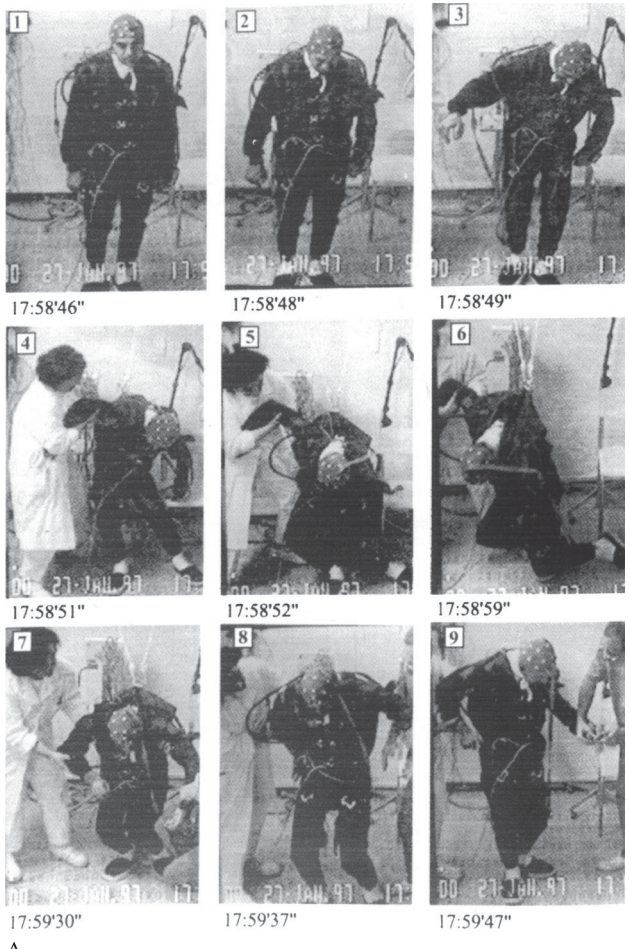

Figure 12–8. EMG in "belly-dancer's" dyskinesias. EMG recording from a 25-year-old woman with abdominal dyskinesias, synchronous in the upper and lower rectus abdominus and alternating between the rectus abdominus and the external oblique. The relatively slow frequency and alternating contractions create an undulating umbilicus suggesting to some the movements of a belly dancer. (From: Marsden's Book of Movement Disorders. Ivan Donaldson, C. David Marsden, Susanne Schneider, and Kailash Bhatia. Chapter 52 Miscellaneous movement disorders. Figure 52.5.)

a synkinesis between the trigeminal and oculomotor nerves.[66] There are multiple variations of this, including ptosis and a variety of ocular deviations that appear with chewing. Synkineses are not limited to the face and can appear between an upper and lower limb (usually ipsilateral).[67]

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Chapter 13

Psychogenic Hyperkinetic Movement Disorders

Roger M. Kurlan

INTRODUCTION

Psychogenic movement disorders[1] are voluntary or due to psychological mechanisms and occur in the absence of organic dysfunction in the brain's motor control system. Psychogenic abnormalities of movement can resemble any of the known hyperkinetic (or hypokinetic) movement disorders but can usually be recognized by qualities of the movements that distinguish them as being atypical or different. Other clues to their presence include the presence of psychodynamic problems in the patient's life, secondary gains (i.e., the movements are associated with positive outcomes, such as personal attention, relief from life's responsibilities, financial gains), a histrionic personality, other psychogenic (nonorganic, nonanatomic) neurological signs, and failure to respond to standard therapies. Psychogenic movement disorders are important to diagnose when present in order to avoid potentially expensive or risky diagnostic tests and treatments and to steer therapy to the underlying psychodynamic problems.

UNDERLYING PSYCHOPATHOLOGIES

Malingering, Fictitious Disorder

The most straightforward underlying disturbance in psychogenic movement disorders is malingering, the conscious faking of a movement disorder in order to achieve a desired outcome. Malingering often occurs for financial profits, such as during lawsuits related to injuries sustained after a fall, on the job, or after a motor vehicle accident. The movements are used to purposely accentuate the appearance of disability and to increase financial settlements. Malingering can be established by clandestine surveillance videotaping (sometimes done by insurance companies) which demonstrate the movements are absent when the individual does not think he or she is being observed. Another form of voluntary manifestation of an abnormal movement is fictitious disorder. In this situation, patients purposely create the movement abnormality in response to emotional and psychological factors but not for specific concrete secondary gain.

Conversion Disorder

The most common psychopathology underlying psychogenic movement disorders is conversion disorder. Conversion disorders are often key components of hysteria, a psychogenic disorder that has been of interest to neurologists and psychiatrists for centuries. A conversion disorder is a motor or sensory neurological sign or symptom that is a manifestation of subconscious psychodynamic conflicts. Blindness, deafness, loss of speech, paralysis, sensory loss, pain, and abnormal gaits are common conversion disorders, but movement disorders are represented as well. A conversion disorder is not associated with organic neurological dysfunction. As viewed from a psychoanalytic perspective, the individual is unable to cope with or sometimes even consciously acknowledge the psychodynamic stresses present and as a defense mechanism subconsciously "converts" the process into a medical symptom. In this way, instead of directly dealing with very challenging psychological issues, the person can focus on what are interpreted as medical (nonpsychological) symptoms. Thus, it may be much easier emotionally to think about tremor or deafness than about abuse, insecurities, or financial or personal stresses. Conversion disorders can be seen in depression and anxiety and may represent symptoms of a more generalized somatization disorder in which a variety of physical symptoms develop in response to underlying psychiatric disturbances. Hypochondriasis, a preoccupation with fears of having a serious illness based on a person's misinterpretation of bodily symptoms and despite appropriate medical evaluation and reassurance, can also be associated with conversion disorders. With conversion disorders, the primary focus of evaluation and ultimately therapy is to identify the underlying psychodynamic processes, bring these to the patient's awareness and develop positive psychological approaches and other supportive measures to better deal with them.

Mass Hysteria

An unusual cause of a psychogenic movement disorder is mass hysteria. This is a phenomenon in which there is rapid spread of symptoms within a group of individuals. Perhaps the most common example is one child in a school classroom thinking they smell a foul odor, followed by feelings of lightheadedness and then many other students in the classroom or school hearing about and experiencing the same symptoms. Symptoms finally resolve when no real odor is found and the group is reassured. Interestingly, this type of event, manifested by tic-like movements, occurred in a school in upstate New York in 2011–2012. Despite reassurances from healthcare professionals about the psychological nature of the problem, news stories about this situation led to community concerns and fears about infections and environmental toxins which likely prolonged the incident.

GENERAL APPROACH TO DIAGNOSIS

A number of historical and clinical features are suggestive of a psychogenic movement disorder of any type. These are summarized in

Table 13–1. The history is often presented in a histrionic fashion, while sometimes the individual maintains a demeanor of indifference despite conveying serious problems. Contrary to most true movement disorders, there is often an abrupt onset, commonly in association with minor trauma or a stressful psychological event. The course is often static, with little fluctuation, although some patients experience an inconsistent course with spontaneous remissions at times. The presence of psychiatric disorders, particularly those associated with conversion disorders such as depression, anxiety, and somatoform disorders, can be helpful in arriving at a proper diagnosis. Psychogenic movement disorders tend to persist in the presence of litigation or compensation hearings and when secondary gains continue. Young women appear to be the demographic group most prone to psychogenic movement disorders, particularly those working in a health field.

Table 13–1 Clinical Clues Suggesting a Psychogenic Movement Disorder

A. History
1. Abrupt onset
2. Static course
3. Spontaneous remissions (inconsistencies in course)
4. Precipitated by minor trauma, psychological stress
5. Presence of psychiatric disorders
6. Multiple somatic symptoms, unexplained conditions
7. Pending litigation
8. Secondary gains evident
9. Young female
10. Employed in a health profession

B. Examination
1. Inconsistent qualities (frequency, direction, amplitude, distribution)
2. Does not fit with recognized patterns of organic movement disorders
3. Bizarre, multiple, difficult-to-classify phenomenology
4. Paroxysmal quality
5. Increase with attention (i.e., suggestible), decrease with distraction
6. Strange or nonphysiological triggers (e.g., trigger points)
7. Functional disability out of proportion to examination findings
8. Deliberate slowness of movement, often associated with moans, groans
9. Presence of other psychogenic signs

C. Response to Therapy
1. Poor response to standard treatments
2. Response to placebo
3. Remission after psychotherapy

A careful physical examination can lead to important diagnostic clues. Probably most important for psychogenic movement disorders compared with other types of conversion disorders is the presence of qualities inconsistent with organic movement disorders. Qualities to focus on are frequency, direction, amplitude, and body distribution. These will be discussed further later in the chapter. Psychogenic movement disorders often have bizarre qualities, are difficult to classify based on standard phenomenology, and may occur as multiple types. A sudden, paroxysmal nature is often seen. Psychogenic movement disorders are often suggestible, increasing when attention is directed to them, and they tend to decrease when the patient is distracted (e.g., performing motor maneuvers [these tend to amplify organic hyperkinetic movement disorders] or counting backward). Psychogenic movement disorders are often precipitated by nonphysiological triggers, like pressing nonexistent trigger points or moving the limb. Patients tend to report functional disability out of proportion to the findings on examination. There is often a deliberate slowness in all movement and the patient attempts to demonstrate difficulty or pain by moaning or groaning or holding parts of the body (e.g., holding on to the low back or a "dysfunctional" hand). The presence of other psychogenic signs helps to support a diagnosis of psychogenic movement disorder, and examples include constricted visual fields (tunnel vision), exact midline split of sensation, give-away weakness, Hoover's sign of psychogenic weakness, astasia-abasia gait, and pseudoseizures.

Psychogenic movement disorders tend not to respond to standard medical therapy but may improve following suggestion or use of a placebo. Physical therapy often is beneficial. Psychotherapy is the most reliable treatment and it may lead to prolonged remissions.

Fahn and Williams have proposed a diagnostic classification for the certainty of diagnosis of a psychogenic movement disorder and this is summarized in Table 13–2.[2] It is important to remember that the accurate diagnosis of a psychogenic movement disorders is based not just on the exclusion of other causes, but is also based on the identification of supportive clinical features indicative of psychogenicity.

Table 13–2 **Diagnostic Classification for Psychogenic Movement Disorders**

A. *Documented*—Complete resolution with suggestion, physiotherapy, or placebo.
B. *Clinically established*—Inconsistent over time or incongruent with the presentation of a classical movement disorder, such as additional atypical signs, multiple somatizations, obvious psychogenic disturbance, disappearance with distraction, and deliberate slowing.
C. *Probable*—Incongruous and inconsistent movements in the absence of any of the other features listed above.
D. *Possible*—Clinical features of a psychogenic movement disorder occurring in the presence of an emotional disturbance.

It is also important to remember that just like epilepsy patients having psychogenic pseudoseizures, psychogenic movement disorders can occur in patients with organic movement disorders as a form of embellishment.

TYPES

Published estimates indicate that between 3.3% and 13.8% of patients seen at an active movement disorder specialty center are diagnosed as having a psychogenic movement disorder.[3] It has been suggested that the incidence of this condition has increased substantially over the past couple of decades. Combined data from a group of movement disorder centers around the world identified the following frequencies for individual types: tremor (40%), dystonia (31%), myoclonus (13%), gait disorder (10%), parkinsonism (5%), tics (2%), and other (5%).[3]

Psychogenic Tremor

Psychogenic tremor[4] can involve any part of the body, but usually it causes shaking of the head or limbs. Voice tremor may occur on a psychogenic basis. The anatomic distribution often changes over time. In assessing psychogenic tremor it is critical to focus on the qualities of the body shaking. Frequency is an important quality. For example, a parkinsonian rest tremor is typically slow with a frequency of 3–5 Hz, essential tremor has a faster rate of about 10–12 Hz, while a psychogenic tremor has varying frequencies when carefully examined. Organic tremors occur in the same directions over and over, while psychogenic tremors change direction. As an entity, tremor is defined by its predictable, rhythmic to-and-fro movement. Psychogenic tremor has inconsistent rhythmicity. Entrainment is a psychogenic phenomenon in which a psychogenic tremor adopts the frequency of a repetitive movement that the patients is asked to do (e.g., finger tapping, opening/closing a hand).[5] Many of these atypical qualities of psychogenic tremor can be confirmed using electrodiagnostic equipment (Figure 13–1).[6,7]

Psychogenic Dystonia

Psychogenic dystonia[8] is probably the most controversial type of psychogenic movement disorder. One reason is that dystonia itself was long linked to hysteria and its genetic and neurological etiologies were not recognized for centuries. For this reason, physicians have been reluctant to apply a psychogenic focus to the disorder. Another controversy that persists today is whether or not organic dystonia can result from bodily trauma. This occurrence is commonly seen in accident- or job-related litigation, often associated with the controversial condition complex regional pain syndrome (reflex sympathetic dystrophy), in which dystonia may occur along with various combinations of pain, edema, coldness, weakness, stiffness, and other symptoms. Fixed, unyielding dystonia/posturing suggests a psychogenic cause.

Psychogenic Myoclonus

Psychogenic myoclonus[9] usually presents with segmental or generalized jerking at rest and with movement. The movements are lessened and become more variable with distraction. Neurophysiological methods are quite useful in distinguishing psychogenic jerks from true cortical or brainstem myoclonus and stimulus-related voluntary jerks from stimulus-sensitive myoclonus.[10]

Psychogenic Tics

Psychogenic tics (pseudotics) can occur in isolation, but are probably most common in patients with Tourette's syndrome (TS) who embellish their condition with these pseudotics.[11] In the

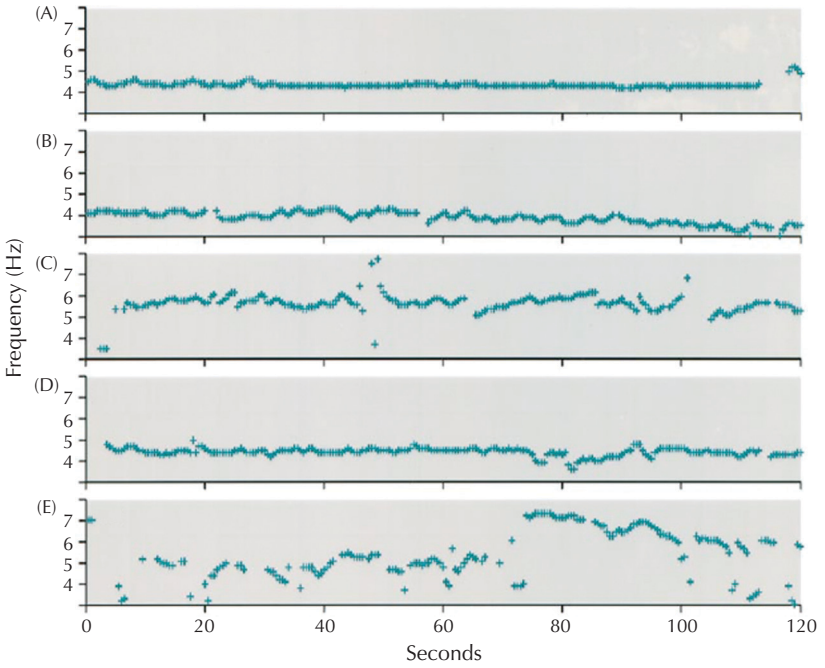

Figure 13–1. Variation in tremor frequency over time. A: Relatively stable Parkinson's disease. B: Gradual slowing of Parkinson's disease rest tremor. C: Small fluctuations of rest tremor in Parkinson's disease. D: Small fluctuations of postural tremor in essential tremor, E: Very large fluctuations in psychogenic tremor. (From O'Suilleabhain PE, Matsumoto JY, Time frequency analysis of tremors. Brain 1998;121:2127–2134, with permission.)

author's experience, pseudotics are most common in children and adolescents who are having problems coping with their TS. Pseudotics are generally manifested by high-amplitude, bizarre movements or loud yells or shouts. They can resemble pseudoseizures and sometimes cause the patient to fall to the floor, which is very rare in true TS. For patients presenting with complex tic-like movements, in TS it is very unusual to see complex motor tics alone, so the absence of accompanying simple tics suggests a psychogenic etiology.

THERAPY

It is important to accurately diagnose a psychogenic movement disorder for a variety of reasons. First, medical and supportive attention can be drawn away from the movements themselves to more appropriately focus on the underlying psychodynamic problems. Second, patients with psychogenic movement disorders should be shielded from frequent, expensive, or risky diagnostic testing and therapies. Third, introducing the appropriate therapeutic interventions can lead to resolution of the movements and provide patients with new psychological insights and coping skills to help avoid future psychogenic symptoms.

The treatment of psychogenic movement disorders depends on the cause. When caused by malingering or a fictitious disorder, simply telling the patient that the actual volitional nature of the condition is evident can end the charade. Insurance companies have used clandestine videotaping to demonstrate the voluntary nature in some cases. With mass hysteria, the best approach is separating the individuals and engaging each in regular psychotherapy. Unfortunately, community fears and anxieties may interfere with this proper treatment.

Conversion disorders are best approached by a psychodynamically oriented therapist who works with the patient to uncover psychodynamic conflicts and to develop more productive psychological skills for dealing with them. In this way the defense mechanism of conversion will no longer be needed or can be replaced by positive behaviors. A variety of dynamic, cognitive-behavioral, and group psychotherapy

approaches have been used. Specific attention may need to be directed toward somatization or hypochondriasis. Sometimes, taking advantage of the tendency for psychogenic movement disorders to be suggestible, repeatedly telling a patient that his or her movements are getting better can lead to improvement. Underlying psychiatric disorders that might be contributing, such as depression or anxiety, can be treated.

PROGNOSIS

While there is little published information about the course and prognosis of psychogenic movement disorders, some exists for conversion disorders in general.[3] Features associated with remission or a better prognosis include: shorter duration of symptoms (<3 months), younger age at onset, the presence of well-defined psychiatric illness, and a change in marital status. Conversion disorders that persist for 18 months or longer remit in only about 25% of cases.[12] Factors reported to be linked to a poor outcome are: presence of an underlying personality disorder, the use of nonpsychotropic medications for the neurological disorder, the ongoing receipt of financial benefits, and ongoing litigation. The few reported follow-up studies of patients with psychogenic movement disorders have generally identified a poor outcome, with persistence of the disorder in 44%–90% of patients after observation periods of up to 5 years.[3]

SUMMARY

Psychogenic movement disorders are purposeful or due to psychological and emotional problems. Malingering and conversion disorder are the most common underlying causes. Psychogenic movement disorders are recognizable based on phenomenological differences from organic movement disorders, the association with other signs of a psychogenic condition, and elucidation of underlying psychopathology. Psychogenic movement disorders can occur on their own or in concert with organic movement disorders as a form of embellishment of symptoms. Once identified, patients should be informed about the psychogenic nature of their symptoms and educated about how psychogenic conditions can develop. This is important so that they can avoid unnecessary therapies and diagnostic tests and engage in appropriate psychological treatment. Unfortunately, prognosis for recovery from psychogenic movement disorders is not good.

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Chapter 14

The Ataxias

Roger M. Kurlan

CLINICAL PHENOMENOLOGY

The term "ataxia" refers to clumsy, poorly coordinated movements that are typically referable to disorders of the cerebellum and its connections. When applied to gait, "ataxia" implies unsteadiness, instability, and imbalance, often with falling, that are not related to feelings of dizziness or vertigo. Patients with an ataxic gait tend to walk slowly with a wide base and shortened strides, and they have difficulty with tandem gait. Such patients may hold on to walls or furniture to avoid falling. Cerebellar dysfunction is also manifested by other motor abnormalities, including hypotonia, dysmetria, past-pointing, impaired ability to check or control movements, dysdiadochokinesia (disturbance of rapid alternating movements), and fatigue. Because of the characteristic problems in motor control associated with cerebellar disturbances, these conditions are often considered to be part of the movement disorders subspecialty field. In addition, ataxic disorders are sometimes associated with hyperkinetic (dystonia, chorea, myoclonus, tremor) or hypokinetic (parkinsonism) movement disorders. Furthermore, cerebellar lesions can cause involuntary movements, including the so-called cerebellar tremor and swaying/titubation of the head or trunk. Cerebellar tremors typically are of the action or postural type and have a slow frequency of 1–3 Hz. They tend to increase as the limb approaches its target (intention tremor). Eye closure sometimes improves this kind of tremor. When a resting component is present and when the intentional quality is of high amplitude, the term "rubral" tremor has

been used, reflecting the fact that lesions involving cerebellar connections in the upper brainstem (near the red nucleus) are often involved. Ataxic patients sometimes exhibit a swaying of their trunk when sitting or standing and at times a more regular tremor-like involuntary movement referred to as "titubation." The postural dyscontrol characteristic of ataxic patients can be seen with the classic Romberg test that shows a worsening when eyes are closed. Ataxic involvement of speech is manifested by dysarthria with clumsy and poorly articulated words. There may be a singular pitch or loudness or an abnormal, seemingly random enunciation or loudness of certain words or syllables (scanning speech). Cerebellar speech can also be slow and reduced in volume.

LOCALIZATION

Virtually any lesion of the cerebellum can cause ataxia. From a functional and clinical standpoint, the cerebellum can be divided into midline, lateral (vermis and hemispheres), and vestibular portions. Ataxia involving the head, trunk, and gait in isolation tend to be due to vermal lesions, while dysarthria typically reflects vermal or hemisphere dysfunction. Cerebellar tremor is seldom due to lesions of the cerebellar cortex alone, as the vermis is typically involved. Generally, ataxia affecting only the limbs unilaterally is due to a lesion in the ipsilateral cerebellar hemisphere. Lesions involving cerebellar inflow or outflow pathways in the brainstem or spinocerebellar tracts in the spinal cord can also cause ataxia.

DIAGNOSIS

As mentioned, essentially any pathological process that affects the cerebellum and its connections can cause ataxia. Thus, the full spectrum of neurological conditions needs to be considered. The differential diagnosis can be narrowed by considering factors such as age at onset, acute versus gradual onset, slow versus rapid progression, sporadic versus familial occurrence, and whether or not other parts of the nervous system are involved. It is useful to discuss the general categories of sporadic and hereditary ataxias. This chapter will focus on the hereditary causes of ataxia because these are the types typically seen by movement disorders specialists.

Sporadic Ataxias

The cerebellum and its connections can be affected by an array of disease processes (Table 14–1).[1] Stroke involving the vertebrobasilar vascular system is a common cause. A variety of tumor types may produce ataxia, most often medulloblastoma, astrocytoma, ependymoma, hemangioblastoma, meningioma, metastatic cancer, and cerebellopontine angle schwannoma. Paraneoplastic forms of ataxia occur, often with detectable anti-Purkinje cell or other antineuronal autoantibodies in the serum (e.g., Yo, Tr, Hu, Ri, CV2, Ma, TA, CARP8, LEMS, CRMPS, GQ1b, amphiphysin, PCA-2, VGKC, NMDA, NMDA receptor [mGluR1], ganglionic acetylcholine receptor antibodies). Ataxia can also be caused by autoimmune processes other than paraneoplastic, such as in association with anti-glutamic acid decarboxylase (GAD65) antibodies (which are more commonly associated with stiff-person syndrome) and the Miller Fisher variant of Guillain-Barré syndrome. Gluten-sensitive enteropathy (celiac disease, sprue) with malabsorption is associated with antigliadin antibodies (IgG and IgA) and can cause ataxia, even in the absence of gastrointestinal disease. Ataxia is a common manifestation of multiple sclerosis. Rubella, *Haemophilus influenza*, and HIV can cause infectious forms of ataxia, and ataxia can also be seen as part of a postinfectious syndrome. There is an ataxic variant of Creutzfeldt-Jakob disease. A variety of toxic/metabolic disorders can cause ataxia, including acute and chronic alcohol intake, hyperammonemia, hypoxia,

Table 14–1 **Sporadic Ataxias**

Stroke
Tumor
Paraneoplastic
Autoimmune
Infectious
Postinfectious
Toxic/Metabolic
Drugs
Other

hyperthermia, vitamin (A, thiamine, folate, B12, E) and zinc deficiencies, endocrine disturbances (hypothyroidism, hypoparathyroidism, hypoglycemia), chemical toxins (e.g., thallium, bismuth, toluene, methylmercury), and prescribed drugs (e.g., antiepileptics, lithium, chemotherapy agents, benzodiazepines). In infants and children a variety of metabolic disorders (e.g., leukoencephalopathies and leukodystrophies, Alexander disease, Gaucher disease, Krabbe disease, some acidemias and acidurias, iron deposition diseases, biotin disturbances) must be considered.

Hereditary Ataxias

One of the biggest recent changes in neurology has been the identification of genetic loci linked to many of the inherited ataxias.[2] This has led to new genetic classifications and the elucidation of molecular genetic mechanisms for many of the conditions.[3,4] The hope is that better understanding of pathogenetic processes for the hereditary ataxias will stimulate the development of new and effective therapies which, to date, have largely been lacking.

AUTOSOMAL RECESSIVE ATAXIAS

The ataxias with autosomal recessive (AR) inheritance are summarized in Table 14–2. They often have early age at onset and are generally thought to be due to reduced translation and loss of a functional protein. Systemic, non-neurologic features are more common in the AR forms compared with those with autosomal dominant inheritance. The AR ataxias can be divided by their major clinical presentations.

Primarily Sensory and Spinal Ataxias

Friedreich's Ataxia (FRDA).[5] With a prevalence of 1–2 per 50,000 people, this is the most common inherited ataxia in the United States and Europe. It is the most common AR and early-onset ataxia. The usual clinical features include juvenile onset (prior to age 25), progressive ataxia of gait and limbs, hypoactive deep-tendon reflexes of the legs, and extensor plantar responses. Patients often have dysarthria, proprioceptive and vibratory sensation loss in the feet, and scoliosis. Systemic manifestations include cardiomyopathy in about two-thirds of cases and diabetes mellitus in about one-third. Later onset variants of FRDA are now recognized. Clinical genetic testing for FRDA is available. It is a GAA triplet-repeat disease affecting a gene on 9q that codes for the protein frataxin. This protein localizes to inner mitochondrial membranes and is deficient in the illness, resulting in a disturbance in iron homeostasis and problems with mitochondrial oxidative phosphorylation. Pathologically, there is degeneration and sclerosis in the posterior columns, spinocerebellar tracts, and corticospinal tracts of the spinal cord. Nerve cells are lost in the dorsal root ganglia and in Clarke's column. Myelinated axons are lost in peripheral nerves, and mild degenerative changes are found in the brainstem and cerebellum. A variety of genetic therapy approaches and treatments aimed at alleviating oxidative stress are under investigation for FRDA. Physical and speech therapy, walking aids, and treatment of associated cardiac disease and diabetes are standard treatments, and genetic counseling should be offered to affected families.

Table 14–2 **Autosomal Recessive Ataxias**

Primarily Sensory and Spinocerebellar
Friedreich's Ataxia (FRDA)
Ataxia with Vitamin E Deficiency (AVED)
Abetalipoproteinemia
Refsum Disease
Spinocerebellar Ataxia with Axonal Neuropathy (SCAN1)
With Oculomotor Abnormalities
Ataxia Telangiectasia (AT)
Ataxia with Oculomotor Apraxia, Type 1 (AOA1) and Type 2 (AOA2)
Primarily Cerebellar
Autosomal Recessive Cerebellar Ataxia, Type 1 (ARCA1)
Marinesco-Sjogren Syndrome
Progressive Myoclonus Epilepsy (PME)
Ataxia with Pigmentary Retinopathy
Ataxia with Hypogonadism
Ataxia with Deafness
Primarily Spastic
Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS)

Ataxia with Vitamin E Deficiency (AVED). This condition is clinically similar to FRDA, with presentation in adolescence or later, progressive ataxia, loss of proprioreception, and arreflexia. Retinitis pigmentosa may be present, and head titubation and dystonia may be more prominent than in FRDA. There may be Babinski signs. Vitamin E (alpha-tocopherol) levels are markedly reduced, and there is a normal lipid and lipoprotein profile. Genetically, there are mutations in the gene for alpha-tocopherol transfer protein (*TTPA*) on 8q13. This results in an impairment in the incorporation of alpha-tocopherol into very low density lipoproteins. Treatment involves high-dose vitamin E repletion. A related condition, Cayman ataxia, has only been reported from the Cayman Islands and also has vitamin E deficiency with early-onset ataxia and psychomotor retardation. It is due to mutations in the gene (*ATCAY*) that codes for caytaxin, a protein that appears to bind lipophilic molecules in a similar fashion to vitamin E.

Abetalipoproteinemia (Bassen-Kornzweig Disease). This disorder also includes vitamin E deficiency along with cholestatic liver disease, malabsorption, and peripheral blood acanthocytes.

Refsum Disease. This is a childhood-onset ataxia disorder with sensory loss, areflexia, neuropathy, retinitis pigmentosa, anosmia, deafness, and ichthyosis. It is due to mutations in the genes *PHYH* and *PEX7*, resulting in the accumulation of phytanic acid and disturbances of peroxisomal and mitochondrial function.

Spinocerebellar Ataxia with Axonal Neuropathy (SCAN1). This disorder also resembles FRDA clinically, with slowly progressive ataxia, dysarthria, axonal sensorimotor neuropathy, distal atrophy, and pes cavus. Nystagmus may be present. Mild hypoalbuminemia and mild hypercholesterolemia may occur. It usually presents in the second decade. The culprit is a mutation in the *TDP1* gene that codes for a single-stranded DNA repair enzyme.

Ataxia with Oculomotor Apraxia

The conditions in this group differ from FRDA by the presence of prominent oculomotor apraxia, the frequent occurrence of chorea and dystonia, and the greater degree of cerebellar degeneration and atrophy.

Ataxia Telangiectasia (AT).[6] This is an early-onset (ages 1–4 years) form of progressive ataxia with oculomotor disturbances (oculomotor apraxia, abnormal saccades, ocular dysmetria, nystagmus) and dysarthria. Hypomimia, drooling, dystonia, chorea, myoclonus, and neuropathy may appear over time. There are also possible systemic manifestations including telangiectasias of the skin and conjunctivae, delayed growth and sexual development, immune abnormalities (recurrent infections, lymphopenia, decreased IgA and IgG), malignancies (most often leukemia or lymphoma), increased sensitivity to ionizing radiation, and premature aging. The gene for AT is for the nuclear protein kinase ataxia-telangiectasia mutated (*ATM*), which mediates the cellular response to DNA damage. Cerebellar Purkinje cell loss is evident. There may be laboratory abnormalities, including elevated alpha-fetoprotein (AFP), increased chorionic embryonic antigen (CEA), and decreased serum IgE and IgG2 levels. There is no established therapy for AT, although the antioxidants vitamin E and alpha-lipoic acid are often given. A number of experimental treatments are under investigation. There is a variant of AT (ATLD) that involves later onset and slower progression, and there are other AR ataxias that appear to be due to problems with DNA repair.

Ataxia with Oculomotor Apraxia (AOA). There are two subtypes of this condition. AOA1 (also known as hereditary motor and sensory neuropathy associated with cerebellar atrophy [HMSNCA]) is characterized by slowly progressive childhood-onset ataxia, oculomotor apraxia, severe axonal motor neuropathy, and hypoalbuminemia.[7] Shortened and atrophic limbs, dystonia and chorea, and hypercholesterolemia are common. The AFP levels are normal. The responsible gene is *APTX*, and it codes for aprataxin, a protein that appears to be involved in the repair of single-stranded DNA. Pathologically, there is cerebellar atrophy with loss of Purkinje cells, degeneration of posterior columns and spinocerebellar tracts, and axonal neuropathy with loss of myelinated fibers.

AOA2 has a later age at onset than AOA1, usually in the teens.[8] Like AT, it also has elevated AFP levels. Oculomotor apraxia, dystonia, chorea, tremor, axonal sensory neuropathy, and pes cavus often occur. The responsible gene is *SETX*. It codes for an RNA helicase.

Primarily Cerebellar Ataxias

Autosomal Recessive Cerebellar Ataxia, Type 1 (ARCA1) has onset in adulthood and is characterized by ataxia, dysarthria, hyperactive reflexes, and slow progression. It is due to a mutation in the *SYNE* gene that encodes a nuclear envelope protein. There may be altered glutamate neurotransmission.

Marinesco-Sjogren Syndrome has infantile onset with ataxia, cataracts, short stature, and mental retardation. The abnormal gene is *SIL1*, resulting in a disturbance of protein folding.

Progressive Myoclonus Epilepsy (Unverricht-Lunborg Syndrome) consists of myoclonus and progressive ataxia (referred to as the "Ramsay Hunt syndrome," which also has other etiologies) and seizures. It is due to a mutation in the gene that codes for cystatin B, resulting in abnormalities in cell protein degradation.

Ataxia with Pigmentary Retinopathy, Ataxia with Hypogonadism, and *Ataxia with Deafness*. These are among other rare AR ataxias.

Spastic Spinocerebellar Ataxias

Autosomal Recessive Spastic Ataxia of Chalevoix-Saguenay (ARSACS) resembles the hereditary spastic paraplegias. It is characterized by the clinical triad of cerebellar ataxia, pyramidal signs, and sensorimotor axonal neuropathy. Nystagmus and dysarthria are often present. Retinopathy and urinary urgency are sometimes seen. Brain MRI often reveals vermian atrophy and linear hypointensities in the pons and middle cerebellar peduncles on T2 sequences. It begins in early childhood and is due to mutations in the gene for sacsin, a molecule that appears to play a role in protein folding. As mentioned above, ARCA1 also can include hyperactive reflexes.[9,10]

X-LINKED ATAXIAS

These are rare conditions with the exception of *Fragile X-associated tremor/ataxia syndrome* (FXTAS).[11] This disorder has adult onset (usually after age 50) in male carriers and includes ataxia and postural or intention tremor. Features may include impaired memory, parkinsonism, neuropathy, and autonomic dysfunction. The MRI shows characteristic increased T2 signal in the middle cerebellar peduncles along with cerebral and cerebellar atrophy. There may be increased T2 signal in the periventricular white matter. Neuronal and astrocytic intranuclear inclusions are seen in the brain. This is a CGG repeat disorder involving the fragile X mental retardation gene. FXTAS involves a premutation number of expansions (55–200 repeats) while mental retardation occurs with >200 repeats.

MITOCHONDRIAL ATAXIAS

Mitochondrial DNA mutations can give rise to ataxias. Examples include *sensory-ataxic neuropathy, dysarthria, and ophthalmoparesis* (SANDO), which is due to a mutation in the gene for a mitochondrial DNA polymerase, and *infantile-onset spinocerebellar ataxia* (IOCA), in which the involved gene codes for a helicase. Mutations in mitochondrial enzymes can cause MERRF syndrome, which is characterized by ataxia, myoclonus, epilepsy, and hearing loss.

AUTOSOMAL DOMINANT ATAXIAS

While earlier classification schemes for the autosomal dominant (AD) spinocerebellar ataxias (SCAs) focused on pathological or clinical features, the current formulation is based on identified genes and involves a sequential numbering system (Table 14–3). Although there are a variety of distinctive features, there are general common features seen with the AD SCAs. They tend to have young- or mid-adult age at onset as compared with the much earlier age for AR ataxias. The initial and most prominent sign is ataxia, often with falls, and dysarthria is often present early. Earlier onset and more severe features (anticipation, potentiation) in succeeding generations are often observed. The same type of mutation, an abnormal expansion of a CAG trinucleotide repeat (polyglutamine coding) in the protein

Table 14–3 **Autosomal Dominant Ataxias**

Disorder	Distinguishing Clinical Features
SCA1	Pyramidal signs, dysphagia, neuropathy, ophthalmoparesis
SCA2	Neuropathy, hyporeflexia, slow saccades, dementia, parkinsonism, dystonia, chorea
SCA3	Ophthalmoparesis, spasticity, weakness, parkinsonism, dystonia, neuropathy
SCA4	Sensory neuropathy, pyramidal signs
SCA5	Slow progression
SCA6	Episodic ataxia, diplopia, downbeating nystagmus, ophthalmoparesis, vertigo, parkinsonism, family history of hemiplegic migraine
SCA7	Retinal degeneration, optic atrophy, ophthalmoparesis, pyramidal signs
SCA8	Severe dysarthria, titubation, ophthalmoparesis, pyramidal signs
SCA10	Slow progression, seizures, neuropathy
SCA11	Slow progression, pyramidal signs, vertical nystagmus
SCA12	Slow progression, action tremor, parkinsonism, dystonia, dementia, dysautonomia
SCA13	Childhood onset, short stature, mental retardation, motor delays, nystagmus, pyramidal signs
SCA14	Myoclonus
SCA15	Slow progression, dysarthria
SCA16	Head tremor, nystagmus
SCA17	Dementia, psychiatric features, parkinsonism, dystonia, myoclonus, chorea, pyramidal signs, seizures
SCA18	Onset in adolescence, neuropathy, pyramidal signs
SCA19	Nystagmus, myoclonus, cognitive decline, sensory neuropathy
SCA20	Slow progression, palatal tremor, pyramidal signs, dentate calcifications on MRI
SCA21	Slow progression, parkinsonism, cognitive impairment, hyporeflexia
SCA22	Slowly progressive
SCA23	Pure cerebellar
SCA25	Sensory neuropathy
SCA26	Slow progression
SCA27	Childhood onset, tremor
SCA28	Ophthalmoparesis
DRPLA	Dementia, myoclonus, seizures, chorea, psychiatric features

coding region of a gene, is seen in a majority of the AD SCAs. This CAG expansion causes disease by altering the coded protein as a toxic gain of function. Like other dominant disorders with trunucleotide repeat expansions, a greater number of repeats is associated with earlier onset. Also, there is meiotic instability, a phenomenon whereby the size of the repeat may change in a parent-to-child transmission. In most cases, repeat expansion is more common during paternal transmission. The autosomal SCAs are discussed below. There is little information available regarding SCA9 and SCA24.

SCA1. The responsible gene is located on 6p23 and has expanded CAG repeats, resulting in dysfunction of the protein Ataxin-1 with its abnormal nuclear aggregation and problems with protein refolding and clearance. Typical age at onset is in the 30s, but there is a wide age range. Distinguishing clinical features include corticospinal tract signs, dysphagia, neuropathy, and ophthalmoparesis.

SCA2. This condition is a relatively common form of AD SCAs worldwide. These patients have CAG expansions in the gene for Ataxin-2, located on 12q24. The protein appears to be involved in mRNA processing and protein translation. Onset is usually in the 20s to 30s but can be variable in age. Characteristic features beyond ataxia and dysarthria include neuropathy, hyporeflexia, slow saccades, and dementia. Levodopa-responsive parkinsonism with a staring gaze, dystonia, and chorea may occur. Until genetic localization, based on pathological findings, this condition had been grouped as part of the olivopontocerebellar atrophies (currently termed "multiple system atrophy-cerebellar type [MSA-C]").

SCA3 (Marchado-Joseph Disease). While first identified in a Portuguese Azorean kindred, this is a fairly common form of AD SCA

worldwide. Progressive ataxia, dysarthria, and ophthalmoplegia are characteristic features. Subtypes have been described based on other clinical features and age at onset. An adolescent-onset form has rapid progression of ataxia with spasticity, parkinsonism, dystonia, and weakness. A mid-adult-onset form has more moderate progression of ataxia, while a late-adult-onset variant has the slowest course with neuropathy. Finally, there is an adult-onset form with ataxia, parkinsonism, and neuropathy. Pathology has a spinopontine localization but may be more extensive. The condition maps to 14q24.3-q31 and involves a CAG expansion in the gene for Ataxin-3, which is involved in ubiquitin-related metabolism. Ubiquinated nuclear proteins can be seen in affected cells.

SCA4. This is an adult-onset disorder with ataxia and prominent axonal sensory neuropathy and corticospinal tract signs. The involved gene is for puratropin-1 on 16q, which appears to play a role in cell signaling and the action of actin in the Golgi apparatus.

SCA5. This condition also has adult onset with a slowly progressive course of ataxia. The mutated gene is located on 11p11-q11 and codes for beta-III spectrin (*SPTBN2*) which is highly expressed in Purkinje calls and functions in glutamate signaling.

SCA6. This is an adult-onset ataxia that is due to a CAG expansion in the gene for an alpha-1A voltage-dependent calcium channel subunit (*CACNA1A*). Interestingly, there are two other phenotypes associated with a mutation in this gene—familial hemiplegic migraine and episodic ataxia type 2 (EA2). The molecular mechanisms involved remain to be clarified. A variety of clinical features may accompany the ataxia, including diplopia, leg cramps, vertigo, nystagmus, hyperreflexia, sensory loss, loss of upgaze, and parkinsonism. Episodic attacks of ataxia may occur before the progressive nature becomes apparent.

SCA7. This condition is due to a CAG expansion of the gene on 3p that codes for Ataxin-7, a protein important in DNA transcription. Age at onset is usually in adulthood but has a wide age range. In addition to ataxia, the condition is marked by the associated retinal degeneration. Loss of yellow-blue color vision may be an early sign and optic disc pallor and macular changes may be seen. Ophthalmoparesis and pyramidal signs may occur.

SCA8. This adult-onset ataxia has a slowly progressive course. Compared with other AD SCAs, severe scanning speech and truncal titubation are often observed early. Ophthalmoparesis and pyramidal signs may be present. Contrary to most of the other triplet-repeat AD SCAs, the trinucleotide repeat is CTG, the repeat length is not closely related to age at onset or severity, allele expansion tends to occur with maternal transmission, and the gene product is a noncoding RNA. The gene resides at 13q21. The molecular mechanisms have not been fully elucidated, although there appears to be downregulation of the adjacent Kelch-like gene (*KLHL1*).

SCA9. This condition is poorly defined.

SCA10. This condition is caused by a pentanucleotide (ATTCT) repeat expansion involving the gene (located on 22q13) for Ataxin-10. It usually begins in adulthood and consists of a largely pure cerebellar syndrome that is slowly progressive and accompanied by seizures. Neuropathy may occur.

SCA11. This adult-onset slowly progressive ataxia maps to 15q14-q21. There may be pyramidal signs and vertical nystagmus. The gene has not yet been identified.

SCA12. This is another adult-onset ataxia with a slow progression. A distinguishing feature is the presence of action tremor. Parkinsonism, dystonia, dysautonomia, and dementia can occur. The gene *PPP2R2B* is located on 5q31-q33 and involves CAG repeat expansions.

SCA13. Mutations in the voltage-gated potassium channel KCNC3 gene (located on 19q13.3-q13.4) causes childhood-onset ataxia with short stature, mental retardation, motor delays, nystagmus, and pyramidal signs.

SCA14. Characterized by a variable age at onset, progressive ataxia, and myoclonus, this disorder is due to a mutation of the protein kinase C gamma gene (19q13.4-qter).[12,13]

SCA15. This slowly progressive ataxia disorder with dysarthria has been linked to a region at 3p26.[14]

SCA16. This disorder includes ataxia, head tremor, and nystagmus and has been localized to 8q22-q24.

SCA17. Onset for this condition can be in childhood or adulthood and includes ataxia, dementia, and psychiatric features. Parkinsonism, myoclonus, dystonia, chorea, pyramidal signs, and seizures may also occur. It is due to a CAG repeat expansion in the TATA-binding protein (*TBG*) gene on 6q27. This gene product is an important factor in initiating DNA transcription.

SCA18. This disorder consists of ataxia and sensorimotor neuropathy, usually with onset in adolescence. There may be pyramidal signs. This condition represents an overlap between the SCAs and the hereditary sensory neuropathies. The genetic locus has been identified at 7q22-q32.

SCA19. Localized to 1p21-q21, this adult-onset condition includes mild ataxia, nystagmus, myoclonus, cognitive decline, and sensory neuropathy.

SCA20. With a variable age at onset, this disorder includes slowly progressive ataxia associated with palatal tremor and mild pyramidal signs.[15,16] Calcifications of the dentate nucleus or other brain regions (pallidum, olives) can be seen on MRI. The condition has been localized to chromosome 11 and may be related to mutations in the *DAGLA* gene that encodes a product important in Purkinje cell synapses.

SCA21. This disorder has been mapped to 7p15-21 and has a variable age at onset (usually prior to 30 years) and includes slowly progressive ataxia with parkinsonism, hyporeflexia, and cognitive impairment.

SCA22. This condition is characterized by a slowly progressive course. The mutation has been localized to 1p21-q23.

SCA23. Mapped to 20p13-p12.23, this is a pure cerebellar syndrome.

SCA24. This condition is poorly defined.

SCA25. Localized to chromosome 2p, this condition includes ataxia with sensory neuropathy. It may resemble FRDA.

SCA26. Characterized by adult onset and slowly progressive ataxia, this disorder has been linked to 19p13.3.

SCA27. Missense mutations in the gene for fibroblast growth factor 14 on 13q34 have been reported to cause this childhood-onset ataxia with postural tremor.

SCA28. Localized to 18p11.22-q11.2, this disorder has onset around age 20 with ataxia and ophthalmoparesis.

Dentatorubropallidoluysian Atrophy (DRPLA). This condition is most often seen in Japan. Clinical features include ataxia and dementia. Earlier onset cases also often show rapidly progressive dementia, myoclonus, and seizures, whereas later onset patients tend to also exhibit chorea, dementia, and psychiatric disturbances, resembling Huntington's disease. The MRI may show atrophy of the cerebral cortex and involved nuclei. The illness is caused by CAG expansions in the *DRPLA* gene on 12p. The gene product is Atrophin-1. Ubiquinated intranuclear inclusions can be found in striatum, pons, inferior olive, and cerebellum.

Diagnostic Testing

For patients presenting with ataxia, particularly sporadic cases, diagnostic testing should focus on excluding potentially treatable acquired causes.[17] This generally involves reviewing prescribed medications, alcohol intake history, potential toxin exposures, checking metabolic parameters with blood testing (T4, TSH, PTH, calcium, lipoprotein profile, vitamin B1, B12, folate, and E levels), excluding infectious and postinfectious causes, and considering immune assays (e.g., paraneoplastic, anti-gliadin antibodies). An MRI will generally reveal tumor or vascular causes. It is important to keep in mind that there is a wide variety of disease processes that can cause ataxia. A complete diagnostic evaluation can be extensive and very expensive. A full discussion of this topic is beyond the scope of this chapter.

If acquired causes of ataxia can be excluded, a genetic cause should be suspected. The age at onset, suspected mode of inheritance, the accompanying other neurological or non-neurological features, and possibly the MRI findings should help narrow the differential diagnosis. For the early-onset cases, AR inherited causes of ataxia must be considered. Given its common nature, genetic testing for FRDA is usually done. If negative, other AR ataxias need to be considered and a battery of tests may be useful in diagnosis, including blood lipids and lipoproteins, very long chain fatty acids, vitamin E level, AFP, CEA, phytanic acid assay, and immunoglobulins. Depending on the clinical presentation, screens for mitochondrial mutations may be useful. Nerve conduction

studies and nerve biopsy may be informative in the presence of clinical signs of neuropathy. Clinical genetic testing[18,19] is available for several of the AR ataxias, including AVED, abetalipoproteinemia, AOA1, AOA2, and ARCAS. Although informative for diagnosis and family genetic counseling, the bulk of AR hereditary ataxias unfortunately do not have available therapies aimed at the primary disease process.

For the AD, usually later onset, hereditary ataxias, genetic testing is generally available, often as part of commercial ataxia genetic panels. Professional genetic counseling should accompany the testing. Again, testing often fails to have practical therapeutic implications, can be expensive, and is often not covered by health insurance companies.

TREATMENT

Most of the treatable causes of ataxia fall within the acquired category. For the hereditary ataxias, AVED and abetalipoproteinemia may respond to vitamin E replacement (sometimes with alpha-lipoic acid) and should not be missed. The episodic ataxia seen with SCA6 may improve with acetazolamide. Symptomatic medications can be used for neurological disturbances that accompany ataxia, such as spasticity, epilepsy, parkinsonism, dystonia, and chorea. Intramuscular injections of botulinum toxin can be useful for dystonia or spasticity. Physical therapy, orthopedic procedures, and gait assistive devices may improve mobility and prevent falls. For some of the disorders, specific systemic features may need attention, such as the cardiomyopathy of FRDA or the avoidance of ionizing radiation and the treatment of infections or malignancies in patients with AT. As more and more information is gained regarding the molecular mechanisms of the inherited ataxias, new specific disease-modifying therapies should emerge.

SUMMARY

Ataxia is a clinical syndrome that results from dysfunction of the cerebellum and its pathways. Unless there is a clear family history, initial diagnosis should focus on sporadic causes, as many of these are treatable. Hereditary ataxias are typically divided by genetic transmission pattern. Autosomal recessive cases tend to present early (infancy or childhood), often have systemic manifestations, and are usually due to loss of function mutations. These can be divided by major clinical presentations, including the following types: primarily sensory/spinal (e.g., FRDA), with oculomotor disturbances (e.g., AT), primarily cerebellar (e.g., ARCA1), and spastic spinocerebellar (e.g., ARSACS). In contrast to AR ataxias, AD ataxias have later age at onset, are often caused by trinucleotide expansions, and result from toxic gain of function. The AD spinocerebellar ataxias are classified by number, corresponding to genetic localization and identified gene. The AD ataxias are generally recognized by their pattern of clinical features, but clinical genetic testing is widely available for many of the types. There are also X-linked (e.g., FXTAS) and mitochondrial inherited forms of ataxia. With a few exceptions, treatment for the hereditary ataxias remains symptomatic. As molecular mechanisms become clarified, a variety of experimental therapeutic approaches are now being applied and hopefully will yield successes.

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Appendix

Resources for Clinicians and Patients

The following websites contain useful information for patients with hyperkinetic movement disorders, their families, and the clinicians caring for them.

GENERAL REFERENCES

www.ataxia.org/

This group provides educational information about ataxia, fund raising activities for research, and information about support groups for patients and their families.

www.clinicaltrials.gov

Patients or physicians seeking information about active clinical research studies related to movement disorders and other medical diseases can search for those that are recruiting new subjects.

www.NIH.gov

This website of the National Institutes of Health, in the section on the National Institute of Neurological Disorders and Stroke (NINDS), provides straightforward educational information about neurological movement disorders and other neurological conditions.

www.wemove.org

This is website of the organization Worldwide Education and Awareness for Movement Disorders and contains educational information and videos of a variety of movement disorders.

www.movementdisorders.org

This is the website of the international professional Parkinson and Movement Disorders Society and contains information about journals and educational events sponsored by the society as well as clinical rating scales.

DISEASE-SPECIFIC REFERENCES

www.autismspeaks.org

The website of Autism Speaks includes educational information about autism spectrum disorders as well as information about research.

www.blepharospasm.org

The website of the Benign Essential Blepharospasm Research Foundation contains educational information about this dystonic disorder and information about research on the condition.

www.dystonia-foundation.org

This website of the Dystonia Medical Research Foundation contains educational and research information regarding dystonia.

www.essentialtremor.org

The website of the International Essential Tremor Foundation has educational information about the disorder.

www.hdfoundation.org

The Hereditary Disease Foundation is a scientific and philanthropic organization aimed at finding better treatments and a cure for Huntington's disease and other genetic disorders.

www.hdsa.org

This website of the Huntington's Disease Society of America contains educational information about the illness as well as information about state chapters.

http://iocdf.org/

On its website, the International OCD Foundation provides educational and other information related to obsessive-compulsive disorder.

www.rls.org

Formerly the Restless Legs Syndrome Foundation and renamed the Willis-Ekbom Foundation, their website provides educational information about restless legs syndrome.

www.rettsyndrome.org

The website of the International Rett Syndrome Foundation contains educational information about the condition as well as information about related research.

www.tsa-usa.org

Individuals with Tourette's syndrome and others interested in learning more about the condition can find educational information on this website.

www.wilsonsdisease.org

The Wilson's Disease Association provides educational information about the disorder on its website.

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