Hyperkinetic Movement Disorders
Differential diagnosis and treatment
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Hyperkinetic Movement Disorders
Differential diagnosis and treatment

EDITED BY

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Preface

Hyperkinetic movement disorders have always puzzled neurologists and other clinicians because of uncertainties about their classification and treatment. At first sight, many hyperkinetic disorders may look alike, but a closer examination of their phenomenology, including pattern, rhythm, and anatomic distribution, usually allows for their proper categorization. Although in general neurology, clinical anatomical correlates are the cornerstone of diagnosis, in movement disorders phenomenology has an essential role. In our training and mentoring experience we enjoy the enthusiasm of young residents and fellows who begin to explore the many facets of hyperkinetic disorders. They soon recognize that proper phenomenological categorization is an essential element in the diagnosis of movement disorders, which then leads to finding the most likely etiology and treatment. Thus, as an example, if the clinician does not recognize patient’s chorea, the appropriate tests, such as Huntington disease DNA test, may not be ordered and the diagnosis may be delayed. Similarly, if one does not recognize a particular hyperkinesia as stereotypy, prior use of dopamine receptor blocking drugs may not be investigated and the diagnosis of tardive dyskinesia can be missed.

Until few years ago treatment options for hyperkinetic movement disorders were limited, but in recent years there has been a remarkable growth in effective and safe medical and surgical treatment strategies. Appropriate diagnosis, however, is critical before the most suitable disease-specific treatment is selected and offered to the patient.

Because of diagnostic challenges in the field of hyperkinetic movement disorders many patients seek multiple opinions. These consultations are sometimes done informally and facilitated by exchanging patient videos. Personal experience and expert knowledge are perhaps more important in this field than other neurological disciplines. Hence, the idea to assemble a unique volume dedicated to hyperkinetic movement disorders, accompanied by instructive videos, was the impetus for this book.

In planning this book we carefully selected true authorities in each field and, fortunately, they have accepted our invitation. As a result, we assembled the most outstanding, internationally renowned, faculty. We wish to thank the authors for their scholarly contributions. We also wish to thank the editorial and management staff of Wiley, particularly Michael Bevan, Julie Elliott, and Martin Sugden. Finally, we express our deep appreciation to our families, who allowed us to dedicate our time and effort to this project.

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PART 1

General Issues in Hyperkinetic Disorders
CHAPTER 1
Distinguishing Clinical Features of Hyperkinetic Disorders

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Introduction

Movement abnormalities can be dichotomized into the two broad categories of hypokinetic and hyperkinetic syndromes. The hallmark of hypokinesias is the loss of voluntary and automatic movements (akinesia), which is combined with slowness (bradykinesia) and stiffness or increased muscle tone (rigidity) in akinetic-rigid or parkinsonian syndromes [1]. In contrast, hyperkinesias are manifested by abnormal, uncontrollable, and unwanted movements. This term should not be confused with “hyperkinetic disorders” used in ICD 10 [2] to describe a behavioral abnormality – typically labeled attention deficit disorder with hyperactivity – occurring particularly in children and often associated with attention deficit and a tendency to move from one activity to another without completing any one. This is often associated with disorganized, ill-regulated, and scattered activity and thinking. This is not the only inconsistency between terminology in adult and childhood disorders, and efforts have been recently undertaken to unify the nosology and diagnostic recommendations in pediatric and adult movement disorders [3].

Hyperkinetic movement disorders include six main phenotypic categories, which can appear in isolation or in variable combinations: tremor, chorea, tics, myoclonus, dystonia, and stereotypies. In addition to these six categories there are other abnormalities of motor control that are also included within the field of movement disorders, such as akathisia, amputation stumps, ataxia, athetosis, ballism, hyperekplexia, mannerisms, myorhythmia, restlessless, and spasticity. The term “dyskinesia” is commonly used to indicate any or a combination of abnormal involuntary movements, such as tardive or paroxysmal dyskinesias or levodopa-induced dyskinesia, but more specific phenomenological categorization should be used whenever possible. In addition, there is a large and important group of peripherally-induced movement disorders, exemplified by hemifacial spasm [4], although any hyperkinetic movement disorder can be triggered or induced by peripheral injury [5]. Some conditions combine hypokinetic and hyperkinetic features, as exemplified by the coexistence of bradykinesia and tremor in Parkinson disease (PD) often referred to by the oxymora “gait disorder with acceleration” [6] or “shaking palsy” [7]. Probably the best examples of coexistent hyper- and hypokinesia is levodopa-induced dyskinesia in patients with PD and chorea or dystonia in patients with Huntington disease, many of whom have an underlying hypokinesia [8].
We describe here the hallmark features and phenomenology of the main hyperkinetic disorders, which are listed according to the time of their medical recognition.

**Historical background**

The importance of recognizing the appropriate phenomenology, not only as a guide to diagnosis but also as a means to study the pathophysiology of the disorder, is highlighted by the following statement attributed to Sir William Osler: “To study the phenomenon of disease without books is to sail an uncharted sea, while to study books without patients is not to go to sea at all” [9].

The characterization and classification of the various hyperkinetic disorders has evolved over a long period of time (Table 1.1). Tremor was a common language word before becoming a medical term. In ancient Greek, the root TRE is a lexical unit to indicate at the same time fear and shaking. Tremor was defined by Galen as an “involuntary alternating up and down motion of the limbs.” Involuntary movements present during action or at rest were also mentioned by Sylvius [10]. Parkinsonian tremor was later described by James Parkinson [7] and further differentiated from kinetic “intentional tremor” by Charcot [11]. The familial occurrence of postural action tremor was recognized shortly afterwards [12].

Epidemics of “dancing mania” emerged in central Europe in the late Middle Ages as local phenomena [13] or in connection with pilgrimages. Coincident with the Black Plague in 1348–50, St Vitus was called upon to intercede, leading to the term “chorea Sancti Viti” (St Vitus dance) to indicate at the same time a request for intercession and an means to expiate. This terminology has entered medical literature after Paracelsus described this syndrome among one of the five that “deprive man of health and reason.” He adopted the term “chorea” into medical jargon and proposed using the expression “chorea lasciva” to describe the epidemics [14]. One century later, Thomas Sydenham observed an epidemic affecting only children which he called “chorea minor” [15] and was later recognized to be a manifestation of rheumatic fever. Adult-onset hereditary chorea was described in the 19th century [16] and later renamed Huntington chorea.

The term “tic” arose in France in the 17th century to describe shivers in horses, particularly of certain breeds, which affect primarily the muscles of the pelvic region, pelvic limbs, and tail [17]. The word was later used by French doctors by analogy. The first medical report on human tics is probably the description of the Marquise of Dampierre, who started having tics at 7 years of age [18]. Later, Trouseau listed tics among choreatic disorders [19] and Gilles de la Tourette provided a separate taxonomic categorization of these phenomena [20].

Essential myoclonus was first described by Friedrich [21], who reported a 50-year-old man with a 5-year history of multifocal muscle jerks affecting both sides of the body symmetrically, but asynchronously. The syndrome was defined as “paramyoclonus multiplex” because of the reported symmetry. Forms of myoclonic epilepsy were later described and Lundborg [22] proposed a classification of myoclonus that remains largely in use today. Asterixis was observed in patients with hepatic encephalopathy [23] and later recognized to be a form of negative myoclonus.

Dystonia was the last main hyperkinetic disorder to be recognized: its name derives from a supposed alteration of muscle tone in patients with generalized distribution [24]. The hereditary nature was noted at about the same time [25].

### Table 1.1 Chronology of first description of the main hyperkinetic disorders.

<table>
<thead>
<tr>
<th>Date</th>
<th>Name</th>
<th>First usage</th>
</tr>
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<tbody>
<tr>
<td>Ancient Greece</td>
<td>Tremor</td>
<td>τρεμω (to tremble, to fear)</td>
</tr>
<tr>
<td>XI Century</td>
<td>Chorea</td>
<td>Choreomania (ritual dance)</td>
</tr>
<tr>
<td>XVII Century</td>
<td>Tic</td>
<td>French horse breeders</td>
</tr>
<tr>
<td>1871</td>
<td>Athetosis</td>
<td>Hammond [71]</td>
</tr>
<tr>
<td>1881</td>
<td>Myoclonus</td>
<td>Friedreich [21]</td>
</tr>
<tr>
<td>1885</td>
<td>Ballism</td>
<td>Kussmaul [72]</td>
</tr>
<tr>
<td>1911</td>
<td>Dystonia</td>
<td>Oppenheim [24]</td>
</tr>
<tr>
<td>1953</td>
<td>Asterixis</td>
<td>Adams [23]</td>
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Phenomenology and classification

Although at first sight involuntary movements resemble each other, each hyperkinetic disorder has a specific phenomenology (signature) that can be identified by direct observation of the patient or videotaped examination. Duration, rhythmicity, topography, and other features must be carefully analyzed and noted in order to make a specific phenomenological diagnosis [26] (Table 1.2).

Tremor

Tremor is an involuntary, rhythmic, oscillation of a body region about a joint axis. It is usually produced by alternating or synchronous contractions of reciprocally innervated agonistic and antagonistic muscles that generate a relatively symmetric velocity in both directions about a midpoint of the movement [27, 28]. The oscillation produced by tremor can be represented by a sinusoidal curve; it is generated by rhythmical discharges in an oscillating neuronal network and maintained by feedback and feed-forward loops. The resulting movement is patterned and rhythmic, characteristics that distinguish tremor from other hyperkinesias [29].

Tremor varies when different voluntary movements are performed or postures are held: it is labeled as a rest tremor, postural tremor, or action tremor according to the condition of greatest severity. Intention tremor, typically associated with cerebellar dysfunction, is characterized by the worsening of tremor on approach to a target, as in a finger-to-nose maneuver. The typical rest tremor of PD has a frequency of 4 to 6 Hz, and is most prominent distally. Its characteristic appearance in the hand is also referred to as a pill-rolling tremor. Parkinsonian rest tremor also typically involves the chin, jaw, and legs, but almost never involves the neck. Indeed, head oscillation should suggest essential tremor or dystonic tremor rather than PD. True rest tremor, however, disappears during complete rest, such as sleep, and is reduced or disappears with voluntary muscle contraction, or during movement. Postural tremor is present with the maintenance of a particular posture, such as holding the arms outstretched in front of the body. It is commonly seen in physiological and essential tremor. Re-emergent tremor refers to a postural tremor that occurs after a variable latency period during which no observable postural tremor is present [30]. This typically occurs in the setting of PD, and most likely represents a parkinsonian rest tremor that has been “reset” during the maintenance of a posture [31].

Task-specific tremor occurs only during execution of a particular task, such as writing, and is considered by many to be a variant of dystonic tremor. Dystonic tremor may occur in the setting of dystonia, and is a rhythmic, oscillation-like, dystonic movement [32]. Position-specific tremors only occur when the affected body part is placed in

Table 1.2  Tremor types can be differentiated based on frequency, amplitude and onset in relation to voluntary movements.

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Tremor type</th>
<th>Amplitude</th>
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<th>Relation to voluntary movement</th>
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<td>1–4 Hz</td>
<td>Cerebellar tremor</td>
<td>Medium–high</td>
<td>Limbs</td>
<td>Postural, action</td>
</tr>
<tr>
<td>3–5 Hz</td>
<td>Task-specific tremor</td>
<td>Low–medium</td>
<td>Hand</td>
<td>Writing, feeding, playing an instrument</td>
</tr>
<tr>
<td>4–5 Hz</td>
<td>Parkinsonian tremor</td>
<td>Medium–high</td>
<td>Limbs, jaw</td>
<td>Rest</td>
</tr>
<tr>
<td>5–8 Hz</td>
<td>Essential tremor</td>
<td>Medium–high</td>
<td>Limbs, head, voice</td>
<td>Postural</td>
</tr>
<tr>
<td>8–12 Hz</td>
<td>Physiologic tremor</td>
<td>Medium</td>
<td>Limbs</td>
<td>Postural</td>
</tr>
<tr>
<td>14–16 Hz</td>
<td>Orthostatic tremor</td>
<td>Low–medium (may not be visible, but can be palpated or auscultated)</td>
<td>Legs, trunk</td>
<td>Standing</td>
</tr>
</tbody>
</table>
a particular position or posture. Orthostatic tremor is an example of a position-specific tremor, and refers to a fast (14–16 Hz) tremor, mainly affecting the trunk and legs, that occurs after standing for a certain period of time [33].

**Chorea**

Chorea is an irregular, unpredictable, involuntary random-appearing sequence of one or more, discrete, involuntary jerk-like movements or movement fragments. Movements appear random due to the variability in timing, duration, direction, or anatomic location. Each movement may have a distinct start and end point, although these may be difficult to identify since movements are often strung together, one immediately following or overlapping another. Movements may, therefore, appear to flow randomly from one muscle group to another, and can involve trunk, neck, face, tongue, and extremities. Infrequent and mild chorea may appear as isolated, small-amplitude brief movements. It may resemble restless, fidgety, or anxious behavior. When chorea is more severe, it may appear to be almost continuous, flowing from one site of the body to another (Figure 1.1).

Although chorea may be worsened by movement, it usually does not stop with attempted relaxation. Chorea is distinguished from tremor and dystonia by its lack of rhythmicity and predictability. Chorea may be difficult to differentiate from myoclonus, but the latter is more intermittent rather than continuous. Chorea is typically a fluent disorder involving contiguous body parts in variable order and direction. It may be associated with hypotonia, hung-up and pendular reflexes, and motor impersistence (inability to maintain a sustained contraction). Examples of impersistence include an inability to maintain prolonged tongue protrusion or handgrip (“milkmaid grip”). The term “parakinesia” refers to the incorporation of the involuntary movements into semipurposeful movements, in a semiconscious attempt to camouflage the chorea. Examples of parakinesia include touching one’s face, adjusting glasses, and other mannerisms that often served to delay the recognition of the involuntary movement.

Ballism is characterized by high amplitude, almost violent, movements that mainly involve the proximal limb joints. It is considered an extreme phenomenological expression of the spectrum of chorea that affects proximal joints such as shoulder or hip. This leads to large amplitude movements of the limbs, sometimes with a flinging or flailing quality. As patients recover from acute ballism, frequently associated with a stroke in the contralateral subthalamic nucleus, the ballistic movements often gradually evolve into chorea or dystonia (see Chapters 10 and 11).

**Tics**

Tics are repeated, individually recognizable, intermittent movements or movement fragments that are almost always briefly suppressible and are usually associated with the awareness of an urge to perform the movement, the so-called “premonitory sensation.” Motor tics often result in either a simple jerk-like movement such as a blink, facial grimace, head jerk, or shoulder shrug, or more complex, stereotyped, semivoluntary, intermittent movements. Tics are usually abrupt in onset, fast and brief (clonic tics), slow and sustained (dystonic tics), or manifested by sudden cessation of movement because of isometric muscle contractions (tonic tics), or inhibition of voluntary movement (blocking tics). The duration of each tic movement is characteristic of that tic, and the duration does not generally vary between different repetitions [34]. Tics can occur during all stages of sleep.

Characteristic features include predictability of both the nature of the movement and its onset, suggestibility, exacerbation during excitement or stress and also after stress (rebound), and brief voluntary suppressibility. Complex motor tics may resemble normal motor acts or gestures, but are generally inappropriately intense and timed [34]. The movements can appear purposeful, such as touching, throwing, hitting, jumping, and kicking, or non-purposeful, such as head shaking or trunk bending. Occasionally tics can be so severe as to cause neurological sequels, with reports of compressive cervical myelopathy resulting from recurrent head thrusting and violent neck
hyperextension tics [35]. Complex motor tics can also include copropraxia (grabbing or exposing one’s genitals) or echopraxia (imitating gestures).

Motor tics are almost invariably accompanied by vocal or phonic tics and many experts view motor and phonic tics are having the same pathophysiologically mechanism. Simple phonic tics can involve brief occurrences of sniffing, throat clearing, grunting, screaming, coughing, blowing, or sucking sounds. Pathological laughter has also been reported as a manifestation of a simple phonic tic [36]. In contrast, complex phonic tics are semantically meaningful utterances and include coprolalia, or shouting of obscenities, profanities, or other insults. Other

Figure 1.1 This photographic sequence (1.5 frames per second) permits an appreciation of the rapid flow of chorea motor fragments in a patient with Huntington disease.
complex phonic tics include echolalia (repeating someone else’s words or phrases) and palilalia (repeating one’s own utterances, particularly the last syllable, word, or phrase in a sentence). Rarely, tics may be continuous and disabling, resulting in a so-called “tic status” [37] or in severe, self-injurious, even life-threatening behaviors, so called “malignant Tourette syndrome” [38]. Because of the broad expression of Tourette syndrome, manifested not only by motor and phonic tics but by a variety of behavioral comorbidities (such as attention deficit with hyperactivity, obsessive-compulsive disorder, and impulsivity), the management depends on establishing an appropriate hierarchy of the various symptoms and targeting the therapeutic strategies to the most troublesome problems [39]. (See Chapters 12 and 13).

**Athetosis**

Athetosis is a slow, continuous, involuntary writhing movement that (1) prevents the maintenance of a stable posture; (2) involves continuous smooth movements that appear to be random and are not composed of recognizable movement fragments; (3) typically involves the distal extremities (hands or feet) more than the proximal and can also involve the face, neck, and trunk; and (4) may worsen with attempts at movement or posture, but can also occur at rest.

Athetosis rarely occurs in isolation but is much more commonly associated with chorea and dystonia. In fact, it is considered a variant of distal chorea or dystonia. Phenomenologically, athetosis is at the opposite end of ballism, resulting in a slow, gentle, and distal motion, resembling slow chorea. The recognition of athetosis often leads to consideration of cerebral palsy or paroxysmal choreoathetosis. Pseudoathetosis refers to a severe distal sensory loss syndrome whereby involuntary, slow, writhing movements are due to loss of proprioception [40].

**Myoclonus**

Myoclonus consists of repeated, often non-rhythmic, brief shock-like jerks due to the sudden involuntary contraction or relaxation of one or more muscles. These “lightning-like” movements differ from epileptic myoclonus and do not affect consciousness [41]. Myoclonus may be synchronous (several muscles contracting simultaneously), spreading (several muscles contracting in a predictable sequence), or asynchronous (several muscles contracting with varying and unpredictable relative timing). When myoclonus affects more than one muscle in an apparently random and varying pattern it is called multifocal; it is called generalized when many muscles through the body are involved simultaneously. Myoclonus is characterized by a sudden unidirectional movement due to agonist contraction (positive myoclonus) or by sudden brief muscle relaxation (negative myoclonus) [42]. The latter is exemplified by asterixis, which typically presents in patients with hepatic and other encephalopathy.

The distinction between myoclonus and other involuntary disorders – particularly tics, chorea, and different varieties of jerks – is not always clear. Tics are usually associated with a generalized, conscious, urge or local premonitory sensation to move and a feeling of relief of tension after the movement. In addition, many tics are suppressible, in contrast to myoclonus. Brief muscle movements in dystonia are often associated with dystonic posturing. Mild chorea may be difficult to distinguish from myoclonus. Sometimes myoclonus is rhythmic and can resemble tremor. When myoclonus is repeated rhythmically it is also called “myoclonic tremor”, but this is a misnomer as rhythmical myoclonus, such as palatal myoclonus [43], is caused by contractions of agonists only, not alternating contractions of antagonist muscles as seen in tremor.

Myoclonus can be caused or worsened by movement and can sometimes occur during sleep. Myoclonus can be categorized as action myoclonus, postural myoclonus, or rest myoclonus on the basis of the condition in which it is observed [44]. It can also be categorized on the basis of the presumed anatomic origin as cortical, subcortical, brainstem, propriospinal, or spinal. Myoclonus may coexist with dystonia (as in myoclonus-dystonia syndrome) or with tremor (as in essential myoclonus) [45]. (See Chapters 14, 15, and 16).
Dystonia
In dystonia, involuntary sustained or intermittent muscle contractions cause twisting and repetitive movements, abnormal postures, or both. The combination of postures and dystonic movements is typical of dystonia [46].

Dystonic postures are repeated and particular patterns or postures are characteristic of each patient at a given point in time. Similar dystonic postures may occur in different patients. Postures can be sustained, particularly at the peak of dystonic movements, or may occur during very brief intervals. Dystonic postures are often triggered by attempts at voluntary movement or voluntary posture, and in some cases they are triggered only in particular body positions or by particular movements as may occur in task-specific dystonia. With the exception of certain seizure disorders [47], dystonic movements or postures are not typically seen during sleep, possibly due to inhibition of movements by spinal mechanisms [48]. Postures tend to occur at intervals determined by voluntary movement and can be sustained for variable lengths of time. Relaxation may be impaired so that the dystonic posture may be maintained well beyond the end of the attempted voluntary movement that triggered it. There may be multiple dystonic postures in the same patient, so that different dystonic postures may be combined.

Dystonic movements may vary in terms of speed, amplitude, rhythmicity, forcefulness, and distribution in the body, but the same muscles are usually involved; hence the term “patterned” movement disorder. Dystonia may occur at rest, during activity or only during a specific motor movement or posture, so-called task- or position-specific dystonia (Figure 1.2) [49]. The most common adult-onset upper limb task-specific dystonia is writer’s cramp [50]. Musician’s cramp occurs while playing a musical instrument [51]. Embouchure dystonia affects the control of the lip, jaw, and tongue muscles, and may be seen in woodwind and brass players [52].

The term “fixed dystonia” is used to indicate persistent, abnormal posture, without a dynamic component. When present but untreated for weeks or longer, dystonia may lead to fixed contractures. Fixed dystonia is often associated with painful contracture, as in post-traumatic, chronic regional pain syndrome [53] or sustained voluntary contraction as in psychogenic dystonia. (see Chapter 24).

Dystonia is typically associated with the occurrence of gestes antagonistes (or sensory tricks), mirror phenomena and overflow [54–56]. Their recognition supports the clinical diagnosis of dystonia [46]. Dystonia can affect any body part, with a wide range in severity from very mild to extremely severe cases (see Chapters 8 and 9).

Stereotypies
Stereotypies are involuntary or unvoluntary (in response to or induced by inner sensory stimulus or unwanted feeling), coordinated, patterned, repetitive, rhythmic, seemingly purposeless movements or utterances [57]. Although stereotypies typically occur in children with autism or other pervasive developmental disorders, they can also occur in adults. Typical motor stereotypies encountered in children with autism include body rocking, head nodding, head banging, hand washing and waving, covering ears, fluttering of fingers or hands in front of the face, repetitive and sequential finger movements, eye deviations, lip smacking, and chewing movements, pacing, object fixation, and skin picking. Phonic stereotypies include grunting, moaning, and humming. In adults, stereotypies are
usually encountered in patients with tardive dyskinesias. In this setting stereotypies are usually in the form of orofacial or lingual chewing movements, pelvic rocking movements and other repetitive coordinated movements. They are often accompanied by akathisia, manifested by motor and sensory restlessness (see Chapters 21 and 22).

Non-motor features
Psychiatric morbidity is higher in patients with hyperkinetic movement disorders than in community samples or in patients with other forms of chronic disease. Behavioral abnormalities have been reported in patients with Tourette syndrome [58], Wilson disease [59], dystonia [60], essential tremor [61], Sydenham chorea [62] and Huntington disease gene carriers [63]. Age at onset is likely to be an important determinant of susceptibility to psychiatric morbidity in many of these conditions.

Given the complexity of basal ganglia functions, it is not surprising that hyperkinetic disorders are frequently associated with behavioral or psychological changes that, in many cases, are considered to have a pathogenic commonality with the motor disturbance. Basal ganglia pathology engenders a wide spectrum of neuropsychiatric symptoms [64], which are thought to involve the associative circuit (focused on the dorsolateral caudate nucleus and the caudoventral putamen) and the emotional circuits (centered in the ventral caudate nucleus, the nucleus accumbens, and the amygdala) [65, 66].

Particularly, chorea, tics, and dystonia are coincident with obsessive-compulsive traits, anxiety, or depression in different combinations and with variable severity. Such coincidence may be due to an underlying basal ganglia dysfunction producing both motoric and behavioral expressivity. Of particular interest is the finding that depression, attention-deficit hyperactivity disorder and vocal tics are significantly more common in children with Sydenham chorea, compared to children who had rheumatic fever without Sydenham chorea [67]. Medication-related adverse effects may be an additional source of depression or anxiety in patients with hyperkinetic movement disorders and cause akathisia or additional hyperkinesias [68–70].

Behavioural features associated with hyperkinetic disorders should not be confounded with psychogenic movement disorders, which are abnormal movements thought to be due to pre-existing psychological or psychiatric disturbances. The borderland between movement disorders and psychiatry is a difficult diagnostic area. It is remarkable that most movement disorders were initially considered psychogenic due to the inexplicability of their phenomenology, such as the paradigmatic case of primary dystonia, featuring bizarre postural abnormalities, relief by gestes antagonistes, task specificity, and normal brain morphology. The organic nature of primary hyperkinetic movement disorder is now unequivocally recognized, although they may not always be easily differentiated from psychogenic hyperkinesias. Chronicity, social impairment, and stigma, however, can affect the ability of patients with hyperkinetic disorders to develop or continue many of their key social roles, such as marital or employment status, thus engendering reactive depression or other secondary behavioral consequences.

Clinical examination and medical recording
Although the expert clinician can quickly attempt to recognize the features of hyperkinetic disorders (Figure 1.3) it is necessary to accomplish a thorough documentation of the observed features to avoid mistakes and allow review and comparison of the phenotype [26, 57].

Examination of patients with a hyperkinetic movement disorder must include a full examination for associated neurological findings. It must also include an assessment of the effect of the movement disorder on overall motor function and quality of life. Observation of the disorder itself should include several components, including the phenomenology of the disorder, the time-course, triggers and suppressibility, and the somatic distribution (focal, segmental, multifocal, and generalized). The phenomenology should be described in terms of duration, speed, amplitude, jerkiness, repeatability, or stereotyped quality, and
the number of different identifiable movements or postures. The time-course should be described in terms of rhythmicity, whether it is intermittent with intervening more normal movement, whether movements are sustained or ongoing, and whether there are discrete submovements or movement fragments or whether the movement appears to be continuously flowing. Possible triggers should be assessed from the history and examination, including attempted movement, posture, rest, and emotional state. Suppressibility can be tested in clinic or assessed from the history, and the presence of an urge to move should be determined.

Distractibility evaluates whether unrelated mental or physical tasks (as opposed to asking the patient to voluntarily suppress) result in movement suppression. Distractibility can be seen in tics, stereotypies, and psychogenic movements.

Given the patient’s consent, it is valuable to take a video of the clinical interview and medical examination. This allows the examiner to review the phenomenology of the hyperkinetic disorder, to seek expert consultation and visually compare phenomenology changes during natural course of the condition. It is particularly important to show as clearly as possible on the video clip the features listed in Table 1.3.

**Table 1.3** General features of hyperkinetic disorders.

<table>
<thead>
<tr>
<th>Movement</th>
<th>Regularity</th>
<th>Rhythmicity</th>
<th>Speed</th>
<th>Suppressibility</th>
<th>Duration</th>
<th>Triggerability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tremor</td>
<td>Yes</td>
<td>Yes</td>
<td>1-16 Hz</td>
<td>Sometimes briefly briefly</td>
<td>Transient or permanent</td>
<td>Position, posture, voluntary movement</td>
</tr>
<tr>
<td>Chorea</td>
<td>No</td>
<td>No</td>
<td>Fast</td>
<td>No</td>
<td>Transient or permanent</td>
<td>Voluntary movement</td>
</tr>
<tr>
<td>Tics</td>
<td>No</td>
<td>No</td>
<td>Slow or fast</td>
<td>Usually</td>
<td>Transient or permanent</td>
<td>Sensory stimuli, stress, thoughts</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>Sometimes</td>
<td>Sometimes</td>
<td>Fast</td>
<td>No</td>
<td>Transient or permanent</td>
<td>Sensory or proprioceptive stimuli</td>
</tr>
<tr>
<td>Dystonia</td>
<td>No</td>
<td>Rarely</td>
<td>Slow or fast</td>
<td>Partial or only briefly</td>
<td>Transient, permanent or paroxysmal</td>
<td>Specific motor tasks</td>
</tr>
</tbody>
</table>

**Figure 1.3** Flow chart for a quick orientation in the differential diagnosis of the five main hyperkinetic disorders.
in Tables 1.3 and 1.4, allowing the specifics of the observed phenomena to be visually evaluated. A well-constructed video recording can convey more accurate information than standard clinical notes.

References

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Distinguishing Clinical Features of Hyperkinetic Disorders


Chapter 1


CHAPTER 2
Pathophysiology and Molecular Pathology of Dystonia and Tics

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Introduction
In this chapter we focus on dystonia and tics as they may share similarities in the pathophysiology; they can be considered as models of: dysfunction of the basal ganglia-cortical pathways; the sensorimotor loop for dystonia; and the motor, associative, and limbic loops for tics and Gilles de la Tourette syndrome.

Dystonia
Dystonia is defined as involuntary, sustained and often repetitive, muscle contractions of opposite muscles that lead to abnormal movements or posture. This definition, although commonly accepted, does not reflect the complexity and variety of syndromes enclosed within the denomination of dystonia. Here, we attempt to update the implication of genetic forms in the pathophysiology of dystonia, explore the animal models, and summarize recent advances in neuroimaging and neurophysiology.

Molecular pathology
Up to 20 genetic forms of dystonia have been identified to date [1]. The phenotype of these forms is presented in Chapter 7. Although the gap between molecular pathology and dystonic phenotype is far from being bridged, identification of the functions of the mutated genes has been possible for some primary dystonia forms providing new insight into the pathophysiological processes underlying the expression of these different clinical patterns (Table 2.1). Interestingly, several recent works have highlighted functional links between the proteins encoded by these genes.

DYT1 dystonia is related to mutations in the TOR1A gene. Torsin A, an AAA+ ATPase, is a protein whose exact cellular function is not yet known. This protein may play a role in cellular membranes (nuclear envelope and endoplasmic reticulum) homeostasis and may be involved in proteins processing/trafficking and excretory pathways. Other potential functions include synaptic vesicles recycling, neurite outgrow and postnatal maturation events involving neurons (especially at the synaptic level) [2] and glia [3].

DYT3 dystonia is caused by complex changes in TAF1/DYT3 transcripts. TAF1/DYT3 comprises at least 43 exons that are alternatively spliced. Alternative splicing of exon 1–38 encodes isoform of TATA box binding protein-associated factor 1 (TAF1). Exons d1–d5 located downstream to exon 38 can either form separate transcripts...
Table 2.1 DYT coding for dystonia genes and locus.

<table>
<thead>
<tr>
<th>Locus name</th>
<th>Inheritance</th>
<th>Chromosome</th>
<th>Gene</th>
<th>Phenotype</th>
<th>OMIM</th>
</tr>
</thead>
<tbody>
<tr>
<td>DYT1</td>
<td>AD</td>
<td>9q34</td>
<td>TOR1A</td>
<td>Early onset idiopathic torsion dystonia</td>
<td>128100</td>
</tr>
<tr>
<td>DYT2</td>
<td>AR</td>
<td>NK</td>
<td>NK</td>
<td>AR torsion dystonia</td>
<td>224500</td>
</tr>
<tr>
<td>DYT3</td>
<td>XL</td>
<td>Xq13.1</td>
<td>TAF1</td>
<td>X-linked dystonia-parkinsonism (Lubag)</td>
<td>314250</td>
</tr>
<tr>
<td>DYT4</td>
<td>AD</td>
<td>Inconnu</td>
<td>NK</td>
<td>Hereditary whispering dystonia</td>
<td>128101</td>
</tr>
<tr>
<td>DYT5a</td>
<td>AD</td>
<td>14q22.1-q22.2</td>
<td>GCH1</td>
<td>Dopa-responsive dystonia (DRD); Segawa syndrome; hereditary progressive dystonia with marked diurnal fluctuation</td>
<td>128230</td>
</tr>
<tr>
<td>DYT5b</td>
<td>AR</td>
<td>11p15.5</td>
<td>TH</td>
<td>Autosomal recessive DRD; AR Segawa syndrome</td>
<td>605407</td>
</tr>
<tr>
<td>DYT6</td>
<td>AD</td>
<td>8p11.21</td>
<td>THAP1</td>
<td>Idiopathic torsion dystonia of 'mixed' type</td>
<td>602629</td>
</tr>
<tr>
<td>DYT7</td>
<td>AD</td>
<td>18p</td>
<td>NK</td>
<td>Adult-onset focal dystonia</td>
<td>602124</td>
</tr>
<tr>
<td>DYT8</td>
<td>AD</td>
<td>2q35</td>
<td>MR1</td>
<td>Non-kinesigenic paroxysmal choreoathetosis (PNKD1)</td>
<td>118800</td>
</tr>
<tr>
<td>DYT9 = DYT18</td>
<td>AD</td>
<td>1p</td>
<td>SLC2A1</td>
<td>Episodic choreoathetosis/spasticity and ataxia</td>
<td>601042</td>
</tr>
<tr>
<td>DYT10</td>
<td>AD</td>
<td>16q11.2-q12.1</td>
<td>NK</td>
<td>Paroxysmal kinesigenic dyskinesia (PKD1)</td>
<td>128200</td>
</tr>
<tr>
<td>DYT11</td>
<td>AD</td>
<td>7q21</td>
<td>SGCE</td>
<td>Myoclonus dystonia</td>
<td>159900</td>
</tr>
<tr>
<td>DYT12</td>
<td>AD</td>
<td>19q12-q13.2</td>
<td>ATP1A3</td>
<td>Rapid-onset dystonia-parkinsonism</td>
<td>128235</td>
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<tr>
<td>DYT13</td>
<td>AD</td>
<td>1p63.32-p36.13</td>
<td>NK</td>
<td>Early onset cranio-facial dystonia</td>
<td>607671</td>
</tr>
<tr>
<td>DYT15</td>
<td>AD</td>
<td>18p11</td>
<td>NK</td>
<td>Myoclonus dystonia</td>
<td>607488</td>
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Table 2.1 (cont’d).

<table>
<thead>
<tr>
<th>Locus name</th>
<th>Inheritance</th>
<th>Chromosome</th>
<th>Gene</th>
<th>Phenotype</th>
<th>OMIM</th>
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<tr>
<td>DYT16</td>
<td>AR</td>
<td>2q31.3</td>
<td>PRKRA</td>
<td>Early onset AR dystonia–parkinsonism</td>
<td>612067</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Protein kinase, interferon-inducible double-stranded RNA-dependent activator:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>signal transduction, cellular proliferation and differentiation; apoptosis</td>
<td></td>
</tr>
<tr>
<td>DYT17</td>
<td>AR</td>
<td>20p11.2-q13.12</td>
<td>NK</td>
<td>AR torsion dystonia (focal)</td>
<td>612406</td>
</tr>
<tr>
<td>DYT18</td>
<td>AD</td>
<td>1p35-p31.3</td>
<td>SLC2A1</td>
<td>Paroxysmal exertion-induced dyskinesia</td>
<td>NK</td>
</tr>
<tr>
<td>DYT19</td>
<td>AD</td>
<td>16q13-q22.1</td>
<td>NK</td>
<td>Paroxysmal kinesigenic dyskinesia (PKD2)</td>
<td>NK</td>
</tr>
<tr>
<td>DYT20</td>
<td>AD</td>
<td>2q31</td>
<td>NK</td>
<td>Non-kinesigenic paroxysmal choreoathetosis (PNKD2)</td>
<td>NK</td>
</tr>
<tr>
<td>DYT21</td>
<td>AD</td>
<td>2q14.3-q21.3</td>
<td>NK</td>
<td>late onset, focal, segmental, generalized dystonia protein</td>
<td>NK</td>
</tr>
</tbody>
</table>

AD: autosomal dominant; AR: autosomal recessive, XL: X-linked; NK: not known.

regulated by separate promoters [4]. or transcripts spliced to some of exons 1–37 of TAF1 [5]. It is not clear how these changes in TAF1/DYT3 transcript system cause the disease but several lines of evidence point to modifications of D2 receptors expression or disruption of various gene expression in the striatum [1].

DYT6 dystonia is caused by mutations in the gene that encodes THAP (thanatos-associated protein) domain-containing apoptosis-associated protein 1 (THAP1) [6, 7]. In addition to the identified mutations, a rare non-coding substitution in THAP1 might increase the risk of dystonia [6]. The THAP1 protein is a sequence-specific DNA-binding factor which regulates cell proliferation and plays roles in cell survival and/or apoptosis [8]. Recently, THAP1 was found to bind two proteins: HCF−1 protein, a potent transcriptional coactivator and cell cycle regulator, and OGT protein, an enzyme which plays an role in a whole host of cellular processes as transcriptional regulation, signaling, proteasomal degradation and organelle trafficking [9].

DYT11 dystonia is related to mutations in the SGCE gene. They result in the synthesis of either aberrant e-sarcoglycan molecules or none at all, and are “loss of function” [10]. The spectrum of myoclonus dystonia-DYT11 associated with mutations within the SGCE gene [11] has been expanded to microdeletion [12] and Silver–Russel syndrome (uniparental disomy of chromosome 7).

Outline of a dystonia molecular network

Links between DYT1 and DYT6
Recent evidence suggests that THAP1 is able to interact with the promoter of DYT1/TOR1A and that THAP1 mutations causing dystonia alter this interaction. However, it was not possible to prove in blood cells or fibroblast lines that DYT1 expression was reduced in THAP1-mutated patients or
increased by THAP1 overexpression. This direct interaction may thus only occur in specific region of the brain or at key developmental steps [13].

**Links between DYT6 and DYT3**
THAP1 shares sequence characteristics, in vivo expression patterns and protein partners with THAP3 [9]. Transcriptional dysregulation leading to increased neuronal vulnerability, may contribute to diseases such as DYT6 and DYT3 (X-linked dystonia-parkinsonism) caused by reduced expression of RNA polymerase II TATA box-binding protein-associated factor 1 (TAF1). In these two diseases, THAP1 (DYT6) and TAF1 (DYT3) are crucial to cell-cycle progression in dividing cells and mutations in either protein is likely to favor cell-cycle arrest and probably cell death [14]. In addition, THAP3 interacts with HCF-1 through a consensus HCF-1-binding motif (HBM), a motif that is also present in THAP1 and the gene encoding the THAP1/DYT6 protein partner OGT maps within the DYT3 critical region on Xq13.1 [9]. A link may also exist between DYT1 and DYT6.

**Dopamine dysfunction: a link between DYT1, DYT11**
A beneficial effect of levodopa has been observed in some myoclonus-dystonia patients [15]. The SCGE gene is also strongly expressed in dopaminergic neurons. Dysregulation of dopamine release has been observed in animal models and reduced dopamine D2 receptor availability was found in patients. The role of dopamine dysfunction in DYT1 dystonia has been emphasized [16–18]: dopamine transporter activity is reduced in DYT1 animal models, with altered dynamics of reuptake and release of dopamine [19]. In addition, reduced striatal D2 receptor binding was found in DYT1 patients [20]. Finally, TAF1, implicated in Lubag (DYT3 dystonia) may also play a role in the regulation of the DRD2 gene, and a decreased expression of the DRD2 gene has been found. Together, these results suggest that alteration in the dopamine signaling pathway may be crucial in various forms of dystonia.

**Animal models**
Several animal models have been developed throughout the years, although none of them can perfectly mimic the complexity of the clinical features observed in humans. These various models basically display dysfunctions within the main motor networks.

**Cortex–basal ganglia loops**
Various types of dystonia, from abnormal postures to phasic movements or myoclonic dystonia [21], have been produced after microinjections of bicuculline (antagonist of GABA-A receptors) into the posterior putamen, corresponding to the sensorimotor territory [22] and the sensorimotor territory of the external globus pallidus (GPe) [23]. Injections within the thalamus [ventral lateralis, nucleus pars oralis (VLo) and ventral anterior nucleus (VA)] induced contralateral dystonic postures, whereas injections in the caudal part [ventral posterolateral nucleus, pars oralis (VPLo) and ventralis lateralis nucleus, pars caudalis (VLC)] induced myoclonic dystonia. This suggested that dystonia might result from a dysfunction of the motor pallidal relay (rostral) but also points to the cerebellar relay (caudal) of the thalamus [21]. Impairment of synaptic plasticity in the striatum is a critical point and has been demonstrated in DYT1 mice models. Abnormal plasticity in the cortex–basal ganglia loop is underlined by aberrant long-term potentiation (LTP) and depression (LTD) phenomena [24, 25] with an unbalanced cholinergic transmission. Systemic 3-NP increased NMDA receptor-dependent LTP at the level of the corticostriatal synapses [26]. At the cortical level, in the SMA proper, there is also an increase in excitability and loss of selectivity [21]. Lesions and pharmacological manipulations of the brainstem (e.g. interstitial nucleus of Cajal, pedunculopontine nucleus, and red nucleus that receives input from the basal ganglia and the cerebellum) may elicit dystonic movements [27].

**Cerebellum–basal ganglia-cortex**
Based on two animal models with dystonic movements originating from cerebellar dysfunctions, the role of the cerebellum in the pathophysiology of dystonia has been emphasized [28]. Additional subclinical lesions of the striatum exaggerated the dystonic attacks [29]. Moreover, in normal mice, when dystonic movements were triggered by a local application of kainic acid on the cerebellar
cortex, microdialysis revealed a reduction in striatal dopamine release [29]. Taken together, these various results in mice support the hypothesis that dystonia may arise from the dysfunction of a motor network involving the basal ganglia, the cerebellum, the cortex, and the dopaminergic system. Apart from the interaction at the cortical level, a disynaptic pathway linking an output stage of cerebellar processing (dentate nucleus) with an input stage of basal ganglia processing (striatum) was recently demonstrated [30]. Cortical areas (the SMA and the pre-SMA) are also the targets of disynaptic projections from the dentate nucleus of the cerebellum and from the GPI [31, 32].

**Sensorimotor disruption**

**Environmental factors**

Some arguments support the fact that there is a link between stereotyped, skilled repetitive movements and the vulnerability to develop task-specific dystonia. In a large case-control study [33], the risk of being affected by writer’s cramp increased progressively with the time spent writing each day and was also associated with an abrupt increase in the writing time during the year before onset, but this finding must be interpreted cautiously because of the strong possibility of a retrospective recall bias.

**Imaging studies**

Although brain MRI was previously thought to be normal in dystonia, structural (VBM, DTI) [34] and functional [35] abnormalities were recently demonstrated within the sensorimotor network (including the putamen, the thalamus, and the cortical representation of the hand) and the cerebellum in various types of dystonia [34, 36]. Additional commonalities between different types of dystonia was supported by the finding of alterations of the fibers connecting: (i) the primary sensorimotor areas with subcortical structures in writer’s cramp [37, 38]; (ii) the thalamic prefrontal connections in a small group of various focal dystonia [39]; and (iii) the pontine brainstem in the vicinity of the superior cerebellar peduncle and the sensorimotor region in DYT1 and DYT6 patients [40].

Sequence learning abnormalities were related to the genotype as reduced performance was observed in DYT1 individuals, regardless of the phenotype (manifesting and non-manifesting carriers), whereas DYT6 individuals had normal performance. This interaction between phenotype (dystonia) and genotype (DYT1 status) was further explored by comparing symptomatic and asymptomatic DYT1 carriers with non-DYT1 dystonic patients (either sporadic or with a family history) [41]. The functional activation was predominant in the lateral cerebellum with relative activation deficits in the bilateral dorsolateral prefrontal cortex, and the left cingulated and dorsal premotor cortex [42], suggesting a shift from the cortico-striato-pallida-thalamocortical to cerebellar pathways. Whether this balance between striatal and cerebellar processing is secondary to functional or structural abnormalities in the basal ganglia, or reflects compensatory mechanisms, is still a matter of debate.

In an important review on the abnormal structure-function relationship in hereditary dystonia [43], the metabolic patterns and anatomical connectivity relative to penetrance and genotype (DYT1 and DYT6) were extensively described: an increased activity pattern distinguished the dystonia-manifesting carriers, across genotypes. A recent study on DYT11 myoclonus-dystonia demonstrated disorganized sensorimotor integration [44]. Measurements of the basal ganglia volumes may have an importance for the phenotypic expression of dystonia (asymptomatic DYT1 carriers and larger than those of symptomatic DYT1 patients [41]) and for the detection of endophenotype (unaffected relatives of patients with sporadic cervical dystonia, who had abnormal sensori-determination, had reduced putaminal gray matter volume bilaterally compared with those with normal SDT [45]). Overall, these findings point toward a pathophysiological core common to several types of genetic or sporadic dystonia.

**Electrophysiological studies**

Abnormal modulation of cortical excitability in sporadic and DYT1 dystonia [46], and abnormal plasticity [47, 48] in DYT1 and sporadic dystonia, are hallmarks of the disease. Other abnormalities appear to be common to sporadic and DYT1 dystonia, such as alterations in sensory processing [49], inner representation of the body (including a non-manifesting carriers) [50], and per-operative
GPI recordings [51]. In contrast, DYT11 myoclonus-dystonia appears different since cortical excitability is normal (hypothetically related to neuron membrane properties) [52].

**An integrative model of the pathophysiology of dystonia**

Despite the multiple phenotypes and genotypes of dystonia, imaging and experimental data points to a disorder of the basal ganglia and the sensorimotor circuits, including, more recently, the cerebellotralamo-cortical pathways [53, 54]. Aberrant plasticity (either maladaptive or developmental) is the hallmark of dystonia at the striatal (with impaired synaptic plasticity – with a role of cholinergic fastspiking interneurons and of dopamine imbalance) and cortical levels [48]. In monogenic forms of dystonia (e.g. DYT1, DYT6, DYT3), imbrications of proteins and genes functions suggest the existence of some common (although poorly understood) pathways. Functional imaging may help to disentangle the mechanisms underlying the phenotypic expression of the disease as activated networks are different in symptomatic and asymptomatic carriers of DYT1 and DYT6 subjects. Neuro-imaging may also open some insight in the compensatory mechanisms (activation studies, striatal volume measures). Finally, animal models may be more useful for studying the pathogenesis of dystonia at the molecular and cellular levels than for mimicking; the phenotypic expressions of the human disease.

**Gilles de la Tourette syndrome**

Tics are sudden, brief, intermittent, repetitive, non-rhythmic stereotyped movements (simple or complex motor tics) or vocalizations (phonic tics, coprolalia, echolalia) that can be voluntarily suppressed (for at least one minute) at the price of an increasing discomfort that is transiently relieved by the execution of the tic [55]. Gilles de la Tourette syndrome (TS) has been arbitrarily defined [56] by the occurrence of multiple motor plus one or more vocal tics that are present not necessarily concurrently, but on most days over at least one year, and without a tic-free period of more than 3 months; the onset of tics must be before the age of 18 (DSM-IV-TR) or 21 (Tourette Syndrome Classification Study Group) depending on the diagnostic criteria applied. TS is in many cases accompanied by comorbid psychiatric features such as obsessive-compulsive symptoms (OCS), attention deficit hyperactivity disorder (ADHD), self-injurious behavior, and other behavioral problems. No single cause of TS has been identified so far. However, genetic, anatomical, neuroradiologic, and animal model studies have shed light on possible pathogenic mechanisms of TS.

**Genetic aspects**

There is strong evidence in favor of a genetic base of TS. Concordance rates for tic disorders are 77–100% in monozygotic twins but only 23% in dizygotic twins. Family studies show a 10- to 100-fold increased risk of having TS in first-degree relatives of TS patients and that chronic tics are more common among first-degree relatives of TS patients than in the general population (for a review see O’Rourke et al. [57]. TS and chronic tic disorders are therefore likely to represent manifestations of different severity that belong to the same disease entity. However, familial aggregation of TS does not prove a genetic cause as family members share a common environment. Comorbid psychiatric conditions are common among patients with TS, and only 12% show a pure movement disorder [58]. OCS and ADHD affect more than 50% of patients with TS [58, 59] – a significantly higher proportion than in the general population.

Linkage analyses showed an association of TS with various markers, including chromosome 2p23.2, 5p, 6p, and 14q [57]. The Slit and Trk-like family member 1 (SLITRK1) was selected as a candidate gene [60]. However, the association between this gene and TS has not been confirmed in several subsequent studies [57, 61]. Other candidate gene studies focused on genes involved with the dopaminergic neurotransmission but failed to identify a causative susceptibility gene for TS. Multiple rare copy number variants (CNVs) including genomic deletions and duplications were associated in a subset of patients with
TS [62]. Recently, a genome wide linkage analysis in a large family with autosomal dominant transmission of TS revealed a mutation in the HDC gene encoding L-histidine decarboxylase, the rate-limiting enzyme in histamine synthesis [63], supporting a role for histamine in the pathogenesis of TS. The relatively disappointing results of genetic research in this highly inheritable condition could be due to the involvement of several genes and complex genetic interactions in the pathogenesis of TS. Moreover, the phenotypic definition of “cases” for linkage studies is difficult because TS is only the extreme manifestation at one end of the broad spectrum of tic disorders, and it is unclear whether mild simple tics, or psychiatric conditions such as OCS and ADHD without tics, represent an attenuated expression of the same genetic condition as TS.

Histological studies
Few brains from patients with TS have been histologically examined, but an increased density of small striatal neurons has been observed. In another case, a decrease of dynorphin, especially in the dorsal part of the external segment of the globus pallidus and the ventral pallidum, pointed toward a loss of dynorphin in the striatopallidal projections [64]. As compared to normal controls, 3 patients with severe TS had a higher total number of neurons in the internal segment of the globus pallidus and a lower number of neurons in the external pallidum and in the caudate. The number and proportion of neurons that were positive for the calcium-binding protein parvalbumin were increased in the globus pallidus internus, whereas the density of parvalbumin-positive neurons was decreased in the putamen and caudate [65]. The same group recently reported a 50–60% decrease of parvalbumin-positive and choline acetyltransferase-positive cholinergic interneurons in the caudate and the putamen in 5 patients with TS as compared to normal controls. Interestingly, the sensorimotor and associative regions, but not the limbic parts of the striatum, were affected. The imbalance in striatal and pallidal neuron distribution with a selective deficit of parvalbumin-positive and cholinergic striatal interneurons points to an alteration of the cortico-striato-pallido-thalamic circuitry in TS with impaired corticothalamic control of striatal neuronal activity [66].

Imaging studies
Structural imaging studies
Neuroimaging studies have provided contradictory findings [67]. Increased proportion of white matter in the right frontal lobe, increased cortical volumes in the dorsal prefrontal and parieto-occipital regions, reduced inferior occipital cortical volumes and frontal and parietal cortical thinning has been described [69, 70]. Reduced gray matter resulting in smaller hemispheric volumes has recently also been demonstrated in the cerebellum of TS patients [71]. Smaller volumes of the basal ganglia (caudate and lenticular nuclei) were observed. The severity of tics in early adulthood correlated with the childhood caudate volumes in a prospective long-term study [72]. Bilateral fractional anisotropy increase was observed in the corpus callosum [73] in the white matter underlying the post- and precentral gyrus, below the left supplementary motor area, and in the right ventro-postero-lateral part of the thalamus. The increase in regional underlying the left postcentral gyrus correlated with tic severity [74]. It was hypothesized that the morphological cortical and subcortical alterations in patients with TS could be cause as well as compensatory process of the disease.

Functional imaging studies
Ligand studies with single photon emission computed tomography (SPECT) or positron emission tomography (PET) have focused on the dopamine and serotonin systems because of the therapeutic implication of these systems in TS. However, several studies did not reveal any differences between patients with TS and healthy controls. Moreover, neuroleptic medication could have altered the results in some patients. An increased dopamine activity has been found mainly in the left striatum, possibly more pronounced in the ventral area [75] and amphetamine challenge has shown a relatively overactive striatal [76] and extrastriatal [77] dopaminergic system.
Studies using fMRI found decreased pallidal and putaminal activity and an increase of activity in the ventral head of the right caudate nucleus [78] and frontostriatal activation [79] during tic suppression. The largest fMRI study in TS [80] used the Stroop test (a test involving mainly the frontostriatal circuits) as a paradigm in a cross-sectional sample of TS patients. There were age-related differences between patients with TS and controls, especially an absence of the relative deactivation of the posterior cingulate cortex with age in TS patients. Moreover, frontostriatal activity increased with age in controls but not in TS patients [80]. A study addressing resting-state functional connectivity in adolescent TS patients [81] suggest abnormal maturation of cingulate and frontostriatal circuits. Increased activity was observed in the paralimbic (anterior cingulate and insula), sensory association (parietal operculum), and premotor (supplementary motor area) cortex during the premonitory phase. At the onset of the tic, the superior parietal lobule, cerebellum, and motor cortex became activated and the activity in the paralimbic cortex and supplementary motor area was reduced [82].

Overall, varied and sometimes contradictory findings of functional imaging in TS point to a complex and dynamic involvement of different cerebral systems, including areas outside the cortico-striato-thalamo-cortical circuitry. Basal ganglia are hypoactive with (possibly compensatory) hyperactivity of the cortical motor and premotor regions. The striatum, mainly its ventral part, is the most commonly involved brain area, and changes are more commonly observed on the left side.

**Animal models**

Since the pathogenesis of TS is incompletely understood, it is difficult to develop an animal model with high construct validity. However, in monkeys, injections of the GABA antagonist bicuculline into the associative part of the external pallidum produced attention deficit and hyperactivity, and injections into the limbic part induced stereotypy [23]. These results suggested the involvement of the associative and limbic parts of the basal ganglia in TS. Moreover, anatomical tracing confirmed the segregated parallel organization of the distinct sensorimotor, associative, and limbic circuits [83] that are topographically connected with prefrontal cortical areas implicated in TS. More recently, bicuculline injections in the ventral striatum of monkeys resulted in either hypoactivity without motor slowing, sexual behavior, or stereotypy, whereas injections in the sensorimotor and associative regions of the striatum led to hyperkinetic manifestations, attention-deficit and impulsivity [22].

**An integrative model of the pathophysiology of TS**

Even though the cause of TS remains elusive, the anatomical, imaging, and experimental data point to a disorder of the basal ganglia and the frontocortical circuits. Mink [84] proposed a model of TS with selective facilitation and surround-inhibition of specific motor and non-motor programs of the basal ganglia and frontocortical circuitry. The execution of unwanted motor programs results in motor or vocal tics; the execution of unwanted associative programs may be related to attention-deficit and hyperactivity; and the execution of unwanted limbic programs may be related to obsessive-compulsive symptoms [85]. The genetic contribution to the disease is complex and may in most cases concern susceptibility to develop the clinical disorder. The therapeutic response to dopamine blocking drugs (or in some cases dopamine agonists) illustrates that the dopaminergic system is pivotal in the pathogenesis of TS although the exact mechanisms remain to be elucidated. The therapeutic response to deep brain stimulation [86–88] in different target in the basal ganglia circuitry (including pallidum and thalamus), as well as the results of functional imaging studies, underline the basal ganglia dysfunction in TS. The anatomical data point to a developmental cause (e.g. altered tangential neuronal migration affecting the neuronal distribution in the basal ganglia) and to additional compensatory consequences (altered cortical volumes and fractional anisotropy).

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CHAPTER 3
Pathophysiology and Molecular Pathology of Tremor, Myoclonus, and Chorea

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Tremor

Tremor is a rhythmical, involuntary, oscillatory movement of a body part [1], sometimes redefined as an approximately rhythmic, roughly sinusoidal involuntary movement [2]. Commonly used clinical classifications relate to the frequency and conditions under which the tremor is activated. However, with progression of the disease, tremulous disorders may often have a combination of various tremor types (Table 3.1).

Tremor mechanisms

Complex combinations of peripheral mechanical-reflex and central generator(s) oscillations are considered responsible for tremor [3, 4].

Peripheral mechanical-reflex oscillations
The mechanical oscillations occur in a body part in response to cardioballistic vibrations produced by ejection and propagation of blood flow at the cardiac systole, and subtetanic motor unit contraction for keeping an antigravity position or weight bearing of the body part. The resonance frequency is determined by inertial, viscous, and elastic properties [2, 3]. The reflex oscillations are elicited by combinations of various peripheral reflex loops: afferents from the spindles to the spinal alphamotor neurons (spinal loop), afferents from peripheral sensors to the motor cortex (transcortical loop), and stretch reflexes [4, 5]. In tremors involving peripheral mechanisms, the tremor frequency can be reduced by adding weight to the appropriate body part [2].

Central generator(s)
The whole motor system is organized by reciprocally innervated circuits from cortical to spinal level [2]. The main neuronal circuits controlling voluntary and involuntary motor movements are: loops between (a) the motor cortex and the basal ganglia, (b) the cerebellum and the brainstem (cerebello-rubro-olivary tract), and (c) the cerebellum, the thalamic nuclei, and the motor cortex (cerebello-thalamo-cortical and cortico-ponto-cerebellar tracts). In addition, there are reciprocal connections with the motor...
networks in the brainstem and at spinal levels (Figure 3.1). It is hypothesized that GABAergic projections from the GPi modulates activity of the motor nuclei of the thalamus with subsequent activation of excitatory glutamatergic projections to the premotor and supplementary motor areas which facilitate movement. Activity of the GPi is modulated by the “direct” and “indirect” pathways. The direct pathway is monosynaptic whereas the indirect pathway runs through the GPe and the subthalamic nucleus. The direct striatopallidal pathway leads to thalamocortical motor facilitation through GPi inhibition, and the indirect pathway leads to thalamocortical inhibition through GPi stimulation [6].

These complex mechanisms can be disturbed by an increase in excitability of the reciprocally innervated neurons by hyperpolarization of the cell membrane or alterations in the intracellular modulators of ion channels [3, 4, 7]. The widespread complex motor networks consist of multiple independent oscillators that tend to couple and contribute to tremor. The various pathological tremors differ by the topography and frequency components in these networks. The debate concerning single or multiple generator structures in the different disorders is yet not finished [3, 8].

**Various types of tremor**

*Enhanced* physiologic tremor is a normal phenomenon that can become evident during precise, fine motor activities, anxiety, or alcohol withdrawal, but is in many persons invisible. Two types of oscillation can be registered, one caused by peripheral mechanical-reflex mechanisms and one of possibly central origin. In certain conditions, like fatigue, anxiety, hyperthyroidism, or use of certain drugs, the tremor is more severe, due to an increase of the stretch reflex. This may be bothersome for the patient, and is called “enhanced” physiologic tremor [2]. Loading the body part with a weight will reduce the tremor frequency [5] and beta-blockers may also reduce this peripheral tremor type [2]. In addition, an 8–12 Hz tremor is registered, and probably originates from the olivo-cerebello-thalamo-cortical pathway [2, 5, 6].

**Rest tremor**

This occurs in a body part that is not voluntarily activated and is completely supported against gravity. Mental stress and movements of another body part may increase the amplitude. [1] Rest tremor is a characteristic symptom in patients with Parkinson disease (PD), SWEDD, Holmes’ tremor, and palatal
tremor: therefore, different mechanisms are assumed to be responsible.

In PD, with implanted DBS electrodes and animal models, coherence studies with EEG, MEG, cortical electrodes, microrecordings, and local field potentials in the basal ganglia nuclei, demonstrate coherent rhythmic activity with a frequency of 4.5–7 Hz between the basal ganglia nuclei, cortical areas, and limb muscles [9, 10]. A number of independent oscillating circuits are assumed within a
widespread tremor-generating network, including cortical, subcortical, spinal centers and the oscillating peripheral limbs [3] (Figure 3.1).

Dopamine deficiency is responsible for rest tremor in PD and, Holmes tremor, supported by 1MPTP studies on primates [5, 9, 10]. In PD, tremor is related to specific loss of dopaminergic neurons located in the mesencephalic A8 area, the retrorubral area, and a loss of other neurotransmitters, such as serotonin [2, 11]. In Holmes tremor a lesion of the nigrostriatal connection will be responsible for a striatal dopamine deficiency. In the case of dopamine deficiency, the subthalamic nucleus (STN) with its dopaminergic afferents from the substantia nigra is probably responsible for the rest tremor due to disruption of these motor neural networks [9–11]. This is in agreement with the favourable results of STN–DBS for parkinsonian tremor [34, 12], and case reports of Holmes tremor patients with favorable outcome of combined DBS in the Vim and STN [13]. Although, on a PET scan, the cerebellum is abnormally active in PD patients with tremor, it appears that the cerebellum is not necessary for producing a parkinsonian rest tremor [7].

SWEDD (Subject Without Evidence of Dopaminergic Deficit) The tremors may be phenomenologically indistinguishable from those of PD patients [14]. The pathophysiology is still unknown, but indicates that a rest tremor can develop without dopaminergic cell loss in the nigrostriatal system. SWEDD is considered to be a form of dystonia [15].

Palatal tremor consists of a rhythmic movement of the soft palate with a frequency of 1–3Hz (see Chapter 7). The pathophysiology of the essential palatal tremor is unknown [16–18]. The secondary form is always accompanied by the olivary hypertrophy, caused by damage of the dentate nucleus, or the fiber tracts forming the Guillain–Mollaret triangle, the crossing dentate-rubro-olivary and olivo-dentate pathways [16–19] (Figure 3.1). The inferior olive (IO) is assumed to be an autonomous central oscillator. The slow rhythmic palatal tremor is the inherent activity of cells within the IO, probably due to loss of dentate-olivary GABA-ergic inhibition of the electronic coupling of the IO neurons. This possibly results in a state of hyperexcitability of Purkinje cells, which re-enhances the olivary oscillations [4, 5]. Only strong external stimuli in test situations can influence the rhythmicity and reset the tremor [16–18].

**Action tremor**

This is defined as any tremor present during voluntary contractions of muscles [1].

*Postural tremor* may occur when maintaining a voluntary position against gravity. When it appears or exacerbates in specific postures it is called ‘position-specific’ tremor [1].

In PD, during sustained action after a short delay of several seconds, (called a re-emergent tremor), often a postural tremor or an action tremor, may develop with an increase in the rest tremor. This re-emergent tremor has about the same frequency as the rest tremor [20]. A combination of rest and action tremors can be produced in MTPT monkeys and therefore the same pathophysiology is assumed for both tremor types [2]. In some PD patients an action tremor develops with a higher frequency of 5–10Hz and without a delay at the beginning of the limb action as in essential tremor (ET). A combination of PD and ET is assumed [21].

**Kinetic tremor**

*Essential tremor* (ET) is the most common movement disorder; it is characterized by a kinetic tremor, and is often accompanied by a postural tremor. The kinetic tremor, as in ET, is probably caused by a functional disturbance of the olivocerebellar circuit with the inferior olive (IO) as the central oscillator. This is supported by the disappearance of the tremor after lesions in parts of the cerebro-cerebellino-cerebral loop, and the finding in the “harmaline animal model” of synchronization of inferior olive cells into rhythmic activity which is transferred through the cerebellum and the reticulo-spinal projections to the spinal motor neurons [22]. Although, the thalamus (VIM) as a central oscillator for the kinetic tremor is still in discussion (based on a patient who developed classical ET with a long delay after hemicerebellotomy [23], the development of an *intention* tremor in about 50% of the ET patients during the progression of the disease indicates a cerebellar involvement in at least part of the patients (see below) [5, 22, 24].
**Intention tremor** is an action tremor with an increase of the amplitude when coming close to the target. A position-specific postural tremor should be excluded [1]. The cerebellar and Holmes tremor, typical representatives of the intention tremor, will be discussed.

**Cerebellar tremor** is characterized by a low-frequency intention tremor, mostly below 5 Hz, and an absence of rest tremor. A postural tremor may be present. In all disorders with an intention tremor a disturbance of the cerebellum and its afferent or efferent pathways can be assumed on the bases of experiments with primates and from the studies of patients [1, 22].

In primate experiments lesions in the globose-emboliform nucleus cause a low-frequency intention tremor by altering the function of peripheral somatosensory reflex pathways [25]. Tremor-related activity can be registered in the motor and somatosensory cortex, and the cerebellar globose-emboliform nucleus. This indicates involvement of transcerebellar and transcortical loops participating in the cerebellar feedback function [22, 25]. Based on the persistence of the intention tremor after deafferentiation, it is argued that a major cause of the intention tremor is caused by a disturbed timing and grading of contractions of antagonistic muscles, called the cerebellar feed-forward control dysfunction, due to lesions in the cerebello-thalamo-cortical pathway at the level of the dentate nucleus, the cerebello-thalamic fibers, or the cerebellar afferences nucleus in the thalamus (VIM) [2, 22, 26, 27]. This mechanism is supported by registrations of enhanced long-latency reflexes in cerebellar disorders [24]. It is not yet clear if a central oscillator is involved [18].

**Holmes tremor** is a condition with a combination of rest and intention tremors. A postural tremor may be present. The tremor has a low frequency (2–4 Hz), and is often irregular. [27]. It is a symptomatic tremor due to lesions involving the dopaminergic nigrostriatal system (rest tremor) and the cerebello-thalamo-cortical system (intention tremor). This may happen at multiple sites and even multiple cortical lesions have been mentioned [22, 28]. There is typically a delayed onset with an interval of weeks to years after the origin of the causal lesion [1], probably caused by a secondary degeneration with functional changes [2, 27]. Only if Holmes tremor is accompanied by symptomatic palatal tremor can a hypertrophic degeneration of the inferior olive be detected [2].

**Neuropathic tremor** This may be assumed in a patient with a tremor in a limb with a peripheral neuropathy, and without other neurological disorders associated with tremors. Demyelinating neuropathies are particularly frequent causes of this condition [22]. A disturbed peripheral reflex mechanism due to the abnormal sensory input seems to be the major pathophysiologic mechanism, supported by the effects of external stimuli on the tremor frequency. An abnormal cerebellar processing of the disturbed sensory input may also be involved – the so-called feedback control [22]. Because only a minority of patients with peripheral neuropathies develop a central tremor, another mechanism, may also be involved.

**Orthostatic tremor** is a tremor syndrome characterized by a typical high-frequency postural weight-bearing limbs tremor of 13–18 Hz, predominantly of the trunk and legs, but upper limbs, neck, and cranium muscles may also be involved [2, 5, 8]. Physiological, neuroimaging (PET, FP-Spect), and transcranial magnetic stimulation (TMS) studies indicate a central generator of the oscillating activity, most likely in the brainstem. The cerebello-thalamo-cortical and the dopaminergic nigrostriatal loops appear to be involved without parkinsonism. However, dopaminergic medications do not improve the tremor, but it can be suppressed by VIM DBS (29, own experience).

**Conclusions**

Various types of tremor can be observed in the same patient in the different kinds of tremor disorder. Besides peripheral mechanisms, especially a dysfunctioning of neuronal circuits involved in motor organization are assumed to be responsible for the generation of the various types of tremor. Hyperexcitability of cell membranes due to various conditions is assumed to be an important mechanism. [For dystonic tremor, SWEDD, and
task-specific tremor, see dystonia syndromes (Chapters 7 and 8).]

### Myoclonus

Myoclonus is a hyperkinetic movement disorder consisting of brief, quick, and involuntary jerks caused by muscle contractions (positive myoclonus) or interruptions of tonic muscle activity (negative myoclonus). The clinical characteristics and etiology of myoclonic jerks are related to the anatomical origin, classified as cortical, subcortical, brainstem, spinal cord, and peripheral nerve myoclonus (Table 3.2) [30].

In this section we will discuss the pathophysiology of myoclonus based on the anatomical classification with a focus on functional aspects. The individual diseases causing myoclonus will not be discussed in detail. The genetic background of different types of myoclonus will be discussed in Chapter 14 [31].

#### Cortical myoclonus

Cortical myoclonus is believed to result from abnormal firing of the sensorimotor cortex resulting in activity that travels through the fast corticospinal pathways to the muscles [31, 32]. EMG-registrations typically show irregular short-lasting bursts (<50 ms) [33]. Diseases known to be associated with cortical myoclonus are focal lesions of the sensorimotor cortex, post-hypoxic encephalopathy or as part of syndromes such as progressive myoclonic ataxia or epilepsy. Cortical myoclonus can also be a relatively minor symptom of different degenerative disorders such as multisystem atrophy (MSA) and Alzheimer disease [34]. Clinically, cortical myoclonus manifests as spontaneous or reflex myoclonus, and is mainly induced by voluntary movements. The jerks can be focal or multifocal [34, 35]. Parts of the body with a large cortical representation, like the mouth, the hands, and the face, are most frequently involved [34, 36].

Pathophysiologically, cortical myoclonus is related to epilepsy and is often associated with generalized convulsions. Continuous isolated muscle jerks of focal cortical origin are described as epilepsia partialis continua (EPC) [37]. In patients with cortical myoclonus, EEG spikes preceding EMG bursts representing the myclonic jerk may be seen in multichannel EEG–EMG recordings. Also, EEG–EMG back-averaging may reveal a “time-locked” biphasic potential on the contralateral sensory cortex, typically preceding EMG bursts with 15–25 ms when recorded from the upper limb, and with 40 ms when recorded from the lower limb [38, 39]. When the myoclonic jerks are continuous and back-averaging is not possible, coherence analysis can reveal the correlation between cortical and muscle activity and between muscles [40]. In cortical myoclonus patients, an exaggerated corticomuscular and intermuscular coherence in the alpha and beta band can be detected with a phase difference consistent with a cortical drive [41–44]. With a magnetoencephalogram (MEG) study, the generator has been localized to the primary motor cortex [45].

Electrophysiologically, cortical myoclonus is characterized by signs of increased cortical excitability, including a giant somatosensory-evoked potential (g-SSEP) and the presence of a cortical reflex (C-reflex). The SSEP N20 component can be

| Table 3.2 Classification of myolonus. |
|-------------------------------|-------------------------------|
| Clinical Clinical presentation | Reflex myoclonus |
| Spontaneous Action-induced |
| Distribution Synchronous in different parts of the body Generalized Segmental (Multi)focal |
| Temporal pattern Irregular Rythmic |
| Anatomical Cortical Subcortical Basal ganglia or Brainstem |
| Spinal Segmental or Propriospinal |
| Peripheral |
| Aetiology Physiological Essential |
| Epileptic Symptomatic |
normal, but the P25/P30 and N35 peaks have enlarged amplitudes [45] (Figure 3.2). The C-reflex response can be seen in cortical myoclonus patients in the ipsilateral thenar muscle with a latency of around 45 ms, and sometimes contralaterally with a delay of 10–15 ms pointing to interhemispheric spread [46].

The precise mechanisms that give rise to cortical hyperexcitability, and their localization in the brain, remain unknown and may range from intrinsic cortical changes to more isolated cerebellar changes resulting in decreased cortical inhibition. A generator in the primary motor cortex is suggested by cortical lesions giving rise to myoclonus and supported by MEG studies [45]. It has been suggested that cortical motor neurons become partly deafferented in neurodegenerative diseases and therefore subtle sensory stimulation may produce paroxysmal activity [47]. In fact, changes in sensory input may play an important role in the generation of cortical myoclonus, as suggested by the stimulus sensitivity and the electrophysiological signs of cortical hyperexcitability, including giant SSEPs. An EMG–fMRI study in patients with FCMTE showed parietal (sensory area) brain activations coupled to involuntary muscle activity [48].

Neuropathological studies in patients with cortical myoclonus show involvement of cerebellum, frontotemporal cortex, hippocampus, thalamus and other areas in various combinations [49, 50]. Interestingly, primary cerebellar changes were observed in cortical myoclonus patients (already described by Hunt [51]), and more recently in patients with celiac disease [52] and FCMTE [50]. In the absence of structural changes, functional cortical changes may exist, for instance as a result of a channelopathy. Channelopathies are recognized in the inherited epilepsy syndromes. It has, however, been suggested that cerebellar...
Subcortical myoclonus

In subcortical myoclonus the source of myoclonus is localized between the cortex and the spinal cord and includes myoclonus-dystonia (M-D), brainstem reticular reflex myoclonus, and orthostatic myoclonus. In contrast to cortical myoclonus, electrophysiological signs of cortical hyperexcitability are not typical and EMG bursts are more variable, ranging from 25 to 300 ms [34, 53].

Myoclonus-dystonia (M-D, essential myoclonus) is characterized by alcohol-responsive jerks in the upper body, mild to moderate dystonia, and commonly autosomal dominant inheritance with often a mutation in the epsilon-sarcoglycan gene (SGCE, chromosome 7q21, DYT11). Myoclonic bursts are variable but mainly short (25–750 ms) [54, 55]. Myoclonus in M-D is supposed to originate from the basal ganglia. Local field potential recordings from the globus pallidus internus (GPi) in M-D patients showed significant coherence between dystonic muscle activity and GPi [56]. Reduced striatal D2 receptor binding was also detected in MD [57]. Electrophysiological studies, including (EMG-)EEG, SSEP, and TMS reveal no changes in cortical excitability [58, 59]. Cortical functional changes have been described in a TMS study, showing polyphasic MEPs possibly reflecting central neuron membrane instability. A functional MRI study revealed disorganized sensorimotor integration consistent with other types of (hereditary) dystonia [58, 60, 61]. These cortical functional changes are possibly secondary to basal ganglia pathology.

Brainstem reticular reflex myoclonus, mainly seen in post-hypoxic encephalopathy and startle syndromes are stimulus sensitive and characterized by abnormal activity that begins in the brainstem and spreads in both rostral and caudal directions, producing generalized jerks due to the bilateral pathways involved. Focal forms are rare, although diaphragm myoclonus can originate from the rostral medulla [62]. In reticular reflex myoclonus, intervals between bursts are shorter as compared to spread of bursts in startle syndromes indicating involvement of different neuronal circuits and pathways. The jerks in reticular reflex myoclonus are thought to originate from the reticular formation. The brainstem motor systems are closely related to subcortical reflex centers, possibly explaining the stimulus sensitivity [30, 34, 36]. Excessive startle reflexes can be part of hyperekplexia, an inheritable mainly autosomal dominant disorder with mutations in the glycine receptor [36, 63–66].

Orthostatic myoclonus is myoclonus induced or increased by the assumption of an upright posture (see also orthostatic tremor). This type of myoclonus has not been formally anatomically classified yet, but is most likely from a subcortical origin. It has been described in elderly patients and usually presents as slowly progressive unsteadiness of gait and stance. It is often associated with an underlying neurodegenerative disease, particularly Parkinson disease. EMG shows non-rhythmic short burst durations (20 to 99 ms) [67, 68].

Spinal myoclonus

Spinal myoclonus is the result of abnormal discharges generated in the spinal cord and can be subdivided in spinal segmental myoclonus and propriospinal myoclonus.

Segmental myoclonus is a rare disorder mostly caused by a lesion in the spinal cord, such as a tumour, syringomyelia, myelitis, or ischemia. It is thought that spinal segmental systems become hyperexcitable, evoking jerks in muscles innervated by this particular segment and one or two contiguous spinal segments. The jerks are continuous, unaffected by voluntary movement and sensory stimulation, and often persist during sleep [69]. The jerks are usually rhythmic with a frequency varying from 1 to 200 per minute. The duration of the EMG-bursts can be up to 1,000 ms. EMG discharges after nerve stimulation were found with different latencies, possibly reflecting involvement of polysynaptic pathways.
Propriospinal myoclonus (PSM) is characterized by both spontaneous and stimulus-sensitive jerks of the trunk and abdominal muscles, often induced by lying down, and without involvement of the facial musculature [70, 71]. PSM is presumed to originate from a spinal generator that elicits activity spreading up and down the spinal cord, supposedly via intrinsic propriospinal pathways [71]. Electrophysiological features include a fixed pattern of muscle activation, slow spinal cord conduction velocity (5–15 m/s), EMG burst duration of less than 1,000 ms, synchronous activation of agonist and antagonist muscles, and no involvement of facial muscles [72]. In some patients lesions in the spinal cord have been reported, but PSM is usually idiopathic [73]. MRI of patients with idiopathic PSM is normal. Diffusion tensor imaging detected associated microstructural abnormalities of the spinal cord [74]. In idiopathic PSM a psychogenic origin might be considered. Recently, in 20 patients diagnosed with idiopathic spinal myoclonus, a bereitschaftspotential (BP) was shown in 15 patients [75]. In another study, axial jerking closely resembling PSM had a psychogenic origin in 34 out of 35 patients [61]. Further prospective studies toward the origin of PSM are required.

Peripheral myoclonus

Peripheral myoclonus driven from the peripheral nervous system includes hemifacial spasm [32] and, described in case reports, myoclonus after lesions of the brachial plexus [76], spinal root, [77], the long thoracic nerve [78], and after amputation (“jumping stump”) [79, 80]. Peripheral myoclonus is limited to one segment of the body, usually the proximal part of a limb or the trunk. Bursts can be triggered by voluntary movement and burst duration varies. In hemifacial spasm, electrical stimulation of one branch of the facial nerve on the affected side in patients elicits a response from muscles that are innervated by another branch (ephaptic transmission).

The origin of myoclonus in patients with complex regional pain syndrome (CRPS) is unknown but is likely to be induced by peripheral trauma. CRPS-related myoclonic jerks are observed at rest, and aggravated during action. EMG burst duration ranges from 25 to 240 ms. Coherence studies showed increased intermuscular coherence in 4 out of 8 patients in the 6–12 Hz band. Significant coherence entrainment was detected in 5 out of 8 patients. The characteristics of myoclonus in CRPS appear to be different from other forms of myoclonus [81].

Chorea

Chorea is defined as a syndrome characterized by the continuous flow of random, involuntary, muscle contractions [82]. Chorea can be associated with a variety of different causes but the most well-known disorder is Huntington disease (HD) (see also Chapters 10 and 11).

Pathophysiology

The pathophysiological mechanisms of chorea is considered to be due to the dysfunction of a complex neuronal network consisting of the basal ganglia and different motor cortical areas [82] The basal ganglia comprise the caudate nucleus, putamen, the internal and external globus pallidus (GPe and GPi), as well as associated structures such as the subthalamic nucleus and the substantia nigra. These corticosubcortical motor circuits are essential to facilitate voluntary movements and stop unwanted movements through parallel pathways that modulate thalamocortical motor projections. Their role has been proposed to be a braking mechanism which facilitates or inhibits motor pattern generators. The model of these motor loops stem from animal studies [6]. According to this model, GABAergic projections from the GPi modulates activity of the motor nuclei of the thalamus with subsequent activation of excitatory glutamatergic projections to the premotor and supplementary motor areas which facilitate movement. Activity of the GPi is modulated by the “direct” and “indirect” pathways. The direct pathway is monosynaptic whereas the indirect pathway runs through the GPe and the subthalamic nucleus. The direct striatopallidal pathway leads to thalamocortical motor facilitation through GPi.
inhibition and the indirect pathway leads to thalamo-cortical inhibition through GPi stimulation [6]. According to this model, chorea is considered to be the result from deficient GPi inhibition to the thalamus resulting in excessive thalamocortical activation. However, several inconsistencies within this model have been reported leading to the assumption that more complex changes in this motor network – i.e. temporal and spatial firing pattern alterations – are involved in the pathophysiology of chorea [83].

Molecular pathology
HD is an inherited neurodegenerative disorder, characterized by progressively worsening chorea, cognitive and psychiatric disturbances involving the basal ganglia and cerebral cortex. HD is an autosomal dominantly inherited disorder caused by CAG trinucleotide expansion from 36 to 121 at the Huntingtin (HTT) gene [83]. Until now, the precise role of HTT in HD is unknown, but the pathology of HD targets medium spiny neurons in the striatum [84]. A number of other disorders can also cause chorea, including neuroacanthocytosis (NA), benign familial chorea (BFC), systemic lupus erythematosus (SLE), Sydenham chorea, and tardive dyskinesia (TD) (see Chapters 10 and 11). All these different types of chorea may be explained by deficient GPi inhibitory output to the motor thalamus as previously mentioned. However, inconsistencies has been demonstrated by several imaging studies. Clinically affected HD patients show severely reduced glucose and oxygen metabolism of the caudate and lentiform nuclei [84]. Caudate hypometabolism is also seen in NA and BFC [85]. In contrast, striatal glucose metabolism has been reported to be normal or elevated in Sydenham chorea, chorea secondary to SLE and TD [86–88]. The medium spiny striatal neurons that degenerate in HD express D1 and D2 receptors. Striatal D2 binding is severely reduced in symptomatic HD patients as demonstrated with IBZM SPECT or C-raclopride PET [89, 90]. Similar changes have been reported in other neurodegenerative choreas, including NA [89]. In contrast, normal striatal D2 binding has been observed in SLE chorea and TD [91]. This finding argues against the hypothesis that TD is the result of striatal D2 hypersensitivity after prolonged exposure to neuroleptics.

Hyperglycemic choreathetosis is often associated with hyperintensity of the putamen on T1 MRI. HMPAO SPECT scan shows hypometabolism of the striatum [91], hence, striatal dysfunction is commonly involved in different causes of chorea. Hypo- but also hyperfunction of the striatum may lead to chorea.

An important characteristic of HD is the particular vulnerability of the caudate–putamen region, despite similar expression of the mutated protein in other brain areas. Several mechanisms have been identified that mediate cell death in HD, including excitotoxicity, transcriptional dysregulation, altered energy metabolism, impaired axonal transport, and altered synaptic transmission [91, 92].

Excitotoxicity
Excitotoxicity involves an enormous increase in intracellular Ca²⁺ concentration in response to the effects of excitatory amino acids (EAA), including glutamate. In particular, the NMDA receptor – a receptor-channel complex permeable to Ca²⁺ – plays an important role in neurotoxicity. Stimulation of this glutamate receptor induces an influx of Ca²⁺ which increases the formation of reactive oxygen and nitrogen by means of proteases and endonucleases, leading to cell damage and cell death. Stimulation of the NMDA receptor is probably the result of an increase of glutamate and glutamate agonist release from the cortex, the decrease of glutamate uptake by glia cells, and hypersensitivity of the postsynaptic NMDA receptors [93, 94].

Recent evidence has shown that excitotoxic degeneration in HD is not only related to corticos-triatal glutamergic input but also to nigrostriatal dopaminergic stimulation. Dopamine is believed to act synergistically with glutamate, making striatal neurons highly sensitive to mutant HTT [95].

Transcriptional dysregulation
Transcriptional dysregulation of multiple genes encoding neurotransmitter receptors, enzymes, and proteins involved in neuron structure, stress responses, and axonal transport has been described
in transgenic mice but recently also in human HD brains. Mutant HTT has been shown to interact with basal transcription factors, including TATA binding protein and transcription factor IIF. Nowadays, the role of histones, highly basic proteins, has been linked to transcriptional activity. In particular, histone methylation and acetylating is regulating transcription factor access to DNA promoter regions [96].

**Mitochondrial dysfunction and altered energy metabolism**

Biochemical studies in HD postmortem tissue have revealed selective dysfunction of components of the mitochondrial tricarboxylic acid cycle and electron transport chain in affected brain regions including complex II, complex IV and aconitase. These changes may lead to reduced O\textsubscript{2} consumption and ATP production rates. This may disrupt the maintenance of Na/K ATPase pumps that regulate ionic and voltage gradients across cell membranes, inducing nitric oxide synthase (NOS) activation and free radical production with a progressive increase of oxidative damage to the mitochondria which ultimately leads to cellular injury. This process is a gradual build-up until a threshold is reached, which explains the slow progressive nature of the disease [94].

**Changes in axonal transport and synaptic dysfunction**

Several studies have shown that HTT is implicated in the control of intracellular processes, including trafficking of vesicles and synaptic transport. In HD the abnormal polyQ expansion leads to a reduction in axonal transport due to the altered interactions between HTT and parts of the motor complex. Of particular interest is the alteration of the brain derived nerve factor (BDNF), because BDNF is crucial for neuronal function and survival [92].

These new insights into the molecular pathology of HD by means of several animal models has given us the motivation to develop new therapeutic approaches which are likely to be a combination of therapies due to the multiplicity of mechanisms underlying HD.

**Epilogue**

In this chapter the pathophysiology and molecular pathology of three different kinds of hyperkinetic symptoms, tremor, myoclonus and chorea, are discussed. Dysregulations of cerebral networks due to many causes and in different diseases may lead to one of these symptoms. Most often abnormal functioning of the basal ganglia circuits is involved, reflected in the often successful application of stereotactic functional neurosurgery. Progression of the knowledge of the molecular pathology will lead to an improvement of the pharmacotherapy.

**References**


CHAPTER 4
Overview of the Medical Treatments of Hyperkinetic Disorders

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Introduction

Hyperkinetic movement disorders encompass a broad spectrum of diseases and neurophysiologies. In the majority of cases they originate in the central nervous system and involve the basal ganglia, although a complete understanding of physiology is lacking in any of these conditions. Hyperkinetic disorders are associated with dysfunction in multiple neurotransmitter systems that cause abnormal data handling within the basal ganglia. In some instances these abnormalities can be mitigated or corrected by medical intervention.

Recognizing the phenotype is the first critical step to diagnosing the underlying condition and eventually choosing the most appropriate treatment (Table 4.1). The detailed phenomenology of each hyperkinetic movement type will be analyzed in the forthcoming chapters. In this chapter, we will present an overview of hyperkinetic disorders and briefly discuss clinical, diagnostic, and physiologic features. We will then discuss treatments used for these disorders.

Motor phenotypes

Hyperkinetic basal ganglia disorders are characterized by the onset of an involuntary movement that can be controlled to varying degrees. On simple observation there can be phenotypic overlap, so additional information is often required for a correct classification. For example, simple demographics are important. Tics almost always start in childhood and lessen with age. Generalized dystonia and chorea/athetosis may begin in childhood but focal dystonias usually appear in midlife. Tremor can occur early but usually presents later and worsens with age. The degree of suppressibility can differentiate hyperkinetic movements. Tics and stereotypies are usually partially suppressible whereas dystonia, action tremor, and chorea usually are not. Clinical history is also important in many cases. Tardive syndromes only occur in the setting of exposure to dopamine receptor-blocking drugs, also referred to as neuroleptics of dopamine antagonists. Hemichorea/ballismus almost always follows a CNS lesion. Many systemic diseases can cause relatively specific movement disorders, i.e. paraneoplastic chorea or ataxia, cerebellar outflow tremors with appropriate CNS lesion, autoimmune chorea, and tics. In some cases specific serologies or imaging is diagnostic. Genetics tests are especially helpful for chorea diseases.

The degree to which hyperkinetic disorders affect quality of life depends upon their severity. Some conditions, such as hemiballismus from a stroke almost always cause severe disability. Most conditions, however, range from mild to severe and affect quality of life accordingly. The best example is essential tremor, which may be barely noticed or result in a complete inability to use the hands.
Pathophysiology of hyperkinetic disorders

Many hyperkinetic disorders are associated with a biochemical rearrangement of neural circuits flowing through the basal ganglia. Some neurotransmitter systems are affected more than others, namely dopaminergic, adrenergic, noradrenergic, GABAergic, and glutamatergic systems. In most cases, it is not simply an absence or overabundance of a single neurotransmitter, but rather neurodegeneration and cell loss that results in altered rhythmic output from the basal ganglia. Many hyperkinetic disorders also show physiological abnormalities outside the basal ganglia, such as increased cerebellar activity in essential tremor and increased cortical representation in dystonia. The main exceptions to neurodegenerative physiology are several metabolic diseases that result in reduced dopamine production. These often present as dystonia and, as would be expected, improve with dopamine supplementation. Other hyperkinetic disorders result from neurotransmitter receptor abnormalities and do not respond well to supplemental neurotransmitters.

Medical treatments of hyperkinetic disorders

Dopamine agonists
Dopamine agonist (DA) drugs include pergolide, bromocriptine, lisuride, pramipexole, ropinirole, cabergoline, rotigotine, and apomorphine; and levodopa most commonly treat parkinsonism, a hypokinetic disorder. That said they usually also improve the rest tremor of Parkinson disease (PD), which may be considered a hyperkinetic component of parkinsonism.

Restless legs syndrome (RLS) is the other common condition that is treated successfully with dopaminergic drugs. The main pathology of RLS is reduced CNS iron. The mechanism by which dopaminergics improve symptoms is unknown, as there is almost no evidence of dopamine deficiency [1, 2]. Nevertheless, initial improvement of RLS with dopaminergics is immediate and among the most dramatic in all of medicine. Long-term complications, including augmentation of symptoms, are common, but dopamine agonists, when appropriately dosed and administered, almost always initially improve idiopathic RLS.

Dopamine-responsive dystonia also dramatically improves with dopaminergics, often for life, without tolerance or complications. This condition usually results from mutations in enzymes that produce dopamine (most commonly GTP cyclohydrolase I) so improvement with dopamine replacement is intuitive. Since testing for these mutations is difficult, it is usually recommended that all cases of generalized dystonia be tried on levodopa or dopamine agonists to assess their effect.

Apomorphine, a short acting DA, is also reported to improve chorea associated with Huntington disease [3], although levodopa was traditionally used to provoke chorea to diagnose chorea in undiagnosed Huntington disease. This apparent anomaly underscores the complexity of specific neurotransmitter interactions in hyperkinetic disorders.
DAs possess a number of side effects, almost all of which are thought to result from the stimulation of dopamine receptors in different parts of the central and peripheral nervous system. Nausea, hypotension, sedation, and peripheral edema are probably the most common. Nasal congestion, constipation, headache are also reported. DAs can cause impulsivity, usually manifested by increased spending, gambling, and increased sexual activity. DA-induced visual hallucinations and choreatic-like dyskinesia are usually seen when used for the treatment of PD. In contrast, nasal congestion related to DAs seems to be more common in RLS.

**Dopamine antagonists**

Dopamine antagonists (neuroleptics) block D2/D3 receptors and, to varying degrees, other dopamine receptors and serotonin, cholinergic, and histaminergic receptors. In general, newer or “atypical” neuroleptics have less dopaminergic and greater serotonergic and histaminergic affinities. These differences result in different efficacy and side effect profiles among the drugs.

Dopamine antagonists remain the mainstay of pharmacotherapy for tics. We prefer fluphenazine and tetrabenazine (TBZ), but pimozide, haloperidol, and other neuroleptics are also used [4]. Dopamine antagonists typically reduce tics by 50–75% from baseline in a dose-dependent manner. Formal data is lacking but newer “atypical” antipsychotics, with less dopamine antagonist affinities, are probably not as effective for tics. Dopamine antagonists can also be used to treat chorea, ballismus, and possibly stereotypies.

Dopamine antagonists possess a number of potentially serious side effects. Most result from the direct blockade of dopamine receptors but others result from effects on other neurotransmitter receptors, especially serotonin. Fatigue, sedation, apathy, and depression are common. The so-called extra-pyramidal side effects include parkinsonism, akathisia, tardive dyskinesia (TD), and neuroleptic malignant syndrome (NMS). TD is particularly problematic as drug withdrawal does not help initially. One advantage of tetrabenazine (a monoamine depleting drug) over other antidopaminergic drugs is that it does not cause TD [4]. Weight gain and the development of type II diabetes is a major concern with some, but is probably related to serotonin and histamine receptor stimulation. Some of these drugs also prolong cardiac QT interval, possibly increasing the risk of cardiac arrhythmias (Table 4.2).

**Tetrabenazine**

Tetrabenazine (TBZ), the best studied and probably most effective antichorea treatment, is most commonly used for chorea associated with Huntington disease [5], but is probably equally effective for chorea of other etiologies. It seems particularly beneficial for chorea with hyperglycemia, an interesting condition associated with very characteristic

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<tr>
<th>High potency</th>
<th>Medium potency</th>
<th>Low potency</th>
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<td>Haloperidol</td>
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<td>Fluphenazine</td>
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<td>Metoclopramide</td>
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<td>Trifluperazine</td>
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¹Higher potency drugs result in greater improvement in hyperkinetic movement disorders but a higher risk of drug-induced movement disorders.

²Does not cross blood–brain barrier.
MRI changes [6]. We have had excellent results with TBZ for stereotypies associated with fronto-temporal dementia. It is also commonly used for hemiballismus and tics. Perhaps the greatest utility of TBZ, however, is the treatment of TD [7]. In short, TBZ probably has good utility for more hyperkinetic disorders than any other single agent.

TBZ is a vesicular monoamine transporter-2 (VMAT-2) inhibitor. It most closely resembles reserpine, except reserpine is also a VMAT-1 inhibitor, which seems to cause greater hypotensive and sedation adverse events. Our anecdotal experience suggests that compared to TBZ, reserpine confers less benefit and increased side effects.

VMAT-2 controls the influx and efflux of monoamines (dopamine, histamine, norepinephrine, and serotonin) to intracytoplasmic vesicles. These neurotransmitters, when free, can be very toxic to cells so a considerable amount of energy is dedicated to compartmentalizing them into the presynaptic vesicles. This is especially true for dopamine which has a vesicle to cytoplasmic ratio of more than 50,000:1. VMAT-2 is also involved with shepherding these vesicles to the nerve junction for release. The end result of TBZ is a reduction of dopamine and histamine > norepinephrine > serotonin release. The improvement in hyperkinetic disorders likely results from reduced dopamine release.

The dose of TBZ ranges from 25 to 150 mg/day. Metabolism of some metabolites, mediated by CYP2D6 enzymes, is highly individualized so the drug is titrated to effect versus side effects rather than a dose. The most common side effects include sedation, fatigue, depression, and insomnia. Like dopamine antagonists, TBZ can cause parkinsonism and akathisia, but these and other side-effects are dose related. TBZ does not cause TD but parkinsonism may occur, particularly when TBZ is used in the treatment of TD.

**Anticholinergic drugs**

Anticholinergics, including trihexyphenidyl (Artane), benztropine (Cogentin), orphenadrine (Norflex), and ethopropazine (Parsidol) are probably the most effective oral medications for dystonia. These drugs block the release of acetylcholine at the neuromuscular junction, resulting in muscle relaxation. Unfortunately they block acetylcholine and histamine in the central nervous system resulting in a robust side effect profile, including sedation, cognitive slowing, including psychosis and delirium, dry mouth, constipation, and heat intolerance. Children tolerate these medicines better than adults so they have their greatest overall utility in young patients with generalized dystonia. They are sometimes used to prevent acute dystonic reactions and treat parkinsonian tremor. Anticholinergics are occasionally prescribed for the “treatment” of chorea and TD, but these drugs can actually exacerbate these hyperkinetic movement disorders. There are no comparative studies among the drugs.

**GABA receptor agonists**

Benzodiazepines, such as baclofen and tizanidine, stimulate gamma-aminobutyric acid (GABA) receptors. The GABA-A receptor is a heterogeneous subunit transmembrane chloride gated ion channel usually composed of 2G, 2H, and 1F units in varying combinations [9]. They possess several distinct binding sites for neurotransmitters and drugs. The actual GABA site straddles the G and H subunits, whereas the benzodiazepine (BZD) site straddles G and F subunits. Benzodiazepine affinity is largely
predicted by the G subtype. Stimulation of the benzodiazepine with agonists facilitates the effect of GABA on the GABA receptors, resulting in chloride ion influx, which usually inhibits synaptic firing.

Benzodiazepines are non-specific muscle relaxants that have been used to treat dystonia, tremor, myoclonus, chorea, and tics. They are generally only moderately effective and formal trials for hyperkinetic disorders or comparisons among drugs are rare. Nevertheless physician familiarity, low cost and a well-described side effect profile make them convenient options for a number of conditions. The main side effect is sedation and mental slowing. They also increase the risk of falls in the elderly.

Baclofen and tizanidine are most commonly used for dystonia but may occasionally help tics.

**Ethanol**

Arguably, the most consistent tremorlytic agent is ethanol. Tremor suppression usually occurs within 20 minutes and lasts for 3–5 hours. This is often followed by a rebound tremor augmentation. The equivalent of one drink appears adequate for this clinical effect but the mechanism by which ethanol improves tremor is not known. The use and abuse of alcohol is probably not increased in ET patients, although this is debated. Other less intoxicating alcohols are currently being studied for ET [10]. Ethanol can also improve a group of overlapping conditions variably named “alcohol responsive myoclonus,” dystonia with lightning jerks, “and myoclonus-dystonia syndrome,” sometimes associated with abnormalities in the epsilon-sarcoglycan gene.

**Topiramate and other seizure medications**

Topiramate was first developed as an antidiabetes drug and later approved as a medication for seizures. There is good data that this drug is useful for tremor [11] and tics [12]. It is also commonly used for migraine headache and for weight loss. The drug has multiple mechanisms of action including sodium, calcium, and potassium channels; at GABA-A and α-amino-3-hydroxy-5-methyl-isoxazole-4-propionate (AMPA)/kainate-type glutamate receptors; and as a carbonic anhydrase inhibitor. Both effect and adverse events are dose dependent with a range from 25 mg to 400 mg/day, usually in two divided doses. Adverse events are common, and include word-finding difficulties and other cognitive slowing, paresthesia, altered taste, especially with carbonated beverages, weight loss, and renal lithiasis.

Gabapentin, gabapentin enacarbil, and pregabalin both demonstrate good efficacy for RLS in controlled trials. They may improve ET but results of trials are mixed. Gabapentin and pregabalin are occasionally reported to improve most other hyperkinetic movement disorders but data is mostly anecdotal and inconsistent. Primidone and, to a lesser extent, its metabolite phenobarbital often help ET. Other seizure medications occasionally help some hyperkinetic disorders (Table 4.3).

**Amantadine**

Amantadine is an old antiviral medication with multiple mechanisms of action. In the early 1970s, it was reported to help PD. Later, amantadine showed benefit against the chorea and stereotypic movements of L-dopa-induced dyskinesia in PD [13]. Subsequently, amantadine also improved HD-associated chorea in controlled trials [14]. Memantine (Namenda), which is marketed for dementia, has also shown some benefit for HD chorea [15]. The antichorea properties of amantadine probably result from its antagonism of N-methyl-aspartate receptors. Amantadine has modest anti-cholinergic properties and side effects (dry mouth, constipation, and cognitive slowing, including psychosis). It also consistently results in livido reticularis, typically after several months of use. This may be associated with problematic peripheral edema.

**Botulinum toxins**

Botulinum toxins (BoNTs) inhibit the release of acetylcholine from the nerve terminal by cleaving one of the required SNARE proteins necessary for the release of acetylcholine into the neuromuscular junction, thus preventing contraction of the muscle. Without functioning neurotransmitters, the nerve terminal and muscle atrophy. The duration of benefit averages between
Clinical results depend upon injection techniques, including dosing, dilutions, and localization techniques. Four different BoNT preparations are currently available: onabotulinumtoxin-A (Botox), abobotulinumtoxin-A (Dysport), rimabotulinumtoxin-B (Myobloc, Neurobloc), and incobotulinumtoxin-A (Xeomin). The type-A toxins differ in the complexing proteins that stabilize the actual 150 Kd protein. Other toxins have been developed but are not commercially available. Potency is based on biological activity rather than mass, and is not interchangeable among the toxins. Gross ratios of potency are also commonly employed by practitioners: uno = 1; inco = 1, abo = 2–5, rima = 40–60.

BoNT injections are first-line therapy for most focal dystonias. Multiple trials have demonstrated efficacy for cervical dystonia and blepharospasm. Hand dystonia, such as writer’s cramp and hemifacial spasm, consistently improve but are less well studied. There are also more than 200 other published uses for BoNT, including a number of hyperkinetic movement disorders. Multiple trials of both arm tremor and head tremor have variably demonstrated the efficacy of BoNT, with more consistent results seen in head tremor. We have found great utility of BoNT for arm tremor that primarily involves the wrists, for task-specific tremors such as writing tremor, for head tremor, and for jaw tremor. BoNT can effectively treat tics in certain anatomies, mostly the upper face (eye blinking, forehead contractions, paranasal movements) and neck (head pulling and rotation, and shoulder shrugging). Therefore, the treatment is reserved for patients with problematic tics in these areas. Interestingly, the treatment usually improves the premonitory sensation, not just the movement. It often results in complete cessation of the injected tic, but some patients subsequently manifest tics in different areas after the injections. BoNT can treat myoclonus, chorea, and stereotype but efficacy depends upon the involved anatomy. In general, smaller muscles and a focal distribution will respond best.

The treatment has minimal systemic adverse events, but can cause focal weakness. Therefore the side effect profile depends on the injected anatomy. Potential non-motor side effects include dry mouth (more common with rimabotulinum toxin-B), flu-like symptoms, and consequences of any injection (bleeding, bruise, site irritation).
Phenol, alcohol, and other destructive agents are occasionally used for dystonia, but more commonly for spasticity. As these agents permanently destroy muscle and nerve, they are reserved for only very refractory hyperkinetic disorders.

**Surgical treatments and physical treatments for hyperkinetic disorders**
Surgical treatments for hyperkinetic disorders will be discussed in detail in subsequent chapters. These can be roughly segregated in ablation/stimulation in the central nervous syndrome or ablation/stimulation in the peripheral nervous system.

Lesioning or deep brain stimulation (DBS) into the VIM thalamus is the most robust treatment for refractory tremor. This is most effective for distal aspects of the appendages, and is less effective for midline tremor. Lesions and DBS of the globus pallidus internus can be very effective for idiopathic generalized dystonia, and some focal dystonias. In general the best efficacy is seen in the appendages, as opposed to midline features, and when the dystonia has a pronounced kinetic (action-induced) component, as opposed to fixed dystonias, which are usually secondary (cerebral palsy and other brain injuries). Targeting the VIM thalamus may be relatively more beneficial in these fixed dystonias. DBS is also used for severe cases of tics. Various targets are used, including the globus pallidus internus, the anterior limb of internal capsule, and several areas of the thalamus [16]. Results in open label series have ranged from modest to dramatic and life changing. This is of course reserved for the most severe and refractory cases.

Peripheral surgical procedures for dystonia include rhizotomy, ramisectomy, peripheral nerve lesioning, and myectomy. These are most commonly performed for cervical dystonia although myectomy is also used for blepharospasm.

Physical measures for dystonia include forceful bracing against the dystonic movement, and braces designed to facilitate the sensory trick (geste antagoniste) seen in many focal/segmental dystonias. For example, a brace that just touches the back of the head may help cervical dystonia. Talking or singing often improves blepharospasm. Various adaptive changes can also lessen task specific dystonia, i.e. using a wide or Y pen for writer’s cramp. Not performing the dystonia-provoking task, sometimes facilitated by casting, often transiently improves the dystonia. This is most commonly employed in musician task-specific dystonia.

**Miscellaneous treatments for specific movement disorders**
Although desirable, behavioral treatments for tics have only occasionally demonstrated consistent efficacy in trials [17]. The most common is habit reversal training, where patients try to replace the tic with an unnoticed movement such as clinching their fist. Anxiety relieving techniques, such as biofeedback, cognitive therapy, and exposure desensitization are also tried. Immunomodulation with plasmapheresis has been advocated for the treatment of tics, but controlled trials were negative.

Treatment of tardive dyskinesia may be difficult if tetrabenazine is ineffective or not available. There is clear data to suggest that TD becomes more refractory if the culpable medication is not withdrawn, therefore discontinuation is recommended whenever possible. TD often acutely worsens with the offending drug’s discontinuation. Vitamin B6 (pyridoxine 300 mg), branched chain amino acids (Leucine, Isoleucine, Valine), and vitamin E (alpha-tocopherol) have controlled trials showing efficacy in TD. However, trials for B6 and amino acids have not been replicated and most vitamin E studies are negative. Other drug-induced movement disorders are variably treated (Table 4.4).

**Summary**
A number of oral, injectable, and surgical treatments exist for hyperkinetic disorders. There is good scientific data supporting several treatments for ET, RLS, for TBZ in chorea, and for BoNT in focal dystonias. There are very few other well-designed trials for dystonia, chorea, myoclonus, ballismus/athetosis, or stereotypies. With few exceptions, these treatments are only symptomatic in nature. Medications are only effective while actively taken and none of the injections or surgeries treat the underlying etiology. As many of these therapeutic
options have serious potential side effects, the symptomatic benefit must in all cases be weighed against side effects and cost.

References


Table 4.4 Phenotypes and treatments of hyperkinetic dopaminergic drug-induced syndromes.

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Prognosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabbit syndrome</td>
<td>4–6 Hz large amplitude mouth tremor</td>
<td>Variable</td>
</tr>
<tr>
<td>Acute dystonic reaction</td>
<td>Upward eye deviation Neck extension</td>
<td>Resolves in several days</td>
</tr>
<tr>
<td>Tardive dyskinesia</td>
<td>Variable Usually mouth, tongue, jaw repetitive smooth movements that lessen with volitional action</td>
<td>Persistent but may gradually lessen over years. Withdrawal TD has a better prognosis</td>
</tr>
<tr>
<td>Acute akathisia</td>
<td>Inner body need to move, pacing, rocking</td>
<td>Improves with drug withdrawal</td>
</tr>
<tr>
<td>Tardive akathisia</td>
<td>Inner body need to move, pacing, rocking</td>
<td>Variable, may persist for years</td>
</tr>
<tr>
<td>Neuroleptic malignant</td>
<td>Rrigidity, autonomic instability (fever), altered mental status</td>
<td>25% mortality; improves over months</td>
</tr>
</tbody>
</table>


CHAPTER 5
Overview of Surgical Treatment Possibilities in Hyperkinetic Disorders

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Introduction

Movement disorders have been grossly categorized into either hypokinetic (e.g., PD, and related disorders) where there is a paucity of movement, or hyperkinetic (dystonia, tremor, choreas, etc.) where there is excessive movement [1–3]. In many cases there is a complexity in the classification as hyperkinetic and hypokinetic components may exist. In this chapter we will provide an overview of, and surgical treatment for, hyperkinetic movement disorders with an emphasis on brain stimulation therapy.

Historical background

Dating back as far as Victor Horsley [4], neurosurgeons have attempted to address HKDs by a variety of destructive, or ablative approaches. The actual process involves unilateral lesioning in the sensorimotor territory of the GPi. This process is called pallidotomy. Generally, it is believed that the success of pallidotomy in reducing the effects of movement disorders is due to an interruption of the abnormal neuronal activity in the GPi. This ablation technique is similar to the removal of a broken part in an electrical circuit. Hence, when the damaged piece is removed, the healthy/remainder of the circuit can continue to function normally. Important refinements in these procedures were introduced in the second half of the 20th century when Spiegel and Wycis utilized the stereotactic head frame technology. This approach was subsequently fine-tuned by clinician-scientists such as Hassler, Cooper, Laitenen, and others [5, 6]. The addition of stereotaxis has allowed surgeons to target subcortical structures on the basis of a relatively simple 3D Cartesian coordinate system [7]. The accuracy of targeting has significantly improved over time, however the pathophysiological basis underlying most basal ganglia disorders remains incompletely understood. Surgical therapy was largely abandoned with the advent of levodopa therapy in 1967 [8]. Surgical therapies re-emerged, however, as dyskinesias and motor fluctuations were recognized as being drug associated, and potentially disabling disease manifestations. Several studies have demonstrated the effectiveness of brain lesion therapy, including thalamotomy for tremor, and pallidotomy for the treatment of idiopathic PD [7, 9].

During pallidotomies and thalamotomies it was observed that high-frequency test stimulation often produced clinically similar effects to the ablative procedure itself [10, 11]. Following Benabid’s successful implantation of a chronic deep brain stimulation (DBS) lead in the thalamus in 1987, the DBS procedure, which was both reversible and programmable, established itself as a potentially safer and
more attractive alternative to ablative approaches. It should be mentioned, however, that ablative lesions are still excellent treatments for many HKDs and are utilized in many of the same targets also used for DBS.

Currently, thalamic DBS is FDA approved in the United States for the treatment of PD, ET, and dystonia. DBS therapy (Medtronic) for essential tremor has been approved in Canada, Europe, and Australia since 1993. DBS therapy for Parkinson disease has been approved in Canada, Europe, and Australia since 1998. In 2009, Medtronic achieved a landmark by receiving the world’s first DBS CE mark approval for a psychiatric condition. Even though there is a lack of understanding of the mechanism of action of DBS, there is reasonable evidence that it is effective in the treatment of many movement disorder symptoms. Specialized centers for the treatment of movement disorders have been established in almost every industrialized nation, and also in some third world countries. Specific symptoms treated by DBS should be tailored to the patient (brain target and symptom) [12]. Neuropsychiatric diseases also have been recently targeted by DBS and the efficacy data is still relatively new and emerging [13–16].

**Phenomenology and clinical features**

HKDs have a wide array of motor and non-motor manifestations. Common features usually include an excess of movement, which may be characterized by involuntary/voluntary, automatic/non-automatic, and purposeful/purposeless intention, but the manifestations can be widely variable.

Although many motor and non-motor features may be addressed by DBS, we will focus this chapter on primary HKDs, or HKDs which have manifestations addressable by DBS (tremor, dystonia, chorea, and tics).

**Physiology, pathophysiology, and neuropathology**

In general, HKDs are thought to arise from pathophysiological changes within the basal ganglia. The main symptoms of HKDs are most likely a result of changes in the neuronal outputs arising from the thalamocortical circuitry. There are several theories about the mechanisms of HKD and their related syndromes. Recordings from the GPi in patients with HD, dystonia, and in levodopa-induced dyskinesia patients, have revealed that the neuronal discharges may be at a lower frequency, and perhaps may be more irregular when compared to PD [17–19]. These changes are, however, perhaps different from patient to patient but a good generalization is that there are significant changes in firing rates and patterns. We will discuss briefly the known pathophysiology of a few of the most common HKDs.

**Stereotactic central nervous system surgery**

**Patients evaluation**

**Initial evaluation**

Practical principles applied for PD surgical candidates can be generally applied for HKDs [20–22], perhaps with the exception of the on/off levodopa challenge test (utilized in PD surgical evaluations). A complete clinical workup of the patient should include a review of the evolution of symptoms, family history, physical and neurological examination and appropriate laboratories (e.g. Wilson disease, rare choreas, workup of mitochondrial disease, tics, ataxia plus syndromes, etc.). The initial assessment should include careful documentation of contractures and limitations in range of motion of any joint as this may impact the outcome (fixed contracture usually do not respond to DBS). Also, neuroimaging can be helpful in the preoperative process to establish diagnosis, and also for evaluating the integrity of potential DBS targets (e.g. some secondary diseases or syndromes may have produced structural changes such as black holes, making targeting a challenge). After the initial neurological assessment and diagnosis, the patient must be evaluated by an interdisciplinary team that usually includes an experienced movement disorders specialist, an experienced neurosurgeon, a neuropsychologist (to evaluate cognitive function), and a psychiatrist (to evaluate for affective disorders). In select cases, social workers,
physical therapists, and speech therapists may be utilized and their roles should be tailored to the patient’s individual need. Cognitive dysfunction and active untreated affective disorders may preclude DBS [12]. The patient and family should be well informed about the possible side effects and realistic expectations of surgery as this may be widely variable in HKDs when compared to other disorders, for example PD. The most frequent postoperative DBS complications as reported from a recent series: headache (15%), confusion (5%), hallucinations (2.8%), nausea and vomiting (1.6%), seizures (1.2%), and these are usually resolved a few weeks following the surgery. Infection (4.4%), cognitive dysfunction (4%), dysarthria (4%), worsening of gait (3.8%), agitation (1.6%), bleeding (1.6–3%), displacement and migration of the lead (2.2%), and suicide (0.1–0.3%) were the most serious and disabling complications, potentially limiting the therapeutic benefits. However, it should be stressed that this is one series and each group may have more or less of a specific complication depending on patient selection/level of difficult cases and experience [23–25].

Scales
When a physician recommends surgery for a patient with a HKD, the first and perhaps most important issue is confirmation of diagnosis. The appropriate scale for pre- and postoperative patient assessment should be tailored to the disease and to the patient. The Fahn—Tolosa–Marin Tremor Rating Scale has been widely used for evaluation of tremor, the Unified Huntington Disease Rating Scale (UHDRS) has been used to evaluate the severity and symptoms of HD, the Burke—Fahn–Marsden Dystonia Rating Scale (BFMDRS) and the Unified Dystonia Rating Scale (UDRS) are commonly utilized to evaluate the severity of dystonia (both scales show an equal reliability as pre and post DBS tools) [26]. The Yale Global Tic Severity Scale (YSGSS) and the Modified Rush Tic Rating Scale are both useful for evaluation of tic disorders such as TS. The Unified Myoclonus Rating Scale (UMRS) is helpful to evaluate symptoms in myoclonus cohorts. It is also common practice to follow patients both pre- and postoperatively with motor, mood, cognition, and quality of life scales as appropriate to the population.

Surgical procedures
Surgical treatment of HKDs may include ablative lesions and also DBS. Lesioning, however, is less frequently used as it is irreversible. Lesioning may be performed unilaterally in the globus pallidus and bilaterally in the STN. Bilateral lesion of GPi can induce a high risk of side effects and it is used or alternatively recommended when the patient has immunological susceptibility, or if there is an issue with access to other treatment options (due to availability, travel, and/or economics). In some cases, patients may prefer lesions (as no wires or hardware issues are involved).

DBS, unlike lesion therapy, is a reversible surgical technique where a quadrapolar lead is implanted in one or more brain targets. The lead is powered by a pulse generator which, at a later point, is implanted (usually subclavicularly in special static cases or in patients with risk of chest trauma can placed in the abdominal wall). Subsequently, the patients undergo multiple programming adjustments over many visits within the office setting. MRI, CT, MRI/CT fusion and ventriculography have all been utilized to aid in targeting with or without the use of microelectrode mapping and macrostimulation [27] (Plate 5.1). Techniques for DBS implantation vary from center to center. In most cases it is preferable to perform the surgical procedure with the patient awake, in a nearly supine position, and off their specific antimovement disorder medication. This procedure will help to evaluate responsiveness to movement in the neuronal population during the microelectrode mapping and stimulation testing. Local anesthesia and light sedation can be administered during application of the frame and this may also serve to relieve severe anxiety [26]. Leads can be implanted unilaterally, or bilaterally, depending on the recommendation of the neurosurgeon and the individual patient’s needs. The four common HKDs currently being treated with DBS are tremors, chorea, dystonia, and tics, but even more HKDs have been used for treatment with DBS including chorea secondary to cerebral
Table 5.1 Summary of DBS outcomes for tremor.

<table>
<thead>
<tr>
<th>Author</th>
<th>Cases</th>
<th>ET Target</th>
<th>Max. ben.</th>
<th>Range Stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graff-Radford, et al. [59]</td>
<td>31</td>
<td>ET VIM</td>
<td>Unilateral: 53%,</td>
<td>Unilateral L 2.7 151 102</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bilateral: 78%</td>
<td>Bilateral R 2.9 149 93</td>
</tr>
<tr>
<td>Zhang K, et al. [61]</td>
<td>34</td>
<td>ET VIM</td>
<td>80%</td>
<td>A: 2.7 151 102</td>
</tr>
<tr>
<td>Stover NP, et al. [65]</td>
<td>1</td>
<td>ET STN</td>
<td>50%</td>
<td>A: 2.6, F: 130 Hz, PW: 90μsec.</td>
</tr>
<tr>
<td>Putzke JD, et al. [67]</td>
<td>24</td>
<td>ET VIM</td>
<td>81%</td>
<td>A: 2.6–2.8, F: 140–180 Hz, PW: 60–90μsec.</td>
</tr>
<tr>
<td>Papavassiliou E, et al. [70]</td>
<td>37</td>
<td>ET VIM</td>
<td>53 ± 36%</td>
<td>A: 1–5.4, F: 130–185 Hz, PW: 60–180</td>
</tr>
<tr>
<td>Kumar R, et al. [72]</td>
<td>5</td>
<td>ET STN</td>
<td>50%</td>
<td>NA</td>
</tr>
<tr>
<td>Fields JE, et al. [73]</td>
<td>40</td>
<td>ET VIM</td>
<td>56%</td>
<td>NA</td>
</tr>
<tr>
<td>Hariz GM, et al. [74]</td>
<td>27</td>
<td>ET VIM</td>
<td>47%</td>
<td>NA</td>
</tr>
</tbody>
</table>


palsy, stroke, trauma, myoclonus-dystonia, focal dystonia, Lesch Nyhan syndrome, paroxysmal non-kineticogenic dystonia, Cockayne syndrome [28, 29]. DBS devices allow for a vast array of configurations for stimulation including potential combinations of pulse width, frequency, and amplitude. Adjustments are usually made by expert teams, and are patient and symptom specific.

**Essential tremor**

Candidates must have a documented medication refractory tremor at maximum doses of tremor medication including a beta-blocker (propanolol is usually the first choice), primidone (or phenobarbital in some countries where primidone is unavailable) and/or benzodiazepines. Medications such as Topiramate, Trazodone, Gabapentin, Pregabalin, Clozapine, Carbamazepine, Trihexyphenidyl, Sine- met, and Leviteracetam can be used but in general have not proven highly efficacious for severe tremor. The usual target for DBS is the ventralis intermedius nucleus of the thalamus (VIM), although other targets including STN have recently been utilized. VIM DBS may address refractory tremors other than ET, but inclusive of PD tremors, MS tremors, mid-brain tremors, orthostatic tremors, and essential tremors previously treated with DBS in another target. Ventralis oralis anterior and posterior (VOA/VOP) thalamic nuclei, STN or other targets including ZI may be used [30]. Double leading (VIM plus VOA/VOP) [31] has become more popular and studies are under way to look at efficacy and whether it helps proximal tremor (Plate 5.2). Contraindications to tremor surgery may include moderate to severe dementia, active alcohol and drug use, and severe untreated affective disorders [12]. A review of tremor outcomes across available studies and targets is provided in Tables 5.1 and 5.2.

**Chorea**

In HD and other hereditary choreas, as well as secondary choreas, there is a wide variation in the response to the usual pharmacological options, in
addition to side effects. This variability in response has opened the door for DBS in a very select group of patients. GPI DBS has shown benefit for chorea and dystonia with lower frequencies (40 Hz), but also with higher frequencies [32, 33] (Plate 5.3). A better control of movement has been observed with higher frequencies; however, an exacerbation of bradykinesia may be observed (remains to be confirmed). Outcomes and long-term efficacy data are scarce; however, new cases are emerging (Table 5.3).
Dystonia

The best candidates for DBS are usually those that have been diagnosed with primary dystonia (generalized or cervical), however this is only based on limited available information [28, 34]. Secondary dystonia (e.g. post-traumatic, infectious, hypoxic, toxic) has been observed to respond less well to DBS, although even this response rate is variable from patient to patient. Prior to undergoing the DBS procedure, dystonia patients should be subjected to medication trials including all potential combinations of anticholinergics, carbidopa-levodopa, muscle relaxants, benzodiazepines, baclofen, tizanidine, and botulinum toxin [35, 36]. Better surgical outcomes in general seem to be achieved in patients who do not have fixed contractures [37]. The duration of dystonia has been raised as an important factor in outcome, with longer durations being associated with less benefit in a recent small surgical series [38]; however, this data, though interesting, remains to be replicated across diverse populations.

A review of all dystonia outcome studies in the literature is provided in Table 5.4 [22]. Interestingly, tardive dystonia/dyskinesia [39], segmental, focal, and task-specific dystonias have all been addressed by DBS of various targets [40]. However, recently the STN as well as thalamic targets have been emerging for different disease presentations [41](Plate 5.4). Currently, the optimal target-symptom selection criteria are unknown in dystonia [42].

### Table 5.4 Summary of DBS outcomes for dystonia.

<table>
<thead>
<tr>
<th>Author</th>
<th>Cases</th>
<th>HKD</th>
<th>Target</th>
<th>Max. ben.</th>
<th>Range stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altermann RL, et al. [133]</td>
<td>15</td>
<td>PD</td>
<td>GPI</td>
<td>76%</td>
<td>A: 2.5, F: 60 Hz, PW: 120μsec.</td>
</tr>
<tr>
<td>Mueller J, 2008 [85]</td>
<td>40</td>
<td>PD</td>
<td>GPI</td>
<td>42–53%</td>
<td>NA</td>
</tr>
<tr>
<td>Parr J, et al. [134]</td>
<td>4</td>
<td>PD</td>
<td>GPI</td>
<td>27–85%</td>
<td>NA</td>
</tr>
<tr>
<td>Cif L, et al. [87]</td>
<td>26</td>
<td>PD</td>
<td>GPI</td>
<td>76% aprox.</td>
<td>A: 0.3–2.1, F: 130 Hz, PW: 450μsec.</td>
</tr>
<tr>
<td>Blomstedt P, et al. [90]</td>
<td>4</td>
<td>PD</td>
<td>GPI</td>
<td>79%</td>
<td>NA</td>
</tr>
<tr>
<td>Isaias IU, et al. [37]</td>
<td>30</td>
<td>PD</td>
<td>GPI</td>
<td>79%</td>
<td>A: 4, F: 60 and 130 Hz, PW 210μsec.</td>
</tr>
<tr>
<td>Woehrle JC, et al. [28]</td>
<td>12</td>
<td>PD</td>
<td>GPI</td>
<td>57%</td>
<td></td>
</tr>
<tr>
<td>Woehrle JC, et al. [28]</td>
<td>2</td>
<td>SD</td>
<td>VIM</td>
<td>57%</td>
<td></td>
</tr>
<tr>
<td>Cersosimo M [93]</td>
<td>10</td>
<td>PD</td>
<td>GPI</td>
<td>32–62%</td>
<td>NA</td>
</tr>
<tr>
<td>Loher TJ, et al. [95]</td>
<td>7</td>
<td>PD</td>
<td>GPI</td>
<td>61–82%</td>
<td>A: 2–5, F: 130 Hz, PW 210μsec.</td>
</tr>
<tr>
<td>Loher TJ, et al. [95]</td>
<td>1</td>
<td>Hemidy.</td>
<td>GPI</td>
<td>61–82%</td>
<td>A: 2–5, F: 130 Hz, PW 210μsec.</td>
</tr>
<tr>
<td>Hung SW [97]</td>
<td>10</td>
<td>PD</td>
<td>GPI</td>
<td>54.8%</td>
<td>A: 3.1±0.7, F: 135±21 Hz, PW: 71±17μsec.</td>
</tr>
<tr>
<td>Moro E [98]</td>
<td>8</td>
<td>PD</td>
<td>GPI</td>
<td>56.7%</td>
<td>A: 2–4, F: 130 Hz, PW: 60–120μsec.</td>
</tr>
<tr>
<td>Martinez-Torres I, et al. [99]</td>
<td>1</td>
<td>PD</td>
<td>GPI</td>
<td>70%</td>
<td>A: 3.3, F: 130, PW: 60μsec.</td>
</tr>
<tr>
<td>Gruber D, et al. [100]</td>
<td>9</td>
<td>TD.</td>
<td>GPI</td>
<td>83%</td>
<td>A: 0.6–3, F: 130–180 Hz, PW: 70–96μsec.</td>
</tr>
<tr>
<td>Markaki E, et al. [102]</td>
<td>1</td>
<td>MS.</td>
<td>GPI</td>
<td>70%</td>
<td>A: 2, F: 185 Hz, PW: 210μsec.</td>
</tr>
<tr>
<td>Cho CB, et al. [42]</td>
<td>1</td>
<td>WC</td>
<td>Vo.</td>
<td>75%</td>
<td>A: 2.3, F: 130 Hz, PW: 60μsec.</td>
</tr>
</tbody>
</table>
Table 5.4 (cont’d).

<table>
<thead>
<tr>
<th>Author</th>
<th>Cases</th>
<th>HKD</th>
<th>Target</th>
<th>Max. ben.</th>
<th>Range stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fukaya C [104]</td>
<td>1</td>
<td>WC</td>
<td>Vo, VIM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coubes P [105]</td>
<td>7</td>
<td>PD</td>
<td>GPI</td>
<td>NA</td>
<td>A: 1.6, F: 130 Hz</td>
</tr>
</tbody>
</table>

PD: Primary dystonia; SD: Secondary dystonia; Seg. D: Segmental dystonia; MS: Meige syndrome; WC: Writer Cramp; CP: Cerebral Palsy; GPi: Globus pallidus Internus; VIM: Ventral Intermedio Nucleus; Vo: Ventralis oralis anterior complex; STN: Subthalamic Nucleus.

Table 5.5 Summary of DBS outcomes for TS.

<table>
<thead>
<tr>
<th>Author</th>
<th>Cases</th>
<th>HKD</th>
<th>Target</th>
<th>Max. ben.</th>
<th>Range stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shalad J, et al. [109]</td>
<td>1</td>
<td>TS</td>
<td>GPi</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dehning S, et al. [111]</td>
<td>18</td>
<td>TS</td>
<td>Cm-Pf, VOA.</td>
<td>65%</td>
<td></td>
</tr>
<tr>
<td>Shields DC, et al. [112]</td>
<td>1</td>
<td>TS</td>
<td>Cm-Pf.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Welter ML [113]</td>
<td>3</td>
<td>TS</td>
<td>GPi, CM-Pf.</td>
<td>65%</td>
<td>A: 1.5–3.5, F: 130 Hz, PW: 60 μsec.</td>
</tr>
<tr>
<td>Servello D, et al. [110]</td>
<td>18</td>
<td>TS</td>
<td>Cm-Pf, VOA.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Porta M [115]</td>
<td>15</td>
<td>TS</td>
<td>Cm-Pf, VOA.</td>
<td>65%</td>
<td></td>
</tr>
</tbody>
</table>

Table 5.6 Summary of hyperkinetic disorders with stimulation of the centro medial parafascicular complex.

<table>
<thead>
<tr>
<th>Author</th>
<th>Cases</th>
<th>HKD</th>
<th>Target</th>
<th>Max. ben.</th>
<th>Range stimulation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shields DC, et al. [112]</td>
<td>1</td>
<td>TS</td>
<td>Cm-Pf.</td>
<td></td>
<td>Significant</td>
<td></td>
</tr>
<tr>
<td>Welter ML [113]</td>
<td>3</td>
<td>TS</td>
<td>CM-Pf+Bilateral GPi</td>
<td>65%</td>
<td>A: 1.5–3.5, F: 130 Hz, PW: 60 μsec.</td>
<td>Substantial reduction of tics</td>
</tr>
<tr>
<td>Ackermans L, et al. [44]</td>
<td>2</td>
<td>TS</td>
<td>Cm-Pf, VOA [1], Cm-Pf, GPi [1]</td>
<td>&gt;90%</td>
<td>A: 3.1–6.4, F: 130–170 Hz, PW: 120–210 μsec.</td>
<td>Two targets in every patient. Follow at 1 year, bennefit in Tics and OC.</td>
</tr>
<tr>
<td>Houeto JL, et al. [106]</td>
<td>3</td>
<td>TS</td>
<td>Cm-Pf, GPi</td>
<td>96%</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

TS: Tourette syndrome; Thal: Thalamus, GPi: Globus pallidus internus; Cm-Pf: Centro medial para fascicular complex; VOA: Ventro oralis anterior complex. Max. ben. in the YGTSS total score. OC: Obsessive compulsive symptoms. QoL: Quality of life. NA: Non-available; A: Amplitude; F: Frequency; PW: Pulse width.
### Table 5.7 Summary of DBS outcomes for “other HKD syndromes”.

<table>
<thead>
<tr>
<th>Author</th>
<th>Cases</th>
<th>HKD</th>
<th>Target</th>
<th>Maximal benefit</th>
<th>Range stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>McMaster J [137]</td>
<td>1 T. Anti-MAG neuropathy</td>
<td>VIM</td>
<td>dramatically improved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foote KD, et al. [31]</td>
<td>1 Holmes tremor</td>
<td>VIM, VOA, VOP</td>
<td>80%</td>
<td>A: 4-4, 1, F: 130–185Hz, PW: 90μsec.</td>
<td></td>
</tr>
<tr>
<td>Yamaamoto T, et al. [68]</td>
<td>12 Poststroke tremor</td>
<td>VIM</td>
<td>major improvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sato K, et al. [124]</td>
<td>1 Multiple HKD</td>
<td>GPi</td>
<td>Control of movements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yamada K, et al. [126]</td>
<td>1 PNKD</td>
<td>GPi</td>
<td>100%</td>
<td>A: 2.8, F: 130Hz, PW: 90μsec.</td>
<td></td>
</tr>
<tr>
<td>Oropilla QJL, et al. [127]</td>
<td>1 Myoclonus-Dystonia</td>
<td>GPi, VIM</td>
<td>81%</td>
<td>A: 2.1, F: 140Hz, PW: 90μsec.</td>
<td></td>
</tr>
<tr>
<td>Kuncel AM, et al. [129]</td>
<td>1 Myoclonus-dystonia</td>
<td>VIM</td>
<td>90%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ET: Essential tremor; TS: Tourette syndrome; PNKD: Paroxismal non-kinesigenic dystonia; GM: Gammapathy monoclonal; Vo: Ventro oralis complex; CM-PF: Centro-medial para fascicular complex; Thal: Thalamus; AIC: Anterior limb internal capsule; Vlm: Ventrolateral thalamus; GPi: Globus pallidus internal; STN: subthalamic nucleus. CS: Cortical stimulation. NA: Non-available; A: Amplitude; F: Frequency; PW: Pulse width.

### Table 5.8 Summary of hyperkinetic disorders with stimulation of other nucleus ans structures.

<table>
<thead>
<tr>
<th>Author</th>
<th>Cases</th>
<th>HKD</th>
<th>Target</th>
<th>Maximal Benefit</th>
<th>Range Stimulation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cho CB, et al. [42]</td>
<td>1 WC</td>
<td>VOA.</td>
<td>75%</td>
<td>A: 2.3 F: 130Hz, PW: 60μsec.</td>
<td>Unilateral implantation. Evaluation with BFMDRS 1/4 sustained benefit after 4 years follow-up</td>
<td></td>
</tr>
<tr>
<td>Berk C, et al. [138]</td>
<td>12 MST</td>
<td>Thal.</td>
<td>63%</td>
<td>NA</td>
<td>Control of tremor but no benefit in QoL (SPF36). Benefit in Tics, OC, and QoL</td>
<td></td>
</tr>
<tr>
<td>Maciuunas RJ, et al. [139]</td>
<td>5 TS</td>
<td>Thal.</td>
<td>44%</td>
<td>A: 3.5–3.6, F: 130–185Hz, PW: 90–210μsec.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 5.9 Summary of hyperkinetic disorders with stimulation subthalamic nucleus.

<table>
<thead>
<tr>
<th>Author</th>
<th>Cases</th>
<th>HKD</th>
<th>Target</th>
<th>Max. ben.</th>
<th>Range stimulation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stover NP, et al. [65]</td>
<td>1</td>
<td>ET</td>
<td>STN</td>
<td>50%</td>
<td>A: 2.6 F: 130 Hz, PW: 90 μsec.</td>
<td>Also with PD, unilateral left VIM benefit 40% in UPDRS. Previous left pallidotomy didn’t help tremors</td>
</tr>
<tr>
<td>Chou KL, et al. [66]</td>
<td>1</td>
<td>ET</td>
<td>STN</td>
<td>80% approx.</td>
<td>A: 2–3.2 F: 185 Hz, PW 90 μsec.</td>
<td>In this case with CD, bilateral implantation also shows benefit.</td>
</tr>
<tr>
<td>Plaha P, et al. [69]</td>
<td>4</td>
<td>ET</td>
<td>STN</td>
<td>80%</td>
<td>A: 1.6–2, F: 160–180 Hz, PW: 100–120 μsec.</td>
<td>No tolerance after one year, benefit also in Global Disability Assessment.</td>
</tr>
<tr>
<td>Kleiner-Fisman G [96]</td>
<td>4</td>
<td>PD</td>
<td>STN</td>
<td>30–50%</td>
<td>A: 1–2.5 F: 100–185 Hz, PW: 90 μsec.</td>
<td>With CD, benefit in QoL, disability and motor according to TWSTRS and BFMDRS evaluation</td>
</tr>
<tr>
<td>Martinez-Torres I, et al. [116]</td>
<td>1</td>
<td>TS</td>
<td>Bilateral STN</td>
<td>97%</td>
<td>A: 3–3.2, F: 130 Hz, PW: 60 μsec.</td>
<td>Patient also had PD with 57% benefit.</td>
</tr>
</tbody>
</table>


Tourette syndrome

The Tourette Syndrome Association has recently published guidelines for TS surgery [43] and, currently, target and patient selection remain largely unknown. The field has however been enlightened by recent studies. The centromedian parafascicular complex of thalamus (Cm-Pf) has been the most utilized target; however, motor and non-motor GPi may also be promising [44, 45]. The Anterior limb of Internal Capsule has been overall less successful in TS [46, 47], but more data will be needed to understand this approach. A summary of DBS outcomes for TS is provided in Tables 5.5 and 5.6, and the targets and outcomes of “other” HKDs and hyperkinetic symptoms addressed by DBS are summarized in Tables 5.7 and 5.8. Further, a summary of DBS outcomes in the STN for HKDs is provided in Table 5.9. Sample trajectories from anatomical targeting of DBS brain targets using MRI scanning are provided in Plates 5.1 to 5.4.

Ventralis intermedius nucleus of the thalamus

VIM is a deep subnucleus of the thalamus that receives fibers from the deep cerebellar nuclei and projects to the cerebral cortex. Like other nuclei, it is arranged in somatotopic areas (face, jaw, arm, and leg from medial to lateral). VIM is surrounded by the ventral oralis anterior and posterior subnucleus (VOA/VOP); this subnucleus receives afferents from the posterior and lateral GPi and projects to the supplementary motor cortex area. Tremor cells are located in the VIM and VOP areas, discharging equal to the patient’s tremor, and respond to passive or active movement of the contralateral somatotopic joint when is recording with microelectrode, specifically in the hand area which is the most favorable target for tremors. Stimulation of VIM, particularly in ET, shows good outcomes and control of tremor varies between 41 and 81%, also with good outcomes in quality of life and global disability. And although some authors report tolerance after 2 years of implantation, VIM is the best target for ET (Table 5.10). Parkinsonian resting tremor can be addressed by stimulation of the VIM, however bradykinesia, rigidity, dyskinesia, and dystonia are not alleviated by DBS in this subnucleus. Other tremors such as tremor secondary to multiple sclerosis, post-traumatic tremor, orthostatic tremor, Holmes tremor, tremor secondary to neuropathy, and even dystonic tremor have been treated with stimulation of the VIM, showing benefit. Chorea, secondary to cerebral palsy, and secondary to Cockayne syndrome, have been
<table>
<thead>
<tr>
<th>Author</th>
<th>Cases</th>
<th>HKD</th>
<th>Target</th>
<th>Max. ben.</th>
<th>Range stimulation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morishita T, et al. [24]</td>
<td>19 ET</td>
<td>VIM</td>
<td></td>
<td>64%</td>
<td>NA</td>
<td>Using mTRS. Immediate improvement in postural and intention tremors may predict successful at 6 months.</td>
</tr>
<tr>
<td>Zhang K, et al. [61]</td>
<td>34 ET</td>
<td>VIM</td>
<td></td>
<td>80%</td>
<td>A: 2.5–3, F: 130–180 Hz, PW: 60–120μsec.</td>
<td>Adjustment in stimulation parameters may help to control tolerance, good response in long term</td>
</tr>
<tr>
<td>Pahwa R, et al. [123]</td>
<td>26 ET</td>
<td>VIM</td>
<td></td>
<td>75%</td>
<td>A: 3.6, F: 158 Hz, PW: 111μsec.</td>
<td>18 unilateral, 8 bilateral implantation. Persistent benefit after 5 years follow-up.</td>
</tr>
<tr>
<td>Lee JY, et al. [64]</td>
<td>18 ET</td>
<td>VIM</td>
<td></td>
<td>75%</td>
<td>A: 0–3, F: 170–185 Hz, PW: 90μsec.</td>
<td>Median follow-up 27 months. Some patients require adjustments in programming setting after 6 months</td>
</tr>
<tr>
<td>Putzke JD, et al. [67]</td>
<td>24 ET</td>
<td>VIM</td>
<td></td>
<td>81%</td>
<td>A: 2.6–2.8, F: 140–180 Hz, PW: 60–90μsec.</td>
<td>Unilateral implant produce benefit in axial involvement of tremor, bilateral stimulation produce adding benefit.</td>
</tr>
<tr>
<td>Yamamoto T, et al. [68]</td>
<td>15 ET</td>
<td>VIM</td>
<td></td>
<td>Major</td>
<td>A: 1.3–2.6, F: 120–180 Hz, PW: 90–210μsec.</td>
<td>In this series also reports 12 patients with poststroke tremor, VIM stimulation with good response</td>
</tr>
<tr>
<td>Papavassiliou, et al. [70]</td>
<td>37 ET</td>
<td>VIM</td>
<td></td>
<td>53±36%</td>
<td>A: 1–5.4, F: 130–185 Hz, PW: 60–180μsec.</td>
<td>Suboptimal placement of the lead is associated to tolerance</td>
</tr>
<tr>
<td>Rehncrona S, et al. [71]</td>
<td>19 ET</td>
<td>VIM</td>
<td></td>
<td>50%</td>
<td>A: 1–3.4, F: 120–190 Hz, PW: 60–90μsec.</td>
<td>Optimal response after 6 and 7 years of follow-up. Response is better with high F (&gt;130 Hz)</td>
</tr>
<tr>
<td>Kumar R, et al. [72]</td>
<td>5 ET</td>
<td>VIM</td>
<td></td>
<td>68–62%</td>
<td>NA</td>
<td>Two patients developed tolerance.</td>
</tr>
<tr>
<td>Fields JA, et al. [73]</td>
<td>40 ET</td>
<td>VIM</td>
<td></td>
<td>56%</td>
<td>A: 2.6–4, F: 120–180 Hz, PW: 60–130μsec.</td>
<td>Good response in long term without impair cognition and with benefit in anxiety and QoL.</td>
</tr>
<tr>
<td>Hariz GM, et al. [23]</td>
<td>27 ET</td>
<td>VIM</td>
<td></td>
<td>47%</td>
<td>NA</td>
<td>Posterior article in 2008 with 19 patients after 1–7 years implanted report decreased effect over time</td>
</tr>
<tr>
<td>Koller W, et al. [141]</td>
<td>49 ET</td>
<td>VIM</td>
<td></td>
<td>Variable</td>
<td>NA</td>
<td>Good response in long term (40.2±14.7 months) in 25 patients, some patients without response.</td>
</tr>
<tr>
<td>Krauss JK, et al. [75]</td>
<td>42 ET</td>
<td>VIM</td>
<td></td>
<td>57%</td>
<td>A: 1–4, F: 130 Hz, PW: 210μsec.</td>
<td>In this series also reports 7 patients with MS, trauma or post-stroke tremor with less effective response.</td>
</tr>
</tbody>
</table>

ET: Essential tremor; SCA: Spino cerebellar ataxia; MST: Multiple sclerosis tremor.
VIM: Ventral intermedio nucleus; Vlt: Ventrolateral thalamus.
mTRS: Modified Tremor Rating Scale.
NA: Non-available; A: Amplitude; F: Frequency; PW: Pulse width.
VAMS: Visual Analog Mood Scale; BDI: Beck Depression Inventory; QoL: Quality of life.
### Table 5.11 Summary of hyperkinetic disorders with stimulation of the ventral intermedius nucleus.

<table>
<thead>
<tr>
<th>Author</th>
<th>Cases</th>
<th>HKD</th>
<th>Target</th>
<th>Max. ben.</th>
<th>Range stimulation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamel W, et al. [140]</td>
<td>2 MST</td>
<td>VIM</td>
<td>68–73%</td>
<td>A: 2–3.6, F: 130–145 Hz, PW: 60μsec.</td>
<td>In a series, report benefit</td>
<td></td>
</tr>
<tr>
<td>Lim DA, et al. [142]</td>
<td>1 MST</td>
<td>VIM+VOA</td>
<td>NA</td>
<td>NA</td>
<td>No benefit with dual electrode stimulation</td>
<td></td>
</tr>
<tr>
<td>Wishart HA, et al. [143]</td>
<td>4 MST</td>
<td>VIM, VOP</td>
<td>NA</td>
<td>A: 1.5–4.8, F: 90–160Hz, PW: 60–120μsec.</td>
<td>This is also a review of 12 authors. Significant improvement in tremor and disability benefit in tremor, myoclonus, ataxia in Cockayne syndrome.</td>
<td></td>
</tr>
<tr>
<td>Fukaya C [104]</td>
<td>5 WC</td>
<td>VOA, VIM</td>
<td>75%</td>
<td>A: 1–3, F: 90–185 Hz, PW: 160–260μsec.</td>
<td>1 Patient also GPI DBS. Good outcome after 3 years in 1 patient.</td>
<td></td>
</tr>
<tr>
<td>Bayreuther C, et al. [121]</td>
<td>1 T. Anti-MAG neuropathy</td>
<td>VIM</td>
<td>NA</td>
<td>A: 3, F: 60–90 Hz, PW: 130μsec.</td>
<td>Tremor and QoL dramatically improved</td>
<td></td>
</tr>
<tr>
<td>Ruzicka E, et al. [145]</td>
<td>1 T. in neuropathy GM</td>
<td>VIM</td>
<td>50%</td>
<td>A: 1.1–1.5, F: 130–145Hz, PW: 60–90μsec.</td>
<td>Good outcome in a Patient 72 years old</td>
<td></td>
</tr>
<tr>
<td>Foote KD, Okun MS [31]</td>
<td>1 Holmes tremor</td>
<td>VIM/VOA, VOP</td>
<td>80%</td>
<td>A: 4–4: 1, F: 130–185Hz, PW: 90 μsec.</td>
<td>Posttraumatic tremor. Two leads produce better and sustained response</td>
<td></td>
</tr>
</tbody>
</table>

MST: Tremor secondary to multiple sclerosis; OT: Orthostatic tremor; CP: Cerebral palsy; WC: Writer’s cramp.
VIM: Ventral intermedio nucleus; VOP: Ventral oralis posterior nucleus; VOA: ventral oralis anterior nucleus; STN: Subthalamic nucleus; LF: Lenticular fasciculus.
SCS: Spinal cord Stimulation.
NA: Non-available; A: Amplitude; F: Frequency; PW: Pulse width.
Table 5.12  Summary of hyperkinetic disorders (dystonia) with stimulation of the globus pallidus internal segment.

<table>
<thead>
<tr>
<th>Author</th>
<th>Cases</th>
<th>HKD</th>
<th>Target</th>
<th>Max. ben.</th>
<th>Range stimulation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vandeoriolla F, et al. [146]</td>
<td>22</td>
<td>PD</td>
<td>GPI</td>
<td>50%</td>
<td>A: 0.3–2.1, F: 130 Hz, PW: 450 μsec.</td>
<td>DYT1 patients. All initially single lead bilateral GPI requires double lead bilateral GPI. 4 non responding. Follow-up 10 years.</td>
</tr>
<tr>
<td>Cif L, et al. [87]</td>
<td>26</td>
<td>PD</td>
<td>GPI</td>
<td>76% aprox.</td>
<td>A: 0.3–2.1, F: 130 Hz, PW: 450 μsec.</td>
<td></td>
</tr>
<tr>
<td>Blomstedt P, et al. [90]</td>
<td>4</td>
<td>PD</td>
<td>GPI</td>
<td>79%</td>
<td>NA</td>
<td>Idiopathic dystonia. Excluded DYT 1, DYT 5-DYT 17. All members of a family.</td>
</tr>
<tr>
<td>Isaias IU, et al. [37]</td>
<td>30</td>
<td>PD</td>
<td>GPI</td>
<td>79%</td>
<td>A: 4; F: 60 and 130 Hz, PW: 210 μsec.</td>
<td>Evaluation at different points in 8 years with sustained benefit. Similar benefit at 60 and 130Hz.</td>
</tr>
<tr>
<td>Moro E [79]</td>
<td>8</td>
<td>PD</td>
<td>GPI</td>
<td>54.5%</td>
<td>A: 2–4, F: 130 Hz, PW: 60–120 μsec.</td>
<td>CD TWSTRS evaluation, improvement with high F (&gt;40Hz). Segmental dystonia. Significant improvement at 6 months and even better after 3 years.</td>
</tr>
<tr>
<td>Woehrle JC, et al. [28]</td>
<td>14</td>
<td>PD</td>
<td>GPI or</td>
<td>57%</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Cersosimo M [93]</td>
<td>10</td>
<td>PD</td>
<td>GPI</td>
<td>32–62%</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Loher TJ, et al. [95]</td>
<td>9</td>
<td>PD</td>
<td>GPI</td>
<td>61–82%</td>
<td>A: 2–5, F: 130 Hz, PW 210 μsec.</td>
<td>1 patient with hemidystonia, 4 CD, 2 Generalized dystonia, 1 Meige, 1 PNKD. Good response in long term [9 years]. In this study authors register pairs of cells simultaneously and use surface EMG to evaluate response in programming settings. 12 with DYT1 dystonia, young onset. Sustained low frequency in every patient. Benefit 89% after 1 year. Also benefit in disability, pain, depression and QoL.</td>
</tr>
<tr>
<td>Magariños-Ascone CM, et al. [92]</td>
<td>10</td>
<td>PD</td>
<td>GPI</td>
<td>65%</td>
<td>A: 2–3, F: 120–150 Hz, PW: 100–120 μsec.</td>
<td>In this study authors register pairs of cells simultaneously and use surface EMG to evaluate response in programming settings.</td>
</tr>
<tr>
<td>Altermann RL, et al. [133]</td>
<td>15</td>
<td>PD</td>
<td>GPI</td>
<td>89%</td>
<td>A: 2.5, F: 60Hz, PW: 120 μsec.</td>
<td></td>
</tr>
<tr>
<td>Hung SW [97]</td>
<td>10</td>
<td>PD</td>
<td>GPI</td>
<td>54.8%</td>
<td>A: 3.1 ± 0.7, F: 135 ± 21 Hz, PW: 71 ± 17 μsec.</td>
<td>CD TWSTRS evaluation</td>
</tr>
</tbody>
</table>
Parr J, et al. [134] 4 PD GPi 27–85% NA Children 8–15 years old, idiopathic dystonia. 42% benefit in disability
Krauss JK, et al. [80] 2 PD GPi 78% A: 3.3, F: 135 Hz, PW: 210μsec. Sustained benefit in non DYT–1 dystonia. In this report 2 patients with chore-atethosis with minimal improvement [23% after 2 years]
Markaki E, et al. [102] 1 MS. GPi 70% A: 2, F: 185 Hz, PW: 210μsec. Functionally blind. Benefit in BFMDRS and Disability score [84%]

PD: Primary dystonia; SD: Secondary dystonia; Seg. D: Segmental dystonia; TD: Tardive dystonia; CD: Cervical dystonia.
MS: Meige syndrome; WC: Writer’s cramp; CP: Cerebral palsy.
GPi: Globus pallidus internal; VIM: Ventral intermedio nucleus; VOA: Ventro oralis anterior complex; STN: Subthalamic nucleus; FL: Frontal lobe.
TWSTRS: Toronto Western Spasmodic Torticollis Rating Scale.
EMG: Electromyography.
NA: Non-available; A: Amplitude; F: Frequency; PW: Pulse width.
<table>
<thead>
<tr>
<th>Author</th>
<th>Cases</th>
<th>HKD</th>
<th>Target</th>
<th>Max. ben.</th>
<th>Range stimulation</th>
<th>Comments</th>
</tr>
</thead>
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<tr>
<td>Biolsi B, et al. [77]</td>
<td>1</td>
<td>HD.</td>
<td>GPi</td>
<td>approx. 50%</td>
<td>A: 1.9, F: 130 Hz, PW: 450μsec.</td>
<td>Sustained benefit in choreic movements after 4 years</td>
</tr>
<tr>
<td>Moro E, et al. [98]</td>
<td>1</td>
<td>HD.</td>
<td>GPi</td>
<td>Considerably</td>
<td>A: 2.5–3.5, F: 40–130Hz, PW: 90–120μsec.</td>
<td>Worsening bradykinesia at high freq. [130 Hz]</td>
</tr>
<tr>
<td>Guehl D, et al. [82]</td>
<td>2</td>
<td>Neuroacanthocytosis</td>
<td>GPi</td>
<td>approx. 50%</td>
<td>F: 40 Hz.</td>
<td>F at 130Hz worsened chorea, dysarthria and drooling</td>
</tr>
<tr>
<td>Ruiz PJ, et al. [83]</td>
<td>1</td>
<td>Chorea-acanthocytosis</td>
<td>GPi</td>
<td>approx. 50%</td>
<td>A: 4.2–4.4, F: 130 Hz, PW: 180μsec.</td>
<td>Also with dystonia, better response with high F.</td>
</tr>
<tr>
<td>Hasegawa H, et al. [84]</td>
<td>1</td>
<td>Hemiballism, hemidyst.</td>
<td>GPi</td>
<td>100%</td>
<td>A: 4.5, F: 130 Hz, PW: 60μsec.</td>
<td>Symptoms caused by bleeding in STN.</td>
</tr>
<tr>
<td>Okun MS, et al. [21]</td>
<td>1</td>
<td>RLS</td>
<td>GPi</td>
<td>Control</td>
<td>NA</td>
<td>Report of side effect, DBS implanted in a patient with dystonia</td>
</tr>
<tr>
<td>Yamada K, et al. [126]</td>
<td>1</td>
<td>PNKD</td>
<td>GPi</td>
<td>0/4</td>
<td>A: 2.8, F: 130 Hz, PW: 90μsec.</td>
<td>Secondary to peripheral trauma. Complete suppression</td>
</tr>
<tr>
<td>Oropilla JQ, et al. [127]</td>
<td>1</td>
<td>Myoclonus-dystonia</td>
<td>GPi, VIM</td>
<td>81%</td>
<td>A: 2.1, F: 140 Hz, PW: 90μsec.</td>
<td>Unilateral implantation, better response with GPi</td>
</tr>
<tr>
<td>Kurtis MM, et al. [128]</td>
<td>1</td>
<td>Myoclonus-dystonia</td>
<td>GPi</td>
<td>Excellent improvement</td>
<td>NA</td>
<td>Sustained clinical and neurophysiological benefit after 2 years</td>
</tr>
</tbody>
</table>

HD: Huntington disease; CP: Cerebral palsy; TS: Tourette syndrome; RLS: Restless legs syndrome; PNKD: Paroxismal Non-kinesigenic dystonia.
GPi: Globus pallidus internal; VIM: Ventral intermedio nucleus; VOP: Ventro oralis posterior nucleus; Subthalamic nucleus.
NA: Non-available; A: Amplitude; F: Frequency; PW: Pulse width.
OC: Obsessions compulsions; QoL: Quality of life.
treated with stimulation in this target, reporting control of myoclonus and tremor. Case reports of writer’s cramp and myoclonus-dystonia have been reported with improvement in the final outcome (Table 5.11).

**Globus Pallidus (GPI)**

This nucleus receives fibers from the striatum (specifically spiny neurons expressing dynorphin and peptide P targeting D1 receptors), STN, and reaches areas of the VOA/VOP and VIM nucleus of the thalamus, pedunculo pontine nucleus (PPN), and lateral habenula among others. Somatotopy of GPI shows face/arm lateral and leg medial, while posterior and lateral areas are sensorimotor, and anteromedial have associated functions. According to microrecordings, the final target for stimulation is the posteroventrolateral portion of the GPI, which is dorsal to the optic tract, where kinesthetic neurons are detected.

Placement of the electrode in this nucleus has been indicated in patients with PD, primary, or secondary dystonia, and some reports of chorea, myoclonus-dystonia, and Tourette syndrome. In patients with dystonia, parameter settings are variable in each case; however, there is a tendency to stimulate with low frequencies those patients with primary dystonia, showing consistent benefit in the long term (Table 5.12). Patients with PD have benefit in improving dyskinesia, dystonic postures, and tremor. Patients with TS, chorea, and other hyperkinetic disorders have been treated with reported good outcomes; however, long-term studies are still being developed (Table 5.13).

**Peripheral nervous system surgery**

Peripheral nervous system surgery is vital in the treatment of abnormal postures such as focal dystonias, spasticity, and also pain syndromes. This procedure is approved for patients not responding to the best pharmacological options and usually those who develop immunoresistance to botulinum toxin [48]. For cervical dystonia, anterior cervical rhizotomy was the standard procedure employed prior to the introduction of botulinum therapy [49]. However, this has been generally abandoned due to the fact that it is not very effective, and has numerous side effects. The original technique of selective peripheral denervation was first introduced by Bertrand [50], but has been modified considerably since then. Two standard approaches include rhizotomy and ramisectomy. Technical details include extradural and intradural nerve sectioning trying to reduce abnormal posture, without losing the normal action of the muscle, and for this purpose electromicrographic guidance is helpful [50, 51].

**Cortical stimulation**

One approach for cortical stimulation is the implantation of a quadripolar electrode in the extradural space above the motor cortex region of the brain, contralateral to the motor symptoms needing to be controlled [52]. This option is proposed for patients with contraindications for receiving a basal ganglia stimulator. The Turin group has found that patients show relief in the cardinal motor symptoms of PD, including gait, balance, and extra movements induced by medications such as dyskinesia – and also benefit in their quality of life. However, concrete evidence is lacking [53–54].

Cortical stimulation of the motor cortex has been used for essential tremor, but the final results are disappointing [55]. Another procedure used in clinical research is the cathodal direct current stimulation. This procedure consists of direct electrical stimulation applied in the motor cortex, with a voltage of 2 mA in 20 minutes. In one study, 10 dystonia patients (Musician's Focal dystonia) showed no benefit in the final task; however, 2 patients, one with focal dystonia of the arm and another with dystonia in the hand, showed benefit after the stimulation [56].

**Transmagnetic cranial stimulation**

Studies of transmagnetic cranial stimulation (TMS) in dystonia patients have been contradictory. A report published by Schneider et al. shows no benefit with rTMS at 5 Hz in the somatosensory
cortex in 5 patients with writer’s cramp, while Havrankova et al. stimulated the same region at 1 Hz in 11 patients, and reported subjective and objective benefits in final tasks, with the effects remaining even after 2 weeks. Another study showed benefit in focal dystonia from stimulation of the premotor cortex at 1 Hz for 10 minutes, with lasting benefit, of up to 10 days.

In patients with ET, TMS has not shown benefit [57]. However in PD patients, TMS seems to help in motor and non-motor symptoms. One study focuses on dyskinesia in patients with PD, showing benefit even 3 days after the stimulation was stopped [58].

Conclusions

There are many reasons to be optimistic about the future of DBS to address HKDs in medication resistant patients. As our understanding of the underlying basal ganglia circuitry expands, we will be in a better position to tailor targets and stimulation parameters for individual patients.

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Overview of Surgical Treatment Possibilities in Hyperkinetic Disorders

PART 2
Tremor Syndromes
CHAPTER 6
Essential Tremor

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Introduction

Tremor is an involuntary, rhythmic, muscle movement involving oscillations of one or more parts of the body, resulting from the contraction of opposing muscle groups [1–4]. Essential tremor (ET) is the most common of the many tremor disorders and is also one of the most common neurological disorders among adults [1–9]. The traditional view of ET, as a monosymptomatic condition, is being replaced, as a spectrum of clinical features, with both motor and non-motor elements, including ataxia, parkinsonism, cognitive impairment, dementia, depressive symptoms, and sensory (e.g. mild olfactory dysfunction and hearing impairment) abnormalities [10], are increasingly being observed and documented. The landscape for ET is shifting in a number of important ways in recent years as clinical and postmortem studies increase our understanding of this common disorder. New insights into the pathogenesis of ET, in particular, could advance the development of effective neuroprotective and symptomatic therapies.

Historical background

References to tremor have been recorded from affected people throughout the course of human existence [11, 12]. The term tremore semplice essenziale (simple essential tremor) was first used by Burresi in Italy in 1874 to describe an 18-year-old man with severe, isolated action tremor. By the mid-20th century, the familial distribution and core motor feature (action tremor of the arms) of ET had already been well-documented by clinicians [11]. By the early 20th century, the term “essential tremor” began to appear in the medical literature with greater frequency [12]. For many years, ET was also referred to as “benign essential tremor” [12]; however, the adjective “benign” is slowly being abandoned in recognition of the often disabling nature of the disorder [1–4].

Phenomenology and other clinical features

General characteristics

The tremor of ET is typically a postural or kinetic tremor (i.e. tremor during voluntary motion) most commonly affecting the arms and hands [1–4]. In most cases, it is slightly asymmetric, with the tremor being of greater amplitude in one arm than the other [13].

During the physical examination, the affected body areas should be identified along with each body area’s activity state when the tremor occurs (e.g. at rest, maintaining an extended posture, or voluntary...
movement) [1–4]. The frequency of the tremor is between 4 and 12 Hz, and is inversely related to age, with older patients generally exhibiting tremor frequencies that are at the lower end of this range [14].

Kinetic arm tremor is the hallmark feature of ET and occurs during a voluntary movement, for instance during finger-to-nose testing, while pouring or drinking, or drawing Archimedes’ spirals (Figure 6.1) [1–4, 14]. The kinetic tremor in ET often has an intentional component; for example, during visually guided movements such as the finger-to-nose maneuver, the amplitude of the tremor increases as the target is approached [15] (see Video 6.1). Kinetic tremor leads to difficulties with eating, drinking, writing, dressing, and various other activities of daily living [1–4, 14]. The amplitude of kinetic tremor is usually greater than that of postural tremor [14]. Postural tremors become obvious when the patient keeps his arms outstretched against gravity in front of his body (e.g. extending the upper limbs horizontally) [1–4].

A rest tremor of the arms is observed occasionally in ET patients. If present, it typically occurs when the arms are supported against gravity and completely at rest (e.g. while the patient is lying down, while he is seated and his hands are resting in his lap, or during normal stance and ambulation) [1–4, 16, 17]. One study showed that patients with rest tremor had kinetic tremor that was more severe, more disseminated, and of longer duration than ET patients without rest tremor [18].

**Medical history**

During the medical history, the clinician should collect several types of data.

**Presence of a positive family history**

Family history of ET-like tremor is commonly noted and, depending on the study, is present in anywhere from 17 to 100% of patients [19]. Most studies indicate the presence of other reportedly affected first- or second-degree relatives in 30–50% of patients, with young onset cases and those ascertained from clinical rather than population-based studies being more likely to report an affected relative [19, 20]. Within families, there can be considerable heterogeneity in terms of tremor distribution, age of onset, and rate of progression [12].

**Age at onset**

ET can begin at any age. However, some data suggest a bimodal distribution in age of onset with peaks in the second decade and sixth to later decades, and other data suggesting only one late-life peak [1–4, 21]. One study compared data from a tertiary referral setting and a population-based setting [21]. In the latter setting, a peak in later life was clearly present but a young-onset peak was barely discernible. By contrast, in the tertiary referral setting, age of onset was clearly bimodal [21]. This appearance of a large early-life peak in clinic-based studies is likely due to the preferential referral to treatment centers of patients with young-onset, familial ET (i.e. a referral bias resulting in the impression of a large, young-onset peak) [21].
Anatomical distribution and severity

The tremor of ET is typically an asymmetric kinetic and postural tremor, most commonly affecting arms and hands, but other areas of the body may be affected, especially the head (i.e. neck), voice, jaw, tongue, and legs [1–4, 22–25]. Head tremor is usually of the side-to-side (no–no) type although it may also be of the up–down (yes–yes) type or a rotational type. In different settings, the proportion of patients with head tremor ranges from 34 to 53%, and with jaw tremor from 7.5 to 18.0% [1–4, 22–25]. Depending on its definition, “isolated” head tremor (i.e. head tremor in the absence of arm tremor) is rarer, occurring in few if any ET patients [26].

In general, ET is a progressive disorder, with disease duration and age each being independent contributors to tremor severity [27–29]. Over time, tremor can spread from the arms to the head (especially in women); the converse (initial involvement of the head with subsequent spread to the arms) is rare and should suggest an alternative diagnosis to ET [1–4, 12].

There are few data on the rate of progression in ET. However, it seems that most ET cases exhibit a progressive worsening in tremor with time. Thus, in a study, the average annual increase in tremor severity from baseline was estimated to be between 3.1% and 5.3% and the median annual increase from baseline was between 1.8% and 2.0% [30]. In a large clinical sample, older age of onset was associated with more rapid tremor progression [31].

ET is not always a benign condition and it may negatively impact on patient’s health-related quality of life (HRQoL) [32–37] and morale [38]. Indeed, more than 90% of ET patients who come to treatment centers for tremor report disability [39], and many patients with severe, advanced ET are unable to perform basic daily activities such as feeding or dressing themselves [12]. Almost one-quarter of patients who seek medical attention are compelled to change jobs or retire, and 60% decide not to apply for jobs or promotions because of disabling shaking [12, 39]. Even among population-dwelling cases, the large majority report disability with more than one daily task [39–41].

Embarrassment is a prevalent feature of ET [42]. In one study, 58.2% of ET cases seen in a clinical setting reported embarrassment [42]. Embarrassment is not only common, but it is also a major motivator for treatment [42]. In a study in New York found that the experience of embarrassment nearly doubled the odds of using tremor medication [42]. An embarrassment questionnaire for ET patients has recently been developed and validated and promises to facilitate the assessment and measurement of embarrassment in ET [43].

Presence of additional symptoms or signs that may suggest an alternative diagnosis

Patients with tremor due to other disorders such as hyperthyroidism, Wilson disease, dystonia or Parkinson disease (PD) frequently have concomitant symptoms or signs that lead the clinician to these diagnoses [1–4]. For example, patients with hyperthyroidism may complain of nervousness, palpitations, hyperactivity, increased sweating, heat hypersensitivity, fatigue, increased appetite, weight loss, insomnia, weakness, and frequent bowel movements (occasionally diarrhea) [44, 45]. Hypomenorrhea may also be present [44, 45]. Signs may include warm and moist skin, tachycardia, widened pulse pressure, atrial fibrillation, irritability, and sweating. Elderly patients, particularly those with toxic nodular goiter, may present with symptoms more akin to depression or dementia (apathetic or masked hyperthyroidism) [46]. Patients with PD often complain of slowness and limb stiffness and, on examination, have two or more cardinal features of PD [1–4]. Psychiatric manifestations often accompany Wilson disease [47, 48], ranging from frank psychosis, delusions and hallucinations, to more subtle signs, such as difficulties with school work or job performance, personality changes, emotionality, loss of sexual inhibition, insomnia, and aggressiveness [43, 44]. Diagnosis relies on a high clinical suspicion, typical neurological symptoms, presence of Kayser–Fleischer rings, and reduced serum ceruloplasmin concentration [47, 48].

Administration of pharmaceutical agents or exposure to toxins that may induce or alleviate tremor

An inventory of all current medications, as well as information on caffeine intake, is also mandatory.
Medications that can exacerbate tremor include amiodarone, bronchodilators, cinnarizine, cyclosporine A, flunarizine, fluoxetine, lithium, methylphenidate, metoclopramide, neuroleptics, nifedipine, phenelzine, phenylpropanolamine, prednisone, procainamide, pseudoephedrine, theophylline, tricyclic antidepressants, and valproic acid [1–4]. The tremor of ET may temporarily abate after ethanol intake [1–4]. The improvement is typically reported to begin after 10 to 15 minutes and continue for approximately 3 hours [1–4, 49, 50].

**Differential diagnosis**
Arriving at the correct diagnosis is dependent on the medical history; the clinical distinction between kinetic, postural, intention, and rest tremors; and the recognition of additional clinical signs. The differential diagnosis includes a number of conditions in which kinetic, postural, intention, or rest tremors occur or in which combinations of these different types of tremors co-occur (Box 6.1) [1–4, 51, 52].

ET may be the most overdiagnosed movement disorder and studies have shown that 30–50% of individuals who are assigned the diagnosis of ET have other neurological diseases (e.g. PD or dystonia) rather than ET [53, 54]. Classically, PD is characterized by a rest tremor that dampens with action, whereas ET is characterized as a kinetic tremor that resolves upon rest [55]. However, this is an oversimplification. Indeed, PD can be accompanied by different forms of tremor. A combination of rest, postural, and kinetic tremors constitutes the most frequent tremor constellation in PD [55, 56]. Yet in PD, kinetic tremor is often mild relative to rest tremor and the patient also has other signs of the disease (e.g. diminished facial expression, a reduction in normal arm swing, and general body slowness) [1–4, 56]. By contrast, when rest tremor occurs in ET patients, it usually does so in the setting of a severe kinetic tremor of long duration [1–4]. In addition, the postural tremor of ET usually produces wrist flexion and extension whereas, in PD, wrist rotation is commonly seen, as is thumb flexion and extension [1–4]. Mild cogwheeling may occur in ET, but this is without rigidity [1–4]. In general, the tremor of PD does not involve the voice and although it rarely involves the head it may involve the chin and perioral structures [1–4, 55].

Enhanced physiologic tremor is an 8–12 Hz postural and kinetic tremor that may occur in the limbs and voice (but not the head) and may be further exacerbated by emotion and by medications [1–4, 57, 58]. Its amplitude is generally lower than that of ET. Although quantitative computerized tremor analysis, with accelerometers attached to the arms, which exists in some tertiary treatment settings, may be useful in differentiating mild ET from marked enhanced physiological tremor, there are limitations, as approximately 8% of young and elderly adults have an electromyography (EMG)-acceleration pattern that is indistinguishable from mild ET [59].

ET must also be differentiated from dystonic tremor (tremor occurring in the setting of focal, segmental, and generalized dystonias) [59]. In some cases, dystonic tremor may be very rhythmic, especially when there is relatively little muscular coactivation [1–4, 59] and, for this reason, mild tremulous cervical dystonia (torticollis) is often misdiagnosed as ET [1–4]. However, there are a number of features that aid in the differentiation of dystonic tremor and ET. In general, in ET patients, head tremor is characterized by rhythmic (i.e. regular) oscillations, whereas in torticollis it tends to be irregular, occurs with tilting of the head or chin, varies in intensity with changes in neck or head position, and may completely disappear when the head is allowed to assume the position of the dystonic pulling (“null point”) [1–4, 59, 60].
There are other neurological findings that may be helpful in distinguishing this entity from ET, including the presence of dystonic posturing in the limbs or torticollis in the neck and hypertrophy of involved dystonic musculature [1–4, 59]. In addition, persistently focal tremor in one extremity, jerky and irregular tremors, gestes antagonistes, or selective responsiveness to antidystonic therapeutic agents should point to the diagnosis of dystonic tremor [1–4, 59].

Also in the differential diagnosis are a series of conditions that may be misclassified as tremor, including myoclonus, clonus, asterixis, and focal motor epilepsy.

Myoclonus is a brief muscle jerk, which may occur in repetitive trains and may be mistaken for tremor. Surface electromyography typically shows periodic muscle burst durations of less than 50 ms [61]. Isolated whole-body tremulousness should raise the suspicion of generalized polymyoclonus, confirmed using routine surface EMG. Recognition is important because the differential diagnosis includes autoimmune disorders and drug-induced myoclonus [61, 62].

Clonus is an involuntary muscular contraction alternating in rapid succession with relaxation. It occurs around joints and is stimulated through the stretch reflex. Passive stretching increases clonus but not tremor, aiding in the differentiation [1–4, 63]. However, in selected cases, action-induced clonus can mimic tremor [64].

Asterixis (negative myoclonus) is a disorder of motor control characterized by brief, arrhythmic interruptions of sustained voluntary muscle contraction; it is usually observed as a brief lapse of posture [65]. It manifests as a bilateral flapping tremor affecting various parts of the body (especially the hands and arms) and occurs with a frequency of 3–5 Hz during active maintenance of posture [65]. Asterixis can be differentiated from tremor on the basis of the irregularity of the movements [65]. In addition, the electromyographic features consist of cessation of electrical activity for 35 to 200 ms in multiple muscles, during which time posture may be overcome by gravity, followed by an equally abrupt reactivation of motor units and a restorative jerk of the affected body part [65].

Epilepsia partialis continua is a rare form of focal status epilepticus that can cause rhythmic muscle jerks in the extremities. Characteristic features enable it to be distinguished from ET [66]. Typical clinical signs of epilepsia partialis continua are as follows: combination of the repetitive myoclonic jerks with hemiparesis or, less frequently, with other cortically-generated deficits; monomorphic, simple, brief excursions of the affected limb; irregular occurrence of the jerks; involvement of very distal muscle groups; and increase in amplitude and frequency after physical exercise or psychic exertion [66]. In addition, electroencephalography often shows abnormal spikes, which help the clinician to arrive at the correct diagnosis [66].

**Laboratory workup**

There are currently no laboratory findings that are unique to ET [1–4]. Hence, the purpose of laboratory investigation is to help to exclude other disorders. Among certain patients, recommended screening investigations include thyroid function tests and, especially if the patient is under 40 years of age, diagnostic studies to exclude Wilson disease (e.g. serum ceruloplasmin) [1–4].

In the last decade, functional imaging of the dopamine transporter (DAT) has been introduced [67, 68]. DAT imaging detects presynaptic dopamine neuronal dysfunction and thereby assists with the differentiation of conditions with and without such dopamine deficits (i.e. parkinsonism vs. ET) [67, 68]. The DAT scan is usually normal in ET [69] (and in drug-induced tremors) whereas it is abnormal in PD or other parkinsonian syndromes [67, 68]. In one study, however, DAT imaging showed that the pattern of dopaminergic loss over time is different between ET and PD, but both disorders exhibit impairment of DAT in the caudate nucleus [70].

In the last several years, transcranial sonography has also been shown to be useful in the differentiation between PD and ET [71, 72]. In a transcranial sonography study, bilateral substantia nigra hyperechogenicity >0.20 cm² was found in 91% of 80 PD patients, 10% of 80 healthy subjects, and 13% of 30 ET patients [72]. Substantia nigra hyperechogenicity in ET patients might correspond
to an increased risk of developing PD later in life [72]. In some tertiary care centers, quantitative computerized analysis of tremor may distinguish enhanced physiological tremor and other tremors from the tremor of ET [1–4, 73].

**Clinical diagnostic criteria**

The diagnosis of ET is based on history and physical examination [1–4]. Several clinical criteria have been proposed, including those proposed in the Consensus Statement on Tremor by the Movement Disorder Society (Box 6.2) [74]; these criteria have also been modified slightly by the Tremor Research Group (Box 6.3) [75]; and those by the National Institutes of Health Essential Tremor Consortium (Box 6.4) [76]. The Washington Heights-Inwood Genetic Study of ET criteria (Box 6.5) are also useful, particularly for genetic and epidemiological studies, in which the distinction between ET and enhanced physiological tremor is important [77–80]. The use of different classification schemes may stimulate discussion among physicians regarding the definition of ET; however, the lack of consensus may be an impediment to tremor research.

**Tremor assessment and health-related quality of life measurements**

Once a diagnosis of ET has been established, the treating physician may identify patients with more severe disease manifestations in order to initiate treatment. There are a several validated scales that are useful in the assessment of tremor severity and disability. In general, clinical rating scales grade tremor amplitude in each body region during specific postures or tasks. Among the preferred scales used to measure the severity of tremor is the Fahn–Tolosa–Marin clinical evaluation scale [81], clinical rating scales designed by Bain et al. [82], and a series of clinical rating scales, disability questionnaires and performance-based tests designed by Louis et al. [77–80].

There is increasing recognition that the global well being of patients with chronic neurological disease is an important outcome in research and clinical practice alike [83, 84]. Subjective (i.e. self-reported) measures of health-related quality of life
Essential Tremor

(HRQoL) may serve to alert clinicians to areas that would otherwise be overlooked [83, 84]. Data on HRQoL in ET have been reported in a small number of studies [32–37]; however, most of these have sampled highly selected ET patients with severe and disabling tremor who were seen in treatment settings. In one community-based study of HRQoL in ET [35], 32 ET cases and 32 matched controls were compared using the Rand-SF36 [35]. The results demonstrated poorer overall HRQoL in ET cases than in controls. Recently, a 30-item, ET-specific HRQoL scale – the Quality of Life in Essential Tremor Questionnaire (QUEST) – was developed [36, 37] and will be useful in terms of assessing and advancing our understanding of ET-specific HRQoL.

Box 6.4 National Institutes of Health essential tremor consortium

Tremor severity scale
0 none
1 minimal (barely noticeable)
2 obvious, noticeable but probably not disabling (<2 cm excursions)
3 moderate, probably partially disabling (2 cm to 4 cm excursions)
4 severe, coarse, and disabling (>4 cm excursions)

Definite essential tremor
2+ amplitude rating for bilateral arm tremor
or
2+ amplitude rating in one arm and 1+ amplitude rating in other arm
or
1+ amplitude rating in at least one arm and predominant cranial/cervical tremor with 2+ amplitude rating

Head tremor is rhythmic with no directional preponderance and without asymmetry of cervical muscles.
Exclusion: obvious secondary causes (coexistent dystonia allowed; coexistent Parkinson’s disease (PD) disallowed)

Possible essential tremor
1+ bilateral arm tremor
or
Isolated 2+ cranial/cervical tremor
or
Convincing history of ET
Exclusion: obvious secondary causes (e.g. enhanced physiologic tremor, drug-induced or toxic tremor, coexistent peripheral neuropathies)
Coexistent dystonia allowed
Coexistent PD allowed if there is a convincing history of pre-existing essential tremor

Possible essential tremor
Isolated 1+ cranial/cervical tremor
or
Task- or position-specific arm tremor
or
Unilateral arm tremor
or
Orthostatic tremor

Unrateable essential tremor
Tremor is coexistent with other neurologic disease, therapy with antitremor or tremor-promoting drugs, untreated thyroid disease, caffeine withdrawal/abstention, etc.

Box 6.5 Washington Heights-Inwood genetic study of ET criteria

Tremor ratings
• 0: No visible tremor
• +1: Low amplitude, barely perceivable tremor, or intermittent tremor.
• +2: Tremor is of moderate amplitude (1–2 cm) and usually present. It is clearly oscillatory.
• +3: Large amplitude (>2 cm), violent, jerky tremor resulting in difficulty completing the task due to spilling or inability to hold a pen to paper.

1. On examination, a +2 postural tremor of at least one arm (a head tremor may also be present, but is not sufficient for the diagnosis).

2. On examination, there must be a +2 kinetic tremor during at least four tasks, or a +2 kinetic tremor on one task and a +3 kinetic tremor on a second task. Tasks include pouring water, using a spoon to drink water, drinking water, finger-to-nose manoeuvre, and drawing spirals.

3. If on examination the tremor is present in the dominant hand, then by report it must interfere with at least one activity of daily living (eating, drinking, writing, and using the hands). If on examination the tremor is not present in the dominant hand, then this criterion is irrelevant.

4. Medications, hyperthyroidism, ethanol, or dystonia are not potential etiological factors.

5. Not psychogenic (bizarre features, inconsistent in character, patient is distractible, other psychiatric features on examination).
**Associated findings**

ET patients demonstrate abnormalities in tandem gait that are milder yet otherwise indistinguishable from those seen in patients with cerebellar diseases [85–89]. These gait disturbances are seen more frequently in ET patients with longer disease duration and who are at an advanced stage of ET [85–89]. These tandem gait abnormalities provide clinical evidence of cerebellar dysfunction in ET [1–4], and these gait abnormalities in ET can temporally improve with ethanol intake [49, 50, 89]. In a study, the ingestion of ethanol to a mean blood level of 0.45% led to a transient improvement of ataxia in ET patients yet produced a worsening of gait parameters in controls [82].

The weight of emerging evidence is indicating that ET is also associated with a series of non-motor manifestations, including cognitive deficits [90–98], dementia [99–101], personality changes [102], depressive symptoms [103], possible mild olfactory dysfunction [104–106], and hearing impairment [107, 108].

Mild cognitive deficits, mainly in frontal-executive function and memory, have been reported to occur in ET patients in 9 studies [90–98], including a population-based case–control study of largely treatment-naive ET patients [95]; these studies indicate that a frontosubcortical-type dysfunction occurs in some ET patients. In one of these studies [95], ET patients were more likely to complain of forgetfulness than were controls, suggesting that these mild cognitive deficits are not completely subclinical and may affect HRQoL. Indeed, in a population-based study of ET in Spain, lower cognitive test scores were associated with more reported functional difficulty, indicating that lower cognitive test scores in ET, rather than being clinically inconsequential, seem to have a clinical–functional correlate [109].

An association between elderly-onset ET and prevalent dementia was found in the above-mentioned population-based study in Spain [99]. ET cases with tremor onset after age 65 years were 70% more likely to be demented than were controls (odds ratio = 1.70, p = 0.03), whereas ET cases with tremor onset ≤ age 65 years and controls were equally likely to develop incident dementia [101]. In a second population-based study of elders in New York, ET was also associated with both increased odds of prevalent dementia and increased risk of incident dementia [100], with ORs and RRs similar to those reported in the study in Spain. In both studies, the large majority of subjects with dementia received clinical diagnoses of Alzheimer disease (AD). Although additional studies are needed, these two studies suggest that the presence of dementia appears to be greater than expected for age (i.e. a disease-associated feature rather than an age-associated feature) and that there are links between ET and AD [99–101].

There is also an accumulating body of evidence documenting the links between ET and PD [110, 111]. Family studies have clearly shown the co-occurrence of the two diseases within some families as well as the presence of action tremor in a disproportionately large number of PD families [111, 112]. In addition, several modern postmortem studies have demonstrated the greater presence of brainstem Lewy bodies in ET cases than in controls [113, 114], raising the possibility that some ET cases have a form of Lewy body disease [113, 114]. The link between ET and PD has been formally quantified in a population-based study in Spain, which demonstrated that the risk of developing incident PD was 4.3 times higher in ET cases than in age-matched controls without ET [115].

Distinct definable personality traits might be present in some ET patients. In a cross-sectional study that used the Tridimensional Personality Questionnaire, ET patients had higher scores than did controls in the personality domain of harm avoidance, suggesting a personality with increased levels of pessimism, fearfulness, and shyness [103]. A study in Germany, which used a different method of assessing personality, also noted case–control differences in personality, with the ET patients showing more passivity than controls [34]. Further studies are needed. Aside from personality features,
depressive symptoms might be more prevalent in ET than in the rest of the population. In a population-based study, prevalent ET cases were twice more likely than controls to report depression and three times more likely to be taking antidepressant medications [103]. In prospective analyses, baseline self-reported depression (adjusted RR = 1.78, p = 0.018) was associated with incident ET. These prospective data suggest that the mood disorder in ET may be more than a secondary response to disease manifestations; this mood disorder may be a primary feature of the underlying disease [103] – as is the situation in both PD and Huntington disease.

Mild olfactory dysfunction has been detected in ET patients in some studies [104–106] but not in others [116]; when observed, this dysfunction is milder than that observed in patients with PD [117]. As in PD, this possible dysfunction does not correlate with disease duration or severity, suggesting that it occurs early in the disease process [104].

Finally, hearing impairment in ET has been reported in two case-control studies [107, 108]. Data from a tertiary referral center showed that ET was associated with both subjective and objective measures of hearing loss [107]. Along the same lines, in a population-based study, ET patients reported more hearing impairment than did matched-controls [108]. The basis for this possible hearing impairment is unknown. However, both central and peripheral nervous system mechanisms have been suggested [107, 108].

Epidemiology

Prevalence and incidence

ET is a global condition, affecting human beings in a variety of settings, ranging from the remote Eastern Highlands of Papua New Guinea to the urban area of Madrid, Spain [6, 118]. The prevalence of ET increases with advancing age [5–7]. In a study of a multiethnic community in northern Manhattan, New York, more than 1 in 5 individuals in the oldest age group (≥95 years of age) had this disease [5].

In general, there are no gender differences among the majority of studies [5–7]. In a review of more than 20 prevalence studies, estimates of crude prevalence varied substantially from 0.008% to 22% (i.e. an approximate 3,000-fold difference between the lowest and highest estimates) [9]. This wide range in estimates may be the result of a number of methodological issues [119]: (1) there is a broad variability of the surveyed populations in terms of age structure, ethnic origin and composition; (2) many studies have not defined populations in the remaining studies have defined it differently; (3) there is no test to validate a clinical diagnosis of ET and therefore final diagnoses depend on the experience of the study personnel; (4) kinetic tremor may be a feature of diverse disorders of the central and peripheral nervous systems [1–4]; (5) kinetic tremor of the arms may be found to some extent as a normal finding in the aging population [1–4]; and (6) referral bias from clinic-based and hospital record-based studies might provide low estimates of ET prevalence. In addition, a major limitation of many of the studies is the use of screening questionnaires rather than the direct examination of subjects to ascertain cases [7]. The range of prevalence estimates in subjects who are greater than 60 years of age is narrower (0.1–0.5%) if one only selects those studies that are population-based and that specify how they define ET [9]. How does the prevalence of ET compare with other neurologic disorders of later life? In a population-based study in central Spain (NEDICES), the prevalence of ET [4.8% (95% confidence interval [CI] = 4.2–5.4)] [6] was higher than the prevalence for all types of parkinsonism [2.2% (95% CI, 1.8–2.6)] [120] and similar to that of cerebrovascular disease, including stroke and transient ischemic attack [4.9% (95% CI 4.3–5.5)] [121]. However, it was slightly less than that of dementia [5.8 (95% CI 5.2–6.5)] [122].

The incidence of ET has been estimated in only two studies [8, 123]. A prospective, population-based study of individuals in Spain (the NEDICES study), who were aged 65 years or older, reported an adjusted incidence of ET of 616 per 100,000 person-years [8]. This incidence estimate was substantially higher than that reported using data from in the Rochester Epidemiology Project (incidence of 58.6 per 100,000 among those aged
60 to 69 years; 76.6 per 100,000 among those aged 70 to 79 years; and 84.3 per 100,000 among those ≥ 80 years) [123]. In the latter study [123], entry into the medical record system as an ET case would have required that the symptoms and signs be severe enough to be recognized by the patient and deemed important enough by the treating medical doctor to require a comment in the medical record [123], and this may have contributed to the lower estimate of incidence. In both studies [8, 123], the incidence increased with advancing age.

**Mortality**

Mortality in ET has not been well studied. In one longitudinal retrospective study that used the records linkage system at the Mayo Clinic, survival of ET patients was similar to that of a historical control group [123]. In that study, the mean age at diagnosis was 58 years, and the mean length of follow-up was 9.7 years; therefore, cases were not all followed into advanced age, when the risk of mortality in ET is likely to rise. By contrast, in a prospective, population-based study in Spain (the NEDICES study), which enrolled a contemporary rather than historical control group, the risk of mortality was slightly but significantly increased in ET cases (adjusted relative risk [RR] = 1.45, 95% CI = 1.01–2.08, p = 0.04) [124], suggesting that ET could be a disease of both increased morbidity and mortality. Deaths from pneumonia were more common in the ET cases than in the controls [124]. Additional prospective, population-based studies are needed.

**Risk factors and etiology**

Aging is the risk factor most consistently associated with an increased incidence and prevalence of ET [5–9]. However, there are no gender differences in most of the studies [5–7]. Little is known about racial differences in the prevalence of ET. In a classic study in the biracial population of Copiah county, Mississippi, prevalence ratios were similar between whites and African-Americans [125]. In a community-based survey in Manhattan, N.Y., the authors found a significant ethnic difference in the prevalence of ET with the prevalence among whites being the lowest [5]. Taking into account that that study [5] did not rely on a screening questionnaire, ethnic differences could exist, although this requires further investigation. The prevalence appeared to be low in the residents of Arabic villages in northern Israel [126]. Another study performed in Singapore, comparing Singaporean Chinese, Malays, and Indians, showed that the prevalence rate of ET was marginally higher in Indians than in Chinese [127]; no Malays with ET were found [127]. Although many kindreds with autosomal dominant inheritance of ET have been described, no ET genes have been identified to date [19]. Three susceptibility loci have been found, on chromosomes 2p22, 3q13, and 6p [128–131]. A genome-wide association study has revealed that the LINGO1 gene is associated with an increased risk for ET in European and American populations [132]. This has been also confirmed in a study in Asians [133]. LINGO1 has potent, negative regulatory influences on neuronal survival and is also important in regulating both central-nervous-system axon regeneration and oligodendrocyte maturation [132, 133].

Current data indicates that non-genetic (environmental) factors may also play an important role in disease etiology [134]. First, in twin studies, pairwise concordance in monozygotic twins was 60% [135] in one study and 77–93% in another study [136]. Second, more than 50% of ET patients report a negative family history [137]. One neurotoxin that has begun to emerge from epidemiological studies is harmane (1-methyl-9H-pyrido[3,4-b]indole) [138–141]. This is based on the published observation that blood harmane concentration was elevated in ET patients from the Neurological Institute of New York compared with control subjects (100 cases and 100 controls in initial sample – 2000–2002) [138] and 150 cases and 135 controls in a replicate sample – 2002–2007 [139]. Harmane is a neurotoxin that is present in the diet (especially in numerous meats such as chicken, beef, fish, and pork, yet also in many vegetables) and it is also produced endogenously; exogenous exposure is thought to be the main source of the body’s harmane [140, 142]. It is known that administration of harmane to a wide variety of laboratory animals produces severe
action tremor resembling ET [142]. Harmane is structurally similar to MPTP, a neurotoxin closely linked with PD [142]. Aside from harmane, blood lead has also been found to be modestly but significantly elevated in ET cases when compared with controls in separate studies in the United States and in Turkey [143, 144]. Lead is a neurotoxin that can cause cerebellar damage and tremor [143, 144].

Controlled, quantitative postmortem studies have demonstrated pathological changes, including Purkinje cell loss, in the cerebellum in ET [106, 107]. Ethanol is often used for symptomatic relief in ET [49, 50, 89]. However, ethanol is a well-established Purkinje cell toxin, resulting in Purkinje cell loss [145]. In a population-based study, higher levels of chronic ethanol consumption were associated with an increased risk of developing ET [146]. Further studies are required to explore whether higher consumption levels are a continued source of underlying cerebellar neurotoxicity in patients who already manifest this disease [146].

It has long been known that PD is inversely associated with smoking cigarettes [147]. Using a population-based, case-control design, cigarette smoking habit was assessed in 221 prevalent ET and 663 matched controls. Smokers were nearly half as likely to have ET as were never smokers (adjusted OR = 0.58, p = 0.004) [148]. In an incidence cohort from the same population, baseline, heavy cigarette smoking was also associated with a lower risk of incident ET (adjusted RR = 0.29, p = 0.03) [149].

The genetic and the non-genetic environmental hypotheses for ET might not be mutually exclusive; for instance, environmental factors might trigger the expression of underlying susceptibility genotypes or underlying susceptibility genotypes might increase the toxicity of environmental exposures. The identification of these environmental factors is important as it would open the way toward primary disease prevention through a reduction in exposure to these factors.

**Pathophysiology**

Clinical and neuroimaging data point to cerebellar involvement in ET, and the tremor of ET is thought to be mediated by a neuronal loop involving cerebello-thalamo-cortical pathways [1–4, 150–158].

A broad array of neuroimaging methods used in a growing number of studies, including functional magnetic resonance imaging studies [150], positron emission tomography [151], [1H] magnetic resonance spectroscopic imaging studies [152], diffusion tensor imaging studies [153], voxel-based morphometry studies [154, 156] and studies using other automated volumetric methods [155] now point to the presence not only of functional and metabolic abnormalities in the ET cerebellum, but of structural abnormalities in both the cerebellar gray and white matter as well.

Moreover, postmortem studies provide evidence of degenerative changes in the cerebellum in many ET cases [113, 114, 157–159], with a six-fold increase in Purkinje cell axonal swellings (torpedoes) (Figure 6.2) and an approximate 40% reduction in the number of Purkinje cells [113, 114, 157–159]. In a quantitative, controlled study comparing 33 ET cases to 21 controls, the mean number of Purkinje cells per 100x field was reduced in ET cases and there were also approximately 7 times as many torpedoes in ET cases [106]. Two cases also had degeneration of the dentate nucleus [113]. Other structural abnormalities in ET cases were Purkinje cell heterotopias and Purkinje cell...
dendrite swellings [113]. Eight (24.2%) of the 33 ET brains had Lewy bodies in the brainstem, mainly in the locus ceruleus, and normal cerebella [113]. Other reports have also noted an increase in brainstem Lewy body pathology in ET cases compared with controls [114] while some others have not [159], so the role of Lewy body pathology requires further study. In general, however, the pathological findings in brains from ET patients seem to be both heterogeneous and neurodegenerative [113, 114, 157–159]. As evidence of clinical heterogeneity and pathologic heterogeneity in ET emerges, this raises the question as to whether it will at some point be possible to reformulate this condition as a cluster of separable clinical-pathological entities, that is, a family of diseases — the essential tremors [160].

**Treatment**

**General considerations**

As with other chronic diseases, it is important to consider the psychological and social impact of the illness on patients. ET patients may be unable to continue full-time work, so financial problems may rise. Physicians should coordinate the help of other healthcare professionals to address these social and psychological issues. The impact of the disease on the patient’s family should also be taken into account. It may be useful for ET patients to bring their spouse or partner to a consultation, to help them better understand the disease and to discuss their difficulties and concerns.

Patient-centered associations may be of help in offering individual and group support, education, and advice. Through such interactions, patients may benefit in learning ways to cope with the many practical day-to-day difficulties that arise for those living with this disease.

There are physical and psychological measures as well as certain lifestyle changes that may be helpful in patients with mild ET. Application of weights to affected limbs may decrease tremor amplitude in some patients; for instance, strapping 1- to 2-pound weights to the wrist could improve hand stability. Furthermore, some patients may experience modest benefits from relaxation methods aimed at alleviating the anxiety or stress that may exacerbate tremor.

Lifestyle changes may be of benefit in some patients. These changes include restricting caffeine intake or other stimulants that may increase symptoms. The transient antitremor effects of ethanol are well known [49, 50, 89]. Ethanol binds to the GABA<sub>α</sub> receptor, thereby enhancing GABAergic neurotransmission [161, 162]. However, tremor can rebound after the effect of ethanol wears off [1–4, 49, 50, 89]. Ethanol should not be recommended as a maintenance therapy for patients who search for tremor reduction throughout the day, because of its known deleterious effects on general health as well as its potential deleterious effects as a Purkinje cell toxin [145].

No medication has been shown to provide a cure in ET patients. However, there are several treatments that can lessen tremor in some patients [1–4]. The issue is that such treatments for ET have side effects and it is important to carefully consider in each patient whether the benefits outweigh any side effects [1–4]. Of interest is that in a study, nearly one of every three ET patients who had been prescribed medication for tremor had discontinued pharmacotherapy [163]. This underscores the inadequacy of current pharmacotherapeutic options for this disorder [163].

Treatment should be initiated when the tremor begins to interfere with the patient’s ability to perform daily activities, or if the tremor is embarrassing to the patient [1–4]. Surgery is the final option for patients who have not responded adequately to medications [1–4]. As a general rule, the four most important rules for physicians when initiating treatment for ET are: (1) to “start low and go slow” in order to minimize adverse drug events and to maximize patient tolerance [1–4]; (2) to select each medication according to patients’ preferences and comorbidity. For instance, a benzodiazepine would be a good choice for ET patients who have comorbid anxiety disorder, a β-adrenergic-receptor antagonist in those patients with associated hypertension, and topiramate for patients with migraine or obesity [1–4]; (3) to gradually taper and withdraw a given medication if it is not useful at a dose that causes adverse effects; and (4) to add a second medication
if the benefit of the first medication is only partial. Some patients require only intermittent tremor reduction (for example, when attending a social event or engaged in a meeting). In these cases, propranolol (10–40 mg orally) approximately half an hour before the event may be of benefit [1–4].

**Pharmacological agents**

Table 6.1 shows the pharmacological agents that are used in the treatment of ET [164]. Propranolol and primidone, administered either as monotherapy or in combination, are the two first-line medications in the treatment of ET [32, 165–172]. Each of these is estimated to be effective in anywhere between 30 and 70% of patients [165]. Propranolol is a non-selective β-adrenoceptor antagonist, whose main action is probably peripheral β₂-receptor antagonism; propranolol may be used as initial therapy to treat limb tremors in ET [165, 166], and perhaps head tremor, although data for this last indication is limited [164]. The initial dosage is 10 mg propranolol, one to three times daily with titration in 10–20 mg increments to an upper limit of 320 mg/day [164, 165]. The dose range for children is less clear, but dosing for other indications, such as migraine, ranges from 1 to −3 mg/kg/day in divided doses [173]. The long-acting once-daily preparation is as effective as conventional propranolol [166]. Long-acting once-daily preparation, in capsules taken once daily in the morning or evening, may be preferred for maintenance [166].

Primidone, an anticonvulsant medication, has also been effective in placebo-controlled trials [32, 167–172]. Tolerability is a frequent problem and it

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**Table 6.1** Pharmacological agents for the treatment of essential tremor.

<table>
<thead>
<tr>
<th>Pharmacological agent</th>
<th>Dosage</th>
<th>Potential side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>60–320 mg/d</td>
<td>Reduced arterial pressure, reduced pulse rate, tachycardia, bradycardia, impotency, drowsiness, exertional dyspnoea, confusion, headache, dizziness</td>
</tr>
<tr>
<td>Long-acting propranolol</td>
<td>80–320 mg/d</td>
<td>Skin eruption, transient dizziness</td>
</tr>
<tr>
<td>Primidone</td>
<td>Up to 1,000 mg/d</td>
<td>Sedation, drowsiness, fatigue, nausea, giddiness, vomiting, ataxia, malaise, dizziness, unsteadiness, confusion, vertigo, acute toxic reaction</td>
</tr>
<tr>
<td>Nadolol</td>
<td>120–240 mg/d</td>
<td>None</td>
</tr>
<tr>
<td>Sotalol</td>
<td>75–200 mg/d</td>
<td>Decreased alertness</td>
</tr>
<tr>
<td>Atenolol</td>
<td>50–150 mg/d</td>
<td>Lightheadedness, nausea, cough, dry mouth, sleepiness</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>120 mg/d</td>
<td>Headache, heartburn, orthostatic hypotension</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>1,200–1,800 mg/d</td>
<td>Lethargy, fatigue, decreased libido, dizziness, nervousness, shortness of breath</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Up to 400 mg/d</td>
<td>Appetite suppression, weight loss, paraesthesias, anorexia, concentration difficulties</td>
</tr>
<tr>
<td>Levitiracetam</td>
<td>1000 mg/d</td>
<td>Behavioral side effects (from hostility to aggressive behaviour)</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>100–200 mg/d</td>
<td>Ataxia, dizziness, somnolence, agitation, anorexia</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>0.75–2.75 mg/d</td>
<td>Sedation, fatigue, potential for abuse</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>0.5–6 mg/d</td>
<td>Drowsiness</td>
</tr>
<tr>
<td>Clozapine</td>
<td>6–75 mg/d</td>
<td>Sedation, potential agranulocytosis (0.8% at one year)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>20 mg/d</td>
<td>Drowsiness, sedation, weight gain, diabetes</td>
</tr>
<tr>
<td>1-octanol</td>
<td>Up to 64 mg/kg</td>
<td>Unusual taste</td>
</tr>
<tr>
<td>Botulinum toxin A (hand tremor)</td>
<td>50–100 U</td>
<td>Hand/finger weakness, reduced grip strength, pain at injection site, stiffness, cramping, haematoma, paraesthesias</td>
</tr>
<tr>
<td>Botulinum toxin A (head tremor)</td>
<td>40–400 U</td>
<td>Neck weakness, post-injection pain</td>
</tr>
<tr>
<td>Botulinum toxin A (voice tremor)</td>
<td>0.6–15 U</td>
<td>Breathlessness, weak voice, swallowing difficulty</td>
</tr>
</tbody>
</table>

Adapted from Zesiewicz TA, Elble R, Louis ED, et al. [164].
is recommended that primidone be initiated with a dose of 12.5 mg/day, and increased gradually to doses of 500–1,000 mg/day as tolerated [32, 167–172]. Drowsiness and unsteadiness, the most common side effects, which sometimes require the withdrawal of the agent, may be seen in approximately 20% of patients [32, 167–172]. Propranolol and primidone seem to be equally efficacious [169]. Other medications may be used with varying efficacy in patients who do not achieve an adequate response with primidone and propranolol in ET (Table 6.1) [164]. Among these medications, other β-adrenoceptor antagonists such as nadolol (120–240 mg/day), sotalol (75–200 mg/day), and atenolol (50–150 mg/day), may have antitremor efficacy in ET patients [174, 175]. Nimodipine, a calcium channel blocker, may be useful to reduce tremor at 30 mg qid [176]. Gabapentin (1,200–1,800 mg/day), an anticonvulsant structurally similar to the GABA, resulted in significant reduction in tremor compared with placebo in two trials [177, 178]; however, a third study identified no difference between gabapentin and placebo [179]. Topiramate (up to 400 mg/day), another anticonvulsant medication that enhances GABA activity, may be useful in reducing tremor in ET [180, 181]. However, adverse effects, such as cognitive difficulty and paraesthesias, may reduce its potential use [182]. Levetiracetam, another anticonvulsant medication, at a single dose of 1,000 mg/day, was of benefit in reducing arm tremor in a double-blind placebo controlled trial [183], but not in another study [184]. Zonisamide (100–200 mg/day) may be useful for modest tremor reduction in some medically refractory ET patients [185], especially those with head tremor [186]. Other GABAergic medications, such as alprazolam (0.75–2.75 mg/day) [187] and clonazepam (0.5–6 mg/day) [188], may improve tremor. However, clonazepam was not useful in another study, and the dropout rate was as high as 40% due to adverse effects such as drowsiness [189]. Antipsychotic medications have also been tested in ET. Thus, clozapine, has been found to reduce tremor at doses of 6–75 mg/day, with a starting dose of 12.5 mg/d po or less, introducing approximately 1/8 of a 25 mg tab and increasing slowly [190, 191]. However, hematologic monitoring is necessary, since this drug is associated with agranulocytosis [192]. Olanzapine (20 mg/day), another atypical antipsychotic, significantly decreased tremor in one study [193]; however, side effects associated with this drug (substantial weight gain, development of dyslipidemia and type II diabetes mellitus) may limit its use [194]. Finally, 1-Octanol (an 8-C alcohol currently used as a food-flavoring agent) significantly reduced tremor in a randomized, placebo-controlled pilot trial of a single oral dose of 1 mg/kg [195]. Intramuscular botulinum toxin A injection may be used in those patients with wrist tremor who fail treatment with oral agents [196, 197]. However, our recommendation is only use botulinum toxin A when the main manifestation of ET is a simple wrist flexion-extension tremor (rather than tremor of the shoulder, elbow or fingers and rather than complex, multi-planar wrist tremors). On the other hand, existing data are insufficient to draw a conclusion on the use of intramuscular botulinum toxin A injection in the treatment of head and voice tremor [198–200]. In general, however, the benefits must be considered in conjunction with the common adverse effect of muscle weakness associated with intramuscular botulinum toxin A injection [196].

**Surgical treatment**

Advances in surgical interventions offer patients an alternative treatment modality when pharmacotherapy is inadequate. Surgical treatment for ET has been used since the early 1950s [201]. The optimal target was determined to be the ventralis intermedius (VIM) nucleus of the thalamus [201], since tremor is thought to be mediated by a neuronal loop involving cerebello-thalamo-cortical pathways [1–4]. Both thalamotomy and thalamic VIM nucleus deep brain stimulation (DBS) offer high rates of tremor reduction in the contralateral arm [202, 203]. In general, the magnitude of improvement from surgery is large, and patients’ disability scores improve dramatically [196, 197]. However, DBS has been shown to have fewer adverse effects [202, 203].
Stereotactic thalamotomy and gamma knife thalamotomy

Stereotactic thalamotomy has been demonstrated to provide long-term efficacy for medically intractable tremor in ET [202–206]. It is less expensive than DBS and no hardware remains in the body [196–200]. Although the efficacy of thalamotomy and thalamic DBS are similar [202, 203], thalamotomy is associated with a higher complication rate, including dysarthria, dysequilibrium, weakness, and cognitive deterioration [202–207]. Bilateral thalamotomy is usually avoided since it is associated with a higher risk of dysarthria and a risk of cerebral hemorrhage [204–207].

Gamma knife thalamotomy for ET is still under study; there is difficulty in targeting a defined area for lesioning because electrophysiologic guidance is not possible [208, 209]. However, recent studies suggest that gamma knife thalamotomy provides tremor relief that is similar to that provided by stereotactic thalamotomy or thalamic DBS, but it is safer than either of these alternatives and, in addition, long-term follow up indicates that relief of tremor is well maintained [208, 209].

Thalamic deep brain stimulation

Thalamic VIM nucleus DBS has replaced thalamotomy in the surgical treatment of parkinsonism and ET because it is reversible, adaptable, and well tolerated even by patients undergoing bilateral surgery [33, 210–213]. The main advantage of thalamic DBS is that it is adjustable and adverse effects from stimulation can be controlled by reducing stimulation. However, it is expensive, there is a foreign body implant, it is necessary to optimize parameters and there is hardware maintenance, including battery replacement [33, 210–213].

Conclusion

ET is one of the most common neurological disorders among adults. For many years, ET was viewed as a monosymptomatic condition, characterized only by a kinetic arm tremor, yet over the last 10 years, a panoply of previously unrecognized motor and non-motor features has emerged. In addition, emerging pathological studies are providing evidence that ET is likely to be a neurodegenerative disease or diseases. As with other progressive neurological disorders of later life (e.g. motor neuron disease and PD), ET might represent a family of related diseases that show heterogeneity at etiological, clinical and pathological levels. Although a small number of medications can provide partial relief from tremor, the pharmacological treatment of ET is not optimal and some patients with severe tremor undergo surgery, which is generally effective. It is necessary to continue the search for newer and better medications that result in greater tremor control and improve HRQoL.

References

Essential Tremor


CHAPTER 7
Other Tremors

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The definition, classification and diagnosis of tremor

The term tremor defines a rhythmic, oscillatory movement caused by alternating or synchronous contractions of antagonist muscles. It is the most common form of involuntary movement, but only a small proportion of patients with tremor look for medical attention.

Tremor has accompanied humanity from the very early beginnings. In the Ayurveda (the literature of the system of health used in India from 5000 to 3000 BC) tremor seemed to be defined by the term kampa. Also in Egypt were found hieroglyphs thought to mean “trembling.” References to tremor also appear in writings of Hippocrates (460 BC), Galen (2nd century), and Galileo (17th century) [1].

Tremors can be classified according to their phenomenology, distribution, frequency, and etiology, but in this chapter tremors are defined and classified following the consensus statement of the Movement Disorder Society on tremor [2].

Rest tremor is produced when the affected part is at rest, without voluntary muscle activation and fully supported against gravity. Rest tremor is the main feature of Parkinson’s disease (PD). In PD rest tremor amplitude increases with mental or motor activity (counting backwards, walking, and contra lateral hand movements) and decreases or disappears during initiation of voluntary activity. Rest tremor can reappear after few seconds when a position is maintained and then is termed re-emergent tremor [3]. Action tremor is that which appears with voluntary muscle contraction and can be postural, isometric and kinetic. Postural tremor is present when maintaining a posture against gravity. Isometric tremor appears with sustained muscle contraction against a rigid object, and can occur in isolation or accompanying other types of tremor. Kinetic tremor can appear during any voluntary movement. There is the simple kinetic tremor which appears during voluntary movements not target directed, and the intentional tremor which is triggered when the limb is reaching a target. Usually, the amplitude of intentional tremor increases when goal-directed movements are performed and has typical amplitude fluctuations. These types of tremor appear when cerebellum or its pathways are involved, and sometimes it is difficult to distinguish intentional tremor and ataxia. Task-specific kinetic tremor is defined as a kinetic tremor that increases or appears predominantly or exclusively during specific tasks, like primary writing tremor which occurs when writing. An example of task-specific tremor can be seen in Video 7.1, which shows tremor appearing in the right hand several seconds after holding a handbag, in a patient otherwise
asymptomatic. An unusual variant of kinetic tremor is position-specific tremor, which appears only in certain postures.

In this chapter, tremors other than essential tremor and psychogenic tremors that are described elsewhere in this book, will be reviewed.

**Enhanced physiological tremors**

Physiological tremor refers to the invisible mechanical vibration of a body parts present in every normal subject. It is usually apparent during action and while maintaining a posture, with an 8 to 12 Hz frequency. Enhanced physiologic tremor (EPT) is a visible, predominantly postural high frequency tremor occurring in absence of any neurological disease that can cause tremor.

This definition includes tremors of different causes, typically those elicited by endogenous or exogenous intoxications producing postural tremor. Mechanical and sometimes central oscillations cause physiological tremor which can be enhanced by emotional stress, fatigue, exercise, hypoglycemia, thyrotoxicosis, alcohol withdrawal, pheochromocytoma, hypothermia, and a number of different drugs.

Treatment of the cause of tremor enhancement is the main issue in EPT, but if such cause is not evident or eliminating it fails to suppress the tremor sufficiently a beta-blocker like propranolol can be recommended. Drug-induced tremor usually responds to beta-blockers like those induced by valproate or lithium; a partial response can be seen in some peripheral neuropathic tremors and in hyperthyroidism and stress-induced tremors.

**Tremor in Parkinson’s disease**

The typical parkinsonian tremor is a rest tremor. It is an asymmetric 3–4 Hz moderate amplitude tremor that usually involves the thumb (the rhythmic movement of this finger against the index finger is called “pill rolling”). It may involve other body parts, such as the forearm pronation/supination movements, the legs (adduction/abduction), and jaw. Head tremor is only rarely seen.

Rest tremor usually worsens with cognitive tasks and tremor of the hand is often brought out by walking.

Some patients with PD do not have tremor while in others tremor is the main symptom and dominates the clinical picture throughout the course of the entire illness. In some of these cases the rest of the motor symptomatology may remain relatively mild and are sometimes called “benign tremulous Parkinson’s disease.” They frequently have a slowly progressive course and a low risk of dementia.

PD patients can also present with postural tremor, defined as a 6–8 Hz moderate amplitude tremor that appears immediately on stretching out the arms and is usually asymmetrical. Some patients exhibit only this kind of tremor and so can be easily misdiagnosed as essential tremor patients. A low-amplitude and high-frequency (8–12 Hz) kinetic tremor is also present in many parkinsonian patients, and is frequently quite disturbing since it interferes with actions such as drinking or eating.

A fourth kind of tremor in PD, called re-emergent tremor, has been described. It consists of an asymmetric 3–4 Hz tremor that appears on stretching out the arms after a few seconds in this new position [3].

The exact origin of the parkinsonian tremors is still unknown and it is unclear whether intrinsic cellular oscillators versus network oscillators underlie the tremor [4].
Other Tremors

18F-fluorodopa PET striatal uptake does not necessarily correlate with tremor severity, suggesting that dopamine is not the only affected neurotransmitter and resting tremor is not always associated with striatal lesions. In PD, the severity of rest tremor has been found to correlate with a decrease in median raphe 5-HT1A receptor binding, as measured by 11C-WAY 100635 PET [5]. This observation suggests that midbrain tegmental rather than nigrostriatal pathology may be more relevant to the pathogenesis of parkinsonian rest tremor.

Antiparkinsonian medications and deep brain stimulation (DBS) are effective treatments for PD postural and rest tremor. Dopaminergic drugs such as L-dopa, dopamine agonists, MAO B Inhibitors, and amantadine are useful in the treatment of tremor [6–8]. Anticholinergic agents (said to have better effect on tremor than on akinetic–rigid symptoms) reduce the tremor but due to their side effects they are considered as second line treatment and not used for elderly patients. Another drug sometimes recommended for refractory rest tremor in PD is clozapine [9].

DBS of the ventral intermediate (VIM) thalamic nucleus was originally proposed as a treatment for tremor in PD [10] and indeed it is efficacious to reduce rest tremor amplitude in PD patients [11]. However, STN and GPi DBS are efficacious not only on tremor, but also on rigidity, bradykinesia, and postural instability, which makes these the preferred neurosurgical targets even in patients where tremor is the predominant symptom [12]. In a recent study comparing different DBS targets in PD there was a trend to a better outcome of motor signs, tremor included, in STN-DBS patients and fewer adverse events in the GPi-DBS group [13]. Occasionally PD patients have a rest tremor that responds poorly or only partially to levodopa. In such cases, even though the lack of levodopa response could be considered a contraindication for surgery, DBS can be recommended if the tremor is disabling [14]. A DAT scan is warranted in such patients, in order to confirm the diagnosis of PD, as a PD-like tremor, possibly related to hand dystonia, has been found to be a cause of Scans Without Evidence of Dopaminergic Deficit (SWEDDs – see below) [15].

Cerebellar tremor syndromes

The most common type of cerebellar tremor is intention tremor, a kinetic, goal-directed, action tremor. The term cerebellar tremor is frequently used as a synonym for intention tremor, although several clinical forms of tremor have been described in cerebellar disorders [16–17].

Intention tremor increases in severity as the extremity approaches its target. When tremor only occurs as the target is reached, it is known as terminal tremor. Classically the cerebellar tremor is elicited by a finger-to-nose and heel-to-shin test. This can be the only minimal sign of cerebellar dysfunction. In cerebellar diseases tremor can initially start with terminal tremor and, as the disease advances, occur during all action movements. Initially the extremities are affected but if it progresses it can involve axial structures. Onset as head tremor is rare.

Cerebellar tremor is usually considered as symptomatic tremor, and other signs of cerebellar pathology – such as abnormalities of gait, speech and ocular movements, alternate movement disturbances, and dysmetria – can be present.

Cerebellar intention tremor has an irregular frequency and amplitude and usually the oscillations are perpendicular to the direction of movement. Commonly the cerebellar tremor is described as 3–5 Hz frequency tremor, but the frequency is inversely proportional to limb inertia, and therefore depends on the part of the body affected. In the upper limbs kinetic tremor has a frequency of 3–8 Hz, and in lower limbs of 3 Hz. When present in the trunk causing a partial sway, the frequency is 2–4 Hz. In cerebellar disorders, postural tremor can also occur, affecting the head and also the limbs. If the action tremor is intense, rest tremor can be seen because the patient is unable to relax completely.

The diagnosis of cerebellar tremor can be done when the following conditions are fulfilled: Pure or dominant intention tremor, unilateral or bilateral; tremor frequency below 5 Hz (mostly below 4 Hz); and postural tremor possibly present but no rest tremor [2].

Another cerebellar tremor is titubation, a low-frequency oscillation of the trunk or the head. This
is usually caused by lesions of the cerebellum or its efferent/afferent pathways. As the amplitude often increases during the movement, it is a very disabling tremor [17].

Other postural and positional tremors are only considered to be cerebellar in origin if other cerebellar signs are present.

Cerebellar tremors are due to lesions of the lateral cerebellar nuclei, the superior cerebellar peduncle, or the pathways where they are involved. Classically, a lesion within a cerebellar hemisphere or nuclei leads to an action tremor on the ipsilateral side of the body. Midline cerebellar disease may cause tremor of both arms, the head, and the trunk.

Multiple sclerosis (MS) is the most common cause of the cerebellar tremor in young people and can contribute to worsen a disability. Other causes of cerebellar tremor include tumors and strokes, as well as cerebellar metabolic and neurodegenerative diseases.

There is no established treatment for cerebellar tremor. Since it is a common source of disability in MS, several medical and surgical treatments are described in patients with this condition with limited evidence of effectiveness. Isoniazide in high doses [18, 19], carbamazepine [20], propranolol [21], glutethimide [22], and ondansetron [23] have been reported to provide some relief. Most trials were of small population and of short duration. One patient with MS and bilateral arm tremor improved with intrathecal baclofen [24]. Oral cannabinoids in large randomized-controlled trials appear to be ineffective [25]. Tremor reduction can be obtained with stereotactic thalamotomy or, more recently, with thalamic deep brain stimulation. It remains unclear whether DBS in multiple sclerosis tremor is superior to thalamotomy and whether patients show an overall improvement in quality of life and activities of daily living since studies were small and information on the long-term functional outcome is scarce [26].

Physiotherapy, tremor-reducing orthoses, and limb cooling can achieve some functional improvement in tremor on MS [27].

One study described improvement in postural cerebellar tremor and dysphagia with vagus nerve stimulation of 3 patients with multiple sclerosis. The authors hypothesized that improvement occurs by stimulating the main brainstem visceral component of the vagus, and the nucleus tractus solitarius, which modulates central pattern generators linked to both olive complex pathway and swallowing [28].

**Dystonic tremor syndromes**

Dystonia is defined as involuntary, sustained, patterned, and often repetitive contractions of opposing muscles that cause abnormal postures, twisting movements, or both [29, 30]. Patients who clinically present rhythmic dystonic movements can be misdiagnosed as essential tremor or parkinsonian tremor rather than primary dystonia. A helpful clinical review has been done recently by Lalli et al. [31].

Dystonic tremor is defined clinically as an action (either postural or kinetic) tremor occurring in a body part which is affected by dystonia. It is a focal tremor, with irregular amplitudes and frequency, usually under 7 Hz, and is not seen during complete rest [2]. Dystonic tremor can occur both in primary and secondary dystonia. Dystonic tremor as a component of dystonia is more obvious when the patient voluntarily attempts to move in the direction opposite to the force of the dystonia. It is exacerbated by muscle contraction and tends to decrease in amplitude with sensory tricks, as in tremulous spasmodic torticollis or dystonic head tremor, which does not happen in essential tremor [32, 33]. Electromyographic recordings show that bursts of muscle contraction occurs in an unsynchronized activity of agonists and antagonists muscles with a variable amplitude (3–12 Hz) and duration (50–300 ms) [34]. These studies can be useful in differentiating dystonic tremor from essential tremor and also in conditions where tremor and dystonia are present. [35] Dystonic tremor may resemble myoclonus if accompanied by jerk-like movements, and is not unusual to find myoclonus in patients with dystonic tremor. In fact, when 45 patients with dystonia and tremor were studied with electromyography (EMG), 15 (33%) had EMG features consistent with myoclonus [36].
Video 7.2 Dystonic head tremor

Head tremor in a patient with mild torticollis and laterocollis, that improves with a sensory trick (touching of the chin).

http://bit.ly/ueqF7o

Video 7.2 illustrates a dystonic head tremor in a young woman with mild cervical dystonia. The tremor improves when the patient touches the chin (example of a “sensory trick”). *Tremor associated with dystonia* is defined as a postural tremor that appears in a body part not affected by dystonia in a dystonic patient. Its etiology remains unclear. About 25% of patients with cervical dystonia have upper limb postural tremor that is undistinguishable from enhanced physiological tremor or essential tremor [37]. Another study compared 11 patients with ET and 19 patients with cervical dystonia (9 “ET-like” and 10 dystonic arm tremors) and showed differences between both dystonic tremors and essential tremor. Moreover, they defined two subgroups of patients with cervical dystonia and arm tremor, one with a late and simultaneous onset of arm tremor and torticollis, and another with an early onset of arm tremor and later development of torticollis. These groups do not correspond to the currently proposed clinical subdivision of “dystonic tremor” and “tremor associated with dystonia” [35].

The main differences between rest parkinsonian tremor, essential tremor, and dystonic tremor can be described in Box 7.1.

Recently, in several randomized trials of dopaminergic medication in early Parkinson disease, 4% to 15% of patients had normal presynaptic nigrostriatal dopaminergic imaging. These cases have been labeled as SWEDDs [15]. Some of these patients have been described as exhibiting a form of dystonic tremor. The tremor in such cases involves mostly the hands, and these individuals have features suggestive of dystonia such as the presence of subtle hand dystonia, thumb extension tremor, lack of true bradykinesia, “flurries” or task/position-specific tremor, head tremor, and dystonic voice (Box 7.2) [38–40].

The lack of progression in these patients to develop features other than tremor and dystonia supports the diagnosis of a non-parkinsonian disorder, and the different outcome of SWEDDs to that of patients with true PD has been reported in several longitudinal studies [40–42].

Finally, tremor as an isolated finding is not uncommon in patients with a family history of dystonia, especially those with a known genetic mutation [43]. Such patients have been classified as having dystonia gene-associated tremor. In some cases, isolated tremor can be the initial manifestation of dystonia [44].

The exact physiopathology of the various dystonic tremors is unknown, but could be related to the same basal ganglia dysfunction observed in dystonia.
Box 7.2 Metabolic and toxic causes of tremor

<table>
<thead>
<tr>
<th>Metabolic diseases</th>
<th>Toxins</th>
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<tbody>
<tr>
<td>Hyperthyroidism</td>
<td>Nicotine</td>
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<tr>
<td>Hyperparathyroidism</td>
<td>Alcohol</td>
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<td>Hypoglycemia</td>
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<td>Hypomagnesemia</td>
<td>Lead</td>
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<tr>
<td>Hypocalcemia</td>
<td>Toluene</td>
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<tr>
<td>Vitamin B12 deficiency</td>
<td>Naphthalene</td>
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<tr>
<td>Hepatic encephalopathy</td>
<td>DDT</td>
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<tr>
<td>Kidney disturbances</td>
<td>Manganese</td>
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<td>Chronic hepatocerebral</td>
<td>Lindan</td>
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<td>degeneration</td>
<td>Arsenic</td>
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<tr>
<td>Eosinophilia myalgia</td>
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<td>syndrome</td>
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<td>Dioxins</td>
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Treatment with botulinum toxin can result in marked improvement of dystonic tremors [45, 46]. Good results have been described with deep brain stimulation of globus pallidus or ventrolateral thalamus in severe generalized dystonia [47]. Subthalamic deep brain stimulation was also beneficial in several cases of tremor and dystonia [48, 49]. Postural tremor associated with dystonia can respond to drugs used in essential tremor, such as beta-blockers or benzodiazepines, as well as botulinum toxin.

Holmes tremor

Gordon Holmes in 1904 published a series of 9 cases with an unusual combination of rest, postural, and kinetic tremors of the extremities and he suggested a lesion of red nucleus as the cause [50]. This unusual tremor has been also known as rubral tremor, midbrain tremor, thalamic tremor, myorysthnia, and Benedikt syndrome.

The key features of the tremor are the presence of rest tremor, an exacerbation by sustained posture, and a further amplification with movement. The tremor is usually accompanied by other neurological signs. A delay in development of tremor is one of the hallmarks of this clinical entity, usually from 4 weeks to 2 years after an initial insult. Stroke and trauma to the midbrain are the most common causes of Holmes tremor. Bithalamic infarction with no midbrain structural lesions has been described as a cause of Holmes tremor [51]. Infectious causes as brain tuberculomas [52], toxoplasmosis [53, 54], and neuroparacoccidiomycosis [55] affecting midbrain structures have been described. A case of HSV-1 cerebral pedunculitis as a cause of Holmes tremor has been reported [56].

Holmes tremor can be caused by midbrain neoplasms [57], can be part of paraneoplastic syndrome [58, 59], and has also been described after radiation therapy in the midbrain region [60].

Usually Holmes tremor results from lesions of the brainstem/cerebellum and thalamus, but lesions affecting pathways in other zones can cause the same clinical features. Pathological [61] and neuro-imaging with PET studies [62] have suggested that concomitant damage to the cerebellothalamic and nigrostriatal systems are needed to cause Holmes tremor [63]. It is now believed that Holmes tremor is most likely a result of the interruption of a combination of pathways in the midbrain tegmentum, namely rubro-cerebello-rubral loop, rubrospinal fibers, dopaminergic nigrostriatal fibers, and the serotonergic brainstem telencephalic fibers [62, 64].

The treatment of Holmes tremor is generally considered to be difficult, although spontaneous improvement may occur. Some patients had acceptable response to levodopa alone [62, 65] or in combination with dopaminergic drugs like cabergoline or ropinirole, clonazepam [66], carbamazepine [67], or anticholinergic drugs. Two reports suggest that levetiracetam can also be useful [68, 69].

Treatment of structural lesions responsible for the tremor may be of help. Heran et al., for example, reported a case of Holmes tremor that improved after the drainage of neuroepithelial cysts [70]. The treatment of infectious diseases is indicated in appropriate cases, but the resolution of underlying lesions may not correlate with improvement of the tremor.

Patients with longstanding tremor and stable medical illness may be considered for stereotactic
thalamotomy or thalamic stimulation in the nucleus ventralis intermedius, from which significant tremor improvement has been reported [71].

**Drug- and toxic-induced tremors**

Drug- and toxic-induced tremors can manifest all kind of different tremors, depending on the causative substance and the patient’s individual predisposition [72]. The list of drugs and toxins that induce or exacerbate tremors is growing each year. The most common presentation of drug-related tremor is an enhanced physiological tremor-like and postural-intentional tremor similar to essential tremor. Drugs causing tremor include sympathomimetics (bronchodilators), cardiovascular drugs (amiodarone, calcium-channel blockers), mood stabilizers (lithium), antiepileptic drugs (valproate, topiramate), or antidepressants (tricyclics and SSRI).

The patients shown in Video 7.4 illustrates an example of a drug-aggravated tremor. In this case the patient has idiopathic cranio-cervical dystonia and longstanding postural and head tremor that markedly worsens while taking citalopram. After the drug is withdrawn the tremor returns to its pretreatment level (Box 7.3).

Antidopaminergic agents like neuroleptics, and often vestibular sedatives (flunarizine) or prokinetic–antiemetic drugs (metoclopramide) can cause rest as well as other tremors. Other dopamine-depleting drugs that can cause tremor and parkinsonism are tetrabenazine, reserpine, and

**Video 7.4 Drug-related tremor in a patient with segmental dystonia**

Patient affected of cranio-cervical dystonia and mild head and arms postural tremor of 10 years’ duration. Tremor worsened markedly after starting citalopram (as shown in the video) and improved to “pre-citalopram” levels after its withdrawal (not shown).


**Box 7.3 Main drugs that can cause tremor**

- Antidopaminergic agents
  - Neuroleptics (haloperidol, risperidone)
  - Gastrointestinal prokinetics (metoclopramide, cimetidine)
  - Tetrabenazine
- Lithium
- Antidepressants (amitriptiline, SSRIs)
- Anticonvulsants: Valproate
- Antiarrhythmics: amiodarone, procainamide
- Bronchodilators (Salbutamol)
- Metixantines (teofiline, caffeine)
- Immunosuppressants (tacrolimus, ciclosporine, α-interferon)
- Drugs (ethanol, cocaine, MDMA, nicotine)
- Chemotherapy drugs (tamoxifen, citarabine, ifosfamide)
- Hormones: adrenaline/epinefrine, medroxiprogesterone
- Antibiotics: co-trimexazole (trimethoprim-sulfamethoxazole), amphotericin B

For additional information see Morgan and Sethi [71]
methyldopa. These drugs can induce rest tremor in drug-induced parkinsonism, rabbit syndrome when the tremor is involving mainly the lips, and tardive tremor. Tardive tremor is a rare tremor seen after the long-term intake of antidopaminergic drugs, and is mainly postural with a 3–5 Hz frequency, although rest and intentional tremor can be present. For these tremors tetrabenazine or clozapine can be useful [73]. Alcohol, known to suppress essential and other forms of tremor [74], can also induce tremor upon withdrawal following chronic ingestion. This alcohol withdrawal tremor might be a variant of the enhanced physiological tremor caused by anxiety or emotional stress, but it is reported that withdrawal tremor had a higher amplitude compared to patients with anxiety or stress-related tremors [75]. Chronic alcoholism results in cerebellar degeneration, where a 3 Hz leg tremor and upper extremity have been demonstrated [76]. Alcohol abuse alone or combined with hepatic encephalopathy can cause various types of tremor, asterixis, and cerebellar dysfunction. Alcohol withdrawal is occasionally complicated by transient basal ganglia dysfunction manifested by parkinsonism or chorea [77]. These syndromes are distinct from the movement disorders complicating acquired hepatolenticular degeneration occurring in some chronic alcoholics [78].

Smoking cigarettes and nicotine has been associated with increased tremor amplitude in normal individuals [79]. Caffeine has been reported that can induce a new onset of tremor or exacerbate a previously existing tremor [80]. Caffeine tremor effect was thought for a long time to result from its inhibition of phosphodiesterase, stimulation of catecholamine release and through its direct effect on muscle. In one survey, however, where doses of 150 and 450 mg/day of caffeine were given to subjects, no increase on tremor was shown if patients followed a normal diet. Only the association of caffeine and starving increased increased postural hand tremor [81]. Measuring tremor with an accelerometer after 375 mg of caffeine did not increase physiologic, essential tremor or parkinsonian tremor at 1, 2, or 3 hours after intake [82].

There are more than 850 neurotoxic chemicals found in workplaces, of which 65 are the most common [83] and the association of the potential tremor-inducing effect of some of these toxins has long been known. Chronic exposure to heavy metals, like mercury and lead, cause mainly postural tremor and ataxia; manganese exposure, instead, can result in a typical rest tremor and parkinsonism. Insecticides and herbicides, like kepone, DDT, dioxin and methylbromide, are known causes of tremor and other neurological disturbances (Box 7.4). Toluene is also a solvent by which chronic exposure causes postural tremor, besides visual impairment, nystagmus, and pyramidal signs [84]. The treatment in drug- and toxic-induced tremors is to avoid exposure to them and sometimes, if that is not enough, drugs for essential tremor can be useful. When tremor occurs in a reasonable time-frame following ingestion of a particular food or beverage, it is considered to be a food-induced tremor which can take the form of an enhanced physiological tremor, and can precipitate or increase essential tremor, cerebellar tremor, or tremor associated to peripheral neuropathy [85].

**Orthostatic tremor**

Orthostatic tremor (OT) is characterized by a subjective feeling of unsteadiness on standing with a rapid
103 tremor of the legs that disappears when walking or sitting. At this frequency, the tremor is best appreciated by the examiner placing his hands on the standing patient’s legs, whereas a noise like a helicopter can be heard by placing a stethoscope on the thighs. The diagnosis is based on electromyographical findings of a unique tremor frequency and high coherence between antagonistic and contralateral muscle groups. OT is generally considered an idiopathic disorder as brain imaging and other investigations are usually normal. Only rarely has OT been described in patients with pontine lesions [86], aqueductal stenosis, or relapsing polyneuropathy [87], cerebellar degeneration, or following head trauma. Orthostatic tremor-plus has been described when additional neurological features are found, like parkinsonism, tardive dyskinesias or RLS [88]. In PD there are two different types of orthostatic tremor that have been described. One type consists of a slow OT (range 4–7 Hz) that is thought to be related to a dopamine deficiency which improves with L-Dopa or a DA-agonist. A fast (13–18 Hz) OT that is not thought to be related to dopamine deficiency and improves with clonazepam has also been described [89–90]. A recent report describes a case of slow OT in a patient with multiple sclerosis with a lesion in the pedunculus cerebellaris medius with bad response to treatment [91].

Idiopathic OT is thought to be caused by a central oscillator which, based on the findings in secondary cases, would be located in the posterior fossa [88]. In primary cases, studies with H$_2$O-PET indicate involvement of the cerebellum, basal ganglia, and cortex [92]. There is no significant difference in $^{123}$I-FP-CIT SPECT findings between controls and patients with longstanding OT [93].

Clonazepam is the most used drug but obtains a partial response. Other antitremoric drugs such as propranolol or primidone have a little effect. In a recent double-blind placebo-controlled crossover study of 6 patients with gabapentin, a symptomatic benefit has been reported [94]. L-Dopa can improve OT associated with PD. Recent reports suggest that patients with severe OT can be successfully treated with bilateral or unilateral thalamic (VIM, ventralis intermedius nucleus) DBS [95–96].

**Palatal tremor**

Palatal tremor (PT), also referred to as palatal myoclonus, is characterized by rhythmic movements of the soft palate, usually vertical oscillations at 1–3 Hz. There are two forms of PT or palatal myoclonus, symptomatic (SPT) and essential (EPT), differing clinical and pathophysiologically. An objective ear click can be found mainly in essential palatal tremor whereas in symptomatic PT about a 30% of patients can present pendular nystagmus and in variable proportions ataxia and dysarthria.

In a series of 287 patients with PT, about a quarter of the cases were essential (tensor veli palatini contraction) whereas the rest were symptomatic (levator veli palatini contraction) due mostly to lesions in the triangle of Guillain and Mollaret (dentate nucleus, red nucleus and inferior olivary nucleus). The etiology in about 70% of cases is a vascular infarct [97–98].

MRI of the brainstem with proton density or T2-weighted images can show a hyperintense signal in the region of the inferior olive that can represent the hypertrophic degeneration of these structures found in the autopsy of patients with symptomatic palatal tremor. It is thought that the lesion of the dentatoo-olivary pathway causes the cells of the inferior olive to synchronize. This rhythm is then carried through the inferior cerebellar peduncle to the contralateral cerebellar hemisphere and, thus, interferes with physiological regulations producing the hyperkinesia of brainstem muscles.

Essential palatal tremor has no currently demonstrable cause, and no accompanying physical or radiological signs, and is almost certainly heterogeneous.

There are some studies that support a central origin, a mechanical/peripheral origin, a voluntary movement, and even a psychogenic disorder as responsible for this problem [99].

In some cases, injection of botulinum toxin into the tensor veli palatini can be useful to reduce the ear click. If there are associated abnormal eye movements, injection of botulinum toxin in these muscles can be useful too. In these last cases responses to clonazepam are described.
Task-specific tremors

Task-specific tremor is a rare type of tremor with unknown pathophysiology. The most studied task-specific tremor is primary writing tremor. In clinical practice there are other task-specific tremors, most of them in musicians or sportspeople who perform very precise repetitive motor tasks [100].

Primary writing tremor is defined as a writing difficulty caused by tremor triggered by active pronation of the forearm. It can be divided into a pure task-induced tremor (that appears only during writing; type A) and another tremor present not only during the writing action but also when the patient’s hand takes the position used in writing (positionally sensitive, type B) [101].

This tremor has a frequency between 5 and –7 Hz, appears with pronosupination of the hand, and is asymmetrical. Sometimes postural tremor or dystonia (“mirror dystonia”) in the contralateral hand or coexisting dystonia can be observed, suggesting a relationship between task-specific tremor and task-specific-dystonia [102]. In neurophysiological studies, alternating tremor in agonist and antagonists muscles or co-contraction of both muscles can be demonstrated, the latter again suggesting a relationship to dystonia [103].

In spite of being the most studied task-specific tremor, even today there is no unanimous opinion about the origin of primary writing tremor and it could be classified as a tremulous form of focal dystonia (writer’s cramp, WC), a form of essential tremor, or a different and primary disorder. Some studies point to these differences, such as Ljubisavljevic et al. who describe distinct changes in central inhibition in PWT compared to those previously reported on writer’s cramp [104]. These results differ from those seen in studies with PET, where the increased activation of premotor cortical and cerebellar areas coincide in PWT, WC, and ET [105, 106].

Propranolol and injections of botulinum toxin have been tested for this disease with generally mixed results. Some patients have a good response to physiotherapy and rehabilitation [107]. In severe cases, thalamotomy or thalamic stimulation might be an option [108–110].

Stroke-induced tremor

Strokes in midbrain, superior cerebellar peduncle, and cerebellum can be frequently followed by tremor, but in other locations are extremely uncommon. In a review of 62 cases of thalamic and subthalamic lesions no case of isolated tremor was found [111]. Isolated tremor secondary to stroke is very rare, and is usually associated with other neurological signs. Intention tremor with cerebellar signs and Holmes tremor are the types more frequently reported, but irregular, low-amplitude and high-frequency tremors – some associated with dystonia after thalamic lesions – have also been described [112]. Immediate onset after stroke has been described, with a better prognosis than late onset, but stroke-related tremor usually begins weeks to months after insult, with secondary neuronal changes probably being involved.

In the management of stroke-induced tremor the associated neurological signs must be considered. In general, in stroke-induced tremor pharmacological treatment is disappointing when there is a cerebellar component. A case with yes–yes head tremor after a right occipital and bilateral cerebellar stroke with response to botulinum toxin A has been reported [113].

Tremor in systemic disorders

Tremor is a well-known symptom of thyrotoxicosis, and is indistinguishable from enhanced physiological tremor clinically or by EMG. Moderate correlation between tremor intensity and thyroid hormone levels have been reported [114]. Treatment of thyrotoxicosis results in rapid improvement.

In hypothyroidism, tremor associated with cerebellar signs can be seen. Tremor is a common manifestation in Wilson disease, being the most frequent sign in several series, but it is not so common as the initial symptom. Postural type tremor is the most prevalent; it usually starts in one limb and may eventually spread to the whole body. It may vary from mild rest tremor in fingers to coarse tremor in all members, trunk, and cephalic segment. “Wing beating tremor” is one of the
Other Tremors

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characteristic symptoms of Wilson disease and consists of a proximal tremor of high amplitude, better seen when the patients stretch the arms. Lesions in dentato-rubro-thalamic tracts are probably involved in the genesis of this tremor (Box 7.5).

In a retrospective study at tertiary centers with HIV patients, a 2–3% incidence of clinically relevant movement disorders was reported [115]. Tremor in AIDS patients may be seen as part of parkinsonian syndrome or may occur as an isolated phenomenon. This typically occurs as a mild bilateral postural tremor, but often is symmetrical and may occur at rest. Tremor is common in patients with HIV-associated dementia, ranging from 5.5 to 44% of patients [116], but can also occur in early stages of HIV infection in the absence of a central nervous system disorder [117]. Holmes tremor has been described in AIDS patients as a result of opportunistic lesions in the midbrain, such as tuberculosis, toxoplasmosis, or lymphoma. Drug-induced tremor may be seen as part of parkinsonian syndrome due to antiemetic or neuroleptic drugs. Trimetoprim-sulfamethoxazole can cause rest tremor or bilateral high-frequency, low-amplitude postural and kinetic tremor [118]. In the management of isolated tremor or parkinsonism in HIV patients, recognition of possible opportunistic infections and drugs causing tremor is important, and it can improve with the treatment of the underlying conditions.

Highly active antiretroviral therapy (HAART) has been shown to be effective in the reduction of neurologic complications of HIV infection, and resolution of parkinsonism with normalization of CD4 count in an AIDS patient with HAART alone has been reported [119].

In certain autoimmune diseases tremor can be a neurological finding, like bilateral tremor in a patient with antiphospholipid syndrome secondary to systemic lupus erythematosus [120]. Tremor as an early manifestation of systemic lupus erythematosus that disappeared with corticosteroid treatment has also been reported.

Isolated tremor in paraneoplastic syndromes is not common, but there is a report of a patient who developed severe orthostatic tremor (OT) as the sole presenting anti-Hu paraneoplastic manifestation of small cell lung cancer (SCLC) [121]. Recently orolinguatal tremor as a presentation of anti-Hu paraneoplastic syndrome has been reported [122].

Other systemic diseases, causing liver dysfunction, like cirrhosis, hemochromatosis [123], and variegate phorphyria [124] have been described as causes of tremor. Metabolic disorders involving renal function or ions can also cause tremor.

**Post-traumatic tremor**

Tremor can be caused by traumatic lesion in several anatomic locations, from cerebral cortex, basal ganglia, thalamus, midbrain, and cerebellum to peripheral nerves. Other neurological findings are usually associated, but CT/MRI may not show such lesions which can occur at a cellular level.

In cases of minor head trauma post-traumatic tremor is generally transient and non-disabling, characterized like an enhanced physiologic or essential tremor [125]. In severe head injury, post-traumatic tremor is usually a delayed sequelae, and can appear a few days to months after injury. The most common form in these cases is a combination of kinetic and rest tremor or Holmes tremor [126].

Post-traumatic parkinsonism with rest tremor caused by repeated head trauma has been described, as in the “punch drunk” syndrome or pugilistic encephalopathy seen in boxers [127].

**Box 7.5 Metabolic disorders that can cause tremor**

- Hyperthyroidism
- Hyperparathyroidism
- Hypoglycemia
- Hyponatremia
- Hypomagnesemia
- Hypocalcemia
- Vitamin B12 deficiency
- Hepatic encephalopathy
- Kidney disturbances
- Chronic hepatocerebral degeneration
- Eosinophilia myalgia syndrome

For additional information see Morganand Sethi [71]
Tremor resulting from peripheral nerve injuries is rare, and is usually associated with dystonia or reflex sympathetic dystrophy (RSD). In a series of RSD, a distal tremor with a 7.2 Hz frequency was observed that disappeared when RSD was treated [128]. Also tremor of the 4th and 5th fingers secondary to ulnar nerve entrapment in Guyon’s canal has been reported, with disappearance after surgery in a typist subjected to repeated hand movement [129].

The mechanisms underlying post-traumatic tremor are not entirely known, but functional changes in afferent neuronal input to the spinal cord and secondary affection of higher brainstem and subcortical centers are probably involved [130].

Midbrain lesions are an identified hallmark of diffuse axonal injury, a frequent finding in rapid deceleration trauma. Initial presentation of diffuse axonal injury is generalized brain edema, and in a series of severe head injuries the presence of kinetic tremor correlated to the presence of brain edema on initial CT [126].

Tremor in post-traumatic parkinsonism stems from presumed midbrain injury as a result of shearing forces produced by repeated rotational impacts of the head [131].

Spontaneous remission of post-traumatic head injury tremor is possible, resolving within 1 year after onset [132]. In a series with a follow-up of 3.9 years after severe head injury, over half of the patients recovered spontaneously from tremor [126].

Whenever and wherever possible, treatment of the cause is often beneficial, like in compression neuropathy and reflex sympathetic dystrophy. If no obvious cause besides a previous traumatism can be found, or other neurological conditions are associated, pharmacological therapies are less beneficial. Clonazepam, carbamazepine, levodopa, propranolol alone or in combination with valproic acid can be tried. Botulinum toxin injections may be helpful to relieve the tremor temporarily, but the secondary weakness of arm muscles may limit the usefulness of this treatment.

Thalamotomy and, lately, thalamic deep brain stimulation can be useful in severe post-traumatic tremor [133, 134].

**Neuropathic tremor**

Neuropathic tremor refers to tremor occurring in association with peripheral neuropathies. Most extensively documented is the tremor occurring in immune-mediated demyelinating and in hereditary peripheral neuropathies, which are the most frequent neuropathic tremors.

In some patients with Guillain–Barré syndrome, specially the rare relapsing form [135, 136], and also in chronic inflammatory demyelinating polyneuropathy (CIDP), tremor has been described [137]. Tremor in CIDP may appear during a relapse and disappear during remission, and can subside with immunomodulating treatment [137].

In Charcot-Marie-Tooth disease, the presence of tremor is known as Rousse-Lévy syndrome and is currently included in the hereditary motor sensory neuropathy (HMSN) type I. In HMSN I tremor is present in 40%, and consists of a postural tremor with rest component but without other Parkinsonism features. It involves mostly the hands, and response to alcohol can be seen [138].

Another neuropathy associated with tremor is the demyelinating neuropathy associated with monoclonal protein, usually IgM. This monoclonal protein typically represents the monoclonal gammopathy of undetermined significance (MGUS). This entity is also known as CIDP-MGUS, IgM neuropathy, or antiyel associated glycoprotein (MAG) neuropathy. Its clinical features are: male predominance, older age of onset, slow progression, predominantly sensory manifestations like sensory ataxia, and poor response to immunomodulating therapies [139]. Upper extremity tremor occurs in 40–90% of patients with IgM demyelinating polineuropathy, and it is mainly a mild postural tremor more distal than proximal, with a frequency of 3–6 Hz. Tremor severity has no relationship to the severity of motor or sensory signs [137, 140].

Tremor may also occur in certain forms of inherited motor neuron disease such as spinal muscular atrophy and X-linked bulbo-spa tial atrophy (Kennedy disease). In Kennedy disease more than 80% of patients had postural tremor [141]. Hypoesthesia, proximal weakness, gynecomastia, and facial/tongue fasciculations can help to the
diagnosis of the last one. Tremor can be seen in peripheral neuropathies associated with diabetes mellitus, uremia, and treatment with amiodarone. Peripheral neuropathies cause slow nerve conduction which increases the delay of a stretch reflex response, leading to enhancement of the tremor. A central component can also be involved in the pathophysiology of tremor associated with peripheral neuropathy, despite normal anatomical neuroimaging. Bain et al. suggested that tremor in patients with IgM paraproteinaemic neuropathy is due to a specific cerebellar functional disturbance caused by the delayed and distorted afferent input rather than to absence of sensory input [142].

Neuropathic tremor is often mild but if bothersome or interferes with activities, therapies such as propranolol or primidone, used for essential tremor, can be an option. Tremor in CIDP and also in IgM demyelinating neuropathy does not respond to immunomodulating therapies and modest improvement from propranolol and clonazepam have been described [137, 142]. Two case reports suggest that pregabaline could be useful to improve tremor in both neuropathies, IgM neuropathy, and CIDP [143, 144].

In few selected cases of severe neuropathic tremor, a beneficial effect of deep brain stimulation of the ventral intermediate thalamic nucleus has been described [145–147].

References

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PART 3
Dystonia Syndromes
CHAPTER 8
Primary Dystonias

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Historical background

Dystonia was one of the last hyperkinetic disorders to be recognized: the name derives etymologically from a supposed alteration of muscle tone. The term was coined in 1911 by Oppenheim, who observed that muscle tone is “hypotonic but also characterized by hypertonia and active contractures, which are especially induced by voluntary movements during standing and walking” [1]. He first stated that dystonia was an organic disease and enriched the clinical observation with some characteristic signs: twisted postures of the limbs and trunk associated with muscle spasms, bizarre alterations in gait, with buckle, bend, and twist of the trunk, rapid jerking and sometimes rhythmic movements, tendency of symptoms to progress until the appearance of fixed postural deformity. He is thought to have observed cases of DYT1 dystonia, as he described the progressive limb and axial involvement in the affected patients.

The hereditary nature of this disorder was mentioned by Flatau and Sterling [2], who also proposed use of the expression “progressive torsion spasm” as they believed that the alteration in muscle tone was not the most characteristic clinical sign of this condition.

In the early sixties Denny-Brown identified dystonia as a basal ganglia disease and considered it “a disturbance of attitude,” which began with instability of posture, “with a tendency to patterned attitudes that at first were labile and gradually became more fixed” [3]. He described two fundamental patterns: one with flexed arms and extended lower limbs, which he called “hemiplegic dystonia” and was considered to be related to putaminal lesions; the other with general flexion, which was associated with damage to the globus pallidum. Following these observations, the term dystonia has also been used to encompass postural abnormalities observed in spastic paralysis or fixed postural abnormalities [3].

The phenomenology of dystonia coincided with the generalised phenotype for many decades, until Marsden and Harrison used the term “torsion dystonia” to describe “a syndrome characterized by dystonic movements and typical posture, regardless of aetiology and related neuropathology” [4]. In June 1975 an international conference chaired by Stanley Fahn in New York City laid the way to the modern era and recognized the clinical features of focal dystonias [5]. David Marsden’s intuition then provided the intellectual glue for lumping together focal dystonia entities that were previously considered independent nosologic forms (e.g. blepharospasm, torticollis, “spastic” dysphonia, and writer’s cramp) [4, 6–9]. In 1984, an ad hoc committee of the Dystonia Medical Research Foundation documented the occurrence in all forms of dystonia “of sustained muscle contractions, frequently causing twist-
ing and repetitive movements, or abnormal postures* [10]; later it was recognized that the association of slow tonic posturing with faster (phasic) movements (sometimes resembling tremor) is the clinical hallmark of this movement disorder [10–12].

**Classification**

The classification of dystonia syndromes has changed over time. Fahn and Eldridge [5] first distinguished primary dystonia (with or without hereditary pattern), secondary dystonia (with other hereditary neurological syndromes or due to known environmental cause), and psychological forms of dystonia. Later, Fahn, Marsden, and Calne proposed a classification of dystonia based on three axes describing, for each patient, age at disease onset (early vs. adult), distribution of involved body sites (from focal to generalized), and etiology (differentiating idiopathic dystonia syndromes, sporadic or familial, from symptomatic ones) [10, 11]. The first two axes remained unchanged until today, whereas the etiological classification was expanded to include four subgroups of dystonia syndromes: primary, dystonia-plus (i.e. dystonia with parkinsonism or myoclonic jerks), secondary, and heredodegenerative [13].

The recently published European dystonia Guidelines [14] retain the three axes (Box 8.1) and refine the etiological axis distinguishing primary (or idiopathic) dystonia syndromes, heredodegenerative (where dystonia is a feature of a genetic

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**Box 8.1 Classification of dystonia based on three axes.**

**By etiology**

- **Primary pure dystonia**: dystonia is the only clinical sign (apart from tremor) and there is no identifiable exogenous cause or other inherited or degenerative disease. Examples are DYT1 and DYT6 dystonias.

- **Primary dystonia-plus**: dystonia is a prominent sign, but is associated with another movement disorder, for example myoclonus or parkinsonism. There is no evidence of neurodegeneration. For example, DOPA-responsive dystonia (DYT5) and myoclonus-dystonia (DYT11) belong to this category.

- **Primary paroxysmal**: dystonia occurs in brief episodes with normalcy in between. These disorders are classified as idiopathic (often familial although sporadic cases also occur) and symptomatic due to a variety of causes. Three main forms are known depending on the triggering factor. In paroxysmal kinesigenic dyskinesia (PKD; DYT9) attacks are induced by sudden movement; in paroxysmal exercise induced dystonia (PED) by exercise such as walking or swimming, and in the non-kinesigenic form (PNKD; DYT8) by alcohol, coffee, tea, etc. A complicated familial form with PNKD and spasticity (DYT10) has also been described.

- **Heredodegenerative**: dystonia is a feature, among other neurological signs, of a heredodegenerative disorders. Example: Wilson disease.

- **Secondary**: dystonia is a symptom of an identified neurological condition, such as a focal brain lesion, exposure to drugs or chemicals. Examples: dystonia due to a brain tumour, off-period dystonia in Parkinson disease.

**By age at onset**

- **Early onset** (variably defined as ≤20–30 years): usually starts in a leg or arm and frequently progresses to involve other limbs and the trunk.

- **Late onset**: usually starts in the neck (including the larynx), the cranial muscles or one arm. Tends to remain localised with restricted progression to adjacent muscles.

**By distribution**

- **Focal**: single body region (e.g. writer’s cramp, blepharospasm)

- **Segmental**: contiguous body regions (e.g. cranial and cervical, cervical and upper limb)

- **Multifocal**: non-contiguous body regions (e.g. upper and lower limb, cranial and upper limb)

- **Generalised**: both legs and at least one other body region (usually one or both arms)

- **Hemidystonia**: half of the body (usually secondary to a structural lesion in the contralateral basal ganglia)

Source: Albanese et al. [14].
disorder characterized by neurodegeneration), and secondary (or symptomatic) syndromes. Based on the phenotype, primary dystonias are further subdivided into primary pure (with dystonia only), primary plus (with other associated movement disorders) and primary paroxysmal forms (characterized by intermittent symptoms). Age at onset defines early-onset forms (variably defined as starting before 20–30 years), which usually start in a leg or arm and frequently progress to involve other limbs and the trunk, and adult-onset forms, which usually start in the neck (including the larynx), the cranial muscles or one arm and present limited progression to adjacent muscles. The distribution axis defines forms as: focal (if a single body region is affected), segmental (if contiguous body regions are affected), multifocal (if non-contiguous body regions are affected), and generalized (if dystonia is present in both legs and at least one other body region).

**Epidemiology**

The prevalence of primary dystonia is difficult to ascertain. The estimates range from 2 to 50 cases per million, for early-onset primary dystonia, and from 30 to 7,320 cases per million for late-onset dystonia. On the basis of the best available prevalence studies, primary dystonia may be 11.1 per 100,000 for early-onset cases in Ashkenazi Jews from New York area, 60 per 100,000 for late-onset cases in Northern England, and 300 per 100,000 for late-onset cases in the Italian population over age 50 [15].

The true prevalence of dystonia is probably underestimated due to a number of reasons. Diagnostic uncertainties and the occurrence of mild phenotypes (so-called formes frustes) [16] lead patients with mild symptoms of dystonia, such as writer’s cramp, not to seek medical advice. Another related explanation is the delay of the clinical diagnosis, which often requires expert evaluation to be appreciated. Conditions that are more common or better acknowledged than dystonia include other movement disorders (such as Parkinson’s disease, essential tremor, myoclonus, tics, psychogenic forms) or other conditions, such as headache or scoliosis [17].

**Phenomenology of primary dystonia**

**Cardinal features**

Following David Marsden’s seminal observation [4], it is commonly accepted that dystonia encompasses a combination of movements and postures to generate sustained muscle contractions, repetitive twisting movements, and abnormal postures (torsion dystonia). Dystonic postures can precede the occurrence of dystonic movements and in rare cases can persist without appearance of the latter (so-called fixed dystonia) [12]. Dystonic movements have specific features that can be recognized by clinical examination: speed of contractions may be slow or rapid, but at the peak of movement it is sustained; movements almost always have a consistent directional or posture-assuming character. Dystonic movements and postures are commonly aggravated during voluntary motion and in milder forms they may only be present with specific voluntary actions (task-specific dystonia).

Dystonic movements may be regular, appearing as tremor (so-called dystonic tremor [18]). When fast and jerky, they may resemble myoclonus. Dystonic tremor may precede clear abnormal posturing thus raising doubts about the actual diagnosis. A tremor similar to essential tremor may occur in dystonia and can be mistaken for non-dystonic tremor, particularly when isolated [17].

The diagnosis of dystonia can be missed or delayed in a number of patients with task- and position-specific tremors, particularly primary writing tremor, occupational tremors, or isolated voice tremor, as typical features of dystonia may develop only many years after onset. Head or voice tremors observed in tremulous forms of cervical dystonia can be very hard to distinguish from essential tremor. In contrast to essential tremor involving the head, dystonic head tremor tends to be more irregular, with directional preponderance, often associated with a null point – a position of the head.
in which the tremor ceases. In some cases, family
history of essential tremor or dystonia may help
with the final diagnosis.

**Associated features**

Dystonia has some unique activation/deactiva-
tion features that can be recognized if appropriatelooked for and serve as a basis for the diagnosis:
gestes antagonistes (or sensory tricks), mirroring,
and overflow. Criteria for identifying these
features, when present, have been published
recently [16].

Gestes antagonistes have been described in
patients with different forms of focal dystonia, who
reduce or even abolish dystonic postures while
making some specific voluntary movements. For
example: cranial dystonia patients can apply
pressure on the eyebrows or touch the skin at the
side of the eyes to relief blepharospasm; cervical
dystonia patients can place a hand on the side of
the face, the chin, or the back of the head or touch
these areas with one or more fingers to reduce
neck contractions; writer’s cramp patients can
touch the affected arm with the opposite hand.
Contrasting with the cardinal signs of dystonia,
gestes are never forceful, but natural and elegant
[16]. The mechanism of action of the gestes is
debated; their action is not associated with a
mechanical correction by counter-pressure [19]. It
has been observed that gestes do not improve non-
dystonic essential head tremor, are uncommon in
early post-traumatic dystonia, and have atypical
phenomenology in patients with psychogenic
dystonia [16]. The geste efficacy may diminish as
the disease progresses.

Overflow and mirroring are two related clinical
phenomena that reveal or enhance dystonia and
prove particularly helpful in cases with mild or
inconstant phenomenology. Overflow is an
unintentional contraction of muscles not primarily
involved by dystonia, and is usually located in
neighboring body sites, which are activated at the
peak of dystonic movements [20]. For example, a
patient with cervical dystonia may have
involvement of the unaffected upper limb by the
occasional spread of dystonia activity. Mirror
dystonia occurs on the affected body side when a

specific task is performed by the homologous
opposite unaffected body part. Usually there are
specific tasks that elicit mirror dystonia; they must
be identified in order to appreciate this feature. For
example, patients with writer’s cramp may present
mirror dystonia of the dominant hand while writing
with the non-dominant unaffected hand [21].
Overflow and mirroring are considered a clinical
expression of lack of inhibition occurring in
dystonia [16].

**Diagnostic algorithm**

A diagnostic algorithm for identifying the features
of primary dystonia has been proposed [16].
According to this schema when all the cardinal
features of dystonia are observed, the clinical
diagnosis is plainly achieved by physical
examination. Otherwise, at least two associated
features must be observed to reach a clinical
diagnosis. EMG observation of features associated
with dystonia is helpful when physical observation
is insufficient (Figure 8.1).

Dystonia can occur at rest, during voluntary
movement or in paroxysmal form following a spe-
cific trigger. These features must be appreciated by
expert clinical examination. To make the clinical
picture more complex, dystonia features can be
combined or intermixed with other movement
disorders in dystonia plus syndromes.
Etiology

It has been shown that both genetic predisposition and environmental factors play a significant role in the etiology of primary dystonia syndromes. An appropriate classification takes into account these two known factors. Genetic defects are known only for a minority of cases presenting with pure dystonia [22]. By contrast, dystonia plus syndromes are by far more precisely classified (Table 8.1). We describe here the most common forms of primary dystonia, without mentioning paroxysmal dystonia syndromes, which are dealt with in Chapter 23.

Genetically classified primary dystonia syndromes

DYT1 dystonia

A common cause of generalized primary pure dystonia is the GAG deletion in the DYT1 gene encoding the protein Torsin A [23]. The disease was originally described among Ashkenazi Jews with a relatively homogeneous phenotype characterized by early limb-onset generalized dystonia [24]. It was later reported that, particularly in Caucasian patients [25], the DYT1 phenotype is broader than originally thought. The “classical” DYT1 phenotype is characterized by early onset in a limb, generalization without spread to the craniocervical region [25]. In a series of patients with early-onset primary dystonia (PD) it has been confirmed that dystonia never starts in the craniocervical region in DYT1 carriers, although craniocervical sites can be involved at later stages [26]. It is remarkable that DYT1 patients who develop severe generalized involvement may carry out their daily activities with significant adaptation in many cases. Extreme cases have also been observed, ranging from asymptomatic status to...
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craniocervical involvement or even status dystonicus [27–30]. Due to phenotypic heterogeneity, it is not possible to identify DYT1 patients based only on their clinical presentation. Five other phenotypes have been described in addition to the classical limb-onset presentation [26, 31]: generalized dystonia with cranial-cervical involvement [32]; generalized myoclonic-dystonia, with a phenotype more severe than that observed in DYT11 myoclonus-dystonia [33]; focal dystonia with slow progression and occasional later spread even several years after onset [34, 35]; late-onset DYT1 forms [27]; rarer cases of DYT1 dystonia with non-limb presentation, that may present cervical, laryngeal, or trunk onset [36, 37].

The gene penetrance is estimated to be around 30% [23, 29], meaning that a high proportion of mutation carriers is asymptomatic. This has

Table 8.1 DYT genotypes associated with dystonias. The gene name is indicated when known; otherwise, the locus is reported.

<table>
<thead>
<tr>
<th>Disease (OMIM)</th>
<th>Map position</th>
<th>Gene</th>
<th>Transmission</th>
<th>Phenotype</th>
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<td><strong>Pure dystonia</strong></td>
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<td></td>
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<tr>
<td>DYT1 (128100)</td>
<td>9q34</td>
<td>TOR1A</td>
<td>AD</td>
<td>Generalized early-limb onset dystonia</td>
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<td>Early-onset generalized dystonia with prominent cranial-cervical involvement</td>
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<td></td>
<td>AD</td>
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<td>8p11.21</td>
<td>THAP1</td>
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<td>AD</td>
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</tbody>
</table>

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; ATP1A3, ATPase, Na+/K+ transporting; GCH1, guanosine triphosphate cyclohydrolase 1, MR1, Myofibrillogenesis regulator 1, PRKRA, double-stranded RNA-activated protein kinase; SGCE, e-sarcoglycan; SLC2A1, Solute carrier family 2 (facilitated glucose transporter), member 1, SPR, Sepiapterin reductase; TAF1, TATA boxing-binding protein associated factor; TH, Tyrosine hydroxylase; THAP1, Thanatos-associated protein; TOR1A, torsin A gene.
prompted the search for potential endophenotypes to help to identify manifesting as well as in non-manifesting DYT1 carriers. Two potential endophenotypes are of interest: reduction of striatal D2 receptor binding shown by PET studies [38], and higher tactile and visuotactile temporal discrimination thresholds or temporal order judgments [39]. These findings need to be confirmed and integrated into a coherent diagnostic protocol.

The DYT1 gene is named *TOR1A* [23]. The disease is caused by a unique mutation that deletes one of a pair of GAG triplets from the carboxyl terminal in Torsin A. This unique DYT1 haplotype originally found in Ashkenazi Jews has also been observed in non-Jewish patients [40] and represents the only pathogenic disease mutation identified in *TOR1A*. An 18-bp deletion has also been found in families with primary dystonia and myoclonus, but its pathogenicity has not been ascertained [41]. Torsin A is a heat-shock and ATP-binding protein and a member of the AAA+ superfamily. The normal protein is widely distributed in many species and is located in the endoplasmic reticulum [42, 43]. Immunohistochemical studies have revealed that Torsin A is a constituent of Lewy bodies [44].

**DYT6 dystonia**

The DYT6 locus was originally mapped in two Mennonite families with primary pure dystonia and autosomal dominant transmission [45]. Mutations in the *THAP1* (Thanatos-associated-domain containing, apoptosis-associated protein 1) gene have been found responsible for DYT6 dystonia with an estimated penetrance of approximately 60% [46]. In American series *THAP1* heterozygous mutations were identified in 9 out of 36 (25%) DYT1-negative families with early-onset non-focal PD [47]. European series reported a lower mutation frequency with an overall prevalence of 1.0–2.5% in PD cohorts from all over Europe [48, 49]. The spectrum of *THAP1* mutations includes missense, nonsense, and frame-shift mutations of all three exons.

*THAP1* is a member of the family of sequence-specific DNA-binding factors. Its function is still poorly understood, recent studies provided evidence that *THAP1* and *TOR1A* are interconnected in a common pathway [50], because wild type *THAP1* represses the expression of *TOR1A* [51].

*THAP1*-associated DYT6 dystonia should be considered in patients with early-onset DYT1-negative generalized or segmental dystonia, particularly if cranial involvement is prominent. On average, age at onset is higher than in DYT1 dystonia, and the topographic distribution differs between the two forms. The prevalence of DYT6 dystonia is still undetermined.

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**Video 8.2 Primary dystonia: DYT1 phenotype**

This 45-year-old patient has DYT1 dystonia. Dystonia started at age 13 in the right lower limb and impaired walking. The disease progressed with dystonia occurring also at rest spreading to generalization. The video shows rest-type tremor and torsional lower limb instability when standing. Gait is grossly abnormal with both legs affected by dystonia. Severe torsional posturing is visible in the right lower limb. A right striatal toe with mild dystonic movements of the left foot is present at rest. Dystonia during handwriting is also shown.

Chapter 8

DYT5: dopa-responsive dystonia

Dopa-responsive dystonia (DRD) is a neurometabolic disorder classified among the dystonia plus syndromes. Onset is infantile in most cases and two different modes of inheritance have been described. In the autosomal-dominant form (DYT5), heterozygous mutations of GTP-cyclohydrolase I (GCH1) cause DRD with reduced penetrance and excellent and sustained response to levodopa. Autosomal-recessive forms (AR-DRD) are caused by homozygous or compound heterozygous mutations of the tyrosine hydroxylase (TH) or the sepiapterin reductase (SPR) gene.

As this is a treatable condition, a particular effort should be made to establish the correct diagnosis early. The most common form is autosomal-dominant DYT5 DRD (also called Segawa’s disease). The classical phenotype presents with walking difficulties before 20 years, and progression to segmental or generalized dystonia, sometimes with additional parkinsonian features and sustained response to levodopa [52]. Parkinsonian features consist of rigidity and rapidly-induced fatigue with repetitive motor tasks, which commonly coexist with dystonia, and increased tendon jerks in the affected limb. By 10–15 years after onset, dystonia gradually spreads to involve all the limbs. The resulting generalized picture typically remains asymmetric and involves the four limbs, being more severe in the legs [53]. One important feature of DRD is the occurrence of diurnal fluctuations: patients are less affected in the morning and more disabled in the evening [54].

Three additional categories of GCH1-linked DRD have been recognized [52, 55]: cases with young-onset (<20 years) and episodic dystonia, toe walking and progressive scoliosis; compound heterozygous GCH1 mutation carriers who develop young-onset severe DRD with early hypotonia, similar to AR-DRD caused by TH mutations; adult-onset DRD manifesting after age 30 years with mild dystonia, resting tremor and non-tremulous parkinsonism. Phenotypic heterogeneity is quite ample and clinical features could not allow the genotype to be predicted even in a large series.

Clinical heterogeneity of DRD is a cause of diagnostic uncertainty. The DRD phenotype can include adult-onset parkinsonism with tremor and levodopa-induced dyskinesias, leading to possible confusion with patients carrying parkin gene mutations, who often develop a dystonic gait disturbance as the initial symptom [56]. The presence of early prominent parkinsonism and severe dyskinesias favours parkin mutations. DAT scan is normal in DRD patients, but not in parkin disease patients [57, 58].

The DRD phenotype can be mistaken for spastic paraparesis because of brisk lower limb reflexes and apparent extensor plantar responses (dystonic toe extension, known as “striatal toe”). Normal motor evoked potentials, unremarkable cranial MRI and positive family history should prompt consideration of a levodopa trial [59]. In one series, up to 24% of DRD patients were misdiagnosed as having cerebral palsy [60]. Particular care should be put in identifying the features of dystonia that lead toward a correct diagnosis.

With screening for gene dosage alterations the rate of detection for GCH1 mutations is over 80% [61, 62]. If genetic testing of GCH1 is negative, other genes of the tetrahydrobiopterin and dopamine synthesis pathways, like TH and SPR, should be considered, especially if inheritance is recessive [56, 62]. TH deficiency is the most frequent cause

Video 8.3 Primary dystonia: DYT6 phenotype

This 19-year-old patient carries a point mutation in the THAP1 gene. At age 16 he presented right upper limb dystonia and hand tremor. Two years later he started to have speech difficulties due to occurrence of oromandibular task-specific dystonia while talking. The videotape shows upper limb dystonic tremor (with right hand side prevalence); speech is impaired by lower cranial dystonia.

of AR-DRD and is associated with a broad phenotypic spectrum, ranging from TH-deficient DRD at the mild end to the levodopa-unresponsive infantile parkinsonism or progressive infantile encephalopathy phenotype at the severe end [59]. In mild cases clinical findings may initially be limited to unilateral or asymmetric limb dystonia, postural tremor, or gait “incoordination.” However, progression over time may result in the classic dopa-responsive dystonic gait disorder. Diurnal variation of motor condition may be present, with worsening in the afternoon or the evening [53]. Brain MRI have not revealed structural or signal abnormality in individuals with TH-deficient DRD who have been on treatment for 35 years [63]. Children at the severe end of the spectrum are profoundly disabled by infantile parkinsonism, with onset before 6 months of age, limb rigidity and hypokinesia, developmental motor delay, and truncal hypotonia. Ptosis and/or oculogyric crises are common. These infants are more difficult to treat and unusually prone to side effects (dyskinesias and gastrointestinal complications) from levodopa therapy [53]. Another phenotype associated with TH deficiency presents with progressive infantile encephalopathy, cerebral and cerebellar atrophy; the patients are severely affected and do not respond to levodopa [64].

Response to a therapeutic trial with levodopa orientates towards the diagnosis of DRD [65]. Studies on pterin and dopamine metabolites from cerebrospinal fluid or a phenylalanine loading test have also been suggested as diagnostic complements [66], but their predictive value is still uncertain and both can only be performed in specialized centres. Because DRD is not easily diagnosed, every patient with early-onset dystonia without an alternative diagnosis should have an early levodopa trial to ascertain the diagnosis [14].

**DYT11: myoclonus-dystonia**

Myoclonus-dystonia (M-D) is a dystonia plus syndrome that also peaks in childhood. The initial symptoms, usually starting in the first two decades, consist of lightning jerks and dystonia mainly affecting the neck and the upper limbs, with a prevalent proximal volvement. M-D has been described to a greater extent in Chapter 14.

In most cases the presenting symptom is myoclonus, which may be isolated or associated with dystonia. Dystonia is the initial manifestation in about 20% of cases [67].

When present, dystonia is usually mild to moderate, with torticollis or writer’s cramp as the most common manifestations. In patients with onset in infancy, gait disturbance, caused by a mixture of lower limb dystonia and myoclonus, have also been described as the initial presentation [68]. The phenotype generally evolves to cause neck-dominant typical M-D. Large studies suggest that screening for SGCE has low yield in patients with pure dystonia [69]. Family history is frequently remarkable, although sporadic cases have also been reported [70].

Usually M-D is compatible with an active life and a normal lifespan. Both myoclonus and dystonia can worsen at any time during the course of the disease, even in old age, and may spread to previously unaffected body regions [71]. A worsening of myoclonus is not necessarily coupled with a simultaneous worsening of dystonia [72]. Myoclonus and dystonia can improve spontaneously or in relation to treatment [71], a possibility to be considered when planning surgical interventions, such as deep brain stimulation (DBS).

Myoclonus is strikingly alleviated by alcohol in many, but not all, patients [73], leading to a risk of abuse [74]. Neuropsychiatric features have also been reported in several M-D patients, who presented with depression, alcohol abuse, obsessive-compulsive disorder, anxiety/panic/phobic disorders, and psychosis. Impaired verbal learning and memory have also been described in some families [74–76].

Mutations in the epsilon-sarcoglycan gene (SGCE, DYT11) can be detected in over 50% of patients with a typical M-D phenotype and age at onset below 20 [69, 77–79]. As in DRD, the rate of SGCE mutation detection is increased by screening for exon or whole gene deletions (gene dosage) [72]. Although SGCE mutations are the commonest known genetic cause, not all individuals with the M-D phenotype carry mutations in the SGCE gene.
supporting the genetic heterogeneity of the disorder [77, 80]. Patients with a typical M-D phenotype have been shown to map to 18p11, a locus called DYT15 [81].

**DYT12: rapid-onset dystonia parkinsonism**

Rapid-onset dystonia parkinsonism (RDP) is a rare dystonia-plus syndrome caused by mutations in the **ATP1A3** gene (DYT12). Onset is in childhood or early adulthood.

The patients develop dystonia, bradykinesia, postural instability, dysarthria and dysphagia over a period ranging from several hours to weeks with triggering factors, such as physical (fever, running, childbirth, excessive alcohol ingestion) or psychological stress in the majority of patients [82]. RDP usually develops over minutes to 30 days and then stabilizes. Delayed worsening of symptoms has been reported to occur in few patients 1–9 years after onset [59]. In addition to rapid onset, other features suggesting RDP are: prominent bulbar involvement and a gradient of dystonia severity with the cranial region being more severely affected than arms and legs. Neither tremor or prominent pain have been described at onset [83].

**DYT16: dystonia parkinsonism**

This dystonia-plus syndrome is caused by mutations in the **PRKRA** (protein-kinase RNA-dependent activator) gene. The phenotypic spectrum is characterized by early onset with focal dystonia leading to walking and writing difficulties. Progression occurs within few years with facial, cervical, laryngeal dystonia and swallowing difficulties. Pyramidal and psychiatric features are also associated. Brain imaging is unremarkable [84].

**Mapped loci**

The DYT7 locus, mapping to the short arm of chromosome 18, was identified in a large German family with autosomal dominant focal pure dystonia phenotype [85]. The mean age at disease onset was 40 years with a prevalent phenotype characterized by focal cervical dystonia. In some patients a segmental distribution has been reported, where cervical dystonia is associated with cranial dystonia or writer’s cramp. No patient had generalized dystonia.

The DYT13 locus was mapped in a large Italian family with prominent craniocervical and upper limb involvement and a pure dystonia phenotype [86, 87]. In the majority of cases onset was in infancy or adolescence. Of the 11 definitely affected individuals, two had generalized dystonia with early onset in the upper limb or in the cervical region [88]. Disability was mild even in generalized cases. A peculiar feature of the DYT13 phenotype is prominent cervical or upper limb involvement, similarly to the DYT6 phenotype, which has nevertheless been excluded in these patients.

The DYT15 locus was mapped in a large Canadian kindred, whose affected 13 members had alcohol-responsive myoclonic dystonia affecting the upper limbs, hands, and axial muscles [81].

The DYT17 dystonia locus was mapped in a single consanguineous Lebanese family with three sisters suffering from recessively inherited primary pure dystonia and onset in adolescence [89]. The site of onset was cervical, with progression to segmental distribution in two of the sisters and generalization in one. Prominent features were dystonia and dysarthria. Dystonic symptoms did not respond to levodopa.

**Video 8.4 Primary dystonia: DYT13 phenotype**

This patient is the proband of an Italian family linking to the DYT13 locus. At age 15 he presented abnormal head movements with a rapid (clonic) component and tonic posturing. The clinical picture slowly progressed to a segmental distribution. At age 54, the patient underwent surgical resection of the right sternocleidomastoid muscle which produced no additional clinical benefit.
Genetically unclassified dystonia syndromes

Classified phenotypes
DYT2 is a recessive pure dystonia phenotype originally described in three consanguineous pedigrees of Spanish Gypsies. The disease was named “autosomal recessive dystonia in Gypsies” and listed as DYT2 [90, 91]. In two of the families the presentation was similar to that of DYT1 dystonia, consisting in early limb onset and progression to generalization; in a third family dystonia presented with prominent oromandibular and cervical involvement [91]. A Sephardic Jewish Iranian family with a similar phenotype and autosomal recessive inheritance has been described separately [92]. Three siblings in this family had PD with limb-onset in childhood, and slow progression to generalization with predominant cranio-cervical involvement.

Two patients first developed in-turning of the foot with gait abnormalities, and all had cervical involvement, facial grimacing, blepharospasm, and involvement of the upper and lower limbs. Two patients also had dystonic dysphagia. A third family with childhood-onset, generalized dystonia, and autosomal recessive inheritance also has the DYT2 phenotype [93].

The DYT4 phenotype refers to a large Australian pedigree with 20 affected members and autosomal dominant inheritance [94]. Penetrance was complete in all the examined obligate gene carriers; age at onset varied from 13 to 37 years. Many patients presented with “whispering dysphonia”, others had cervical dystonia. Most patients eventually developed generalized dystonia. Wilson’s disease coexisted in the same pedigree, but was excluded as a cause of dystonia in the affected individuals [95].

Unclassified phenotypes
A number of scattered pedigrees not carrying the DYT1 mutation have been described. In some of these families recently discovered dystonia loci (e.g. DYT6) have not been excluded. Linkage studies have not been performed or have not been informative, leaving these pedigrees unmapped.

A non-Jewish American family presented with adult-onset DYT1-negative PD [96]. The disease started in the neck in 6 cases and in a leg in 1. All patients developed cervical dystonia, and language impairment (dysarthria or dysphonia) occurred in 5. Four patients developed generalization of symptoms. In another Swedish family transmission was autosomal dominant with a heterogeneous phenotype [97]. There was involvement of the face and larynx, and generalization occurred in 3 of the 10 patients. A family from South Tyrol had 6 affected individuals, 4 of whom developed generalization approximately 5 years after onset [98]. Limbs were involved at onset in all cases but 1, who started with cervical dystonia. Upper body involvement was observed in 3 of the 4 generalized cases. An Italian family had 6 affected individuals, 1 of whom had severe segmental dystonia [99]. The prevalent phenotype was with adult-onset cranio-cervical dystonia with occasional axial involvement but no generalization.

In a series of 43 Italian patients with non-DYT1 early-onset dystonia a common phenotype was identified [26]. This was characterized by cervical involvement, frequent non-limb onset, relatively benign course and uncommon generalization. This finding suggests that these non-DYT1 Italian families may share a common genetic defect. Their peculiar phenotype is similar to the phenotype associated with the DYT6 genotype, which was ruled out in these subjects.

A focal dystonia with onset in adulthood can be the only clinical sign in many patients, who usually have no or mild progression to a segmental pure dystonia. The most frequent forms of dystonia with typical sporadic occurrence that remain genetically unclassified are: blepharospasm, oromandibular dystonia, spasmodic dysphonia, cervical dystonia or occupational upper limb dystonia. Figure 8.2 shows the appearance of some focal and generalized dystonia phenotypes.

Cervical dystonia is the most common among these forms. Various abnormal head positions can occur, including horizontal head rotation (torticollis), head tilting (laterocollis), head flexion (anterocollis), or head extension (retrocollis). These postures can be combined variably depending on the neck muscles involved. Pain occurs in 75% of patients with cervical dystonia [100]. Cranial dystonias are less prevalent than cervical forms.
Spasmodic dysphonia affects the vocal folds and may result in abnormal adduction, which causes a strained, strangled voice, or, less frequently, it may result in vocal cord abduction, in which the voice sounds whispery and breathy.

Patients with blepharospasm have abnormal contraction of the orbicularis oculi; mild cases are characterized by a simple increase of blink rate and occasional flurries of blinking; in more severe cases forceful eye closure can interfere with vision leading to functional blindness. In oromandibular dystonia there is abnormal activity in lower facial, tongue, jaw, and pharyngeal muscles that can interfere with speaking or swallowing. Brachial dystonia is a form of focal dystonia that can be primarily, or exclusively, present with writing (writer’s cramp).

Segmental dystonia can affect the upper and lower cranial muscles, as in the combination of blepharospasm with oromandibular dystonia, sometimes called Meige syndrome. In cranial-cervical dystonia, another type of segmental dystonia, the cranial districts are involved together with the neck muscles.

**Pathophysiology**

The pathophysiology of dystonia has been reviewed in Chapter 2. The core feature is an abnormal co-contraction of agonists, and antagonists muscles worsened by certain task-specific actions and are sometimes relieved by some sensory tricks. The abnormal co-contraction is thought to be caused by a dysfunction either at the spinal or cortical level or both [101]. Reciprocal inhibition is the central nervous system process in which a muscle is inhibited when its antagonist is activated. A decreased reciprocal inhibition at different levels of the central nervous system might contribute to
the excessive movement seen in dystonia. Another research area suggests that dystonic patients may have faulty processing within the inhibitory interactions between antagonist muscles at the sensory-motor cortex level.

An emerging line of evidence indicates that dystonia could be a disorder of neuroplasticity. In some susceptible individuals, during the acquisition of new motor skills, the mechanisms of neuroplasticity are subtly abnormal. In the presence of such predisposition, several environmental factors, such as repetitive training or peripheral nervous system injury, can trigger an abnormal maladaptive plasticity, which can lead to an overt dystonia particularly in patients with a predisposing genetic background [101].

Although primary dystonias are traditionally considered not to be associated with morphological brain abnormalities, voxel-based morphometry studies have shown increase in gray matter density or volume in various areas, including cerebellum, basal ganglia, and primary somatosensory cortex, which might represent plastic changes secondary to overuse [102–106]. Diffusion MRI studies have found signal abnormalities in various brain areas (including corpus callosum, basal ganglia, pontine, brainstem, and prefrontal cortical areas) in cervical dystonia, writer’s cramp and primary generalized dystonia, but not blepharospasm [107–110]. It is difficult to reconcile these morphological evidences that may pick up some epiphenomena related to prolonged functional changes in the brain motor systems.

Data on genetically defined forms also provides insights on the neuropathology of primary dystonia. It has been observed that symptomatic DYT1 mutation carriers have a smaller basal ganglia size compared to non-carriers or asymptomatic carriers, and the severity of dystonia correlates negatively with basal ganglia size in DYT1 carriers [111]. A significant reduction in caudate and putamen D2 receptor availability and reduced \(^{11}C\) raclopride binding has also been described in the ventrolateral thalamus of DYT1 and DYT6 carriers [112]. Other studies failed to observe neuropathological changes in the basal ganglia of DYT1 patients [113], but perinuclear inclusion bodies have been detected in the midbrain reticular formation and periaqueductal gray matter of DYT1 patients [114].

**Treatment**

There is no etiologic or neuroprotective treatment for primary pure dystonia syndromes. Etiologic remedies are instead available for some dystonia plus syndromes of metabolic origin, such as DRD, or non-primary forms, such as Wilson disease. Symptomatic treatments aim to relieve involuntary movements, correct abnormal posture, prevent contractures, reduce pain and embarrassment, and improve function [115]. Botulinum toxin is the first choice treatment for most types of focal dystonia. Neurosurgical treatments have a growing role in the symptomatic treatment plan. Evidence-based guidelines have been recently published by the European Federation of Neurological Sciences [14].

**Etiologic treatments**

In metabolic disorders the knowledge of the biochemistry and metabolic pathway involved in the pathogenesis can help to identify etiologic treatments, such as enzyme-replacement therapy to rescue cellular function or systemic delivery of a missing metabolite. A growing number of genes are being found to cause familial forms of dystonia and, consequently, the molecular diagnosis of these disorders is becoming increasingly important.

An etiologic treatment is available for DRD. Reduced activity of \(GCH1\), \(TH\), or \(SPR\) is thought to cause symptoms by depleting dopamine, consistently with the pronounced therapeutic effect of levodopa, even in patients who have been severely incapacitated for several years [116].

Patients with DRD typically experience a marked long-term benefit with low doses of levodopa [117]. The optimal regimen varies among patients; while some respond magnificently to small doses, others require higher dosages. In the largest available series, clinical benefit was observed at a mean dose of 343.8 mg daily for patients who developed dyskinesias, and 189.1 mg daily for patients without dyskinesias [117]. The overall long-term responsiveness to levodopa was excellent in \(GCH1\)-DRD and the prescribed doses had to be increased only in a minority of patients. Long-term observations have shown that side
effects such as dyskinesias or motor fluctuations are unlikely to occur [52]. In contrast to patients with GCH1 mutations, TH-DRD patients may show a delayed and incomplete levodopa response with occurrence of dyskinesias [59].

**Botulinum toxins**

Botulinum neurotoxins (BoNTs) inhibit the vesicular release of acetylcholine at the neuromuscular junction, resulting in a transient, localized impairment of neurotransmission. Different type A and one type B BoNT are available for clinical use [118].

In properly adjusted doses, BoNTs are effective and safe treatments of cranial and cervical dystonia [119]. According to one systematic review, no conclusions can be drawn on the efficacy of BoNTs for different types of spasmodic dysphonia [120], although uncontrolled studies have found this treatment efficacious. BoNT/A has also been proven efficacious for the treatment of writing dystonia [121].

BoNT injections can be performed by direct inspection, EMG- or ultrasound-guided targeting and there is no consensus on which is the most appropriate practice. In recent years long-term studies on the efficacy and safety of BoNT/A have become available, new formulations of BoNT/A have been marketed, and new studies on BoNT/B have been performed.

The efficacy and safety profile of BoNT treatments has been evaluated in long-term observational studies. BoNT/A was found to be effective and safe in treating blepharospasm, with long-lasting efficacy up to 15 years of follow up [122]. In patients with different dystonia types followed for over 12 years there was no decline of efficacy and the main side effects consisted in muscle weakness in or around the injected region [123]. Onabotulimumtoxin A immunogenicity was found to be low in long-term use [124]. A meta-analysis found that adverse events are more frequent among children with cerebral palsy than in individuals with other conditions [125]. BoNTs are safe when repeated treatments are performed over many years, but doctors and patients should be aware that excessive cumulative doses may be dangerous, particularly in children.

**Systemic treatments**

Little evidence-based information is available for other medical treatments of primary dystonia.

Anticholinergic drugs at high dosage are reported to be effective in the treatment of childhood-onset primary or secondary generalized dystonias [126, 127]. This therapy is generally well tolerated when the dose is started low and increased slowly. Trihexyphenidyl should be titrated up to a dosage of 30–40 mg per day but some patients might require up to 60–100 mg per day, although dose-related side effects (e.g. drowsiness, memory difficulty, and urinary retention) might limit its usefulness, especially in adults.

Non-controlled trials are available on the effects of antidopaminergic drugs. Tetrabenazine was initially found to be effective in a small double-blind randomized cross-over study [128]. The positive effect of this treatment on dystonia was confirmed in a large series of patients with different types of movement disorders, including dystonia, followed up retrospectively for a mean duration of 3.0 years [129].

**Deep brain stimulation**

Long-term electrical stimulation of the globus pallidum internum (GPI) is now established as an effective treatment for primary generalized or segmental (mainly cervical) dystonia [130, 131]. Surgery is indicated after medications or BoNT have failed to provide adequate improvement. There is limited experience on targets different from the GPI [132] such as the thalamus, the subthalamic nucleus [133], and the cerebral cortex [134]. Chronic stimulation in dystonia uses both higher pulse width and voltage than in PD resulting in earlier battery depletion: replacement may be needed sometimes every 2 years or less. GPI DBS, in general, is less effective in secondary dystonia. This procedure requires a specialized expertise and a multidisciplinary team, and is not without side effects. Other indications are still being explored, such as status dystonicus, task-specific dystonias, camptocormia, secondary hemidystonia, pantothenate kinase-associated neurodegeneration, Lesch-Nyhan and cerebral palsy-related dystonia-choreoathetosis.
According to a National Institute for Clinical Excellence (NICE) guideline [135], GPi DBS provides marked benefit with improvement of dystonia motor scores, ranging between 34 and 88%, and disability scores, between 40 and 50%. A meta-analysis using a regression analysis published in 2006 revealed that longer duration of dystonia correlated negatively with surgical outcome [136]. Improvement of dystonia after DBS commonly follows a specific pattern, with phasic (clonic or tremulous) elements improving earlier than tonic features, the latter often with a delay of weeks or months [137–139]. Overall, the most beneficial results with pallidal DBS were reported in children with primary generalized dystonia, particularly in DYT1 dystonia, which improves in the range of 40 to 90% [140–142]. Long-term efficacy was reported to be sustained after more than 5 years of follow-up [143]. In patients with cervical dystonia, GPI DBS has so far been used primarily in those who were thought not to be ideal candidates for peripheral denervation, including patients with head tremor and myoclonus, or marked phasic movements [144].

Safety aspects which have to be considered include surgery-related complications, stimulation-induced side effects and hardware-related problems. Recently, it was noted that GPI DBS in patients with segmental dystonia may induce a parkinsonian gait or bradykinesia in extremities which were not affected by dystonia at chronic stimulation with high voltage [145, 146]. Bilateral pallidal stimulation does not impair cognitive performance [147].

Other neurosurgical procedures
According to NICE guideline for selective peripheral denervation in cervical dystonia [148], this procedure requires a specialized expertise, it is safe with infrequent and minimal side effects and is indicated exclusively in cervical dystonia. Intrathecal baclofen has been used in patients with severe generalized dystonia. Since this treatment is burdened by medication-related side effects, it is currently indicated only in patients where secondary dystonia is combined with spasticity [149].

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CHAPTER 9
Secondary Dystonias

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Historical background
Dystonia is a hyperkinetic movement disorder defined by involuntary twisting and repetitive movements resulting in abnormal postures [1].

Historically, one of the first descriptions of the condition may be that by Destarac from 1901 who reported generalized dystonia affecting the neck, arm, pelvis muscles, and feet in a teenage girl. Soon after, in 1908, Schwalbe described several patients, some of whom had a suggestion of hereditability. The term “dystonia” itself was coined by Oppenheim. Much was written following this, documenting the details of the clinical phenotype and the disease course, the underlying different etiologies and pathophysiology, and outcome.

Dystonia syndromes can be classified by onset age, distribution of symptoms, and the underlying etiology. With respect to the latter, dystonic syndrome’s primary and secondary forms can be broadly distinguished. Secondary forms may be due to strategic brain lesions, metabolic disease, neurodegenerative conditions, or following exposure to drugs (in particular dopamine antagonists) or toxins [2–4]. In particular, postmortem studies gave insight into which brain areas and neuronal networks associated with dystonia. However, because making a diagnosis can be challenging, clinical red flags are an important aid to the clinician. Examples of clinical clues pointing towards a secondary etiology are summarized in the following (see also Box 9.1) and syndromic associations will be discussed in the following.

Box 9.1 Clinical features suggestive of secondary dystonia
- Sudden onset and/or rapid progression
- Unusual distribution such as:
  - Hemidystonia
  - Cranial onset in childhood
  - Adult-onset of leg dystonia
- Unusual disease course such as:
  - Restriction to focal or segmental dystonia in patients with childhood-onset
  - Progression to generalized dystonia of adult-onset dystonia
- Prominent orobulbar involvement
- Absence of “sensory tricks”
- Other neurological or systemic signs (except tremor)
Phenomenology and other clinical features

Sudden onset of symptoms
In primary dystonia onset is usually slow (with the exception of the genetic form of “Rapid Onset Dystonia Parkinsonism”, DYT 12). When symptoms develop acutely, a secondary cause, such as a vascular event or a metabolic disequilibrium, should be investigated for. Psychogenic dystonia can also have a sudden onset.

An unusual distribution
The group of primary dystonias has been reviewed in the preceding chapter [5]. In recent years there have been advances in neurogenetics and the clinical phenotypes of the genetic dystonia forms have been delineated, for example of DYT1 dystonia where symptoms usually begin in childhood in the lower limbs and later become generalized [5]. Indeed, being aware of the classic phenotypes is important to recognize patients in whom the distribution either fits the patterns associated with genetic forms and who should thus be considered for genetic testing, or patients in whom the distribution is atypical and who should be thoroughly investigated for a secondary cause. An example for the latter may be the onset of leg dystonia in an adult, or hemidystonia. The latter may be a hint toward a brain lesion. (See Video 9.1.)

Dystonia with prominent orobulbar involvement
While some primary dystonias may have laryngeal involvement, prominent orolingualbuccal dystonia is uncommon in primary dystonia and a secondary or heredodegenerative form should be considered [6], particularly when severe.

Primary dystonias with prominent orobulbar involvement include DYT4 (“whispering dystonia,” the underlying gene remains unknown), DYT6 (due to mutations in the THAP1 gene, as recently identified), DYT12 (“rapid-onset dystonia parkinsonism”) due to mutations in the ATP1A3 gene and DYT17 (recessively inherited, linked to the chromosome 20, gene not yet identified) dystonia [7–10].

Among the group of secondary dystonias, particularly previous neuroleptic intake should be thought of; but also certain genetic disorders such as pantothenate kinase-associated neurodegeneration (PKAN, also known as Hallervorden–Spatz disease) due to mutations of the PANK2 gene, neuroacanthocytosis, neuroferritinopathy, and Lesch–Nyhan syndrome can produce dystonia with marked orobulbar involvement [6]. With the exception of neuroferritinopathy (autosomal dominant inheritance) these latter genetic diseases follow autosomal recessive inheritance and family history may thus be negative for a similar disorder, but there may be a history of consanguinity (see Video 9.2).

Ocular motor signs and fundus oculi
We expect patients with primary dystonia to have normal eye movements and the presence of an eye movement disorder may hint toward a secondary form of dystonia. Ocular motor dysfunction can, for example, manifest as supranuclear gaze palsy and this has been observed in Niemann–Pick type C and PKAN, both inherited autosomal recessively. In the neurovisceral lipid storage disorder Niemann–Pick type C supranuclear gaze palsy was in fact present in 75% of adult-onset cases and a presenting sign in 8% of cases [11].

The presence of retinitis pigmentosa is another useful sign to narrow down the list of differential diagnoses in patients with dystonia. Most importantly,
PKAN (or the allelic disorder referred to as HARP syndrome – characterized by hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration), GM2 gangliosidosis, and metachromatic leukodystrophy should be considered.

**Hearing loss**

The combination of “dystonia and deafness” is characteristic of the mitochondrial disorder Mohr–Tranebjaerg syndrome associated with mutations in the *DDP1* gene [12]. Other mitochondrial diseases may produce a complex phenotype consistent of neurological features with movement disorders, visual problems (blindness), hearing impairment and heart problems [13].

Another complex disorder with phenotypic similarities to mitochondrial disease is the autosomal recessively inherited disorder with the name of Woodhouse–Sakati syndrome for which the underlying cause was recently identified. The full function of the associated gene, *C2orf37*, and the encoded nucleolar protein remain unknown [14]. The phenotype is characterized by hypogonadism, alopecia, diabetes mellitus, mental retardation, and extrapyramidal features (Figure 9.1) [15, 16]. However, there is phenotypic and genetic variability.

**Dystonia and peripheral neuropathy**

The presence of neuropathy is not a feature of primary dystonia, although the pathophysiological role of the sensory system is being discussed. Hallett has suggested that dystonia may be a sensory disorder [17] and others are investigating the presence of subclinical impairment of sensory discrimination as a possible endophenotype of dystonia [18].

Neuropathy may be secondary to diabetes mellitus and the combination of dystonia and diabetes is seen in acerulplasminemia (a rare genetic disorder with autosomal recessive inheritance due to mutations of the ceruloplasmin gene which is characterized by movement disorders, dementia, and diabetes...
mellitus), mitochondrial disease and the Woodhouse–Sakati syndrome (for these see above). Once diabetes has been excluded, but ataxia is additionally present, there are also a number of differentials to consider. This includes the common recessive forms of ataxia, such as Friedreich’s ataxia [19] and ataxia telangiectasia [20, 21] and their differential diagnoses [22]. In all these ataxia, dystonia and peripheral neuropathy may be present. For example, in a study of 70 ataxia telangiectasia patients, dystonia was present in 55 and peripheral neuropathy 50 of them [20]. A less common cause of this combination is the young-onset variant of Niemann–Pick type C disease [11]. Because the presence of vertical gaze palsy is also characteristic (see above) in Niemann–Pick type C, which is present in 75–80% of patients, this should also be looked for. A further clue toward this diagnosis may be hepato- or splenomegaly which are present in about 30 to 90% of cases [11, 23]. Notably, the combination of dystonia, neuropathy and ataxia has also been reported for some of the autosomal dominant spinocerebellar ataxias [24], e.g. SCA 3 [25]. Furthermore, the combination of peripheral neuropathy, progressive dystonia and ataxia, as well as a cognitive decline is seen in metachromatic leukodystrophy caused by mutations in the arylsulfatase A gene [26].

Finally, patients with complex regional pain syndrome (CRPS) may have additional dystonia. CRPS, formerly referred to as reflex sympathetic dystrophy is defined as regional, post-traumatic, neuropathic pain problem affecting one or more limbs [27] and patients may experience hyperesthesia, hyperalgesia or allodynia, temperature asymmetry, or abnormal sudomotor (sweating) activity. In addition there may be local edema, changes of skin color, hair, or nails. Particularly in type I CRPS, motor dysfunction including dystonia, often fixed, may occur [28, 29] (see Video 9.3). The pathogenesis of CRPS and the relation to dystonia remain poorly understood. An association with small fibre neuropathy has been discussed [30]; however, there is also an ongoing debate regarding a possible psychogenic nature of dystonia in CRPS [28].

### Video 9.3 Complex regional pain syndrome

This patient is 47 years old. At age 46, she noticed rigidity and tension in the right hand and gradually developed a clenched fist over the following week. Local skin changes mainly consisted in swelling and dyschromia. A clinical diagnosis of complex regional pain syndrome was made. The videotape shows the clenched fist due to fixed dystonia of the right hand. The patient is asked to open her fingers and raise her arms. Then, the patient is asked to lay down the fingers and open her hands. There is no impairment in the left hand, whereas on the right hand side the patient can only move the thumb. No overflow or mirroring are detected during hand movements. [Video courtesy of Alberto Albanese, MD, Milan, Italy]

http://bit.ly/v17UZg

### Dystonia and parkinsonism

In addition to pure dystonic and pure parkinsonian syndromes, there are conditions with an overlapping phenotype of these symptoms. First, dystonic conditions may have superimposed parkinsonism, as seen in dopa-responsive dystonia or Wilson disease. Second dystonia may be a seen in (or even be the presenting feature of) various parkinsonian disorders. Dystonia in a drug-naive patient with features of idiopathic parkinsonism would however be atypical. Its presence may, on one hand, be a red flag toward an atypical parkinsonian syndrome like progressive supranuclear palsy (PSP), multiple system atrophy (MSA), or corticobasal degeneration (CBD) [31]. Dystonia may then manifest as axial dystonia and blepharospasm (levator inhibition) causing the starring expression associated with PSP; antecollis and facial dystonia in MSA; or the dystonic arm posture seen in CBD. On the other hand, parkinsonism associated with dystonia may be seen in some of the genetic disorders. For example, in early-onset parkinsonism, including the parkin-associated variant, dystonia may intermittently be present as so-called exercise-induced paroxysmal
foot dystonia, and this may precede signs of parkinsonism by some years [32]. The combination of young-onset dystonia and parkinsonism is also seen in other neurodegenerative diseases like the rare autosomal recessive disorders with nigrostriatal-pallidal-pyramidal degeneration, including Kufor Rakeb disease (PARK9) or PLA2G6-associated neurodegeneration (PARK14) [33] (also see review by Schneider et al. [34]).

Most frequent, however, is dystonia in the context of parkinsonism as a complication of dopaminergic treatment, for example as peak-dose dystonia, diphasic dystonia, and off-dystonia [31].

**Dystonia with progressive dementia**

Progressive dementia is not a feature of the primary dystonias like the young-onset DYT1-related dystonia or the adult-onset sporadic forms. Progressive dementia is, however, one of the core features of Huntington disease and the Huntington disease-look like syndromes (including HDL4/SCA17), as well as neuroacanthocytosis and PKAN. Indeed, chorea is the main movement disorder in these conditions, however, prominent dystonia can occur. A further condition to consider is Creutzfeldt–Jakob disease, a rare neurodegenerative disease characterized by rapidly progressive dementia, mutism, ataxia, and extrapyramidal and pyramidal involvement [35]. The movement disorder is typically characterized by focal or generalized myoclonus (present in 80–100% of cases), but dystonia occurs and may rarely be a presenting sign [35–37] (see Video 9.4). Dystonia in Creutzfeldt–Jakob disease is then usually unilateral and distal but may become generalized in later stages of the disease [35]. Overall, the course of the disease is progressive, which should alert the clinician to this diagnosis. Furthermore, HIV encephalopathy is a cause of dementia, and dystonia may be present [38].

Finally, dementia may also be a symptom in the complex autosomal recessive dystonia parkinsonian syndromes mentioned above [34].

**Neuroimaging features**

Investigations will confirm or exclude the suspected clinical diagnosis. Neuroimaging, for example, can reveal patterns that are characteristic of certain conditions.

First, strategic lesions in the basal ganglia, brainstem, cerebellum, or cortical areas (parietal and frontal) can result in dystonia [39–47] and should be looked for; however, not all basal ganglia lesions necessarily result in neurological symptoms or signs. If present, there may be a relationship between the distribution of dystonia and the localization of such lesion: for example, thalamic lesions are more likely to result in hand dystonia, while brainstem lesions are associated with cranial dystonias such as blepharospasm, and putaminal lesions, were found in patients with hemidystonia or limb dystonia. As mentioned above, in hemidystonia, lesions are often unilateral, contralaterally to the dystonia.

The cause of strategic lesions is variable and includes vascular causes, space-occupying lesions, trauma, inflammation, atrophic changes in the context of neurodegeneration or accumulation of metals (such as iron, copper, manganese, etc.; see Box 9.2).

In particular, metal deposition disorders have attracted interest in recent years. It is known that the basal ganglia host high concentrations of metals
including iron, copper, and manganese which act as cofactors for metabolic activity. In the case of excessive metal accumulation, however, this may cause dysfunction and disease. Such metal deposition can be detected by neuroimaging on CT (e.g. copper) or MRI (e.g. iron or manganese). In recent years, in particular, iron deposition disorders have received growing attention and a new term referring to these disorders, “syndromes of neurodegeneration with brain iron accumulation” (NBIA), has been coined. This group entails the condition of PKAN (NBIA type 1, also known as Hallervorden–Spatz disease), PLA2G6-associated neurodegeneration (NBIA type 2, PARK 14) [33], neuroferritinopathy, and aceruloplasminemia [48, 49]. In addition, there is recent evidence that Kufor Rakeb disease (PARK 9) and FA2H-associated neurodegeneration may also belong to this group of the NBIA's [50, 51].

McNeill et al. [52] proposed that the different NBIA syndromes may be distinguished with gradient recalled echo (GRE) T2*-weighted and fast spin echo T2-weighted brain MRI. The authors find that in PKAN iron deposits are localized within the globus pallidus interna and can be depicted as hypointense signal (representing iron) with a central hyperintensity (probably representing fluid accumulation or edema). On axial slides, this radiological pattern resembles an eye-of-the-tiger [48] (Figure 9.2) and there may be a high correlation with the presence of PANK2 gene mutations [48, 53]. NBIA type 2 is associated with mutations in the PLA2G6 gene on chromosome 22q13 encoding a calcium-independent phospholipase. The clinical phenotype is heterogeneous and includes infantile neuroaxonal dystrophy and adolescence/adult-onset dystonia parkinsonism, and it is a key differential diagnosis of PKAN. As in PKAN there is iron deposition on MRI imaging, however there is no classical eye-of-the-tiger sign, but there is only a hypointensity in the globus pallidus, whereas the central hyperintensity is lacking. Notably, however, normal MRI imaging has also been reported in a gene-proven case of PLA2G6-associated neurodegeneration and the disorder should thus also be considered when iron is absent [33]. T2*-weighted MRI scans of neuroferritinopathy fall into two groups [52]: first, those with basal ganglia hypointensity; and, second, those with confluent hyperintensity (probably

### Box 9.2 Differential diagnosis of basal ganglia metal deposition

| Iron: | - NBIA type 1 (pantothenate kinase-associated neurodegeneration, previously known as Hallervorden–Spatz disease)  
- NBIA type 2 (PLA2G6-associated neurodegeneration, PARK 14)  
- Kufor Rakeb disease (PARK 9)  
- Aceruloplasminemia  
- Neuroferritinopathy |
| Copper: | - Wilson disease  
Manganese: | - Exposure to manganese as seen in mine workers or after illicit drug use  
- Chronic liver dysfunction |
| Calcium: | - Hypoparathyroidism  
- Infections (e.g. toxplasmosis, rubella, cytomegaly, herpes, HIV)  
- Following carbon monoxide poisoning  
| Familial, Fahr disease (striopallidodentate calcinosis) |

**Figure 9.2** Eye of the tiger sign on T2-weighted axial brain MRI in a genetically proven PKAN patient.
cavitation) of the globi pallidi and the putamen with hypointensity of the substantia nigra and dentate nuclei. In a recent study, a subset of patients had additional caudate or thalamus involvement. An eye-of-the-tiger sign indistinguishable from that seen in PKAN has also been observed in gene-proven neuroferritinopathy cases [52]. Finally, in the case of Kufor Rakeb disease reported by Schneider et al. [50], iron deposition affected the putamen and caudate rather than the globus pallidus as seen in NBIA types 1 and 2. Thus, there is an overlap of features between the different syndromes. Furthermore, there are other patients with iron deposition on MRI who do not carry mutations in any of the associated genes, suggesting the existence of yet unrecognized NBIA disorders.

Copper deposition also shows as hyperintense signal on T2-weighted scans. Copper deposition in the putamen and globus pallidus, liver, and cornea are characteristic of Wilson disease, an important differential diagnosis of secondary dystonia, particularly in young patients [54, 55]. This is known as the “face of the giant panda” sign (referring to the combination of high signal intensity in the tegmentum except for the red nucleus, with preservation of signal intensity of the lateral portion of the pars reticulata of the substantia nigra, and hypointensity of the superior colliculus) [56].

Manganese accumulation has been associated with secondary parkinsonism following manganese exposure (for example, in miners or after illicit drug use) [57] or with chronic liver failure [58]. In the basal ganglia manganese accumulates symmetrically within the globus pallidum and is depicted as hyperintensity on T1 sequences. Dystonia may also be prominent [59–62].

Calcium deposition can be easily detected by CT imaging as high-intense lesions and incidental calcifications are relatively frequent (up to 1.5% of CT scans). Within the basal ganglia, calcium most commonly affects the globus pallidus and is usually benign, in most cases idiopathic or age-related [63]. In view of this, it has been proposed that presence of globus pallidus calcifications only requires further elaboration when the patient is younger than 40. In addition, all patients, irrespective of their age, should be further investigated where other basal ganglia or brain areas are affected. The differential diagnosis is wide and includes metabolic, infectious, toxin-induced, and degenerative causes [63]. Among the metabolic disorders, idiopathic or surgical hypoparathyroidism is probably the most common cause of symmetric basal ganglia calcifications, and dystonia as presenting feature may occur [64]. Infections (including congenital forms) by toxoplasmosis, rubella, cytomegalovirus, herpes, and HIV may result in basal ganglia damage with calcifications and secondary dystonia [65, 66]. Following carbon monoxide poisoning, movement disorders including dystonia may develop as a part of delayed encephalopathy [67] and imaging may reveal basal ganglia calcifications [68]. Neurodegenerative causes include Wilson disease [69].

Last, but not least, familial causes of basal ganglia calcifications with autosomal dominant inheritance have been recognized (and also referred to as striopallidodentate calcinosis or Fahr disease), and dystonia has been observed [69].

**Prevalence and etiology**

How common is secondary dystonia? Prevalence data on secondary dystonia are limited. A Brazilian study of 122 patients with a dystonic syndrome, 46 (38%) were found to have a symptomatic form [70]. Among these, the most frequent causes were tardive dystonia (35%) and perinatal cerebral injury (30%). Other causes included stroke (13%), encephalitis (6.5%), and Wilson disease (4%). Causes were more common in certain age groups: Younger patients tended to have had perinatal cerebral injury or encephalitis preceding their dystonia. In older patients stroke and exposure to drugs (tardive dystonia) were more common. In a recent study of a total of 706 patients studied by Wenning et al. [71] of 16 elderly patients with dystonia, 10 (62.5%) were classified as having a secondary form. Of these, 8 were drug-induced dystonias, highlighting the importance of this etiology. This is in line with a large study of more than 3,000 dystonia patients, 29% of which had a secondary form: tardive dystonia was the leading cause [72, 73].
Treatment

Therapy depends on the underlying etiology. Space-occupying strategic lesions should be removed surgically, if possible. Infectious causes should be treated with antibiotic, antiviral, or antifungal treatment as appropriate. Similarly, metabolic and hormonal imbalances should be addressed by resetting hemostasis. In secondary dystonia due to drug or toxin exposure, the triggering factors should be withdrawn.

If symptoms remain, symptomatic treatment can be explored [74]. There are three main therapeutic routes which include medication, surgical interventions, and supportive methods. The goal is to correct abnormal postures, prevent contractures, reduce pain, and improve function and quality of life [75]. Anticholinergic agents (such as trihexyphenidyl) is the drug of choice for generalized dystonias. On failure, muscle relaxants like baclofen can bring benefit. All young-onset patients should also have a trial of levodopa to exclude dopa-responsive dystonia. For patients with focal dystonia botulinum toxin is the drug of choice, injected into the affected muscle [76]. For severe or treatment-resistant cases, surgical interventions like deep brain stimulation can be promising. Last, but not least, patients benefit from additive supportive therapy such as physiotherapy and speech therapy.

Conclusion

While the presence of tremor is compatible with a diagnosis of primary dystonia, there are other clinical features which point away from this diagnosis but may be suggestive of a secondary or hered degenerative etiology causing dystonia as a predominant feature or as a part of a syndrome. Clinical red flags include eye movement disorders, retinitis pigmentosa, or peripheral neuropathy, to name a few. Syndromic associations, some of which have been outlined in this chapter, can thus be useful and help the clinician to narrow down the list of differential diagnosis. Investigations such as a peripheral blood smear to screen for neuroacathocytosis, or neuroimaging, may help to reach at the correct diagnosis.

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PART 4
Chorea Syndromes
CHAPTER 10
Huntington Disease and Other Genetic Choraeas

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Historical background

The clinical syndrome of Huntington disease (HD), an autosomal dominant neurodegeneration [1], was first delineated in 1872 by George Huntington, who reported:

“Hereditary chorea … confined to certain and fortunately a few families, and has been transmitted to them, an heirloom from generations away back in the dim past. It is spoken of by those in whose veins the seeds of the disease are known to exist, with a kind of horror … There are three marked peculiarities in this disease: 1. Its hereditary nature. 2. A tendency to insanity and suicide. 3. Its manifesting itself as a grave disease only in adult life” [2]

The degeneration of the striatum was recognized as the essential neuropathologic feature around the turn of the century [1, 3–5]. The gene for HD was the first human gene to be localized by linkage analysis using restriction fragment length polymorphisms [6], and the mutation was discovered to be an expansion of a trinucleotide repeat in a novel gene on the short arm of chromosome 4 [7]

Phenomenology and other clinical features

HD is an autosomal dominant, neurodegenerative disease that causes disorders of motor control, emotional control, cognitive ability, and involuntary movements, classically choreic [1, 8]. The mean age at onset is approximately 40 years, but there are descriptions of individuals who became symptomatic during infancy and as late as 9th decade of life. Juvenile cases (less than 20 years of age at onset) constitute about 5.4% of all cases of HD [9].

Premanifest HD

Because of its serious implications, the diagnosis of manifest HD is reserved for at-risk persons who have developed chorea or another movement disorder. A number of individuals, however, have prominent mood, thought, or personality disorders that present in the years prior to onset of definitive motor signs. Cognitive changes may also precede onset of motor definitive symptoms [10]. The earliest cognitive indicator of HD is emotional recognition, which may be detected in gene-positive individuals more than 15 years from the predicted motor diagnosis. Within 15 years of the predicted motor diagnosis, a number of cognitive measures may detect additional impairments, including time production and speed of processing [11]. Mild cognitive impairment may be present in nearly 40% of individuals with prediagnosed HD, with higher rates in individuals closer to the HD diagnosis [12]. One study examining prodromal HD patients who were estimated to be less than 9 years from their clinical diagnosis found significantly poorer performance scores on nearly all cognitive tests compared with a control group [13]. Individuals who had an estimated 9–15 years
before their clinical diagnosis had poor performance scores on about half of their cognitive tests. In one study, prediagnostic CAG expanded individuals appeared to demonstrate a more rapid decline in some (but not all) neurocognitive and psychomotor measures, as they approached the estimated onset of disease [14].

Psychiatric symptoms may also be evident in premanifest individuals. One study identified specific psychiatric symptom dimensions (obsessive-compulsive, interpersonal sensitivity, anxiety, paranoid ideation, and psychoticism) that differentiate non-mutation carriers from individuals in the early preclinical stages of HD who are either symptom free or have minor non-specific motor abnormalities [15].

Other signs that may portend onset of clinically manifest HD include increased motor restlessness, slowing of saccadic eye movements, and slowing or dysrhythmic production of rapid, repetitive movements of the fingers or tongue [16, 17]. Abnormalities in saccadic latency have been demonstrated in premanifest HD patients, with significant changes seen from year to year [18]. Oculomotor defects may be seen in presymptomatic patients with a predicted time to clinical onset of up to 10 years [19]. Variability in speeded and metronome tapping tasks were also reported in manifest and premanifest HD in one cross-sectional study, and were more pronounced in the later stages [20]. The speeded tapping variability in HD and premanifest HD correlated with the UHDRS total motor score. In addition, tapping variables were associated with gray matter atrophy and cortical thinning. Such deficits may provide a possible outcome measure for use in future preventative clinical trials [21].

Weight loss, which is a well-recognized manifestation of established HD, has also been demonstrated in individuals in the early stages of HD, who do not yet have a clinically apparent movement disorder [1]. In addition, caloric intake may need to be increased to maintain body mass index in clinically unaffected gene carriers, suggesting increased energy expenditure due to subtle motor impairment or a hypermetabolic state [22].

**Motor manifestations**
The appearance of a motor disorder in the presence of a positive family history heralds the onset of clinically manifest HD. This is confirmed by genetic testing. The prototypical movement disorder is chorea, which interferes with voluntary motor control and causes progressive physical disability [23]. Chorea, from the Greek word meaning, “to dance,” is an involuntary movement defined as a relatively continuous abnormal involuntary movement produced by jerk-like contractions of muscles that move randomly from one part of the body to

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**Video 10.1 Mild generalized chorea in Huntington disease**
This woman with Huntington’s disease is 35. She had a positive family history with autosomal dominant transmission from her mother. Disease onset was at age 30. The videotape shows a florid choreatic disorder that is activated by speech and voluntary movements. Chorea is also evident during walking, where it gives the appearance of a dance-like attitude. The involuntary movement causes disability in performing even simple tasks, such as fastening and unfastening the watch belt. [Video courtesy of Alberto Albanese, MD, Milan, Italy]


**Video 10.2 Moderate chorea in Huntington disease**
Young woman with HD and moderate generalized chorea.

http://bit.ly/vr0xt8
Chorea in Huntington disease
Patient with HD showing generalized, perioral and upper facial chorea, due to irregular, random, asymmetrical, unpredictable frontalis contractions.


Chorea also impairs the ability to produce sequences of movements and to rhythmically produce rapid repetitions of a single movement [24]. Apraxia, particularly ideomotor apraxia, is often present even at the onset [25], although language skills remain mostly intact. Patients are unable to learn complicated motor skills. Loss of voluntary motor control continues throughout the course of the illness until it causes complete inability to perform any purposeful motor act.

Other motor signs include bradykinesia, dystonia, imbalance, and speech disturbances. Bradykinesia generally coexists with chorea in the adult form of illness [26]. Juvenile cases and occasional young adult cases can present with prominent parkinsonism or rigidity-dystonia with little or no chorea (Table 10.1).

A parkinsonian state with marked slowing of eye movements is seen in the juvenile-onset cases (Westphal variant); seizures and myoclonus commonly complicate the course of juvenile-onset HD. Deep tendon reflexes are typically hyperactive, hung-up, and pendular [27]. Motor impersistence is another characteristic feature of HD, and may be demonstrated by the inability to maintain tongue protrusion.

The movement disorder in adult-onset HD changes with time. Chorea gradually decreases in amplitude and may be replaced by dystonia-rigidity in the end stages. Patients can develop fixed dystonic contraction of limb and axial muscles leading to contractures and immobility. Speech and swallowing dysfunction develop mid-stage of the illness and ultimately lead to inability to communicate.

### Table 10.1 Clinical features.

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<tr>
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<th>Adult onset</th>
<th>Juvenile onset</th>
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<tr>
<td>Age at onset</td>
<td>35–55 (mean age 40)</td>
<td>Before 20</td>
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<tr>
<td>Initial features</td>
<td>Chorea, personality changes.</td>
<td>Personality changes, deterioration</td>
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<tr>
<td></td>
<td>May have mild cognitive impairment.</td>
<td>of school performance, rigidity,</td>
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<td></td>
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<td>bradykinesia, dystonia.</td>
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<tr>
<td>Late features</td>
<td>Dementia, abnormal eye movements, dystonia, rigidity, bulbar dysfunction</td>
<td>Dementia, dysarthria, abnormal eye movements, tremor, seizures, ataxia, myoclonus</td>
</tr>
<tr>
<td>Duration</td>
<td>15–30 years</td>
<td>5–15 years</td>
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and swallow. Autonomic dysfunction may also be seen in patients with HD [28].

Falls are common in patients with HD. In a study of 45 early- to mid-stage HD patients, falls occurred more commonly in patients with higher scores for chorea, bradykinesia, and aggression, as well as lower cognitive scores [29]. In addition, HD patients had decreased gait velocity and a decreased stride length; fallers had increased stride length variability and a significantly greater trunk sway in the mediolateral direction compared to non-fallers. Another study showed that over 50% of HD patients had fallen more than twice in the previous 12 months [30]. They tended to have an increased risk of falls if the Timed “Up & Go” test scores were 14 seconds or more or if the Berg Balance Scale scores were 40 or less. Individuals with HD exhibit slower stepping response times, poorer dynamic balance, mobility and motor performance when compared with controls [31]. Subtle postural deficits in the setting of changing sensory conditions have also been reported in one study, involving not only manifest HD individuals, but also premanifest HD individuals up to 5 years before estimated disease onset [32]. The Tinetti Mobility Test has been examined in one study as a potential tool for assessment of balance and falls risk in individuals in the ambulatory stages of symptomatic HD [33].

**Psychiatric and behavioral manifestations**

George Huntington described a “tendency to insanity and sometimes that form of insanity that leads to suicide, is marked.” Psychiatric disorders are prevalent in patients with HD. A variety of disturbances have been observed, including psychosis and hallucinations, delusional thought disorder, mood lability, anxiety, irritability, mania, obsessive behavior, or rigidity of thought. Severe psychiatric problems occur in one fifth of individuals. This includes suicidal ideation and attempts, and irritability/aggression. Frank psychosis is relatively unusual, although delusions may occur. A study by the Huntington Study Group reported the probability of obsessive compulsive symptoms is approximately three times greater in patients with clearly manifest disease than in those with no apparent motor abnormalities [34]. Changes in temperament or personality with irritability are common and often troublesome for family members. Disabling or overwhelming apathy from frontal lobe dysfunction is not unusual. Depression is the most common psychiatric manifestation of HD and may be accompanied by emotional irritability with outbursts of disruptive behavior. Health-related quality of life in patients with HD appears to be determined by the depressive mood and greater functional incapacity, more so than by decreased motor and cognitive functions [35]. Suicide occurs in 5 to 10% of HD patients, and there is an increased
risk of suicide for those at-risk for the disease [36]. Paulsen and colleagues suggest that there are two critical periods for increased risk of suicide in HD. The first is immediately before receiving a formal diagnosis of HD, and the second is in stage 2 of the disease, when independence diminishes [37]. The depression subscale of the Hospital Anxiety and Depression Scale and the Depression Intensity Scale Circles have been found to be good screening measures for depression in the HD population in one study [38].

**Cognitive manifestations**

Cognitive decline occurs in all patients and may be more, less, or equally as disabling as the motor disorder in different patients [1, 39]. Decline in cognitive ability most closely relates to the number of years affected by HD [40]. Patients tend to be disorganized and suffer from lack of initiative. Some may show no awareness of their movement or cognitive disorder. The cognitive profile is typically characterized by attention deficits, cognitive slowing, impaired planning and problem solving, and visuoperceptual and construction deficits. In contrast to the cognitive impairment seen in Alzheimer disease, other cognitive deficits appear to contribute to functional impairment in HD before the memory disturbance [41]. There is usually a more rapid decline in visuospatial function as compared to verbal skills. Also, a more dramatic drop in performance IQ as opposed to verbal IQ scores is seen [42]. One study demonstrated evidence of impaired explicit motor sequence learning in premanifest and early HD, whereas implicit motor sequence learning was preserved [43]. The Montreal Cognitive Assessment (MoCA) has been shown to achieve higher sensitivity without sacrificing specificity in many domains relative to the Folstein Mini Mental State Exam in mild to moderate cognitive impairment in HD [44].

**Other manifestations**

Progressive weight loss and muscle wasting is another feature of HD. Weight loss is likely to result from a hypermetabolic state, and has been linked to CAG repeat length [45]. Energy expenditure also appears to increase with disease duration [46].

Weight loss, and alterations in sexual behavior and wake-sleep cycle, frequently found in patients with HD, have been attributed to involvement of the hypothalamus even in early stages of HD as demonstrated by PET and postmortem studies [47].

**Epidemiology**

The prevalence of HD is geographically heterogeneous, probably related to the diaspora after the founder mutation in the Middle Ages in southeast England. Thus, in certain regions of the world the prevalence is as high as 560 per 100,000 (Moray Firth, Scotland) and 700 per 100,000 (Lake Maracaibo, Venezuela) [27]. The prevalence of affected individuals in the United States has been estimated to be at 5 to 10 per 100,000 [48]. However, there are concerns that the prevalence of HD may actually be underestimated due to a variety of reasons, such as stigma associated with the disease [49, 50], low expectations of medical interventions, and potential discrimination from employers or insurers [51]. The effect of the baby-boomer birth cohort, and the occurrence of new mutations may also play a contributory role [52]. The All Party Parliamentary Group on Huntington’s disease, aimed to promote HD research and care, also plans to investigate the true prevalence of HD” of the true prevalence of HD [53]. Approximately two to four times as many individuals have inherited the mutation but are as yet asymptomatic. As an autosomal dominant disorder, there is no gender predisposition and the disease is present worldwide. Prevalence is correlated with European ancestry. HD is rare in Japan and China, and is seen infrequently in African Americans. A nationwide population-based epidemiologic study in Taiwan found an average annual incidence rate of 0.1 per 100,000 [54]. Although the incidence rates and prevalence were much lower compared with estimates from Caucasian populations, the age distributions were similar.
**Etiopathogenesis**

HD is an autosomal dominant disorder, and results from an expanded and unstable trinucleotide repeat in the *IT15* gene on the short arm of chromosome 4 [7]. There is a 50% chance of inheriting the Huntingtin (*HTT*) gene from an affected parent. Three nucleotides, cytosine—adenine—guanine (CAG), normally form a trinucleotide and are repeated in this gene. The gene produces a protein called huntingtin (Htt). A normal person may have as many as 35 repetitions of the CAG trinucleotide in the *HTT* gene.

Laboratory guidelines for HD Genetic Testing from the American College of Medical Genetics/American Society of Human Genetics Huntington Disease Genetic Testing Working Group define the CAG repeat range of 40 or more to be consistent with HD [55]. Individuals with 36–39 repeats are categorized as HD allele with reduced penetrance, and those with 27–35 are considered to have mutable normal alleles. The HD allele with reduced penetrance range, with CAG repeats between 36 and 39, is considered abnormal. However, the HD phenotype is not always penetrant. A conservative estimate of penetrance in one observational study calculated that in this CAG repeat range, an individual has at least a 40% chance of being asymptomatic at age 65 years and at least a 30% chance of being asymptomatic at age 75 years [56]. Such individuals may have offspring with clinical HD who have a more expanded CAG repeat length in the *HTT* gene [57, 58]. The mutable normal allele (27–35 CAG repeats), otherwise referred to as intermediate alleles or high normal alleles, is defined as having a normal phenotype. Males with mutable normal alleles are at risk of transmitting an HD allele with reduced or full penetrance (≥36) to offspring, even though they themselves will not develop the disease [59]. Hendricks et al. estimated that the probability that a male with intermediate or “high normal” (27–35) CAG repeats in one allele will have an offspring with an expanded penetrant allele ranges from 1/6,241 to 1/951. In recent years however, there has been some emerging evidence of clinical disease in this group. Observations derived from the Prospective Huntington Disease At-Risk Observational Study (PHAROS) found that patients with intermediate repeat length expansions overlapped on some behavioral measures of the Unified Huntington’s Disease Rating Scale (UHDRS) with HD patients [60]. Kenney and colleagues reported a 65-year-old male with autopsy-proven HD and 29 CAG repeats, suggesting that in rare cases, HD phenotype can occur in the normal CAG repeat range [61]. Other cases of HD phenotype with intermediate CAG repeats have been reported [62]. Motor and behavioral abnormalities have been identified in individuals with intermediate length CAG repeats in the Cooperative Huntington’s Observational Research Trial (COHORT) [63].

CAG repeat length is the major determinant of age at onset for HD with larger expansions responsible for earlier-onset disease [64, 65]. Individuals with shortest CAG expansions appear to have the best prognosis [66]. Variability in age at onset occurs after controlling for repeat length, especially in individuals with CAG repeat between 40 and 50, where the repeat only determines 44% of the variability. In Venezuelan HD kindreds, the variance in age of onset was attributable to genes other than the *HTT* gene and environmental factors [67]. Genome-wide linkage analysis targets 2p25, 2q35, 6q22 [68]. Other suggested regions are on chromosome 5 (5p14 and 5q32). The Huntington disease MAPS study showed linkage for modifier of age at onset at 6q23–24. Evidence for linkage was also found at 18q22 [69].

The gender of the affected parent also modifies age at onset with an earlier age at onset seen with paternal inheritance [65]. Children with juvenile onset have greater expansions typically between 60 to 100 CAG repeats. Most juvenile-onset cases (90%) have inherited HD from an affected father. It has been determined that marked expansion of the repeat length likely occurs in spermatogenesis, accounting for this sex-of-parent effect on the inheritance of juvenile-onset HD [70, 71].

The pathogenic cause of the progressive neurodegeneration in HD is not known, but studies point to free radical toxicity [72], glutamate toxicity [73], and caspase activation [74–77] as potential factors in pathogenesis. The neurodegeneration affects the striatum prominently, but entire brain
weight is decreased, and neuronal loss in cortex and other nuclei has been documented. In the striatum there is predominant loss of spiny projection neurons with preservation of the aspiny interneurons and large aspiny acetylcholinesterase positive neurons [77]. This pattern has been produced in animals by excitotoxic lesions and by the systemic or local injection of mitochondrial toxins [79]. For example, intrastriatal injections of quinolinic acid, a glutamate agonist, into rat brain also reproduces closely the neurodegenerative changes found in HD [80] and serves as a model of an excitotoxic lesion. Intraperitoneal administration of the mitochondrial toxin 3-nitropropionic acid also causes progressive cell death in the striatum of rodent and non-human primates. Garcia and colleagues describe activation of the c-Jun N-terminal kinase pathway during chronic 3-nitropropionic acid infusion leading to dorsolateral striatal cell death. In addition, they found that the activation of c-Jun N-terminal kinase pathway caused phosphorylation of c-Jun in vivo and in vitro models, which supports the role of phosphorylated c-Jun in causing selective striatal cell death [81]. The authors postulate that similar activation of this pathway may take place in HD brains by interactions with free radicals or glutamate toxicity.

Mitochondrial dysfunction and abnormal energy metabolism is well documented in HD. However, the precise cause and mechanism has not been clearly defined. Data from a number of studies suggest that the mutant huntingtin (Htt) protein impairs mitochondrial function directly as well as and indirectly by dysregulation of transcriptional processes [82]. The resulting defects include reduced Ca\(^{2+}\) uptake capacity, defects in the electron transport chain (ETC) activity, and increased sensitivity of mitochondria to Ca\(^{2+}\)-induced permeability transition pore (mPTP) opening. Changes in mitochondrial permeability can cause cytochrome c release and subsequent caspase activation leading to apoptotic cell death. Cell models have demonstrated defects in mitochondrial complex II/III activity and to a lesser extent complex IV activity [83]. Evidence of mitochondrial respiratory chain defects has also been identified in HD tissue [84]. The role of peroxisome proliferator-activated receptor-coactivator 1 (PGC–1α), a transcription cofactor that regulates mitochondrial biogenesis and function, may provide a link between transcription dysregulation and mitochondrial dysfunction in HD [85]. In addition, there is evidence that mutant Htt protein impairs intracellular trafficking of mitochondria, providing further evidence for a possible pathogenic role of mitochondrial dysfunction in HD [86].

Magnetic resonance spectroscopy (MRS) has documented an increase in brain lactate in patients with HD as might be expected in the case of mitochondrial dysfunction or increased excitatory stress [87, 88]. The size of the Htt gene repeat has been reported to affect mitochondrial function and may play as a disease modifier of other neurodegenerative disorders. In the GenePD Study, there was no effect on age at onset of familial Parkinson disease, although 5.2% of the sample had repeats in the intermediate range (27 to 35 repeats), suggesting a relatively high prevalence of intermediate allele carriers in the general population [89]. In juvenile HD patients, MRS has documented elevated glutamate, mainly in the striatum but also in extrastriatal areas, and low striatal creatine [90]. In adults, the glutamate elevations occur in preclinical and manifest patients, but low creatine levels were found only in preclinical patients [91]. Evidence of mitochondrial dysfunction has also been demonstrated in peripheral tissue. HD patients subjected to incremental cardiopulmonary exercise were found to have a lower anaerobic threshold on ventilatory and cardiometabolic parameters associated with an increase in plasma lactate, compared with controls [92].

The mRNA for the Htt gene is widely expressed in all tissues [93]. The mutated form of Htt protein is found in both affected and unaffected regions of the brain [94]. Thus, the regional specificity of the neuropathology is not explained by a differential expression of the Htt gene in the brain. In a study using samples of caudate and whole blood from HD patients, it was shown that transcription is deregulated in large genomic regions in coordinated fashion and that transcription in these regions is associated with disease progression [95]. This supports the notion of a common genome-wide
mechanism of disruption of RNA transcription in the brain and periphery of HD patients [96]. Indeed, there is growing evidence that HD is not merely a brain disease but a systemic disorder [97].

Htt is a cytoplasmic protein. It is believed to play an important role in a number of biological processes, including synaptic transmission, intracellular transport, and neuronal transcription [98]. Using biochemical and live cell imaging, Marcora and Kennedy demonstrated that wild-type Htt also stimulates the transport of nuclear factor k light-chain-enhancer of activated B cells (NF-kB) out of dendritic spines and supports active NF-kB in neuronal nuclei. Also intriguing is the discovery that normal Htt protein helps support brain-derived neurotrophic factor production in cortical neurons that is then transported to striatal neurons. A recent study also demonstrated a role of Htt in mitotic spindle orientation in Drosophila and mouse models [99].

The proteolytic products of abnormal Htt containing the expanded polyglutamine sequences are sequestered in the nucleus where they interfere with gene regulation [98]. Neuronal intranuclear inclusions occur in a mouse model transgenic for the HD mutation [100]. These insoluble inclusions contain a cleavage product of Htt formed only when polyglutamine stretches are pathologically expanded [101]. Subsequent ultrastructural study of postmortem brain tissue from affected HD patients revealed similar neuronal intranuclear inclusions containing Htt [102]. These inclusions are specific to regions of the brain affected in HD. The microtubular system of the cell may aid mutant Htt protein to gain access to the nucleus and help to form inclusions [103, 104]. One laboratory study demonstrated altered cell survival in response to microtubule depolymerizing agents, with different responses depending on the presence or absence of mutant Htt [105]. The mutant Htt protein’s abnormal stretch of polyglutamines may confer new properties to the protein and allow altered interactions with other proteins. For example, transglutaminase has been shown to crosslink with the pathologically expanded polyglutamine segment of Htt to help to form neuronal intranuclear aggregates. Several other proteins have been described that interact with Htt [76, 106–111], and these interactions may possibly interfere with normal cell activity in select neurons (Figure 10.1).

Mutant Htt interferes with the function of the cAMP responsive element binding protein (CBP), which is required for neuronal health; its absence results in selective neuronal vulnerability and death [112]. CBP is an acetyltransferase enzyme that activates transcription of important cell-sustaining genes through acetylation of histones. Mutant Htt binds with CBP and prevents its normal function, thus interfering with gene transcription by reducing histone acetylation [113]. Further research in a Drosophila model of HD has shown that inhibiting histone deacetylase, thus increasing

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**Figure 10.1** Possible pathogenesis of HD.

- Toxic gain
- Mitochondrial dysfunction
- Dysregulation of neuronal signaling capabilities
- Transcriptional dysregulation
- Decreased neurotrophic support
overall histone acetylation, can retard progression of neuronal cell loss and improve survivability of the model [114]. Other examples of Htt disruption of transcriptional regulation are its action in decreasing D2 receptor gene expression [115] and mRNA data in transgenic mice that demonstrate alterations in several genes, including those for neurotransmitter receptors and intracellular signaling systems [116]. Additionally, there is relative loss of brain-derived neurotrophic factor production, thus neurotrophic support, due to down regulation of transcription by mutant Htt, that may lead to selective vulnerability in striatal neurons [117]. The role of adenosine A(2A) receptors in modulating synaptic functions and maintaining levels of brain-derived neurotrophic factor has also been explored [118].

Thus, mutant Htt protein potentially causes cell death through pathways involving increased oxidative stress, mitochondrial dysfunction, dysregulation of neuronal signaling capabilities, or gene expression and decreased neurotrophic support. Interaction of the mutated Htt protein with various other proteins, such as the small guanine nucleotide-binding protein Rhes, localized to the striatum, leads to cytotoxicity and may contribute to the localized neuropathology of HD [119].

The development of mouse models in HD has been tremendously exciting and has rapidly expanded our understanding of the disease process. It has been discovered that the absence of Htt causes embryonic death in mice [120], and that deletions within chromosome 4 that involve the Htt gene do not cause HD, suggesting that the mutant protein exerts its effect through a gain in function rather than a loss of function [121]. Transgenic mice expressing exon 1 of the mutant human Htt gene develop a progressive neurologic syndrome similar to that seen in humans [122]. This and other murine genetic models exhibit also some pathological changes seen in HD, making these mouse lines excellent models for preclinical evaluation of novel therapeutic approaches.

A number of potential new therapeutic targets for HD have been investigated in animal and cellular models of HD [123]. However, further studies would be required before such findings can be translated to clinical medicine. Autophagy, which enhances the clearance of misfolded protein, may provide a potential treatment strategy in neurodegenerative proteinopathies [124]. Inducers of neuronal autophagy have been studied as potential therapeutic targets [125]. Inhibition of type 2 transglutaminase, which is involved with apoptosis and autophagy regulation, may also provide an avenue for future therapeutic studies [126]. McConoughey and colleagues demonstrated that transglutaminase inhibition attenuated degeneration in a Drosophila model of HD, and also protected mouse HD striatal neurons from excitotoxicity [127]. Proteases belonging to the matrix metalloproteinase (MMP) family may play a role in the cleavage of mutant Htt, thus indicating a potentially important role of MMPs in Htt proteolysis and toxicity [128]. Inhibition of sirtuin 2 (SIRT2) may possibly alter sterol biosynthesis and decrease mutant Htt toxicity in cellular and invertebrate models of HD [129].

In one study, nicotinamide was demonstrated to increase mRNA levels of brain-derived neurotrophic factor (BDNF) as well as peroxisome proliferator-activated receptor gamma co-activator 1-alpha (PGC–1α), and improve motor deficits in a mouse model [130]. One study using mouse models also demonstrated restoration of Htt function in BDNF transport with the calcineurin inhibitor FK506 [131]. A recent study showed that Meclizine suppressed apoptotic cell death in a murine cellular model of polyglutamine toxicity [132]. Hsp70 and Hsp40, two major cytosolic molecular chaperones, suppress mutant Htt toxicity in animal models [133]. One study demonstrated inhibition of polyglutamine (polyQ) protein aggregation by human cytomegalovirus UL97 kinase in a cellular model of HD [134]. The role of type 1 cannabinoid receptors has also been studied. In mouse models, receptor deletion aggravated the symptoms, neuropathology and molecular pathology of HD, while pharmacological administration of the cannabinoid Δ(9)-tetrahydrocannabinol ameliorated those parameters [135].

Recent studies have also provided further insights into possible mechanisms related to clinical manifestations of HD. Neuropathological studies have shown loss of oxytocin- and vasopressin-expressing
neurons, with increases in the number of cocaine- and amphetamine-regulated transcript (CART)-expressing neurons [136]. These alterations in peptide expression of hypothalamic neurons may influence the emotional and metabolic disturbances seen in HD. Studies of motor cortical plasticity in HD gene carriers (premanifest and very early manifest gene carriers) have revealed evidence of reduced inhibition to continuous theta burst stimulation [137]. Early cognitive deficits are probably related to synaptic and cellular dysfunction [138]. A postmortem neuropathological study found an association between motor dysfunction and cell loss in the primary motor cortex, as well as between major mood symptomatology and cell loss in the anterior cingulate cortex [139]. A polymorphism in an autophagy-related gene (Atg7) was found to possibly modify age of disease onset in one study [140].

Neuropathology

HD affects both subcortical and cortical areas. The striatum, particularly the medial region of the caudate followed by the putamen, is most severely affected [141, 142]. Other areas such as the globus pallidus, thalamus, and amygdala are involved to a lesser extent [143, 144]. The hippocampus is relatively spared [145]. The cell loss in the striatum preferentially affects the medium spiny GABAergic neurons, which also contain enkephalin, substance P, and calbindin [27]. The neurons containing enkephalin appear to be affected before those containing substance P. On the other hand, the cholinergic and somatostatin-containing neurons are spared (Figure 10.2). A particular class of striatal interneurons, characterized by immunoreactivity for the calcium-binding protein calretinin, was found to be selectively increased in HD brains compared with controls [146]. It has been postulated that the preferential loss of striatal neurons projecting to the lateral globus pallidus gives rise to the clinical manifestation of chorea. The rigid- akinetic symptoms, on the other hand, may be a consequence of the additional loss of striatal neurons projecting to the medial segment of the pallidum [147]. Another possibility may be related to neuronal dysfunction, which occurs before cell death [123]. A neuropathological classification system devised by Vonsattel and colleagues graded the severity of HD pathology based on microscopic and macroscopic criteria in the striatum [148]. The severity correlated with the degree of clinical disability. The grades ranged from Grade 0, which consisted of no gross or microscopic abnormalities, and Grade 1, which involved mild to moderate microscopic evidence of gliosis in the putamen and caudate respectively without macroscopic changes, to Grade 4 disease, with severe caudate, putamenal and pallidal atrophy, with severe gliosis and neuronal loss throughout the caudate and putamen and moderate gliosis in accumbens.

![Figure 10.2 Pathology of Huntington disease.](image-url)
Subsequent studies revealed evidence of more widespread disease with cortical involvement [143–144, 149]. The degree of cortical atrophy is less severe than in the striatum. There is an approximate 20–30% reduction in cross-sectional area in the frontal, anterior parietal, anterior temporal, and posterior temporal regions [145]. The large pyramidal neurons in deeper cortical layers V and VI are preferentially affected. Pathologically, there is no significant astrogiosis involved in cortical degeneration, in contrast to the findings in the striatum [148, 150]. The cortical volume loss has been found to correlate with the neuropathological grade of disease severity. In addition, the rates of cortical and subcortical atrophy correlates with CAG repeat length [151]. Intranuclear inclusion bodies may also be found in the cortex and striatum of patients with HD [152]. They may be seen in all cortical layers and in the medium-sized neurons of the striatum, but not in the neurons of the globus pallidus or cerebellum [102]. These inclusions contain truncated, ubiquitinated Htt protein. The frequency of the cortical intranuclear inclusions correlated directly with the size of CAG expansion but was inversely related to the age at onset and death [152]. Other CAG trinucleotide disorders such as dentatorubropallidoluysian atrophy may also demonstrate similar inclusions, consisting of polyglutamine protein [153]. The finding of dystrophic neurites has also been reported, predominantly in cortical layers V and VI in HD brains [102]. DiFiglia and colleagues postulated that these dystrophic neurites were distended axon terminals. Increased basal ganglia iron levels have also been identified on magnetic resonance imaging in HD, and its distribution may be related to the pattern of neurotoxicity observed in HD [154].

**Imaging**

Serial MRI scans to assess basal ganglia volume [155] or specialized MRI scans to assess cortical thickness [156] may some day be useful to follow the progression of disease and effects of potential neuroprotective interventions. A report of voxel-based morphometry MRI revealed patterns of gray and white matter loss in gene-positive patients without motor evidence of disease, indicating that the pathological changes of HD begin before clinical onset [157]. Using volumetric measurements of caudate, putamen, total striatum, globus pallidus, thalamus, total gray and white matter, one study demonstrated that there were faster rates of atrophy in striatum, total brain, and cerebral white matter in prodromal individuals compared with controls [158]. Using the gray matter segment of MRI scans, Klöppel and colleagues explored the usefulness of a multivariate support vector machine to automatically identify presymptomatic HD gene mutation carriers in the absence of any a priori information [159]. Presymptomatic HD gene mutation carriers close to estimated diagnostic onset were successfully separated from controls on the basis of single anatomic MRI scans. A study of 523 prodromal HD subjects found evidence of volume decrement, particularly affecting the posterior and superior cerebral regions, even in the “midway to onset group” with an estimated proximity to clinical onset of 9–15 years [160]. Paulsen and colleagues assessed brain morphology by MRI in preclinical HD subjects [161]. Preclinical participants had substantial morphologic differences from controls throughout the cerebrum. Volume of the cerebral cortex was significantly increased in preclinical HD, whereas the basal ganglia and cerebral white matter volume were substantially decreased. In another study, not only were the volumes of the caudate nucleus and putamen reduced in premanifest HD long before predicted onset (>10.8 years), but atrophy of the accumbens nucleus and pallidum was also apparent in premanifest HD [162]. In addition, the 12-month whole-brain atrophy rates were greater in early HD individuals as well as premanifest gene-positive carriers less than 10.8 years from predicted diagnosis compared with controls [163]. All gene-positive groups also showed faster rates of caudate and putamen atrophy over 12 months compared with controls. The whole-brain and caudate atrophy rates were found to correlate with the UHDRS total functional capacity score as well as with cognitive and quantitative motor measures. MRI changes in the hypothalamic region have also been demonstrated before clinical onset [164]. A study using
magnetization transfer MR imaging demonstrated degeneration of the subcortical and cortical gray matter in HD gene carriers, with correlations between regional magnetization transfer ratios and several clinical variables [165]. Nopoulos and colleagues found evidence of reduced intracranial volumes in prodromal HD compared with controls, lending support to the theory of abnormal neurodevelopment in HD [166].

**Treatment**

Treatment of patients with HD requires a coordinated effort on the part of a medical, psychiatric, social service, and physical or occupational therapy team [167–170]. Treatment is tailored to the treatable symptoms and cannot be generalized to all patients or to an individual patient over all stages of the illness (Figure 10.3).

**Disease-modifying therapy**

For those who are gene-positive and asymptomatic or early symptomatic, focus should be on treatments that may potentially slow disease progression. CARE-HD, the first national trial exploring two of these interventions, showed that neither remacemide nor CoQ10 given alone or in combination had any significant effect on progressive functional decline [171]. However, the CoQ10 treatment arm showed a trend toward slowing the disease, with participants able to handle daily finances and domestic chores longer. In addition, patients had improved

![Figure 10.3](image-url)
attention and were less distressed. A follow-up study, 2CARE, aims to assess higher doses of CoQ10 and will be the largest therapeutic clinical trial in HD to date. A safety and tolerability study of higher dosages found that CoQ10 was well tolerated, with over 80% of subjects achieving the target dosage of 3,600 mg/day [172]. The most common adverse events were gastrointestinal symptoms. A pilot study conducted to study the effect of minocycline in delaying disease progression showed that it was well tolerated and had no serious adverse events [173]. Although minocycline at 200 mg/day was well tolerated and safe over 18 months of treatment, there was no meaningful slowing of the rate of functional decline [174]. A recent futility study of minocycline showed that although futility was not supported by the primary analysis, the data provided insufficient evidence to justify a larger and longer trial of minocycline in HD [175]. The PREQUEL study will evaluate CoQ10 in gene-positive, preclinical HD patients [176].

**RNA interference and antisense technology** has shown efficacy in animal models for the silencing of molecular targets in HD and is being explored as a potential therapeutic strategy in HD [184].

**Symptomatic therapy**

Psychiatric symptoms should be addressed as part of the multidisciplinary approach to HD. Depression often responds partially to treatment with standard antidepressants. Carbamazepine or valproate may improve patients with a manic disorder. Delusions and paranoia often respond to neuroleptics. Neuroleptics also decrease chorea, but care is needed not to increase to doses that impair the individual’s functional level. Low doses of neuroleptics are often well tolerated, whereas high doses are rarely helpful and may impair motor function, such as swallowing, and cognitive function. Irritability and emotional dyscontrol are common in patients with HD and can cause great disturbance in their families or living situation. Behavioral modification on the part of the patient and caregiver can alleviate such stressful situations. Carbamazepine, selective serotonin reuptake inhibitors, clonazepam, propranolol, valproate, and clomipramine are just some of the medications that may be helpful. Risperidone may be useful for the management of psychiatric disorders in patients with HD [185].

Chorea in HD may be treated with neuroleptics effectively. Other agents used include tetrabenazine, benzodiazepines, and propranolol. In a prospective
open-label study, high dose olanzapine (30 mg/day) was found to be useful in chorea [186]. In another randomized trial, amantadine hydrochloride treatment at doses of 300 mg/day had no effect on Huntington chorea, although most patients felt subjectively better [187]. An open-label pilot study suggested that levetiracetam may be efficacious in reducing HD chorea in doses up to 3,000 mg/day [188].

In August 2008, tetrabenazine was approved by the Food and Drug Administration (FDA) for the treatment of chorea in HD patients. Tetrabenazine’s exact mechanism of the antichorea effects is unknown but is believed to be related to its effect as a depletor of monoamines by reversibly binding to the type 2 vesicular monoamine transporter (VMAT2) [189]. Tetrabenazine has more than 75% bioavailability and is 82 to 85% protein-bound. It is metabolized hepatically by the CYP 450 enzymes. In the pivotal clinical trial, 84 patients were randomized to either tetrabenazine up to 100 mg/day or placebo for 12 weeks [189]. Tetrabenazine effectively lessened chorea in ambulatory patients. The treatment effect was 3.5 UHDRS points, with 69% having at least a 3-point decline in total chorea score and 19% having at least a 10-point decline (28-point maximum). The clinical global improvement scores showed 44% of active treatment and 7% of placebo were very much improved or much improved. Serious adverse events included suicide and restlessness. When using strong CYP2D6 inhibitors, the dose of tetrabenazine should be halved. The FDA suggests CYP2D6 genotyping when considering doses of more than 50 mg/day. Also, tetrabenazine has a risk evaluation and mitigation strategy with goals of minimizing the risk of drug-associated depression and suicide, promoting informed prescribing, titration, and dosing, and minimizing the risk of interactions with other drugs. In another trial, 68 patients were treated with tetrabenazine for a mean period of 34.4 months [190]. Tetrabenazine was well tolerated and produced long-term clinical benefit, but the magnitude was reduced, despite a progressive increase of the doses. In a withdrawal study, 30 patients treated with tetrabenazine were assigned to be withdrawn in a double-blind, staggered fashion [191]. The chorea scores of subjects withdrawn from tetrabenazine treatment increased by 5.3, whereas the scores of the group with partial or no withdrawal of tetrabenazine treatment increased by 3.0 units (P = 0.0773). A post hoc analysis of the linear trend was positive for re-emergent chorea (P = 0.0486). No serious adverse events were reported after abrupt withdrawal of tetrabenazine treatment. The trend for the re-emergence of chorea supports the effectiveness of tetrabenazine in reducing chorea. Another publication by Kenney and colleagues also outlines its efficacy in treatment of hyperkinetic disorders including HD chorea [192]. In a small study of 6 HD patients, aripiprazole was compared to tetrabenazine [193]. Both had similar effects on UHDRS chorea scores, but aripiprazole was associated with less sedation and was better tolerated. There was a slight trend for improvement in depression with the aripiprazole-treated patients, but this was not significant. In a multicenter, placebo-controlled trial, riluzole 200 mg/day decreased the intensity of chorea without improving functional capacity [194]. It caused reversible liver transaminase abnormalities that required long-term monitoring. Deep brain stimulation of the bilateral globus pallidus may have the potential to optimize motor response in HD, improving chorea without worsening bradykinesia [195]. In a small report of 2 HD patients who underwent pallidal DBS, sustained improvement in chorea was seen after 2 years follow-up. However, one patient had returned to his pre-operative level of functioning due to progressive deterioration in gait, bradykinesia and dystonia. In addition, both patients experienced further decline in neurocognitive functioning [196]. Dystonia and rigidity may complicate end-stage disease and if it is uncomfortable, or if there is interference with hygiene or care of the patient, then excessive tone can be treated with local injections of botulinum toxin type A [168–170].

Frequent awakening during sleep may become problematic and sleep cycles may reverse. Disturbed night-time sleep and a delayed sleep phase can occur in HD, and these may be associated with...
depression and lower cognitive and functional performance [197]. Avoidance of daytime sleeping and other basic good sleep hygiene practices as well as medications, such as clonazepam, trazodone, or amitriptyline at bedtime can help to modify this problem. Because of impulsivity and excessive movements some patients will need to be placed in modified floor beds at night and may need special chairs (e.g. Broda chair) for daytime seating.

Juvenile cases of HD are often treated with carbidopa and levodopa to reduce prominent bradykinesia, posture abnormalities, rigidity, and dystonia. One case report cites success in such a case using the dopamine agonist, pramipexole [197].

Nutrition is important in HD patients as their caloric requirements may be increased. At the end stage, patients are bed-bound, mute, and rigid. Eventually dysphagia and aspiration become problematic. Changing the shape of cups and stable posture, in consultation with a speech therapist, may lessen the chance of aspiration [199]. The patient’s wishes regarding gastric tube feeding should be ascertained in preparation for this stage of illness. Longer CAG repeat lengths are associated with earlier age at nursing home placement as well as earlier age at percutaneous endoscopic gastrostomy placement, but the interval from the onset of HD symptoms to either of these endpoints is similar regardless of CAG repeat length [200].

**Box 10.1 Phenocopies of HD**
- HDL1 – AD (prion protein, PRNP; 20p12)
- HDL2 – AD (junctophilin, JPH3; 16q24.3)
- HDL3 – AR (4p16.3)
- DRPLA – AD (c-Jun NH-terminal kinase, JNK, 12p)
- Neuroacanthocytosis – AR (VPS13A, 9q21)
- McLeod syndrome – X-linked (HK, Xp21)
- Mitochondrial encephalomyopathies
- Benign hereditary chorea – AD (TIF1-1, 14q13.1–q21.1)
- Ataxia-Chorea:
  - o SCA2 (ataxin–2, 12q24.1), SCA1, SCA3, SCA12
  - o SCA17 – AD (HDL4) (TATA-Box binding protein, 6q27)
  - o Friedreich’s ataxia (GAA repeat expansion in frataxin, 9p13)
  - o Ataxia telangiectasia (ATM gene, 11q22–23)
- Neurodegeneration with brain iron accumulation (NBIA)
  - o Pantothenate-kinase-associated neurodegeneration (PKAN)
  - o Neuroferritinopathy
- Psychogenic chorea
- Wilson disease

### Other genetic causes of chorea

A number of genetic causes of chorea may mimic the HD phenotype, and may be clinically indistinguishable from HD. HD phenocopies should be considered in the setting of a compatible clinical picture with negative HD gene testing (Box 10.1).

**Dentatorubral-pallidoluysian atrophy (DRPLA)**

DRPLA is an autosomal dominant neurodegenerative condition, caused by an unstable CAG expansion on chromosome 12 [201]. The unstable CAG repeats also exhibit the phenomenon of

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**Video 10.7 Chorea in ataxia telangectasia**

This 10-year-old patient had a normal birth. She had normal early development milestones, except walking, that started at the age 2. At 18 months she developed mild choreiform movements involving limbs and trunk. She remained stable until the age 9, when she started to present gait ataxia. She also developed recurrent infections of the upper and lower respiratory tract. Immunodeficiency with lymphopenia was detected. Telangiectasias on the bulbar conjunctiva appeared bilaterally. A brain MRI showed cerebellar atrophy. Chromosomal instability was then detected, leading to a diagnosis of ataxia telangectasia. The videotape shows small jerks of the hands and feet that look like fidgeting. Lower limbs are held unstably against gravity. Instability and hyperkinetic features are visible while standing, walking and running.

[Video courtesy of Nardo Nardocci, MD, Milan, Italy]

anticipation. DRPLA is particularly prevalent in Japan, although cases have also been identified in European and African-American families [202, 203]. Similar to HD, the age of onset is correlated with CAG repeat length, accounting for 62% of the observed variation in age at onset [204]. The mean age of onset is in the fourth decade, and the condition manifests as cerebellar ataxia, choreoathetosis, dystonia, rest and postural tremor, parkinsonism, and dementia [203]. Early-onset DRPLA, typically presenting before 20 years of age, may manifest with variable features of myoclonus, epilepsy, and mental retardation.

Huntington-like diseases (HDLs)
The mutation causing Huntington disease-like 1 (HDL1) has been mapped to the prion protein (PRNP) gene on chromosome 20 [205]. The mean age of onset is 20 to 45 years [206]. Clinical features include involuntary movements, incoordination, dementia and psychiatric symptoms [207]. Seizures have also been described in this condition [208].

Huntington disease-like 2 (HDL2) is another autosomal dominant condition with similar clinical features to HD. It is caused by a CTG/CAG trinucleotide repeat expansion within the junctophilin–3 (JPH3/HDL2) gene [203]. The disorder occurs predominantly in individuals of African origin. It classically presents in the fourth decade, and consists of abnormalities of movements such as chorea, dystonia, bradykinesia, rigidity, tremor, gait abnormalities, as well as dysartria, hyperreflexia, psychiatric symptoms, and dementia. Huntington disease-like 3 (HDL3) is an autosomal recessive disorder that has been described in one family. The symptoms typically begin at age 3–4 years. Clinical manifestations include chorea, dystonia, gait disorder, spasticity, seizures, mutism, intellectual impairment, and bilateral frontal and caudate atrophy. Spinocerebellar ataxia type 17 (SCA 17), also referred to as Huntington disease-like 4 (HDL4), is an autosomal dominant disorder. It is caused by a mutation of the TATA box-binding protein (TBP) gene on chromosome 6, resulting in abnormal CAG triplet repeats. Similar to HD, the age of onset is inversely correlated to the CAG repeat length. The mean age of onset is between 19 and 48 years [208]. Clinical features include ataxia, dementia, psychosis, dystonia, chorea, parkinsonism, pyramidal signs, and seizures [209].

Neuroacanthocytosis
This autosomal recessive disorder is caused by mutations in the VPS13A gene on chromosome 9q21 [199]. It typically presents in the third and fourth decades of life, although its age of onset may range from 8 to 62 years. Clinical features include orolinguial (eating) dystonia, chorea, tics, stereotypies, as well as cognitive and personality disturbances, seizures, dysphagia, dysarthria, vertical ophthalmoparesis, parkinsonism, amyotrophy, areflexia, and elevated serum creatine kinase [203]. Eating dystonia, involving tongue protrusion during eating, was present in 16% of individuals in one series [210]. The presence of this uncommon symptom is highly suggestive of the diagnosis [199]. McLeod syndrome is an X-linked recessive form of acanthocytosis. It may cause depression, bipolar disorder and personality disorders, in addition to chorea, involuntary vocalizations, seizures, liver disease, hemolysis, motor axonopathy, and elevated creatine kinase levels [211–213].

Video 10.8 Chorea in Neuroacanthocytosis
This patient is 39 years old. At age 29 she developed generalized choreic movements with prevalent cranial involvement that progressed mildly. A brain MRI showed mild atrophy of cerebellum and caudate, laboratory investigations showed increased level of creatine phosphokinase and acanthocytosis (with 10% of acanthocytes). Her parents were consanguineous and she had a brother and a sister with mild adult-onset dyskinesias and increased creatine kinase levels. A chorein deficiency was identified by Western blot leading to the diagnosis of neuroacanthocytosis. The videotape shows mild choreic movements which are observed at rest. An occasional negative myoclonus of the lower limbs is present when standing or walking. [Video courtesy of Alberto Albanese, MD, Milan, Italy]
Neurodegeneration with brain iron accumulation

Pantothenate-kinase-associated neurodegeneration (PKAN) and neuroferritinopathy, two other conditions that may present similarly to HD, have characteristic features on brain MRI. PKAN, also referred to as neurodegeneration with brain iron accumulation type 1, or NBIA1, is an autosomal recessive condition caused by mutations in the pantothenate kinase (PANK2) gene. It typically presents in childhood, with dystonia, dysarthria and rigidity. Atypical cases involving late-onset and slowly progressive symptoms have also been described [214]. MRI appearances in PKAN consist of global pallidal hypointensity with a central region of hyperintensity, and are often referred to as the “eye of the tiger” sign. Neuroferritinopathy, caused by mutations in the FTL gene, has a mean age of onset of 40 years. MRI findings include symmetrical cystic degeneration of the globus pallidus and putamen, and abnormal iron deposition [215, 216]. NBIA is covered in greater detail in Chapter 8.

Benign hereditary chorea (BHC)

The earliest report of hereditary non-progressive chorea of early onset described two brothers who developed a non-progressive syndrome of inherited childhood-onset chorea [217]. Subsequent descriptions were heterogeneous in their clinical manifestations [218]. In some cases there was delayed motor development, with one report of child who was wheelchair-bound until the age of 9 [219, 220]. Intellectual impairment was also reported in some cases [221]. Associated symptoms of intention tremor [222] and sensorimotor hearing loss [223] have also been described. The diagnostic accuracy of the syndrome has been reviewed critically in several reports [218, 224–226]. In a follow-up study on 11 families originally diagnosed with benign hereditary chorea, the diagnoses were subsequently changed in 9 [218]. These alternate diagnoses included HD, myoclonus dystonia, idiopathic torsion dystonia, and ataxia-telegiectasia. This raised the concern that benign hereditary chorea may not be an etiological diagnosis, but rather a syndrome requiring further investigation. The identification of the locus for BHC on chromosome 14 [227, 228], and the subsequent finding of mutations in the TITF1 gene [229] have allowed for a more accurate characterization of the disease. The TITF1 gene, which is involved in the organogenesis of the lung, thyroid, and the basal ganglia, is inherited in an autosomal dominant manner. The neurological symptoms typically begin in childhood, but usually become less severe or even disappear in adulthood. There has been limited success with pharmacological treatments, although symptomatic improvement with levodopa therapy has been reported in 2 siblings [230]. Mutations in the TITF–1 gene have also been found in individuals with chorea, congenital hypothyroidism, and pulmonary dysfunction [231]. The term “Brain-Thyroid-Lung syndrome” was coined in reference to the multisystem involvement that may be seen with TITF1 mutations, distinct from the classic presentation of BHC [232, 233].

Psychogenic chorea

Rarely, chorea can be a component of a psychogenic movement disorder or can be seen in patients who have family history of HD and become convinced that they are developing early stages of HD, even in the setting of negative DNA test for HTT mutation [234].

Conclusion

Huntington disease is an autosomal dominant neurodegenerative condition that causes disorders of motor control, behavioral and cognitive function, and involuntary movements. Cognitive and behavioral changes may occur years prior to the onset of definitive motor signs. The management of HD involves a multidisciplinary approach, taking into account cognitive impairment, psychiatric disturbances, motor symptoms, sleep disturbances, and nutrition, in addition to genetic and social issues. Treatment of HD currently remains symptomatic, chiefly directed against chorea, but treatment of various comorbidities, including anxiety and depression, is also often required. In the setting of a compatible clinical picture and a negative
gene test. HD phenocopies should be considered, although these account for only a small proportion of cases.

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CHAPTER 11
Acquired Choreas

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Historical background

The clinical phenomenon of chorea has been recognized for many centuries, and has been attributed variously to psychological or organic causes [1]. The term derives from the Greek word χορεία which describes a type of traditional circle dance, and suggests the rapid, jerk-like, albeit irregular and unpredictable quality of the movements. The involuntary movements were first described as dance-like by the physician and alchemist Paracelsus in the 16th century. Paracelsus used the term “St Vitus’ dance” (Chorea Sancti Viti) to refer primarily to epidemics of “dancing mania” which occurred in Europe in medieval times. This dancing mania was also known in various locations as St John’s chorea, dansé de St Guy (the French name of St Vitus), or the dancing procession of Echternach. A form of this latter manifestation persists as an annual celebration in Luxembourg [2]. This attribution of dancing mania to St Vitus may have been because sufferers were cured after dancing in a chapel dedicated to St Vitus [3] (now known as the patron saint of dancers), although other explanations can be found. Several of these epidemics were described in various countries in the middle ages, and resulted in significant fatalities from exhaustion, stroke, and heart attack. They clearly appear to have been psychogenic in origin [2,4]. The theory that these epidemics were due to ergotism appears unlikely as chorea is not a feature of ergot toxicity.

In the 17th century the English physician Thomas Sydenham noted the development of chorea in children, and attributed this to a local epidemic of dancing mania, hence the somewhat confusing term “St Vitus’ dance” [3]. This childhood disorder was also known as chorea minor, to distinguish it from the wider epidemics of dancing mania in adults, chorea major. The connection with rheumatic fever, and the use of the eponym “Sydenham’s chorea” was only made later by Charcot in 1887 [1]. The hereditary nature of an adult-onset form chorea in families on Long Island, New York, was reported by George Huntington in 1872, although this was disputed by Charcot who believed that most forms of chorea were variations of a similar inherited condition [1]. Clarification of different forms of hereditary and acquired chorea was made by William Osler in 1894 (On Chorea and Choreiform Affections) [1].

Phenomenology

Chorea refers to involuntary movements of limbs, trunk, neck, or face, which rapidly flit from region to region without regular pattern. Mild chorea can appear as subtle fidgetiness or restlessness, of which
the patient may not even be aware. Involuntary movements may be disguised as purposeful movements, such as scratching the ear or fiddling with clothing (parakinesia). Unlike dystonia, where the same muscle groups are activated repetitively, body parts are involved in an irregular manner. There is an inability to maintain a fixed posture, “motor impersistance,” which appears to be due to lapses in the ability to perform the task, as the converse of the intrusions of fragments of movements into voluntary tasks. This phenomenon results in the “milkmaid’s grip,” as if squeezing the udders of a cow, and the “trombonist’s tongue,” which moves back and forth in the mouth.

Chorea may occur with, but should be distinguished from, athetosis, which is a slower, writhing movement, and dystonia, in which abnormal movements are repeated, or there is a sustained abnormal posture.

Although it strictly means “abnormality of movement,” the term “dyskinesia” usually refers more specifically to movements which are choreiform, most commonly “tardive dyskinesia” or “l-dopa-induced dyskinesia.”

### Epidemiology

The epidemiology of chorea reflects that of the underlying disorders. In addition to the ever-increasing list of relatively rare genetic disorders which manifest with chorea, this movement

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Acquired Choreas

Disorder can be seen as an infrequent complication of many common disorders. The underlying pathophysiology is likely to be an imbalance of the direct and indirect basal ganglia pathways. It is unclear why this happens in such a wide variety of clinical conditions, but also why it does not happen more often in common disorders, such as stroke involving the basal ganglia. The causative diagnosis may be suggested by features of the patient’s history and examination (Table 11.1). The work-up of the patient with chorea can be extensive (Figure 11.1), and yet some patients invariably remain undiagnosed.

Etiology

Structural causes

A large variety of structural causes have reported to produce chorea in adults. In these cases chorea is typically unilateral, due to a focal lesion of the contralateral basal ganglia. Vascular etiologies may

Figure 11.1 Flow chart for the evaluation of the patient with acquired chorea. This algorithm assumes that genetic causes have been excluded, and should be used as a guide, taking clinical context into account, rather than strictly followed.

Abbreviations: ab, antibody; ASO, antistreptolysin O antibody; CSF, cerebrospinal fluid; hgb, hemoglobin; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; Pb, lead; PLEDs, periodic lateralizing epileptiform discharges; PTH, parathyroid hormone; RPR, rapid plasma reagin; SLE, systemic lupus erythematosus; TSH, thyroid-stimulating hormone.
include stroke, vasculitides, moya-moya disease, cavernous angioma, or arteriovenous malformation. Hypoperfusion may be demonstrated in the absence of a structural lesion (Figure 11.2; Video 11.1). Space-occupying lesions due to tumor or infection may present with chorea. Multiple sclerosis is a rare cause [5]. Although it is usually accepted that chorea originates in disruption of basal ganglia pathways, cases of reversible chorea associated with herniated cervical discs have been reported [6].

In children, cerebral palsy (CP) is a common cause of hyperkinetic movement disorders, including dystonia and chorea. The history should be diagnostic, of neurological deficits due to pre- or perinatal lesions evolving from a spastic di- or quadriplegia to a hyperkinetic disorder over several years. Chorea may be acutely exacerbated in the setting of metabolic stress such as infection and fever, and may require emergent intervention such as general anesthesia or neurosurgical procedure. Another condition occasionally seen in children (and very rarely in adults) is post-pump chorea which may occur following open-heart surgery on cardiopulmonary bypass. This may be due to microemboli or a hyperviscosity syndrome, and appears to be reducing in incidence with improvements in technology [7].

**Metabolic**

The most commonly reported metabolic cause of chorea is in diabetic patients with non-ketotic hyperglycemia who may present acutely with hemichorea. For unknown reasons this appears to be common in older, Asian, female, patients, and is typically unilateral. Neuroimaging demonstrates hyperintensity of the contralateral putamen on T1- and T2-weighted MRI [8], suggestive of breakdown of the blood–brain barrier due to inflammation and edema [9], hyperviscosity [10], or ischemia [11]. The movement disorder should resolve with correction of the hyperglycemia, but has been reported to persist for months [12]. Chorea has been reported in a non-diabetic patient following chronic sucrose ingestion [13]. Hypoglycemia can occasionally result in chorea, which is usually bilateral.
Imbalance of most electrolytes has occasionally been reported to cause chorea, although this appears to be relatively uncommon. These include hyper- and hyponatremia [15], hyper- and hypocalemia [17], and hypomagnesemia. Chorea also been reported following correction of hyponatremia causing central pontine myelinolysis [18].

Disturbances of calcium levels as seen in hypoparathyroidism [19] and pseudohypoparathyroidism [20] are also reported to be associated with chorea, which may be paroxysmal. In addition, the deposition of calcium in the brain known as Fahr disease may cause a variety of movement disorders, including chorea, likely due to the structural lesion caused by calcium deposition in the putamen. The term “Fahr disease” describes a number of different disorders, including those of calcium and mitochondrial metabolism.

Patients with end-stage liver disease can develop acquired hepatocerebral degeneration (Video 11.2, resulting in a mixed movement disorder, often with prominent orofacial hyperkinesia, in addition to ataxia, parkinsonism, and tremor [21]. The pathophysiology is likely to be similar to that of Wilson disease. Manganese is deposited in the caudate–putamen, although this does not appear to be a direct cause of the movement disorder [21].

Video 11.2 Movement disorder of acquired hepatocerebral degeneration
This man has end-stage liver disease following viral hepatitis. He has prominent orofaciolingual and truncal chorea, dysarthric speech with cerebellar components, difficulty initiating saccadic gaze, bradykinesia of the feet, and negative myoclonus (asterixis) with arms outstretched. [Video courtesy of John C. Morgan, MD, PhD, and Kapil Sethi, MD, FRCP(UK), Augusta, Georgia]


Other endocrine causes of chorea include hyperthyroidism [22, 23], and chorea gravidarum, seen in pregnancy. A similar pathophysiology, possibly sensitization of dopamine receptors by estrogens, may be responsible for chorea sometimes observed with the use of estrogens [24, 25].

Vitamin B12 deficiency is reported as a reversible cause of chorea [26, 27].

Autoimmune disorders
Certain components of neurons of the putamen appear to be especially susceptible targets for autoantibodies. As the chorea seen in various disorders due to autoantibodies is not associated with tissue destruction, it is likely that the autoantibodies interfere with neuronal signaling, perhaps by blocking specific receptors.

Sydenham chorea is a relatively common childhood chorea, occurring following a streptococcal throat infection. The recognition of basal ganglia neurons by antistreptococcal antibodies appears to be the cause [28, 29]. As with other autoimmune etiologies, it is not known why the putamen is particularly vulnerable to autoantibodies. This disorder is usually self-limited and resolves within a few weeks, but may sometimes result in bizarre and violent movements requiring medication.

A number of autoimmune disorders have been reported to cause a range of movement disorders, both hypokinetic and hyperkinetic. These include systemic lupus erythematosus [30, 31], Sjögren syndrome [32], and others. The association of chorea with antiphospholipid antibodies (including anticardiolipin antibodies and lupus anticoagulant) is recognized, as part of an “antiphospholipid antibody syndrome”. Polycythemia vera may present with chorea [36, 37], although it is unclear whether this is due to the presence of autoantibodies or to hyperviscosity resulting in basal ganglia ischemia.

Celiac disease has been associated with a number of neurologic complications, typically ataxia or peripheral neuropathy, but occasionally chorea (Video 11.3) which responds to a gluten-free diet [38].

Paraneoplastic chorea has been reported in patients with renal, small cell lung, breast, Hodgkins and non-Hodgkins lymphoma [39–43], due to anti-CRMP–5/CV2 [42, 44], anti-Hu [43], and anti-Yo [45] antineuronal autoantibodies.
The syndrome associated with anti-NMDA-receptor antibodies involves encephalopathy and complex, repetitive stereotypies with components of dystonia and chorea [46, 47]. In some cases a causative ovarian teratoma has been identified, although in others the etiology remains obscure. The outcome may be surprisingly good despite a prolonged disease course.

**Drug-induced choreas**

A form of chorea commonly seen in neurologic practice is that induced by levo-dopa in Parkinson disease (PD). This is mentioned here because an understanding of the pathophysiology of l-dopa-induced dyskinesias (LIDs), both in humans and in animal models of PD, may shed light upon mechanisms in chorea of other etiologies.

The underlying cause of LIDs is a hyperdopaminergic state in the setting of underlying dopamine depletion, as can be inferred from the relationship to dosing with dopaminergic medications. However, more complex changes occur at the neuronal level. Alterations of a large number of parameters relating to different neurotransmitters within the striatum have been reported, and agents with a variety of mechanisms of actions have been reported to reduce LIDs in animal models. Changes in glutamate NMDA receptors play a major role in the development of LIDs [48], correlating with the fact that NMDA-receptor antagonist amantadine reduces LIDs. Loss of plasticity at glutamatergic corticostriatal synapses plays a critical role [49], and may lead to the loss of selection of signals via the D1-stimulated direct pathway. The increase in activity of this (direct) pathway would lead to a decrease in GPi activity [50, 51].

Two different forms of LIDs are observed in PD patients. Peak dose dyskinesias are seen when l-dopa is at its highest blood level, and are choreiform in nature, involving the arms, trunk, and neck [52]. On–off dyskinesias tend to involve the legs, and have a dystonic component. One possible mechanism underlying the generation of these dyskinesias may be imbalance in the dopaminergic levels of adjacent striatal regions. This would be seen particularly in advanced disease when loss of presynaptic dopamine terminals leads to reduced dopamine storage and, hence, impaired buffering of dopamine levels.

The term “tardive dyskinesia” (TD) is used to refer to a movement disorder caused by exposure to dopamine-receptor blocking drugs. It may manifest as various forms of hyperkinesia, including chorea, although the typical orofacial-lingual dyskinesia, with coordinated, repetitive, patterned movements, is best characterized as a stereotypy. Any dopaminergic antagonist may be responsible, including the first, second, and third generation antipsychotics, and some anti-emetics, such as metoclopramide [53]. Although promoted as having a lower risk of TD, the atypical antipsychotics are increasingly reported to cause TD [54]. One form of drug-induced chorea is the withdrawal emergent syndrome, typically seen in children treated with neuroleptics [55]. Tardive chorea may be mixed with tardive dystonia, which is often more debilitating. Other medications with different mechanisms of action have been reported to cause TD, including selective serotonin reuptake inhibitors (SSRIs), lithium, and anticonvulsant medications.
Acquired Chorea

Stimulants, both those used therapeutically [56] and those used recreationally, such as amphetamine, cocaine, and specifically crack, may result in chorea (“crack-dancing”). The release of catecholamines is probably the explanation for the appearance of the movement disorder.

Anticonvulsants such as gabapentin [57, 58], lamotrigine [59], and lithium [60], may cause chorea. The use of estrogens in the contraceptive pill and as hormone replacement therapy [25] may result in chorea, presumably by the same mechanism which causes chorea gravidarum. However, contradictorily, suppression of estrogen with LHRH may also result in chorea [61].

Methotrexate is recognized as a cause of chronic neurotoxicity, but also can cause acute, reversible chorea, especially after intrathecal administration [62, 63].

Infectious and postinfectious

HIV infection may cause a variety of movement disorders [64] due to a mass lesion, such as lymphoma or abscess, or as a direct effect of HIV encephalopathy [65, 66]. Syphilis should be considered as a very rare but treatable cause of chorea [67]. Creutzfeldt-Jakob disease, particularly the new variant related to bovine spongiform encephalopathy, should be considered, especially if the course is of subacute deterioration over months [68,69].

In children, striatal necrosis may occur as a complication of measles encephalitis [70] or following undefined febrile illness [71]. A similar picture can be seen after mycoplasma pneumoniae infection [72], with a mixture of chorea and dystonia, hyperreflexia and encephalopathy. Chorea has also been reported in the setting of encephalopathy due to parvovirus infection [73], and following herpes simplex encephalitis [74].

Psychogenic

While mass psychogenic chorea, as a manifestation of the “dancing mania,” was reported in medieval times [2, 4], and more recently [75], this seems at present to be an uncommon occurrence. In general, chorea is found in less than 10% of patients with psychogenic movement disorders [76, 77], thus this diagnosis should be made with caution. Rarely, patients with a strong family history of Huntington disease (HD) may present with psychogenic chorea even though their genetic testing is negative [78].

Pathophysiology

The model developed by Albin, Young, and Penny [79], despite its limitations [80, 81], can be used to understand many of the pathophysiological aspects of chorea. The direct pathway may be responsible for the activation of a motor program following an input from the motor cortex. The indirect pathway then focuses and selects the movements [82] (Figure 11.3[A]). As a wide variety of pathophysiologicals can cause chorea, it is likely that imbalance of these pathways can occur at many levels, within the caudate–putamen, subthalamic nucleus (STN) (causing hemiballismus; Figure 11.3[B]), and the globus pallidus internal (Gpi) segment.

From the model, chorea is due to a decrease in activity of the indirect pathway from the caudate–putamen to the external segment of the globus pallidus (GPe) (Figure 11.3[C]) [79, 83]. This results in overactivity of this nucleus with increased inhibition, and thus decreased activity of its projection targets, the STN, the Gpi, and the substantia nigra pars reticulata (SNr). This correlates with the fact that lesions of the STN cause chorea (hemiballismus). A decrease in activity of the indirect pathway from the STN to the Gpi results in a loss of selection of motor signals that have arrived from the striatum via the direct pathway [82]. The inhibited Gpi/SNr consequently has decreased inhibition of the motor thalamus, thus there is an increase in thalamocortical signaling.

Treatment

If possible, treatment should be directed at the underlying disease process. If this is not possible, treatment is symptomatic, to the extent that movements are disabling or distressing (which may not be the case). Reduction in chorea may not result in an improvement in function. Most
Figure 11.3  During normal function of the basal ganglia, the direct pathway from the striatum inhibits neurons of the GPi, disinhibiting the motor pattern generator, consisting of the motor thalamic nuclei and their projections to the cortex. The neurons which select the motor program are represented as being surrounded by a network, controlled by the indirect pathway, which reduces the generation of unwanted movements. [B] Damage to the subthalamic nucleus results in decreased drive of the GPi, loss of inhibition of the motor thalamus, and the appearance of involuntary movements. STN lesions typically cause severe hemichorea, known as hemiballismus. The thickness of lines indicates the relative degree of activity. [C] Lesions affecting the neurons of the indirect pathway are a probable cause of chorea from striatal pathology. There is decreased surround inhibition of the thalamus via the indirect pathway, with a similar effect as in [B].
experience has been obtained with HD, and can be extrapolated to other choreiform conditions due to the presumed similarity of pathophysiology.

Medical therapies aimed at decreasing dopaminergic function are the main line of therapy at present. There is some evidence that drugs with other modes of action, such as NMDA-receptor antagonism, may be useful. A small number of cases who underwent surgical therapies, specifically deep brain stimulation (DBS) or lesioning, have been reported, with mixed outcomes.

**Dopamine-blocking and dopamine-depleting agents**

An excess of dopaminergic function is believed to underlie the mechanism of chorea in many cases, thus the first line of treatment is usually to reduce activity at dopamine receptors. The atypical antipsychotic agents are widely used, as there is less concern about the potential side effects of parkinsonism or tardive dyskinesia with these agents, which is felt to outweigh the possible metabolic effects. Although, so far, there is little published data, clinical experience suggests that quetiapine, olanzepine, and clozapine may be useful. Aripiprazole [84], ziprasidone [85], and tiapride [6, 89], may also be helpful in reducing chorea.

Tetrabenazine has been shown to be effective in HD, and may be tried in other disorders. It depletes monoamines from presynaptic terminals [86] and may be useful in a variety of hyperkinetic movement disorders [87–89]; however, the side effects of depression and parkinsonism may limit therapy. The use of reserpine carries the same caveats as tetrabenazine, and it may occasionally play a role in the treatment of TD [90, 91].

**Anticonvulsants**

Levetiracetam is reported to be beneficial in TD [92–94] and may be worth a therapeutic trial. Other anticonvulsants have been used with some positive results, possibly related to a membrane-stabilizing effect. Sodium valproate and carbamazepine can be used in Sydenham chorea [95, 96].

**Glutamate NMDA-receptor antagonists**

Amantadine has been shown in some studies to reduce chorea in HD [97, 98], and may be of use in chorea of other etiologies. The mechanism of action is presumed to be similar to that in levodopa-induced dyskinesias in PD, in which it appears to be beneficial, by reducing glutamatergic neurotransmission, either in the caudate–putamen or in the Gpi/SNr. Studies of the symptomatic (as opposed to neuroprotective) effects of riluzole in HD were positive [99], but sometimes not sustained [100], and the reduction in chorea did not necessarily result in improved function [101].

**Intrathecal baclofen**

In chorea due to cerebral palsy, intrathecal baclofen (ITB) has proven useful [102]; however, this may be due to an upper motor neuron component of the condition, as ITB is not of clear benefit in hyperkinetic disorders of other etiologies [103].

**Immune modulators**

Chorea of autoimmune etiologies may respond specifically to immunosuppressive modalities, such as intravenous immunoglobulin, plasmapheresis, or corticosteroids; however, symptomatic therapy with dopamine-blocking agents, etc., is often adequate.

**Surgical therapies**

DBS or lesioning of the STN or the Gpi have been used to treat chorea of various etiologies in small numbers of cases, usually of genetic etiologies. Results are often mixed and overall benefit to the patient is unclear. The motor thalamus has also been proposed as a potentially promising site for DBS in “senile chorea” [104] and chorea from CP [105] and has been reported as being beneficial in a patient with chorea-acanthocytosis [106]. The optimal site and frequency of stimulation for treatment of chorea remain to be identified, but this therapy may be considered in intractable chorea from any cause.

**Non-medical therapies**

In the absence of effective medical therapies to reverse or reduce the symptoms, adjunctive non-medical therapies are invaluable. The pharyngeal musculature is often affected by hyperkinetic movement disorders and thus an evaluation of swallowing is very important to avoid aspiration and to maintain adequate oral intake. If the
patient is at high risk for aspiration, placement of a feeding tube may be necessary. Dysarthria may also be significant and patients may benefit from speech therapy. Physical therapy aimed at improving gait and balance may be useful to improve stability. Assistive devices for walking, which provide a wheeled frame in which the patient can stand or sit, are unwieldy but are very stable, and may enable patients with a moderately advanced disease to stay mobile.

**Conclusion**

Chorea is a commonly-seen movement disorder which may arise from a multiplicity of acquired causes, with a wide variety of potential mechanisms. Details of the medical history and neurological examination may be informative, yet a number of patients typically remain undiagnosed.

Approaches to understanding the underlying pathophysiology focus primarily upon the caudate-putamen, yet the precise mechanism for the generation of involuntary movements remains obscure. Treatment is often challenging and is essentially based upon empiric observations, awaiting further developments in our understanding of the etiology of this symptom.

**References**

Acquired Choreas


CHAPTER 12
Tics and Tourette Syndrome

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Historical background

In 1885 Georges Albert Édouard Brutus Gilles de la Tourette, a 28-year-old student of Jean-Martin Charcot, published A Study of a Neurological Condition Characterized by Motor Incoordination Accompanied by Echolalia and Coprolalia [1]. Gilles de la Tourette (abbreviated in the literature and in this manuscript as Tourette) described 9 patients (including the Marquise de Dampierre, previously reported by Itard in 1825, as a reclusive aristocratic lady who “ticked and blasphemed” from the age of 7 until her death at the age of 80) and noted that all 9 patients shared one feature – they all exhibited brief involuntary movements (motor tics); additionally 6 made noises (phonic tics), 5 shouted obscenities (coprolalia), 5 repeated the words of others (echolalia), and 2 mimicked the gestures of others (euchopraxia). They likened tics to Jumping Frenchmen and the echopraxic syndromes of Myriachit and Latah, that had been previously described. Shortly after the tragic death of his young son and of his mentor, Charcot, Tourette was shot in the head in his consulting rooms by a paranoic young woman who had been a patient at the Salpêtrière and claimed that she had been hypnotized by Tourette against her will. After 1900, Tourette’s behavior became erratic and bizarre, probably due to neurosyphilis, and his wife had to commit him to an asylum in Switzerland where he remained until his death in 1904.

Although Tourette considered the disorder he described to be hereditary, the etiology was ascribed to psychogenic causes for nearly a century following the original report. The perception of TS began to change in the 1960s when the beneficial effects of neuroleptic drugs on the symptoms of TS began to be recognized. This observation helped to refocus attention from psychogenic to central nervous system etiology [2].

Phenomenology of tics and other clinical features of Tourette syndrome

Tics, the clinical hallmark of TS, are relatively brief and intermittent movements (motor tics) or sounds (vocal or phonic tics). Recognition of the full spectrum of phenomenology of tics is critical to the diagnosis of TS [3, 4]. Currently accepted criteria for the diagnosis of TS require both types of tic to be present. This division into motor and vocal/phonic tics, however, is artificial, because vocal/phonic tics are actually motor tics that involve respiratory, laryngeal, pharyngeal, oral, and nasal musculature. Contraction of these muscles may produce sounds by moving air through the nose, mouth, or throat,
hence the term “phonic” rather than “vocal” tic is preferred. According to the criteria outlined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) – which is currently under revision and DSM-5 is expected to be released by 2013 – in order to make a diagnosis of definite TS the following features must be present: (1) both multiple motor and one or more phonic tics are present at some time during the illness, although not necessarily concurrently; (2) the tics occur many times a day (usually in bouts), nearly every day or intermittently throughout a period of more than 1 year without a tic-free period of more than 3 consecutive months; (3) the onset is before age 18 years; and (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 disease or postviral encephalitis).

Tics may be simple or complex. Simple motor tics involve only a small group of muscles, causing a brief, jerk-like movement. They are usually abrupt in onset and rapid (clonic tics), but they may be slower, causing a briefly sustained abnormal posture (dystonic tics) or an isometric contraction (tonic tics). Examples of simple clonic motor tics include blinking, nose twitching, and head jerking, while simple dystonic tics include blepharospasm, oculogyric movements, bruxism, sustained mouth opening, torticollis, and shoulder rotation (Video 12.1). Tensing of abdominal or limb muscles is an example of a tonic tic. Tics and dystonia rarely occur in the same family or the same patient [5].

Complex motor tics consist of coordinated, sequenced movements resembling normal motor acts or gestures that are inappropriately intense and timed (Video 12.2). They may be seemingly non-purposeful, such as head shaking or trunk bending, or they may seem purposeful, such as touching, throwing, hitting, jumping, and kicking. Additional examples of complex motor tics include gesturing “the finger” and grabbing or exposing one’s genitalia (copropraxia) or imitating gestures (echopraxia). Burping, vomiting, and retching, and air swallowing are other complex tics seen in patients with TS [6].

In addition to motor tics, patients with TS exhibit simple phonic tics, such as sniffing, throat clearing, grunting, squeaking, screaming, coughing, blowing, and sucking sounds or complex phonic tics manifested by linguistically meaningful utterances and verbalizations, such as shouting of obscenities or profanities (coprolalia) [7], repetition of someone else’s words or phrases (echolalia), and repetition of one’s own utterances, particularly the last syllable, word or phrase in a sentence (palilalia). Some TS patients also manifest sudden and transient cessation of all motor activity (blocking tics) without alteration of consciousness.

Motor (particularly dystonic) and phonic tics are preceded by premonitory sensations in over 80% of patients [8, 9]. This premonitory phenomenon consist of sensations or discomforts, such as a burning feeling in the eye before an eye blink, tension or a crick in the neck that is relieved by stretching of the neck or jerking of the head, a feeling of tightness or constriction that is relieved
by arm or leg extension, localized to one body part of more generalized feeling of an urge to perform the tic [10]. The presence of premonitory sensations helps to differentiate tics from other abrupt, jerk-like, hyperkinetic movement disorders such as myoclonus and chorea (Box 12.1). Furthermore, in contrast to other hyperkinetic movement disorders that are usually completely suppressed during sleep, motor and phonic tics may persist during all stages of sleep [11].

Although TS typically occurs in children, it can also affect adults. We reviewed 43 adults with TS referred to our Movement Disorders Clinic over the past 5 years and compared them with 100 TS patients 18 years old or younger [12]. We found that adult TS patients had significantly more facial and truncal tics, as well as a greater prevalence of substance abuse and mood disorders, but fewer phonic tics, and lower rates of ADHD and oppositional behavior than children with TS. Furthermore, adult TS largely represented a re-emergence or exacerbation of childhood-onset TS. During the course of TS, phonic and complex motor tics, self-injurious behaviors, and ADHD tend to improve, but facial, neck, and trunk tics dominate the adult TS phenotype.

Tics, although rarely disabling, can be quite troublesome for TS patients because they cause embarrassment, interfere with social interactions, and at times can be quite painful or uncomfortable. Rarely, cervical tics may be so forceful and violent, the so-called “whiplash tics,” that they may cause secondary neurologic deficits, such as cervical artery dissection, and compressive or non-compressive cervical myelopathy [13]. Patients with life-threatening tics, self-injurious behavior,
and other severe symptoms of TS have been labeled as having “malignant” TS [14, 15].

In addition to ADHD and OCD, patients with TS often manifest a large variety of behavioral comorbidities, particularly impulse control disorder, oppositional defiant disorder, anxiety, depression, conduct disorder, severe temper outbursts, rage attacks, inappropriate sexual behavior, and other psychiatric problems. Some of these features are being captured in the Tourette International Consortium Database [16].

Epidemiology

Epidemiological studies of TS have been hampered by the lack of a disease-specific, diagnostic, marker and other challenges including different study populations, methodological problems, which has resulted in a marked variability in the reported prevalence and incidence. Some prevalence figures suggest that up to 24% of children may have tics at some time during their childhood [17, 18]. Most epidemiological studies have shown that 20–30% of children exhibit tics at some time during childhood and 2–3% of children develop some features of TS, although the worldwide prevalence of TS in children has been reported to range from 0.3 to 0.8% [19].

Etiology

TS has been considered a genetic disorder since its first description, but the causative gene or genes have eluded the scientists, despite intensive efforts by many geneticists and consortia. Two genes have been recently identified as potentially causative genes: the Slit and Trk-like 1 (SLITRK1) gene on chromosome 13q31.1 [20] and the L-histidine decarboxylase (HDC) gene located on 15q21.1–15q21.3 [21]. No mutations in these two genes, however, have been found in large populations of TS patients, thus it is unlikely that the reported mutations are relevant to the pathogenesis of most cases of TS. One possible explanation for the lack of known gene(s) for TS is the observation that bilineal transmission, which violates the standard principle of one-trait, one-locus, may play a role in a large proportion of all TS cases.

Although genetic factors are thought to account for the majority of tics, particularly in children, tics and other features of TS may also be caused by a variety of etiologies such as infection, trauma, stroke [22], multiple sclerosis, cocaine and neuroleptic drugs, static encephalopathy, autistic spectrum disorders, neuroacanthocytosis, pantothenate kinase-associated neurodegeneration, head trauma, and peripheral injury [23]. The study of the mechanisms of the secondary tourettism could provide insights into the pathogenesis of TS as TS symptoms have been reported to be exacerbated by various structural lesions involving the basal ganglia and the limbic system [24].

The potential role of immunologic mechanisms in the pathogenesis of tics has attracted a great deal of attention over the past few decades. Several studies have suggested that exacerbations of TS...
symptoms correlated with an antecedent group A β-hemolytic streptococcus (GABHS) infection (demonstrated by elevated antistreptococcal titers) and the presence of serum antineuronal antibodies. Variably referred to as pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) or pediatric infection-triggered autoimmune neuropsychiatric disorders (PITANDS), this area is one of the most controversial topics in pediatric neurologic and psychiatric literature [25, 26]. In a case-control study of a large primary care database of 678,862 patients with an average follow-up of 5.08 years, no support was found for a strong relationship between streptococcal infections, neuropsychiatric syndromes such as OCD, or TS or PANDAS [27]. This and other recent studies cast doubts on the proposed link between GABS and TS.

Pathophysiology

Although the pathogenic mechanisms of TS are still unknown, the weight of evidence supports an organic rather than a psychogenic origin, probably involving the basal ganglia circuitry [2, 24, 28]. Although direct evidence is still lacking, TS is currently viewed as a disorder of synaptic transmission involving disinhibition of the cortico-striatal-thalamic-cortical circuitry. Several studies have provided evidence in support of the notion that the basal ganglia, particularly the caudate nucleus, and the inferior prefrontal cortex, play an important role in the pathogenesis not only of TS but also of comorbid disorders, particularly OCD. Although there are no animal models of TS, studies of stereotypies in animals may provide insight into the pathogenesis of habits, rituals, tic-like, and impulsive behaviors in humans [29, 30].

Conventional neurophysiological investigations have found that TS patients have defective inhibitory mechanisms. Functional MRI showed decreased neuronal activity during periods of suppression in the ventral globus pallidus, putamen, and thalamus and increased activity in the right caudate nucleus, right frontal cortex, and other cortical areas that are normally involved in the inhibition of unwanted impulses (prefrontal, parietal, temporal, and cingulate cortices). Examining the resting-state functional connectivity MRI (rs-fcMRI) in 33 adolescents with TS, Church et al. [31] found anomalous connections primarily in the fronto-parietal network, suggesting widespread immature functional connectivity, particularly in regions related to adaptive online control. Transcranial magnetic stimulation studies have demonstrated that TS children have a shorter cortical silent period but that their intracortical inhibition was not different from that of controls, although intracortical inhibition is reduced in children with ADHD [32].

Although standard anatomic neuroimaging studies in TS are unremarkable, by using special volumetric, metabolic, blood flow, ligand, and functional imaging techniques, several interesting findings have been reported that have strong implications for the pathophysiology of TS. Careful volumetric MRI studies have suggested that the normal asymmetry of the basal ganglia is lost in TS. Caudate volumes have been reported to correlate significantly and inversely with the severity of tic and OCD in early adulthood [33]. An MRI-DTI study of monozygotic twins showed that the mean fractional anisotropy values were significantly lower particularly in the posterior portion of the corpus callosum in the twin affected with TS [34]. Using tractography of the fronto-striato-thalamic circuit, TS patients were found to have significantly lower probability of connection between caudate nucleus and anterior-dorsolateral-frontal cortex on the left [35]. Additional imaging studies have identified frontal and parietal cortical thinning, most prominent in ventral portions of the sensory and motor homunculi in patients with TS [36].

Positron emission tomography (PET) scanning has shown variable rates of glucose utilization in basal ganglia as compared to controls. In one study, [18F]fluorodeoxyglucose, PET has shown evidence of increased metabolic activity in the lateral premotor and supplementary motor association cortices and in the midbrain (pattern 1), and decreased metabolic activity in the caudate and thalamic areas (limbic basal ganglia-thalamocortical projection system) (pattern 2) [37]. Pattern 1 is reportedly
associated with tics, and pattern 2 correlates with the overall severity of TS. In a follow-up study involving 12 TS adult patients (untreated for >2 years) and 12 controls, the investigators found a TS-related metabolic pattern which was characterized by increased premotor cortex and cerebellum activity and reduced resting activity of the striatum and orbitofrontal cortex [38].

In contrast to dystonia – which is characterized by lentiform nucleus-thalamic metabolic disassociation, attributed to overactivity of the direct striatopallidal inhibitory pathway – the pattern of TS is characterized by concomitant metabolic reduction in striatal and thalamic function. The authors suggested that this pattern can be explained by a reduction in the indirect pathway resulting in reduction in subthalamic nucleus (STN) activity. This is in part consistent with another study that found evidence of increased activation in the direct pathway, but the activity in the prefrontal cortex and STN has been found to be increased presumably as a result of compensatory activation [39]. Using PET to study metabolic activity, robust activation of cerebellum, insula, thalamus, and putamen was found during tic release [40].

An autopsy study of three TS brains found consistent increases in DAT and D2 receptor as well as D1 and α-2A density, suggesting that dopaminergic hyperfunction in the frontal lobe may play a role in the pathophysiology of TS [41]. Another pathological study showed a marked increase in total number of neurons in the globus pallidus internum (GPI) and decreased number in the globus pallidus externa (GPe) and in the caudate nucleus of brains of patients with TS [42]. Furthermore, an increased number and proportion of the GPI neurons were positive for the calcium-binding protein parvalbumin in tissue from TS subjects, whereas lower densities of parvalbumin-positive interneurons were observed in both the Cd and putamen of TS subjects. These abnormalities have been interpreted as indicating a developmental defect in the migration of some GABAergic neurons. PET with the vesicular monoamine transporter type 2 ligand \(^{11}\text{C}\text{[dihydrotetraphenazine]}\) that binds to type 2 vesicular monoamine transporter (VMAT2) to quantify striatal monoaminergic innervation and \(^{11}\text{C}\text{[methylphenidate]}, a ligand for dopamine transporter (DAT), in 33 adults with TS no differences between subjects with TS and controls were found [43]. In a study of 8 patients with TS and 8 controls \(^{11}\text{C}\text{[FLB 457}}\) PET in conjunction with an amphetamine challenge used to evaluate extrastriatal D2/D3 receptor binding and DA release, TS patients showed decreased \(^{11}\text{C}\text{[FLB 457}}\) binding potentials bilaterally in cortical and subcortical regions outside the striatum, including the cingulate gyrus, middle and superior temporal gyrus, occipital cortex, insula, and thalamus [44]. Furthermore, amphetamine challenge induced widespread increased DA release in TS patients, which extended more anteriorly to involve anterior cingulate and medial frontal gyri. The authors suggested that “reductions in D2/D3 receptor binding in both frontal cortex and thalamus are consistent with recently published preliminary data demonstrating similar abnormalities of D2/D3 binding in TS patients using a different PET ligand.” Reduced metabolism or blood flow to the basal ganglia, particularly in the ventral striatum, most often in the left hemisphere, has been demonstrated in majority of the studies involving TS subjects. These limbic areas are thought to be involved in impulse control, reward contingencies, and executive functions, and these behavioral functions appear to be abnormal in most patients with TS. The radioligand studies have been less consistent, but they provide some support for increased D2 receptor density in the caudate nucleus. Imaging studies of presynaptic markers such as dopa decarboxylase, dopamine, and dopamine transporter have produced results that are even less consistent. Future imaging and ligand studies should include children, since this population has been largely excluded because of ethical considerations. The studies should also rigorously characterize comorbid disorders and should take into consideration potential confounding variables, such as the secondary effects of chronic illness and medications.

**Treatment**

The first step in the management of patients with TS is the proper education of the patient, relatives, teachers, and other individuals who frequently
interact with the patient about the nature of the disorder [2, 4, 45]. In addition, the parents and the physician should work as partners in advocating the best possible school environment for the child. This might include extra break periods and a refuge area to allow release of tics, waiving time limitations on tests or adjusting timing of tests to the morning, and other measures designed to relieve stress. National and local support groups can provide additional information (e.g. www.tsa-usa.org) and can serve as a valuable resource for the patient and his or her family.

Because of the broad range of neurologic and behavioral manifestation and varying severity, therapy of TS must be tailored specifically to the needs of the individual patient (Box 12.2). The most troublesome symptoms should be targeted first. Medications should be instituted at low doses, titrated gradually to the lowest effective dosage, and tapered during non-stressful periods (e.g. summer vacations). Another important principle of therapy in TS is to give each medication and dosage regimen an adequate trial. This approach will avoid needless changes made in response to variations in symptoms during the natural course of the disease. While an evidence-based approach, based on double-blind, placebo-controlled studies is desirable to objectively evaluate the efficacy of a drug, long-term observational studies provide useful information not only on the drug's efficacy but also on its safety.

Before discussing the pharmacologic therapy of TS symptoms, it is appropriate to make a few remarks about behavioral therapy. Different forms of behavioral modification have been recommended since the disorder was first described, but until recently, very few studies of behavioral treatments have been subjected to rigorous scientific scrutiny. The behavioral intervention, called Comprehensive Behavioral Intervention for Tic (CBIT) disorders is primarily based on HRT which employs competing response training, which is different from deliberate tic suppression in that it teaches the patient to initiate a voluntary behavior to manage the premonitory urge. CBIT also includes relaxation training and a functional intervention. In a multicenter study designed to test the efficacy of CBIT, 126 children aged 9 to 17 with moderate to severe TS were randomly assigned to receive either CBIT or supportive counseling and education about TS [46]. The success of this behavioral management is critically dependent on active involvement by the parents and the therapist, both of whom must be well trained and skilled in the various CBIT techniques [10]. Given the demands on time and effort on the part of the patient, the therapist, and parents, it is unlikely that all parties will be able to maintain the needed compliance with the training program to provide sustained benefit. There is also some concern as to whether the mental effort required to fully comply with the various components of CBIT could actually interfere with the patient’s attention and learning.
While there has been a great deal of effort exerted over the last several decades making the scientific, clinical, and lay community understand the biological basis of TS, the reported response to behavioral therapy may be misinterpreted by some as evidence that tics and TS are of psychological etiology. This is one reason why behavioral therapies are often not covered by insurance or other third party payers. Thus, only a limited number of patients will be able to access this behavioral therapy as compared to pharmacologic treatment, which actually may be more effective. Nevertheless, behavioral therapies are useful ancillary techniques in patients whose response to other therapies, including pharmacotherapy, is not entirely satisfactory.

Placebo-controlled and open-label, observational trials have found that the dopamine receptor-blocking drugs (neuroleptics) are clearly most effective in controlling motor and phonic tics (Box 12.2). Although haloperidol and pimozide are the only neuroleptics that have actually been approved by the Food and Drug Administration (FDA) for the treatment of TS, we rarely used them because of sedation, weight gain, school phobia, and other potentially serious adverse effects, including prolonged QT interval torsades de pointes. We prefer fluphenazine or risperidone as these neuroleptics appear to be relatively well tolerated. All neuroleptics, however, block dopamine receptors and may, therefore, cause tardive dyskinesia. Even though the second- or third-generation (atypical) neuroleptics have been promoted to have a lower risk of tardive dyskinesia, all have been reported to cause this side effect.

Tetrabenazine – which is a monoamine-depleting drug that acts by inhibiting VMAT2, and was approved in 2008 for the treatment of chorea associated with Huntington disease – has been shown to be a powerful antictic drug [47]. The drug is well tolerated, although some patients experienced drowsiness (32.6%), nausea/vomiting (8.7%), depression (7.6%), insomnia (6.5%), akathisia (5.4%), and other less frequent, dose-related side effects. It has the advantage over the conventional neuroleptics in that it does not cause tardive dyskinesia.

Several non-neuroleptic treatments have been reported to be effective in the treatment of tics. These include clonazepam and topiramate [12]. Motor tics may be also successfully treated with botulinum toxin injections in the affected muscles [48, 49]. Such focal chemodenervation ameliorates not only the involuntary movements but also the premonitory sensory component. The so-called “whiplash” tics that involve the neck muscles and potentially cause compressive myelopathy or radiculopathy, can be effectively treated with injections of botulinum toxin into neck extensor muscles [14, 49].

CNS stimulants, such as methylphenidate, dextroamphetamine, levoamphetamine, pemoline, and lisdexamfetamine dimesylate are clearly the most effective agents in the treatment of ADHD. Although CNS stimulants may exacerbate or precipitate tics in up to 25% of patients, the National Institute of Mental Health (NIMH) Collaborative Multimodal Treatment Study of Children with Attention Deficit Hyperactivity Disorder found that CNS stimulants were safe in the setting of TS and were superior to behavioral treatment [50].

Other classes of drugs reported to effective in the treatment of ADHD and other behavioral comorbidities associated with TS include the α2-adrenergic agonists and tricyclic antidepressants. Clonidine, a presynaptic α2-adrenergic agonist, has been found to improve not only symptoms of ADHD, but also impulse control problem. Although initially reported to be marginally effective in controlling motor tics, clonidine has not been found to be an effective antitic agent in other studies. Side effects include sedation, light-headedness, headache, dry mouth, and insomnia. Because of its sedative effects, some clinicians use clonidine as a night-time soporific agent. The Available also as a transdermal patch, it can cause local irritation, but it seems to be overall better tolerated than oral clonidine. Another drug that is increasingly used in the treatment of ADHD and impulse control problems is guanfacine. Pharmacologically similar to clonidine, guanfacine may be effective in patients in whom clonidine failed to control the behavioral symptoms and may have some advantages over
clonidine in that it has a longer half-life, it appears to be less sedating, and it produces less hypotension. It also seems to be a more selective \(\alpha_2\)-noradrenergic receptor agonist and binds more selectively to the postsynaptic \(\alpha_2A\)-adrenergic receptors located in the prefrontal cortex. While both clonidine and guanfacine appear to be effective in the treatment of attention deficit with and without hyperactivity, they appear to be particularly useful in the management of oppositional, argumentative, impulsive, and aggressive behavior.

Although imipramine and desipramine have been reported to be useful in the treatment of OCD, the most effective drugs are the selective serotonin reuptake inhibitors (SSRIs) [51]. These include fluoxetine, fluvoxamine, clomipramine, paroxetine, sertraline, venlafaxine, citalopram, and escitalopram, and citalopram. Sertraline, particularly when combined with cognitive behavioral therapy, has been found to significantly reduce anxiety in a randomized-controlled trial involving 488 children with anxiety disorder [52].

Surgical treatment of TS should be reserved for patients with disabling symptoms unresponsive to medical therapy. While the overall experience of stereotactic ablative surgery in the treatment of tics has been rather disappointing, an increasing number of reports have provided evidence that deep brain stimulation (DBS) involving the thalamus, the globus pallidus and other targets may be a very effective strategy to treat uncontrollable tics [53–55]. Careful selection of patients, experience with the DBS procedure, and comprehensive assessments at baseline and at follow-up visits are essential for the successful outcome of DBS in TS [56]. Based on a double-blind assessment of 5 patients with TS undergoing bilateral thalamic DBS, there was a significant (\(p < 0.03\)) reduction in the modified Rush Video-Based Rating Scale score (primary outcome measure) and improvement was also noted in motor and phonic tic counts as well as on the Yale Global Tic Severity Scale (YGTSS) and TS Symptom List scores (secondary outcome measures) [57]. In addition, there was evidence of improvement in the quality of life indices and 3 of 5 patients had marked improvement according to all primary and secondary outcome measures. In the largest reported series, 18 TS patients underwent bilateral DBS of the centromedian parafascicular (CM-Pfc) and ventralis oralis (Vo) complex of the thalamus [58]. Followed up to 18 months, most patients apparently showed improvement in tics as well as OCD, self-injurious behavior, and other comorbidities. In a prospective 24-month follow-up of 15 of the original 18 patients, there continued to be a marked improvement in tics, OCD, anxiety, and depression with subjective perception of improved social functioning and quality of life [59]. Finally, the observation that vagal nerve stimulation also favorably modifies the frequency and intensity of facial tics suggests that the brainstem plays a role in generation of modulation of tics [60]. Further studies are needed to determine which TS patients are best candidates for stereotactic surgery and which targets may be most appropriate for particular symptoms.

**Conclusion**

TS is a complex neurobehavioral disorder manifested by phonic and motor tics as well as a variety of behavioral comorbidities, particularly ADHD, OCD, and poor impulse control. Genetic factors clearly play a role in the pathogenesis of this disorder even though no causative gene mutation applicable to most patients with TS has been found. The pathophysiology of TS is not well understood but disinhibition of the cortico-striatal-thalamic-cortical circuit has been suggested by physiological and functional imaging techniques. While the selection of therapy must be individualized for each patient, antidopaminergic drugs and local injections of botulinum toxin have been found to be most effective in the treatment of tics. Even though CNS stimulants may possibly transiently exacerbate tics they are not absolutely contraindicated in the treatment of ADHD associated with TS. SSRIs and other pharmacologic and behavioral therapies are also useful in the management of TS. DBS targeting thalamus of GPI is considered the best surgical approach to patients with extremely severe TS.
References


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APPENDIX

Tourette Syndrome Association (TSA)
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Website: http://neuro–www2.mgh.harvard.edu/tsa/tsamain.ncl

Other Relevant Websites
http://www.tsa.org.uk
http://www.ed.gov

http://www.nih.gov
http://www.wemove.org
http://www.cw.bc.ca/childrens/mhrev05/cats/catsdrug.html

Obsessive Compulsive Foundation
http://www.ocfoundation.org/

Children and Adults with Attention–Deficit Disorder
http://www.chadd.org/
http://www.ets.org/disability/adhdplcy.html
CHAPTER 13
Secondary Tics

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Introduction

The aim of this chapter is to provide an overview of secondary tics or tourettism according to their presumed cause. Tics represent one of the most common movement disorders, reported to occur in up to one quarter of children [1–4]. Although the majority of patients have primary tics associated with Tourette syndrome (TS) (see Chapter 12), in a few patients this movement disorder is associated with an underlying structural abnormality of the brain or some external cause. The term tourettism has been used to describe secondary tics [5–7]. To the author's knowledge, there are no epidemiological studies of the prevalence of secondary tics.

The literature of secondary tics must be interpreted with caution since, in most instances, the causal relationship between the movement disorder and the associated condition is not firmly established since the studies are reports of a few cases. Moreover, in some of the reports, it is not clear whether the patients display features commonly found in tics, such as the ability to suppress them as well as a premonitory urge [8].

Tics and infections

Encephalitis lethargica pandemic, also known as Von Economo disease (named after the Austrian physician who described it), is the classical infectious cause of tics. The disease started spontaneously in several different central European cities around 1916. Over the next 11, it spread relentlessly around the world, leaving an estimated half a million people dead or disabled. From the outset, it became established that a subset of surviving patients developed postencephalitic parkinsonism [9]. As mysteriously as it began, this disease virtually disappeared. Curiously, its causative agent remains unknown to date. It is uncertain whether recent cases with similar clinical pictures represent the same condition described by von Economo [10,11]. Although parkinsonism was the most common movement disorder found in those patients, a subset of subjects presented with motor, vocal, or other phonic tics. Interestingly, similarly to what happens in TS, some patients with postencephalitic parkinsonism also had obsessive-compulsive disorder (OCD) [9].

There are reports of tics associated with herpes simplex encephalitis [12] as well as HIV encephalopathy [13]. However, more recent studies on a possible relationship between infections and tics have focused on streptococcus. PANDAS (pediatric autoimmune neuropsychiatric disorder associated with streptococcus) is a controversial concept, according to which infection with group A beta-hemolytic streptococcus may induce tics, OCD, and other neuropsychiatric disturbances. The following working diagnostic criteria for this condition have been proposed: (1) presence of OCD...
or a tic disorder, (2) prepubertal symptom onset, (3) episodic course of symptom severity, (4) association with group A beta-hemolytic streptococci infections, and (5) association with neurologic abnormalities. According to a description of 50 patients who met these criteria, the onset of tics and OCD had a mean age of 6.3 and 7.4 years respectively [14]. There remain many doubts whether there is indeed a solid causal relationship between streptococcal infection and some of these clinical phenomena, and more recent studies have even challenged the existence of a relationship between streptococcal infections and PANDAS [15, 16].

A related issue is the presence of tics in patients with Sydenham chorea (SC). There are reports of a common occurrence of tics in SC. Caution is warranted to interpret these claims since it is virtually impossible to distinguish simple tics from fragments of chorea. Even vocal tics, which were found in 70% or more of patients with SC in one study, cannot be easily diagnosed in patients with hyperkinesias [17]. Those physicians who are experienced in movement disorders are well aware that involuntary vocalizations may result from dystonia or chorea of the pharynx and larynx [8]. In these circumstances the vocalization lacks the subjective feeling (premonitory urge or sensory tic), so characteristic of idiopathic tic disorders such as TS. In a cohort of 108 SC patients carefully followed up at our unit, we identified vocalizations in just 8% of subjects. We have avoided the term “tic” because there was no premonitory sign or complex sound and, conversely, the vocalizations were associated with severe cranial chorea. Taken together, these findings suggest that the involuntary sounds that were present in a few patients with SC result from choreic contractions of the upper respiratory tract muscles rather than being true tics [18]. The results of this study further weaken the hypothesis of a causal relationship between streptococcus infections and tics and related disorders.

**Tics and drugs**

Box 13.1 contains a list of some of the drugs implied in the development or worsening of tics. This is an area where it is particularly difficult to interpret the data of the studies. In many cases, the articles contain a description of a limited number of cases without proper controls. In other instances, the reported patients already had pre-existent tic disorders which renders it difficult to accept the causal relationship between the use of the medications and the worsening of the movement disorder since TS and other idiopathic tic disorders are characterized by fluctuation of their severity [19]. For instance, there are reports describing the onset of tics in patients treated with carbamazepine [20, 21]. Some of the subjects had a pre-existent movement disorder and the tics persisted after the withdrawal of the antiepileptic drug [20], suggesting that they had an idiopathic tic disorder. Other antiepileptic agents implied in triggering or worsening tics are phenytoin and phenobarbital [6, 7]. Similar problems are found in the literature describing the association of tics and antidepressants such as imipramine, clomipramine, desipramine, fluoxetine, sertraline, fluvoxamine, and buproprion [6]. Not only did all the patients have TS or some other idiopathic tic disorder, but whenever controlled trials were performed, such as with desipramine and clomipramine, no association was found between the use of these drugs and the onset or worsening of tics [22, 23]. Similarly, despite reports of tardive tourettism as a complication of prolonged use of typical neuroleptics [24, 25], in a review of 100 patients with tardive dyskinesia we have not been able to identify any patient with tics [26].

There is a great deal of interest in the relationship between the induction or worsening of tics and the use of stimulant agents [27], which are the main methods of treating attention deficit and hyperactivity disorder (ADHD) – a comorbid

<table>
<thead>
<tr>
<th>Box 13.1 Drugs associated with onset of tics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamines</td>
</tr>
<tr>
<td>Anticholinergics</td>
</tr>
<tr>
<td>Antidepressants</td>
</tr>
<tr>
<td>Antiepileptics</td>
</tr>
<tr>
<td>Antihistamines</td>
</tr>
<tr>
<td>Antipsychotics</td>
</tr>
<tr>
<td>Atomoxetine</td>
</tr>
</tbody>
</table>

*Albanese_c13.indd 201* 12/24/2011 7:05:16 AM
feature in up to 60% of patients with idiopathic tic disorders [28]. In several reports – including some on the more recent agent, atomoxetine – there are descriptions of worsening or even induction of tics with stimulant drugs used to treat ADHD [6, 7, 29–31]. However, when controlled studies were performed, there was no definite evidence supporting the notion that stimulant drugs have the potential to induce tics. This led to the conclusion that it is safe to treat patients with ADHD and tic disorders with stimulants [27, 32, 33]. Finally, we and others have described that patients with TS who use cocaine may experience worsening of their tics [34].

**Tics and structural lesions**

There are reports of a new onset of tics after vascular lesions of the brain [6, 7, 35]. In the sole instance where there is a clear description of the topography of a stroke, Jankovic reports one child with an onset of contralateral hemidystonia and facial tics after an infarction of the middle cerebral artery involving the basal ganglia [35, 36]. The discrepancy between the common occurrence of vascular lesions and the rarity of tics in this context suggests that there might be some underlying genetic predisposition.

Rarely, trauma of the brain [6, 7, 37–39] or a peripheral injury [40] can cause tics. In most instances, the patients underwent severe central nervous system lesion resulting in a myriad of neurological findings, including tics. There are, however, reports describing the onset of tics after relatively minor peripheral injuries [6,40]. Since mild traumas and tics are common, these reports are difficult to interpret. It is possible that the presumed association merely reflects a recollection bias. Furthermore, some of these patients may have a psychogenic movement disorder [4, 42].

Carbon monoxide poisoning induces necrotic pallidal lesion often associated with movement disorders [43]. There is one report in which the authors describe a patient who, after recovery of an acute coma induced by CO poisoning, developed tics [44]. Finally, recently there is one case report describing a child with a large temporal lobe oligodendroglioma extending to the basal ganglia who developed _de novo_ tics, ADHD, and OCD [45].

**Tics and other neurodegenerative disorders**

There are reports of the occurrence of tics in Huntington disease (HD) [6, 7, 46–48]. Although choreic contractions of the upper respiratory musculature can be associated with vocalizations, the reported cases appeared to have phonic tics as well as motor tics. Both motor and phonic tics have also been described in patients with neuroacanthocytosis, an autosomal recessive disorder characterized by chorea and other movement disorders, self-mutilatory oromandibular dyskinesia, seizures, peripheral neuropathy, and acanthocytes in the peripheral blood [49]. Some patients with a clinical diagnosis of neurodegeneration associated with brain iron accumulation type 1 (NBIA-1), formerly known as Hallervoden–Spatz disease, may also exhibit tics [ 6, 7, 50]. There is a wide phenotypic variation related to this condition and not every patient with NBIA-1 has the “eye of the tiger” sign in a MRI of the brain, and this radiological finding is not specific to NBIA-1 [51].

Most cases of dystonia are primary, and unrelated to neurodegenerative diseases [52]. Nevertheless, the possible association between this movement
disorder and tics will be discussed in this section. There are reports suggesting that patients with dystonia are at risk of developing tics [6, 7, 53]. Conversely, in a survey of a large database of TS patients, the authors demonstrated that dystonia has a prevalence of 1,352 per million [54]. This finding suggests that the frequency of dystonia in the TS population falls within the range described for the general population [55].

Miscellaneous

Clinicians have described that patients with autism spectrum disorder may present with clinical features, which meet the criteria for TS [6, 7]. In some series, the authors have described 29 children with such an association, leading them to suggest a pathogenic link between TS and autism [56, 57]. Regardless of the underlying mechanism, more recent data confirms that there is an association between the two disorders. For instance, in one study of 112 consecutive children with autism spectrum disorder, the authors diagnosed chronic tic disorder in 6% of subjects, a figure higher than the 1% prevalence expected for the general population [58].

Older literature describes the presence of tics in non-treated schizophrenic patients [6, 7, 59]. It is not easy to assess this data since definitions of the phenomenology of movement disorder have evolved along the years, less recent studies could have included patients with postencephalitic parkinsonism, and more recent reports are potentially confounded by exposure to neuroleptics. Nevertheless, a recent study describes that 2. 5% of a cohort of 399 TS patients meet the criteria for schizophrenia, whose rate in the general population is 1%. The difference was statistically significant [60]. It remains to be determined whether these patients truly have idiopathic TS or another condition that mimicks it.

Psychogenic tics (pseudo-tics) are a well-recognized entity [6,7]. Two recent studies demonstrate that 4 to 6% of all patients with psychogenic movement disorder present with tics [61, 62]. Similar to seizure disorders, patients with TS may also present with psychogenic tics [63].

Finally, there are reports describing the coexistence of tic disorders with a number of chromosomal abnormalities: Down syndrome, Kleinfelter syndrome, XYY karyotype, fragile X syndrome, triple X and 9p mosaicism, 9p monosomy, partial trisomy of 16, 18q syndrome, 3q24 deletion, and XXYY syndrome [6, 64–66].

Management

If the cause of the secondary tic cannot be removed or treated, then the symptomatic therapy of secondary tics is generally similar to that of primary tic disorders, discussed in Chapter 12. In some instances, however, it is possible to address the specific cause. For example, withdrawal of the offending drug may improve tardive tics, although tetrabenazine may be needed to further improve the tic [67]. Tics associated with SC may be treated with a combination of valproic acid and secondary prophylaxis of streptococcus infection with penicillin. Antidopaminergic drugs and immunosuppressive measures are left for patients who fail to improve with the other measures [68].

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PART 5
Myoclonus Syndromes
CHAPTER 14
Inherited Myoclonus Syndromes

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Historical background

This chapter focuses on the myoclonus-dystonia (M-D) syndrome, which has previously been referred to as familial myoclonia, essential familial myoclonus, benign essential myoclonus, and alcohol-responsive myoclonic dystonia. M-D should be distinguished from (i) inherited myoclonic dystonia, which comprises primarily dystonic disorders with myoclonus occurring in body parts affected by dystonia, usually intermingled with dystonic spasm and resulting in myoclonic-like fast dystonic movements [1–3]; and (ii) inherited neurometabolic or heredodegenerative disorders in which secondary myoclonus or myoclonic dystonia is usually part of a more complex phenotype [4–6] (Tables 14.1 and 14.2). Myoclonus of these patients usually have neurophysiological characteristics distinct from those of M-D patients (see Figures 14.1, 14.2, and 14.3). Following reports of isolated families, Mahloudji and Pikielny provided the first thorough description of the M-D syndrome in 1967 [7], and their initial diagnostic criteria have only undergone minor revisions [8]. The major M-D culprit gene, the epsilon-sarcoglycan gene (\(SGCE\)), was identified in 1997 and linked to M-D in 2001 [9]. Several attempts have been made over the last decade to unravel the genetic basis of M-D, to identify genotype/phenotype correlations, and to gain insights into the complex pathogenesis of this disorder.

Phenomenology and other clinical features

A positive family history is frequent, and dominant paternal transmission is the rule. The disorder usually occurs in childhood, with symptom onset at a mean age of 6 years [10]. Onset tends to occur earlier in girls than in boys, regardless of the underlying genetic abnormality [11]. Onset after age 20 is very unusual, although onset as late as in the eighth decade has occasionally been reported [12]. In most cases the presenting symptom is myoclonus, which may be isolated or associated with dystonia (see Video 14.1). Isolated dystonia is the initial manifestation in the remaining 20% of cases [10, 11, 13–15]. The presenting symptoms are not related to sex or age [10]. Myoclonus is usually the main and most disabling feature. The typical phenotype consists of very brief, “lightning-like” myoclonic jerks, which may be either isolated or associated with mild to moderate dystonia and generally predominate in the upper body [10, 16] (see Video 14.2).
Myoclonus is often present at rest; it is aggravated by posture and action, and is generally stimulus-insensitive. The most frequent pattern is one of axial myoclonus with predominantly cervical involvement associated with upper-limb myoclonus [14]. Myoclonus of the lower limbs is also found in about 25% of cases [10, 13, 14, 16, 17]. Myoclonus usually predominates in the proximal segment of the limbs, although predominantly distal involvement is also observed [12]. Myoclonus involves the...
Inherited Myoclonus Syndromes

Figure 14.2 Polymyographic features in myoclonic dystonia, differing from those of DYT11 M-D

(a) Glutaric aciduria. Dystonic spasms (arrows) intermingled with myoclonus (35 ms length) recorded in the feet in the standing position; b: Idiopathic hemi-myoclonic dystonia. Continuous dystonic spasms (arrows) composed of or intermingled with myoclonus (30-70 ms length), wrist outstretched. c: Rett syndrome. Rhythmic (6 Hz) myoclonus (95–195 ms length) and dystonic pattern recorded during hand stereotypia production. Abbreviations: EDB, extensor digitorum brevis muscle, ECR: extensor carpi radialis, FCR: flexor carpi radialis.

Figure 14.3 Agonist/antagonist patterns during flexion/extension of the wrist in myoclonic dystonia as compared to DYT11 M-D.

In myoclonic dystonia (a), note that dystonic spasms (arrows) observed in both FCR and ECR impair the alternating agonist/antagonist physiological activation expected for a normal movement, thus producing a co-contracting pattern. In DYT11 M-D (b), note the brief myoclonus (asterisks) occurring in the FCR during both extension (E) and flexion of the wrist, interfering with the continuity of the movement.

Abbreviations: ECR: extensor carpi radialis, FCR: flexor carpi radialis.

Video 14.1 Myoclonus-dystonia phenomenology

This 7-year-old girl has a myoclonus-dystonia due to SGCE mutation. She has postural and action myoclonus of the upper body associated with very mild dystonia of the neck and upper limbs, one year after disease onset.


face and/or voice in about 25% of cases [10, 14, 16, 18]. When present, dystonia is usually mild to moderate – cervical dystonia and writer’s cramp being the most common manifestations. The lower limbs are sometimes involved and can be affected first [17]. Laryngeal dystonia is rarely present [13, 17]. As in most movement disorders, psychological or physical stress can lead to transient aggravation of the motor manifestations. Severity and the rate of progression are both variable and unpredictable, ranging from severe motor disability in adolescence to mild, non-progressive symptoms lasting decades, and onset in old age. Clinical signs may evolve over
time in a given individual, particularly in childhood or adolescence. It is noteworthy that limb dystonia can improve spontaneously before adulthood [10, 19]. The motor disorders usually remain fairly stable during adulthood and are compatible with an active life and normal lifespan [20]. In some cases, however, M-D may be progressive [21, 22], and can worsen in severity at any time during the course of the disease (even in old age), or involve body regions that had previously been unaffected [10]. This may occasionally lead to considerable functional disability.

Alcohol responsiveness is a striking feature of M-D, most patients having a drastic symptom improvement in response to alcohol ingestion, and rebound worsening on alcohol withdrawal [16]. For this reason there is a real risk of alcoholism in M-D patients, likely owing more to self-treatment of motor symptoms than to a direct effect of the underlying genetic defect.

The place of non-motor manifestations in the M-D phenotype is controversial. There is growing evidence that M-D patients are more prone to develop psychiatric disorders, including anxiety disorders, depression, emotional instability and obsessive-compulsive disorder [23–27], but further work is needed to determine whether these are part of or secondary to the M-D phenotype. Likewise, M-D patients may have subtle cognitive dysfunction: mild impairment of verbal learning and memory have been reported in a limited number of patients [13], but a larger study showed no cognitive defects [25].

## Epidemiology

The overall incidence of M-D is unknown. The largest series have been reported in Europe and North America, but the disorder seems to occur worldwide.

## Etiology

The M-D syndrome is genetically heterogeneous and has been linked to at least two loci: DYT11 in chromosome region 7p21, corresponding to the location of the epsilon-sarcoglycan gene (SGCE; OMIM# 604149); and DYT15 in chromosome region 18p15, in which the culprit gene remains to be identified [9, 28–34]. M-D patients can be divided into three groups with respect to the underlying genetic defect: (i) patients with mutations or deletions within the epsilon-sarcoglycan SGCE gene, which account for about 40% of cases,
(ii) patients with SGCE deficiency due to rare genetic abnormalities, including large interstitial deletions encompassing the entire SGCE gene of paternal origin and maternal disomy of chromosome 7; and (iii) a heterogeneous group of patients with a similar M-D phenotype in the absence of SGCE deficiency.

Mutation or deletion of the SGCE gene is detected in only about 40% of patients with the typical phenotype, reflecting the genetic heterogeneity of the disorder [31, 34]. SGCE is an ubiquitous membrane protein widely expressed in central nervous system neurons [35–38]. Its exact function is unknown. In M-D families with mutation or intragenic deletion of SGCE, inheritance is autosomal dominant with reduced penetrance. Transmission is almost always paternal, due to imprinting (and thus silencing) of the maternal allele by methylation of CpG dinucleotides within the promoter region of SGCE [39–41]. De novo mutation of SGCE can occasionally occur in patients with apparently sporadic M-D [42]. In addition, the family history may be hidden by maternal imprinting in the case of maternal transmission of the mutated allele over successive generations [43].

In rare patients, M-D is part of a contiguous gene syndrome due to interstitial microdeletions (up to 16 Mb) encompassing the entire SGCE gene of paternal origin and adjacent genes on chromosome arm 7q. In this case the manifestations accompanying M-D depend on the deletion breakpoints and frequently include mental retardation, microcephaly, facial dysmorphism, and intrauterine and postnatal growth retardation [34, 44–47]. Finally, M-D syndrome due to SGCE deficiency can result from maternal uniparental disomy of chromosome 7 owing to methylation, silencing the two maternal alleles [41]. Such patients may have additional manifestations due to abnormal expression of other imprinted genes located on chromosome 7, or to the unmasking of recessive mutations within isodisomic segments.

M-D without SGCE deficiency is also likely to be due to a variety of genetic defects. Basically, the phenotype of these patients is very similar to that of patients with SGCE deficiency [33, 48], although subtle differences have been reported [10, 15].

Pathophysiology

The pathogenesis of M-D has not yet been elucidated. However, several abnormalities point to primary dysfunction of the basal ganglia. Biochemical studies in a mouse model of M-D, and human neuroimaging studies with 123I-IBZM SPECT, suggest an altered dopaminergic neurotransmission in the striatum [49, 50]. Clinical neurophysiological studies have revealed signs of a subcortical origin of the myoclonus, including: (i) a polymyographic pattern (Figure 14.1), (ii) lack of stimulus sensitivity of the myoclonus, (iii) negative C-reflex, (iv) absence of premyoclonic cortical potential on EEG jerk-locked back averaging, and (v) absence of giant somatosensory evoked potentials [10, 14, 51–53]. In particular, dysfunction of the internal globus pallidus may play a key role in M-D pathogenesis, as: (i) M-D patients are dramatically improved by deep brain stimulation of the internal globus pallidus [54]; (ii) increased coherence between the local field potentials of the GPi and muscle activity has been found in M-D patients [55, 56]; (iii) a correlation between myoclonic jerk muscle activity and neuronal activity within the GPi has been observed in one M-D patient [57]. One hypothesis is that the M-D phenotype is related to increased synchronization of neuronal activity in the basal ganglia network [55].

Experimental neurophysiological studies are scarce and include only a small series of patients. They have shown subtle cortical dysfunctions, but it is difficult to determine whether these abnormalities are primary or secondary to basal ganglia or brainstem dysfunction. Transcranial stimulation (TMS) studies suggest that the GABAergic cortical inhibitory system is intact in M-D, as short-interval (mediated by GABA_A receptors) and long-interval (mediated by GABA_B receptors) intracortical inhibition (SICI and LICI, respectively) is normal [52, 58, 59]. Intracortical facilitation (ICF), reflecting the excitability of glutamatergic cortical interneurons, is consistently normal in M-D patients [53, 58, 59]. Contrasting with the normal GABAergic and glutamatergic synaptic transmission, changes in the properties of ion channels in neural membranes are suspected, based on the increased variability of
short-interval intracortical facilitation (SICF) [59] and decreased active motor thresholds (aMT), which reflect membrane-related excitability of cortico-cortical axons [58]. SICF is thought to be mediated by successive activation of different groups of cortical interneurons by transcranial stimulation [60]. However, these findings need to be replicated in a large series of patients. One interesting finding is the enhancement of the recovery curve of the R2 component of the blink reflex, suggesting brainstem interneuron hyperexcitability [53]. Finally, an EEG–EMG coherence study of 20 M-D patients failed to detect the normal cortical drive to the muscles in the beta band during sustained contractions of the arm muscles [61]. Conventional MRI is normal in M-D patients. A study of a limited number of patients showed an abnormal activation pattern in the cortex and cerebellum during a standardized motor task, in keeping with disorganized sensorimotor integration [62]. This is consistent with findings in other hereditary dystonias [63, 64]. Other studies of isolated cases, using single-photon emission computed tomography or functional MRI, have shown inconsistent functional abnormalities in the cortex, striatum, thalamus, or cerebellum [65–67].

**Treatment**

There is no etiological treatment for M-D, and symptomatic pharmacological treatments are usually disappointing. Benzodiazepines and anticholinergics should be tried first. Interestingly, these drugs can be effective not only on dystonia and but also on myoclonus. Many other drugs have been proposed, including antiepileptics (piracetam, levetiracetam, valproate, barbiturates, primidone, carbamazepine, gabapentine, topiramate, zonisamide), L-dopa and dopamine agonists, serotonic agents, beta-blockers, tetrabenazine, amantadine, and zolpidem [8, 51]. One striking feature of M-D is the marked symptom alleviation experienced by most patients after alcohol ingestion, but there is currently no alcohol analogue or equivalent for therapeutic use. Hydroxybutyrate, a drug used for ethanol withdrawal in chronic alcoholics as well as for excessive daytime sleepiness in Parkinson’s disease or narcolepsy, and for binge eating, shows promise in this setting [68, 69]. The sodium salt form, sodium oxybate, may be an interesting option for M-D patients, but most countries restrict its use because of safety concerns. Other possible treatments include botulinum toxin injection for focal dystonic postures (particularly cervical dystonia), physical therapy, and relaxation methods.

Deep brain stimulation of the internal globus pallidum is a safe and effective option for patients with severe and disabling M-D. Although they have not been formally evaluated, the benefits seem to be at least equivalent to those seen in patients with other primary dystonias [70–72], with a motor and functional improvement usually exceeding 60% [54, 73]. Interestingly, this treatment is effective on both myoclonus and dystonia (see Video 14.4). Deep brain stimulation of the ventral intermediate thalamic nucleus has also been reported to be effective [73].

**Other inherited myoclonus disorders**

Besides the myoclonus-dystonia syndrome, inherited myoclonic disorders include myoclonic forms of dystonic disorders as well as neurometabolic or
heredogenenerative disorders, in which myoclonus is part of a complex neurological picture. The main possible etiologies to be considered are listed in Tables 14.1 and 14.2.

Among these disorders, progressive myoclonic epilepsies and progressive myoclonic ataxia (PME/PMA) represent an important syndromic entity. Onset usually occurs in childhood or adolescence. The clinical phenotype is characterized by action- and stimulus-sensitive, severe, multifocal or generalized myoclonus. Myoclonus is usually associated with severe epilepsy and progressive neurological deterioration, typically with cerebellar ataxia and dementia [74]. Clinical severity and the rate of progression vary widely from one patient to the next, mostly depending from the underlying etiology. It ranges from severe disability in adolescence to mild symptoms and normal social interactions with survival into old age.

### Table 14.1 General characteristics of inherited progressive myoclonic epilepsies.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Inheritance</th>
<th>Gene</th>
<th>Protein</th>
<th>Associated abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unverricht–Lundborg disease</td>
<td>AR</td>
<td>EPM1A</td>
<td>Cystatin B</td>
<td></td>
</tr>
<tr>
<td>Lafora disease</td>
<td>AR</td>
<td>EPM2A</td>
<td>Laforin</td>
<td></td>
</tr>
<tr>
<td>Neuronal ceroid lipofusciniosis</td>
<td>AR</td>
<td>EPM2B</td>
<td>Malin</td>
<td>Retinopathy</td>
</tr>
<tr>
<td>Neuropathogenic myoclonic epilpsies with ragged red fibers</td>
<td>Maternal</td>
<td>MTK</td>
<td>tRNALys</td>
<td></td>
</tr>
<tr>
<td>Sialidosis</td>
<td>AR</td>
<td>NEU1</td>
<td>Alpha-neuraminidase</td>
<td>Deafness, Myopathy</td>
</tr>
<tr>
<td>Type 3 Gaucher disease</td>
<td>AR</td>
<td>GBA</td>
<td>Glucocerebrosidase</td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td>Juvenile dentorubral-pallidoluysian atrophy</td>
<td>AD</td>
<td>Atrophin</td>
<td>Atrophin</td>
<td>optic atrophy, Cardiomyopathy</td>
</tr>
<tr>
<td>Juvenile Huntington disease</td>
<td>AD</td>
<td>IT15</td>
<td>Huntingtin</td>
<td>Diabetes mellitus, Lipomatosis</td>
</tr>
<tr>
<td>Encephalopathy with neuroserpin inclusions</td>
<td>AD</td>
<td>SERPINI1</td>
<td>Neuroserpin</td>
<td>Macular cherry-red spot</td>
</tr>
<tr>
<td>PME linked to KCTD7</td>
<td>AR</td>
<td>KCTD7</td>
<td>KCTD7</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>PME linked to PRICKLE 1</td>
<td>AR</td>
<td>PRICKLE 1</td>
<td>Prickle 1</td>
<td>Bone involvement</td>
</tr>
</tbody>
</table>

1 Can accompany the classical manifestations of progressive myoclonic epilepsy: epilepsy + myoclonus +/- cerebellar signs +/- cognitive impairment.

2 When the culprit gene is known.

AR: autosomal recessive; AD: autosomal dominant; PPT1: palmytoyl protein thioesterase; TPP1: tripeptidyl peptidase; KCTD7: potassium channel tetramerization containing domain 7; MFSD8 major facilitator superfamily domain containing protein 8.
## Table 14.2 General characteristics of various inherited dystonic disorders that can manifest as myoclonic dystonia1.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Inheritance</th>
<th>Gene2</th>
<th>Protein</th>
<th>Associated abnormalities3</th>
</tr>
</thead>
<tbody>
<tr>
<td>DYT1 primary dystonia</td>
<td>AD</td>
<td>TOR1A</td>
<td>Torsin A</td>
<td>Parkinsonism, Tremor</td>
</tr>
<tr>
<td>DYT5 primary dystonia</td>
<td>AD</td>
<td>GCH1</td>
<td>GTP cyclohydrolase 1</td>
<td>Tremor, akinetorigid parkinsonism</td>
</tr>
<tr>
<td>Wilson’s disease</td>
<td>AR</td>
<td>ATP7B</td>
<td>ATP7B</td>
<td>Dementia, psychosis</td>
</tr>
<tr>
<td>Glutaric aciduria</td>
<td>AR</td>
<td>GCDH</td>
<td>Glutaryl CoA dehydrogenase</td>
<td>Mental retardation</td>
</tr>
<tr>
<td>GM1 gangliosidosis</td>
<td>AR4</td>
<td>GLB1</td>
<td>Beta-galactosidase</td>
<td>Macrocephaly</td>
</tr>
<tr>
<td>Lesch-Nyhan disease</td>
<td>X linked recessive</td>
<td>HPRT</td>
<td>Hypoxanthine-guanine phosphoribosyl transferase</td>
<td>Mental retardation</td>
</tr>
<tr>
<td>Creatine deficiency</td>
<td>AR</td>
<td>GAMT</td>
<td>Glycine amidinotransferase4</td>
<td>Epilepsy, Mental retardation</td>
</tr>
<tr>
<td>Mitochondrial disorders</td>
<td>Various</td>
<td>Various</td>
<td>Various</td>
<td>Various associated movement disorders</td>
</tr>
<tr>
<td>GLUT1 deficiency</td>
<td>AD</td>
<td>GLUT1</td>
<td>GLUT1 glucose transporter</td>
<td>Multisystem involvement</td>
</tr>
<tr>
<td>Niemann Pick C disease</td>
<td>AR</td>
<td>NPC1</td>
<td>Niemann Pick C 1</td>
<td>Ataxia, Chorea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NPC2</td>
<td>Niemann Pick C 2</td>
<td>Mental retardation, Epilepsy</td>
</tr>
<tr>
<td>Type3 Gaucher disease</td>
<td>AR</td>
<td>GBA</td>
<td>Glucocerebrosidase</td>
<td>Psychiatric disorders</td>
</tr>
<tr>
<td>Pantothenate kinase associated neurodegeneration5</td>
<td>AR</td>
<td>PANK2</td>
<td>Pantothenate kinase 2</td>
<td>Parkinsonism, Pyramidal syndrome</td>
</tr>
<tr>
<td>Rett syndrome6</td>
<td>X-linked dominant</td>
<td>MECP2</td>
<td>Methyl-CpG-binding protein 2</td>
<td>Mental retardation, Epilepsy, Microcephaly</td>
</tr>
<tr>
<td>Spinocerebellar ataxia 14</td>
<td>AD</td>
<td>PRKCG</td>
<td>Protein kinase C gamma</td>
<td>Ataxia, nystagmus</td>
</tr>
</tbody>
</table>

1 Note that virtually all dystonic disorders can occasionally manifest as myoclonic dystonia including primary dystonia (DYT1, DYT5) and dystonia secondary to neurometabolic disorders. In this setting, myoclonic dystonia is usually not isolated but part of a complex phenotype.

2 When the culprit gene is known.

3 Can accompany myoclonic dystonia.

4 Dystonia related to cerebral creatine deficiency is usually secondary to GAMT deficiency (although other genes can be involved in cerebral creatine deficiency).

5 and other neurodegeneration with brain iron accumulation.

6 Note that most cases are sporadic.

AR: autosomal recessive; AD: autosomal dominant.
PME/PMA encompasses a large group of genetic disorders, mostly with autosomal recessive inheritance (Table 14.1). The differential diagnosis of PME/PMA is dominated by five main disorders: Unverricht–Lundborg disease (EPM1) [75], Lafora body disease (EPM2) [76], neuronal ceroid lipofuscinosis [77], sialidosis [78], and mitochondrial encephalomyopathy with ragged-red fibers (MERFF) [79]. The predominant manifestation associated with myoclonus (epilepsy, ataxia, dementia) and additional features (retinal abnormalities, deafness, myopathy, polyneuropathy) vary across the disorders and may guide the clinician to the most likely cause. For example: (i) early or severe cognitive deterioration is rather suggestive of Lafora body disease or neuronal ceroid lipofuscinosis, whereas cognition is relatively preserved in sialidosis or Unverricht–Lundborg disease; (ii) occipital seizures are typically observed in Lafora body disease; (iii) macula cherry-red spot are seen in sialidosis; and (iv) myopathy or deafness are good clues to the diagnosis of mitochondrial encephalomyelopathy.

There is currently no way of preventing or even slowing the course of the neurological decline associated with PME/PMA. The treatment thus consists in symptomatic management of epilepsy and myoclonus associated with supportive and rehabilitative measures. Treatment of myoclonus and seizures is difficult in the setting of PME/PMA as both tend to be refractory. Although their efficacy has not been proved, various antiepileptic drugs are used including combinations of valproate (except for mitochondrial disorders), phenobarbital, benzodiazepine, piracetam, levetiracetam, and zonisamide [74]. It is noteworthy that some antiepileptic drugs can aggravate the clinical condition of PME/PMA patients and should thus avoid phenytoin (particularly in EPM1 patients), carbamazepine, vigabatrin, and gabapentin [74].

Conclusion

Inherited myoclonus-dystonia is a clinical and neurophysiological entity resulting in mild to severe disability due to a combination of myoclonus and dystonia. Precise diagnosis is necessary for etiological investigations and treatment. Knowledge of the clinical, neurophysiological and genetic aspects of myoclonus-dystonia has greatly improved in recent years. However, the function of the protein encoded by the epsilon-sarcoglycan (SGCE) gene, which is defective in nearly 50% of cases, is largely unknown. Ongoing basic and clinical research is providing novel insights into the complex mechanisms responsible for the motor disorders characteristic of M-D, and point to a dysfunction of the basal ganglia network. Drugs are poorly effective. Deep brain stimulation of the...
Chapter 14

Internal globus pallidus is a safe and very effective therapeutic option for severely affected patients.

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References

Inherited Myoclonus Syndromes


CHAPTER 15

Segmental Myoclonus

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Introduction

Segmental myoclonus is an uncommon neurological disorder, but it is a common form of myoclonus based on an epidemiological study [1]. Classically, segmental myoclonus has a specific clinical appearance that consists of, (1) rhythmic or semirhythmic involuntary activation of muscles corresponding to its brainstem/spinal segment(s) generator, (2) persistence that is relatively unaffected by state of consciousness, motor activity, or stimulus [2]. In theory, cortical myoclonus may also have a limited segmental distribution, but the classic clinical properties stated above have become intertwined with the definition of “segmental myoclonus” as a clinical entity. Moreover, the implied segmental generator has given the term “segmental myoclonus” implied physiological properties as well. However, recent observations have challenged the classic appearance and definition. Myoclonic movements that have a segmental generator do not always have persistence nor remain unaffected by external influences (i.e. consciousness, motor activity, or stimuli). Many of these examples involve the abdomen and/or respiratory apparatus as well as occasional more classic palatal and spinal phenotypes. Moreover, the putative “segmental generator” may use non-pyramidal pathways to transmit the abnormal excitation to their circumscribed motorneuron pools. This chapter will discuss the spectrum of myoclonus that is unified by the existence of a circumscribed segmental generator and has circuitry which can generate movements without stimulation from cortical motor systems.

Definition

For the purpose of this chapter, we will use the definition of Jankovic and Pardo, rhythmic or semirhythmic involuntary contractions of muscle groups supplied by one or several contiguous segments of the brainstem and/or spinal cord [2]. More specifically, our definition will imply an abnormal central generator which arises from localized segmental interneuron pools along the craniospinal neuraxis that are normally concerned with circumscribed segmental muscle control. Thus, we exclude genesis from control centers that use pyramidal long-tract descending pathways and exclude lesions that create “release phenomena” which generate abnormal movements at distant caudal muscle segments by severing control from higher integrative centers. This definition includes segmental myoclonus that may spread from a segmental generator via intersegmental or from a higher location via non-pyramidal tract pathways. The involvement of contiguous muscle segments and generation from a central localized segmental origin is key to the definition of segmental myoclonus.
myoclonus. Non-invasive electrodiagnostic studies on segmental myoclonus cases classically show rhythmic or semirhythmic surface electromyographic (EMG) discharges that are typically synchronous with stereotypic duration and frequency. Occasionally, affected muscles that are far apart may not be synchronized nor have the same frequency. There is no evidence of cortical hyperexcitability demonstrated on electroencephalography (EEG) or its back-averaging, somatosensory evoked potentials (SEPs), or transcortical reflexes that elicit EMG responses. These characteristics differentiate segmental myoclonus physiology from cortical, cortical-subcortical, subcortical/non-segmental, and peripheral types [3].

**Palatal myoclonus**

Palatal myoclonus is the most common type of segmental myoclonus [1]. The movement is rhythmic and usually bilateral with a rate between 1 and –4 Hz, with a reported range of 0.1 to 7 Hz [4]. A distinction is made between “essential palatal myoclonus” (EPM) and “symptomatic palatal myoclonus” (SPM) [5]. EPM is idiopathic and usually isolated. SPM is secondary to a definable cause and usually has other clinical manifestations associated. Some experts prefer the term “palatal tremor” over “palatal myoclonus” on the basis of the rhythmic nature of the palatal movements. Even though this terminology change has been proposed for about 20 years, “palatal myoclonus” is still the more commonly used term. Rhythmicity is not uncommon in myoclonus, and the definition of myoclonus does not exclude rhythmic character. For the purpose of this chapter, the term “palatal myoclonus” will be used to refer to this segmental movement disorder.

**Diagnosis and evaluation**

There are important differences between EPM and SPM, and we are indebted to Deuschl’s work for a comprehensive study of this issue [5–7]. Although many of the clinical characteristics of these entities overlap, the differences are strong enough to suggest that EPM is indeed distinct from SPM. EPM is usually caused by contractions of the tensor veli palatini, but isolated idiopathic “essential” middle ear myoclonus is caused by contractions of the tensor tympani and/or stapedius muscle [8–11]. EPM is associated with no identifiable MRI lesion, and is unlikely to involve other muscles. The EPM patients may have tinnitus or ear clicking, and these patients are likely to state that their ear click is the chief complaint [12, 13]. EPM patients are usually younger than those with SPM. SPM is usually caused by the levator veli palatini, although other palatal muscles can also be involved. Brainstem stroke causes about half of the SPM cases. Other etiologies are listed in Box 15.1 [2, 5, 14–29]. Associated synchronous movements may be seen in eye movements, eyelid, tongue, larynx, neck, diaphragm, trunk, and limbs [4]. SPM patients are usually more concerned with the other associated neurological problems (e.g. cerebellar ataxia) rather than the palatal movements per se.

**Clinical neurophysiology of palatal myoclonus**

Palatal myoclonus demonstrates characteristics of a segmental myoclonus physiology [3]. The EEG and SEP are normal. Brainstem auditory evoked potentials (BAEP) have had abnormal findings in some individuals with palatal myoclonus [4, 30]. These inconsistent BAEP abnormalities probably represent the same lesion type, but not the same exact location, as that responsible for the palatal myoclonus pathophysiology. Important differences...
in neurophysiological testing have also been found between EPM and SPM [6]. EPM shows a complete suppression with sleep, but sleep only produces mild variations in rate with SPM. The palatal movement cycle in SPM exerts remote effects on tonic EMG activity of extremity muscles. As shown by studies of blink reflex activity, jaw jerk, and masseter silent period, EPM had only polysynaptic brainstem reflex abnormalities, whereas SPM patients can have abnormalities of monosynaptic, oligosynaptic, and polysynaptic brainstem reflexes.

**Pathophysiology of palatal myoclonus**

The exact pathophysiology of palatal myoclonus has been elusive. EPM is idiopathic and the lesion location is unknown. Classically, SPM is thought to be due to a lesion within a nucleus or tract in the Guillain–Mollaret triangle, i.e. dentate–rubro–olivary circuitry [31]. Figure 15.1 summarizes the circuitry of these pathways and important pathophysiology aspects of SPM. Deuschl concludes from his significant work on EPM and SPM that the pathophysiology of these two entities seems different [7]. fMRI studies shows abnormal activity in the brainstem/cerebellar structures for SPM, but prominent activation of the putamen was shown in EPM [32–34]. It is interesting that EPM has been reported in monozygotic twins, but the exact significance of this finding is not known [10]. Commonly, olivary enlargement or atrophy may be evident on MRI scan in SPM [35, 36]. Pathology may show a neuronal cytoplasmic vacuolation and astrocytic hyperplasia [37, 38]. These changes are believed to result from a transsynaptic degeneration due to deafferentation of the inferior olive. Many of the fibers leaving the dentate nucleus that ascend to the red nucleus do not synapse in the parvocellular portion of the red nucleus. Rather, the fibers ascend in the superior cerebellar peduncle, cross at the midbrain and then loop under the red nucleus to descend via the central tegmental tract to the inferior olive (Figure 15.1). Lesions of either the ascending or descending part of this dentato–olivary pathway are associated with SPM and hypertrophic degeneration of the inferior olive secondary to presumed deafferentation and transsynaptic degeneration. The inferior olive projects fibers to the contralateral dentate nucleus and cerebellar cortex via the inferior cerebellar peduncle. However, lesions of the inferior cerebellar peduncle (base of the “triangle”) have not been associated with SPM. In animal models, it has been demonstrated that the inferior olive possesses gap junctions which have a tendency to oscillate [39, 40]. The prevailing theory is that deafferentation increases the amplitude of the oscillations and/or causes them to be abnormally transmitted to motorneurons to generate SPM [39, 41]. This may be due to removal of the dentato–olivary GABAergic input to the inferior olive [42]. However, hypertrophic degeneration of the inferior olive is not always present in SPM cases, and hypertrophic degeneration may be present

### Box 15.1 Causes of palatal myoclonus

- Vascular
  - Brainstem infarct [14]
  - Brainstem hemorrhage [15]
  - Cerebral vasculitis [16]
  - Ectatic vertebral artery compression [17]
  - Posterior circulation aneurysm [17]
- Essential [5]
- Neoplasm [18]
- Trauma [19]
- Demyelination [20]
- Infection [21]
- Neurodegeneration
  - Spinocerebellar degeneration [22]
  - Progressive supranuclear palsy [23]
  - Neurodevelopmental abnormality (e.g. Arnold–Chiari) [17]
- Syringobulbia [21]
- Hydrocephalus [24]
- Alexander’s disease (presumed) [25]
- Krabbe disease [26]
- Cerebrotendinous xanthomatosis [27]
- Celiac disease [28]
- Anoxia [29]
without SPM [43, 44]. Rarely, other lesions are associated with SPM [45]. Some authors have suggested that a dentato-olivary lesion in the brainstem may be associated with other areas being affected, and the dysfunction in those areas more directly cause SPM [46]. The dorsolateral reticular formation of the brainstem has been proposed as the top candidate for an alternative to the inferior olive as a pathogenic site for the genesis of SPM [47] (Figure 15.1). Whichever site is primary, abnormal oscillations reach the motor nuclei of the nucleus ambiguous to drive the levator palatini in SPM. The movements that are sometimes associated with SPM must also variably have their motor nuclei so affected. Rarely, palatal myoclonus may occur as a tic in the setting of Tourette syndrome [47(a)] or as a psychogenic movement disorder [47(b)].

Treatment
Palatal myoclonus is difficult to treat. All treatment of palatal is “off-label” with little controlled evidence. As a result, standard dosages and precautions as well as the list of potential side effects for the drug should be considered before a treatment trial. The list of drugs with anecdotal success in palatal myoclonus includes but is not limited to clonazepam, carbamazepine, baclofen, anticholinergics, tetrabenazine, valproic acid, phenytoin, lamotrigine, sumatriptan, and piracetam [8, 9, 48, 49]. Most commonly, palatal myoclonus fails these treatments. Because the ear clicking is so disabling when it occurs in palatal myoclonus, surgical treatments including tensor veli palatini tenotomy and occlusion of the Eustachian tube have been tried with variable success [50]. Middle ear myoclonus has been treated with tensor tympani and/or stapedius tenotomy as well as placement of ventilation tubes [11–13].

Botulinum toxin injections have been reported as effective in palatal myoclonus in a growing number of cases [51–62]. In particular, the obnoxious clicking sound experienced by certain cases is a common indication to use this therapy. Because the evidence is from case reports, it cannot be considered to be proven effective or safe. Both of the botulinum toxin A preparations available in North America have been used. Starting doses for Botox have been 4 and 5 units per side, while for

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**Figure 15.1** Coronal illustration of the brainstem showing nuclei and pathways that are important in the pathogenesis of symptomatic palatal myoclonus (SPM). Dentato-olivary pathway disruption is believed to be the most important lesion type for leading to SPM. The dorsolateral reticular formation has also been proposed as being involved in SPM pathogenesis. In SPM, the nucleus ambiguous provides nerve supply that provides the abnormal excitation to the levator palatini muscle.
Dysport has been 10–20 units per side. There is a wide range of reported response durations from weeks to several months. Repeat injections have been required but may be associated with a higher risk of side effects. The literature currently contains a lack of follow-up in these cases so it is not certain how often injections are needed or in how many instances the palatal myoclonus does not truly recur after the initial injection. Side effects may be significant and consist of nasal regurgitation, dysarthria, dysphagia, among others. Other considerations are,

- Botulinum toxin is not yet proven safe nor effective in palatal myoclonus
- Injections should be performed by a qualified Ears, Nose, Throat surgeon
- Electromyography guidance is considered useful
- Patients should be informed about the uncertainty/side effects of this therapy.

**Oculofacialmasticatory myorhythmia**

Sporadic focal myoclonic jerks have been reported in Whipple’s disease, but segmental myoclonus is the most characteristic myoclonus form noted for this disorder [63–65]. The common location for the segmental myoclonus is an oculofacialmasticatory distribution. This movement has also been termed “myorhythmia” because of its <3 Hz frequency. Treatment for the Whipple’s disease may improve the myoclonus. A rostral brainstem tegmentum lesion location has been suggested for the pathophysiology of this abnormal movement [66]. The appearance of oculofacialmasticatory myorhythmia should trigger an evaluation for Whipple’s disease.

**Spinal segmental myoclonus**

Spinal segmental systems may become hyperexcitable, often by viral infection, structural lesions, vascular insults, among other causes (Box 15.3) [2, 67–78]. The muscle jerks may be rhythmic or semi-rhythmic and occur at a typical frequency range of 1–3 Hz. Classically, the myoclonus involves one or several contiguous spinal myotomes and is peculiarly resistant to supraspinal influences, such as voluntary movement or sleep. However, a few recent cases have been reported to be subject to position, emotional distress, various stimuli, and altered consciousness [79–81]. The vast majority of cases have persistent movements, but some are intermittent or even paroxysmal. Certain patients may have had their clinical manifestations change over time. Upper or lower extremities, or even trunk muscles may be affected. Sometimes, pain with the muscle contractions is a significant symptom.

**Diagnosis and evaluation**

MRI of the whole spinal cord and brain is warranted to search for the segmental lesion responsible as well as other possible lesion sites (e.g. neoplasms). Other testing may be needed to determine if a systemic or diffuse neurologic disorder is present that may help to explain the segmental myoclonus,
Box 15.3 Causes of spinal segmental myoclonus

- Infection (viral-Herpes Zoster, HIV, Polio, Nipah [67]
- Stroke (infarct or hemorrhage) [2]
- Neoplasm [68]
- Demyelination [2]
- Neurodevelopmental abnormality [69]
- Trauma [70]
- Spondylosis [2]
- Peripheral nervous system lesion (root, plexus, sympathetic ganglion) [2]
- Arteriovenous malformation [71]
- Neurodegenerative [72]
- Electrical injury [2]
- Paraneoplastic syndrome [73]
- Intrathecal catheter [74]
- Contrast media [75]
- Amputation and soft tissue surgery [76]
- Spinal anesthesia [77]
- Syringomyelia [78]

Clinical neurophysiology of spinal segmental myoclonus

Clinical neurophysiology studies have provided information that is consistent with a segmental generator. The surface EMG shows synchronous rhythmic or semirhythmic discharges in muscles supplied by the corresponding spinal segmental generator (Figure 15.2). The polygraphic surface EMG study usually shows synchronous activation of the affected muscles. The typical frequency is in the range of 1–3 Hz with a broad reported range of 0.2–8 Hz, and the typical surface EMG discharge duration varies widely between 50 and ~500 ms [60, 70, 78, 82]. Needle electromyography may show signs of denervation in lesioned segments, but this is exceptional since the movements are believed to depend on intact motorneurons. Spinal segmental myoclonus physiology is without evidence of abnormal cortical excitability [3]. No EEG abnormalities have been detected, back-averaging never elicits a cortical correlate, and no cortical waves are abnormal in the SEP. However, some responses to sensory stimulation are abnormal and may show insight into the segmental physiological defect. In spinal segmental myoclonus, mixed nerve stimulation can evoke EMG discharges in the affected muscles at latencies longer than 40 ms, but such findings are variable and the latency values vary from case to case. These reflex discharges may reflect hyperexcitability of polysynaptic pathways that contribute to the generation of the myoclonus [83, 84]. Somatosensory evoked spinal potential recovery curves were abnormal in a case of segmental myoclonus involving the L2–L4 myotomes. The authors interpreted this finding as suggesting that dorsal horn interneurons are abnormally hyperactive and are involved in the pathophysiology of spinal segmental myoclonus [85].

Video 15.2 Segmental myoclonus
This patient presents with a post-thoracotomy stimulus-sensitive segmental myoclonus. [Video courtesy of Joseph Jankovic, MD, Houston, Texas]


Video 15.3 Segmental myoclonus
This patient presents with segmental myoclonus following a breast implant. [Video courtesy of Joseph Jankovic, MD, Houston, Texas]

http://bit.ly/tAiNTc
Pathophysiology of spinal segmental myoclonus

Early studies demonstrated that synchronous jerks could develop in the muscles that were innervated by the same spinal segments that had also received a lesion. Experimentally, the lesion was produced initially by 5% phenol in dogs by Turtschaninow in 1894 [86]. Supraspinal or infraspinal isolation of the affected spinal segment did not alter the movements. Proximal or distal sections of the corresponding nerve roots or motor nerves eliminated the movements. L’Hermitte described a patient in case in 1919 in which complete section of the spinal cord had occurred [87]. Campbell and Garland reported cases in which there was a presumed viral infection of the spinal cord [88]. Pathological examination showed changes in the spinal cord gray matter without obvious damage to anterior horn cells. Shortly thereafter, in 1959, Luttrel et al. injected the virus of Newcastle disease into the spinal cord of cats which produce rhythmic myoclonus [89]. Topical penicillin applied to the spinal cord of cats elicits myoclonus with similar results [90]. Cervical segmental myoclonus was reported secondary to a C3–C5 spinal glioma in 1968. In this patient, the myoclonus was relatively unaffected by external stimuli and persisted during sleep [68]. All these papers put forth the basic concepts that were used in subsequent reporting of spinal segmental myoclonus.

In later work, Davis et al. and Howell et al. separately demonstrated selective destruction of small and medium-sized neurons in the spinal gray matter at the appropriate level in their cases of spinal segmental myoclonus [91, 92]. Using these observations and their own, Parisi et al. argued that altered inhibitory functions of the interneurons at the segmental level allowed anterior horn motor neurons to be hyperexcitable enough to produce spinal segmental myoclonus. It was also suggested that such disruption of neuronal circuitry could occur in different ways [93]. Peripheral lesions have been associated with segmental myoclonus. In these instances, it is posited that central reorganization occurs at that spinal segment which produces the abnormal movements [94].

These combined observations allow us to speculate on how spinal segmental myoclonus is generated, but our confidence needs to be tempered by the lack of detail about our assertions and the significant remaining questions. It seems likely that segmental myoclonus can be produced by an abnormal segmental generator that exists within contiguous levels of spinal gray matter which serve contiguous myotomes. This concept also easily incorporates the possibility of influences from supraspinal or peripheral inputs. We know clinically that such influences are real because of the sometimes reported effects of emotional excitement and sensory stimuli. The abnormality in the

**Figure 15.2** A surface EMG recording that shows left anterior tibialis and medial gastrocnemius discharges from a patient with left L5–S1 spinal segmental myoclonus. Note the rhythmic and synchronous character of the discharges.
segmental generator could be due to abnormal circuitry in the interneurons of dorsal, intermediate, or ventral gray matter of the spinal cord. There is considerable evidence that interneuron circuits, when denied afferent input or have partial loss of intrinsic interneurons, begin to have abnormal oscillations. In many cases, these changes may occur through plasticity changes, accounting for the delay between the segmental circuit lesion and clinical manifestations. It is presumed that these abnormal oscillations are transmitted to anterior horn neurons in the corresponding myotomes. The clinical result may be rhythmic or semirhythmic relatively low frequency movements of segmental myoclonus. Drug treatments, when effective, are able to dampen these transmitted oscillations by augmenting still intact inhibitory mechanisms. Other successful treatments may restore the balance between oscillatory and non-oscillatory interneuron network activity.

Rothwell points out that abnormal activity in spinal interneurons may more often result in rigidity and sustained contractions of muscle rather than the intermittent contractions of segmental myoclonus, although sometimes it results in both [95]. He hypothesized that myoclonus occurs when strong enough inhibitory mechanisms still exist so that the muscle activity stops periodically and accounts for synchronization among the myotomes. In addition, Rothwell believes that in some instances, pathologically altered motorneurons may have their intrinsic electrical properties affected to contribute to the abnormal oscillations [95].

Spinal segmental myoclonus cases vary with regard to how widespread, or how many segments or myotomes are involved in the jerking. The Newcastle disease virus cat model of segmental myoclonus demonstrated that the movements can be induced for several segments even though the virus had not spread to those spinal interneuron segments [89]. It may be that the spinal interneuron abnormality may induce a similar abnormality above and below the initial segment through entrainment of the otherwise normal segments. For other cases, intersegmental fiber tracts (e.g. propriospinal) may carry the abnormal physiology to more widespread areas similar to propriospinal myoclonus physiology.

Spinal segmental myoclonus can be caused by a wide variety of pathological processes. Infectious/inflammatory, neoplastic, and vascular lesions are common etiologies, but multiple other etiologies have been reported (Box 15.3) [2, 67–78]. However, only a fraction of cases for any lesion type result in segmental myoclonus. Most often, these lesions cause the clinical syndrome of myelopathy without involuntary movement. This suggests that the lesion type is not nearly as important for generating spinal segmental myoclonus as the particular profile of the interneuron lesion that is the result of the pathology. Moreover, segmental myoclonus in patients may change over the clinical course, and in some cases is modified or completely disappears with treatment. This may suggest that the interneuron circuit abnormality (ies) that causes spinal segmental myoclonus may be capable of changing over time, perhaps through plasticity.

**Treatment**

All treatments of spinal segmental myoclonus are off-label. Clonazepam, in dosages up to 6 mg daily, is the favored drug for the initial choice in spinal segmental myoclonus but usually leads to only partial improvement when there is an effect [96]. Nevertheless, complete suppression of the myoclonus has been reported [94]. Levetiracetam has recently been reported to provide relief [82, 97]. Topiramate, also an antiseizure medication, has had some success [76]. Tetrabenazine is useful in cases refractory to other treatments [76]. Diazepam, carbamazepine, other antiseizure medication has been tried historically with no clear pattern of success. Botulinum toxin injections used for the pain associated with spinal segmental myoclonus may be useful [98]. More recently, botulinum toxin injections also have been reported to dramatically suppress the movements as well [79]. Since the disease process causing the myoclonus sometimes evolves and has a natural history to remit, one must be careful in determining that a presumably symptomatic treatment cures the underlying pathophysiological process.
Diaphragmatic myoclonus

This disorder is believed to represent what was reported by Leeuwenhoek in 1723, who described this movement disorder in himself [99]. He described himself as being “seized” by a violent movement disorder around the diaphragm. In present day, fluoroscopy is necessary to diagnose diaphragmatic myoclonus, so it may be difficult to know exactly what afflicted the father of microscopy. Diaphragmatic myoclonus is referred to as involuntary repetitive brief contractions of the diaphragm and other inspiratory muscles. The movements are rhythmic or semirhythmic. Numerous names for this disorder have been used such as diaphragmatic flutter, respiratory myoclonus, Leeuwenhoek’s disease, as well as other terms using convulsions, flutter-fibrillation, cramps, rumbles, pulsations, and spasms [100].

Diaphragmatic myoclonus may just involve the diaphragm or be associated with movements of other muscles which are involved with inspiration, scalenes; intercostal and abdominal muscles. The oscillatory movements are usually bilateral and synchronous between muscles. In most reported cases, the observation is made that these movements are superimposed on a normal breathing pattern [101]. In some cases, voluntary breath-holding or hyperventilation can alter or suppress diaphragmatic myoclonus [102]. However, there can be prominent symptoms of epigastric pulsations, dyspnea, hyperventilation, hiccups, and belching. Fluoroscopy, in addition to confirming the diagnosis, can also be used to study the relationship of normal breathing and symptoms to the involuntary movements [100]. This condition can occur in paroxysmal bursts lasting a few minutes or persist for several hours or days. Its presence during sleep is variable. Some case series show sensitivity to sensory stimulation around the chest and abdomen, both in terms of triggering the movements or in other cases suppressing them.

Clinical neurophysiology of diaphragmatic myoclonus

Electromyographic studies have complemented the information gained by fluoroscopy in these cases [103]. EMG discharges have been reported over a wide range of 0.5–15 Hz but a 1–5 Hz range is the most common. The discharges often have some irregularity, and vary in frequency and amplitude from discharge to discharge within a given case enough to give the movement an irregular appearance, thus adding to its categorization as “myoclonus.” The contractions observed by EMG are often bilateral and synchronous as would be expected from the movement appearance, but in certain instances more distant muscles from the diaphragm may not be synchronous or have a different frequency. Certain authors have argued that the higher frequency cases (>9 Hz) have clinical differences, but with a small number of cases this is not certain. The EMG discharge duration is almost never below 100 ms and a range of 100–300 ms is typical. Longer durations up to several hundred milliseconds are possible. Evidence of cortical hyperexcitability or dysfunction causing diaphragmatic myoclonus is non-existent.

Pathophysiology of diaphragmatic myoclonus

Most cases of diaphragmatic myoclonus are idiopathic. The known causes consist of encephalomyelitis, trauma, tardive forms, and “irritation” of the phrenic nerve or diaphragm [104]. Neither the idiopathic nor the uncommon causes give much insight with regard to pathophysiology of diaphragmatic myoclonus. Various authors have offered arguments on an empiric basis with citing evidence for where the generator should not be. The medullary respiratory center has been suggested for the origin of diaphragmatic myoclonus, since that such an origin could explain involvement of multiple respiratory muscles that are innervated by multiple segments of the spinal cord [105]. An alternative view suggests that it arises from more rostral centers, while others believe that spinal interneuron abnormalities create the movement and recruitment of other muscles occurs via intersegmental pathways [101, 104]. A combination of these sources is also plausible. However, until more direct information about the pathophysiology of diaphragmatic myoclonus is available, both the source and mechanism are unknown.
Treatment of diaphragmatic myoclonus is difficult, off-label, and the rare occurrence of this condition only provides anecdotal reports on treatment efficacy. Therefore, neither effectiveness nor a side effect profile for a given patient can be reliably predicted, and caution is required. Clonazepam is the most frequently cited symptomatic treatment with favorable results, although it is often not a complete response. Diazepam and phenytoin, sometimes given intravenously or orally, have had limited success [100, 106]. Carbamazepine, gabapentin, and haloperidol have also had some efficacy [104, 107, 108]. Quinidine and Benzhexol have each been reported to be effective in one case [109]. Narcotics and muscle relaxants have been tried but are not effective. Lesion or block of the phrenic nerve has been reported in a case where only the left side was affected [110]. The possible side effects of these treatments need to be carefully considered and monitored. Remissions do occur but are not predictable.

Abdominal/truncal myoclonus

Abdominal myoclonus is believed to be a form of segmental myoclonus arising from the spinal cord, but it will be discussed separately due to some distinct characteristics. Other names for this entity are abdominal flutter and belly dance myoclonus [84]. It is distinguished from diaphragmatic myoclonus by variable involvement of the diaphragm. When the diaphragm is affected in abdominal myoclonus, other muscles besides those involved with inspiration are involved. It may be difficult to determine solely on clinical grounds whether there is active diaphragmatic movement, since movement of the abdominal contents alone may secondarily move the diaphragm. Fluoroscopy is an effective way to evaluate whether the diaphragm is involved. Assessment by diaphragmatic needle EMG may be risky even by experienced electromyographers in the presence of quick involuntary unpredictable diaphragm movements. Abdominal myoclonus should also be distinguished from other quick movements of the abdominal wall such as seizure, tardive dyskinesia, axial dystonia, and “belly dancer’s dyskinesia” [84].

Symptoms of abdominal myoclonus can be similar to diaphragmatic myoclonus. Although usually bilateral, significant asymmetry may occur. In contrast to diaphragmatic myoclonus, abdominal myoclonus often involves more widespread areas, such as paraspinal and proximal extremity muscles, even without involvement of the diaphragm by fluoroscopy [111, 112]. When the diaphragm is not involved, voluntary breath-holding or hyperventilation produces less dramatic changes on the physical appearance of the movements. The myoclonus may begin abruptly, be paroxysmal, sensitive to somatosensory stimulation of the trunk, and be present or absent during sleep [113]. Emotional excitation has also been reported to evoke an episode of the movements. Patients may notice some effect of body posture on the intensity, frequency, and even the presence of the movements.

Surface EMG studies may show similar discharges as what has been reported for diaphragmatic myoclonus. An example of surface EMG discharges in a case of abdominal myoclonus is shown in Figure 15.3. Discharge duration is most commonly between 50 and 400 ms and can be somewhat shorter when compared to diaphragmatic myoclonus [84, 113, 114]. The activation of abdominal muscle is synchronous, although more distant muscles to the abdominal muscles may not be synchronous. The involvement of paraspinal and proximal extremity muscles is often best documented by electrode placement over these muscle groups. Stimulus sensitivity of these abnormal electromyographic discharges has been documented [84]. Evidence of cortical hyperexcitability or dysfunction is non-existent.

Abdominal myoclonus is usually idiopathic. Cases with known causes are B12 deficiency, association with pregnancy, Graves’s disease and syringomyelia [111, 114]. Clonazepam is cited as being effective in suppressing the abdominal wall movements [113, 114]. Other antiseizure agents have also been tried but assessing their effectiveness is difficult. Spontaneous remission may occur.
Conclusion

The clinical spectrum of segmental myoclonus has grown in recent years. Propriospinal myoclonus is usually considered to be a non-segmental type of spinal myoclonus [96]. However, propriospinal myoclonus arises from similar lesion types as does spinal segmental myoclonus. It occurs in a paroxysmal fashion and is sensitive to sensory stimuli, while segmental myoclonus is usually considered to be continuous and relative insensitive to stimuli or mental state. The movement in propriospinal myoclonus may be a single jerk or a short train of jerks with EMG discharge duration between 100 ms and a few seconds. Showing some clinical similarity to propriospinal myoclonus, recent reports of spinal segmental myoclonus have cases with intermittent jerks and sensitivity to both sensory stimuli, mental state, and movement [79, 81]. In some instances, patients first develop movements on a sporadic or paroxysmal manner, but then subsequently evolve to more continuous segmental myoclonus [94]. Abdominal and diaphragmatic myoclonus, as discussed above, typically have paroxysmal and stimulus sensitivity present. Palatal myoclonus is particularly noted for being persistent. However, voluntary suppression and intermittency of typical palatal myoclonus movements has been observed [115, 116]. These combined observations suggest the possibility that both clinically and physiologically, segmental myoclonus exhibits a spectrum. On one end of the spectrum, segmental myoclonus is intermittent and stimulus sensitive, and on the other end is completely persistent and insensitive to modulation by any outside influence or stimuli. More physiological information about segmental interneuron circuits will help us to understand the clinical variability that is seen among segmental myoclonus patients. The ultimate goal will be to use this information to design improved and more specific treatments for segmental myoclonus.

References


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CHAPTER 16
Other Jerks and Startles

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Introduction

Hyperkinetic disorders that do not conveniently fit into the standard classification of movement disorder are grouped in this chapter. They all involve excessive movement, a predisposition to startle, or a combination of the above. Some of the entities described are myoclonic in nature, others are various startle syndromes, and others are related to peripheral nerve pathology. We also include here otherwise unclassified jerks or startles.

Myoclonias

Myoclonus can be defined as a sudden, brief movement. It can be positive, caused by muscle contraction, or negative, due to brief loss of muscle tonus [1]. Etiologic classifications can be complex and daunting, but considering broad categories, the myoclonias can be divided into physiologic (jerks occurring in certain circumstances in normal subjects) and symptomatic (as manifestations of underlying disease) [2]. Inherited and segmental myoclonus have been considered in earlier chapters (Chapters 14 and 15, respectively), and we will consider other entities. Epileptic myoclonus can be classified separately as a standalone entity. Symptomatic myoclonus may be the most common category of myoclonus [3].

Sleep myoclonias and other physiologic myoclonias

The hypnic jerk is part of the normal sleep–wake transition motor phenomena. It consists of a single short (<1 s), non-periodic, non-rhythmic whole body myoclonic jerk produced by contractions of large and/or axial muscles, rarely accompanied by an utterance [4, 5]. These “startles” are often accompanied by a subjective sensation of falling.

Another normal sleep phenomenon is fragmentary myoclonus (or physiologic hypnic myoclonus), which consists of small multifocal jerks. It was first described by De Lisi in 1932 [6], and occurs not only in humans, but also in other species, notably dogs and cats [7]. These phenomena are very common, occurring in at least 70% of the general population. Hypnic myoclonus has been investigated electrophysiologically in a few small studies. In a study of young male volunteers, Montagna et al., using electromyography (EMG), found that the jerks are associated with single motor units or short bursts, lasting less than 100 ms, occurring asynchronously in the different muscles investigated. Single motor units can mimic fasciculation potentials [8]. The jerks occur not only at the transition from wakefulness to sleep, but in all stages of sleep as well as in relaxed wakefulness. They do, however, occur most frequently in stage I and in REM sleep [8, 9]. Dagnino and collaborators conclude that the
incidence of hypnic myoclonus appears inversely related to the degree of EEG synchronization, given the findings of reduced incidence with deeper stages of sleep. The muscles most reliably displaying EMG activity are the distal limb and facial muscles. No EEG correlate was found for the hypnic jerks, both during direct analysis and with back-averaging techniques [8, 9, 10]. The findings of a normal peripheral nervous system and lack of EEG correlates point to a likely brainstem generator for hypnic myoclonus.

While fragmentary myoclonus is a physiologic occurrence and does not require therapy, instances of excessive fragmentary myoclonus have been described and are considered to be pathologic [10, 11]. These may cause sleep onset insomnia, and can be representative of underlying pathology. Treatment consists of correction of the underlying cause, when present, and, if needed, symptomatic therapy, with clonazepam the agent most likely to provide relief.

Singultus, or hiccups (or hiccoughs) consists of a sudden inspiration immediately followed by active glottis closure generating a characteristic sound. It is essentially universal, but its physiologic purpose is unknown. Physiologically it can be regarded as a slow, semirhythmic diaphragmatic myoclonus, occurring at various intervals for each patient, between 4 and 60 per minute. A possible reflex arc has been proposed, with the afferent arm including the phrenic and vagus nerves, closing centrally in the brainstem, involving the respiratory and glottis closure centers, and an efferent arm consisting mainly of the phrenic nerve. Askenasy proposed as a mechanism for hiccups a failure of reciprocal inhibition between inspiration and glottis closure, with the two phenomena occurring at the same time [12]. Phylogenetically, singultus may represent a persistent archaic motor pattern, shared with lower vertebrates. Its persistence in mammals, including humans, may be related to the generation of functions such as suckling and eupneic breathing [13].

Pathologic or excessive hiccups may be indicative of phrenic or vagus nerve irritation (caused, for example, by gastric, diaphragmatic, cardiac, or mediastinal pathology), brainstem disturbance (commonly multiple sclerosis, vascular, or neoplastic lesion), epilepsy, or a large number of iatrogenic causes. A number of folk remedies are anecdotally reported to interrupt bouts of hiccups, but no formal studies have been undertaken for these. Our favorite remedy for common hiccups is a slow continuous sipping of water, but for intractable hiccups, more intervention is needed. The only FDA-approved pharmacologic intervention for hiccups is chlorpromazine, a phenothiazine antipsychotic, but other agents have been shown to give potential benefit [14].

Other physiologic myoclonias include anxiety-induced myoclonus, exercise-induced myoclonus, and benign infantile myoclonus with feeding [15].

**Symptomatic (secondary) myoclonias**

Symptomatic myoclonus is the most common of the broad etiologic categories of myoclonus, and it manifests in the setting of an identifiable underlying disorder. It is typically progressive and associated with encephalopathy or ataxia. We are excluding from this category the myoclonias associated with an epileptic syndrome, in which seizures dominate, as these deserve a separate nosologic entity.

A wide variety of causes can be responsible for symptomatic myoclonus [16, 17, 18]. Table 16.1 presents the major categories of secondary (symptomatic) myoclonus. Some of the entities listed are covered in other chapters.

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**Video 16.1 Focal myoclonus**

This is a 27-year-old patient who suffered of severe perinatal distress with early occurrence of seizures that are now well controlled. The video shows a focal myoclonus of the left hand, with position-specific jerks of variable amplitude. [Video courtesy of the Neurophysiology Unit, Carlo Besta Institute, Milan, Italy]

Table 16.1 Causes of secondary myoclonus.

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<tr>
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<td>• Gangliosidosis (GM1 and GM2)</td>
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<td>• Neurodegeneration with brain iron accumulation type I</td>
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<td>Dementias</td>
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<td>• Frontotemporal dementia</td>
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<td>• Multiple carboxylase deficiency</td>
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<td>• Heat stroke</td>
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<td>Exaggerated startle syndromes</td>
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<td>• Sporadic</td>
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<td>Multiple system degenerations</td>
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<td>• DiGeorge syndrome</td>
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<td>Others</td>
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<td>• Rasmussen encephalitis</td>
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Adapted from [16], [2], and [15].
Pathophysiologically, secondary myoclonus is most often cortical in origin. Electrophysiologically, cortical myoclonus is associated with EMG discharges of short duration (typically <50 ms), EEG spikes closely preceding the myoclonus localized to the contralateral motor region for the muscle group involved, and enhanced early components of somatosensory-evoked potentials, often accompanied by enhanced C-reflexes [1, 19]. See Figure 16.1.

Progressive myoclonic ataxia includes a heterogeneous group of progressive disorders dominated by myoclonus and ataxia, and has some overlap with progressive myoclonic epilepsy. Most myoclonic-ataxic syndromes are caused by inborn errors of metabolism. Most commonly identified is Unverricht–Lundborg myoclonus, or EPM1, due to a mutation in the gene for cystatin B. Dementing and parkinsonian syndromes often include myoclonus in their late stages, but early prominent myoclonus with parkinsonism usually suggests corticobasal degeneration [20]. Periodic myoclonus associated with rapidly progressive encephalopathy is suggestive of Creutzfeldt–Jacob disease. Post-anoxic myoclonus can have a variety of forms, including action and negative myoclonus, and the same is also true for other myoclonias induced by physical agents was given to the left median nerve while the finger flexor muscles are tonically active. There may be a small positive myoclonic response in the muscle, but the main response is negative myoclonus. Again the EEG shows a giant somatosensory-evoked potential. (Courtesy of Dr Camilo Toro, MD.)

Figure 16.1 Enhanced somatosensory evoked potential in cortical myoclonus. (A) Taps were delivered to the left finger flexors and EMG and EEG are recorded. The left finger flexor muscles show a myoclonic response (C reflex) and the EEG at the contralateral sensorimotor area (C4) shows a giant somatosensory evoked potential. (B). In a similar recording situation, an electric shock

(Video 16.2). Opsoclonus–myoclonus is a myoclonic syndrome associated with characteristic eye movements [21], and can be paraneoplastic or associated with other causes. The paraneoplastic variety is most often associated with neuroblastoma in children and with ovarian, lung, or breast cancer in adults [22]. Rasmussen encephalitis is typically associated with epilepsy partialis continua, but focal myoclonus has also been described among the various movement disorders caused by the condition [23].

Treatment of symptomatic myoclonus rests primarily on correction of the underlying cause,
where possible [24]. Special mention in this regard is the opsoclonus–myoclonus syndrome. Of course, an underlying tumor should be treated if identified. Failing that, attention can be directed to the autoimmune nature of the illness.

Beyond correction of the underlying causes, symptomatic treatment employs agents used for treatment of myoclonus of any origin. Benzodiazepines are the most widely used medication class for myoclonus of most subtypes, with clonazepam the most frequently used. The antiepileptic valproate is also widely used, particularly for the treatment of cortical myoclonus [17]. Levetiracetam is a newer generation antiepileptic with notable antimyoclonic activity. It modulates GABA-mediated neurotransmission and is effective primarily in cortical myoclonus [25–28]. γ-hydroxybutirate (GHB) modulates both GHB receptors and GABA neurotransmission and has been shown to effectively treat certain types of myoclonus [29, 30]. Its use is strictly regulated due to the potential for abuse, and, at present, should be considered only experimental. Other agents more rarely used for selected types of myoclonus include 5-hydroxytryptophan, tetrabenazine, zonisamide, and botulinum toxin [17, 18, 23, 24, 31, 32]. Myoclonus can be very difficult to treat, and it is often necessary to use more than one oral agent. Negative myoclonus can continue even with successful treatment of positive myoclonus, and there are virtually no agents that influence negative myoclonus consistently.

**Startle syndromes**

Exaggerated startle syndromes, or hyperekplexia, consist of an exaggerated motor response (sometimes called a jump) to unexpected stimuli, most often auditory [33–35]. The startle reflex is a phylogenetically conserved physiological response [36], and the exaggerated startle syndromes refer to conditions with abnormally enhanced response, although quantification is often difficult [37]. Clinically, a typical startle response consists of facial grimacing, flexion of the neck and trunk, and raising of the arms or generalized limb flexion [36, 2].

Anatomically, the origin of the startle response is in the medullopontine reticular formation, the nucleus reticularis pontis oralis, as shown in both animal and human studies [38, 39]. Functional imaging studies show changes in regional blood flow at this location with startle in normal subjects [40, 41]. In addition to exaggerated magnitude of response to stimulation, the abnormal startle also displays abnormal habituation characteristics and this is the usual way of documenting the abnormality [42, 43].

Broadly, hyperekplexia can be subdivided into hereditary hyperekplexia, secondary hyperekplexia, and the culturally linked startle syndromes, including Latah.

**Hereditary hyperekplexia**

Hereditary hyperekplexia was first described in a Dutch pedigree that demonstrated exaggerated startle responses transmitted in an autosomal dominant fashion [33]. Two different forms are recognized since the first descriptions, a major and a minor form.

The major form is diagnosed by the presence of the following cardinal features [44, 45]:
- Generalized stiffness following birth, worsened by handling and disappearing in sleep, improving in the first years of life [46]
- Excessive startle with unexpected, particularly auditory, stimuli, without alteration of consciousness, present from birth
- Brief (seconds) generalized stiffness following a startle response, sometimes causing falls with preserved consciousness [47].

Minor hyperekplexia is characterized by excessive startle without stiffness, and it can include excessive hypnic jerks and PLMS [48, 34]. These additional features can also be part of the major form. Another characteristic feature for both forms is the “head retraction response,” consisting of brisk, involuntary backward jerking of the head with light face tapping [33, 49].

The first abnormal gene identified in relation with hereditary hyperekplexia is a point mutation in the α-1 subunit of the glycine receptor gene (GLRA1) [50, 51], and this remains the major genetic cause to date. Several missense and nonsense mutations have been identified as causing the
disease, and exon deletions have also been found to cause the phenotype [52]. Other genes known to be associated with hereditary hyperekplexia include: SLC6A5, encoding the presynaptic glycine transporter 2; GLRB, encoding glycine receptor subunit β; GPHN, encoding the glycinergetic clustering molecule gephrny; ARHGEF9, X-linked gene encoding collybistin ([34, 45, 53–56].

Glycine is an inhibitory neurotransmitter in a number of spinal interneurons as well as medullopontine reticular neurons. A lack of inhibitory glycinergetic neurotransmission can explain the exaggerated motor startle response in major hyperekplexia, given the common anatomophysiological substrate of the normal and pathologic startle [37, 57]. In addition, abnormal reciprocal inhibition in the spinal cord can explain the infantile hypertonia and the stiffness of major form hereditary hyperekplexia [58]. It should be noted that the pathophysiology of the minor form of hyperekplexia is significantly different from the major form, and many of the details remain unknown [59, 48, 60, 34, 2]. There is some controversy in regard to the minor form, which might actually be a phenocopy of the major form on a psychogenic basis.

**Secondary hyperekplexia**

Secondary, or symptomatic hyperekplexia, is due to an identifiable underlying neurologic condition. Most cases described have involved various types of insult affecting the brainstem, which is in keeping with the pathophysiology of the syndrome and the role of the medullopontine reticular structures. These have included:

- Stroke [61]
- Encephalopathy [62, 63]
- Malformations [64, 65]
- Extrinsic mechanical compression [66, 41].

In addition to brainstem pathology, other diffuse cerebral insults or generalized disease states have also been associated with symptomatic hyperekplexia. It is worth noting that in many of these cases the brainstem is also involved, blurring the distinction. Reported cases include:

- Cerebral palsy [39, 67]
- Stroke [68]
- Multiple sclerosis [69]
- In-born errors of metabolism [70]
- Other genetic syndromes [71]
- Stiff-person syndrome.

Increased startle is associated with anxiety and other psychiatric pathology, particularly post-traumatic stress disorder (PTSD) [72]. Increased startle is even sometimes used as a diagnostic aid for PTSD. Psychogenic hyper-startles have also been described [73, 74]. This category can overlap with the culturally-linked startles described next, and the classification has been the subject of extensive controversy in the literature. The differentiation of psychogenic from organic etiologies can be difficult with hyperekplexia, but organic startle has a specific EMG signature that can be helpful [43, 60].

**Latah syndrome and other culturally-determined startle syndromes**

A number of culturally-determined startle syndromes have been described [75]. All involve non-habituating hyper-startle responses to auditory or tactile stimuli, and are associated with complex but stereotyped motor or behavioral abnormalities following the startle reaction, lasting several seconds.

Latah is the syndrome described in Indonesia and Malaysia, known in the local culture since the 15th century and in Western medicine since the late 19th century [76]. Those affected exhibit exaggerated startle responses accompanied by involuntary utterances, echolalia, echopraxia, and forced obedience, provoked by sudden touch or loud noises. The complex behavior following the startle can involve involuntary striking out, coprolalia, and an emotional response. Onset is typically in adulthood and the episodes are often preceded by vivid dreams.

The other culturally-bound startle syndromes appear to represent the same entity in different cultural contexts. The Jumping Frenchmen of Maine were described in 1878 by George Beard [77] among French Canadian lumberjacks. Those affected exhibit a startle reaction consisting of jumping, vocalizations, throwing objects, forced obedience, echolalia, and echopraxia, provoked by loud noises or sudden commands or gestures [78].
The other similar syndromes include Myriachit in Siberia, Imu in Japan, Goosey in Southern USA [79], and Ragin’ Cajuns in Louisiana [76].

Given the striking similarity between all these syndromes, it is likely that they share a neurophysiologic substrate. No physiology studies are available in any of these syndromes, so their classification with the other startle syndromes is based on their clinical manifestation. One accepted view is that they represent an exaggerated startle syndrome modulated by a cultural context determining socially acceptable behavior [80, 75], although overlap with tic disorders, stereotypies and psychogenic conditions can be argued [34].

**Treatment**

Treatment of hyperekplexia depends on the etiology. When secondary causes are present, these should be addressed. The psychogenic and culturally-determined syndromes should theoretically benefit from psychotherapy and counseling. In the autosomal-dominant hereditary forms genetic counseling is important. In terms of pharmacotherapy, the benzodiazepines have the highest chance of success, and clonazepam has been shown in a double blind placebo-controlled study to be effective in treating hyperekplexia [81]. Clonazepam facilitates GABAergic neurotransmission and appears to compensate for the loss of glycine.

**Syndromes with peripheral injury**

While most hyperkinetic movement disorders have central nervous system causes, occasionally lesions of the peripheral nervous system can cause abnormal movements. A variety of insults can be responsible for inducing abnormal movements, and here we will cover the major syndromes. Criteria have been proposed for diagnosing a movement disorder as peripherally induced from a specific injury, but these are arbitrary [82–85]:

- Trauma severe enough to cause local symptoms for at least 2 weeks or requiring medical evaluation within 2 weeks after trauma
- Initial manifestations of the movement disorder related to the site of injury
- Onset of the movement disorder within days or months (up to 1 year) after the injury.

These criteria are meant to be used as guidelines only, and are not a strict requirement for classification of a movement disorder as peripherally induced.

**Hemifacial spasm**

Hemifacial spasm (HFS) is the best known example of a peripherally-induced abnormal movement. It consists of unilateral, involuntary, intermittent, irregular, tonic or clonic synchronous contractions of muscles innervated by cranial nerve VII [86]. The extent of involvement is variable, but typically the periorcular region is most severely (and earliest) involved. Chronic isolated eyelid myokymia is an important differential diagnosis, as it is a benign condition requiring no treatment [87].

Cases of bilateral HFS have been described, indicating that the contractions on the two sides are not synchronous. HFS is a sporadic disorder, although rare familial cases have been described, and it is generally confined to the adult population. While HFS is common, good epidemiologic data is scarce. In one study in Olmstead County, MN, the prevalence was 14.5/100,000 in women and 7.4/100,000 in men [88] and a Norwegian study found the overall prevalence in Oslo to be 9.8/100,000 [89]. It is more common in women and much more common in Asians [90].

In the vast majority of cases, HFS is associated with a vascular compression of the facial nerve [91]. Even when a direct insult to the nerve is not found on imaging, it is likely that all cases involve a degree of impingement on the facial nerve root, and surgical exploration can find compressions that had not been apparent on imaging. Most often the insult consists of vascular compression by an ectatic, ectopic, aneurismal, or atherosclerotic anterior or posterior cerebellar artery or vertebral artery at the root exit zone [91–93]. In addition, the nerve compression can be due to various cerebellopontine angle tumors [94], arachnoid cyst [95], or parotid tumors [96]. In some cases, an apparent trigger event is identified as a precipitant, such as acute facial palsy, but most cases start without an identifiable precipitant.
Pathophysiological, the theory of ectopic excitation and ephaptic transmission asserts that the area of demyelination at the site of compression is the origin of abnormal discharges and the pathologic manifestations [97–99]. Ectopic discharges occur at sites of demyelination, and lateral transmission occurs between adjacent demyelinated nerves (ephaptic transmission), which explains the synchronous involvement of the entire face. This improves after surgical decompression of the nerve [100]. An alternative hypothesis is based on findings of a hyperexcitable blink reflex in HFS, and proposes that the discharges arise from a hyperexcitable facial nucleus, induced in turn by the peripheral lesion [101, 103].

Oral treatment of HFS can be attempted but it is usually of limited value. Agents attempted in the past included carbamazepine, baclofen, clonazepam, anticholinergics, and first generation antipsychotics [104, 93]. Recently, two newer generation antiepileptics have been added to the list of potentially useful agents: gabapentin [105, 106] and levetiracetam [107].

For most patients, the treatment of choice is a focal injection of botulinum neurotoxin (BoNT). It has been shown to have efficacy around 95% in open trials, and the benefit is maintained for years [108–111]. Treatments are repeated at approximately 3 month intervals (the duration of action of the botulinum toxin) and are well tolerated. The actual targeted sites of injection depend on the distribution of the spasm, but in most patients it appears that targeting the periocular region (orbicularis oculi) is most effective, and sometimes diffuse hemifacial spasm is symptomatically controlled only with orbicularis oculi injections. The pattern of injection in orbicularis oculi is the one commonly accepted for treatment of all spasms, including blepharospasm [112]. Injections are made away from the midline on the upper eyelid to avoid the levator, and away from the medial aspect of the lower lid to avoid loss of control of tears. (See Figure 16.2, white arrows.)

In our practice, the next most common injections beyond the eye area are in the zygomaticus or risorius when lateral and upward movement of the corner of the mouth is prominent (black arrows in Figure 16.2). Caution is needed with zygomaticus since excessive weakness will lead to an asymmetrical smile, a bad cosmetic result.

Surgical treatment, consisting of vascular decompression, is used either as an additional option for patients who do not have satisfactory results with BoNT, or as an initial approach, depending on the circumstances, patient preferences, availability of an experienced surgical center, and identification of a clear anatomic abnormality on imaging. Large long-term studies show a "cure" rate, generally defined by absence of residual spasms, between 90 and 95% [114, 115]. The most common complications are temporary or permanent hearing loss or facial palsy, each of these permanent in approximately 1% of cases [114, 116]. Intraoperative multimodal electrophysiology monitoring has been shown to increase the rate of success and help the early detection of complications [117, 118].

**Focal myoclonus due to peripheral nerve injuries**

Several examples of focal myoclonus caused by root, plexus, or peripheral nerve injuries have been...
described. The Table 16.2 lists peripheral etiologies reported in association with focal myoclonus.

Clinically, all myoclonias of peripheral origin are confined to the muscles innervated by the affected nerves, and they are spontaneous and rhythmic, often persisting in sleep [128].

Pathophysiologically, myoclonus induced by peripheral lesions may well originate from the corresponding spinal segment by enhanced neuronal excitability, thus sharing a mechanism with spinal segmental myoclonus [129, 2], although an origin within the nerve itself is possible (analogous to HFS). EMG investigation of a case of focal myoclonus caused by brachial plexus injury showed the origin of the contractions in a segment of the posterior cord of the brachial plexus [123].

Treatment of peripheral focal myoclonus relies on correction of the underlying cause when possible and benzodiazepines for symptomatic therapy, with limited success. Clonazepam is the agent most frequently used.

### Table 16.2 Focal myoclonus due to peripheral injuries.

<table>
<thead>
<tr>
<th>Putative causative insult</th>
<th>Myoclonus distribution</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thoracic root tumor</td>
<td>Paraspinal muscles</td>
<td>[119]</td>
</tr>
<tr>
<td>Lumbosacral radiculopathy</td>
<td>Legs and hips</td>
<td>[120]</td>
</tr>
<tr>
<td>Lumbar laminectomy</td>
<td>Proximal unilateral leg</td>
<td>[120]</td>
</tr>
<tr>
<td>Brachial plexus electrical injury</td>
<td>Proximal arm</td>
<td>[120]</td>
</tr>
<tr>
<td>Femoral nerve sarcoma</td>
<td>Quadriceps</td>
<td>[121]</td>
</tr>
<tr>
<td>Distal CN XI lesion</td>
<td>Bilateral trapezius</td>
<td>[122]</td>
</tr>
<tr>
<td>Axillary radiotherapy; abduction trauma of the shoulder</td>
<td>Upper limb</td>
<td>[123]</td>
</tr>
<tr>
<td>Deep peroneal nerve trauma</td>
<td>First dorsal interosseus muscle of the foot</td>
<td>[124]</td>
</tr>
<tr>
<td>Palmar digital branch of the median entrapment</td>
<td>Hand</td>
<td>[125]</td>
</tr>
<tr>
<td>Long thoracic nerve trauma</td>
<td>Scapula, serratus anterior muscle</td>
<td>[126]</td>
</tr>
<tr>
<td>Elbow/ulnar nerve trauma</td>
<td>4th dorsal interosseus muscle</td>
<td>[127]</td>
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</tbody>
</table>

A number of involuntary movements have been associated with CRPS. These include myoclonic jerks, dystonia, tremor, and spasms [135–137, 128]. Dystonia is the most common of these movements, accounting for over 90% of the abnormal movements in some series, and the onset interval is very variable, as is the course [138, 139]. It can lead to deforming spasms, and cases have been described of “mirror” involvement of the contralateral side of the body.

The mechanism for the movement disorders is the subject of extensive controversy. Primary sympathetic involvement certainly appears doubtful. There are some data pointing to central generators for the involuntary movements in CRPS. Disturbances of body representation have been identified in CRPS patients, suggesting the possibility of a mechanism akin to other dystonias for the abnormal movements [140]. Functional imaging in CRPS shows evidence of reorganization in central
somatosensory and motor networks [141]. Other studies however did not show any abnormalities of sensorimotor integration in CRPS-associated dystonia, while these are characteristic in other forms of dystonia [142]. Furthermore, many of these patients exhibit extensive psychiatric pathology and many of the movement disorders may in fact be psychogenic [143, 144], leading to a strong current of opinion questioning the organic nature of CRPS-associated movements [145, 146]. The issue is far from settled and the subject of ongoing debate in the neurologic community [147, 148]. We advise that at the very least the abnormal movements associated with CRPS be interpreted with caution.

The treatment of CRPS-associated movement disorders remains largely unsatisfactory. Multimodal therapies have probably the highest chance of working, and if a psychogenic component is found to play a large role, cognitive behavioral therapy and other forms of psychotherapy should be attempted. Various medications, including benzodiazepines, antiepileptics, antidepressants, and oral baclofen showed no sustained benefit [137]. Intrathecal baclofen showed benefit in 6 out of 7 patients in a double-blind, placebo-controlled crossover trial [149], but reproducibility of this finding has not yet been demonstrated.

**Dystonia associated with peripheral nerve injury**

Multiple reports exist of associations of peripheral nerve pathology with dystonia. Caution is warranted when interpreting causality, as dystonia can often be the cause rather than the consequence of peripheral nerve pathology. Reports include peripheral nerve lesions causing arm dystonia [82], lumbar canal stenosis causing lower extremity dystonia [150], and ulnar nerve entrapment causing hand dystonia [151, 152].

A more common and better characterized association is that of trauma with onset of dystonia. In a large series of patients with dystonia, 9% of the patients had had some form of preceding injury [153]. In other series, a preceding neck trauma was found in 10–20% of patients with cervical dystonia (CD) [154, 85]. Preceding insults have also been described in oromandibular dystonia [155, 156], blepharospasm [157, 158], focal limb dystonia following electrical injury [159], and writer’s cramp [160].

Of course, an association does not imply causality, and it is fair to point out that the vast majority of patients who suffer trauma do not develop dystonia, and most dystonias are not preceded by trauma. In many patients with genetically-proven familial dystonia, trauma is identified as a putative precipitant at the onset. In a study of 104 patients with various forms of dystonia, 85% of the cases had a variable penetrance autosomal dominant genetic cause for the dystonia, yet over 16% of these cases identified a traumatic event preceding or precipitating the dystonia [154, 161]. Similar observations have been made by Jankovic and Van der Linden in a smaller series, where approximately 25% of the patients identified preceding trauma [162]. It is conceivable that trauma may trigger focal dystonia in patients who go on to develop generalized dystonia on a genetic basis. It is also possible that the association is an artifact of recall bias, with the patients identifying otherwise unrelated trauma as related to the onset of the dystonia.

Tarsy separated post-traumatic cervical dystonia into two variants [163]. The first is an acute onset variant, occurring immediately after the trauma, which is different from idiopathic CD in that it is associated with significant pain, does not respond to sensory tricks, and does not increase with activation. The second is a delayed onset post-traumatic CD, occurring 3–12 months after the trauma, and is phenomenologically identical to idiopathic CD. Shoulder elevation in posttraumatic CD may represent a particular subset, associated with shoulder trauma or accessory nerve injury [164, 165].

The mechanism by which peripheral trauma can induce dystonia is not entirely elucidated and remains the subject of ongoing study and controversy. Peripheral lesions have been found to affect signal patterns in higher order neurons in the spinal cord, brainstem, basal ganglia, and cortex, and can induce chemical changes in thalamic nuclei [166, 167]. This can lead to the abnormalities of sensorimotor integration known to have a causal association with idiopathic dystonia [83, 128]. On
the other hand, using paired pulse transcranial magnetic stimulation, we have also found evidence for the thesis that trauma simply acts as a precipitant on a terrain of predisposing abnormal cortical hyperexcitability, demonstrating abnormal intracortical facilitation not only in patients who had developed focal dystonia after trauma, but also in their family members who were not affected at the time of the study [168].

Treatment of dystonia associated with peripheral nerve injury relies on multidisciplinary approaches, including physical and occupational therapy and rehabilitation efforts. BoNT therapy can be symptomatically effective as in other forms of dystonia, while oral medication has limited use. Deep brain stimulation (DBS) is resorted to in cases unresponsive to other therapies, and while data exist showing efficacy in traumatic dystonia [169, 170], it needs to be remembered that, in general, secondary dystonia and post-traumatic dystonia are less responsive to pallidal DBS than primary dystonia [171, 172].

“Jumpy stumps”
Weir Mitchell is credited with the first description of “jumpy stumps,” in addition to the description of causalgia, in the same 1872 work, referring to the spasms and jerks observed in the residual stumps following amputation [131]. A number of cases have been described in the literature [173–176, 127]. The movements consist of jerking or spasms of the amputation stump, sometimes associated with tremor, and the term used to describe the characteristic movements is “jactitation”. Transient jerking of amputation stumps in the post-operative period is common, but the cases of pathologic “jumpy stumps” involve prolonged abnormal movement, lasting at times for decades [175]. The motor phenomena are typically associated with severe pain, consistent with the phantom limb sensory experience.

The epidemiology is hard to estimate, given the rarity of the phenomenon, but incidence has been estimated at approximately 1% of amputations [177]. Pathophysiologically, most authors consider it a form of spinal segmental myoclonus, and electrophysiology studies appear to validate this proposal [174, 178, 127]. Functional and structural changes may occur at spinal or supraspinal levels as a result of altered sensory inputs following deafferentation. Notably, the phenomenon of phantom dyskinesia has also been described as a form of tardive dyskinesia in an amputated limb following exposure to metoclopramide [179] and as a psychogenic movement disorder [180].

No large treatment trials exist, but anecdotal reports of effective treatments can be found. Baclofen at 20–40 mg daily has successfully treated the movements in two patients [181], and gabapentin was effective in one case [182]. It is not known if BoNT could provide any relief. One intriguing study reports highly effective treatment with thalamic high-frequency stimulation targeting the nucleus ventralis posterolateralis [183]. This involved older approaches to deep brain stimulation, prior to the emergence of the modern hardware, but the paradigm may be worth revisiting, particularly given the recent renewed interest in thalamic DBS for limb dystonia.

“Belly dancer’s” dyskinesia
The term “belly dancer’s dyskinesia” describes a syndrome of involuntary writhing movements and contractions of the abdominal wall muscles [184]. The movements have a sinuous, writhing, and flowing character, and typically entrain oscillatory movements of the umbilicus. Electrophysiology data in the original report by Iliceto et al. showed alternating contractions in the recti and obliques.

Video 16.3 Belly dancer’s dyskinesia
Seven-year-old girl with history of quasi-continuous writhing, flowing movements of her abdominal muscles. A thoracic spinal glioma was identified on imaging. Surgical intervention was not successful. The case has been previously reported [185].

explaining the circular umbilical movements. Diaphragmatic flutter can be associated.

The etiology of the condition is not clearly known. Many, but not all, patients have a history of pre-existing local trauma [186]. A case has been reported in association with basal ganglia lesions from central pontine and extrapontine myelinolysis following hyponatremia [187]. A spinal generator with a mechanism similar to segmental myoclonus has been proposed and the scant electrophysiologic data available is consistent with this [188].

No systematic therapeutic studies exist. One group reported significant benefit with transcutaneous electrical stimulation (TENS) [186], but it should be noted that this case may have represented a tardive syndrome, and spontaneous resolution could have coincided with the therapeutic intervention [189]. BoNT has been successful in alleviating the movements in one case [190] and one group reported long-term success in one patient with pallidal DBS [191].

**Painful legs and moving toes**

The syndrome of painful legs and moving toes was described by Spillane and colleagues in 1971 [192]. Subsequently a number of case reports have emerged, as well as several larger case series [193, 194]. It is a condition of adulthood or late life, and consists of pain (usually the presenting symptom) with a deep aching or burning quality, associated with involuntary, athetoid, “wriggling” movements of the toes, in a combination of flexion, extension, abduction, and adduction patterns, typically at a rate of 1–2 Hz [193, 192]. Pain is commonly the predominant symptom and the one prompting medical contact in most patients. The condition is rare and appears to be heterogeneous, having been described in association with a number of presumed causative insults, and on occasion without an identified cause. Etiologies described to date include:

- generalized peripheral neuropathy of various etiologies – the most common cause [193–195], with a particular subgroup of well-described association with HIV neuropathy [196, 197]
- lumbosacral root pathology, cauda equina mechanical, or inflammatory pathology [192, 198, 193]
- focal peripheral nerve pathology, including trauma [199–203]
- unknown [192, 200, 193].

The syndrome has also been described as a manifestation of tardive movement disorders following exposure to neuroleptics [204].

The etiology of the condition is not clear. Peripheral nerve pathology is found in most cases, and some physiology studies pointed to peripheral generators, either in the nerves themselves or in the dorsal root ganglia [198]. Others proposed distinct spinal oscillator circuits as the origin for the movements [205, 206] and even supraspinal mechanisms cannot be excluded. Involvement of the sympathetic nervous systems has been proposed as a mechanism, primarily for the pain component [207], and is supported by reports of sympathetic blockade effect in treating pain. It has been proposed that the syndrome is in fact a heterogeneous entity, with several possible causes [205, 128].

A clinically and electrophysiologically similar condition has been described in which pain is absent, and this is referred to as “painless legs and moving toes” [208]. It is less disabling than the painful variant, and it also appears to be heterogeneous, but most cases described appear to have a central cause [209, 199].

No large treatment trials exist, as the condition is rare. Several oral medications have been tried with limited impact [93], and most positive results have been reported with Baclofen [199, 193, 210]. There is one report of good results with adenosine.
infusion [211], but this has not been duplicated. Sympathetic blockade had been used with limited success [192, 199, 198, 193], but now is largely abandoned. Lumbar epidural block and epidural cord stimulation have both been reported to provide short-term relief [212, 213]. After initial disappointing results, botulinum toxin treatment is being revisited with promising results [214, 215]. It is notable that BoNT provides pain relief primarily (through unknown mechanisms) and provides limited alleviation of the movements.

Painful hands and moving fingers
A syndrome similar clinically to painful legs and moving toes, but affecting the upper extremity, has been described, with few cases reported to date [216, 217]. The finger movements have similar characteristics to the toe movements described above, with flexion–extension combined with abduction–adduction, and pain in the limb is commonly associated. Most cases described had an associated peripheral nerve insult. The mechanism may involve central (spinal or supraspinal) plastic changes induced by peripheral nerve pathology, further resulting in abnormal sensorimotor integration, which is ultimately responsible for the abnormal movements [206, 218]. Treatment is as difficult as in the case of painful legs and moving toes, and recently BoNT has been reported effective in one case [219].

Miscellaneous other jerks and startles

Episodic focal lingual spasms
Several cases of episodic involuntary spasms of the tongue have been reported. One of the most comprehensive descriptions is by Edwards et al. in a woman exhibiting spontaneous episodic tightening of one side of her tongue, lasting up to 2 minutes, multiple times a day [220]. No etiology was apparent in this case. Other cases were presumed dystonic, although still without a clear etiology [221]. These appear very similar to the cases dubbed “galloping tongue”, consisting of rhythmic 3Hz partial tongue movements following head trauma [222]. A recent case of similar tongue movements has been described in a patient with anoxic encephalopathy demonstrating thalamic anoxic lesions [223], and the movements resolved spontaneously, along with the lesions on imaging. The authors propose a basal ganglia-thalamic circuitry dysfunction analogous to dystonia mechanisms as a possible etiology, but the issue is far from settled.

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Other Jerks and Startles


PART 6
Ataxias
CHAPTER 17
Clinical and Pathophysiologcal Features of Cerebellar Dysfunction

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Anatomical background

The cerebellum overlies the posterior parts of the pons and medulla, occupying a large part of the posterior fossa. Structurally, the cerebellum consists of four pairs of nuclei – from medial to lateral: fastigial, globosus, emboliformis, and dentate – embedded in white matter, and surrounded by a cortical mantle of gray matter [1].

The cerebellar cortex is composed of Purkinje cells, granule cells, and inhibitory interneurons (Figure 17.1). The cortex is organized in a trilayer structure with the Purkinje cell layer (ganglionic layer) separating the outer molecular from the inner granular layer. Purkinje cells are GABAergic and thus inhibitory [2]. Their axons project to the cerebellar nuclei and vestibular nuclei. The corticocerebellar innervations of the cerebellum is dense [3]. Purkinje cells receive a glutamatergic projection through the climbing fibers originating from the inferior olive [4]. This is one of the most powerful synapses in the brain. The inferior olive receives projections from the spinal cord, motor cortex, sensory root of the trigeminal nerve, and red nucleus [1]. In addition, the inferior olive receives an inhibitory signal from cerebellar nuclei (nucleo-olivary pathway). Purkinje cells also receive numerous items of information, mainly somesthetic, vestibular, acoustic, visual, and cortical through the mossy fibers arising from a large spectrum of ipsilateral and contralateral sources. Granule cells present about four to five dendrites and a thin unmyelinated T-shaped axon whose branches constitute the parallel fibers running between the Purkinje neurons [5]. Inhibitory interneurons are located both in the molecular (basket cells and stellate cells) and in the granular layer (Lugaro cells and Golgi cells). Their function is to balance the excitatory activity targeting the Purkinje cells (Figure 17.1).

Nucleofugal fibers are excitatory except for the inferior olive. Nuclei project back to the cerebellar cortex. These nucleocortical projections reach mostly the areas from which they receive Purkinje cells axons [6–8]. The cerebellar output arises exclusively from the cerebellar nuclei (except for the vermal Purkinje cell axon to the lateral vestibular nucleus).

Afferent fibers enter the cerebellum through three pairs of peduncles: the inferior peduncle (restiform body): the large middle peduncle (brachium pontis):and the superior peduncle (brachium conjunctivum). Efferent fibers from the cerebellar nuclei leave the cerebellum through the superior and inferior peduncles.

Jansen has divided the human cerebellum into three main parts: the anterior lobe, the posterior lobe,
Figure 17.1 Scheme of the anatomical connections of the cerebellar circuitry. Purkinje neurons (PN) inhibit cerebellar nuclei and vestibular nuclei (VN). Stellate cells (sc), basket cells (bc) and Lugaro cells (lc) are inhibitory interneurons of the cerebellar cortex. Golgi cells are not represented. Climbing fibers (CF) originate exclusively from the contralateral inferior olivary complex. The origin of mossy fibers (MF) is more diffuse. These latter target granule cells (GC), whose ascending axon gives rise to parallel fibers (PF) making numerous synapses with PN. Ret.ST: reticulospinal tract. Rub.ST: rubrospinal tract (this tract does not extend beyond the cervical segments in human). Hypothal.: hypothalamus. +: excitatory. -: inhibitory.

and the paraflocculus/flocculus [9]. On the basis of mossy fiber projections to the cerebellar cortex, three areas can be considered [10]: the flocculonodulus (vestibulocerebellum): the vermal portion of anterior and posterior lobes with mainly spinal connections (paleocerebellum); and a mediolateral part having principally cortico–ponto–cerebellar connections (neocerebellum). Pontocerebellar and spinocerebellar afferents are mixed in the intermediate zone. Connections between the cerebellum and the cerebral cortex are segregated in re-entrant loops running in parallel (Figure 17.2). From a functional point of view, the cerebellar cortex can be divided into three zones: a vermal zone projecting to the fastigial nucleus, an intermediate zone projecting to the interpositus nucleus (globus and emboliformis), and a lateral zone projecting to the dentate nucleus (Figure 17.3).

Physiology of the cerebellum

The cerebellum contains more neurons than any other region of the brain and the number of afferent fibers exceeds the number of efferences by a ratio of about 40:1, hence the enormous computational
Clinical and Pathophysiological Features of Cerebellar Dysfunction

Figure 17.2 Illustration of the segregated loops between the cerebellum and prefrontal cortex, parietal cortex, paralimbic cortex, and superior temporal sulcus.

Figure 17.3 Comparison of anatomical connections of the vermal zone (A); the intermediate zone (B); and the lateral zone of the cerebellum (C). The midline zone and the intermediate zone receive direct information from the spinal cord, unlike the lateral cerebellum. Abbreviations: IOC, inferior olivary complex; LVN, lateral vestibular nucleus; FN, fastigial nucleus; NI, nucleus interpositus; DN, dentate nucleus. (From Manto [11].)
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voluntary movements of the extremities, including reaching and grasping [14]. The dentate nucleus regulates reaction time through initiation of movements triggered by vision or mental percepts, and accuracy of single-joint and multi-joint goal-directed movements. Neurons in the interpositus nucleus typically fire when a position is perturbed in reaction tasks aiming at keeping the segments of the limbs in a fixed position [15]. Limb movement representations in the interpositus nucleus may be instrumental for the control of goal-directed movements such as grasping or precise foot placement during gait. The interpositus neuronal activity can parse out the directional from the scalar component (i.e. the movement speed) of a velocity vector associated with movements. A differential role for the anterior and posterior portion of interpositus in encoding movement kinematic parameters is emerging. The activity of the posterior interpositus is associated with changes of movement speed [16].

Clinical features of the cerebellar dysfunction and underlying mechanisms

Neurological signs and symptoms occurring in cerebellar diseases can be grouped into five categories [17, 4]: oculomotor disturbances, speech deficits, deficits of limb movements, abnormalities of gait and posture, and cognitive disturbances. Deficits of limb movements include dysmetria, dysdiadochokinesia, tremor, decomposition of movements, loss of check and rebound, and disorders of muscle tone. Cerebellar ataxia is defined as the jerky or poorly coordinated character of motion. It appears in the absence of muscle weakness or sensory deficit, although fatigability is a common complaint in cerebellar patients.

Oculomotor disturbances

The oculomotor alterations observed in cerebellar diseases are, mainly: instability of gaze and nystagmus, hypermetria/hypometria of saccades, saccadic pursuit, skew deviation (ocular misalignment), and disorders of vestibulo-ocular reflex (VOR) and optokinetic responses (Table 17.1).

<table>
<thead>
<tr>
<th>Oculomotor disturbances</th>
<th>Localization of the lesion</th>
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</thead>
<tbody>
<tr>
<td>Dysmetria of saccades</td>
<td>Dorsal vermis/Fastigial nucleus</td>
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<tr>
<td>Saccadic pursuit</td>
<td>Flocculus/paraflocculus</td>
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<td>Gaze-evoked nystagmus</td>
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<td>Rebound nystagmus</td>
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<td>Downbeat nystagmus</td>
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<tr>
<td>Saccadic pursuit</td>
<td></td>
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<tr>
<td>Abnormal gain of VOR</td>
<td></td>
</tr>
<tr>
<td>Periodic alternating nystagmus</td>
<td>Nodulus, ventral uvula.</td>
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</table>

Adapted from Manto [19].

The stability of gaze is estimated clinically by holding the index finger in front of the patient at a distance of about 30 cm and in a lateral position (no more than 30 degrees), in upward and downward position. Nystagmus consists of rhythmic oscillatory movements of one or both eyes, with a fast and a slow component in opposite directions. Latency, precision, and velocity of saccades are estimated by asking the patient to look laterally at one and the other fingers located in each temporal visual fields [4]. Ocular hypermetria, defined as an inaccurate saccade with overshooting of the target, is very suggestive of cerebellar disease [18]. The use of a rotating chair is required to test the VOR. When the chair is rotated at constant velocity and the subject fixates on an object that moves synchronously with head movement, intermittent deviations of the eyes with corrective saccades are observed. In a healthy subject a compensative rotation of the head suppresses the VOR.

In cerebellar diseases abnormal ocular movements are usually due to a lesion at the level of the dorsal vermis or fastigial nucleus (i.e. dysmetria of saccades, saccadic pursuit), the flocculus and paraflocculus (i.e. saccadic pursuit, nystagmus, abnormal VOR, and optokinetic response), and or the uvula and nodulus (i.e. periodic alternating nystagmus) [20–23]. The fastigial nucleus plays a key role not only for eye movements, but also for control of the head position. The rostral fastigial nucleus controls head orientation and eye–head gaze shifts [24] whereas the caudal fastigial nucleus regulates oculomotor aspects, such as saccades or smooth pursuit [25].
By comparison with cerebellar disorders, the main extrapyramidal disorders are characterized by the following oculomotor abnormalities:

- In Parkinson disease, multiple step hypometric saccades are abnormally frequent [26]. Peak saccadic velocities are significantly reduced. Brief corrective intervals occur after hypometric saccades. They are attributed to internal (non-visual) efference copy feedback of eye position errors. Saccadic reaction times and post-saccadic refractory periods are prolonged. Smooth pursuit gain is abnormally low in patients during tracking sinusoidal targets. Frequent square wave jerks are also one of the features of Parkinson disease, but they lack specificity and are nearly always present in case of extrapyramidal disorder.

- Huntington disease (HD) is characterized by impaired initiation of saccades and slow saccades [27]. Early HD shows three types of significant abnormalities while performing memory guided and antisaccade tasks: increased error rate, increased saccade latency, and increased variability of saccade latency [28].

- Vertical saccade paralysis and supranuclear defects of VOR are suggestive of progressive supranuclear palsy (PSP) [29]. Analysis of refixation saccades shows hypometria, slow velocity/amplitude relationships, and profound prolongation of duration. The pursuit abnormality, characterized clinically by cogwheel eye movements, represents the inability to match eye velocity to target velocity.

Dysarthria and mutism

Dysarthria

Clarity, rhythm and fluency of speech are impaired in cerebellar patients. Speech tends to become slow with slurring. Comprehension is spared and paraphrasias are absent. Words may be unintelligible because of the temporal dysregulation of muscles activities [30]. Speech is often explosive, with a staccato rhythm and a nasal character. The scanning aspect is the most easily recognized deficit [31, 32], with hesitations, accentuation of some syllables, omission of appropriate pauses, and addition of inappropriate pauses. A disturbance in the melodic aspect of speech (dysprosody) may also occur.

Lesions of the superior paravermal region are commonly associated with speech deficits [33]. It has been suggested that, as a result of an asymmetric development of language, damage to the left intermediate cerebellar cortex might be one of the main causes of the cerebellar dysarthria [34, 35]. Two separate networks might supervise speech motor control [36]: the supplementary motor area, the dorsolateral frontal cortex, including the Broca area, anterior insula, and superior cerebellum would constitute a preparative loop; the executive loop would include the sensorimotor cortex, basal ganglia, thalamus, and inferior cerebellum.

Mutism

Mutism occurs mainly as a consequence of posterior fossa surgery (see also “Posterior fossa syndrome” below). It is more common in pediatric patients [37]. Mutism is characterized by an absence of speech without other aphasic signs or alteration of consciousness [38–41]. In most cases, it appears 12–48 hours after surgery and lasts about 12 weeks. After resolution of muteness, cerebellar dysarthria is observed. Hydrocephalus and postsurgical edema might contribute to the pathogenesis [42], but a genuine cerebellar contribution is slowly emerging in the literature.

Disturbances of limb movements

The so-called cerebellar syndrome relates to impairment in performance of limb movements, including various combinations of dysmetria, dysdiachokinesia, postural and kinetic tremor, decomposition of movement, and disorders of muscle tone. Motor deficits are lateralized to the side of the cerebellar lesion.

Dysmetria

Limbdysmetria is a cardinal sign in cerebellar disease. Holmes defined dysmetria as an error in trajectory due to a disturbed range, rate and force of the movement [43–45]. Hypermetria designates the overshoot of the target and is associated with a delayed onset latency of the antagonist EMG activity (Figure 17.4). There is a good correlation between the AS20 score (a clinical rating score of ataxia) on the one hand, and the severity of hypermetria and the delayed onset latency of the antagonist EMG activity on the
other [46]. Hypermetria is largest when the movement is made as fast as possible and when the inertia of the moving limb is increased [47–49]. Cerebellar patients show also deficiencies to adapt to artificial damping [50]. Hypometria is less common. Hypometric movements are characterized by a premature arrest before reaching the aimed target. Dysmetria is often followed by corrective movements. In most cases, dysmetria occurs both for proximal and distal joints [51]. Lesions of the dentate nuclei are typically associated with an overshoot of the target and a decomposition of multi-joint movements [52, 53]. Cerebellar patients are still able to describe the direction of the movement without looking at the moving limb, unlike patients with impaired position sense [35].

(A) Single-joint movements

1. Fast monodirectional movements

2. Fast reversal movements

Figure 17.4 (cont’d)
Figure 17.4 (cont’d) A. (1) Electromyographic (EMG) deficits associated with fast monodirectional single-joint movements in a control subject (left panel) and in a cerebellar patient (right panel). The onset latency of the antagonist EMG activity is delayed and the rate of rise of EMG activities is depressed. (2) Fast reversal movements during artificial modification of the damping characteristics of movement in a control subject (left panel) and in a cerebellar patient (right panel). The first phase of movement is normal in this patient. However, movement is dysmetric during the return to the initial position and the patient is unable to adapt the EMG activities to artificial damping.

B. Effects of increasing velocities on kinematics of the upper limb pointing movements in a control subject (upper panels) and a cerebellar patient (lower panels). Subjects are seated and comfortably restrained in order to allow only shoulder and elbow movements. They are asked to perform a vertical pointing movement towards a fixed target at various speeds. The target is located in front of the subjects at a distance of 85% of total arm length. In the patient, deficits in angular motion are enhanced with increasing velocities, especially the increased angular motion of the elbow resulting in overshoot (hyperextension of the elbow). Black lines: angular position of the elbow; grey lines: angular position of the shoulder. Abbreviations: sh, shoulder angle; elb, elbow angle.

C. Long-latency EMG responses to stretches of the first dorsal interosseous muscle in a cerebellar patient (black line) and in a control subject (gray line). Latencies of averaged rectified EMG responses are normal, but the M3 response is increased in the cerebellar patient. Surface EMG rectified and averaged 200 times. Responses are calibrated in arbitrary units (a.u.). (From Manto [11].)
Dysdiadochokinesia

Adiadochokinesia (or dysdiadochokinesia) designate the inability to perform rapid successive movements [54]. Dysdiadochokinesia is mainly characterized by irregularly irregular and slow alternating sequential movements [4]. An abnormal sway of the elbow is often present in advanced cases during successive pronation/supination tasks. Errors in timing and magnitudes of muscles activities contribute to the errors in the metrics of motion (see also “Dysmetria” below).

Tremor

Tremor associated with cerebellar diseases is mainly composed of low-frequency oscillations, usually with a kinetic component. Many cerebellar patients exhibit a concomitant postural tremor. Isometric tremor as well as titubation of the trunk may also occur [55]. The tremor may be bilateral, but in most cases, tremor is ipsilateral to the cerebellar lesion. In parkinsonian patients, tremor occurs while the body segment is maintained at rest and may disappear with action, although this is not a consistent finding. Rest tremor is typically in the 3–6 Hz frequency range, is usually asymmetrical and often starts distally in the arms. Typically, parkinsonian tremor in the upper limbs recalls the “pill rolling” movement. In some cases patients can reduce the tremor by holding one hand with the other or crossing their legs [56]. Lips and jaw can be affected.

Kinetic tremor in ataxic patients appears during the execution of a movement. It is assessed during the finger-to-nose and the knee-to-tibia tests. The frequency of kinetic tremor is usually between 4 and 12 Hz. Tremor appears immediately but increases in amplitude after a few seconds, in the line of gravity. The oscillations appearing during the heel-to-knee test rapidly evolve into lateral sways in severe cases. Eye closure and body displacements tend to enhance the oscillations. Postural tremor in cerebellar disease can be further described as: (a) precision tremor – usually due to lesions of cerebellar nuclei – with a frequency of 2–5 Hz, occurring during the execution of precision tasks and involving the distal musculature; (b) asthenic tremor – in case of hemispherical lesion – precipitated by fatigue; (c) axial postural tremor; and (d) midbrain tremor associated with midbrain lesions [60]. A postural tremor of the shoulder may be precipitated by fatiguing tasks in patients presenting a large cerebellar malformation.

Action tremor is often suggestive of anterior lobe cerebellar pathology. However, it may be observed also in diffuse cerebellar diseases such as idiopathic late-onset cerebellar atrophy (ILOCA) or hereditary spinocerebellar ataxias (SCAs) [61–64].

Both discontinuities in movements and tremor could result from impaired stretch reflexes and disorganized servo-assistance mechanisms, with a contribution of transcortical pathways [65, 4]. A detailed analysis of firings of neurons has revealed that the neuronal populations discharging strongly in relation to cerebellar tremor respond markedly and reciprocally to limb perturbation. However, the 3–4 Hz cerebellar tremor is not driven by a purely central oscillator [66]. Atrophy of the anterior lobe of the cerebellum may be associated with a very suggestive 3 Hz leg tremor in alcoholic patients.

The recent developments of wearable sensors as well as the advent of sensor fusion approaches (integration of various sensors) will very likely change our appraisal of the mechanisms underlying the various forms of tremor encountered in ataxic patients [67].
Figure 17.5 Postural tremor in a patient presenting a cerebellar stroke in the territory of the superior cerebellar artery. Top: Axial MRI of the posterior fossa; stroke (arrow) in the territory of the superior cerebellar artery. [Abbreviations: B, brainstem; C.H., cerebellar hemisphere; V, vermis. The lesion involves the outflow tract of the cerebellar nuclei.] Bottom: Data from a monoaxial accelerometer and from a surface electromyographic (EMG) sensor are shown, as well as the corresponding power spectra. Note the waveform characteristic, which is characterized by asymmetry. (From Grimaldi and Manto [56], with permission.)

**Decomposition of movement**

Ataxic movements tend to be decomposed into elementary components, with a lack of synergy between joints resulting in a lack of fluidity in motion [68]. Decomposition of movement is often accompanied by an inability to generate independent finger movements. For slow multi-joint movements, decomposition is manifested by errors in the...
direction and rate of the movement. The lack of coordination cannot be explained by a simple summation of the elemental deficits observed during single-joint movements. Deficits in adaptation of the interaction torques generated in a multi-degree of freedom human arm have been demonstrated in cerebellar patients [69] (see Figure 17.4B).

Check and rebound
Impaired check is assessed by asking the patient to maintain the upper limbs extended with the hands pronated [19]. The examiner exerts a tap on the wrist. A large displacement of the limb is observed, immediately followed by an overshoot of the initial position and oscillations around the initial position. Impaired check causes a large movement called excessive rebound [19]. The lack of check can be evaluated during the Stewart–Holmes maneuver. The patient is asked to perform a forceful flexion of the elbow while the examiner attempts to extend the joint. When the forearm is suddenly released, the patient hits himself with his hand. This is due to a combination of prolonged activity if the biceps muscle (agonist) and delayed onset latency of the braking activity of the triceps muscle (antagonist).

Disorders of muscle tone
Hypotonia is usually associated with severe cerebellar damage. The decline in resistance to the passive manipulation of limbs tends to be more pronounced in proximal joints. Pendular tendon reflexes, characterized by limbs oscillating around the position at rest, may be found. Nevertheless, amplitude and velocity of tendon reflexes are normal as well as cutaneous reflexes. Hypotonia is associated with decreased excitability the stretch reflex excitability, because cerebellum tunes the activity of gamma motor neurons [32]. Differential diagnosis of cerebellar hypotonia includes extensive brainstem lesion, spinal shock, anterior horn cell disease, polyradiculitis/polyneuropathy, floppy syndrome in children [4]. Cerebellar fits are spasms associated with intermittent opisthotonos [70]. They are associated with posterior fossa tumors, Chiari malformations, and stroke involving the cerebellar cortex but sparing the nuclei [4]. The mechanism is presumably an extensor tone disinhibition [71]. Cerebellar fits are included in the category of “cerebellar seizures,” which include also hemifacial seizures associated with a dysplastic cerebellar tumor in infants [72]. Ganglioglioma of the cerebellum may be associated with paroxysmal facial contractions [73]. Similar symptoms may be observed in children with hamartoma of the floor of the fourth ventricle [4].

Posture and gait
Cerebellar patients present a broad-based stance with an increased body sway. They may also exhibit distorted anticipatory adjustments and defective postural response to external forces [74]. Gait may be seen as resulting from a combination of balance and locomotor activities. Balance tasks include standing in an upright position (antigravity task), anticipatory adjustments preceding movements, as well as postural responses triggered by external forces. Locomotor tasks include the integration of the body to the changing environment, taking into account the rhythmic character of locomotion. Balance and locomotor tasks may be defective in ataxic patients.

Ataxia of stance
Ataxia of stance is characterized by an inability to maintain the body in a stationary position. Body sway is increased and the trunk tends to lurch from side to side or to drift on one side [45]. This lateropulsion is usually towards the site of the lesion [75]. The wide-base character of stance is typical in cerebellar disorders. The increased spread of the feet in natural position might result from the increased body sway and/or might be used as a compensatory strategy aiming at lowering the center of gravity of the body [19]. The assumption that ataxia of stance in isolated cerebellar diseases is not influenced by eye closure is false, although the exacerbating effect of closing the eyes might be less evident than in proprioceptive deficits or in the so-called vestibular ataxia [62, 76, 17]. Cerebellar patient may also present with titubation (rhythmic oscillations of the head, trunk or entire body) [43]. Oscillations occur in the anterior–posterior plane, in the lateral plane or are rotatory-like. Lesions of the anterior lobe are associated with a 3 Hz sway predominating in
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the anterior–posterior direction, whereas vestibulocerebellar lesions tend to produce a low-frequency sway (<1 Hz) in all directions [76, 4].

Sitting, stance, and gait are usually impaired in midline cerebellar lesions. Lesions in the medial and intermediate zones of the cerebellum, especially in the anterior lobe, disturb movements necessarily linked to the equilibrium function [74]. Lower vermal lesions often cause pluridirectional increased body sway at low frequencies and high amplitudes, whereas lesions in the upper vermal zone tend to induce anterior–posterior oscillations at higher velocities and lower amplitudes [77, 78].

The cerebellum controls the adequate scaling of anticipatory postural responses during standing postural perturbations [74]. Cerebellar circuitry tunes the magnitudes of long-latency reflexes (LLRs) in four limbs (see Figure 17.4C). LLRs are involved in the stabilization of postural activities in limbs and contribute to stability of trunk [79]. Cerebellar–cortical loops related to LLRs are especially involved in adapting postural responses based on prior experience [80]. We have found recently that the ratios of intensities of LLRs divided by intensities of short-latency reflexes (SLRs) are correlated with the onset latencies of antagonist EMG activities, suggesting that similar mechanisms might be involved [81].

Ataxia of gait
Gait is tested clinically during a 10 m test including a half-turn. The maneuvers that can unravel a subtle gait deficit are: walking in a line, walking in tandem, walking backwards. Ataxic gait is irregular and broad based. Successive steps are spaced in a staggering way, followed by corrections or falls. The rhythm is distorted and speed is often reduced. The cerebellum regulates step and stride length and cadence and attenuates the variability of gait during successive cycles. Walking trajectory veers erratically in cerebellar patients, with difficulties in initiation, stops, or turns.

Due to its anatomical connections, each cerebellar zone influences gait: the medial cerebellar zone integrates spinal and vestibular inputs to influence vestibulospinal and reticulospinal tracts; the intermediate zone integrates spinal and cortical inputs to influence walking via projections to motor cortical areas; the lateral cerebellum influences walking via cortical interactions and contributes to the voluntary modifications of the locomotor cycle [78].

Lesions at the level of the flocculonodular lobe cause an unsteady gait. An important role of the posterior inferior cerebellar vermis in tandem gait has been shown by Bastian and colleagues who reported an isolated abnormal tandem gait with preserved regular gait and stance in children with surgical transection of the posterior inferior cerebellar vermis [82]. Abnormal patterns of gait include irregular timing of peak flexion at one joint with respect to the other joints and/or joint–joint decomposition, which can be seen as a reduction in the movement at one joint during movement of another joint [78]. The analysis of goal-directed leg placement demonstrates that the interposed and the adjacent dentate nuclei are more frequently affected [83]. The intermediate zone seems to play an important role for multi-joint limb control both in goal-directed leg movements and in locomotion.

Cerebellum and learning
The cerebellum plays several key roles in learning [4]. The cerebellar circuits are involved in many aspects of memory, in particular in non-declarative memory [84]. This latter includes procedural learning (skills and habits): priming and perceptual learning, basic associative learning including simple classical conditioning of emotional and skeletal muscle responses, and non-associative learning [85, 4]. While the corticostriatal systems deals with learning of new sequences, the cerebrocerebellar systems are primarily engaged in the motor adaptations phases of learning [86]. Cerebellar circuits coordinate event sequences.

The cerebellum is critical to the adjustments required facing environmental changes or perturbations [87]. The prototype of adaptation learning is the gain of the vestibulo-ocular reflex (VOR), which refers to the amplitude of the eye movements due to head motion. Cerebellum and brainstem are two of the key players in the adaptation of the VOR [88]. Selection of the gain is a learning phenomenon, but no apparent new skill is required when
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the gain changes [89]. The VOR operates in conjunction with other systems such as smooth pursuit. Another typical example of adaptation to environmental change is the prism adaptation. In this task, the subject has to adjust movements while wearing prism glasses which displace vision. Subsequently, the prisms are removed and the subject has to readjust movement once again. Cerebellar patients have difficulties in both tasks. The recalibration of misaligned reference frames due to perturbed visual input is dependent upon a network of cortical (anterior cingulate, anterior intraparietal region) and cerebellar regions [90].

Cerebellar lesions are associated with impaired eyeblink conditioning [91, 92]. Acquisition of eyeblink conditioning is abnormal in various disorders in which the cerebellum plays a key role, for instance in essential tremor. Impairment of more complex forms of eyeblink conditioning (for example, trace eyeblink conditioning) and delay conditioning of other aversive responses (for example limb flexion response) in cerebellar subjects suggest a general role of the cerebellum in associative learning [85]. Globally, the cerebellum is involved in acquisition, timing and extinction of conditioned eyeblink responses.

Cerebellum and cognitive deficits

Cerebellum contributes to neural processes beyond the motor domain. Cerebellar patients may present cognitive and behavioral changes. Because these deficits may be subtle and are not detected by a conventional neurological examination, they are overlooked. A comprehensive neuropsychological evaluation is recommended when deficits are suspected. Two entities have been well delineated. They are described below.

Cerebellar cognitive affective syndrome

The concept of cognitive dysmetria has been proposed, by extension to the observations of motor deficits [93]. The terminology of “cerebellar cognitive affective syndrome” (CCAS) includes impairment of executive functions including planning and working memory, deficits in visuospatial skills, linguistic deficiencies such as agrammatism, and inappropriate behavior [94]. Executive dysfunction is commonly encountered in cerebellar patients [4]. Tasks requiring planning/initiation, sustaining and inhibiting activity, inferring, judging and shifting set are often abnormal in inherited ataxias, but premorbid state might influence strongly their severity and mode of presentation. Some patients with autosomal dominant spinocerebellar ataxia (SCA) may exhibit a clear intellectual decline, especially in SCA17 or dentato-rubral-pallidoluysian atrophy (DRPLA). Mood disorders and personality changes are not rare. Lexicosemantic knowledge may be impaired in subjects with advanced SCA, suggesting that language is affected as the disorder progresses. Attentional deficits are congruent with the hypothesis of a role of the cerebellum in providing attentional resources allotted in a rapid way [4]. Speech may be characterized by a vocal instability, reduced rate, and monotony, complicating dysarthria [95].

The constellation of these cognitive/behavioral deficits is suggestive of a disruption of the cerebellar modulation of neural circuits that link prefrontal, posterior parietal, superior temporal, and limbic structures including the amygdala, hippocampus, and septum [96]. Nearly all regions of the associative and paralimbic cortices project to pontine nuclei in a segregated manner, and pontine nuclei send mossy fibers to the cerebellum. The prefrontal cortex projects to medial and dorsomedial regions of the pons, the association areas of the temporal lobes project to the lateral pons, the superior regions of the parietal association cortices project to the central pons, the inferior parietal regions send projections to the rostral pons, and paralimbic regions project to medial and lateral pontine nuclei. A “limbic cerebellum” has even been suggested [97]. Impaired performance in Wisconsin Card Sorting Task (WCST) points toward a damage to the dorsolateral prefrontal cortex and/or its subcortical connections including the cerebellar circuits [98]. Behavioral changes might be more common in patients presenting lesions of the posterior cerebellar lobe and the vermis. Attention errors and abnormal visuospatial skills are reported repeatedly in these patients. Visuospatial deficits might be more common in case of left side lesions.
Positive effects of electric cerebellar stimulation on mood in psychiatric disorders has been reported, suggesting a role of cerebellum in human emotion [99]. Indeed, damage to the vermis has been associated with emotional dysregulation [100]. Which form of emotional process is handled by cerebellar circuitry is still an open question [96, 101].

**Posterior fossa syndrome**

The so-called posterior fossa syndrome can be considered as a very acute form of CCAS [4]. The syndrome affects mainly children between the age of 2 and 10 years. Following resection of a midline tumor of the cerebellum (see Figure 17.6 for an example), children show mutism, buccal and lingual apraxia, apathy and poverty of movements [102]. Mutism usually develops 1–5 days after the resection. Post-surgical mutism evolves into speech disorders or language disturbances similar to agrammatism, and behavioral disturbances ranging from irritability to behaviors reminiscent of autism, often with emotional lability (irritability, emotional reactions, agitation) and regressive personality changes [4]. When the lesion involves the vermis and spares the hemispheres, mutism quickly develops into dysarthria, which will improve markedly. When both the vermis and the right cerebellar hemisphere are involved, the recovery of speech is slow and speech often becomes monotonous and telegraphic, reminiscent of speech deficits found in frontal lobe lesions [4]. Concomitant cognitive deficits are common: impairment in the shifting of attention, perseveration, difficulties in problem-solving.

**Theories and computational models of cerebellar function**

Several major theories are influencing our concepts of cerebellar function (Table 17.2). According to the “sensory” theory, the cerebellum provides an online monitoring of sensory information [103] and tunes the sensory motor coupling in a given condition combining reflexes and voluntary movement [104]. The relation between sensory signals guiding motion and the movement itself depends on the relative position of limb segments, the position of the body in the gravitational field, and the external forces interacting with the
movement. The theory of the sensorimotor coordinate transformer assumes that the cerebellum implements the correct input–output in sensory motor transformations (mathematical computation of motor commands on the basis of sensory signals), thus transforming an intended movement vector into a given motor command [105]. The possibility that sensorimotor cortex and its cerebellar connections behave as pairs of reciprocally coupled oscillators is strongly suggested by (a) the coupling between the cerebellum and contralateral thalamic nuclei and primary cortex [106], and (b) the coherent oscillations between sensory cortex and cerebellar cortex [107]. Cerebellofugal fibers might even trigger oscillations in thalamic nuclei and motor cortex [108].

The “timing theory” considers that the cerebellar circuitry provides an internal timing system required to perform sensorimotor tasks accurately [115]. A main goal of the olivocerebellar system and the cerebellar microcircuits would be to provide a precise temporal representation [116]. Interactions between cerebellum and inferior olive are likely involved in the generation of complex temporal patterns producing intervals between movements. Data consistent with the idea that the cerebellum contributes to time processing in both perceptual and motor aspects come in particular from functional MRI (fMRI) studies. The right lateral cerebellum (lobule VI) is active during a time discrimination task, whereas the left cerebellum (lobule VI) is activated during a timed movement generation task [117].

The accurate control of joint torques is a prerequisite for normometric movements (see also “Disturbances of limb movements” above). Intensities of forces are scaled to the square of movement speed, providing a possible explanation for the increase in clumsiness when patients perform quicker movements. Cerebellar circuitry might keep an internal representation of the biomechanical properties of each body segment, regularly updated by peripheral sensory information [118]. This representation might be defective in cerebellar disorders.

**Internal models**

One leading theory proposes that the cerebellum houses neural representations, called “internal models,” to mimic fundamental natural processes such as a joint movement and body motion [119–121]. Some of the most convincing evidence

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### Table 17.2 Main theories of cerebellar functions.

<table>
<thead>
<tr>
<th>Theory</th>
<th>Principles</th>
<th>References</th>
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<tbody>
<tr>
<td>Sensory processing</td>
<td>The cerebellum monitors and adjusts the acquisition of sensory inputs</td>
<td>Bower [109]</td>
</tr>
<tr>
<td>Adaptive filter</td>
<td>Based upon Marr-Albus theory. Transformation of sets of signals into others. Components are weighted individually and then recombined to minimize the errors in performance caused by unavoidable noise.</td>
<td>Fujita [110]</td>
</tr>
<tr>
<td>Cerebellar timer</td>
<td>Cerebellum is the main site of temporal representation of action. Timing of sensorimotor activities are under the control of the cerebellar circuitry. Cerebellar circuitry behaves as a regulating clock.</td>
<td>Braitenberg [111]</td>
</tr>
<tr>
<td>Tonic reinforcer</td>
<td>The cerebellum tunes the intensities of agonist/antagonist/synergist muscles. Cerebellum exerts an excitatory influence upon extracerebellar targets such as thalamic nuclei or reticular nuclei.</td>
<td>Eccles et al. [5] Bastian and Thach [14] Oulad Ben Taib and Manto [113]</td>
</tr>
<tr>
<td>Internal models</td>
<td>The cerebellum contains neural representations to emulate movement. Internal models reproduce the dynamic properties of body parts.</td>
<td>Wolpert et al. [114]</td>
</tr>
</tbody>
</table>

Adapted from Manto [50].
that the nervous system uses internal forward models in human motor behavior comes from studies dedicated to the control of grasping forces during manipulation of objects [120]. This theory is based in particular on the inherent time delay of sensory feedback to update motor commands [122]. Sensorimotor delays vary according to the modality and context and may be in the range of 50 to 400 ms. The cerebellum may function similarly to a “forward model” by using efference copies of motor orders to predict sensory effects of movements. Cerebellar circuitry would be necessary to learn how to make appropriate predictions using error information about the discrepancies between the actual and predicted sensory consequences, not only for limb movements, but also for postural adjustments [123, 50, 4]. The cerebellum could compute an expected sensory outcome, which would be sent to cerebral cortical areas via excitatory connections to the thalamus and to the inferior olive via inhibitory connections (Figure 17.7). The inferior olive would operate as a comparator, sending signaling errors back to the cerebellar cortex.

Accurate predictions would decrease the dependence on sensory signals. Purkinje cell firings have several features suggestive of a forward internal model of the arm. Experimental data suggest that Purkinje neurons from lobules IV to VI encode position, directional parameters, and velocities of arm movements [124]. A subset of the parallel fiber synapses contacting Purkinje cell would control its output by causing a weakening of the strength of the synapses activated during an erroneous motor command [125]. A simulated regulation of smooth pursuit eye movements has been obtained in a model of the cerebellum by minimizing its inputs from parallel fibers, which carry various signals including error and efference copy. In minimizing both error and efference copy, this model demonstrates how cerebellar learning through parallel fibers renders movements more accurate and more efficient [126].

Inverse models
According to this theory, the cerebellum would lodge an “inverse model.” In this scheme the input to the cerebellum would be the aimed trajectory, and the output would be a motor co-
mand. In order to train this type of model, error information would be best characterized in motor coordinates in three directions. Both clinical and neurophysiological data support the existence of inverse models. Cerebellar patients exhibit difficulties in adapting to external force field, in agreement with the inverse dynamics hypothesis [127]. Shidara and colleagues have shown that Purkinje cell activity during ocular movements is consistent with signals of an inverse model [128]. Nevertheless, some doubts exist about the capability of Purkinje cells to really code for dynamic information (i.e. muscle commands) [129]. A majority of Purkinje cells do not exhibit any modulation in the patterns of discharges as a function of force type or load. In addition, the spatial tuning pattern seems unaffected, strengthening the idea of uncoupling between Purkinje cell firing and electromyographic activity in limbs.

Forward models and inverse models can be seen as two interrelated models. Forward models are required for the acquisition of a behavior. During learning of a given behavior, an inverse model is created, allowing skilled motion at an unconscious level [130]. The cerebellum interacts permanently with supratentorial areas, especially the premotor cortex, the motor cortex, the posterior parietal cortex, and the primary sensory cortex, in order to generate the appropriate encoding of force and direction of motion (Figure 17.8).

**Figure 17.8** Overview of the motor control strategy for limb movements. The cerebellum builds internal models and corrects motor commands, comparable to a system identification function. The basal ganglia ensures an optimal control of motion, facilitating motor commands. The parietal cortex integrates proprioceptive and visual outcomes, as well as sensory feedback, playing a role of state estimator. The premotor cortex and the motor cortex transform predictions into sets of motoneuronal discharges, encoding for force and direction of movement. (Reproduced from Manto [50] with permission from Springer.)

**References**


Clinical and Pathophysiological Features of Cerebellar Dysfunction


CHAPTER 18
Inherited and Sporadic Ataxias

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Introduction

Ataxia is a broad term, commonly referring to motor incoordination [1]. Ataxias may be classified as (i) cerebellar, when the cerebellum and its afferent or efferent projections are affected; (ii) sensory, when the proprioceptive pathways are affected; (iii) frontal, a form related to cerebellofrontal disruption; (iv) thalamic, due to cerebellothalamo-cortical loop damage; and (v) vestibular, due to labyrinthine dysfunction. Patients with cerebellar ataxia commonly show unbalanced gait and station, dystasia, dysmetria, intention tremor, dysdiadochokinesia, dyssynergia, decomposition of the movement and scanning dysarthria (see Video 18.1). Additionally, they may show titubation, hypotonia, pendular reflexes, loss of check, nystagmus and saccadic and pursuit disorders of oculomotor movements, and cerebellar cognitive affective syndrome [2, 3].

Cerebellar ataxias can be classified into hereditary, sporadic and symptomatic (secondary) varieties. Hereditary cerebellar ataxias are further classified into disorders of autosomal recessive (ARCA), autosomal dominant (ADCA), X-linked and mitochondrial inheritance. Sporadic cerebellar ataxias are those without identifiable heritability of the disease. Thus, recessive disorders, mitochondrial disorders, and other hereditary cases with de novo mutations, non-paternity or unrecognized adoption may present as sporadic cerebellar ataxias. However, most sporadic cerebellar ataxias remain as idiopathic degenerative cerebellar ataxias, which include the cerebellar form of multiple system atrophy (MSA-C), and sporadic adult-onset cerebellar ataxia of unknown etiology (SAOA; also known as idiopathic late onset cerebellar ataxias or idiopathic sporadic cerebellar ataxia) [3–5]. Symptomatic (secondary) cerebellar ataxias are caused by acquired disorders, such as vascular, toxic, neoplastic, paraneoplastic, immune-mediated, nutritional, infectious, traumatic, and endocrine disorders [1].

Video 18.1 Ataxia phenomenology
Ataxic gait (wide base, awkward turning, inability to perform tandem gait), abnormal standing (astasia; able to stand with normal stance and toes together but not with feet in the tandem position), normal sitting, mild dysarthria, dysmetria on the finger chase test, intention tremor on the nose-finger test, and abnormal heel-to-shin test.

Some patients with idiopathic cerebellar ataxias have congenital disorders with no progression of the disease after birth. These patients may have some forms of cerebral palsy or other developmental disorders. In this chapter we focus on progressive cerebellar ataxias of non-congenital onset. The OMIM number in Tables 18.1 and 18.2 links each disease to an extensive genetic, phenotypic and mechanistic description of the disease in the Online Mendelian Inheritance in Man database of the National Center for Biological Information (NCBI). Readers should also visit the NCBI GeneReview database for information, diagnosis and treatment. The GeneReview site also links to GeneTest, which provides information regarding where and how DNA testing of hereditary ataxias can be obtained. Descriptions of ataxic disorders that are not referenced in this chapter can be found in these databases.

**Autosomal Recessive Cerebellar Ataxias (ARCAs)**

ARCAs are typically characterized by cerebellar and spinal cord degeneration with a relatively early age at onset (Table 18.1) [6, 7]. The pathogenesis of ARCAs most commonly involve “loss of function” of proteins related to mitochondrial function, DNA repair, cerebellar or brain stem development, structural maintenance, or cell cycle and homeostasis [8].

**ARCA due to mitochondrial dysfunction**

These are disorders caused by nuclear genes encoding mitochondrial proteins (see “Mitochondrial ataxias” below).

**Friedreich ataxia**

Friedreich ataxia (FA), described in 1863 by Nicholaus Friedreich, is the most common form of ARCA in Caucasians, with the prevalence of 2–4/100,000 [9]. In FA, the defective upright instability is primarily attributable to sensory ataxia due to the degeneration of dorsal root ganglia, dorsal column and spinocerebellar tract. Although signs of cerebellar ataxia are clinically detectable, cerebellar atrophy is not prominent on MRI. The genetic and clinical description on FA is summarized in Table 18.1. Square wave jerks on oculomotor examination often provides a diagnostic clue. Although ataxia and hyporeflexia have been traditionally thought to be the clinical hallmarks of FA, many patients with documented FA have hyperreflexia, spasticity and a variety of hyperkinetic movement disorders including tremor, myoclonus, chorea and dystonia [9A].

Frataxin is a mitochondrial protein whose loss due to the intronic expansion of the GAA repeat leads to excess free radical production, disrupted iron-sulfur clusters and mitochondrial iron accumulation. [10, 11]. Antioxidants, such as idebenone (Coenzyme Q10 analogue), pioglitazone (PPAR gamma ligand), A0001 (alpha-tocopherolquinone), iron chelators, such as desferrioxamine and deferiprone, and, carbamylated erythropoietin have been already in clinical trials (www.clinicaltrials.gov). Histone deacetylase (HDAC) inhibitors have

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**Video 18.2 Friedreich ataxia**

This patients is affected by Friedreich ataxia (GAA trinucleotide repeat expansion in the FXN gene). Hypermetric saccadic movements are visible. [Video courtesy of Alberto Albanese, MD, Milan, Italy]
<table>
<thead>
<tr>
<th>ARCA</th>
<th>OMIM #</th>
<th>Gene, Locus</th>
<th>Mutated protein/mutation</th>
<th>Age at onset (years)</th>
<th>Phenotype description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Friedreich's Ataxia (FA)</td>
<td>#229300</td>
<td>FTX, (FRDA2, 9q13–21 9p23–p11)</td>
<td>Frataxin/ 90–1300 GAAs (normal 6–36); 5% of FA patients are compound heterozygotes with an expansion on one allele and a point mutation on the other. (Protein and mutation unknown for FRDA2)</td>
<td>Typically &lt;25, later in late onset FA (LOFA)</td>
<td>Ataxia (sensory ataxia and cerebellar ataxia); hypo-or areflexia, (reflexes retained in FARR); sensory loss with axonal neuropathy; square wave jerks on oculomotor exam; pyramidal weakness with extensor plantar reflexes - often accompanies cardiomyopathy, diabetes mellitus, pes cavus, scoliosis, sensorineural deafness and optic atrophy.</td>
</tr>
<tr>
<td>Ataxia Telangiectasia (AT)</td>
<td>#208900</td>
<td>ATM, 11q22–23</td>
<td>Phosphatidylinositol 3-kinase-type enzyme</td>
<td>Ataxia at 2–4, Loss of ambulation &lt;10</td>
<td>Ataxia, conjunctival telangiectasias (Figure 1), oculomotor apraxia, hyperkinesia, hyporeflexia, malignancies, reduced levels of IgA, IgE, and IgG, elevated serum α-fetoprotein, and gray hair and skin keratoses.</td>
</tr>
<tr>
<td>Ataxia with oculomotor apraxia 1 (AOA1)</td>
<td>#208920</td>
<td>APTX, 9p13.3</td>
<td>Aprataxin</td>
<td>2–6</td>
<td>Ataxia followed by oculomotor apraxia, distal muscle weakness and atrophy, and proprioceptive sensory loss, occasional dystonia, hypomimia and mental retardation.</td>
</tr>
<tr>
<td>Ataxia with oculomotor apraxia 2 (AOA2)</td>
<td>#606002</td>
<td>SEXT, 9q34</td>
<td>Senataxin</td>
<td>10–22</td>
<td>Ataxia, hyperkinesia, peripheral neuropathy and areflexia. Oculomotor apraxia in ~20% of cases. Skeletal and foot deformities. Elevated α-fetoprotein, gamma-globulin, and creatine kinase levels in the serum.</td>
</tr>
<tr>
<td>Spinocerebellar ataxia with axonal neuropathy (SCAN1)</td>
<td>#607250</td>
<td>TDPI, 14q31</td>
<td>Tyrosyl-DNA phosphodiesterase-1</td>
<td>Early childhood</td>
<td>Ataxia, axonal neuropathy with distal amyotrophy, pes cavus, mild hypercholesterolemia and hypoalbuminemia.</td>
</tr>
<tr>
<td>Abetalipoproteinemia</td>
<td>#200100</td>
<td>MTP, 4q22–24</td>
<td>Microsomal triglyceride transfer protein</td>
<td>6–12</td>
<td>Ataxia, areflexia, distal amyotrophy and loss of proprioception, with lipid malabsorption, achalasia, retinopathy.</td>
</tr>
<tr>
<td>Ataxia with primary vitamin E deficiency (AVED)</td>
<td>#277460</td>
<td>α-TTP, 8q13</td>
<td>α-tocopherol-transporter-protein</td>
<td>Typically &lt;25</td>
<td>Similar to FA without cardiomyopathy or impaired glucose metabolism. Titubation may be present in 1/3 of cases. Plasma vitamin E level &lt;10% of normal.</td>
</tr>
<tr>
<td>Cayman cerebellar ataxia</td>
<td>#601238</td>
<td>ATCAY, 19p13.3</td>
<td>Caytaxin</td>
<td>At birth</td>
<td>Hypotonia, mental and physical retardation, non-progressive ataxia.</td>
</tr>
<tr>
<td>Spastic ataxia of Charlevoix-Saguenay</td>
<td>#270550</td>
<td>SACS, 13q11</td>
<td>Sacsin</td>
<td>&lt;13</td>
<td>Ataxia and spasticity with distal muscle wasting, finger/foot deformities and hypermyelination of retinal nerve fibers.</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>ARCA</th>
<th>OMIM #</th>
<th>Gene, Locus</th>
<th>Mutated protein/mutation Information</th>
<th>Age at onset (years)</th>
<th>Phenotype description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marinesco-Sjögren syndrome</td>
<td>#248800</td>
<td>SIL1, unknown, 5q31 18pter</td>
<td>SIL1 Unknown gene or protein for this 2nd locus</td>
<td>&lt;1</td>
<td>Ataxia, congenital cataracts, short stature and mental retardation with neuromuscular disorders (demyelinating polyneuropathy and recurrent rhabdomyolysis.)</td>
</tr>
<tr>
<td>Refsum disease</td>
<td>#266500</td>
<td>PHYH, 10pter–p11</td>
<td>Phytanoyl-CoA hydroxylase</td>
<td>Early childhood-50s</td>
<td>Ataxia, retinitis pigmentosa (night blindness polyneuropathy, high cerebrospinal fluid protein without pleocytosis, and elevated phytanic acid.)</td>
</tr>
<tr>
<td>Infantile Refsum disease</td>
<td>#266510</td>
<td>PEX1, PEX2, PEX26 7q21–q22 8q21.1 22q11.21</td>
<td>Peroxin 1(peroxisome biogenesis factor 1) Peroxin 2 (peroxisomal assembly factor 1) Peroxin 26</td>
<td>&lt;1</td>
<td>A phenotype similar to adult-onset Refsum disease; atypical retinitis pigmentosa, peripheral neuropathy and cerebellar ataxia with elevated phytanic acid but associated with severe deafness, mental and growth retardation, facial dysmorphism and hepatomegaly with elevated very long chain fatty acids (VLCFA).</td>
</tr>
<tr>
<td>Cerebrotendinous xanthomatosis</td>
<td>#213700</td>
<td>CYP27, 2q33-pter</td>
<td>Sterol 27-hydroxylase</td>
<td>&lt;10</td>
<td>Diarrhea, jaundice, hepatitis, cataracts, optic disk pallor, and premature retinal senescence with retinal vessel sclerosis and hypermyelinated retinal nerve fibers in the first decade of life, xanthomas on tendons and neurological signs with mental retardation, dementia, hyperkinesias, and cerebellar ataxia in 2nd and 3rd decades.</td>
</tr>
<tr>
<td>Posterior column ataxia and retinitis pigmentosa (AXPC 1)</td>
<td>%609033</td>
<td>unknown, 1q31</td>
<td>Unknown</td>
<td>Childhood (ataxia in the 2nd decade)</td>
<td>A ring scotoma gradually leading to blindness, sensory ataxia, proprioceptive sensory loss, amyotrophy, weakness and areflexia.</td>
</tr>
<tr>
<td>Ataxia of the Beauce</td>
<td>#610743</td>
<td>SYNE1, 6q25</td>
<td>Synaptic nuclear envelope 1</td>
<td>Typically middle age</td>
<td>Pure cerebellar ataxia with occasional lower limb hyperreflexia.</td>
</tr>
<tr>
<td>SeSAME syndrome</td>
<td>#612780</td>
<td>KCNJ10, 1q23.2–q23.3</td>
<td>Inwardly rectifying potassium channel</td>
<td>&lt;1</td>
<td>Seizures, sensorineural deafness, ataxia, mental retardation and electrolyte imbalance.</td>
</tr>
</tbody>
</table>
been proposed to reduce the mitochondrial iron overload. Idebenone has been suggested to show a
dose-related neurologic benefit in a phase II trial. However, the current clinical management of
patients with FA largely depends on symptomatic and supportive treatments although the manage-
ment of cardiomyopathy, diabetes and dysphagia may be of particular importance.

**ARCA due to coenzyme Q10 deficiency**
Coenzyme Q10 (CoQ10), or ubiquinone, is a
mobile lipophilic electron carrier critical for electron
transfer in the mitochondria. While primary CoQ10
deficiency has variable phenotypes, the ataxic form
is characterized by childhood-onset and cerebellar
atrophy, reduced levels of muscle CoQ10, lactic
acidaemia, elevated serum creatine kinase (CK) and
episodic myoglobinuria. Additional features include
seizures, myoclonus, mental retardation, muscle weakness, fatigability, hyporeflexia and
pyramidal signs. Oral high-dose CoQ10 may
dramatically improve the clinical manifestations
[12]. Primary CoQ10 deficiency is cause by muta-
tions in the decaprenyl diphosphate synthase
subunit–2 (PDSS2), PDSS1, CABC1, COQ2 and COQ9,
and possibly, APTX genes [13].

**ARCA due to DNA repair defects**

**Ataxia telangiectasia**
Ataxia telangiectasia (AT), described in 1941 by
Louis-Bar, is the second most common cause of
progressive cerebellar ataxia in childhood, after
FRDA, with a prevalence of 1 in 10^5 live births [14].
Clinical manifestations, including telangiectasia
(Figure 18.1), are summarized in Table 18.1. Brain
imaging shows cerebellar atrophy. Most patients
die by 20, usually from bronchopneumonia or
malignancy. Treatment with conventional dosages
of radiation can be fatal in AT patients. Patients
with “variant” AT have an extended lifespan with a
milder disease.

The **ATM** gene encodes a nuclear phosphoprotein
(phosphatidylinositol 3-kinase-type enzyme) that
acts in DNA-damage checkpoint processes and
repair. The precise pathogenic role of **ATM** for ataxia
is unknown.

**Ataxia with oculomotor apraxia**
Ataxia with oculomotor apraxia 1
Clinical and genetic characteristics of AOA1 [15]
are summarized in Table 18.1. AOA1 often
accompanies axonal neuropathy, cerebellar and
brainstem atrophy, hypoalbuminemia and hyper-
cholesterolemia. AOA1 is the most frequent recessive
ataxia in Japan, while it is the second most
common, after FRDA, in Portugal.

**Ataxia with oculomotor apraxia 2**
Ataxia with oculomotor apraxia type 2 (AOA2)
[15] represents ~8% of non-FA ARCA. Clinical and
genetic features are summarized in Table 18.1.
Additionally, cerebellar atrophy and axonal sensory
neuropathy are often found. Senataxin possibly
acts in the DNA repair pathway and splicing
machinery. Dominant mutations in **SETX** gene
cause ALS4, an autosomal dominant form of
amyotrophic lateral sclerosis.

**Spinocerebellar ataxia with axonal
neuropathy (SCAN1)**
See reference [16] and Table 18.2.

**ARCA due to vitamin E deficiency
and related disorders**
Vitamin E is an antioxidant, which scavenges
peroxyl radicals in cell membranes. Of various forms
of vitamin E, α-tocopherol has the highest biological
activity. In the liver, the α-tocopherol-transfer-protein
(TTPA) incorporates $\alpha$-tocopherol in the very-low density lipoproteins (VLDL).

Deficiency of vitamin E may also be a consequence of lipid malabsorption, abetalipoproteinemia (ABL), or primary vitamin E deficiency. In these conditions, ataxia is usually part of a multisystem disorder caused by multiple defects of other lipid-soluble vitamins and essential factors, such as vitamin A in ABL. Early treatment with high-dose vitamin E and other supplements can delay the disease progression or even prevent the onset of neurological deficits [17].

**Abetalipoproteinemia (Bassen Kornzweig disease)**

See Table 18.2.

**Ataxia with primary vitamin E deficiency (AVED)**

AVED was first described by Burck in 1981 in cases with a phenotype similar to FA. The disease is frequent in North-Africans and other Mediterranean populations with distinct nonsense mutations. Plasma vitamin E levels are usually less than 10% of normal values, and daily supplementation with high dosage of vitamin E is necessary and effective.

**Cayman cerebellar ataxia**

Cayman cerebellar ataxia (CCA) was identified in an isolated population from Grand Cayman islands. Caytaxin, the protein mutated in Cayman cerebellar ataxia, contains a CRAL-TRIO domain, which is also present in TTPA [17].

**ARCA due to chaperon protein deficiency**

**Spastic ataxia of Charlevoix-Saguenay**

Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS, see Table 18.1) [18] was described by Bouchard in 1978 in the Charlevoix-Saguenay-Lac-Saint-Jean region of Quebec (carrier frequency, 1 in 22 individuals). Main pathological findings comprise atrophy of the upper vermis and loss of Purkinje cells in the cerebellum. Rare patients with ARSACS lack spasticity.

In a single gigantic exon spanning 12,794 bp of the SACS gene, 29 different mutations have been found in Quebec, Turkey, Tunisia, Italy, Spain, Japan, Belgium, and Holland.

**Marinesco-Sjögren syndrome (MSS)**

MSS was described in 1931 by Marinesco, Draganesco, and Vasiliu'. In addition to core features described in Table 18.1 [19, 20], patients show often laboratory abnormalities, including sustained or episodic elevation of serum creatine kinase and hypergonadotropic hypogonadism. Treatment is symptomatic, and cataractectomy and hormonal replacement therapy may be needed. Patients survive to old age with varying disability.

**Other ARCAs with known mutations**

Other ARCAs with known mutations include Refsum disease, cerebrotendinous xanthomatosis, SeSAME syndrome (seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance), recessive ataxia of the Beauce (SYNE1 ataxia), and posterior column ataxia with retinitis pigmentosa (Table 18.1; also see OMIM4 and GeneReview5).

**Other autosomal recessive ataxias with unknown genetic loci**

There are many autosomal recessive ataxias in which neither genetic loci nor mutations are known. Among them, some disorders appear to be phenotypically distinct but they are almost certainly genetically heterogeneous.

**Hyperkinetic movement disorders in ARCAs**

Chorea, dystonia, myoclonus, and tremor are often seen as extrapyramidal signs of ARCAs. Patients with FA may show generalized or primarily upper body chorea – in some cases even without cerebellar signs. Some patients with FA may also show dystonia, myoclonus, and head tremor. Chorea is

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<table>
<thead>
<tr>
<th>ADCA</th>
<th>OMIM #</th>
<th>Gene, Locus</th>
<th>Primary Pathogenic Gene Product Mutation</th>
<th>Harding's ADCA type/Anticipation</th>
<th>Age at Onset (years)</th>
<th>Phenotype Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCA1</td>
<td>#164400</td>
<td><em>ATXN1</em>, 6p23</td>
<td>Ataxin-1 40–82 CAGs (normal 6–44; CAT interruptions in large normal alleles)</td>
<td>ADCA 1 Anticipation (+)</td>
<td>5–70</td>
<td>Ataxia, spasticity, dysarthria, ophthalmoplegia, hypermetric saccades, nystagmus, optic atrophy, pyramidal tract signs; rare extrapyramidal; signs; some have dementia; neuropathy and slow saccades occur late</td>
</tr>
<tr>
<td>SCA2</td>
<td>#183090</td>
<td><em>ATXN2</em>, 12q24</td>
<td>Ataxin-2 33–64 CAGs (normal 14–31, intermediate 34–35 with CAA interruptions)</td>
<td>ADCA 1 Anticipation (+)</td>
<td>9–44</td>
<td>Ataxia, dysarthria, muscle cramps; slow saccades/ ophthalmoplegia; hyporeflexia, dementia in some; no pyramidal or extrapyramidal features except for dopa-responsive parkinsonism at young ages with a small CAG expansion. An infantile form suggested.</td>
</tr>
<tr>
<td>SCA3 or Machado-Joseph disease,</td>
<td>#109150</td>
<td><em>ATXN3</em>, 14q24.3–q31</td>
<td>Josephin (Ataxin-3) 52–86 CAGs (normal 12–44, intermediate 45–51 with reduced penetrance)</td>
<td>ADCA 1 Anticipation (+)</td>
<td>17–72</td>
<td>Ataxia, dysarthria, ophthalmoplegia; type I onset in mid 20s with facial-lingual myokymia, pyramidal and extrapyramidal features; type II onset in 40s; type III onset in mid 40s with peripheral neuropathy (weakness and atrophy)</td>
</tr>
<tr>
<td>SCA4</td>
<td>%600223 Gene unknown, 16q22.1 (same region as #117210 below)</td>
<td></td>
<td></td>
<td>ADCA 1 or 3</td>
<td>19–72</td>
<td>Pure ataxia in some cases, most have sensory axonal neuropathy; deafness in some</td>
</tr>
<tr>
<td>SCA5</td>
<td>#600224</td>
<td><em>SPTBN2</em>, 11p13</td>
<td>Spectrin beta chain, brain 2</td>
<td>ADCA 3 Anticipation has been reported</td>
<td>10–68</td>
<td>Downbeat nystagmus; ataxia, dysarthria, impaired smooth pursuit, and gaze-evoked nystagmus; slow progression; both vermian and hemispheric cerebellar atrophy, normal life expectancy</td>
</tr>
<tr>
<td>SCA6</td>
<td>#183086</td>
<td><em>CACNA1A</em>, 19p13</td>
<td>Voltage-dependent PI/Q-type Ca^{2+} channel alpha-1a subunit 19–33 CAGs (normal 4–18)</td>
<td>ADCA 3 Anticipation (−)</td>
<td>22–71</td>
<td>Ataxia, dysarthria, nystagmus, distal sensory loss, normal life expectancy</td>
</tr>
<tr>
<td>SCA7</td>
<td>#164500</td>
<td><em>ATXN7</em>, 3p21.1–p12</td>
<td>Ataxin-7 37–300 CAGs (normal 4–27, intermediate 28–35)</td>
<td>ADCA 2 Anticipation (+)</td>
<td>0–50</td>
<td>Pigmentary retinal degeneration, ataxia, dysarthria, ophthalmoplegia, slow saccades, pyramidal tract signs</td>
</tr>
<tr>
<td>SCA8</td>
<td>#608768</td>
<td><em>ATXN8OS</em>, 13q21</td>
<td>ATXN8OS RNA 3’UTR (CUG)n and opposite-strand PolyQ 107–250 CTG/CAG (normal 16–91)</td>
<td>ADCA 3 Anticipation (−)</td>
<td>20s–70s</td>
<td>Ataxia, dysarthria, nystagmus, impaired smooth pursuit</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>ADCA</th>
<th>OMIM #</th>
<th>Gene, Locus</th>
<th>Primary Pathogenic Gene Product Mutation</th>
<th>Harding’s ADCA type/Anticipation</th>
<th>Age at Onset (years)</th>
<th>Phenotype Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCA9</td>
<td>Unassigned category</td>
<td>ATXN10, 22q13</td>
<td>Ataxin-10 intron RNA 850–4500 ATTCTs (normal 10–29; reduced penetrance 280–850)</td>
<td>ADCA 3 Anticipation (+)</td>
<td>10–50</td>
<td>Ataxia, dysarthria, dystonia, epileptic seizures; to date only found in Mexican and Argentinean families</td>
</tr>
<tr>
<td>SCA10</td>
<td>#603516</td>
<td>SCA11, 15q14–q21.3</td>
<td>Tau-tubulin kinase 2</td>
<td>ADCA 3 Anticipation (-)</td>
<td>20–40</td>
<td>Ataxia, dysarthria, nystagmus</td>
</tr>
<tr>
<td>SCA11</td>
<td>#604326</td>
<td>PPP2R2B, 5q31–q33</td>
<td>Ser/thr protein phosphatase 2A, 55-kd regulatory subunit B, beta isoform 55–78 CAGs in 5'UTR (normal 7–32)</td>
<td>ADCA 1 Anticipation (-)</td>
<td>8–55</td>
<td>Upper extremity and head tremor, gait ataxia, ophthalmoplegia, hyperreflexia, bradykinesia, dementia</td>
</tr>
<tr>
<td>SCA12</td>
<td>#605259</td>
<td>KCNC3, 19q13.3–q13.4</td>
<td>Voltage-gated K+ channel, subfamily C member 3</td>
<td>ADCA 3 Anticipation (-)</td>
<td>4–82</td>
<td>Ataxia, dysarthria, mental retardation; slow progression, seizures</td>
</tr>
<tr>
<td>SCA13</td>
<td>#605361</td>
<td>PRKCG, 19q13.4</td>
<td>Kinase C, gamma type;</td>
<td>ADCA 3 Anticipation (-)</td>
<td>Child to 60</td>
<td>Ataxia, dysarthria, nystagmus; younger patients (&lt;27 y) also had intermittent axial myoclonus prior to ataxia</td>
</tr>
<tr>
<td>SCA14</td>
<td>#606658</td>
<td>ITPR1, 3p26.1–p25.3</td>
<td>Inositol 1,4,5-triphosphate receptor type 1 Large deletion</td>
<td>ADCA 3 Anticipation (-)</td>
<td>10–66</td>
<td>Slowly progressive pure cerebellar ataxia, dysarthria, tremor; may have head titubation, nystagmus, oculovestibular reflex abnormalities, mild hyperreflexia</td>
</tr>
<tr>
<td>SCA15 SCA16</td>
<td>#607136</td>
<td>TBP, 6q27</td>
<td>TATA-box-binding protein 47–63 CAGs (normal 25–44, 46–47 with reduced penetrance); CAA interruptions</td>
<td>ADCA 1 Anticipation (+)</td>
<td>7–49</td>
<td>Ataxia, pyramidal, extrapyramidal, and, possibly autonomic dysfunction; dementia, psychosis, degeneration of caudate, putamen, thalamus, frontal cortex, temporal cortex, and cerebellum</td>
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<tr>
<td>SCA17</td>
<td>#607458</td>
<td>SCA18, 7q22–q32</td>
<td>Unknown; IFRD1 has been a candidate</td>
<td>ADCA 1 Anticipation (-)</td>
<td>20s–30s</td>
<td>Sensorimotor axonal neuropathy with ataxia; gait abnormality, dysmetria, hyporeflexia, muscle weakness and atrophy, decreased vibratory and proprioceptive sense</td>
</tr>
<tr>
<td>SCA18</td>
<td>#607346</td>
<td>1p21–q21</td>
<td>Unknown</td>
<td>ADCA 3 Anticipation has been reported</td>
<td>12–40</td>
<td>Ataxia, hyporeflexia, dysphagia, dysarthria, and gaze-evoked horizontal nystagmus; cerebellar atrophy on MRIs</td>
</tr>
<tr>
<td>SCA19 SCA22</td>
<td>#608687</td>
<td>11p13–q11</td>
<td>Unknown</td>
<td>ADCA 1 or 3 Anticipation (-)</td>
<td>19–64</td>
<td>Dysarthria, gait and upper limb ataxia, slow progression; more variable features are mild pyramidal signs, hypermetric saccades, nystagmus, palatal tremor, slow cognitive decline; CT scan shows dentate calcification</td>
</tr>
<tr>
<td>SCA21</td>
<td>%607454</td>
<td>SCA21, 7p21–15</td>
<td>Unknown</td>
<td>ADCA 1</td>
<td>6–30</td>
<td>Cerebellar ataxia, limb ataxia and akinesia, dysarthria, dysgraphia, hyporeflexia, postural tremor, resting tremor, rigidity, cognitive impairment, cerebellar atrophy</td>
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<tr>
<td>SCA23</td>
<td>%610245</td>
<td>20p13–12.3</td>
<td>Unknown</td>
<td>ADCA 1</td>
<td>40s–50s</td>
<td>Slow progression; gait and limb ataxia, dysarthria (varies), slow saccades and ocular dysmetria, decreased vibratory sense, pyramidal signs; severe cerebellar atrophy</td>
</tr>
<tr>
<td>SCA25</td>
<td>%608703</td>
<td>SCA25, 2p21–p13</td>
<td>Unknown</td>
<td>ADCA 1</td>
<td>1–39</td>
<td>Invariable features are cerebellar ataxia; variable features are lower limb areflexia, peripheral sensory neuropathy, nystagmus, decreased visual acuity, facial tics, extensor plantar responses, urinary urgency, and gastrointestinal symptoms</td>
</tr>
<tr>
<td>SCA26</td>
<td>%609306</td>
<td>19p13.3</td>
<td>Unknown</td>
<td>ADCA 3</td>
<td>26–60</td>
<td>Pure cerebellar signs, including ataxia of the trunk and limbs, dysarthria, and irregular visual pursuit movements; intelligence normal; MRI shows atrophy of cerebellum, sparing pons and medulla</td>
</tr>
<tr>
<td>SCA27</td>
<td>#609307</td>
<td>FGF14, 13q34</td>
<td>Fibroblast growth factor 14</td>
<td>ADCA 1</td>
<td>12–20</td>
<td>Cerebellar ataxia, tremor, low IQ, aggressive behavior, eye movement abnormalities are nystagmus, cerebellar dysarthria, head tremor, orofacial dyskinesias, cerebellar atrophy, pes cavus, axonal sensory neuropathy, neuronal loss in cerebral cortex, amygdala, and basal ganglia</td>
</tr>
<tr>
<td>SCA28</td>
<td>%610246</td>
<td>AFG3L2, 18p11.22–q11.2</td>
<td>AFG3-like protein 2</td>
<td>ADCA 1</td>
<td>12–36</td>
<td>Imbalance and mild gait incoordination; gaze-evoked nystagmus, slow saccades, ophthalmoparesis, and, often, ptosis; frequently lower limb hyporeflexia</td>
</tr>
<tr>
<td>SCA29</td>
<td>%117360</td>
<td>3p26 Genetic heterogeneity?</td>
<td>Unknown</td>
<td>ADCA 3</td>
<td>Birth</td>
<td>Non-progressive cerebellar ataxia</td>
</tr>
<tr>
<td>SCA30</td>
<td>%613371</td>
<td>4q34.3–q35.1</td>
<td>Unknown</td>
<td>ADCA 3</td>
<td>45–76</td>
<td>Slowly progressive gait and appendicular ataxia, hypermetric saccades, some with hyporeflexia</td>
</tr>
<tr>
<td>SCA31</td>
<td>#117210</td>
<td>BEAN, 16q21–q22</td>
<td>Brain-expressed associated with NEDD4 2.5–3.8 kb insertion containing pentanucleotide repeat including (TGGAA)n</td>
<td>ADCA 3</td>
<td>45–72</td>
<td>Pan-cerebellar ataxia, decreased muscle tone, horizontal gaze nystagmus</td>
</tr>
</tbody>
</table>

(continued)
Table 18.2 (cont’d).

<table>
<thead>
<tr>
<th>ADCA</th>
<th>OMIM #</th>
<th>Gene, Locus</th>
<th>Primary Pathogenic Gene Product Mutation</th>
<th>Harding’s ADCA type/Anticipation</th>
<th>Age at Onset (years)</th>
<th>Phenotype Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dentatorubral-pallidolysian atrophy (DRPLA)</td>
<td>#125370</td>
<td>DRPLA, 12p13.31</td>
<td>Atropin-1-related protein 49–88 CAGs (normal 3–36)</td>
<td>ADCA 1 Anticipation (+)</td>
<td>1–70</td>
<td>Myoclonic epilepsy, dementia, ataxia, choreoathetosis, degeneration of dentatorubral and pallidolysian systems</td>
</tr>
<tr>
<td>Episodic ataxia type 1, EA1</td>
<td>#160120</td>
<td>KCNA1, 12p13</td>
<td>Kv1.4 voltage-gated channel (A1)</td>
<td>Episodic ataxia Anticipation (−)</td>
<td>Early childhood</td>
<td>Continuous muscle movement (myokymia) and periodic ataxia</td>
</tr>
<tr>
<td>Episodic ataxia type 2, EA2</td>
<td>#108500</td>
<td>CACNA1A, 19p13</td>
<td>Voltage-dependent P/Q-type Ca(^{2+}) channel alpha-1A subunit</td>
<td>Episodic ataxia Anticipation (−)</td>
<td>Before 10</td>
<td>Ataxia, downbeating nystagmus dizziness treated with acetazolamide; no progression after childhood; cerebellar atrophy</td>
</tr>
<tr>
<td>Episodic ataxia type 3, EA3</td>
<td>%606554</td>
<td>1q42</td>
<td>Unknown</td>
<td>Episodic ataxia Anticipation (−)</td>
<td>1–42</td>
<td>Vestibular ataxia, vertigo, tinnitus, interictal myokymia</td>
</tr>
<tr>
<td>Episodic ataxia type 4, EA4</td>
<td>%606552</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Episodic ataxia Anticipation (−)</td>
<td>20–50</td>
<td>Recurrent attacks of vertigo, diplopia, and ataxia; some with slowly progressive cerebellar ataxia with defective smooth pursuit and gaze-evoked nystagmus</td>
</tr>
<tr>
<td>Episodic ataxia type 5, EA5</td>
<td>+601949</td>
<td>CACNB4, 2q22–q23</td>
<td>Voltage-dependent L-type calcium beta-4 subunit</td>
<td>Episodic ataxia Anticipation (−)</td>
<td>20–30</td>
<td>Ataxia similar to EA-2; severe episodic lasting hours to weeks; interictal gait and truncal ataxia with mild dysarthria; nystagmus (downbeat, spontaneous, gaze evoked); seizures</td>
</tr>
<tr>
<td>Choreo-athetosis spasticity episodic, CSE</td>
<td>%601042</td>
<td>12p13</td>
<td>Unknown</td>
<td>Episodic ataxia Anticipation (−)</td>
<td>2–15</td>
<td>Paroxysmal choreoathetosis with episodic ataxia and spasticity</td>
</tr>
<tr>
<td>Autosomal dominant spastic ataxia, SPAX1</td>
<td>%108600</td>
<td>SAX1, 12p13</td>
<td>Unknown</td>
<td>ADCA 3 Anticipation (−)</td>
<td>10–20</td>
<td>Lower limb spasticity, generalized ataxia, impaired ocular movements, gait abnormalities; brain and cord MRIs normal; neuropathology shows midbrain neuronal loss</td>
</tr>
</tbody>
</table>
the most frequent extrapyramidal sign in AT; however, early-onset dystonia and myoclonus have also been found in AT. Patients with AOA1 typically show chorea in addition to ataxia; however, dystonia, myoclonus, and tremor seem to be rare. In contrast, about 15% of patients with AOA2 show tremor and dystonia, but chorea is less common in AOA2 than in AOA1. In AVED head tremor and dystonia are most common extrapyramidal signs. Palatal myoclonus, tremor, and dystonia may be found in some patients with cerebrotendinous xanthomatosis.

**Autosomal dominant cerebellar ataxias (ADCAs)**

ADCAs constitute a large, complex, group of heterogeneous autosomal dominant diseases of the cerebellum and its afferent and efferent connections, which may be accompanied by extracerebellar signs such as ophthalmoplegia, pyramidal signs, movement disorders (including parkinsonism, dystonia, myoclonus, and chorea), dementia, epilepsy, visual disorders (including pigmentary retinopathy), lower motor neuron disease, and peripheral neuropathy. There have been many excellent reviews on ADCAs but the most recent reviews are by Durr [21] and Teive [5].

**Harding’s classification of ADCAs**

Harding classified progressive neurodegenerative ADCAs into four basic types [22]:

- Type 1: ADCA with extracerebellar signs such as ophthalmoplegia, dementia, amyotrophy, and extrapyramidal signs.
- Type 2: ADCA with retinal degeneration and can be accompanied by other extracerebellar signs.
- Type 3: ADCA with “pure” cerebellar ataxia.
- Type 4: ADCA with deafness and myoclonus.

**Hyperkinetic movement disorders in ADCAs**

Chorea, dystonia and myoclonus are seen in patients with ADCA type 1, most commonly in SCA7, SCA17, and DRPLA but also in SCA1, 2, 3, especially in patients with an early-onset disease or in an advanced stage. These hyperkinetic movement disorders in SCA7, SCA17, and DRPLA resemble those of Huntington disease although cerebellar ataxia is a key feature in these diseases, and visual loss distinguishes SCA7 from others. Upper limb action tremor is frequently seen in patients with SCA2, SCA12, SCA21, and Japanese patients with SCA15 although less prominent tremor may be detected in other SCAs. Patients with SCA12 may show dystonia in addition to tremor. Isolated cases of SCA8, SCA10 and, SCA14, which belong to ADCA type 3, have been reported with dystonia. Chorea may also be a rare sign of SCA14. In SCA20, palatal tremor and myoclonus may be prominent features in some family.

**Genetic classification and nomenclature of ADCAs**

In Human Genome Organization (HUGO) database, the nomenclature of spinocerebellar ataxia (SCA) is reserved for ADCAs whose locus has been mapped; the number following “SCA” has been given primarily in the order of identification of the locus, hence SCA1 is the first one mapped. Currently, the number is up to 31, and specific genetic mutations have been identified in SCAs types 1–3, 5–8, 10–17, 27, and 31. For the remaining types – SCAs 4, 18–26, 28, 29 and 30 – the disease locus is defined but the genes and mutations associated with them have not been identified. While SCA9 and SCA24 were recessive ataxias and have been removed from the SCA group, dentatorubral pallidoluysian atrophy (DRPLA) is usually counted as a SCA. Mutations for SCAs 1–3, 6–8, 10, 12, 17, 31, and DRPLA involve short-tandem repeats (also known as microsatellite repeats), whereas SCAs 5, 11, 13–16, and 27 are caused by point mutations. SCA 16 has been identified as being identical to SC15. SCAs 29 and 15, and SCAs 22 and 19, may represent different allelic forms of the same gene [5, 21].

**Epidemiology of SCAs**

The prevalence of SCAs has been estimated as 1 to 5 per 100,000. SCA3 is the most common worldwide; SCAs 1, 2, 6, 7, and 8 have greatly varying prevalence depending on the ethnic background of the population [5, 21]. SCAs 12 and 17 are relatively
rare, and most patients with SCA12 have been seen in India. SCAs 10 and 31 are rare but may be the second most common SCA in the Latin America and Japan, respectively. SCAs 4, 5, 11, 13–15, 18–23, and 25–30 are very rare.

Clinical and genetic diagnosis of SCAs

Diagnosing specific SCA types based on clinical findings alone is a difficult task. There are some useful clues for clinically diagnosing some of these SCAs. However, they are often overlapping with each other, and neither the specificity nor the sensitivity of these findings can accurately determine the SCA type. Genotype determination by DNA testing offers accurate and economical diagnosis when the result is positive. The DNA testing may identify SCA types in ~60% of patients with an autosomal dominant family history and ~5% of patients with no family history. Table 18.2 summarizes core clinical features, genetic loci, mutations, and proteins of SCAs. Readers may wish to examine the clinical diagnostic algorithms (Box 18.1) [23].

Some supplemental information is described below.

Clinical and genetic characteristics SCAs

See Table 18.1.

**Box 18.1 ALGORITHM FOR ASSESSING PATIENTS WITH SPINOCEREBELLAR ATAXIA (SCA):**

I – AUTOSOMAL DOMINANT CEREBELLAR ATAXIA + SPECIFIC CLINICAL DATA (A to Q):

A- EPISODIC ATAXIA (EA): EA1,2,3,4,5,6 and 7.
E- MYOCLONUS + CHOREA + DEMENTIA: DRPLA and SCA17.
F- OCULOMOTOR SIGNS: GO TO PART II – SCA1,2,3.
I- HEAD TREMOR: SCA12 and 16.
K- PERIPHERAL NEUROPATHY: SCA2,3,4,10,18,24, and 25.
O- POSTURAL TEMOR + DYSKINESIAS: SCA17.
Q- PURE CEREBELLAR ATAXIA: SCA 5,6,8,10,11,12,14, 16,22,23,26,30 and 31.

II – OCULOMOTOR SIGNS (R, S, and T):

R- NYSTAGMUS + HYPERMETRIC SACCADIES (Associated to pyramidal signs): SCA type 1.
S- SLOWED SACCADIC EYE MOVEMENTS + HYPOREFLEXIA: SCA type 2.

DRPLA = Dentatorubral-Pallidoluysian Atrophy.

**Video 18.3 SCA2 ataxia**

This video shows two patients with SCA2 (expanded CAG trinucleotide repeat in the ataxin-2 gene). The finger-to-nose maneuver reveals dysmetria and trunk instability. Ocular movements are slowed in all directions. Gait is wide-based with instability and tandem gait is not possible without holding the handrail. [Video courtesy of Alberto Albanese, MD, Milan, Italy]

**Video 18.4 SCA3 ataxia**

The phenomenology of ataxia is shown in this patient affected by SCA3. He sits in a chair as is unable to walk or stand autonomously. The following features are illustrated: mixed scanning and spastic dysarthria, abnormal finger-to-nose and heel-to-toe, intention tremor, dystrophic finger chase, slowing of pronation-supination alternating movements.
Neuroimaging studies
Neuroimaging, particularly magnetic resonance imaging, reveals cerebellar atrophy (Figure 18.2), with or without brainstem involvement, roughly corresponding to Harding’s classification. Cerebral cortical atrophy may be seen in cases in which dementia is a part of the SCA phenotype.

Pathogenic mechanisms of ADCAs
ADCAs caused by expanded polyglutamine-coding CAG repeats
SCAs 1, 2, 3, 6, 7, and 17 and DRPLA are known as polyglutamine expansion diseases and share some clinical, histopathological and molecular features with each other and with Huntington disease, which is also caused by an expansion of a CAG repeat encoding a polyglutamine repeat (“polyQ”) tract. The CAG repeat size inversely correlates with the age of onset and generally correlates with the severity of the disease. Expanded mutant alleles are mostly unstable with tendency to further expand in successive generations, causing anticipation, i.e. the progressively earlier onset with increasingly severe disease in successive generations in affected families. Existing evidence suggests that the mutant protein product containing an expanded polyglutamine tract causes neurodegeneration by a gain of toxic function [24].

ADCA caused by expansion or insertion of non-coding short tandem repeats
A second group of SCAs, which includes SCAs 8, 10, 12, and 31, is caused by an expansion of a non-coding microsatellite repeat [21, 25]. Clinical and genetic characteristics of these SCAs are summarized in Table 18.2. SCA8, 10, and 31 cause the disease by producing toxic RNA with expanded untranslated CTG and ATTCT repeats transcribed from their respective genes, although the pathogenic mechanism of SCA8 may also involve the polyglutamine tract expansion derived from the complementary strand (see GeneReview). In addition to ataxia, SCA8 may be associated with myoclonus and migraine headaches [25A]. In SCA12, an expansion of 5’UTR CAG appears to deregulate the activity of protein phosphatase 2 (PP2), an enzyme that has an important function in Purkinje cells.

ADCA caused by point mutations
This group of SCAs (SCA5, 11, 13, 14, 15, and 27) involves changes in the amino acid composition of
the following proteins: βIII spectrin in SCA5, tau tubulin kinase (TTBK2) in SCA11, potassium channels (KCN3) in SCA13, protein kinase C gamma (PRKCG) in SCA14, inositol 1,4,5-triphosphate receptor, type 1 (ITPR1) in SCA15, and fibroblast growth factor 14 (FGF14) in SCA27. Most, if not all, of these diseases are caused by a loss-of-function of the respective genes [21].

**Hereditary episodic ataxias**

Hereditary episodic ataxias (EAs) are characterized by recurrent episodes of ataxia and vertigo, as well as progressive CA. To date, seven forms of EA have been identified, the most common been type 1 (EA1) and type 2 (EA2), which are both secondary to genetic mutations coding for membrane proteins that constitute ion channels and transporters. Clinically, EAs are characterized by childhood-onset episodes of ataxia, lasting from seconds to minutes, triggered by physical exertion and stress, and interictal myokymia. EA2 is an allelic disorder of familial hemiplegic migraine type 1 and SCA6, which are all caused by mutations in the \( CACNA1A \) gene. EA2 is characterized by episodes of ataxia (lasting hours to days), and interictal nystagmus, with childhood or adolescence onset [26].

**X-Linked ataxias**

The most clinically relevant and common form is the fragile X/tremor/ataxia syndrome (FXTAS) described by Hagerman in 2001 [27]. The syndrome occurs predominantly in males, over 50 years of age, and is characterized by the presence of action tremor with prominent kinetic component, cerebellar ataxia, cognitive dysfunction, and occasionally parkinsonism and autonomic dysfunction. MRI shows increased T2 signal intensity in the middle cerebellar peduncles in the majority of patients. FXTAS is caused by intermediate expansions (between 50 and ~200 repeats) of a CGG trinucleotide in the fragile X mental retardation 1 (\( FMR1 \)) gene, the same gene that causes fragile X syndrome [27].

**Mitochondrial ataxias**

Mitochondrial ataxias usually combine cerebellar and sensory ataxia, among other features, due to abnormalities of the mitochondrial DNA. They are maternally inherited ataxias due to point mutations in genes coding for RNAs, respiratory chain subunits, or deletions/duplications of the mitochondrial DNA. This group includes myoclonic epilepsy associated with ragged-red fibers (MERRF), neuropathy, ataxia and retinitis pigmentosa (NARP), KSS, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), infantile-onset spinocerebellar ataxia (IOSCA), and mitochondrial recessive ataxia syndrome (MIRAS). MIRAS is caused by the mutation in the mitochondrial DNA polymerase gamma (POLG) [28].

**Sporadic ataxias**

Sporadic ataxias with adult onset represent a challenging group of acquired ataxias and idiopathic degenerative ataxias. Autosomal recessive, X-linked, and mitochondrial ataxias may be presented as sporadic cases. Even in autosomal dominant ataxias, non-paternity, unrecognized adoption, reduced penetrance and de novo mutation may result in apparent sporadic cases. About 5% of adult-onset ataxias without positive family history may have positive genetic testing for one of the SCAs. Conversely, phenocopies have been found when an individual with ataxia shows a negative genetic testing while his/her affected family members have documented SCA by genetic testing. Among acquired ataxias, there are rare but treatable causes, which should not be missed.

**Acquired ataxias**

Among the acquired or secondary cerebellar ataxias, it should be stressed that neuroimaging studies, especially using MRI, are of capital importance in defining focal lesions of the cerebellum and its connections, including neoplastic, inflammatory, demyelinating, and vascular disorders. Hypothyroidism and Hashimoto encephalopathy
Inherited and Sporadic Ataxias

(with elevated serum thyroperoxidase antibodies), drugs, such as alcohol (alcoholic cerebellar degeneration) [28A], chemotherapeutic agents (fluorocytosine arabinoside sp?), phenytoin, mercury, lead, thallium, lithium, solvents, several infectious disorders (HIV associated ataxia, mumps virus, infectious mononucleosis virus – Epstein-Barr virus – syphilis, Lyme disease, Whipple disease) and dietary deficiency of vitamins, such as thiamine, tocopherol, and B12 can cause cerebellar, or sensory ataxia should be considered [1].

Miller Fisher syndrome, a Guillain-Barré syndrome variant and paraneoplastic cerebellar degeneration (PCD) are immune-mediated cerebellar disorders. In PCD there are several types of autoantibodies directed against neuronal antigens, the most common being anti-Yo (PCA–1), associated with breast and gynecological cancer; anti-Hu (ANNA–1) associated with small-cell lung cancer, and anti-Tr (Hodgkin’s lymphoma), among others. Antibodies against glutamic acid decarboxylase (GAD), which are originally described in patients with stiff-person syndrome but may also be found in insulin-dependent diabetes mellitus and thyroid diseases. Also antigliadin antibodies have been associated with ataxia and celiac disease [28B]. Anti-GAD ataxia, Miller Fisher syndrome, and PCD are variably responsive to intravenous immunoglobulins and steroids. Gluten ataxia, in which the antigliadin antibody is positive in 100% of the patients, responds to gluten-free diet. Finally, prion diseases, such as Creutzfeldt–Jakob disease (sporadic or hereditary), Gerstmann–Sträussler–Scheinker (familial), fatal familial insomnia, and variant Creutzfeldt–Jakob disease also cause cerebellar ataxia [1].

**Non-genetic degenerative ataxias**

Idiopathic cerebellar degeneration includes a group of disorders of unknown etiology, such as MSA-C and SAOA. In a series of 112 sporadic ataxia patients from Germany, 29% had MSA-C, 58% had SAOA, while FA and SCAs (SCA1, 3, and 6) were found respectively in 4 and 9%. In Japan, a population-based epidemiological study of sporadic ataxias showed that OPCA is the most common form (64.7%) [28C]. In Brazil, in a follow-up study of 15 years with 55 patients, 64% had SAOA and the remaining 36% were diagnosed with MSA-C, SCAs, FA, and acquired ataxias [1, 5, 29].

**Multiple system atrophy (MSA)**

MSA is a sporadic and progressive neurodegenerative disease characterized by parkinsonism, cerebellar ataxia, and autonomic failure [29]. There is no etiology known and neuropathologically MSA is a sinucleinopathy, with the presence of argyrophilic filamentous glial cytoplasmic inclusions (GCIs). In most Western populations, the clinical picture showed a predominance of parkinsonian features (defined as MSA-P) whereas the remaining MSA patients had cerebellar ataxia as the main motor disorder (defined as MSA-C). However, in Japan, there is a predominance of MSA-C (83.8%).

**Sporadic adult-onset cerebellar ataxia (SAOA)**

The original definition of SAOA is a non-hereditary degenerative adult-onset (after 20 years of age) ataxia disorder distinct from MSA. Clinically, however, most patients with SAOA exhibit slowly progressive pure cerebellar ataxia, with onset after the age of 50 years although subtle non-cerebellar signs, such as chorea, pyramidal, and sensory signs, can be found. Thus, in practice, SAOA resembles a disorder previously known as cerebello-olivary degeneration or pure cerebello-olivary degeneration of Marie, Foix, and Alajouanine. The diagnosis is one of exclusion, after acquired/secondary, genetic ataxias and MSA have been investigated [1].

**Sporadic olivopontocerebellar atrophy (sporadic OPCA)**

The nomenclature of OPCA is confusing [29A]. The diagnosis of OPCA has been used for some of the genetic ataxias while it has also been given to patients with MSA-C. However, as MSA-C and SAOA has become relatively well-defined entities, the diagnosis of Sporadic OPCA may be given to patients with sporadic cerebellar ataxia associated with prominent clinical extracerebellar features and atrophy of the cerebellum and brainstem on imag-
ing studies in the absence of autonomic failure or parkinsonism. However, the original definition of SAOA includes such a disorder. Furthermore, some of these patients may turn out to have MSA-C as they develop autonomic failure later in the course of the disease. It should be noted that genetic OPCA largely overlaps with the SCAs of the ADCA type 1 phenotype although some recessive and X-linked disorders have also been classified as OPCA [1].

References

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PART 7
Other Hyperkinetic Disorders
CHAPTER 19

Dyskinesias in Parkinsonian Syndromes

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Introduction

Dyskinesia is an involuntary hyperkinetic movement disorder that includes chorea, dystonia, tics, myoclonus, stereotypies, and mixed movements with both choreic and dystonic components, termed choreoathetosis [1]. In rare instances, the movements can be large amplitude and ballistic in character. This chapter will discuss the variety of dyskinesias associated with primary or idiopathic Parkinson disease (PD) as these types of involuntary movements are much less likely to be encountered in secondary or atypical forms of parkinsonism. Dyskinesias may occur as a feature of the underlying disease or as an effect of drug treatment for the disease. The chapter is organized to deal with PD first and to discuss dyskinesias that occur as part of PD itself and then to discuss the larger topic of dyskinesias encountered in the context of drug treatment. The second part of the chapter will address the other parkinsonian syndromes, again dealing first with dyskinesias seen as part of the core disease and second the dyskinesias that can develop during drug treatment. Chapter 20 focuses on drug-induced dyskinesia in non-Parkinsonian patients treated with antipsychotic or dopamine receptor blocking medications.

Parkinsonism is a hypokinetic movement disorder, consisting of at least two of the following four signs: rigidity, bradykinesia, tremor, postural instability. By far, the most common cause of primary parkinsonism is PD which is usually characterized by an asymmetric onset of parkinsonism and a slow progression of disability over many years. Patients with PD typically have a good response to levodopa and other dopaminergic drugs, but often develop drug-associated dyskinesias after years of treatment. Whereas these dyskinesias were formerly known as Levodopa-Induced Dyskinesias or LID, dyskinesias can occur with dopamine agonists as well and can be exacerbated by agents such as monoamine oxidase inhibitors or catechol-O-methyl transferase inhibitors (COMTI) when used with levodopa. Although the term “LID” is still historically used by some authors to cover all dyskinesias associated with any dopaminergic agent, the terminology for these dyskinesias that will be used throughout this chapter will be “dopaminergic drug-associated dyskinesias.”

It is important to recognize the different forms of dyskinesias in parkinsonian disorders, because the different forms require different treatment strategies. Further, some forms of dyskinesia are more typical of the non-PD parkinsonian syndromes than PD, and the presence of these special forms of dyskinesia may help in establishing a solid diagnosis. The pathophysiology of dyskinesias likely differs
among the different parkinsonian syndromes, and treatment strategies need to be tailored to the type of dyskinesia and the underlying parkinsonian syndrome.

**Parkinson disease**

**Dyskinesia as a manifestation of PD**

Dystonia may appear in early, untreated PD. In young patients, foot dystonia is particularly common. In this case, the foot cramps and the usual dystonic posture is foot inversion with hyperextension of the big toe [2]. Some patients develop calf spasms with minor foot twisting in the early morning before or immediately after rising from bed. The involved dystonic foot is on the same side of the predominant parkinsonian signs of bradykinesia, tremor and rigidity [3]. Some patients experience additional or isolated exercise induced dystonia, also called kinesiogenic foot dystonia. Whereas foot dystonia is often present in the context of other demonstrable parkinsonian signs, sometimes the foot cramping develops months or even years prior to the onset of other motor symptoms [4]. Since idiopathic dystonia in adults usually affects the head, neck, or upper extremities, a presentation of leg dystonia in an adult should raise the suspicion for early PD [3].

**Dopaminergic drug-associated dyskinesia in PD**

As PD progresses, brain dopamine levels decline, and dopamine cells become markedly reduced in quantity. Consequently, patients become more dependent on exogenous dopamine and its smooth delivery for normal motor function [5]. Motor fluctuations or an irregular response to medication over a given medication cycle include wearing-off of benefit near the end of a drug cycle and drug-induced dyskinesia. With wearing off, patients find that they alternate between periods of good response to medicine with little PD related disability called the ON state, and periods when symptoms of parkinsonism return, called OFF state. Dyskinesias can occur in both ON or OFF states, as described below.

**Phenomenology of dopaminergic drug-associated dyskinesias in PD**

Peak-dose dyskinesia occurs when dopaminergic activity levels are high and when patients are experiencing good clinical benefit from levodopa. This type of dyskinesia is usually stereotypic or choreic (random, flowing, dance-like movements), although it can be dystonic, or a combination of chorea and dystonia during the high-peak phase. As such, lip-smacking, neck jerking, and random movements of the extremities are highly typical of the choreic dyskinesias at peak dose, whereas neck twisting of a more sustained nature (torticollis) or foot inversion may occur as dystonic forms of peak-dose dyskinesia. These movements occur at rest, but are exacerbated by mental stress, speaking, and some voluntary movements. Peak-dose dyskinesia tends to affect the upper body, and usually is most marked on the side of the body more affected by PD symptoms (Figure 19.1).

Diphasic dyskinesia occurs when dopaminergic drug activity is rising or descending relative to the peak medication effect. These movements typically involve lower extremities and trunk, and may coexist with mild OFF symptoms (parkinsonism), because the patient is in a transition phase between full ON and full OFF. As such, patients with diphasic dyskinesia often complain of movements immediately after taking the dose of dopaminergic drug and at the very end of the dose cycle. In

**Video 19.1 Peak dose dyskinesia**

This man has peak dose dyskinesia. There are involuntary choreic movements of his hands, neck, and legs at rest. Movements are present on both sides, but are more marked on his right side.

between these two periods, the same patient often has peak-dose dyskinesia, but the movements switch from trunk and leg distribution of diphasic dyskinesias to head, shoulder and upper extremities during the peak-dose abnormal movements.

**OFF dyskinesia** occurs when levodopa or other dopaminergic activity is low. This type of dyskinesia is usually dystonic, and affects the foot of the more affected side, often causing painful toe extension [6].

**Run-away dyskinesias after neurotransplantation.** A particular form of dyskinesia has also been reported after fetal mesencephalic cell transplantation, and this topic is discussed later in the chapter.

**Dyskinesias in Parkinsonian Syndromes**

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![Diagram showing dyskinesias and levodopa levels](image)

**Figure 19.1** Type of dyskinesia varies in relationship to timing of dopaminergic medicine.

**Table 19.1** Clinical characteristics of dopaminergic drug-associated dyskinesia in Parkinson disease.

<table>
<thead>
<tr>
<th>Type</th>
<th>Distribution</th>
<th>Movement</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levodopa induced dyskinesia</td>
<td>Upper body</td>
<td>Stereotypy &gt; chorea &gt; dystonia</td>
<td>Peak-dose effect when parkinsonism is maximally treated</td>
</tr>
<tr>
<td>Diphasic dyskinesia</td>
<td>Lower body</td>
<td>Flinging leg and truncal jerking</td>
<td>Beginning and end of dose cycle when patient is in between ON and OFF</td>
</tr>
<tr>
<td>Off dystonia</td>
<td>Foot</td>
<td>Dystonic</td>
<td>End of dose or before first morning dose: Patient is OFF and parkinsonian</td>
</tr>
</tbody>
</table>

**Video 19.2 Diphasic dyskinesia**

In the first half of this video the patient is ON with peak dose dyskinesia, characterized by involuntary movements of her arms and face. In the second half of the video she is at the end of her dopaminergic dose cycle. She has marked lower extremity movements consistent with diphasic dyskinesia.

Risk factors for dyskinesia include age at PD onset, PD severity, levodopa dose, and duration of treatment. Because several of these risk factors are linked, the relative importance of individual factors, such as the influence of PD severity and duration versus levodopa dose and treatment duration, have been disputed. Evidence that disease severity, not levodopa dose or treatment duration, is most important comes from observations that patients with a long duration of untreated disease have a short latency to onset of dopaminergic drug-associated dyskinesias [7].

Other evidence for the role of disease severity comes from the observation that time to onset of dyskinesia is related to stage of disease. In one study, patients with early PD (stage I) had a median time to dopaminergic drug-associated dyskinesias of 66 months compared to more advanced patients (stage III) who developed dyskinesias after 14 months of treatment [8]. Younger patients are more likely to develop dopaminergic drug-associated dyskinesias than elderly PD subjects [9, 10]. After 5 years of drug treatment, dyskinesia occurs in 50% of patients with PD onset at age 40–59, compared with only 16% of PD patients whose disease onset occurred after age 70 [11].

Women are more likely to develop dyskinesias during the course of the disease than men [12]. Specific hormonal influences have not been studied, and the influence of menstrual fluctuations, hormone replacement therapy and menopause remain undefined. One study suggests that estrogen replacement in postmenopausal women lessens dyskinesia [13]. Whereas most dopaminergic drug-associated dyskinesias are increased by movement, excitement, and stress, no studies have focused on interventions related to altering these environmental factors.

Clinical impact

The clinical impact of dyskinesia is variable. When mild, dyskinesia may be unnoticed by patients [14]. When more marked, it can adversely impact activities of daily living and cause spilling, imbalance and falls. Additionally, dyskinesias can lead to fatigue, pain, and clinically pertinent social isolation. In spite of disabling dyskinesias, however, most patients prefer to be ON even with severe dyskinesia rather than to be OFF and experiencing parkinsonian symptoms [14]. Quality of life studies have confirmed these clinical observations, so that when dyskinesia is mild and non-disabling, it is not generally associated with reduced quality of life [15]. However, when it is more severe or painful,
Dyskinesias in Parkinsonian Syndromes

Dyskinesia is associated with poor quality of life and increased cost of care [16]. Many clinicians underdose dopaminergic medicine out of fear of inducing dyskinesias, but when those patients are compared to patients with adequate benefit from levodopa even with dyskinesia, the later group has better quality of life scores [17]. One study showed that while 59% of patients have dyskinesia after 10 years of drug treatment, less than half of the dyskinetic patients required medication adjustment to reduce dyskinesias [18].

Rating scales

Dopaminergic drug-associated dyskinesia is notoriously difficult to measure. Several different approaches have been used to quantify dyskinesia. Clinical rating scales aim to estimate the severity of dyskinesia based on examiner observations. However, many scales are of limited clinical utility because they only capture certain aspects of dyskinesia, and therefore lack sensitivity [19]. For example, individual scales focus on either the intensity, anatomical distribution, phenomenology, or disability, but do not provide an accurate measure of the diversity of dyskinetic movements. The new version of the Unified Parkinson Disease Rating Scale, developed by the Movement Disorder Society (MDS-UPDRS), includes several items designed to capture levodopa-related motor complications [20]. Recently, the Unified Dyskinesia Rating Scale (UDysRS) has been designed to assess and quantify the diverse nature of dyskinetic movements and to incorporate patient perceptions of disability from dyskinesia [21].

Patients’ self evaluation diaries are sometimes used in clinical studies to record the amount of time that dyskinesia is present during the day. Because this methodology relies on patient’s self report, some have challenged the accuracy of these diary-based tools. However, accuracy can be improved with patient training, and data from these diaries are accepted by the Food and Drug Administration (FDA) as a clinical end point [22].

In addition to clinical rating scales, objective measures are used to help quantify dyskinesia. The goal of objective measures is to provide unbiased, sensitive ways to quantitate dyskinesia. Several techniques have been studied, including, analysis of digitized spiral drawings [23], use of accelerometers [24], force transducers [25]. These measures can be cumbersome, carry the risk of including tremor movements within the dyskinesia registration, and may fail to accurately capture the complicated phenomenology and variability of dyskinesia. If small and portable, however, they may have the advantage of collecting data over long epochs and even 24 hours [26].

Pathophysiology

More than dopamine

The development and persistence of dyskinesia depends on a variety of pathophysiological changes at several levels in the dopaminergic and cortico-subcortical pathways. Dyskinesia is not solely a hyperdopaminergic phenomenon; instead, a combination of effects likely occurs related to an increase in synaptic dopamine, changes in cortico-subcortical loops, the underlying dopaminergic deinnervation of PD, and a progressive development of intermittent rather than continuous dopaminergic stimulation. Together, these alterations cause downstream changes in gene/protein expression in postsynaptic cells [6]. Nigral degeneration is required for the occurrence of dyskinesia. Patients on chronic levodopa therapy for dopa responsive dystonia, as well as normal controls exposed to levodopa, do not develop dyskinesia [6]. The occurrence of dyskinesia is not a simple reflection of dopaminergic levels being too high, as increasing doses of levodopa prolong dyskinesia duration, but do not change the quality of the ON state or severity of dyskinesia [27, 28].

Dopamine transporter changes

Early in PD, the expression of the dopamine transporter (DAT) is down-regulated as a result of loss of nigrostriatal terminals and as a compensatory mechanism for low presynaptic dopamine. This
allows the synaptic dopamine to stay in the synapse longer. PET (positron emission tomography) studies of DAT show that patients with dyskinesia have a lower ratio of DAT to dopaminergic nerve terminals than patients without dyskinesia [29]. This finding suggests that patients with the most robust compensatory mechanisms are the most likely to develop dyskinesia. Other PET studies show that patients with dopaminergic drug associated dyskinesias have greater change in synaptic dopamine release in response to levodopa than patients without dyskinesia [30]. Whereas synaptic levels of dopamine are not higher in dyskinetic patients compared to nondyskinetic subjects, this observation suggests that dyskinetic patients have a larger change in dopamine levels induced by levodopa.

Animal models show an upregulation of the D3 receptor in dopaminergic drug associated dyskinesia [31]. Whereas D3 antagonists cause parkinsonism, a D3 partial agonist, reduced dyskinesia without worsening parkinsonism in a primate model of PD [32].

Non-dopaminergic influences
A large body of evidence suggests that other neurotransmitter systems besides dopaminergic function are important to the development of dyskinesia. Multiple neurotransmitter systems have been implicated, such as changes in N-methyl-D-aspartic acid (NMDA) and (α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate (AMPA) glutamergic receptors, adenosine, and opiate receptors. The glutamatergic system, in particular the NMDA receptor, has been the focus of antidyskinetic drug development, since the most effective antidyskinetic drug to date, amantadine, likely acts by antagonizing the NMDA receptor [33]. Alterations in the A2a adenosine receptor and opiate receptors have been well described, but to date pharmacological modification of these receptors have not improved dyskinesia [34, 35].

Brain derived neurotropic factor (BDNF) has a role in synaptic plasticity, and has a modulatory effect on D1, D3, NMDA, and γ-Aminobutyric acid (GABA)ergic receptors. A common BDNF polymorphism (vall66met) has been associated with LID [36]. Patients who are homozygous for this polymorphism developed LID earlier in the course of dopaminergic treatment for PD.

Differing mechanisms for different dyskinesias
Several pharmacological observations suggest that distinct mechanisms may be at play in different types of dyskinesia. For instance, histamine H3 agonists reduce peak dose dyskinesia but not dystonia, cannabinoid CB1 agonists reduce diphasic dyskinesia of an antiparkinsonian dose of levodopa, but not peak-dose dyskinesia, while α-2 adrenergic antagonists reduce dopaminergic drug associated peak-dose dyskinesia but not dystinesia elicited by apomorphine [37]. These differences suggest that antidyndyskinetic drugs may need to be tailored to the type of dyskinesia that most disables any individual patient (Figure 19.2).

Treatment
The most important aspect of treating dopaminergic drug-associated dyskinesia is correct recognition of the type of dyskinesia (timing in relationship to medicine), as different treatment approaches are required for each type of dyskinesia.

Painful OFF-period dystonia can improve with the same therapeutic measures used for motor fluctuations when the therapeutic emphasis is the reduction of OFF time. Examples include changes in the dosage or in the frequency of administration of levodopa preparations, the addition of oral dopamine agonists, the adjunctive treatment with COMT inhibitors [38] and monoamine oxidase (MAO)-B inhibitors (selegiline, rasagiline) [39] are common therapeutic approaches to reduce OFF time. Sustained release levodopa given at bedtime may be useful to treat nocturnal akinesia and early-morning dystonia [40]. In some cases, the injections of botulinum toxin may alleviate prolonged painful foot dystonia [41]. Subcutaneous injections of apomorphine may also be used to treat sudden, unexpected off period dystonia [42].

The first step in treating peak-dose dyskinesias is to reduce individual levodopa doses temporally associated with dyskinesia. Reduction of the
amount of an individual dose, however, may decrease the duration of clinical benefit and can result in more severe OFF periods. As a result, patients with peak-dose dyskinesias typically need more frequent levodopa doses in order to maintain ON time without prominent dyskinesia. Peak-dose dyskinesia can often be lessened by changing sustained release levodopa to standard levodopa. The sustained release formulation often causes a cumulative effect such that dyskinesia peaks late in the day, after several doses. Similarly, treatment of peak-dose dyskinesia may require discontinuation of COMT or MAO-B inhibitors.

Diphasic dyskinesia are the most difficult to treat. Higher individual doses of levodopa, may be of benefit [43].

**Antidyskinetic drugs**

Amantadine is a glutamate antagonist that is active at NMDA receptors and has shown antidyskinetic effects in patients with PD. Small, randomized, placebo-controlled studies performed in parkinsonian patients with motor fluctuations and dyskinesias have documented that oral amantadine reduces dyskinesia severity and decreases the percentage of time patients experience dyskinesias, without reducing ON time [44–46]. Amantadine is commonly used at doses of 200 to 300 mg/day. Elderly patients, or those with reduced renal function are particularly susceptible to the side effects which include: confusion, worsening of hallucinations, edema of the feet and livedo reticularis. Amantadine is currently the only drug considered efficacious in the treatment of dyskinesia by evidence-based review techniques [47]. Its antidyskinetic effect in PD gives support to the glutamatergic hypothesis as a pathogenic mechanism of dopaminergic drug-associated dyskinesias.

Clozapine has been reported to reduce the severity of dyskinesia in some open studies and in one randomized, double-blind, parallel-group, placebo-controlled multicenter study. In the latter [48],

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**Figure 19.2** Treatment algorithm for different types of dyskinesia in Parkinson disease.
50 parkinsonian patients were treated with a mean dose of 39 mg/day of clozapine for 10 weeks. The mean daily ON time without dyskinesias increased 1.7 hours. Potential adverse effects of clozapine are agranulocytosis (white cell count monitoring is needed), somnolence, seizures, myocarditis, and orthostatic hypotension. At present, there is insufficient evidence to support or refute the efficacy of clozapine in reducing LID [49].

A variety of other drugs have been reported to reduce LID but lack evidence from double-blind, randomized, controlled trials. These drugs include: dextromethorphan, riluzole, istradefylline, memantine, remacemide, and propranolol [50]. Sarizotan, a dopamine agonist that also binds to 5-hydroxytryptamine1A receptors, showed promise in early studies, but two large studies failed to demonstrate antidyskinetic properties [51].

**Stereotactic surgery**

Pallidotomy was the first major surgical target intervention for dyskinesias. Unilateral pallidotomy reduces dyskinesia severity by 75% in the contralateral limbs [52], and a mean increase of 2.8 hours in daily ON time without dyskinesias [53]. Bilateral pallidotomy often results in side effects such as dysarthria, dysphagia, cognitive changes, and falls. Therefore deep brain stimulation surgery (DBS) has largely replaced lesion therapies in the treatment of PD.

Bilateral DBS of the subthalamic nucleus (STN) is currently the most commonly performed surgical procedure in patients with PD and severe motor complications that include dyskinesias [54]. Reviews of the large number of uncontrolled studies and the few randomized, double-blind crossover trials [55] have found that bilateral DBS of STN increases ON time without dyskinesias, reduces OFF time, and improves all clinical patterns of dyskinesias (OFF period dystonia, peak-dose and diphasic dyskinesias). In addition, DBS of STN allows a reduction in antiparkinsonian medication, which in part may contribute to dyskinesias improvement. The average reduction in dyskinesias severity following surgery is estimated to be 70% [56]. Further, the clinical motor improvement, including reduction of dyskinesias, induced by bilateral DBS of STN may last up to 5 years [57, 58].

Bilateral stimulation of the internal globus pallidus (GPI) has been explored as a treatment for LID. There was an overall improvement of dyskinesia severity by 41 to 87% [59] with a significant increase in ON time without dyskinesias [60]. A recent multi-center study showed similar efficacy of STN DBS when compared to GPI DBS for the treatment of PD [61].

The mechanism of action by which each surgical target reduces dyskinesia is likely to be quite different. STN DBS allows for about at 50% reduction in levodopa dose, and this dose reduction is thought to account for the reduction in dyskinesia. In contrast, patients who undergo GPI DBS do not have a significant reduction in levodopa dose post operatively, but still have a reduction in dyskinesia. This improvement appears to be due to direct antidyskinetic effects of GPI stimulation [58, 60].

Adverse effects related to DBS of STN include intracranial hemorrhage that can appear in 4% of patients and infections in 1.5%. Device malfunction, migration, and fracture of leads are also reported, and other side effects directly related to the stimulation such as dysarthria, diplopia, paresthesias, weight gain, and psychiatric and cognitive symptoms can occur [62].

**Runaway dyskinesia after transplantation**

Dyskinesia has proven not only to be a troublesome side effect of drug treatment in advanced PD, but to be a severe complication of fetal nigral transplantation for PD.

Dyskinetic movements developed in 50% of patients who received transplants. They occurred in both the ON and OFF states. ON dyskinesias were choreic, while OFF dyskinesias affected the lower extremities, suggesting its mechanism may be similar to that of diphasic dyskinesia. Patients who were most sensitive to levodopa’s beneficial and adverse effects preoperatively, were the most likely to develop this post transplant OFF-dyskinesia [63].
Based on electrophysiological recordings, the pathophysiology of post-transplantation dyskinesias is likely to differ from that of dopaminergic drug-associated dyskinesia under normal conditions; firing rates in the GPi decrease in the ON state, and with dyskinesia. However, in patients with post-transplant OFF dyskinesia, firing rates were not reduced and were typical of a PD patient in the OFF state [64]. Therapeutically, DBS of the GPi, but not STN has been effective at treating these dyskinesias [65].

**Non-PD parkinsonian syndromes**

**Dyskinesia as part of the primary parkinsonian syndrome**

Cervical dystonia, specifically anterocollis, is considered a clinical hallmark of multiple system atrophy (MSA). The exact etiology of this abnormal posture is not fully understood, although it probably represents a combination of dystonia and rigidity rather than extensor myopathy [66, 67]. In a cohort of clinically diagnosed MSA patients, as many as 46% had dystonia prior to the onset of treatment, most commonly limb dystonia or anterocollis [68]. Tongue movements have occasionally been observed in untreated MSA as well [69].

Dystonia is also a common feature of untreated progressive supranuclear palsy (PSP). In a retrospective study of clinically diagnosed PSP patients, 46% had dystonia during their illness: 27% limb, 24% blepharospasm, 17% retrocollis. Limb dystonia often occurs early in the disease and is either hemidystonia, or involves a single limb (usually arm). Patients who present with arm dystonia, may be mistaken for corticobasal degeneration (CBD), and indeed a minority in the study had coexistent CBD or vascular pathology at autopsy. Retrocollis is the most commonly reported and recognized dystonic feature of PSP. Some argue, however, that the neck rigidity and retrocollic posture do not represent dystonia, as the neck is not mobile, and lacks a sensory trick or other features typical of dystonia. Blepharospasm, a focal dystonia causing involuntary eye closure, is usually a late disease manifestation of PSP [70]. About half of patients with blepharospasm have coexistent apraxia of eyelid opening. Blepharospasm can render a patient functionally blind, but should not go unrecognized, as it often treatable.

Dystonia and myoclonus occur commonly in CBD. In this disorder, limb dystonia usually involves one upper extremity and over time leads to a painful, fisted hand that can eventually develop contractures. In one published series, more than half of the patients developed dystonia [71].

**Dyskinesia in association with drug treatment in non-PD parkinsonism**

By definition, atypical parkinsonian disorders have a minimal or an unsustained clinical improvement with dopaminergic treatment. As such, in late disease, most patients with these disorders (PSP, MSA, CBD) are either not treated with dopaminergic medication doses or only receive small daily doses. In the early and mid-phases of the diseases, however, clinicians may prescribe high doses of these drugs in order to maximize a clinical response. In this instance, drug-associated dyskinesia can develop. For instance, while anterocollis can be a manifestation of untreated MSA, it may also occur in response to treatment. Several authors have reported patients who developed anterocollis after treatment with a dopamine agonist that resolved after stopping the drug [72]. Most drug-induced dyskinesia in MSA is confined to face, lips, and neck [68]. Drug-induced dyskinesia can also occur in patients with PSP, and there are rare reports of oromandibular dystonia induced by levodopa, which resolved off levodopa [73].

**Future perspectives**

Certainly, more pharmacological treatments are needed that can reduce dyskinesia severity without worsening parkinsonism. There are several reasons why such drug discovery has remained elusive. First, the underlying mechanism of dyskinesia likely involves multiple interconnected subcortical pathways, and neurochemical substrates. Second, dyskinesia is notoriously difficult to quantify, and more refined measurement tools may allow for better efficacy documentation. As such, considerable research...
is currently targeted at developing more sensitive and reliable measures of dyskinesia. Lastly, recent research has shown a placebo-induced improvement in dyskinesia during double-blind placebo controlled trials. Therefore, open-label studies of antidyasekinetic drugs often produce misleadingly positive results, as was the case with sarizotan [74, 75].

Recent PD research has focused non-motor symptoms such as autonomic dysfunction, cognitive and behavioral changes. Some of the behavioral changes associated with chronic dopaminergic drugs include dopamine dysregulation disorder and punding. Punding describes purposeless, repetitive behaviors such as arranging or disassembling and reassembling objects. There is some evidence that some of these behavioral changes may be comorbid with dyskinesia, and may share some of the same underlying pathophysiology. Patients with punding have more severe dyskinesia than those without punding, and the severity of punding correlated with severity of dyskinesia, even after controlling for medication dose [76]. It is expected that a better understanding of both the behavioral and motor changes in advanced PD will lead to new treatments for PD.

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Chapter 19


CHAPTER 20

Restless Legs Syndrome

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Historical background

Restless legs syndrome (RLS), formerly termed Ekbom syndrome, is a sensorimotor disorder first described by Thomas Willis in the 17th century [1]. Initially thought to be a form of neurosis, in 1923, Oppenheim suggested the condition could be a genetic neurological disorder [2]. In 1945 Ekbom coined the term “Restless Legs” and reported the findings of a large number of patients in a doctoral thesis entitled “Restless legs: a clinical study of a hitherto overlooked disease in the legs characterized by peculiar paresthesias and occurring in two main forms, asthenia crurum paraesthetic and asthenia crurum dolorosa” [3]. In his publication he described previously published similar cases by Wittmack in 1861, Bing in 1913, Code and Allen in 1936 and Allison in 1943 when various descriptive terms were used such as anxietas tibiarum and leg jitters [3]) Prior to his use of the term “Restless Legs,” Ekbom himself had previously used the term “irritable legs” [4]. In 1974 Karl Ekbom Jr and K.A. Ekbom reported a previously overlooked case of restless legs syndrome described by Magnus Huss in Huss’s extensive writings on chronic alcoholism, published in 1849 [5].

In 1979 and 1990 The Diagnostic Classification Steering Committee of the American Association of Sleep Medicine developed RLS diagnostic criteria. The criteria were published in two respective versions of the International Classification of Sleep Disorders: Diagnostic and Coding Manual (ICSD) In the early 1990s a group of interested physicians and researchers formed the International RLS Study Group (IRLSSG), which published the original consensus definition of RLS in 1995 [6]. In 2003 the definition was updated for better clarity [7]. Although all of the important clinical features of RLS were documented by Ekbom, except for “Nocturnal Myoclonus” later termed “Periodic Limb Movements in Sleep” [8], he did not make an attempt to divide the clinical features into essential and non-essential criteria. Neither the 1979 nor the 1990 version of the ICSD listed all four of the current minimal criteria as essential. In addition, the 1979 and 1990 versions included some criteria as essential that are currently considered non-essential. The 2003 definition by the International RLS Study Group was soon adopted by the new ICSD in 2005 [7]. This updated definition has been universally accepted and a severity scale that was validated by the IRLSSG in 2003 was instrumental in the development of FDA-approved medications for RLS [7, 9].

Clinical features

RLS typically involves the lower limbs but can involve the upper limbs, trunk, and occasionally the face. If sensory symptoms are present, which is true in the majority of cases, patients describe the sensory sensations by various terms and phrases.
such as ants crawling in my legs, heebie jeebies, painful, etc. The symptoms are experienced as coming from deep within the legs and not as superficial [3]. Large parts of the calves, thighs, or both are usually affected [3]. Although this description is typical of familial/idiopathic RLS, we have observed that RLS associated with peripheral neuropathy or radiculopathy may not always follow this pattern and may involve smaller parts of the thighs or calves and may sometimes be felt as superficial rather than deep. The onset of discomfort follows a circadian pattern with discomfort beginning or worsening in the evening or just before bedtime and resolving or absent in the morning. With increasing severity, sensations may lose the circadian pattern and occur earlier in the day [9, 10].

In patients older than 12 years of age, the diagnosis of RLS requires the presence of four essential features [7]: (1) an urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs; (2) the urge to move, or the unpleasant sensations, may begin or worsen during periods of rest or inactivity such as lying or sitting; (3) the urge to move, or the unpleasant sensations, may be partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues; and (4) the urge to move, or the unpleasant sensations, may worsen, or only occur in the evening or night. When the diagnosis is questionable, the presence of supportive clinical features may resolve uncertainty. Supportive clinical features include: positive family history of RLS, a positive therapeutic effect to very low doses of dopaminergic medications, and periodic limb movements [7]. When the diagnosis is in doubt, associated features are also helpful when confirming the diagnosis. Features associated with RLS include:

1. The natural clinical history. When the onset of RLS occurs in patients under 50 years, the onset is often insidious. In patients older than 50 years, symptoms often occur abruptly.
2. Sleep disturbance.
3. The medical evaluation/physical examination. The physical examination is generally normal and does not contribute to the diagnosis except for those cases where RLS may be co-morbid with other conditions, i.e. peripheral neuropathy or radiculopathy [7] (Box 20.1).

A periodic limb movement is defined as a limb movement of at least 0.5 second duration and a maximum duration of 10 seconds. In addition, Periodic Limb Movements require the occurrence of a minimum series of four limb movements with a period of between 5 and 90 seconds. In addition, limb movements must be associated with an increase in electromyogram (EMG) amplitude of a minimum of 8 μV above the baseline EMG (Figure 20.1) [12]. Nearly 90% of patients with RLS have periodic limb movements during sleep with two nights of polysomnographic recording [13]. Periodic limb movements (PLMs) can occur during sleep and wakefulness. PLMs occurring during wakefulness are strongly associated with RLS.

If the patient is cognitively impaired, RLS cannot be definitively diagnosed. The patient is diagnosed with "probable RLS" in the presence of five criteria: (1) signs of leg discomfort such as rubbing or kneading the legs and groaning while holding the lower extremities; (2) excessive motor activity in the lower extremities such as pacing, fidgeting, repetitive kicking, tossing, and turning in bed, slapping the legs on the mattress, cycling movements, foot tapping, rubbing the feet together, and an inability to remain seated; (3) signs of leg discomfort are exclusively present or worsen during periods of rest or inactivity; (4) signs of leg discomfort decrease with activity; and (5) criteria (1) or (2) occur only in the evening or night or are more severe than during the day [7] (Box 20.1).
Children 2 to 12 years of age can be diagnosed with RLS when all four adult criteria are present and the child relates a description in his or her own words that is consistent with leg discomfort. If the child meets all four adult criteria but is unable to describe the symptoms in his/her own words, the child must have at least two of the following: a sleep disturbance greater than expected for his or her age, immediate biological relative with RLS, or a periodic limb movement index of five or more during sleep documented by polysomnography [7]. As in the case of adults, when the essential diagnostic criteria cannot be clearly identified in children, supportive criteria can be useful and definitions for probable and possible RLS in children have been defined [7] (Box 20.1).

Restless legs syndrome (RLS) is classified as either primary or secondary. RLS is classified as primary if a precipitating medical illness, neurological disorder or medication side effect cannot be identified and is considered secondary if such an association can be identified. Although primary RLS can occur sporadically, is most probably genetic when it occurs at a young age, and there is a family history of RLS.

Secondary RLS is associated with an underlying medical disorder, neurological abnormality, or medication side effect (1) Any medical condition associated with iron deficiency can precipitate secondary RLS (2) Peripheral neuropathy and radiculopathy are in the differential diagnosis of RLS but they may also occur with RLS (3) Use of antidepressant medications, such as selective serotonin reuptake inhibitors (SSRIs), may also aggravate and sometimes be the sole apparent cause of RLS (4) RLS occurs in pregnancy but disappears after delivery (5) RLS can be more frequently comorbid with fibromyalgia, diabetes, uremia, rheumatoid arthritis, multiple sclerosis, hypertension, heart disease,
attention deficit hyperactivity disorder, anxiety, and depression [7]. In the case of the more frequent association of anxiety or depression with RLS, we assume that the reverse is true – i.e. the RLS leads to anxiety and depression, and not vice versa.

Restless legs syndrome must be differentiated from conditions that mimic RLS as certain conditions unrelated to RLS may occasionally satisfy all RLS diagnostic criteria. As an example, patients with leg cramps or positional leg discomfort may meet all four RLS diagnostic criteria but do not have RLS [14] (Box 20.2) In leg cramps the legs go into an actual spasm that is usually brief and relieved by dorsiflexion of the foot on the floor. This is not true of RLS patients even if they complain of a cramp-like sensation, as is sometimes the case. In positional discomfort, e.g. due to pain from hip discomfort, the pain may be localized to a small area and relieved by a brief simple shift of position. This is quite different from idiopathic RLS where large parts of the thighs, calves, or both are usually involved. RLS is different from both positional discomfort and leg cramps in that walking or other activities to relieve leg discomfort is more prolonged in RLS. Restlessness related to habit or anxiety may mimic RLS but is less likely to be worse at night.

**Box 20.2 RLS Mimics**
- Positional discomfort
- Restlessness related to habit or anxiety
- Leg cramps
- Local leg injury
- Arthritis

**Figure 20.1** Periodic Limb Movements. A limb movement of at least 0.5 second duration and a maximum duration of 10 seconds, requires the occurrence of a minimum series of four limb movements with an intermovement interval between 5 and 90 seconds. Limb movements must be associated with an increase in electromyograph (EMG) amplitude of a minimum of 8μV above the baseline EMG.
Peripheral neuropathy and radiculopathy are in the differential diagnosis of RLS if the patient does not meet the criteria for RLS. If a patient with peripheral neuropathy or radiculopathy meets the diagnostic criteria for RLS, the patient is considered to have RLS associated with peripheral neuropathy or radiculopathy. Sleep transitional movements, which includes hypnic jerks, are in the differential diagnosis of the periodic movements during wakefulness that is sometimes seen in RLS.

Epidemiology

In 1945 Ekbom reported a 5.2% prevalence of RLS in a study population of Swedish subjects. Prevalence was slightly higher among women [2]. In 2002, Ohayon and Roth studied the prevalence of Periodic Limb Movement Disorder (PLMD) and RLS in 18,980 subjects from 15 to 100 years of age living in five countries: United Kingdom, Germany, Italy, Portugal, and Spain. Using specific diagnostic criteria from the International Classification of Sleep Disorders: Diagnostic and Coding Manual (1990 edition), the researchers found a prevalence of 5.5% for RLS and 3.9% for PLMD [15]. Högl et al. reported a prevalence of RLS among residences of Bruneck, an “entirely white” Italian population. In this community-based study of subjects 50–89 years of age the prevalence of RLS was 10.6% and more than twice as frequent in women compared to men [16].

In a study by Tison and colleagues of 10,000 French subjects, among all subjects, RLS had a prevalence of 8.5%. The prevalence was 10.8% among women [17]. Previously the prevalence of RLS among African-Americans was thought to be rare but a recent study suggests that it the same as the prevalence among Caucasians [18]. In Asian countries the prevalence of RLS is 1–2%. In 2000, Rothdach et al. studied the prevalence of RLS among German subjects 65–83 years of age. The prevalence of RLS was 6.1% among men and 13.9% among women [19]. The prevalence of clinically significant RLS, defined as symptoms occurring at least twice per week that are moderate or severely distressing, is 2.7% [20]. The prevalence of RLS decreases in older men but remains stable in older women.

Hypertension, heart disease, and stroke

RLS may be associated with an increase prevalence of stroke [21]. It has been shown that PLMs are a manifestation of sympathetic activation. Heightened sympathetic activity is associated with elevations in pulse rate and blood pressure. Changes in sympathetic activation occurring in RLS and associated PLMs may be a risk factor for stroke [21].

The relationship of RLS to hypertension is unclear. Some researchers report a relationship between RLS and hypertension [21]. Högl did not find a relationship between RLS and hypertension [16]. Studies by Winkelman demonstrate an association between RLS and cardiovascular disease but not hypertension [22, 23]. A review of the Wisconsin Sleep Cohort study by Winkelman et al. found that persons with daily RLS symptoms were more likely to have a history of cardiovascular disease [22]. This finding was confirmed in a later study by Winkelman et al. using the International RLS Study Group diagnostic criteria for RLS [23].
Childhood restless legs syndrome and attention deficit hyperactivity disorder

Brenning performed the first study documenting a relationship between childhood “growing pains and RLS-like symptoms” [24]. The Peds REST study examined the prevalence and impact of restless legs syndrome in children using data collected from 10,523 families. Moderate or severe RLS occurred in 0.5% of children 8–11 years of age and 1.0% in children 12–17 years of age [25]. Eighty percent of children with RLS in this study presented with growing pains [25].

Attention deficit hyperactivity disorder (ADHD) occurs more commonly in children and adults with RLS and vice versa. Kotagal and Silber reported that 8 of 25 children with RLS demonstrated inattentiveness [26]. In 2005 Cortese et al. reported that up to 44% of children with ADHD have RLS or symptoms of RLS [27]. Zak et al. studied 30 adults with ADHD and found a 20% prevalence of RLS [28].

Iron deficiency

Secondary RLS (symptomatic RLS) has been linked to conditions causing iron deficiency such as pregnancy and blood donation [29, 30].

Gastrointestinal disease

RLS has been linked to gastrointestinal disease. In 2009, Weinstock et al. studied 85 patients with celiac disease. The incidence of RLS among patients with celiac disease was 35% and prevalence was 25% [31]. Restless Legs Syndrome has been described as an extra-intestinal manifestation of Crohn’s disease. In a multicenter study of 272 subjects from outpatient gastrointestinal clinics the incidence of RLS in patients with Crohn’s disease was 43% (93 of 218 patients) The prevalence of RLS in patients with Crohn’s disease was 30% (82 of 272 patients) [32].

End stage renal disease (ESRD)

Studies estimate the prevalence of RLS among dialysis patient from 6.6 to 21.5%. Nearly 20% of dialysis patients discontinue dialysis due to RLS symptoms [33].

Etiology

Genetics

The etiology of RLS is unknown but primary RLS is thought to be genetic. Linkage studies in RLS families identified eight loci: chromosomes 12q (RLS1), 14q (RLS2), 9p (RLS3), 20p (RLS4), 2q (RLS5), 4q, 17p, and 19p [34]. In 2007 genome-wide association studies completed by two different groups of researchers identified a common variant in an intron of BTBD9 on chromosome 6p [35, 36]. In addition, Winkelman et al. identified genomic regions: MEIS1 on chromosome 2p and a region on chromosome 15q containing MAP2K5 and LBX1C1 [36]. The MEIS1 gene is believed to be related to limb development [37]. Schormair et al. identified an association between RLS and protein tyrosine phosphatase receptor type delta (PTPRD) at 9p23–24 [38]. A gene promoter region favoring monoamine oxidase A activity, which would cause more rapid elimination of dopamine from the synapse, is associated with RLS in women but not men [39]. This latter observation is consistent with the hypodopaminergic hypotheses of RLS and the observation that RLS is more common in women than men.

Pathophysiology

Iron and dopamine

The pathophysiology of RLS is unknown but appears to involve the central nervous system metabolism of iron, the neurotransmitter dopamine (DA), and genetic factors. There is up regulation of tyrosine hydroxylase and down regulation of D2 receptors [40].

Ultrasound studies demonstrate hypoechogenicity in the substantia nigra of patients with RLS consistent with decreased iron content [41]. Using a special MRI measurement (R2) to assess brain iron content, Allen et al. found a significant decrease in brain iron within the substantia nigra, and a somewhat less significant reduction in the putamen, both in proportion to RLS severity [42]. This may indicate iron deficiency.

As to iron metabolism, iron is stored in the body by ferritin and transported within the body by
transferrin. Transferrin is manufactured in the liver and brain. Peripheral transferrin does not cross the blood–brain barrier. When CSF levels of iron, ferritin, and transferrin of patients with RLS are compared to normal controls, patients with RLS have lower CSF ferritin and iron levels and higher transferrin levels [42–44]. When symptoms occur in patients 45 years of age and younger, there is a correlation between the age of symptom onset and ferritin level. The earlier the age of onset, the lower the ferritin level [45].

Iron is essential to the production and utilization of DA. Iron is a cofactor to tyrosine hydroxylase, the rate-limiting enzyme in the transformation of tyrosine to levodopa. Levodopa is a precursor to dopamine. It is possible that defective acquisition or utilization of iron within brain cells leads to dopamine deficits in patients with RLS. Researchers, studying the neuropathological changes of 7 brains from individuals with RLS and 5 age-matched controls without RLS, found a reduction in iron and H-ferritin staining in the substantia nigra. Cells staining for L-ferritin were morphologically different from the cells of the controls. Transferrin receptor staining on neuromelanin-containing cells was decreased in the RLS brains compared to normal. The researchers concluded that RLS may be a functional disorder secondary to impaired iron acquisition by neuromelanin cells [46].

Several researchers posit that a diencephalospinal pathway is involved in RLS. The diencephalospinal pathway originates in the A11 dopaminergic cell group of the hypothalamus and terminates in the intermediolateral cell column of the spinal cord. The intermediolateral cells of the spinal cord are also innervated by excitatory neurons descending from the serotonergic dorsal raphe. When dopamine is reduced, sympathetic tone is increased because of the relative increase of serotonergic activation. One hypothesis is that this leads to over stimulation of skeletal muscles and irritation of muscle spindles. The increased input to the muscle spindle would lead to increased activation of nearby sensory fibers which project to the spinal cord. The nociceptive input to the spinal cord would then be referred to the cortex where it might be perceived as the abnormal sensations associated with RLS [21].

**Endogenous opioid system**

We have recently completed a preliminary autopsy study of RLS patients showing decrements in the endogenous opioids beta-endorphin and metenkephalin in the thalamus of RLS patients versus controls suggesting that hypofunctioning of the endogenous opioids system may be pathogenetic to RLS [47].

**Immunity and inflammation**

Most recently we have noted that RLS patients have an increased prevalence of Irritable Bowel Syndrome (IBS) and an increased prevalence of Small Intestinal Bacterial Overgrowth (SIBO) compared to controls [48]. This led us to review the 40 or so secondary causes of RLS. Independent of RLS, the vast majority of these secondary causes are associated with either iron deficiency, SIBO, or inflammatory/immune abnormalities. This suggests that inflammation and immune attacks on the peripheral or central nervous system in RLS could be pathogenetic to RLS [48]. An alternate explanation is that inflammation may lead to iron deficiency which may in turn lead to RLS.

There is a significant association between RLS and multiple sclerosis (MS) In a study of 164 patients with MS, 19% had symptoms of RLS at least twice per week. It is hypothesized that inflammatory damage associated with MS may trigger RLS [49]. Interestingly, idiopathic RLS in the absence of MS or any other autoimmune disease responds to steroids under double-blind conditions [50] and RLS may undergo remissions just like MS [7, 8].

RLS has also been associated with rheumatoid arthritis. Salih et al. studied patients with osteoarthritis and rheumatoid arthritis. RLS was associated with rheumatoid arthritis but there was no significant association with osteoarthritis. The researchers posited that RLS was secondary to iron deficiency due to anemia of a chronic disease which occurs with rheumatoid arthritis but the autoimmunity associated with rheumatoid arthritis, and not osteoarthritis, is a possible pathogenic risk factor [51].

An overall approach to the management of RLS is listed in Box 20.3 and Figure 20.2.
Box 20.3  A Step Approach to the pharmacologic management of patients meeting RLS diagnostic criteria

Step 1. Classification of symptoms

Intermittent: Frequency of symptoms does not warrant daily medication. However, when present, symptoms are troublesome enough to justify treatment.

Daily: Symptoms occur more than 14 days per month

Refractory (Malignant RLS): Daily RLS treated with a dopamine agonist with one or more of the following outcomes:
1. Inadequate response to appropriate medication dosage
2. Loss of control of symptoms despite increasing amounts of medication
3. Presence of unacceptable adverse affects
4. Uncontrollable augmentation

Step 2. Review medications for drugs that contribute to RLS symptoms: antidepressants, neuroleptics agents, dopamine-blocking antiemetics, sedating antihistamine. Prudently consider discontinuation of medications that contribute to RLS symptoms.

Step 3. Identify co-morbid conditions that interfere with response to RLS therapy

1. Ferritin level less than 50ug/mL (investigate etiology)
2. Neuropathies (may benefit from gabapentin or pregabalin)
3. Renal disease (may respond to clonidine)

Step 4. Initiate nonpharmacologic therapy to all patients and simultaneously initiate pharmacological therapy

Step 5. Selection of pharmacologic agent

(A) Intermittent RLS

Ferritin level less than 50 ug/mL

Yes

Ferrous sulfate + Vitamin C

1. Look for etiology of low ferritin level
2. Continue iron therapy of three months then re-evaluate

Symptoms resolved

Yes

Nonpharmacologic strategies

No

Initiate one of the following:
1. Carbidopa/levodopa
2. DA
3. Low-potency opioids
4. Tramadol
5. Benzodiazepine
6. Anticonvulsant
7. Transcutaneous electrical nerve stimulation/pneumatic compression device
8. Valerian root

Figure 20.2 (cont’d).
(B) Daily RLS
Ferritin level less than 50 ug/mL

Yes

Ferrous sulfate + Vitamin C

No

1. Look for etiology of low ferritin level
2. Continue iron therapy of three months then re-evaluate
3. Simultaneously initiate additional therapy

Levodopa or dopamine agonists

Symptoms controlled

Yes

No

Continue therapy

Change to another DA

Symptoms controlled

Yes

No

Add or change to alternative therapy which includes: Gabapentin, Pregabalin, low-potency opiates, benzodiazepine

Symptoms controlled

Yes

No

Continue therapy

see Refractory RLS

Figure 20.2 (cont’d).
Combination therapy: DA plus one additional agent from one or two of the other classes of medications used to treat RLS:
1. Benzodiazepine
2. High potency opioid
3. Anticonvulsant

Symptoms controlled

Yes
Continue therapy

No
Trial of intravenous iron
Or change medication to methadone

Symptoms controlled

Yes
Continue therapy

No
Consider
1. Intrathecal morphine
2. Intravenous iron therapy

*Abrupt discontinuation of levodopa and DA is not recommended

Figure 20.2 (cont’d) (A) Intermittent RLS. For intermittent RLS medication is administered as needed usually 45 minutes before engaging in activities known to precipitate RLS such as long plane rides sitting down for extended periods of time such long plane flights going to the theater (B) Daily RLS (C) Refractory RLS. [Adapted from: Silber et al. (2004) An algorithm for the management of Restless Legs Syndrome. Mayo Clinic Proceedings, 79:916–22, with permission.]

Treatment

Non-pharmacologic strategies may resolve mild or intermittent symptoms and possibly reduce symptoms in other patients. All patients should be encouraged to use non-pharmacologic strategies. A non-pharmacologic approach includes: use of alerting mental activities such as games, crossword puzzles, or playing a musical instrument; abstinence from caffeine, nicotine, and alcohol; and, when medically possible, discontinuing medications known to exacerbate RLS symptoms such as certain antidepressants, neuroleptics, dopamine-blocking antiemetics, or sedating antihistamines [52]. For some individuals, working in the afternoon or night shift can be helpful when activity can suppress the symptoms at a time when the symptoms are most likely to occur.

The serum ferritin level should be evaluated in all patients with RLS. A serum ferritin level less than 50 micrograms/L is often associated with RLS symptoms and should be treated simultaneously with the initiation of more definitive therapy [53, 54]. We recommend ferrous sulfate 325 mg tid with Vitamin C 500 mg tid to aid absorption. The
etiology of iron deficiency should be investigated. Patients with neurologic findings of peripheral neuropathy or radiculopathy and symptoms of RLS should be evaluated by electromyography and nerve conduction studies [54].

Of the pharmacologic agents used to treat RLS, only pramipexole and ropinirole are approved by the United States Federal Drug Administration (FDA). All medications used to treat RLS should be started at the lowest dose and increased as needed to the maximum dose (see Table 20.1).

**Dopaminergics**

In 2004, the Standards of Practice Committee of The American Academy of Sleep Medicine published guidelines for the use of dopaminergics in the treatment of RLS. Levodopa with decarboxylase inhibitor, pramipexole and ropinirole are all effective treatments. The only FDA approved medications for treatment of RLS are the non-ergot dopamine agonists ropinirole and pramipexole [2]. We have reviewed the dopaminergic therapy of RLS elsewhere in detail [2].

The ergot dopamine agonists, bromocriptine and pergolide, are also effective but because of their association with pleuropulmonary fibrosis and cardiac valvulopathy, are no longer recommended.

Rotigotine is a non-ergot dopamine receptor agonist with strong affinity to D3, D2, and D1 receptors and lesser affinity to D5 and D4 receptors [55]. Previously available in the United States as a silicon transdermal patch, Rotigotine effectively reduced RLS symptoms. Due to problems with crystallization, Rotigotine is currently unavailable in the United States but is available in Europe.

Ropinirole should be started at 0.25 mg administered 1–3 hours before bedtime or 90–120 minutes before the onset of symptoms. Ropinirole can be increased by 0.5 mg every 7 days as needed to a maximum dose of 4 mg per day. The therapeutic range is 0.25 mg to 4 mg per day. The mean dose is 2 mg per day. Syncpe, sometimes associated with bradycardia, hypotension, and hallucinations, are reported side effects [56].

Pramipexole should be started at 0.125 mg. If symptoms are not controlled in 4–7 days, pramipexole can be increased to 0.25 mg after 4–7 days and increased to 0.5 mg after an additional 4–7 days if needed. The usual prescribed dose is 0.5 mg per day but we have used doses up to 3 mg/day in divided dosages over the evening time [57].

Levodopa/carbidopa, has a relatively short half-life and, as such, may be used to control mild symptoms that occur only in association with prolonged sitting or intermittently. The routine night-time dosing of levodopa/carbidopa, however, should be avoided as it can lead to gradual loss of efficacy and augmentation and rebound (see below).

Cabergoline is an ergot-derived long-acting D2 agonist seldom used in the United States due to cost and side effects. In a meta-analysis of randomized clinical trials of dopaminergic agents (DA) used to treat RLS, Zintzaras et al. reported that cabergoline and pergolide had greater efficacy than non-ergot dopaminergics [58].

All dopaminergics are potentially associated with augmentation and rebound. Augmentation is defined by the presence of an increase in the frequency or severity of symptoms, slightly earlier onset of symptoms or the onset of symptoms in previously uninvolved body areas, but the earlier onset of symptoms is the key feature [59]. Augmentation is associated with daily administration of levodopa or administration of 300 mg per day or more. Augmentation occurs less often with dopamine agonists than L-Dopa but is still a significant clinical problem with dopamine agonists. Rebound is a withdrawal symptom and occurs when the medication is wearing off at a time that is compatible with the half-life of the drug. Rebound may lead to the emergence of symptoms during early morning hours after the administration of night-time medications [60]. Rebound must be distinguished from augmentation because treatment of these phenomena differs. In augmentation the symptoms appear at a time incompatible with the half-life of the drug when medications are long out of the blood stream. For example, if symptoms previously began at 6 pm and were treated at 5 pm with a dopaminergic agent with a 6 hour half-life, the symptoms may start to begin at 4 pm as a side effect of the drug itself. With mild augmentation an earlier dose of medication may sometimes be helpful. However, with recurrent augmentation the medication should be reduced or
discontinued. Rebound can be treated by increasing the medication dosage at bedtime or changing to an extended release form of medication.

**Table 20.1** Behavioral manifestations of dopamine dysregulation syndrome in RLS patients.

<table>
<thead>
<tr>
<th>Behavior*</th>
<th>Definition</th>
<th>Diagnostic Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compulsive gambling (Pathological gambling)</td>
<td>The presence of five or more of the following in a persistent and recurrent maladaptive behavior:</td>
<td>DSM IV</td>
</tr>
<tr>
<td></td>
<td>1. Preoccupation with gambling</td>
<td></td>
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<td></td>
<td>2. to maintain level of excitement, gambles with increasing amounts of money</td>
<td></td>
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<td></td>
<td>3. repeated unsuccessful attempts to control, reduce or stop gambling</td>
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<td></td>
<td>4. attempts to reduce or stop gambling are associated with restlessness or irritability</td>
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<td></td>
<td>5. uses gambling to escape from problems or to elevate mood</td>
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<tr>
<td></td>
<td>6. attempts to recoup gambling losses by returning on another day to get even</td>
<td></td>
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<tr>
<td></td>
<td>7. conceals extent of gambling</td>
<td></td>
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<tr>
<td></td>
<td>8. engages in illegal acts such as forgery, fraud, theft or embezzlement to finance gambling</td>
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<td></td>
<td>9. risk loosing or has lost a significant relationship, job or educational or career opportunity due to gambling</td>
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<tr>
<td></td>
<td>10. depends on others for money to elevate dire financial problems caused by gambling</td>
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</tr>
<tr>
<td>Hypersexuality (Sexual Dysfunction)</td>
<td>Disturbance in the processes of one or more of the phases of the sexual response cycle (desire, excitement, orgasm, resolutions) or by pain associated with sexual intercourse.</td>
<td>DSM IV</td>
</tr>
<tr>
<td>Punding</td>
<td>Complex prolonged, purposeless stereotyped behavior associated with central stimulants. Often involves repetitive handling of objects.</td>
<td>Rylander</td>
</tr>
<tr>
<td>Drug hoarding</td>
<td>Fear of discarding something useful or that may become useful in the future</td>
<td>Winsberg et al.</td>
</tr>
<tr>
<td>Shopping</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traveling</td>
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</tbody>
</table>

*Patients may develop more than one type of impulsive behavior.

**Dopamine dysregulation syndrome**

Dopamine dysregulation syndrome (DDS), also known as hedonistic homeostatic dysregulation, is an iatrogenic neurobehavioral disorder thought to be secondary to excessive stimulation of the central dopamine reward pathway [61]. Behaviors observed in DDS are similar to behaviors observed in patients who abuse central stimulants such as amphetamines and cocaine. Behaviors associated with DDS include pathological gambling, shopping, hyperphagia, traveling, punding, and hypersexuality (see Table 20.1).

DDS is thought to be secondary to excessive stimulation of the central dopamine reward system [63]. DDS has been reported in patients treated with pramipexole, ropinirole, pergolide, bromocriptine, and levodopa monotherapy [61–66]. Initially thought to only occur in association with large doses of dopaminergic agents such as those used to treat Parkinson disease [61], DDS has been reported in patients taking low doses of levodopa and dopaminergic agents to control RLS symptoms. In 2007, Quickfall et al. and Tippman-Beikert et al. reported the onset of compulsive gambling in 4 RLS...
patients treated with pramipexole (0.125 to 0.75 mg/day) and ropinirole (0.5 mg/day) [65, 66]. In 2010, Kolla et al. reported two additional cases of new onset compulsive behavior disorder in 2 patients with RLS treated with dopamine agonists. One patient experienced hypersexuality and the other case was complicated by the patient’s suicide attempt due to an inability to control gambling [67]. Salas et al. reported the onset of drug hoarding as an atypical manifestation of DDS in a patient with RLS [68]. Increased shopping and traveling around the country were reported by Ondo and Lai [69].

**Punding**

“Punding” is a term coined by Rylander to describe the automatic behaviors associated with high doses of central stimulant drugs [70]. Punding is complex, prolonged, purposeless stereotyped behavior first observed in chronic amphetamine users. Rylander observed that the behavior is generally something that the patient is accustomed to doing or something that the patient enjoys. Examples of punding behavior include manipulation of technical equipment such as radios or engines, repetitive cleaning of a room or object, and excessive attention to personal hygiene [70]. Initially reported as a side effect in patients taking high doses of amphetamines, punding has been reported in patients taking dopaminergic agents. In 2009, Evan et al. described punding in a 65-year-old female with RLS and a familial history of RLS. The patient was initially prescribed pergolide 0.10 mg per night. Over a period of 6 years the medication was increased to 1.5 mg three times per day. Approximately 6 months after starting pergolide the patient voluntarily terminated employment and began gambling. She later developed hypersexuality and punding. Punding behavior consisted of spending many hours attending to her garden, painting her house, often the same room multiple times, and engaging in aimless repetitive cleaning such as polishing furniture more often than necessary. The dose of pergolide was reduced and the patient was given a trial of cabergoline to no avail. Punding, hypersexuality, and gambling stopped abruptly with the discontinuation of all dopaminergic agents [71].

DDS is treated by decreasing the dosage or discontinuing dopamine or dopamine agonists. Therapy is then continued with off label medications.

**Iron therapy**

The most common cause of secondary RLS is iron deficiency [29, 30]. Any condition associated with iron deficiency may trigger RLS symptoms in patients predisposed to RLS. Serum ferritin and iron levels should be evaluated in all patients with RLS. Unless iron is contraindicated for other reasons, patients with a ferritin level less than 50 mcg/L should be given supplemental iron [41]. We recommend 325 mg of ferrous sulfate administered orally with 500 mg of vitamin C three times per day for three months. Ferritin and iron levels should be determined again after three months of therapy. An attempt to determine the etiology of iron deficiency is indicated. Oral iron therapy will not work immediately and is dependent on raising iron stores. Because iron crosses the blood brain barrier poorly this may take a few months and for severe patients concomitant therapy with medications is recommended.

Intravenous iron therapy may be helpful in patients with refractory RLS who are unable to tolerate oral iron. After intravenous administration of high molecular weight iron dextran, Ondo noted improvement in patients with refractory RLS symptoms. The clinical effect of intravenous iron is delayed by approximately three days. Intravenous iron must be given with caution due to the risk of anaphylaxis [72] (Box 20.4).

**Second line treatments**

**Opioids**

The opioid oxycodone decreased RLS symptoms and PLMs in a double-blind study [76]. Opioids are effective long-term therapy [77]. The mechanism of opioid effectiveness in RLS is thought to be opiate receptor specific as the opiate receptor blocker naloxone reverses the therapeutic benefit of the opioids [78]. Methadone has been used for refractory RLS and in patients unable to tolerate dopaminergics [79]. In addition to its effect upon the mu opiate receptor subtype, methadone uniquely antagonizes N-methyl-D-aspartate
Box 20.4 Pharmacologic agents for treatment of RLS

<table>
<thead>
<tr>
<th>Classification and Name of medication</th>
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<tbody>
<tr>
<td><strong>Dopaminergic agents</strong></td>
</tr>
<tr>
<td>Ropinirole</td>
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<tr>
<td>Pramipexole</td>
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<tr>
<td>Levodopa/carbidopa</td>
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<tr>
<td>Cabergoline</td>
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<tr>
<td>Rotigotine</td>
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<tr>
<td>Bromocriptine</td>
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<td>Pergolide</td>
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<tr>
<td><strong>Opioids</strong></td>
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<tr>
<td>Codeine</td>
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<tr>
<td>Hydrocodone</td>
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<tr>
<td>Methadone</td>
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<tr>
<td>Oxycodone</td>
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<tr>
<td>Oxycodone XR</td>
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<tr>
<td>Propoxyphene</td>
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<tr>
<td>Tramadol</td>
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<tr>
<td>Morphine (Intrathecal)</td>
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<tr>
<td><strong>Anticonvulsants</strong></td>
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<tr>
<td>Gabapentin</td>
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<tr>
<td>Pregabalin</td>
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<tr>
<td>Lamotrigine</td>
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<tr>
<td><strong>Antihypertensives</strong></td>
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<tr>
<td>Clonidine</td>
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<tr>
<td><strong>Herbal Preparations</strong></td>
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<tr>
<td>Valerian</td>
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<tr>
<td><strong>Minerals and Supplements</strong></td>
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<tr>
<td>Iron (oral)</td>
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<tr>
<td>Iron (intravenous)</td>
</tr>
<tr>
<td>Magnesium</td>
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<tr>
<td><strong>Antihypertensives</strong></td>
</tr>
<tr>
<td>Clonidine</td>
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<tr>
<td><strong>Herbal Preparations</strong></td>
</tr>
<tr>
<td>Valerian</td>
</tr>
<tr>
<td>Only ropinirole and pramipexole are FDA approved for treatment of RLS</td>
</tr>
</tbody>
</table>

Benzodiazepines

Long-acting benzodiazepines, such as clonazepam, reduce RLS symptoms and frequency of periodic limb movements and promote sleep because of their hypnosedative properties [85]. Short-acting benzodiazepines (such as triazolam) or intermediate acting benzodiazepines (such as temazepam) are less likely to be effective [86]. There are reports of benzodiazepines precipitating sleep apnea. Benzodiazepines, taken in low to moderate doses, have sustained efficacy with low risk for adverse effects, dosage escalation or abuse in sleep disorder patients without a previous history of addiction [87].

Third line treatment

Clonidine

Clonidine is a centrally acting alpha adrenergic agonist. Clonidine 0.1–0.3 mg at bedtime can be used to reduce sleep latency. Clonidine relieves the leg discomfort of RLS but does not reduce periodic limb movements [88].

Alternative therapies

Herbal therapy

When allopathic therapies do not relieve symptoms, 67% of patients with RLS try complementary and alternative medical therapies (CAM) [89]. In a blinded pilot study of 48 patients with RLS, Cuellar reported that RLS symptom severity decreased and sleep quality improved in patients given 800 mg of Valerian an hour before bedtime for 8 weeks. Valerian is thought to be a safe herbal product associated with few side effects. Reported side effects include gastrointestinal disturbances, fatigue/mental sluggishness, vivid dreams, agitation/restlessness, headache, dizziness, and rash [90].

Acupuncture

In 2007 Cui et al., reviewed the Cochrane Central Register of Controlled Trials, Medline, EMBASE, several Chinese databases and a Korean database for evidence of effectiveness of acupuncture for RLS (91) There is limited data on the use of the various acupuncture methods in the treatment of RLS. The authors found case reports and small studies that support effectiveness of acupuncture.
for RLS, but no reports of acupuncture being more effective than allopathic therapy including FDA-approved medications. They concluded “there is insufficient evidence to support the hypothesis that acupuncture is more effective in the treatment of RLS than no treatment or other therapies. There are insufficient well-designed randomized controlled trials and the safety of acupuncture methods for RLS is unknown” [70]. In 2009 Stanislao et al. reported the results of a retrospective case study of 30 Italian adults with RLS. Most had some benefit, and some had relief of symptoms for up to 6 months after 10–12 acupuncture sessions [92].

The effectiveness of acupuncture is complex because there are several methods of acupuncture. Methods of acupuncture include body acupuncture, auricular acupuncture, scalp acupuncture, electro-acupuncture, laser acupuncture, acupressure, and acupoint injection therapy, which is the injection of medication into acupoints.

**Transcutaneous electrical nerve stimulation**

In 1990, Krueger reported that transcutaneous electric nerve stimulation may be beneficial [93]. There is, however, limited literature on treating RLS with transcutaneous electric nerve stimulation.

**Enhanced external counter pulsation**

Enhanced external counter pulsation (EECP) increases collateral circulation to the legs and other body parts and has been used in the treatment of angina. In an open label study, 6 patients with RLS were treated with EECP [94]. Changes in severity of RLS symptoms were measured by the International RLS Study Group severity scale. The patients’ score on the severity scale decreased and EECP appeared to be a promising treatment. The open label study was followed by a parallel double-blind placebo-controlled study with long-term subjective follow-up for 6 months. EECP did not show long-term improvement of RLS symptoms [95].

**Spinal cord stimulation**

For more than 40 years, spinal cord stimulation (SCS) has been a therapeutic option for treatment of chronic pain [96]. SCS alleviates or reduces pain associated with a variety of pain syndromes including failed-back syndrome, neuropathic pain, radiculopathic pain, phantom limb and ischemic leg pain [97]. There is limited information available regarding the use of SCS for RLS. Jakobsson and Ruuth reported failure of SCS to improve RLS symptoms in a 52-year-old woman with refractory RLS [73].

**Deep brain stimulation (DBS) and pallidotomy**

In 1999, Rye reported a patient with RLS and PD who experienced resolution of RLS symptoms after pallidotomy for severe symptoms of Parkinson disease [98]. Okun et al. described eliminating RLS symptoms in a patient with dystonia and comorbid RLS after bilateral internal segment of the globus pallidus (GPI) deep brain stimulation (DBS) [99]. In a study by Ondo, involving patients with essential tremor and RLS, stimulation of the ventralis intermedius nucleus (VIM) of the thalamus did not improve the RLS symptoms [100].

In 2004 Kedin et al. reported the emergence of RLS in 11 patients with Parkinson disease treated by subthalamic DBS and a reduction in dopaminergic therapy. The authors concluded that their unmasking of the RLS symptoms was due to a reduction in dopaminergic medications [101]. A similar study by Driver-Dunckley et al. reported contradicting results. They found an improvement in RLS symptoms post-subthalamic stimulation, and attributed the positive benefit to a slower taper of dopaminergic therapy, a longer post-operative period of observation and different programming parameters of the stimulators [102].

**Infrared light**

Mitchell et al. evaluated the effectiveness of monochromatic near-infrared light treatment in decreasing RLS symptoms. Thirty-four subjects with RLS were randomly assigned to one of two groups: infrared therapy or sham therapy. The legs were exposed to infrared lights or sham lights for 20 minutes. Therapy was given at the same time on Monday, Wednesday, and Friday. If a subject missed a session, the session was made up on another day of the week. Response to therapy was monitored...
by the RLS severity rating scale developed by the International Restless Legs Syndrome Study Group. Subjects treated by infrared therapy showed significant improvement compared to subjects receiving sham therapy [103].

Supplements and vitamins

Magnesium
In 1998 Hornyak reported findings from an open trial study of 10 patients with RLS and or PLM. Patients were administered 12.4 mmol (approximately 300 mg) magnesium each evening for 4–6 weeks. Polysomnography documented a reduction in PLMs and patients reported improvement in RLS symptoms [104]. Magnesium decreases smooth muscle contraction and dilates blood vessels [105]. Walters et al. measured total serum and CSF magnesium levels in patients with RLS and controls. There was no statistical significant difference between patients and controls for either serum or CSF magnesium [106].

Folate
Botez et al. described 3 patients with RLS and folate deficiency whose RLS symptoms improved after treatment with folate [107] According to Lee et al. a reduction in folate may be associated with RLS symptoms during pregnancy [108].

Antibiotic treatment
RLS patients with comorbid celiac disease and irritable bowel syndrome (IBS) may have a reduction in symptoms after treatment with antibiotics. In a study by Weinstock, 10 of 13 patients with RLS and IBS treatment with 10 days of rifaximin had a reduction in RLS symptoms [109]. Weinstock et al. propose two hypotheses regarding the relationship between chronic gastrointestinal infections and RLS. One hypothesis is that RLS may be caused by an immunologic mechanism precipitated by infection. An alternative hypothesis is that SIBO is a chronic infection associated with poor gastrointestinal iron uptake [31]. Volunteers given bacterial lipopolysaccharides, develop elevated cytokine levels. Cytokines, such as interleukin-6, up-regulates hepcidin, a hormone produced by the liver that regulates iron absorption. Hepcidin induces degradation of ferroportin. Ferroportin is the only known mechanism for the export of intracellular non-heme-associated iron, and ferroportin and hepcidin are critical to iron homeostasis [110]. The degradation of ferroportin leads to iron deficiency. The association between iron deficiency and RLS is well established [42–45].

Pneumatic compression devices
Pneumatic compression devices work on a principle distinct from the EECP mentioned above. In EECP leg devices compress and decompress in relationship to cardiac cycles, whereas with pneumatic compression devices this is not the case. In a double-blind study where 35 subjects were enrolled, true compression was compared to sham compression, and there was a significant improvement in severity of RLS symptoms, quality of life, and sleep quality. The devices were applied for at least 1 hour prior to the usual onset of symptoms and the authors conclude that pneumatic compression devices should be considered as a useful adjunct to pharmacotherapy [111].

Conclusions
The expanding body of medical research has redefined RLS from a rare disorder affecting only older persons of European descent, to a common disorder affecting nearly every ethnic group. The IRLSSG’s standardization of diagnostic criteria and validation of an RLS severity scale are instrumental to ongoing research and provide valuable aid to clinicians.

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Chapter 20


CHAPTER 21

Tardive Dyskinesias

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Historical background

Tardive dyskinesia (TD) is an iatrogenic movement disorder resulting from exposure to dopamine receptor blocking agents (DRBAs) for a period of at least 3 months [1] (one month in patients older than 60 years). [2] The first typical (first generation) antipsychotic, chlorpromazine, was found to be effective for the treatment of psychosis in a small clinical trial conducted in 1952 [3] and approved by the FDA in 1954. In 1957, the first reported cases of TD were described in the medical literature when three elderly women developed lip-smacking dyskinetic movements after 2–8 weeks of exposure to this drug (4). TD was believed at that time to be rare, with only scattered cases appearing in the medical literature [5, 6]. It was in the late 1960s when larger studies began to reveal that it was probably more common than initially believed. The term “tardive” dyskinesia was coined in 1964 by Faerbye et al. [7] based upon the observation that dyskinetic movements usually appear late in the course of neuroleptic exposure. TD became widely accepted as an iatrogenic condition in the early 1970s, and the first therapeutic trials for TD occurred shortly thereafter [8–10].

The first atypical (second generation) antipsychotic, clozapine, was developed in the 1950s but did not become available until 1989 after the FDA approved its use for treatment-resistant schizophrenia. Throughout the 1990s and early 2000s, additional presumed atypical antipsychotics became available and largely replaced the typical agents for the treatment of schizophrenia and other forms of psychosis. The atypical agents have also been used extensively, especially with off-label prescribing, as mood stabilizers, adjunctive agents in the treatment of refractory depression, for agitation in dementia, and in variety of other psychiatric conditions. Based upon preclinical data, the atypical antipsychotics were expected to carry a dramatically reduced risk of extrapyramidal side effects (EPS) including tardive syndromes. It was expected that TD would ultimately disappear. A recent review has suggested this expectation to be true as a drop in reports on TD (reflecting decreased interest) were seen in the literature when second generation agents became available [11]. However, it has become apparent that, while they may carry lower risk for EPS and tardive syndromes, they are not free of these side effects and numerous case reports and case series have suggested that all atypical agents, including clozapine, carry a risk for TD [11A].

Epidemiology

A wide range of incidence and prevalence estimates can be found in the literature for TD. Reasons for the variability across studies include differences in the definition of TD, ascertainment of TD diagnosis,
inclusion of all phenotypes, and methodological approaches. In addition, heterogeneity of subjects across studies with regard to diagnosis, risk factors and exposure to neuroleptics, treatment practice variations between sites, and failure to control for the rate of spontaneous dyskinesias.

In a review of 56 early studies (conducted between 1959 and 1979), Kane and Smith reported an average point prevalence of 20% (range 0.5%–65%) [12]. Kane and Smith also reviewed 19 prior studies that estimated the prevalence of spontaneous dyskinesias in untreated samples. They found an average prevalence of 5% for spontaneous dyskinesias. Subtracting this from their overall TD prevalence of 20%, they concluded that the true prevalence of TD was likely closer to 15% [12]. A later review of 76 studies conducted through 1989 by Yassa and Jeste indicated an overall TD prevalence of 24.2% (range 3.3–62%) [13].

In 1988, Kane et al. conducted a prospective study of 908 patients, estimating a 5% annual incidence of TD from their cohort [14]. Their data also suggest that, at least for the first 4–5 years of neuroleptic exposure, the cumulative incidence of TD increases linearly with increasing duration of exposure. Both of these findings were later confirmed by Chakos et al [15]. In 1993, Glazer et al. presented long-term risk estimates for TD in a prospective cohort study of 362 psychiatric outpatients who were free of TD at baseline and were maintained on neuroleptics [16]. They also estimated the risk of TD to be 5% per year, in keeping with prior studies. They also estimated long-term risks of 25% after 5 years, 49% after 10 years, and 68% after 25 years.

More recent epidemiological studies have sought to compare the incidence of TD in patients treated with typical versus atypical antipsychotic agents. In 2004, Correll et al. reviewed 11 studies lasting at least a year and involving samples of at least 20 subjects. A total of 1235 patients, on different atypical antipsychotics, were included. For the adult sample, the weighted mean annual incidence of TD for atypical antipsychotics was 0.8% compared with 5.4% for haloperidol [17]. In a subsequent review of 12 trials published between 2004 and 2008, Correll and Schenk found the annual incidence of TD to be 3.9% for atypical antipsychotics versus 5.5% for typical agents (p = 0.0001). Prevalence rates were 13% among subjects on atypical agents and 32% among subjects on typical agents (p = 0.0001) [18]. The conclusion from these studies is that atypical antipsychotics are not without risk of TD, but the risk appears lower than what is observed with typical agents like haloperidol.

Other factors (besides drug class) related to drug exposure such as dose and blood levels have been difficult to correlate with risk of TD. However, it is generally agreed that longer exposure and high doses add to the risk of developing TD [19]. Though once advocated, drug holidays have been shown to increase risk and worsen prognosis after withdrawal [20, 21]. This is a practice that has been disappearing.

Advancing age is a well-established risk factor for the development of TD. Several studies have demonstrated higher vulnerability of the geriatric population to the development of TD following neuroleptic exposure [22–24]. Elderly patients are also likely to develop more severe forms of TD. In a study of 99 elderly subjects (mean age 73.5) naïve to neuroleptics at study inception, Yassa et al. reported a TD prevalence 35.4% after 5 years of follow-up [22]. In a prospective longitudinal study of 266 outpatients over 45 years of age, Jeste et al. found a cumulative incidence of TD of 26%, 52%, and 60% after 1, 2, and 3 years respectively [23]. These numbers contrast sharply with those reported in a prospective study of 850 young adults (mean age 29), which reported a cumulative incidence of TD of 5%, 19%, and 26% after 1, 4, and 6 years of treatment [25].

Conflicting results have been published with regard to gender as a risk factor. In their review of 75 studies, 6 of which were stratified by age groups, Yassa et al. reported excess risk for women older than age 51 with a more evenly distributed risk in younger age groups [13]. This suggests a possible interaction between age and gender.

Studies conducted in other countries have also reported wide variations in TD rates [26–31]; however, differences in prescribing practices, cultural and environmental factors, and methodological differences make interpretation of such
Tardive Dyskinesias

In the US, African-Americans and other non-whites are more susceptible than Caucasian Americans of European descent, even after adjustment for neuroleptic dose and duration of exposure [32, 33].

Diabetes mellitus has been implicated as a risk factor for the development of TD [34, 35], with one study reporting a risk ratio of 2.3 for diabetics compared to non-diabetics exposed to neuroleptics [35]. Elderly diabetics appear to be at particularly high risk [35]. Diabetics may also be more likely to manifest more severe forms of TD [34]. There are some studies that did not relate such findings [36].

An increased incidence and prevalence of TD has been noted among neuroleptic-treated patients with affective disorders compared to schizophrenia [37]. Other potential risk factors such as substance abuse, smoking, exposure to other drugs like anticholinergics and lithium, and the presence of previous structural brain damage remain controversial [38].

Family studies have supported the notion that there is genetic susceptibility for TD. First, they have demonstrated concordance for TD among first-degree relatives of patients [39, 40]. This was followed by the search for the genetic determinants which has yielded a number of potential candidate gene polymorphisms. Table 21.1 summarizes the currently known associations. Though discussion of all the candidate genes is beyond the scope of this chapter, a few consensus associations warrant further discussion.

Steen et al. reported a high frequency (22–24%) of homozygosity for the Ser9Gly variant (2–2 genotype) of the dopamine D3 receptor gene (DRD3) gene among subjects with TD in both cross-sectional and longitudinal studies, as compared with the relative underrepresentation (4–6%) of this genotype in patients with no TD [41]. Subsequent studies also demonstrated an association between TD in schizophrenic patients and the D3 receptor gene [42, 43]. Some studies reported that a serine to glycine polymorphism in the first exon of the DRD3 gene was a risk factor for the development of TD [43–45]. A meta-analysis of genetic studies reported an odds ratio of 1.17 for developing TD associated with the serine to glycine polymorphism in the D3 receptor gene [46].

Table 21.1 Associations of candidate gene polymorphisms with TD.

<table>
<thead>
<tr>
<th>Gene and Polymorphism</th>
<th>Association</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRD3 Ser9Gly</td>
<td>Gly allele confers susceptibility</td>
<td>Bakker et al. [46]</td>
</tr>
<tr>
<td>DRD2 Taq1A</td>
<td>A2 variant of Taq1A SNP associated with higher risk</td>
<td>Bakker et al. [53]</td>
</tr>
<tr>
<td>DRD4</td>
<td>Long allele protective</td>
<td>Lattuada et al. [176]</td>
</tr>
<tr>
<td>CYP2D6*10</td>
<td>Association 120bp duplication marker</td>
<td>Srivistava et al. [177]</td>
</tr>
<tr>
<td>CYP1A2*1F</td>
<td>Associated with greater severity</td>
<td>Basile et al. [51]</td>
</tr>
<tr>
<td>MnSOD Ala9Val</td>
<td>Ala-Val and Val protective</td>
<td>Bakker et al. [53]</td>
</tr>
<tr>
<td>COMT</td>
<td>Val-Met heterozygosity confers protection</td>
<td>Bakker et al. [53]</td>
</tr>
<tr>
<td>5-HTR2A T102C</td>
<td>Associated with TD</td>
<td>Segman et al. [178]</td>
</tr>
<tr>
<td>GSTM1</td>
<td>Absence associated with TD</td>
<td>De Leon et al. [180]</td>
</tr>
<tr>
<td>NQ01 609C/T</td>
<td>T allele associated with increased risk</td>
<td>Pae et al. [181]</td>
</tr>
<tr>
<td>NOS3</td>
<td>T–4B-Glu haplotype protective</td>
<td>Liou et al. [182]</td>
</tr>
<tr>
<td>RGS9 7SNPs</td>
<td>AGG haplotype associated</td>
<td>Liou et al. [183]</td>
</tr>
<tr>
<td>MAO A &amp; B</td>
<td>No associations identified</td>
<td>Matsumoto et al. [184]</td>
</tr>
</tbody>
</table>

1 Where available, meta-analyses, rather than individual studies, are cited.
Chen et al. found a significant association between TD and the dopamine D2 receptor gene (DRD2) Taq1A polymorphism [47]; several later studies and a meta-analysis later supported the association [48].

Certain polymorphisms in the CYP2D6 gene, which encodes a cytochrome P450 enzyme, have been reported to be positively associated with TD. Specifically, there are data supporting allele *10 [49, 50]. Other CYP genes such as the CYP1A2*1F have also been shown to be potentially associated with TD severity [51].

The notion that deranged superoxide dismutase (SOD) activities might be a risk factor for schizophrenia and/or TD led to studies of the manganese superoxide dismutase gene (MnSOD). Hori et al. reported that the –9Ala MnSOD allele (high activity) may play a role in protecting against susceptibility to TD in schizophrenics [52], a finding later supported by a subsequent meta-analysis of pooled genetic data [53].

**Phenomenology and other clinical features**

Though various phenotypes of TD exist which also differ with regard to pathophysiology, epidemiology, and pharmacology, there are commonalities, including exposure to dopamine-blocking agents and their tendency to persist, in most cases after the offending agent has been removed. The term “tardive” was originally used to denote the late onset of the disorder (DSM criteria suggest 3 months of exposure is needed except in the elderly where one month is adequate). However, it is now accepted that this disorder may appear relatively early in the course of treatment with dopamine-blocking agents (with few doses) and there is no clinical distinction between the earlier- and later-onset subtypes [54]. Some experts, however, have suggested that young males are more likely to exhibit tardive dystonia, particularly involving the trunk and upper extremities, whereas middle-aged and elderly women typically exhibit the classical, oral-buccal-lingual movements. In the classical form, TD as described by Fahn [55] has oral-buccal-lingual masticatory movements; also referred to as bucco-lingual-masticatory syndrome [56]. Video 21.1 features these classical oral-buccal-lingual movements. There are variations of TD characterized by dystonia, chorea, tics and myoclonus [57] in isolation or in combination with TD. It is beyond the scope of this chapter to review all of them but they are listed in Table 21.2.

Classical TD tends to involve the face and the mouth region. Usually the upper face is less involved, though in some patients blepharospasm, increased blinking, arching of eyebrows and oculogyric movements [57A] may be noted as well. The limb and the trunk are less involved and even when involved, much less affected than the face and the mouth. The movements are usually stereotypic but can be choreic like the random and often unpredictable movements of Huntington disease. In TD the movements of the mouth are rhythmic, repetitive complex chewing motions and may involve puffing of the cheeks, protruding of the tongue, lip smacking, puckering, pursing, and chewing [58]. TD movements when involving other distal portions of the body can be rhythmic and repetitive as well. Dyskinesia in the fingers may look as if the patient is playing an invisible guitar or piano. In the lower extremities these may appear as repetitive foot tapping, crossing and uncrossing the legs, and when, lying down, repeated abduction and adduction movements of the thigh. These movements in general are worsened by anxiety, stress, agitation, or concentration on other voluntary movements. TD can be suppressed by voluntary activation of the affected muscles, relaxation or sedation and, like most other hyperkinetic
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Movement disorders, disappears during sleep. TD needs to be distinguished from other movements that involve the orofacial region. (Box 21.1). Many patients may be unaware of these movements which rarely interfere with basic functions such as chewing, speaking, or swallowing. Occasionally, in some cases it may cause food to be pushed out of the mouth, interfering with eating, and at times patients may develop sores from the constant movement of the tongue over the teeth [59].

When involving the trunk, these movements may appear as rhythmic rocking or pelvic thrusting motions (so-called copulatory dyskinesia [60]). Video 21.2 features TD with prominent pelvic thrusting. Some patients exhibit grunting and moaning which is believed to be due to involvement of the upper air passages. Respiratory movements may also be affected with altered rhythmical patterns leading to hyper and hypoventilation. These respiratory tardive dyskinesias may not be medically significant although may look alarming [61] however, in some cases, may be considered life threatening [62]. Video 21.3 features respiratory TD. Horiguchi et al. described rare cases of esophageal dyskinesia associated with lingual dykinesias leading to increased intraesophageal pressure and death in one patient [63].

Tardive dystonia is the second most frequently observed TD variant (approximately 25% of TD cases) and can often be indistinguishable from idiopathic torsion dystonia. Tardive dystonia can be focal, segmental or generalized. In a study conducted by Molho et al [64] comparing 20

### Table 21.2 Tardive dyskinesia variants.

<table>
<thead>
<tr>
<th>Classical tardive dyskinesia</th>
<th>Rapid repetitive stereotypical movements involving the oral, buccal and lingual areas.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tardive dystonia</td>
<td>Can be indistinguishable from idiopathic torsion dystonia. Focal dystonias are the most common manifestation but segmental dystonia may be noted; generalized dystonia is rare.</td>
</tr>
<tr>
<td>Tardive akathisia</td>
<td>Characterized by feelings of inner restlessness and objectively manifested by semi purposeful movements.</td>
</tr>
<tr>
<td>Tardive tics</td>
<td>May manifest as invariant tics or may fulfill criteria for Tourette syndrome [185]. This is a common cause of adult onset tics.</td>
</tr>
<tr>
<td>Tardive tremor</td>
<td>Postural and kinetic tremor that persists despite withdrawal of dopamine blocking agents [186]</td>
</tr>
<tr>
<td>Tardive myoclonus</td>
<td>Myoclonic movements may occur in isolation or in combination with tardive dystonia or akathasia. [187, 188]</td>
</tr>
<tr>
<td>Tardive complex</td>
<td>Three or more tardive movement disorders in same patient</td>
</tr>
</tbody>
</table>

Adapted from Fahn [58], pp 480–518.

### Box 21.1 Differential diagnosis of orofacial dyskinesia [58, 145, 189]

**Orofacialcervical tremors**
- Essential tremor – head and jaw
- Parkinsonian tremor involving lips, jaw and tongue
- Cerebellar tremor
- Palatal myoclonus – with synchronized ocular, shoulder and head movements

**Orofacial myoclonus**
- Facial myoclonus (as seen with Creuzfeld-Jacob disease)
- Hemifacial spasm
- Facial myokimia

**Orofacial tics**
- Transient or chronic simple tics
- Tourette syndrome

**Orofacial chorea**
- Huntington disease
- Sydenham chorea
- Hepatocerebral degeneration
- Idiopathic basal ganglionic calcification
- Neuroacanthocytosis
- Encephalitis lethargica
- Cerebellar infarction
- Edentulous malocclusion
- Tumors (primary or metastatic)
- Spontaneous oral masticatory syndrome

**Orofacial dystonia**
- Meige syndrome-blepharospasm and oromandibular dystonia

**Drug-induced chorea dystnesia**
- Levodopa, amphetamine, cocaine, TCAs, cimetidine, cinnarizine, flunarizine, phentolamine intoxication, antihista-mines, anticholinergics, benzodiazepines and lithium

**Others**
- Synkinesis due to faulty regeneration of facial nerve
- Psychogenic
patients with tardive cervical dystonia to 77 patients with idiopathic cervical dystonia, patients with tardive cervical dystonia were found to have extracervical involvement, retrocollis and spasmodic head movements more frequently than those with idiopathic cervical dystonia. Truncal dystonia may be characterized by opisthotonic arching of the torso, often accompanied by pronation and extension of arms at elbows [65].

**Predisposing factors and clinical course of tardive dyskinesia**

The natural history of classical TD is difficult to determine as it is affected by a variety of host and treatment factors. Furthermore, the dopamine receptor blocking agents that cause TD also tend to suppress these movements. Age seems to be most consistently associated with the development, severity and persistence of TD [14, 66, 67]. In a study conducted by Smith and Baldessarini it was found that both the prevalence and severity ratings for TD tend to increase with age almost linearly between 40 and 70 years [68]. Younger patients are not immune to TD; however, in children the course may be more benign and often spontaneously remits [68A]. TD, though rare in infants, has been reported; possibly the youngest being that of a 9 month old who developed TD secondary to treatment with metoclopramide [69].

The spectrum of TD varies widely from mild transient dyskinesia that emerges during withdrawal to irreversible TD after the offending drug has been withdrawn [58]. The syndrome may take days or weeks to develop, and early cases may actually remit in weeks to months after discontinuation of the offending agent. Reports have described complete remission occurring as late as 2 years or more after discontinuation of the offending agent [70]. TD may worsen transiently after discontinuation before finally disappearing. The term “withdrawal emergent syndrome” or “dyskinesia” has been used to describe this type of TD [68A].

Many studies concerning reversibility have been conducted in patients who continued to receive DRBA, while few studies have examined remission of TD once the offending agent has been discontinued [71–73]. Currently there is no definitive data that, once established, TD will continue to progress in severity with continuation of the offending drug [74–76]. Gardos et al. [77] conducted a study in 122 neuroleptic-treated patients, and 63 patients were followed up at 5- and 10-year intervals. No progression of TD was noted in the second 5-year follow-up, as compared to the initial 5 years of the study; however, 11 patients had remission and 12 patients who did not have TD at baseline developed TD over the 10-year period. In another study conducted by Fernandez et al. [78], 53 patients were assessed over a 14-year period. TD improved and parkinsonism worsened.
in the patients who continued to receive neuroleptic medications. In general it is suggested that 30% of cases are reversible but this depends on the age of the patient [19]. About 10% of cases of TD progress to a severe level. Given the available data, it would be prudent, especially in the elderly, to use the smallest dose of drug for the shortest time as there appears to be a strong inverse correlation between rates of spontaneous remission and age [68, 79].

**Etiology**

Traditionally, TD has been defined as a clinical syndrome caused specifically by chronic exposure to DRBA, particularly first generation agents (FGAs). It has been defined as occurring after 3 months of exposure but can be seen after a single exposure to DRBA. Although, the incidence has diminished with the advent of second generation agents (SGAs), TD continues to be a problem, even with these newer agents. Video 21.4 features TD due to the SGA risperidone. Quetiapine and clozapine are the SGAs with the lowest risk of causing TD; however, they too have been reported to result in TD [80–91]. Dopamine-depleting agents like reserpine and tetrabenazine have not been reported to cause TD in humans [91A]. Non-antipsychotic DRBAs that can cause TD include antiemetics (metoclopramide [92, 93], promethazine [94], prochlorperazine [95, 96]), antidepressants (amoxapine [97–102]), and calcium channel blockers are thought to have some dopamine-blocking effects (flunarizine and cinnarizine) [103]. Since not all patients exposed to chronic DRBAs develop symptoms of TD, and some appear to be particularly susceptible, theories emerged suggesting that other factors superimposed upon DRBA exposure are necessary for the development of TD. Risk factors for TD have been identified and include age, duration of DRBA exposure, and genetic susceptibility. Furthermore there is evidence to support that DRBA exposure may not be necessary at all for the development of TD, and that dopamine and its receptors may not play such a central role in the pathophysiology of TD. In support of this theory are reports of spontaneous dyskinesias in psychotic patients not exposed to DRBAs [104], in elderly patients that were neither psychotic nor exposed to DRBAs [105], and in rodents and non-human primates [106]. It is important to note that spontaneous dyskinesias are thought to be phenomenologically distinct from classic TD, and do not meet the definition of TD which requires DRBA exposure; therefore, they are likely to represent a distinct clinical entity. Candidate causes implicated in the etiopathology of TD will be discussed in more detail in the following section.

**Pathophysiology**

The pathophysiology of TD remains under investigation. Multiple hypotheses have been proposed, but none yet has been able to reconcile the fundamental features of this disorder. Any theory proposed must explain why TD (1) emerges after chronic use of DRBAs, (2) occurs in only a fraction of exposed patients, (3) persists after the withdrawal of the offending agent, and (4) responds to DRBAs and worsens with dopaminergic therapy. At first glance, it is counterintuitive to think of TD as a hyperkinetic movement disorder arising from dopamine blockade. However, clinical evidence supports TD as a relative hyperdopaminergic state; examples include the withdrawal emergent syndrome and the amelioration of symptoms with higher DRBA dose [107, 107A].

One of the earlier and prevailing theories proposes an up-regulation of D2 receptors with a subsequent hypersensitivity and increased affinity to dopamine. If, in fact, there are a greater number of D2 receptors and greater sensitivity, this model would explain why the hyperkinetic disorder develops, and why it responds to greater dopamine blockade and/or depletion of dopamine pharmacologically. Furthermore, it explains the withdrawal emergent syndrome since there would be a greater number of receptors with greater affinity to dopamine that would bind endogenous dopamine once they are no longer under blockade. However, this model does not explain why
only a fraction of patients develop the condition, since one would expect that hypersensitivity is present in all (also evidenced by animal models), nor does it explain why the onset is years after exposure since hypersensitivity itself is present within days to weeks (as demonstrated in rodent models). Another issue is that TD is persistent, yet hypersensitivity diminishes over time, and dopamine receptor numbers return to baseline after DRBAs are withdrawn [108]. Studies in rats treated with DRBAs (short term) show that the up-regulation of D2 receptors occurs universally after exposure and reverses once DRBAs are withdrawn [109]. When rodents are exposed for longer periods of time, symptoms can persist longer but remain reversible [110]. These models are clearly not equivalent with TD in humans, but continue to be used to answer questions about its pathophysiology. To explain the delay in onset of symptoms others have postulated that interactions from multiple peptide systems including enkephalins and neurotensin take place, and these changes take longer to occur [109]. Efforts to study dopamine receptors using imaging and immunohistochemistry in humans and animal models have not been able to consistently confirm either up-regulation or hypersensitivity of dopamine receptors in patients exposed to DRBAs [106, 111–113]. For this reason, some have suggested that an increased ratio of D1/D2 receptor function may be a more accurate way of representing the underlying pathophysiology [114]. Structural or pathological changes have not been demonstrated consistently in humans or animal models through autopsy or neuroimaging.

To explain the difference in side effect profile between typical and atypical DRBAs the rapid dissociation hypothesis has been proposed. Here, a truly atypical agent (the prototypes being clozapine and quetiapine) are thought to bind post-synaptic D2 receptors in the striatum loosely, then dissociate, while the typical DRBAs like haloperidol are thought to bind tightly and have long-lasting effects on the receptor. In this theory, the atypical agents bind just long enough to have antipsychotic action, but not long enough to cause extrapyramidal symptoms (indicative of decreased D2 affinity) [115, 116]. The duration of receptor binding is highly correlated with lower potency. However, antipsychotic effects are thought to occur as a function of dopamine receptor occupancy, not duration of binding, and even clozapine has been reported to cause EPS at high enough doses [117].

Alternate theories suggest a more complicated process involving multiple receptors and neurotransmitters. Glutamic acid decarboxylase (GAD) and gamma-aminobutyric acid (GABA) have been found to be diminished in the substantia nigra and external pallidum in animal models and in CSF in TD patients [118], and these levels were found to correlate in rodents with increased vacuous chewing movements (VCMs) [119]. However, these findings have not been consistently replicated [106, 120]. In support of this theory are reports of suppression of TD with GABAergic agents [118, 121].

Opioid peptides (enkephalin and dynorphin) and their receptors have also been implicated in the pathophysiology of TD. Increased mRNA levels of both peptides have been reported following exposure to neuroleptics [122–124]. Furthermore, administration of selective opioid receptor antagonists into specific basal ganglia structures in rodents not only attenuate VCMs, but do so in such a way as to suggest that increases in dynorphin in the direct pathway, and enkephalin in the indirect pathway, contribute significantly to the pathophysiology of TD [125]. In addition, recent studies show significant changes in norepinephrine and serotonin by brain region in rats exposed to neuroleptics [126]. Evidence in further support of a role for serotonin in TD include the potentiation of haloperidol-induced catalepsy with co-administration of 5HT re-uptake inhibitors [127], non-selective agonists [128], and lesions in the medial raphe protected against neuroleptic-induced catalepsy [129].

Another neurotransmitter that has been under investigation is glutamate. Some have hypothesized that glutamatergic transmission is enhanced by presynaptic dopamine blockade. In support of this theory are CSF studies in patients with TD showing higher levels of
N-acetylaspartate, N-acetylaspartylglutamate, and aspartate compared with controls. These levels also correlated with severity of symptoms [130]. Studies in a rat model of TD with haloperidol-induced VCMs support the notion that glutaaerergic transmission is affected [131]. Co-administration of N-methyl-D-aspartate (NMDA) receptor blockers with haloperidol allowed rats to recover sooner than those not receiving NMDA blockers, implicating NMDA receptor overstimulation as a contributing factor [132]. Other evidence suggests the involvement of oxidative stress in the pathophysiology of TD, including (1) the finding that mitochondrial complex I activity is inhibited by neuroleptics, but more so by FGAs [133], (2) the finding that increased reactive oxygen species is seen in rats exposed to haloperidol in vitro [134], and (3) the reduction in erythrocyte Cu, Zn-superoxide dismutase activity in patients exposed to neuroleptics with TD [135]. The neurodegenerative hypothesis of TD proposes that damage to GABAergic neurons leads to disinhibition of the nigrostriatal tract, resulting in a hyperdopaminergic state. Such neuronal damage may result from oxidative damage generated from increased dopamine turnover in the face of neuroleptic exposure [136]. In support of this hypothesis there is one early study of 28 patients with TD and 28 psychiatric controls showing neurodegeneration and gliosis of the basal ganglia of TD patients [137]. Studies attempting to replicate these results have been limited by sample size, lack of controls, and methodology [136].

Another factor thought to play a significant role in the pathogenesis of TD is genetic susceptibility which, when present in patients who are exposed to DRBAs, would result in TD. This could explain why only selected exposed patients are afflicted. Potential candidates for susceptibility genes are determined, in part, based on whether they affect the metabolism of the drug (pharmacokinetiics) or the ability of the drug to interact with its target or receptor (pharmacodynamics). The major enzymes involved in the metabolism of DRBAs have been clearly elucidated. CYP3A4 and CYP2D6 are responsible for the metabolism of up to 80% of the DRBAs most commonly prescribed, but many other enzymes have also been identified. These enzymes have been found to be highly polymorphic. In terms of pharmacodynamics the dopaminergic pathway has been the primary focus of investigation. Another potentially related category of genes is involved in the oxidative stress pathway.

To date, associated genetic polymorphisms have been identified in all these pathways. Of these, the PM phenotype of the CYP2D6 has been reported in several populations to be associated with severity of symptoms. In fact, these data are being used in clinical trials and commercial testing is approved by the FDA [138]. In the dopaminergic pathway several groups have reported an association of DRD2 variants with TD. The A2 variant of Taq1A SNP has been confirmed independently and its association with TD has been further supported by two meta-analyses [139]. In addition, replication of DRD3 Ser9Gly has been reported to be associated with TD by eight independent studies and one meta-analyses [140]. DRD3 is an autoreceptor known to control the phasic activity of dopaminergic neurons, expressed in the limbic area primarily. Postmortem studies have reported an increase in D2 receptors in the basal ganglia in patients exposed to neuroleptics. Furthermore the glycine allele has been shown to be associated with higher dopaminergic activity [138]. In the oxidative stress pathway the Ala9Val polymorphism in the mitochondrial targeting sequence of the MnSOD gene holds the most promise [52]. If present, this allele would lead to impaired detoxification of superoxide radicals. Confirming its relevance one study found the Ala9 allele to be protective against TD while another found the Val/Val genotype to increase the risk of development of TD tenfold. A meta-analysis contradicted these findings showing a protective effect for Val carriers [138]. Although many hypothesize that it is likely that several genes interac to result in the TD phenotyp, studies to understand these interactions are limited [138]. Genotype-phenotype correlation studies have not been fruitful either. One genotype wide association analysis was performed revealing eight genes from the GABAergic pathway [141].
Treatment

TD is an iatrogenic disorder and, as such, is preventable. Undoubtedly, DRBAs are effective treatment modalities for a group of patients with severe and debilitating symptoms, particularly schizophrenia. The use of DRBAs is warranted in this patient population and others including Tourette’s syndrome and Huntington disease. However, using the lowest effective dose, monitoring for side effects routinely, reassessing the need for treatment periodically in order to limit duration of exposure if possible, using alternative non-DRBAs therapies concurrently, and utilizing the atypical antipsychotics are important strategies in terms of prevention. Of the atypical antipsychotics it should be stressed that clozapine and quetiapine carry the lowest risk for TD. DRBAs should be avoided, particularly chronic use, in conditions where alternative agents are effective, such as depression, anxiety, sleep disorders and others.

When TD arises, the first consideration should be withdrawal of the offending agent. This is a widely accepted practice among experts in the field with data demonstrating remission rates from 8 to 33% supporting this practice [110]. However, no randomized controlled trials (RCTs) have been performed to provide further proof of this approach [142]. If DRBAs are absolutely necessary, consideration should be given to switching to clozapine or quetiapine if they are on typical or other atypical agents. With clozapine in particular the question has arisen, because of its unique pharmacology whether the improvement seen is direct therapeutic effect or just a removal of the dopamine blockade from the causative agent or simply masking of the TD [143]. The answer remains unclear. If it is not possible to use these agents, or they do not adequately control symptoms for which the DRBA was being prescribed, then treating TD with another agent will need to be considered. Generally, the use of typical DRBAs will alleviate TD symptoms by masking them; however, most experts fear it will eventually lead to worsening of symptoms, and/or the requirement for higher doses. In fact, this hypothesis has not been supported by data [144]. Nevertheless, continuing DRBAs will inevitably worsen prognosis by eliminating any chance for remission.

Whether the DRBA is removed or not many patients will need therapeutic intervention. First line agents for the treatment of TD are dopamine depleters both for their effectiveness, and the fact that they have never been reported to cause TD. These agents reduce dopamine levels thereby reducing TD symptoms without inducing dopamine blockade. Reserpine and tetrabenazine (TBZ) are both synthetic benzoquinolizines that inhibit the vesicular monoamine transporter (VMAT), keeping monoamines in the nerve terminal vesicles where they are metabolized by monoamine oxidase and depleted. Reserpine depletes catecholamine stores in both central and peripheral (sympathetic) nerve terminals as it irreversibly blocks VMAT 1 and 2, and for this reason has more peripheral related side effects including orthostasis [145]. TBZ is thought to reversibly inhibit VMAT 2, primarily in the CNS, and also has dopamine-blocking activity. For these reasons, it is less likely to cause orthostasis than reserpine and depression is more likely to be less protracted. Both drugs can cause parkinsonism, akathisia, and sedation at higher doses, which are reversible. Multiple studies examining efficacy with reserpine were reported in the 1980s, including a double-blind trial with 30 patients showing 50% improvement in symptoms [146]. This was confirmed by a meta-analysis which showed that 64–96% of patients treated showed such improvement [67]. Some of these studies have used α-methy-para-tyrosine in conjunction with reserpine to reach the reported clinical effect. This compound is a competitive inhibitor of tyrosine hydroxylase, which can augment the dopamine-depleting effect of reserpine. TBZ has been studied in one early placebo-controlled trial [8], several open label, one large retrospective, and one single-blind trial, showing safety and significant improvement in TD symptoms, even at long term [147, 148]. A recent RCT showing safety and efficacy in the treatment of chorea in Huntington disease led to FDA approval of this drug in the US [149] in 2008. Video 21.4 features a patient with severe TD before and after treatment with TBZ.
Multiple agents have been studied in relatively small controlled trials, case series, and case reports as possible therapies for TD (Table 21.3). General categories of therapeutic agents investigated include: benztropine, biperiden, chlorprothixene; cholinergics (deanol, lecithin, meclofenoxate); benzodiazepines (diazepam, clonazepam); catecholaminergics (celiprolol, tiapride); GABA agonists (baclofen, valproate, prograbide, THIP); neuroleptics (haloperidol, quetiapine); dopamine agonists (bromocriptine); and antioxidants (vitamin E). Other agents that have been less well studied include propranolol, clonidine, buspirone, phenylalanine, estrogen, lithium, insulin, gamma-linoleic acid, levetiracetam, acetazolamide, amantadine, and ceruletid. To date, no study has been able to provide high-quality convincing evidence supporting its use as definitive therapy in TD [142].

Alternatives to medical therapy for TD include botulinum toxin injections and deep brain stimulation (DBS). Several open label reports of improvement have been reported in the literature, particularly for cases of severe lingual movements where genioglossus injections of botulinum toxin were administered [150–154]. One small single-blind study showed benefit after correcting for adjustments in neuroleptics [155]. Multiple case reports have shown significant improvement in TD with DBS [156–158]. One small, prospective, phase two, multicenter study with double-blind evaluations showed a mean decrease of 50% in TD symptoms according to validated rating scales [159].

As evidenced by the above findings, treatment for TD remains complicated, and although multiple safe and effective modalities are available to the clinician, there is still much research to be done to determine which therapy is best. Each case of TD should be evaluated carefully and treatment should be individualized depending on multiple patient specific and treatment specific variables.

In our practice we wean all non-psychotic patients off of DRBAs first. Patients with significant psychosis are switched to either quetiapine or clozapine. If they are on anticholinergics these are discontinued since they can exacerbate symptoms [160, 161]. Once this transition is made, they are re-evaluated and if further medical therapy is warranted they are generally tried on propranolol and vitamin E concurrently. If the syndrome is very focal and refractory to initial therapy, botulinum toxin is considered early. If the syndrome is severe, and depression is not of particular concern, tetrabenazine is considered early. Levitiracetam and amantadine are generally considered next, followed by the benzodiazepine clonazepam. If symptoms remain severe and refractory to multiple medical therapies bilateral GPI DBS is considered. Figure 21.1 outlines this treatment approach.

**Metoclopramide**

The drug metoclopramide deserves special attention in this chapter for several reasons: (1) it is a major cause of TD in non-psychiatric patients; (2) it may be associated with unique clinical features and perhaps a more severe form of TD; (3) it recently had a label change pointing to its importance in relation to TD and addressing the role of chronic therapy, and (4) it has been the subject of substantial medical litigation. Videos 21.2 and 21.3 feature TD due to metoclopramide.

Metoclopramide is a substituted benzamide derivative with-D2 blocking effects similar to chlorpromazine [93]. Its indications include post-operative or chemotherapy-induced nausea and vomiting, gastroesophageal reflux, and
Table 21.3 Medical therapies for tardive dyskinesia.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Type of trials</th>
<th>Effective?</th>
<th>Worth trying?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dopamine depleters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetrabenazine</td>
<td>1 early placebo controlled trial [8]</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>6 small early open label</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 large retrospective [190]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 single blind [147]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reserpine</td>
<td>Early double blind trial with alphamethyldopa [146]</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Early meta-analysis [67]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anticholinergic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class (withdrawal)</td>
<td>Two Small RCTs [160, 191]</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Meta-analysis [192]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benztropine</td>
<td>Small controlled trial [161]</td>
<td>No, worsened symptoms</td>
<td>No!</td>
</tr>
<tr>
<td><strong>Cholinergics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class</td>
<td>Meta-analysis [193]</td>
<td>Insufficient evidence</td>
<td>No</td>
</tr>
<tr>
<td>Donepezil</td>
<td>1 small open label trial [194]</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>GABA agonists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>2 small blinded studies [195]</td>
<td>Insufficient evidence</td>
<td>Yes</td>
</tr>
<tr>
<td>Baclofen and Valproate</td>
<td>Cochrane review [196]</td>
<td>No</td>
<td>No</td>
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<tr>
<td><strong>Neuroleptics</strong></td>
<td></td>
<td></td>
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<tr>
<td>Haloperidol</td>
<td>1 small single blind RCT [197]</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>1 small single blind RCT [197]</td>
<td>Yes</td>
<td>Yes (schizophrenics)</td>
</tr>
<tr>
<td>Clozapine</td>
<td>2 small double blind 4 open label [143]</td>
<td>Yes</td>
<td>Yes (schizophrenics)</td>
</tr>
<tr>
<td><strong>Dopamine agonists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>1 early, small double blind, controlled trial [198]</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Antioxidants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin E</td>
<td>14 small blinded studies (4 negative) Large RCT (negative) [199]</td>
<td>Insufficient evidence</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Branched chain amino acids</strong></td>
<td>1 small RCT [200]</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>valine, isoleucine, leucine</td>
<td>Multiple early reports, small open label trials [201–214]</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Noradrenergic antagonists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>Multiple early reports, small open label trials [201–214]</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Celiprolol</td>
<td>1 early, small, blinded, controlled trial [215]</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Clonidine</td>
<td>Two early, small, blinded, controlled trials [216, 217]</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leviteracetam</td>
<td>1 recent, small, RCT [218]</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>2 open label trials Multiple case reports</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amantadine</td>
<td>Multiple case reports 9 small open label 1 small blinded (neg.) 1 small RCT (positive) [219]</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
gastroparesis. It is also used for a variety of reasons by anesthesiology, although this is diminishing [162], and neurology for migraines. How it works for such purposes has been reviewed elsewhere [93, 162]. Most cases of TD occur after chronic therapy although short-term high-dose metoclopramide used as an antiemetic in cancer patients has also been reported to cause it [92, 163]. The incidence and prevalence of TD secondary to this drug in non-psychiatric populations has not been formally studied. Estimates for frequency range from <1% to nearly 30%. The low estimates are based on prescription databases and adverse event registries, methods that notoriously underestimate the frequency [164, 165]; higher figures are based on smaller studies of less than 100 patients which certainly could result in overestimation because of population biases [166, 167]. Reports of TD from metoclopramide dropped from 1993 to 2000 when cisapride was available for gastroparesis, but picked up again when this drug was removed from the market due to cardiac adverse effects [168]. It is reasonable to think that the prevalence of TD is lower with metoclopramide than the first generation neuroleptics if used chronically, considering the fact that a 10- to 20-fold increase in dose is required for it to have antipsychotic effects. As discussed elsewhere in this chapter, there are a number of risk factors for the development of TD in psychiatric patients, particularly related to their psychiatric disease. If the patient is treated with metoclopramide, this is not an issue. The primary risk factors are age (elderly), sex (female), chronicity of therapy, and diabetes mellitus [169, 170]. Of course, it could be that elderly women with diabetes develop gastroparesis and are simply treated more often with this drug. This data is from retrospective evaluations. Like TD secondary to antipsychotics, cases caused by metoclopramide are also frequently persistent (50–70% in 6 months) [170, 171]. Because the physicians prescribing these drugs do not typically see TD in their practices, it is reasonable to think that it is under-recognized in this setting [93, 169, 170].

There have been several suggestions that the TD caused by metoclopramide might differ from that of antipsychotics. Most subtypes of TD have been described [62, 92, 94, 96, 172, 173], but Swell and Jeste [170] suggested that metoclopramide may more frequently affect the face and lips and less frequently the limbs than antipsychotics. Lang [60] indicated that pelvic thrusting and respiratory dyskinesia are significantly more common with metoclopramide than antipsychotics, and that dystonia was less common. It is the respiratory dyskinesia that has been considered to be life threatening and if more common with metoclopramide adds to the importance of understanding
the phenomenology [62]. These findings have not been confirmed.

Metoclopramide was approved by the FDA in 1979 and the first case of TD caused by it was reported in 1978 [174]; nevertheless, it was not until 2009 that a label change was made and a black box warning was added regarding this complication. The warning focused on the chronic use of the drug. The recommendation is for up to 12 weeks of therapy. The warning states, among other things, that chronic use is linked to TD, chronic use should be avoided, the development of TD is directly related to length of time patient is on it, and the number of doses taken.

We suspect that because TD generally occurs in the psychiatric population treated chronically with antipsychotics, and that chronic therapy is often warranted, such cases have not aroused much activity in the medicolegal world with some exceptions. However, the occurrence of TD in non-psychiatric cases is another story. One paper in 1992 discussed the growing number of court cases related to metoclopramide [170] and this was revisited in 2006 [169]. The grounds often cited for legal action include: (1) the physician did not obtain appropriate consent for patients; (2) the off label use of the drug; (3) a lack of monitoring for TD; and (4) a lack of the early neurology referral. However, the most important reason relates to uses of the drug of more than 12 weeks since most cases occur with this scenario [92, 169]. This is no small target since an examination of the Caremark Dimension Rx program showed that 15% of patients treated with this drug received prescriptions for a period of greater than 90 days. These patients tended to be elderly females [175]. With the change in labeling and with the advent of television commercials seeking patients who developed TD while on metoclopramide, there has been an increase in medicolegal cases.

Conclusions

TD represents a crisis in neurology and psychiatry. Despite its being first described over 50 years ago it remains underrecognized and its impact underestimated. With the approval of second generation atypical antipsychotic drugs, many expected the disappearance of this disorder; however, newer DRBAs continue to result in TD at alarming rates, and the use of these agents has increased because they are marketed as having substantially lower risk. DRBAs are now used for the treatment of many psychiatric disorders – not just schizophrenia, including depression, anxiety, and others – and their use for gastrointestinal conditions and other neurological conditions, including migraines and sleep disorders, has become routine. Although significant advances have been made, we do not yet have a cohesive theory to explain the pathophysiology of this condition, nor do we have sufficient evidence to support definitive therapy. Many physicians continue to use neuroleptics to mask the symptoms, even in non-psychiatric patients, when it makes little intuitive sense to do so. Clearly this practice can only worsen prognosis. Continued research to elucidate the underlying pathophysiology of TD and determine the natural history of this condition definitively (including its reversibility), in conjunction with well-designed prospective double-blind controlled trials of therapeutic agents, are necessary for the development of adequate and appropriate therapy. Furthermore, physicians should not lose sight of the fact that this is a preventable condition, and that even the newest DRBAs continue to have the potential of causing TD and other tardive syndromes, even clozapine. These agents should be used with restraint, particularly when effective therapeutic alternatives are available.

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CHAPTER 22
Stereotypies and Other Developmental Hyperkinesias

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Introduction

Children exhibit a variety of hyperkinesias that consist of stereotyped, repetitive movement patterns. Many of these share features that allow them to be grouped together under the category of stereotypies. Others have features in common with stereotypies, but occur at specific developmental stages and are usually transient. Indeed, the developing nervous system produces a variety of motor patterns that would be considered pathologic in older children and adults, but are simply a manifestation of CNS immaturity. Like many of the so-called “primitive reflexes” (e.g. grasping, rooting, sucking, placing, tonic neck reflexes), these motor patterns disappear as neuronal connectivity progresses and myelination matures. Some transient hyperkinetic movement disorders in childhood may be manifestations of abnormal neural function, but do not correlate with serious underlying pathology. These are typically associated with complete resolution of the abnormal movements and ultimately normal development and neurological function. Others are symptomatic of more serious underlying disorders. This chapter is focused on stereotypies, but other transient hyperkinesias of childhood will also be described.

Stereotypies

Phenomenology and other clinical features

Definition

Stereotypies are broadly defined as involuntary, patterned, coordinated, repetitive, non-reflexive movements that are typically rhythmic and occur in the same fashion with each repetition. [1–3]. These movements can vary considerable across individual patients, but within each patient are characterized by a fixed and repetitive pattern that does not change over time. Stereotypies are not preceded by a premonitory urge and in many cases the child is unaware he or she is making the movement until it is pointed out. Stereotypies are not preceded by a premonitory urge and in many cases the child is unaware he or she is making the movement until it is pointed out. Stereotypies typically arise from a background of normal movement and have sudden onset and offset. They are most often seen when the child is excited, anticipating something, or engrossed. Common stereotypies include hand waving, arm flapping, finger wiggling, head nodding, and body rocking. Stereotypies can be divided into simple or complex types. Simple stereotypies include body rocking, head nodding, walking in circles, hand flapping or clapping, and facial grimacing. Complex stereotypies are more complicated in nature, such as sitting and rising...
from a chair. In children, hand flapping is the most common primary stereotypy (48%), followed by clenching stiffening (38%), and ritualistic behaviors (13%) [3]. The most common body part involved is the arms in 70% of children, followed by face-hand-mouth (53%) and hands-fingers (48%). Two-thirds of children used more than one body part in their stereotypy, and 57% made multiple movements each time [3].

Differentiating stereotypies from tics is central to making a definitive diagnosis of stereotypies [3–4]. The major distinguishing features are presented in Table 22.1. Tics are non-rhythmic, discrete, brief movements that fluctuate in location and type over time. Their frequency and severity also waxes and wanes, and they can be either simple or complex. Compared to tics, stereotypies tend to be longer and more rhythmic in nature. Tics are more likely to involve head, shoulder, and eye movements, such as eye blinking or shoulder jerking, are typically non-rhythmic, and are often preceded by a premonitory sensation [5]. In contrast, stereotypies involve more limb movements, such as hand flapping, and are typically rhythmic.

Other considerations in the differential diagnosis of stereotypies are mannerisms, akathisia (Chapter 1), compulsions, paroxysmal dyskinesias (Chapter 23), and self-gratification behavior (masturbation). Mannerisms are habits unique to an individual that are attached to normal activity, such as an athlete’s routine before a game. They are typically unique to the individual, are brief, rarely repetitive, and are less complex than stereotypies [4]. Akathisia is a syndrome of motor restlessness that typically includes both a subjective sense of inner restlessness and outwardly observed repetitive movements such as rocking or repeatedly crossing and uncrossing the legs while sitting. Although the movements may appear similar to stereotypies, the associated sensations and common association with neuroleptic medications help distinguish akathisia from stereotypies [6]. Compulsions are repetitive purposeful behaviors (such as hand washing) that the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly [7]. Compulsions are often acknowledged as being excessive or unreasonable, but this may not be the case in children. Paroxysmal dyskinesias are a group of movement disorders that are episodic, usually arising out of a background of normal movement and behavior [8]. They usually consist of chorea, dystonia, athetosis, or a combination and may be associated with specific triggers. Masturbation, also known as self-stimulation or gratification behavior, is a normal sexual behavior that can begin at any age [9].

Table 22.1 Factors distinguishing stereotypies from tics.

<table>
<thead>
<tr>
<th></th>
<th>Tics</th>
<th>Stereotypies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset:</td>
<td>6–7 years</td>
<td>&lt;2 years</td>
</tr>
<tr>
<td>Pattern:</td>
<td>Variable, changing in type and complexity over time</td>
<td>Fixed, identical, patterned, predictable</td>
</tr>
<tr>
<td>Movements:</td>
<td>Blink, grimace, twist, shrug</td>
<td>Arms/hands (flap, wave), body rocking, pacing</td>
</tr>
<tr>
<td>Vocalizations:</td>
<td>Sniffing, throat clearing</td>
<td>Moaning, humming</td>
</tr>
<tr>
<td>Rhythm:</td>
<td>Rapid, sudden, random</td>
<td>Rhythmic</td>
</tr>
<tr>
<td>Duration:</td>
<td>Intermittent, brief, abrupt</td>
<td>Intermittent, continuous, prolonged</td>
</tr>
<tr>
<td>Precipitant:</td>
<td>Excitement, stress</td>
<td>Excitement, stress, also when engrossed</td>
</tr>
<tr>
<td>Suppression:</td>
<td>Brief, voluntary (but have increased “inner tension”)</td>
<td>With distraction, rare conscious effort</td>
</tr>
<tr>
<td>Distraction:</td>
<td>Reduction of tics</td>
<td>Stops</td>
</tr>
<tr>
<td>Family history:</td>
<td>Frequently positive</td>
<td>May be positive</td>
</tr>
<tr>
<td>Treatment:</td>
<td>Alpha-2 agonists, antidopaminergic drugs, behavioral therapy</td>
<td>Poorly responsive, may respond to behavioral therapy</td>
</tr>
</tbody>
</table>

Source: Mahone et al. [3]
Stereotypies and Other Developmental Hyperkinesias

include repetitive movements such as dystonic posturing of the lower extremities, rocking, and grunting.

In children under the age of 2 years, other developmentally specific conditions should also be considered. These are discussed at the end of this chapter.

Etiology

Stereotypies can be classified into two etiological categories: primary (or physiological), and secondary (see Box 22.1).

Primary stereotypies

Primary stereotypies are those that are not due to an identifiable underlying cause and typically occur without other neurologic signs or symptoms. Primary stereotypies can be further subdivided into (a) common stereotypies (such as body rocking, head banging, and hair twirling), (b) head nodding, and (c) complex hand and arm stereotypies [2, 10]. Head nodding may represent a specific developmental case, as discussed at the end of this chapter. In general, primary stereotypies have a typical onset before 3 years of age in 90% of patients. They are more common in males, with a M:F ratio of 3:2. Symptoms occur at least once daily in 90%, are triggered by excitement in 70%, and stopped when cued in 98%. The movements cease when cued or distracted [11]. A family history of stereotypies is common; 25% of children with motor stereotypies have an identified family history of motor stereotypies in one study [12].

Primary stereotypies typically occur in normally developing children. The type of stereotypy can vary with developmental stage, such as thumb sucking in the younger child versus college students who may exhibit more body rocking or playing with pens [13]. Some children may have a past history of delayed milestones despite currently normal development [2, 11–14]. Cognitive and behavioral comorbidities have been identified, including attention deficit hyperactivity disorder (ADHD) in 25% and a learning disability in 20% [3].

It has been argued that normal motor development in infants is characterized by a number of stereotypies, primarily involving legs, arms and torso [15–16]. These developmental patterns may include head rolling, head banging, and body rocking [17]. In typically developing pre-school children, other stereotypies identified by parents included thumb sucking (25%), and nail biting (23%), both correlating with negative mood states [18].

Secondary stereotypies

Secondary stereotypies are those associated with neurological or sensory impairment. They have classically been associated with autism, which is defined as impaired social interaction and communication associated with restricted repetitive and stereotyped patterns of behavior, interests, and activities [7]. Thus, stereotyped and repetitive motor mannerisms can be central diagnostic features of autism. Young children with autism, particularly those aged between 3 and 4 years, tend to display more stereotypic behaviors than age-matched peers [19]. One observational study reported stereotypies in 25% of children with autism, and more prevalent in the lower functioning autism subtype [20], but others have reported that as many as 100% of autistic subjects had stereotypies [21–22]. Autistic stereotypies include body movements involving the hands (such as clapping) or whole body (such as...
Chapter 22

swaying or rocking). There may also be a fascination with the movement of other objects which may be incorporated into the stereotypy, such as the spinning wheels of toys or other rapidly revolving object. However, one observational study demonstrated the lack of predictive value in stereotypies with autism, as both autistic and non-autistic children were found to have a similar degree of stereotypies [23]. A high degree of abnormal repetitive behaviors have been identified in individuals with autism and in those with cognitive impairment in the absence of autism. Autistic individuals were associated with more frequent and more severe stereotypies than those with mental retardation without autism [24]. However, compared to individuals without mental retardation, a greater proportion of individuals with mental retardation engaged in stereotypies, such as body rocking [25].

Rett syndrome is a regressive disorder of psychomotor development following a normal early history till 5 months of age. It is characterized by developmental arrest or regression associated with loss of communication skills. The loss of previously acquired purposeful hand skills between ages 5 and 30 months are often seen, with the subsequent development of stereotyped hand movements [7]. Hand stereotypies are a hallmark of Rett syndrome (RS), particularly hand washing stereotypies, although a variety of motor stereotypies have been described in RS [26] (Video 22.1). These include most frequently bruxism, mouthing, pill rolling, and twisting of the trunk. Although initial reports suggested that children with RS who are MeCP2 positive are more likely to have diverse stereotypies that diminish with age [26], more recent reports suggest that hand stereotypies in adults can persist, and may help in making a diagnosis of RS [27].

Sensory deprivation, particularly visual impairment, has been associated with stereotypies. Specific impairments may be associated with distinctive stereotypies. For example, eye-poking and pressure on the eyeball appears to be relatively specific to children with a vision impairment, and especially to those with an intact optical nerve but a damaged cornea [28], and rocking is strongly associated with retinopathy of prematurity [29–30]. Stereotyped behaviors most frequently observed in children who were blind included body rocking, repetitive handling of objects, hand and finger movements, eye pressing, eye poking, lying face downwards, and jumping.

A study of non-handicapped children in residential care identified a prevalence of stereotypies in 58.5 % of the children studied [28]. However, the types of stereotypies seen were not different to that identified in the normal and autistic populations.

Various metabolic disorders associated with stereotypic movements have been reported. These include Lesch–Nyhan disease [31], neuroacanthocytosis [32], Wilson disease [33], and ornithine transcarbamylase deficiency [34]. In Lesch–Nyhan disease and neuroacanthocytosis, the stereotypic movements are often self-injurious in nature due to orofaciolingual movements, such as self-biting. Typically, metabolic disorders do not present with stereotypies in isolation, and are usually accompanied by other clinical features of the underlying condition.

Stereotypies can accompany psychiatric disorders such as anxiety or other affective disorders, obsessive compulsive disorder, Tourette syndrome, tardive dyskinesia, schizophrenia, and akathisia [14] (Video 22.2).

**Pathophysiology**

The underlying origins of stereotypies are still being investigated, but many explanations have been put forward. Basal ganglia circuit dysfunction has been implicated in the underlying pathogenesis of stereotypies. Rhythmic stereotypies are manifesta-
Stereotypies and Other Developmental Hyperkinesias

Stereotypies and Other Developmental Hyperkinesias...tions of the immature brain, reflecting incomplete cortical control of the motor system [15]. Immature circuitry is also suggested by onset of stereotypies in 90% of a population of children aged before 3 years [3], with improvements reported over time. Studies involving administration of a dopamine receptor agonist to rats induced motor stereotypies, and correlated with an activation of striatal neurons [35–36]. Deep brain stimulation (DBS) in two primates of the anterior, or limbic, subthalamic nucleus resulted in a dramatic reduction in stereotypies [37].

Volumetric magnetic resonance imaging studies in children with complex stereotypies have demonstrated a reduction in volumes of frontal white matter disproportionate to the total cerebral white matter, and in the caudate nuclei compared to age-matched controls [38]. This supports the view that dysfunction in the cortico-striatal-thalamo-cortical circuitry may underlie stereotypies. Indeed, stereotypic behaviors are often seen in patients who have evidence of frontal-subcortical dysfunction such as seen in fronto-temporal degenerations and other tauopathies [39] (Video 22.3).

Neurotransmitter dysfunction may also be involved. Stereotypies characterized by sniffing have been reproduced following injection of dopamine agonists into the anterior ventral striatum of rats [36] or d-amphetamine and meth.

Video 22.2 Tardive stereotypies
This is a 72 year old man previously treated with haloperidol for 5 years for anxiety gradually developed “nervous rubbing” of the right thumb and index finger, which progressed to more generalized stereotypies as part of tardive akathisia. Both the motor and sensory components improved markedly with tetrabenazine.

[Video courtesy of Joseph Jankovic, MD, Houston, Texas]

Videoclip of a 72 year old man previously treated with haloperidol for 5 years for anxiety gradually developed “nervous rubbing” of the right thumb and index finger, which progressed to more generalized stereotypies as part of tardive akathisia. Both the motor and sensory components improved markedly with tetrabenazine.

A positive family history of stereotypies has been identified in 25% of children with complex stereotypies, suggesting a possible genetic predisposition [3].

It has been suggested that stereotypic movements in normal infants allow them to experience kineesthetic sensations [17]. Deficient sensory processing has been implicated in various studies as a cause of stereotypies in autism [42].

Wing and Gould described a triad of features in autism, and suggested that impaired imagination is linked with restricted repetitive behaviors [43], the latter acting to compensate for the deficits in the former. More recent studies have identified a negative correlation between the amount of repetitive behavior, including motor stereotypies, in children with autism and the amount of time engaged in play activities, suggesting a possible association between repetitive behaviors and imagination [44].

Whether this is a behavioral “function” of stereotypies has been debated. Troster studied 142 non-handicapped children in residential care, and classified four types of situations which correlated with an increase in certain stereotypies: concentration and nail or lip biting; boredom and thumb sucking and hair twisting; frustration/concentration and face pulling or scratching oneself, and stimulation, in which no specific stereotypy was identified [28]. However, we favor the view that stereotypies are akin to other hyperkinetic movement disorders in which the movements are involuntary and arise from abnormal neuronal discharge patterns [45]. These patterns reflect underlying pathophysiology and not underlying psychopathology. In non-autistic, non-retarded children, it is quite common for children to be unaware that they are doing the stereotypies unless that is pointed out to them [3]. Stereotypies typically cease when...
the child is distracted or redirected. This apparent unawareness of stereotypies is similar to what has been observed for chorea in Huntington disease and dopa-induced dyskinesia in Parkinson disease [46]. A careful investigation in patients with Huntington disease was able to reject any psychodynamic contribution to the reduced self-awareness of involuntary movements [46]. Similarly, many patients with tic disorders are unaware of some or all of their tics, if they are mild [47]. These findings suggest that low awareness of certain kinds of involuntary movements is common and supports the idea that involuntary movements are not done for functional reasons.

**Treatment**

For primary stereotypies, usually education and reassurance is sufficient. For secondary stereotypies, treatment should be targeted at the underlying condition when possible. The efficacy of behavioral techniques for stereotypies has been studied, particularly for stereotypies considered less socially acceptable such as head weaving [48]. The various behavioral techniques are divided into aversive procedures or positive procedures. Aversive procedures include electric shock, physical restraint, aversive physical consequences, aversive music, overcorrection, timeout from positive reinforcement, and verbal punishment. In addition to the unethical nature of some of these techniques, there have been no long-term studies demonstrating sustained efficacy outside of isolated case reports. Positive procedures to reduce stereotypies includes habit reversal and awareness training, self-stimulation tokens, and differential reinforcement of other or incompatible behaviors. There are reports that combined use of habit reversal and differential reinforcement of other behavior is beneficial in reducing motor stereotypies in non-autistic children who were followed for a mean period of 12 months [49]. Besides this however, no long-term efficacy studies in these areas have been conducted. In children with sensory deprivation, a reduction in stereotyped behavioral traits was achieved by stimulating appropriate adaptive behavior [50].

There have been no controlled therapeutic trials examining the efficacy of benzodiazepines, alpha-adrenergic agonists, opiate antagonists, beta-blockers, antiepileptic medications, antipsychotics, monoamine depletors, such as tetrabenazine, and selective serotonin reuptake inhibitors (see [4] for review). Isolated reports have reported some improvement with selective serotonin reuptake inhibitors [51], clonazepam [52], clonidine [53], and dopamine depleting agents [54].

**Prognosis**

Few long-term follow up studies characterizing the outcome of children with stereotypies have been performed, and many of these have suggested that stereotypies are less likely to resolve than once suspected. Harris et al. followed a clinical cohort of children with motor stereotypies for a mean period of 12 months.
of 6.8 years [12], and 94% of children continued to have stereotypies at their most recent follow-up, suggesting stereotypies had a more chronic course, particularly if arm or hand movements were involved. Mahone et al. [10] found that only 5% of the children in their study had resolution of their stereotypy after a mean interval of 6.5 years after age of onset, despite studying a population of children without mental retardation. 50% of these children continued to have stereotypies that were unchanged in frequency and severity. Several comorbidities associated with stereotypies were also identified from these studies, including attention deficit hyperactivity disorder (30%), tics (18%), and obsessive compulsive traits (10%) [3].

A similar study of stereotypies in 10 children by Tan et al. found that stereotypies resolved in only 2 children [55]. Both parents and teachers reported a decrease in stereotyped behaviors associated with nervousness (thumb sucking, nail biting) with age [18]. Conversely, certain stereotypies such as thumb sucking and rocking were found to persist into adulthood more than other stereotypies, particularly if there were comorbid anxiety or affective disorders [14]. Many of these studies were performed at referral centers and may be associated with substantial ascertainment bias.

Other developmental hyperkinesias

A variety of largely benign hyperkinesias have been described in infants and toddlers. Many of these disorders may belong more properly to the spectrum of stereotypies, but they have been defined based on the nature of the movements.

Shuddering

Shuddering episodes are characterized by periods of rapid tremor of the head, shoulders, and arms that resemble shivering [56–57]. Age at onset is typically during infancy or early childhood. The episodes last several seconds and can occur up to 100 times each day. During a spell, there is no change in consciousness. Similarity to benign myoclonic epilepsy in infancy has been suggested [56, 58]. Parallels to stereotypies include age at onset in infancy and early childhood, rhythmicity of movements, and common association of facial grimacing. However, the movement frequency is usually slower in stereotypies, the duration of stereotypies tends to be longer (up to minutes), and stereotypies tend to persist into late childhood, or longer. Shuddering episodes typically resolve as the child grows older. The prognosis for development and neurological function is uniformly good. Some investigators (e.g. Vanasse et al. [69]; Kanazawa [56]) have suggested that “shuddering attacks” of infancy might be the initial manifestation of essential tremor, but a true link has not been proven.

Head nodding

Head nodding without accompanying nystagmus can occur as paroxysmal events in older infants and toddlers [59]. These head movements can be lateral (“no–no”), vertical (“yes–yes”), or oblique. The frequency (1–2 Hz) is slower than that of shuddering. They typically occur many times a day. The movements do not occur when the child is lying, but can occur in the sitting or standing position. The movements typically resolve within months, but can persist longer. Some children with head nodding have a prior history of shuddering spells; others may have a family history of essential tremor [60]. However, it is unclear whether there is any etiological relationship with these other conditions. An unusual head nodding epileptic syndrome has been described in sub-Saharan Africa. This head-nodding epilepsy syndrome appears to be associated with hippocampal sclerosis and may be related to infection with O. volvulus [61]. Developmental and neurological outcome are benign in idiopathic head nodding. Although the literature has referred to “head nodding” as a specific entity, we prefer to regard it as a simple primary stereotypes (see Box 22.1).

Spasmus nutans

Spasmus nutans is a condition beginning in late infancy (3–8 months) that is characterized by a slow head tremor (approximately 2 Hz) that can be horizontal (“no–no”) or vertical (“yes–yes”). The
head movements are indistinguishable from head nodding stereotypies. However, in spasmus nutans, the head movements are accompanied by a small-amplitude nystagmus that can be dysconjugate, conjugate, or uniocular [62]. The nystagmus is typically pendular with high frequencies (up to 15 Hz) and low amplitudes (0.5–3 degrees) and is most commonly dysconjugate [63]. When the child fixates on an object, the nodding may increase. If the head is held still, the amplitude of the nystagmus typically increases. Spasmus nutans generally resolves within several months, but the majority of patients continue to have a fine, subclinical, nystagmus until at least 5–12 years of age [64]. Long-term outcome is good.

Thus, ophthalmologic evaluation is recommended for children with spasmus nutans. Neuroimaging abnormalities, including tumor and aplasia of the cerebellar vermis, have been described in patients with spasmus nutans, but this is an uncommon association [65–67]. Routine neuroimaging in the absence of other evidence for intracranial pathology has limited yield [68].

Conclusions

Stereotyped repetitive behaviors are one of the more common forms of hyperkinetic movement disorder in childhood. Although commonly associated with autism and other developmental disorders, they occur in many children with no other neurologic disorders. The primary stereotypies are likely to have a generally good outcome. The neural basis of stereotypies is not known, but is likely to involve basal ganglia and frontal cortical circuits. Whether stereotypies are purposeless or “self-stimulating” is controversial, but it seems in non-autistic individuals with stereotypies that the movements are not done for any specific “purpose.” Behavioral and pharmacologic therapies have been reported in small studies, but there is no consensus regarding efficacy. Disorders that substantially resemble stereotypies have been defined as specific age-related syndromes. However, it is likely that many of these represent a developmentally specific part of the stereotypy spectrum.

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CHAPTER 23

Paroxysmal Dyskinesias

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Paroxysmal kinesigenic dyskinesia

Historical background

In 1901 Gowers described choreoathetotic attacks triggered by sudden movement without loss of consciousness [1], but considered them to be an epileptic phenomenon. An even earlier description exists, by Shuzo Kure (1892), who reported a 23-year-old man with brief episodes of involuntary movements triggered by sudden movement. Given the absence of previous reports at that time, the Japanese physician made a diagnosis of “atypical” myotonia congenita [2].

The term “paroxysmal kinesigenic dyskinesia” (PKD) was first coined in 1967 [3] when Kertesz reported 10 new cases and reviewed 31 cases from the literature.

Phenomenology and other clinical features

The current diagnostic criteria for PKD include an identified kinesigenic trigger, short duration of attacks (<1 minute), and no loss of consciousness or pain during the attacks. Interictal neurologic examination is normal and attacks are well controlled with phenytoin or carbamazepine [4]. The age of onset is between 1 and 20 years and a higher prevalence in males has been reported (up to 8:1) [5–7].

Video 23.1 Infantile paroxysmal kinesigenic dyskinesia

This is a 7-month-old child with early onset paroxysmal kinesigenic dyskinesias. He is taken while playing with a toy. Paroxysmal dystonia is induced by the voluntary movement of pushing the toy button. [Video courtesy of Nardo Nardocci, MD, Milan, Italy]

http://bit.ly/tETZw4

The typical trigger of the attacks is a sudden movement, such as standing up from a sitting or lying position, but also the simple intention to move or focal movements of the limbs can trigger an attack. Other rare precipitants include menstruation, cold weather, humidity, hunger, external motion, and startle.

A premonitory sensation preceding the attacks (aura) is reported in up to 82% of cases [4]. Typically, it is a general feeling of malaise, but also focal numbness and tingling of the extremities can be felt before the attacks; some patients can abort an attack, avoiding the movement when they feel the premonitory sensation.

Clinically, attacks are characterized by dystonia (the most common manifestation), chorea, ballismus, or a combination of these. Attacks are mostly unilateral, but can also be bilateral or alternating in distribution. Frequency ranges from a few attacks per year to more than 40 per day. More than 50% of patients report a spontaneous remission or significant reduction in the frequency after the age of 20 years [4]. Attacks last less than 1 minute in most cases but a duration of up to 5 minutes has been reported. Unlike epileptic seizures, consciousness is always preserved during the episodes and there is no postictal confusion or drowsiness. However, speech disturbances (dysarthria or anarthria), probably related to facial involvement, can occur.

**Epidemiology**

PKD is a rare neurological disorder and the precise prevalence is unknown, although it is estimated at 1:150,000.

**Etiology**

PKD can be primary or secondary. Most cases are primary — either sporadic or familial. In a recent series, 67% of patients had a family history with an autosomal dominant pattern of inheritance, sometimes with reduced penetrance [4]. Secondary PKD, due to structural cerebral lesions or other identifiable causes, have been described in 7.6% of patients [6]. Blakeley and Jankovic found that 17/76 (22%) patients with paroxysmal dyskinesias had a secondary underlying cause [8]. Of these, only 2 had PKD and 5 had intermediate symptoms between PKD and PNKD. Secondary causes of PKD include multiple sclerosis, vascular lesions, central or peripheral trauma and metabolic decompensation [2] (see Box 23.1). Psychogenic PKD have been reported as well [9].

Several patients with PKD also present infantile convulsions (Infantile Convulsions and Choreaathetosis, ICCA syndrome) and in 1997 a locus in the pericentromeric region of chromosome 16 was
reported for the first time [10]. This linkage for the PKD and ICCA syndrome has subsequently been confirmed by several groups to chromosome 16 (DYT10) [11–13], although no genes have been identified so far [14]. ICCA and PKD are now believed to be different manifestations of the same disorder, given the overlap of the genetic loci. Moreover, a Sardinian family with Rolandic epilepsy, paroxysmal exercise-induced dystonia, and writer’s cramp (RE-PED-WC) was also found to share the same locus on chromosome 16. A different locus (EKD2) on chromosome 16 has been identified in an Indian family with PKD [15] and a British family not linked to either of these loci has been described, providing evidence for a third locus (EKD3) [16]. Interestingly, some patients with episodic ataxia-1, caused by mutations in the \textit{KCNA1} gene on chromosome 12 encoding a potassium channel [17], can also present PKD and the two conditions share several features, including age of onset, triggering factors, and duration of the attacks.

Pathophysiology
The paroxysmal nature of PKD attacks, along with the frequent presence of an aura and the dramatic response to anticonvulsants, led some to consider PKD as a form of reflex epilepsy arising from a subcortical focus [18, 19], but surface EEG is usually normal during attacks and EEG changes (rarely reported) are of a questionable significance [19–21]. An involvement of basal ganglia (BG) is supported by the observation that secondary PKD occurs in conditions affecting the basal ganglia and response to levodopa has been described [22]. During attacks, accordingly, discharges from the caudate nucleus [23] as well as an increased metabolism in the BG with photon emission tomography (PET) [24] have been demonstrated. Furthermore, Single-photon emission computed tomography (SPECT) studies have shown an increased perfusion in the contralateral basal ganglia [25] that normalizes between attacks and an ictal hyperperfusion has been detected in the thalamus [26]. On the other hand, a bilateral hypometabolism in the ventral striatum has been shown in late-onset PKD [27] and ictal hypoperfusion in the caudate nuclei has been reported [28]. In this regard, diffusion tensor imaging (DTI) showed ultrastructural abnormalities in the thalamus of 7 PKD patients [29]. The exact neurophysiological mechanisms of PKD are still unknown but various defects in cortical and spinal inhibitory mechanisms have been described, including extended surround inhibition (see [30] for review).

Therapy
Patients with PKD have a particularly good response to low doses of carbamazepine (100–200mg daily) or phenytoin. Other anticonvulsants (oxcarbazepine, hydantoin, lamotrigine, topiramate) can also be effective in reducing the number of attacks, which often completely cease after initiation of therapy.

Paroxysmal non-kinesigenic dyskinesia
Historical background
In 1940 Mount and Reback reported the first family with paroxysmal non-kinesigenic dyskinesia (PNKD), calling it \textit{familial paroxysmal choreoathetosis}. The patient described had attacks of involuntary flexion of the arms and posturing of the legs lasting up to 2 hours without loss of consciousness. Richards and Barnet [31] introduced the term “paroxysmal dystonic choreoathetosis” for long-lasting attacks not triggered by sudden movement; this definition was also used by Lance in 1977 [32]. The term “paroxysmal-non kinesigenic dyskinesia” was first used by Demirkiran and Jankovic [33] in the currently used classification of paroxysmal movement disorders.

Phenomenology and other clinical features
PNKD is characterized by intermittent attacks of dystonia, chorea, or ballismus involving the extremities, trunk, and face. A combination of dystonia and chorea is the most frequent presentation [34]. Attacks mostly start in infancy and early childhood with mean age at onset reported to be 12 years in a large review of cases [35] and 4 years in \textit{MR-1} gene mutation carriers (see “Etiology” below).
Up to 41% of patients report an aura-like sensation (stiffening or numbness, internal feeling of anxiety) before the attacks [34] that typically last from 10 minutes to few hours. Frequency ranges from a few per year to several per day and tends to decrease with aging and during pregnancy. Typically, attacks are triggered by coffee, alcohol, and emotional stress; other precipitants include exercise, fatigue, heat, hunger, and menstruation [34, 36, 37]. Sleep benefit (attack resolved if the patient goes to sleep) is reported by several patients [34, 38]. Consciousness is always preserved during the episodes and transient dysarthria and dysphagia can be present during severe attacks.

**Epidemiology**

Idiopathic (primary) PNKD is a rare disorder and its exact prevalence is unknown. However, familial cases are more frequent than the sporadic ones. PNKD was described in 52% of patients with secondary paroxysmal dyskinesias reported by Blakeley and Jankovic [8].

**Etiology**

Primary PNKD is transmitted as an autosomal dominant trait with a 98% penetrance [34]. In 2004, two disease-causing missense mutations in the myofibrillogenesis regulator-1 gene (MR-1, also referred to as PNKD or DYT8) on chromosome 2 were found in patients with familial PNKD [39, 40]. These have been confirmed in other families [34] and recently another mutation in the same gene has been reported [41]. A second locus (PNKD2) has been described on chromosome 2q31 in a Canadian family but no gene has been identified. Affected subjects of this family differ from those with MR-1 mutations in that coffee and alcohol do not trigger attacks [42]. MR-1 mutation carriers show a homogeneous clinical phenotype and specific diagnostic criteria to individuate these subjects have been proposed [34].

Secondary causes of PNKD include stroke, central and peripheral trauma, kernicterus, multiple sclerosis, hypoglycemia, encephalitis [8], Fahr disease [43], and coeliac disease [44]. Psychogenic PNKD must also be taken into account [32, 45] (see Box 23.1).

**Pathophysiology**

The pathophysiology of PNKD remains controversial. The gene MR-1 encodes MR-1, a protein expressed in three different isoforms (MR1-1L, MR1-1M, MR1-1S) by alternative splicing. MR1-1L is specifically expressed in the brain and is homologous to hydroxyacylglutathione hydrolase, an enzyme involved in the detoxification of methylglyoxal, a by-product of oxidative stress also found in coffee and tea, thus a mechanism whereby alcohol, caffeine, or stress may precipitate attacks has been suggested [40]. According to recent findings, MR1-1L and MR1-1S are proteins imported into mitochondria through a mitochondrial targeting sequence that contains the mutations discovered so far [41]. However, the exact function of the protein and its role in neuronal excitability as well as the mechanisms by which MR-1 mutations cause PNKD remain unknown.

Alterations of the basal ganglia, such as striatal dopaminergic dysfunction, have been postulated as an underlying mechanism but 11C-dihydrotetabenazine PET imaging failed to reveal an abnormal binding, thus ruling out an altered density of nigrostriatal innervation [46]. On the other hand, a marked reduction in the density of postsynaptic dopamine D2 receptors has been shown by 18F-dopa PET and 11C-raclopride PET [47]. Moreover, ictal SPECT showed hyperperfusion on the right caudate and thalamus of a patient with PNKD, supporting the notion that the basal ganglia are the anatomical

---

**Box 23.1 Secondary causes of paroxysmal dyskinesia**

- Multiple sclerosis
- Stroke and TIsA (thalamus, putamen, medulla), moyamoya
- Infections (CMV encephalitis, syphilis, HIV)
- Central and peripheral trauma
- Metabolic disorders (hypoglicemia, hyperglicemia, hypocalcemia)
- Migraine
- Neurodegenerative diseases, such as Parkinson disease and Fahr disease
- Others: kernicterus, coeliac disease
substrate of this disorder [48]. Finally, a mutation in KCNMA1 on chromosome 10q22 encoding a calcium-activated potassium channel has been identified in a family with various combinations of epileptic seizures and PNKD [49].

**Treatment**

Although PNKD has been traditionally considered difficult to treat, in contrast to the dramatic response of PKD to anticonvulsants, Bruno, et al. [34] reported that 97% of MR-1 mutated patients responded to benzodiazepines (clonazepam, diazepam), while antiepileptic drugs (valproate, carbamazepine, phenytoin) were less effective. MR-1 negative patients tend to have a partial response either to benzodiazepine or to anticonvulsants. Lorazepam has been reported to abort the attacks within 5 minutes from onset if administered sublingually [50]. Deep brain stimulation (DBS) of the ventrointermediate thalamus and of the internal globus pallidus has been successful in 2 cases of secondary PNKD [51, 52]. Bilateral internal globus pallidus DBS was successful in a case of primary PNKD who, however, also had other neurological and psychiatric features [53].

**Paroxysmal exercise-induced dyskinesia**

**Historical background**

In his classification of paroxysmal movement disorders, Lance defined an intermediate form including attacks lasting 5 to 30 minutes that were triggered by continuous exertion rather than sudden movement [32]. The term “paroxysmal exertion-induced dyskinesia” (now named paroxysmal exercise-induced dyskinesia, PED) was first used in Demirkiran and Jankovic’s classification in 1995 [33].

**Phenomenology and other clinical features**

PED is characterized by dyskinesias induced by prolonged exercise of 15- to 60-minute duration. Other precipitating factors include stress, starvation, and sleep deprivation, as reported for GLUT1 gene-mutated patients (see “Etiology” below) [54]. Alleviating factors encompass eating (especially sugar) and rest. Mean age of onset is 8 years (range 3 to 30 years). The attacks last minutes to hours with a median duration of 15 minutes. Dystonia of the exercised limb with distal involvement (feet and hands) is the most common presentation, sometimes spreading to the adjacent muscles. Chorea affecting axial and orobuccal muscles has also been reported [55]. Episodes are mostly symmetrical but can be unilateral, with a frequent hemidystonic presentation [7]. Frequency of the attacks varies from daily to monthly. Autonomic symptoms (sweating, pallor, hyperventilation), an uncomfortable epigastric sensation, anxiety, and paresthesias are reported by some patients prior to the onset of the attacks. Neurological examination is normal between attacks, although interictal myoclonus and dystonia have been described [56]. PED can be isolated or part of more complex phenotypes, including various combination of epilepsy, hemolytic anemia, ataxia, spasticity, cognitive problems, migraine, and other interictal movement disorders (dystonia, tremor, myoclonus) with different degrees of severity (see [55] and [57] for reviews).

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**Video 23.5 GLUT1 deficiency**

This patient has a GLUT1 deficiency syndrome. Segment 1 shows the patient at age 19 years presenting with dysarthria, ataxia, hyperreflexia in lower limbs, and mild choreoathetoid movements of arms. Segment 2 shows the patient during an exercise-induced paroxysmal dyskinesia, characterized by dystonic posturing of legs and trunk and choreoathetoid movements of arms. The case has been previously reported [58]. [Video courtesy of Nardo Nardocci, MD, Milan, Italy]

Epidemiology

PED is a rare disorder with unknown prevalence and incidence, and cases reported worldwide are biased by the awareness of the disorder. Incidence/prevalence of GLUT1 deficiency in Queensland, Australia, has been estimated at approximately 1:90,000 by Coman, et al. [58].

Etiology

Most cases of PED are primary, familial or sporadic. PED can also be secondary to different underlying conditions, including peripheral trauma, Dopa-responsive dystonia, Parkinson’s disease [59, 60]. In Parkin mutations carriers PED can be the presenting symptom (see Box 23.1).

Recently, mutations in SCLA1 (DYT18) have been identified in patients with PED alone or in combination with epilepsy and hemolytic anemia [54, 61], with some patients exhibiting a mild mental retardation. SCLA1 encodes the glucose transporter type 1 (GLUT1), expressed in red blood cells and in the blood–brain barrier (BBB). Mutations in this gene are now thought to be responsible for a spectrum of disorders with different degrees of severity, ranging from the so-called GLUT1 deficiency syndrome (epilepsy, deceleration of head growth, developmental delay, spasticity, dystonia and ataxia) described by De Vivo in 1991 [62] to pure PED [57]. SCLA1 mutations are inherited as an autosomal dominant trait; penetrance is generally complete but 3 unaffected carriers have been reported [54].

The absence of SCLA1 mutations in some familial cases suggests the involvement of other genes in the pathogenesis of PED.

Pathophysiology

Reduced transport of glucose across the BBB when the energy demand of the brain overcomes its supply after prolonged exertion is thought to be the pathophysiological mechanism responsible for the attacks in SCLA1 mutation carriers; accordingly, patients display hypoglycorrachia and a reduced CSF/serum glucose ratio. A decreased availability of glucose could thus result in a transient basal ganglia dysfunction. This hypothesis is supported by PET studies showing thalamocortical and cerebellar hypometabolism and increased metabolism in the putamen [54, 61]. Ictal SPECT has shown hyperperfusion of the putamen and leg cortical areas [54]. EEG is generally normal during attacks.

Treatment

Beneficial effect of a ketogenic diet (high fat, low carbohydrate) has been noted. Ketones produced through fatty acid oxidation, in fact, can cross the BBB providing an alternative energy substrate for brain metabolism. Ketogenic diet markedly improves seizures and complex motor disorders in the classical GLUT1 deficiency syndrome [57]. Its effect on PED is variable, ranging from complete remission of symptoms [54, 61] to no improvement, although a general improvement of gait has been observed in a recent series [55].

Other paroxysmal movement disorders

Episodic ataxias

The first cases of familial periodic ataxia were probably reported in 1946 by Parker; in the 1990s the first gene locus of an episodic ataxia (EA) was mapped to chromosome 12p. EAs are characterized by intermittent attacks of ataxia and vertigo [63] and are infrequent autosomal dominant disorders with unknown prevalence. EA2 is the most frequent form, followed by EA1. Ictal and interictal myokymia is a hallmark of EA1. Interictal nystagmus and slowly progressive ataxia are common in EA2, that is allelic with Familial Hemiplegic Migraine type 1 and Spinocerebellar Ataxia type 6, explaining the frequent clinical overlap [63, 64]. A comparative summary of EAs is shown in Table 23.1.

Other causes of paroxysmal ataxia: intermittent attacks of ataxia have been reported in multiple sclerosis [66–68], Behçet disease [69], Hartnup disease [70], maple syrup urine disease [71], and pyruvate decarboxylase deficiency [72, 73].
<table>
<thead>
<tr>
<th>Locus, gene</th>
<th>Age of onset (years)</th>
<th>Typical duration of attacks</th>
<th>Triggers</th>
<th>Ictal features</th>
<th>Interictal features</th>
<th>Effective treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>EA1</td>
<td>12p13, KCN1A</td>
<td>2–15 Seconds to minutes</td>
<td>Stress, startle, fatigue, hunger, exertion, sudden movement</td>
<td>Ataxia, vertigo, dizziness, dysarthria, head titubation, tremor, oscillopsia, diplopia, nausea, headache, myokymia</td>
<td>Myokymia, sometimes seizures</td>
<td>Acetazolamide, carbamazepine, valproic acid</td>
</tr>
<tr>
<td>EA2</td>
<td>19p13, CACNA1A</td>
<td>2–20 Hours</td>
<td>Anxiety, exercise, heat, fever</td>
<td>Ataxia, vertigo, nausea, migraine</td>
<td>Nystagmus, progressive cerebellar ataxia</td>
<td>Acetazolamide, 4-aminopiridine</td>
</tr>
<tr>
<td>EA3</td>
<td>1q42</td>
<td>1 minute to 6 hours</td>
<td>Stress, exertion, fatigue, head movements, bending, arousal from sleep</td>
<td>Ataxia, vertigo, tinnitus, nausea, visual blurring, headache, diplopia, myokymia</td>
<td>Congenital nystagmus, coloboma, seizures</td>
<td>Acetazolamide</td>
</tr>
<tr>
<td>EA4</td>
<td>Unknown</td>
<td>23–60 Minutes</td>
<td>Sudden change in head position, fatigue</td>
<td>Ataxia, vertigo, diplopia</td>
<td>Defective smooth pursuit, gaze-evoked nystagmus</td>
<td>Acetazolamide is unhelpful</td>
</tr>
<tr>
<td>EA5</td>
<td>2q22–23, CACNB4</td>
<td>20–30 Hours</td>
<td>None reported</td>
<td>Ataxia, vertigo</td>
<td>Downbeat and gaze-evoked nystagmus, mild dysarthria, ataxia</td>
<td>Acetazolamide (transient benefit)</td>
</tr>
<tr>
<td>EA6</td>
<td>5p, SLC1A3</td>
<td>Months to 14 years</td>
<td>Hours to days Fever, stress, fatigue, exercise, alcohol, caffeine</td>
<td>Hypotonia (infancy), ataxia, slurred speech, diplopia, blurred vision, alternating hemiplegia, aphasia, seizures, migraine, nausea, phonophobia, photophobia, fluctuating alertness</td>
<td>Ataxia, hyperreflexia</td>
<td>Acetazolamide</td>
</tr>
<tr>
<td>EA7</td>
<td>19q13</td>
<td>&lt;20 Hours</td>
<td>Exercise, excitement</td>
<td>Ataxia, vertigo, dysarthria, weakness</td>
<td>None</td>
<td>None reported</td>
</tr>
<tr>
<td>LOHEA</td>
<td>Unknown</td>
<td>48–56</td>
<td>1 minute to 2 hours Coffee, alcohol, emotion, overwork, head movements</td>
<td>Ataxia, vertigo, diplopia, slurred speech</td>
<td>Progressive ataxia, nystagmus, cerebellar atrophy in MRI</td>
<td>Poor response to acetazolamide</td>
</tr>
</tbody>
</table>
Psychogenic paroxysmal movement disorders (P-PMDs)

Classical clues pointing to a diagnosis of a psychogenic movement disorder (abrupt onset, intermittent symptoms, variability) can all occur in organic PMDs, making the diagnosis challenging. Other information may be particularly useful for a positive diagnosis of a P-PMD, for instance secondary gain (e.g. litigation), distractibility, other physical findings (e.g. give-way weakness), and improvement or remission with suggestion, placebo or psychotherapy [74, 75].

Other episodic disorders that can be confused with paroxysmal movement disorders

Epileptic disorders

Epileptic disorders with motor manifestation should be considered in the differential diagnosis of PxD, especially when consciousness is preserved during the motor events. Juvenile myoclonic epilepsy is characterized by myoclonic jerks especially in the upper limbs appearing upon awakening. These patients occasionally drop objects, thus being labeled as clumsy [76]. Focal motor seizures are also a possible differential diagnosis of paroxysmal dyskinesias [77].

The so called hypnogenic paroxysmal dyskinesias are now recognized as part of the nocturnal frontal lobe epilepsy (NFLE) spectrum. Attacks occur at night and are characterized by tonic and dystonic postures of the limbs, trunk, pelvis, sometimes accompanied by vocalizations and automatisms. An autosomal dominant family history is frequently observed and mutations in CHRNA3, CHRNA5, and CHRN4, encoding α3, α5, and β4 subunits of the nicotinic acetylcholine receptor have been reported in familial and sporadic cases [78].

Limb-shaking transient ischemic attacks

Shaking movements of an arm or leg resembling focal motor seizures can occur in contralateral transient brain ischemia (carotid stenosis or occlusion [79], Moyamoya disease [80]), without EEG abnormalities. Accurate diagnosis is mandatory, since adequate investigation, treatment, and preventive measures are warranted.

Tonic spasms

They consist of intermittent uni- or bilateral dystonic posturing usually lasting less than 2 minutes, occurring in a stereotyped fashion in each patient, sometimes several times per hour; pain often coexists (painful tonic spasms). Preceding auras are common, and triggers include movement, hyperventilation and emotions. Tonic spasms have been mainly reported in multiple sclerosis. Symptoms are thought to result from ephaptic spreading of spontaneous discharges originating from demyelinated axons in various locations along the motor pathway. Corticosteroids and carbamazepine have been used for the treatment [81, 82].

Superior oblique muscle (SOM) myokymia

They consist in sudden, intermittent, involuntary, unilateral SOM contractions and corresponding eye movements, usually lasting seconds, resulting in oscillosia or vertical diplopia. Patients complain of “jumpy”, “shaky” or “vibrating” vision. Many cases are idiopathic, but vessels contacting the trochlear nerve have also been found [83]. Carbamazepine and propranolol are usually effective [84]; success with memantine has also been reported. Surgery has been beneficial in severe refractory cases [85].

Disorders of infancy and childhood

Benign paroxysmal torticollis of infancy (BPTI) is characterized by torticollis, head tilting, and occasional
Paroxysmal Dyskinesias

Paroxysmal dyskinesia is a rare condition characterized by involuntary movements of the body, typically involving the head, neck, and trunk. The condition is associated with a genetic predisposition and often occurs in children. The movements are often triggered by stress or fatigue and can be accompanied by irritability and crying.

The Sandifer syndrome is a condition characterized by gastroesophageal reflux disease (GER) and paroxysmal abnormal movements of the head, eyes, neck, and trunk. These movements include ocular and cephalic version, head tilting, torticollis, retrocollis, and trunk dystonia. Irritability and crying usually accompany the episodes, which may occur several times a day. Sandifer syndrome is more common in young males (2 months to 5 years); motor growth retardation was found in some patients, but normal neurological examination is the rule. Treatment of GER generally leads to improvement of abnormal movements.

Paroxysmal tonic upgaze (PTU) of childhood is an uncommon condition usually emerging before 1 year of age and remitting by 5 years, characterized by involuntary tonic upward ocular deviations, associated with compensatory neck flexion and downbeating saccades when attempting downgaze. Fever triggers the episodes and sleep provides relief. Ataxia and mild developmental cognitive difficulties can be present. Differential diagnosis includes iatrogenic oculogyric crisis, brainstem lesions, epileptic events, but consciousness is unimpaired; cases associated with absence epilepsy have been reported. A two-generation family has been described with individuals affected by either PTU, EA or BPTI, and one patient with both PTU and EA: a point mutation in CACNA1A gene was found. Levodopa is helpful in some cases.

Childhood masturbation is a normal behavior that may resemble a PMD, sometimes prompting long and unproductive diagnostic efforts. The episodes are fairly stereotyped, with the child exerting pressure on the perineum or suprapubic area, accompanied by typical lower limb posturing and rhythmic pelvic movements; facial flushing, diaphoresis and grunting are common, but genital manipulation is rare. Age of onset ranges from 3 months to 3 years. No impairment of consciousness is observed, interruption of behavior occurs with distraction, and the examination is normal.

Conclusion

Paroxysmal dyskinesias are uncommon hereditary disorders. Three major syndromes are now recognized: PKD, PNKD, and PED. A causative gene has been found for two of these. A number of other disorders that manifest intermittently with motor disturbance are important to be considered in the differential diagnosis. Management and prognosis of each disorder specified in this text is quite different, rendering diagnostic accuracy imperative.

References

1. Gowers WR (1901) Epilepsy and Other Chronic Convulsive Diseases; Their Causes, Symptoms and Treatment. JAMA; XXXVII (13):848.


CHAPTER 24
Psychogenic Movement Disorders

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Introduction

Psychogenic movement disorders (PMDs) are caused by psychologic factors rather than by an organic etiology. Other terms such as “functional,” “non-organic,” and “medically unexplained symptoms” have been used. Although the term “functional” might be more convenient to convey to patients and their families – because of old stigmas regarding having a psychologic disorder – the term “psychogenic” describes the condition best because it places the emphasis on etiology and thereby guides the physician toward appropriate treatment. The term “functional” is ambiguous because it has been used in the past to denote organic diseases in which a specific cause could not be determined, and to organic illnesses considered physiologic rather than anatomic, such as chorea, epilepsy, and neuralgias [see historical reviews by Fahn [1] and Munts and Koehler [2]. The terms “organic” means “not due to a psychogenic or voluntary mechanism.” Thus, non-organic refers to a psychogenic or voluntary etiology. A non-epileptic seizure is also being designated as psychogenic rather than the less satisfying term of pseudoseizure [3, 4].

PMDs are not uncommon. In one large movement disorder clinic, such patients account for 10% of all non-parkinsonian new patient visits [5]. Although young women are often thought to be particularly vulnerable to PMDs, the disorder certainly affects both genders and may be manifested even in children [6, 7]. Typically, patients are diagnosed by the predominant movement feature, e.g. psychogenic tremor, psychogenic dystonia, psychogenic myoclonus, etc. When categorized this way, tremor is the most common psychogenic phenomenology, followed by dystonia (Table 24.1).

Diagnosis

The diagnosis of a PMD is a two-stage process [8]. First, the clinician makes a positive diagnosis that the movements are psychogenic and not due to an organic illness. The second step is to identify the nature of the psychiatric disorder that could explain the etiology of the abnormal movements and prepare the way to deciding the best course for therapy of the individual patient. Deciding between abnormal movements due to a psychogenic cause and an organic one can be extremely difficult. Never having seen strange movements before and pronouncing them to be psychogenic is insufficient and prone to error. Not even a senior movement disorder specialist who has seen a whole gamut of organic abnormal movements has seen all there is. An organic cause of the movements needs to be
excluded, but this alone is insufficient. Rather, the diagnosis of a psychogenic disorder depends on finding positive criteria and not simply the failure to find an organic cause.

The degree of certainty that the abnormal movements are psychogenic in origin was first proposed by Fahn and Williams [9] and categorized into four sections.

**Documented PMD.** The movements are relieved by psychotherapy, by the clinician utilizing psychological suggestion including physiotherapy, or by administration of placebos, or the patient must be witnessed as being free of symptoms when left alone, supposedly unobserved. Surveillance monitoring has been utilized by insurance companies to guard against fraudulent malingering [10], but this approach is rarely used by clinicians.

**Clinically established PMD.** The movements are inconsistent over time (i.e. the features are different when the patient is observed at subsequent examinations) or are incongruent with a classical movement disorder. If only one of these is witnessed, then one or more additional features are needed: fake weakness (i.e. give-way weakness), false sensory findings, self-inflicted injuries, multiple somatizations, deliberate slowness, excessive fatigue, movements disappear with distraction, or electrophysiologic evidence that the movements do not fit with an organic pattern of movement. The last item applies principally to the analysis of myoclonus and tremor, since other movements can be easily duplicated by voluntary movements.

**Probable PMD.** The movements are inconsistent over time or are incongruent but the other features listed above are lacking.

**Possible PMD.** Suspicion that the movements are psychogenic and the presence of a definite psychiatric disturbance.

### Psychiatric classification

In addition to the neurologist making the diagnosis of a PMD, the psychiatrist needs to evaluate the patient to explore psychodynamics and relevant environmental contingencies [8]. PMDs can be due to one of the following three categories.

**Somatoform disorder.** The physical symptoms are linked to psychological factors, yet the symptom production is *not under voluntary control*, i.e. *not consciously produced*. The two main types of somatoform disorders producing psychogenic neurologic problems are *conversion disorder* and *somatization disorder*, the latter also being known as hysteria or Briquet syndrome. A somatization disorder involves recurrent and multiple complaints of several years duration for which medical care has been sought, but which are apparently not due to any physical disorder. The dynamics are presumably the same as those of conversion disorder and the symptoms may emerge from chronic, recurrent, untreated conversion disorder. It should be noted that depression commonly accompanies somatoform disorders.

**Factitious disorder.** The physical symptoms are intentionally produced (hence under voluntary control) due to psychological need. This group includes Munchausen syndrome. Factitious disorders are due to a mental disorder. They are generally associated with severe dependent, masochistic, or antisocial personality disorders.

**Malingering.** The physical symptoms are voluntarily produced in pursuit of a goal such as financial compensation, avoidance of school or work, evasion of criminal prosecution, or acquisition of drugs. Malingering is not considered to be a

### Table 24.1 Predominant movement feature in psychogenic movement disorders.

<table>
<thead>
<tr>
<th>Predominant movement feature</th>
<th>N</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tremor</td>
<td>467</td>
<td>37.5</td>
</tr>
<tr>
<td>Dystonia</td>
<td>365</td>
<td>29.3</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>146</td>
<td>11.7</td>
</tr>
<tr>
<td>Gait disorder</td>
<td>114</td>
<td>9.2</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>60</td>
<td>4.8</td>
</tr>
<tr>
<td>Tics</td>
<td>29</td>
<td>2.3</td>
</tr>
<tr>
<td>Other</td>
<td>64</td>
<td>5.1</td>
</tr>
<tr>
<td>Total</td>
<td>1,245</td>
<td>100</td>
</tr>
</tbody>
</table>

Data from Lang [13]. A tabulation of psychogenic movement disorders seen at eight centers; most centers report their patients by a single primary motor feature, but some report multiple features if more than one is present.
Psychogenic Movement Disorders

It is listed as a PMD, not because of a psychologic cause, but because it is voluntary and not due to an organic cause.

Somatoform disorders are the most easily treated, while factitious disorders persist until the patient is psychologically ready to give up the abnormal movements. Malingering may be impossible to treat until the patient’s gain is obtained or the patient voluntarily gives up the symptoms.

In some psychiatric conditions, abnormal involuntary movements are part of the clinical spectrum. These abnormal movements should not be considered as PMDs. Some of the movements seen are not equivalent to abnormal movements that can be seen as part of some psychiatric condition. Table 24.2 lists some of these movement difficulties seen as part of the psychiatric condition, such as stereotypies in schizophrenia or autism. The condition of “fear of falling” has been considered psychogenic [11]. But, patients with this condition have usually fallen in the past and now have a genuine fear of falling. It’s possible that the fear is excessive and is due to unrealistic anxiety. But in that situation, the condition is a psychiatric one and the gait disorder is not a conversion reaction. Thus, it seems reasonable to consider the gait abnormality of “fear of falling” to be classified as a psychiatric disorder.

Clues suggesting the presence of a psychogenic movement disorder

Often there are clues from the history and neurologic examination that lead the clinician to suspect a diagnosis of a PMD. If present, these clues should alert the observant clinician to consider the possibility that the abnormal movement could have a psychogenic etiology.

### Historical

1. Abrupt onset
2. Spontaneous remissions
3. Onset after minor trauma
4. Multiple somatizations of undiagnosed conditions
5. Obvious psychiatric disturbances
6. Employed in the health profession or in health insurance claims
7. Presence of secondary gain, including continuing care by a “devoted” spouse
8. Litigation or compensation pending

### Clinical examination

1. Inconsistent movements (changing characteristics over time; pattern, body distribution, rapidly varying severity)
2. Incongruous movements and postures (movements don’t fit with recognized patterns or with normal physiological patterns
3. Presence of rhythmic shaking
4. Bizarre gait including knee-buckling
5. Deliberate slowness carrying out requested voluntary movement
6. Bursts of verbal gibberish
7. Delayed or excessive startle (bizarre movements in response to sudden, unexpected noise or threatening movement).
8. Presence of additional types of abnormal movements that are not known to be part of the primary or principal movement pattern that the patient manifests.
10. Movements decrease or disappear with distraction
11. Disappearance of tremors when handling treasured objects

<table>
<thead>
<tr>
<th>Abnormal movements that occur in specific psychiatric disorders</th>
<th>Psychiatric disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychomotor slowness</td>
<td>Depression</td>
</tr>
<tr>
<td>Obsessional slowness</td>
<td>Obsessive compulsive disorder</td>
</tr>
<tr>
<td>Compulsive movements</td>
<td>Obsessive compulsive disorder</td>
</tr>
<tr>
<td>Catatonia</td>
<td>Schizophrenia, depression</td>
</tr>
<tr>
<td>Stereotypies</td>
<td>Obsessive compulsive disorder, autism, schizophrenia</td>
</tr>
<tr>
<td>Fear of falling</td>
<td>Anxiety, agoraphobia</td>
</tr>
</tbody>
</table>

Table 24.2 Movement disorders that are part of the symptom complex of specific psychiatric disorders.
12 Entrainment of the tremor to the rate of the requested rapid successive movement the patient is asked to perform.
13 Response to placebo, suggestion or psychotherapy
14 Dystonia beginning as a fixed posture
15 Manifestation as a paroxysmal disorder
16 Dystonia beginning as a rest dystonia or as a fixed posture
17 Twisting facial movements that move the mouth to one side or the other (Note: Organic dystonia of the facial muscles usually does not move the mouth sidewise, whereas organic jaw dystonia can move the jaw sidewise)
18 Fake weakness
19 False sensory complaints
20 Self-inflicted injuries

**General clinical features**

Besides the specificities of the abnormal movements there are some demographic features that have been observed in patients with PMDs. In their review of 131 cases of documented or medically established PMDs, Williams and colleagues [12] observed that: the mean age at onset was 36.9 years (range: 4–73 years); the female gender predominates (87%); an organic component occurred in 13%; 75% of cases had previously received an organic diagnosis; 79% had more than a single type of abnormal movement; the movements were paroxysmal in 55%; onset was abrupt in 60%; and symptoms spread from the original site to other sites in 43%. They also reported that the psychiatric diagnosis was conversion disorder in 75%, somatization disorder in 12.5%, factitious disorder in 8.3%, and malingering in 4.2%. Depression was seen in 71% and anxiety in 17%.

**Psychogenic tremor**

Rhythmical shaking occurs in the majority of patients with PMDs. When tremor is the only abnormal movement or the predominant one, the patient is classified as having psychogenic tremor. This was the most common PMD diagnosis reported by Lang [13] and by Jankovic and Thomas [14]. The tremor tends to be present equally at rest, with posture holding and with action. Distracting the patient with a disappearance of the tremor is a helpful sign that the tremor is psychogenic [15], but it is not specific enough. Many patients with organic tremor can temporarily suppress the tremor, such as with parkinsonian tremor; furthermore, distractibility is often difficult to observe. Many patients are sophisticated, and it is difficult to eliminate their tremor with distraction. Entrainment of the tremor to a new frequency may sometimes be seen by having the patient touch thumb to the different fingers in a dictated pattern either in the involved hand or in the opposite hand. Of 12 patients with psychogenic tremor compared to 33 with organic essential tremor studied by Kenney and colleagues [16], psychogenic tremor was significantly more likely to start suddenly and was more likely associated with spontaneous remissions compared to essential tremor. McKeon and colleagues [17] followed up their 62 patients with psychogenic tremor; 33 responded over time. The outcome was good (mild or no tremor) in 36%, moderate in 24%, and severe in 40%. Five patients with the good outcome had spontaneous improvement without psychotherapy.
Psychogenic Movement Disorders

Deuschl et al. [18] observed that finger tremor is usually absent in psychogenic tremors. They also reported the “coactivation sign” in which psychogenic tremors often show an increase of tremor amplitude, when a weight is applied to the involved limb. This contrasts to a reduction in tremor amplitude with applied weights in organic tremors. Accelerometers applied to the affected body part can be helpful. Psychogenic tremors show larger tremor frequency changes and higher intraindividual variability while tapping [19]. Motor control physiology can be useful to distinguish psychogenic from organic tremor [20].

Psychogenic dystonia

Psychogenic dystonia is the second most common type of PMD. Psychogenic dystonia is difficult to diagnose since there are no laboratory tests, such as EMG, to establish the diagnosis of organic primary idiopathic dystonia. Simultaneous contractions of agonist and antagonist muscles, the EMG hallmark for organic dystonia, can be easily duplicated voluntarily. Both organic and psychogenic dystonia patients show a reduced cortical and spinal inhibition [21–23]. However, cortical plasticity has been found in organic dystonia, but not in psychogenic dystonia [23], and if this is replicated, testing for plasticity might turn out to be a useful test.

For many years after dystonia was first described, many cases had been considered psychogenic, 52% in the series by Eldridge et al. [24], 43% seen by Marsden and Harrison [25], 25% reported by Cooper and his colleagues [26], and 44% in the series by Lesser and Fahn [27]. With the wider recognition of dystonia by neurologists, and with the knowledge that most cases are primary, not secondary dystonia, it seems that psychogenic dystonia is currently underdiagnosed. The clinical clues listed above and reported by Fahn and Williams [9] should help the clinician to suspect psychogenic dystonia when it is encountered.

Idiopathic torsion dystonia usually begins with action dystonia [28], but psychogenic dystonia often begins with a fixed posture. Fixed postures are sustained postures that resist passive movement, and the presence of such fixed postures are highly likely to be due to a psychogenic dystonia [9, 29–31]. Fixed posture dystonia is rare and when encountered it is often psychogenic in origin; the evaluation of fixed postures requires the aid of anesthesia to see if contractures are present [32]. The posture can manifest so much rigidity that it is extremely difficult to move the limb about a joint. Often, such psychogenic fixed dystonia resembles reflex sympathetic dystrophy (complex regional pain syndrome, CRPS) because there is accompanying pain, tenderness (alldynia) and skin changes [29–31, 33–36]. Nerve injury leading to pain, shiny red skin and fixed postures was called causalgia by Mitchell et al. [37]. Charcot [38] considered the disorder hysterical (see Munts and Koehler [2]). The term “reflex sympathetic dystrophy” was coined by Evans [39] because the phenotype could occur in the absence of trauma to a major nerve and might be due to sympathetic nerves. “Complex regional pain syndrome “ was the recommended term in 1994, with Type 1 being reflex sympathetic dystrophy and Type 2 being causalgia [40]. Some cases of
CRPS have been proven to be psychogenic; it’s possible that some cases are organic. This is a highly controversial topic. A recent proposal that small fiber neuropathy might be responsible for CRPS [41] has been countered that the patient had the phenomenology of a psychogenic dystonia [42].

To make matters confusing, sometimes organic dystonia of a body part can be preceded by an injury to that body part [43–47], so it can be difficult to distinguish between organic and psychogenic dystonia. Fixed painful postural torticollis following trauma is not uncommon, and determining whether it is organic or psychogenic may be difficult [48].

The prognosis of fixed dystonia is often poor [49], but it depends on recognizing this disorder as likely to be a psychogenic one and then applying treatment according to the principles described below.

**Psychogenic myoclonus**

Psychogenic myoclonus should be relatively easy to distinguish from organic myoclonus if access to a motor control physiology laboratory is available [50, 51]. The short duration of a myoclonic jerk (usually less than 100 ms) is almost impossible to duplicate voluntarily. The EMG pattern of voluntary jerks exhibits a triphasic pattern of activity between antagonistic muscles, whereas cortical myoclonus consists of short-duration 25–50 ms bursts of cocontracting antagonist muscles [52]. Furthermore, the latency of reflex myoclonus is physiologically short (40 to 100 ms) whereas abnormal reactive voluntary jerks are much longer [52].

In the 18 patients with psychogenic myoclonus reported by Monday and Jankovic [50], the jerks were segmental in 10, generalized in 7 and focal in 1. Inconsistency with continuously changing pattern anatomically and temporally were common. The movements often increased with stress, anxiety, and exposure to noise or light. A Bereitschaftspotential preceding muscle jerks was found in 5 of 6 patients with a diagnosis of psychogenic myoclonus [53]. A case of propriopsinal myoclonus was presumed be of psychogenic etiology when it disappeared after some minor procedure [54].
Psychogenic Movement Disorders

Psychogenic gait disorder

An abnormal gait is a common feature in patients with a psychogenic movement disorder. Of 279 patients with a PMD, 118 (42%) had an abnormal gait [55]. Of these, 102 (86%) had other psychogenic movements. Slowing of gait (18.6%), dystonic gait (17.8%), bizarre gait (11.9%), astasia–abasia (11.9%), and buckling of the knee (7.6%) are the most common gait abnormalities when other abnormal psychogenic movements are present. Among the pure psychogenic gait disorders, buckling of the knee was the most common feature (31.3%), followed by astasia–abasia (18.8%).

In Keane's report of 60 cases [56] with psychogenic gaits, the most common was “ataxia.” Others had trembling, knee buckling, “dystonia,” truncal “myoclonus,” and camptocormia (markedly stooped posture). In a video review of psychogenic gaits, Hayes and colleagues [57] emphasized certain features of the gait: exaggerated effort, extreme slowness, variability throughout the day, unusual or uneconomic postures, collapses, convulsive tremors, and distractibility. On the other hand, it is possible to misdiagnose as psychogenic an abnormal gait that is organic.

Psychogenic parkinsonism

Psychogenic parkinsonism is a rare cause of parkinsonism, but it does occur. Lang et al. [58] reported 14 patients with this disorder. Eleven had tremor at rest, but the tremor did not disappear with movement of the limb, and the frequency and rhythmicity varied. Rigidity was present in 6 patients, but without cogwheeling. All 14 patients had slowness of movement (bradykinesia) without the typical decrementing feature of organic bradykinesia. Dopaminergic SPECT imaging has helped to distinguish this diagnosis from pure psychogenic parkinsonism [59–61].

Besides tremor, dystonia, myoclonus, gait disorders, and parkinsonism, many other phenomenologies, including tics and chorea [62] can present as PMD.

Physiologic brain changes in psychogenic disorders

Mentioned above in the discussion of psychogenic dystonia was the observation of abnormal cortical and spinal inhibition in both psychogenic and organic dystonia. Abnormal neuroimaging has also been found in psychogenic disorders, indicating that the brain may physiologically respond to the abnormal disarray of motor function. Reduced regional cerebral blood flow and fMRI has been reported in psychogenic blindness [63] and sensory loss [64, 65]. In one study utilizing fMRI, the right temporoparietal junction (TPJ) hypoactivity and lower functional connectivity between the right TPJ, sensorimotor regions, and limbic regions was hypothesized to relate to the perception that the conversion movement is not self-generated [66].

Video 24.5 Psychogenic gait disorder

45 year old man with acute onset of right side weakness, extreme fatigue, and “confusion”. He exhibits psychogenic dysarthria, gait, athetosis, tremor, and dystonia, with marked distractibility. He responds to a self-induced sensory trick, tuning fork accompanied by a powerful suggestion. [Video courtesy of Joseph Jankovic, MD, Houston, Texas]


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secure that an organic basis for the symptoms has not been overlooked.

When explaining the diagnosis to the patient, it is usually helpful to state firmly that he/she has a movement disorder (specifically identify the disorder - e.g. dystonia, tremor, etc.). Then state that “such disorders are caused by many different etiologies. Structural damage to the brain can be one cause, but that is not seen in your situation.” It is very helpful to use the analogy of a computer problem and explain that “instead of a hardware problem, you have a software problem. The brain can react physiologically to stress to produce this type of movement, which is the cause in your case.” Also emphasize the positive news that “because the symptoms are not due to a structural lesion, the chance for reversing the abnormal physiology is great.”

Treatment is a three-pronged approach, with the psychiatrist playing the major role with psychotherapy and exploring the psychodynamics [67]. A coexisting depression or anxiety should be treated with appropriate pharmacotherapy. A second prong is intensive physiotherapy, such as retraining an abnormal posture to restore it to its proper alignment, overcoming any weakness. If there is excess startle, “desensitization” techniques should be used. Use a gentle stimulus that doesn’t trigger the abnormal jerk, and then gradually increase the strength of the stimulus until the jerks are no longer present. The third prong is the part of the neurologist who makes the diagnosis and reinforces the benefits of the above treatments. After making the diagnosis the neurologist explains to the patient that s/he can get better only if he or she is willing to work hard with physiotherapy. The neurologist plays the role of a “bad cop,” emphasizing to the patient that improvement must be seen each day of treatment. This adds the onus to the patient to work with the therapies to show such improvement. The psychiatrist takes the “good cop” role and reinforces the need for improvement to please the neurologist and keep the neurologist involved. Such an approach between the neurologist and the psychiatrist can hasten improvement.

Admitting the patient to the hospital is the best way to provide intensive physiotherapy and psychotherapy, with the patient seen each day by the neurologist to keep emphasizing the treatment and provide encouragement. Such encouragement is important to keep the patient motivated.

After the patient has improved, maintaining the improvement is not always easy because the patient returns to the same environment that led to causation of the movement disorder. Continual psychotherapy will be necessary.

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