

Hyperkinesia, dystonia, and tics

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Introduction

Movement disorders can be classified into two broad categories of akinetic/rigid and hyperkinetic disorders. Hyperkinetic movement disorders (hyperkinesias) are manifested by abnormal, uncontrollable, and unwanted movements. Hyperkinesias include different phenotypic categories, which can appear in isolation or in variable combinations [1]. Some conditions combine hypokinetic and hyperkinetic features, as exemplified by the coexistence of bradykinesia and tremor in Parkinson's disease (PD) or levodopa-induced dyskinesia in patients with PD and chorea or dystonia in patients with Huntington's disease, many of whom have an underlying hypokinesia. The crucial role of the basal ganglia is increasingly recognized, not only in hyperkinetic movement disorders, but also in motor control, muscle tone, posture, behavior, and cognition.

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. The hallmark features and phenomenology of the main hyperkinetic disorders are reported in Table 18.1, and a detailed review can be found in [1].

Phenotypic categories of hyperkinesia

As previously mentioned, the main phenotypic categories of hyperkinesias are: 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, restlessness, 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.

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 [2, 3]. 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; they may, therefore, appear to flow randomly from one muscle group to another [1]. 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 [1]. 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” [4]. Athetosis is a slow, continuous, involuntary writhing movement that prevents the maintenance of a stable posture, involves continuous smooth movements that appear to be random and are not composed of recognizable movement fragments and typically involves the distal extremities [1]. Myoclonus consists of repeated, often non-rhythmic,

Table 18.1 Distinctive features of main hyperkinetic disorders (modified from [1])

Hyperkinetic disorder	Clinical pattern	Typical features	Associated features
Tremor	Rhythmic oscillation of a body part around one or more joints	Regular, oscillatory	Cog-wheeling (postural tremor)
Chorea	Brief purposeless and quick movements that often progress from proximal to distal segments (fluency)	Random, arrhythmic, rapid, occasionally suppressible	Hypotonia Motor impersistence
Ballism	Violent flinging (usually unilateral) movements involving one limb and the shoulder in a coordinated way	Arrhythmic, rapid, non-suppressible	Hypotonia
Tics	Stereotyped intermittent movements (motor tics) or sounds (phonic tics) with abrupt onset	Arrhythmic, rapid, suppressible	Temporarily suppressible by will
Athetosis	Slow writhing movement or sequence of postures involving the fingers, hand, and wrist	Arrhythmic, slow, sustained, non-suppressible	
Myoclonus	Sudden brief muscle jerks (positive myoclonus) or releases (negative myoclonus) of one or more motor units	Arrhythmic, rapid, non-suppressible	
Dystonia	Sustained patterned repetitive movements, often torsional, occasionally rhythmic, associated with abnormal postures	Arrhythmic, sustained, patterned, non-suppressible	Gestes antagonistes Mirroring
Stereotypies	Patterned, coordinated, repetitive, non-reflexive movements that are typically rhythmic and occur in the same fashion with each repetition	Rhythmic, intermittent, continuous, prolonged	

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 [5]. 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 [6]. 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 [7].

Dystonia

Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation [6].

Following David Marsden’s seminal observation [8], 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). Dystonia may occur at rest, during activity, or only during a specific motor movement or posture, so-called task- or position-specific dystonia. The most common adult-onset upper limb task-specific dystonia is writer’s cramp [9]. Musician’s cramp occurs while playing a musical instrument [10]. Embouchure dystonia affects the control of the lip, jaw, and tongue muscles, and may be seen in woodwind and brass players [11].

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. They have specific features that can be recognized by clinical examination: speed of contractions may be slow or rapid, but at the peak of movement are sustained; movements almost always have a consistent directional or posture-assuming character. Dystonic movements may be regular, appearing as tremor (so-called dystonic tremor) [12]. 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 [6].

Dystonic postures can precede the occurrence of dystonic movements and in rare cases can persist without appearance of the latter (so-called fixed dystonia) [13]. Dystonic postures are repeated. 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. 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. The term “fixed dystonia” is used to indicate persistent, abnormal posture, without a dynamic component. When present but untreated for weeks or longer, fixed dystonia may lead to painful contractures, as in post-traumatic, chronic regional pain syndrome [14].

Dystonia has some unique activation/deactivation features that can be recognized when looked for and these can serve as a basis for the diagnosis: gestes antagonistes (or sensory tricks), mirroring, and overflow. Criteria for identifying these features, when present, have been recently published [6, 15]. 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 some cases, family history suggests the correct diagnosis, particularly if family members are ascertained to have dystonia.

Classification

A new classification of dystonia has been recently proposed [6]. This two-axis classification distinguishes the clinical features (axis I) and the etiology (axis II) of dystonia. The combination of these two sets of descriptors provides meaningful information for any dystonia patient and serves as a basis for the development of research and treatment strategies (Table 18.2).

Table 18.2 Classification of dystonia (from [6])

Axis I. Clinical characteristics	
Clinical characteristics of dystonia	
Age at onset	- Infancy (birth to 2 years) - Childhood (3–12 years) - Adolescence (13–20 years) - Early adulthood (21–40 years) - Late adulthood (>40 years)
Body distribution	- Focal - Segmental - Multifocal - Generalized (with or without leg involvement) - Hemidystonia
Temporal pattern	- Disease course - Static - Progressive - Variability - Persistent - Action-specific - Diurnal - Paroxysmal
Associated features	
- Isolated dystonia or combined with another movement disorder - Occurrence of other neurological or systemic manifestations	- Isolated dystonia - Combined dystonia - List of co-occurring neurological manifestations
Axis II. Etiology	
Nervous-system pathology	- Evidence of degeneration - Evidence of structural (often static) lesions - No evidence of degeneration or structural lesion
Inherited or acquired	- Inherited - Autosomal dominant - Autosomal recessive - X-linked recessive - Mitochondrial - Acquired - Perinatal brain injury - Infection - Drug - Toxic - Vascular - Neoplastic - Brain injury - Psychogenic - Idiopathic - Sporadic - Familial

Axis I: clinical features

The clinical characteristics describe the phenomenology of dystonia in a given patient. Five descriptors are utilized to specify clinical characteristics: age at onset, body distribution, temporal pattern, coexistence of other movement disorders, and other neurological manifestations. This structure is also useful for prognostic purposes and for identifying management strategies.

Dystonia may occur in isolation or in combination with other movement disorders. The resulting syndromes may give rise to recognizable associations, such as isolated dystonia or dystonia with myoclonus, parkinsonism, or other movement disorders (Figure 18.1). In isolated dystonia, dystonia is the only motor feature, with the exception of tremor; in combined dystonia, dystonia is combined with other movement disorders (such as myoclonus, parkinsonism, etc.). Isolated dystonia encompasses many cases previously described as “pure” or “primary”, whereas most patients previously classified under “dystonia plus” or “heredodegenerative” would now be classified as having combined dystonia. Unlike previous classifications, in the new classification the term isolated or combined refers to the phenomenology, and does not carry implications about the underlying etiology. In combined forms, dystonia does not necessarily have to be the predominant movement disorder and may not be the prominent motor phenomenology (e.g. foot dystonia in PD, mild dystonic features in myoclonus dystonia).

In addition to movement disorders, the presence of other neurological or systemic features may be associated

with dystonia. Non-motor features have been recently described in cases of dystonia with different etiologies [16]. Cognitive decline is typically observed in degenerative or progressive dystonia syndromes. Wilson disease is a disorder where dystonia is typically combined with other neurological or psychiatric symptoms and liver disease [17].

Axis II: Etiology

Autopsy studies of what previously was called “primary dystonia” have indicated that there are no obvious degenerative changes or other structural defects. However, these studies are not as yet sufficient to exclude subtle cell loss or minor structural defects. Human neuroimaging studies have consistently revealed subtle abnormalities in several brain regions in syndromes of isolated dystonia involving the basal ganglia, cerebellum, cortex, brainstem, and thalamus. These studies reveal changes in the volume or integrity of both gray and white matter and suggest that some underlying structural defect may exist. Furthermore, autopsy studies of isolated generalized DYT1 gene-linked dystonia have indicated some of such changes: one autopsy study described inclusion bodies in the brainstem, while another described enlarged dopamine neurons in the midbrain [18].

These findings raise questions regarding the criteria used to define neuropathological defects, which may not require frank neuronal degeneration, but instead may involve dystrophic cells, axonal or dendritic loss, synapse loss, pathological inclusions, or merely alteration of axonal or dendritic branch

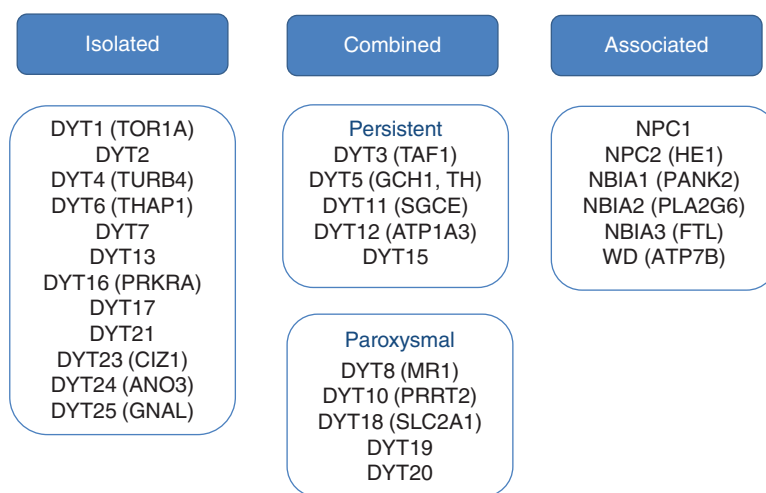


Figure 18.1 Monogenic dystonias: prevalent phenotype. The name of the genes is shown in parentheses. Abbreviations: NPC1, Niemann-Pick type C1; NPC2, Niemann-Pick type C2; NB1A1, Neurodegeneration with brain iron accumulation type 1; NB1A2, Neurodegeneration with brain iron accumulation type 2; NB1A3, Neurodegeneration with brain iron accumulation type 3; WD, Wilson disease.

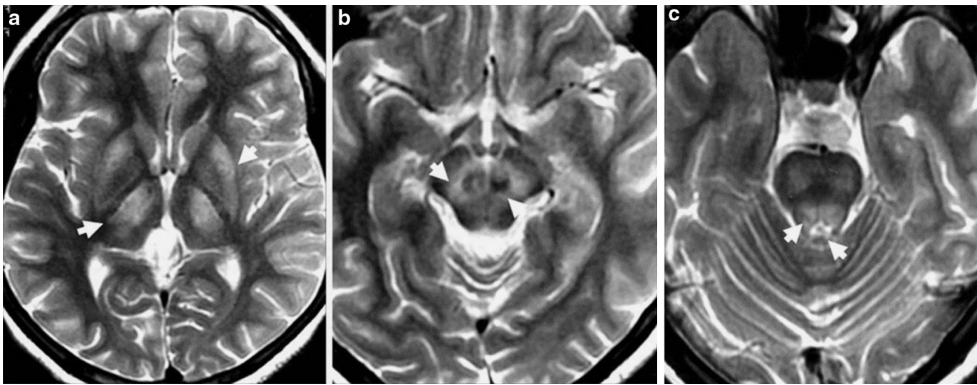


Figure 18.2 Wilson disease. Wilson disease from copper accumulation in multiple organs is diagnosed based on characteristic clinical, biochemical, and genetic testing and is often accompanied by neurological findings including dystonia. T2-weighted axial MRI demonstrates (a) symmetric hyperintense signals in the putamen, posterior internal capsule, and thalami (arrows), (b) “face of the giant panda” in the midbrain with high signal in tegmentum and normal red nuclei (arrows), and (c) “face of the panda cub” in the pons with hypointensity of central tegmental tracts with hyperintensity of aqueductal opening to the fourth ventricle (arrows). From [19].

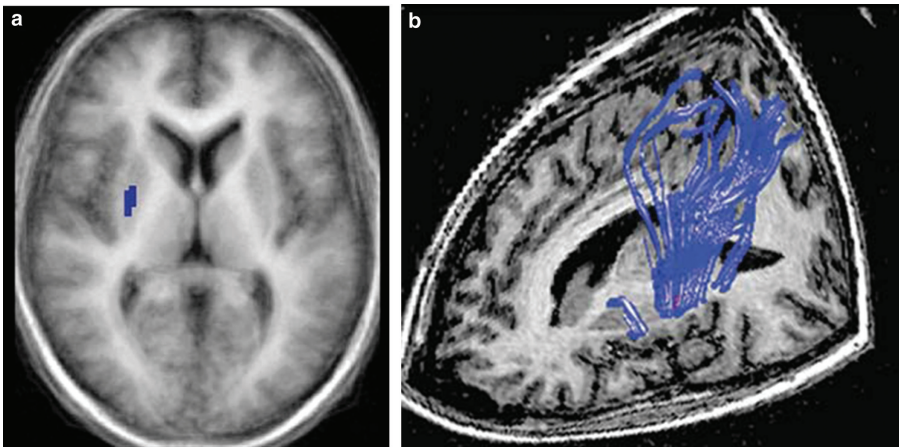


Figure 18.3 (a), (b) Localization of lesions resulting in secondary dystonia in 14 patients with basal ganglia infarct. Lesions were manually segmented on three-dimensional T1-weighted images. The area of overlap of all lesions was determined after normalization in the Montreal Neurological Institute (MNI) space. The overlap area (in blue) is superimposed to the mean normalized anatomical images of the patients. The overlap was located in the posterior sensorimotor part of the putamen (Delmaire *C et al.*, unpublished data). Diffusion-based tractography using this overlap area as the seed region showed that this region was connected to the primary sensorimotor and premotor cortex. Adapted from [20].

structure and complexity. Evidence of degeneration, either at the gross, microscopic, or molecular level, provides a useful means to discriminate subgroups of dystonia into degenerative and non-degenerative forms. Dystonic syndrome may be characterized by degeneration (progressive structural abnormality, such as neuronal loss; Figure 18.2), static lesions (non-progressive neurodevelopmental anomalies or acquired lesions, Figures 18.3, 18.4), or by the absence of evidence of degeneration or structural lesion.

Acute dystonia

Hyperkinetic disorders usually have a slow progressive onset with stabilization and occasional worsening (or remissions). Acute onset is rare and characteristic of few hyperkinetic conditions. Acute dystonic reaction is most commonly seen after exposure to dopamine receptor blockers, both neuroleptics and anti-emetics [22]. Acute dystonic reactions are more common in young men [23], while tardive dyskinesia and drug-induced parkinsonism are more common in

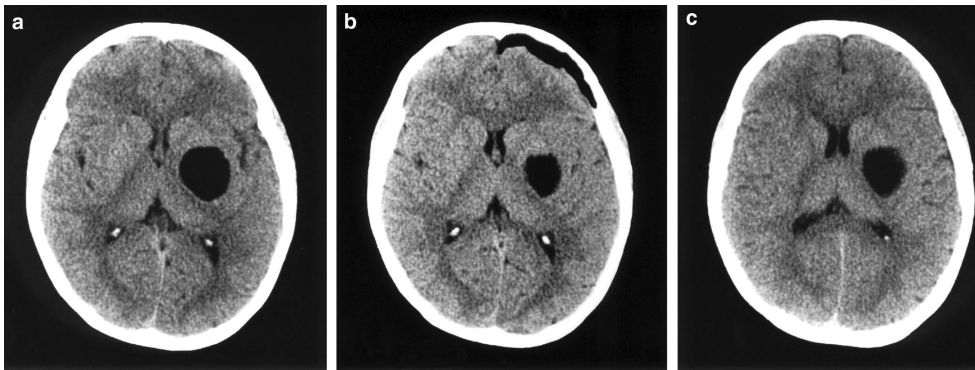


Figure 18.4 Patient with movement disorders affected by neuroepithelial cysts in the basal ganglia. 1: Sequential CT. (a) Pre-operative basal ganglia cyst at the time of the acute symptomatic presentation. (b) Immediate post-operative imaging demonstrating reduction of cyst size and creation of its wall. This corresponded to symptomatic improvement. (c) Delayed re-accumulation of cyst fluid corresponding to symptomatic worsening. From [21].

elderly individuals. Clinical manifestations are diverse, usually affecting the head and neck. Laryngeal dystonia, blepharospasm, cervical dystonia, oculogyric crisis, and focal limb dystonia have all been reported. Dystonia begins within 24 hours of exposure, and usually occurs within 5 days [24]. Acute dystonic reactions affect approximately 6% of patients exposed to “typical” neuroleptics and 1–2% of those exposed to “atypical” neuroleptics [25].

Acute non-traumatic torticollis occurs more commonly in children than adults and should be considered a medical emergency. Conditions that can determine acute torticollis in children include posterior fossa tumors, cervical cord tumors, and infection [22]. Acute torticollis in children should be differentiated from Grisel syndrome that is a pseudodystonia due to atlantoaxial rotatory subluxation. Physical examination may reveal painful, fixed torticollis following an infection or recent surgical procedure in the head and neck area [26]. Another cervical pseudodystonia in children is Sandifer syndrome, which is characterized by acute/subacute abnormal posturing secondary to gastroesophageal reflux [27].

Tics

Tic disorders start in childhood and are characterized by multiple sudden, rapid, recurrent, and non-rhythmic movements (motor tics) or utterances (vocal tics), or both. The best studied chronic tic disorder is Tourette syndrome, which has a prevalence of 0.3–1% in the general pediatric population. The syndrome is

characterized by multiple motor tics as well as one or more vocal tics over a period of more than 1 year [28]. Broad expression of Tourette syndrome is 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) [1]. The European Clinical Guidelines for Tourette syndrome and other tic disorders were recently compiled and published by the European Society for the Study of Tourette Syndrome [29–33]. The take-home message of these guidelines is that tic disorders are common and complex neuropsychiatric conditions.

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, semi-voluntary, 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 [4].

The movements can appear purposeful, such as touching, throwing, hitting, jumping, and kicking, or non-purposeful, such as head-shaking or trunk-bending. 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 [4]. 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 [34]. 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 as having the same pathophysiological 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 [35]. In contrast, complex phonic tics are semantically meaningful utterances and include coprolalia, or shouting of obscenities, profanities, or other insults. Other 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).

Acute tics

Even though it is rare for tics to present with acute onset they can exacerbate and lead to neurologic compromise. Tic disorders wax and wane and some factors lead to marked exacerbation of tic severity including fatigue, stress (physical or emotional), infection, and medications. When this occurs, the dramatic increase in severity (amplitude, violence, or frequency) may be quite alarming to patients and their families. Medications used to treat attention-deficit/hyperactivity disorder or obsessive-compulsive disorder, such as stimulants and antidepressants, are often reported to exacerbate tics [36, 37], although a controlled trial did not confirm this [38]. Rarely, tics may be continuous and disabling, resulting in a so-called "tic status" [39] or in severe, self-injurious, even life-threatening behaviors, so called "malignant Tourette syndrome" [40].

In the emergency department, tics should be diagnosed, and potential exacerbating factors including psychiatric ones should be identified and removed. Pharmacologic treatment, if needed, can be initiated. Initial treatment for debilitating tics uses a neuroleptic or a dopamine-depleting agent. Patients with focal tics may benefit from botulinum toxin injections [41]. Neurologic compromise secondary to tics is uncommon; however, severe tics can cause both compressive neuropathies and cervical myelopathy [34, 42].

Imaging

A large number of neuroimaging studies have been performed in patients with hyperkinetic movement disorders. The high spatial resolution combined with the high contrast-to-noise ratio of MRI enables in vivo demonstration of lesions of central nervous system (CNS) structures. However, the pattern of abnormal MRI findings is rarely pathognomonic of a specific type of hyperkinetic movement disorder (Table 18.3). Imaging studies do not point to a single dominant anatomic brain region for a given disorder. This is in agreement with network models of movement disorders, suggesting that a given disorder can be associated with a dysfunction in one or several node(s) of a distributed circuit that may include multiple interconnected areas within the CNS [44]. Furthermore, a dysfunction in one node can cause a combination of different movement disorders in the same patient. An example of this is the combination of chorea, athetosis, and dystonia after thalamic stroke [43].

Brain imaging techniques beyond structural MRI have been exploited in the diagnostic work-up of hyperkinetic movement disorders, including functional MRI, positron emission tomography, or single photon emission computed tomography (CT), but these modalities are not routinely performed in an emergency setting. The pathophysiology of these disorders has also been studied by advanced imaging approaches in groups of patients compared to normal control populations, but these studies have not proven useful as yet for diagnostic purposes at the individual level.

Nevertheless, imaging is an integral part of the diagnostic work-up of dystonia and provides the basis for the morphological classification on Axis II. Acquired dystonia syndromes often have abnormal imaging, such as the MRI lesions observed in dystonia following perinatal brain injury, vascular pathology, or brain trauma. In familial dystonias, imaging may show usually more subtle abnormalities that indicate morphological changes detected in genetically determined forms. Wilson disease, pantothenate-kinase-associated neurodegeneration (PKAN), and other familial dystonias combined with other movement disorders or associated with other neurological features typically display relevant neuroimaging abnormalities. More subtle white-matter abnormalities have also been reported in myoclonus dystonia associated to mutations in the DYT11 gene [45] and even in isolated dystonia associated to DYT1 gene mutations [46].

Table 18.3 Summary of focal lesions of the CNS or supplying arteries associated with hyperkinetic movement disorders (modified from [43])

Dystonia	Lenticular nucleus Thalamus Brainstem (midbrain/pons) Cerebellum Cerebral lobes (parietal) Cervical cord
Tics	Striatum Cerebral lobes (frontal/parietal) Limbic circuit Midbrain
Chorea	Striatum Pallidum Thalamus Subthalamic nucleus Cerebral lobes (frontal/temporal) Vascular abnormality (e.g. Moya-moya disease)
Ballism	Striatum Thalamus Subthalamic nucleus Cerebral lobes (parietal)
Cerebellar outflow tremor	Thalamus Cerebellum and dentatorubrothalamic tract Striatum Cerebral lobes (frontal/parietal)
Holmes tremor	Midbrain Cerebellum Mesencephalo-thalamic region
The bobble head doll syndrome	Third ventricle Suprasellar region Sylvius aqueduct stenosis Dandy Walker syndrome
Myoclonus	Brainstem (midbrain/pons) Thalamus Striatum
Exaggerated startle syndromes	Brainstem (pons)
Asterixis	Thalamus Striatum Cerebral lobes (frontal/parietal) Brainstem Cerebellum
Transient dyskinesia	High-grade stenosis or occlusion of the internal carotid artery/vertebrobasilar arteries
Stereotypies	Thalamus Striatum Cerebral lobes (frontal/parietal) Cerebellum
Akathisia	Posterior thalamus

Although there are rare case reports of association of tics and structural brain lesions, for example after trauma, or associated with brain tumors, and infection, structural imaging is not likely to reveal an etiology. CT and/or MRI may be beneficial when there are unexpected associated clinical/neurological findings, or for unusual presentations, principally to exclude treatable pathology. Mechanistic studies in groups of patients such as by functional MRI include evaluation of the cortico-striato-thalamo-cortical circuits [47], adaptive control mechanisms [48], and functional connectivity [49], but these are not as yet relevant to clinical evaluation of the individual patient presenting with a tic disorder.

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