Chorea

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REVIEW ARTICLE

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ABSTRACT

PURPOSE OF REVIEW: This article provides an overview of the approach to chorea in clinical practice, beginning with a discussion of the phenomenologic features of chorea and how to differentiate it from other movement disorders. The diagnostic approach, clinical features of important acquired and genetic choreas, and therapeutic principles are also discussed. Practical clinical points and caveats are included.

RECENT FINDINGS: C9orf72 disease is the most common Huntington disease phenocopy, according to studies in the European population. Anti-IgLON5 disease can present with chorea. The role of immunotherapies in Sydenham chorea has increased, and further clinical studies may be useful. Benign hereditary chorea is a syndrome or phenotype due to mutations in several genes, including *NKX2-1*, *ADCY5*, *GNAO1*, and *PDE10A*. New-generation presynaptic dopamine-depleting agents provide more options for symptomatic treatment of chorea with fewer adverse effects. Deep brain stimulation has been performed in several choreic disorders, but features other than chorea and the neurodegenerative nature should be taken into consideration. Studies on genetic interventions for Huntington disease are ongoing.

SUMMARY: Clinical features remain crucial in guiding the differential diagnosis and appropriate investigations in chorea. Given the complexity of most choreic disorders, treating only the chorea is not sufficient. A comprehensive and multidisciplinary approach is required.

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RELATIONSHIP DISCLOSURE:
Dr Termsarasab serves as associate editor of the *Journal of Clinical Movement Disorders* and on the editorial board of *Brain Science Journal*. Dr Termsarasab has received personal compensation for speaking engagements for the American Academy of Neurology and Novartis AG and receives publishing royalties from MedLink Neurology.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Termsarasab discusses the unlabeled/investigational use of the current recommended treatments of chorea, none of which are approved by the US Food and Drug Administration except the use of deutetrabenazine for the treatment of chorea associated with Huntington disease and tardive dyskinesia, tetrabenazine for the treatment of chorea associated with Huntington disease, and valbenazine for the treatment of tardive dyskinesia.

INTRODUCTION

Chorea is derived from the Greek word χορεία, meaning dance. It is characterized by the random and flowing quality of the movements, giving it a dancelike appearance. Randomness is the key phenomenologic feature in the identification of chorea. The movements typically flit from one body region to another in an unpredictable fashion.

The differential diagnosis of chorea is broad. However, with clinical features including demographic data, time course, associated medical and neurologic features, and known prevalence, the search for the etiology of chorea can be performed efficiently. A "shotgun approach" can be reserved for when no diagnostic clues are present. This article discusses the general diagnostic approach to chorea, clinical clues to common and important choreic disorders, and therapeutic principles.

The first section of the article discusses general phenomenologic features of chorea and how to differentiate chorea from other movement disorders. The next section covers the general approach to chorea, beginning with the three body

distributions that can be an important clue. A proposed practical approach to chorea is presented, and how other clinical information can serve as diagnostic clues is discussed. Selected important acquired and genetic etiologies of chorea are discussed in subsequent sections, and paroxysmal movement disorders that can present with chorea are also briefly discussed. Therapeutic principles of chorea are delineated in the final section.

PHENOMENOLOGIC FEATURES OF CHOREA

In addition to the two main phenomenologic features of randomness and a flowing quality, patients with chorea often blend or incorporate the chorea into their normal movements, as if they are attempting to hide it. This phenomenon is called *parakinesia*. For example, when chorea is present in the arm, a patient may try to blend chorea by lifting or moving the arm to a target in the same direction as the choreic movements.

Another feature of chorea is motor impersistence. This is not only seen in Huntington disease (HD) or Sydenham chorea but also in other causes of chorea. It is defined by an inability to perform sustained motor activities. Two tasks that should be examined clinically include tongue protrusion and handgrip. Tongue protrusion cannot be maintained, and the tongue retracts back into the mouth after several seconds. For handgrip, when a patient attempts to squeeze an examiner's fingers, waxing-and-waning grip strength (called *milkmaid's grip*) can be felt.

Ballism is a variant of chorea characterized by large-amplitude flinging movements involving proximal extremities (**VIDEO 6-1**, *links.lww.com/CONT/A351*). The diagnostic and treatment approaches for ballism are the same as for chorea. Athetosis ("without fixed position"), originally described in 1871 by William Hammond, remains controversial. While some experts categorize athetosis as a variant of chorea, it has been argued to be a form of dystonia by others.[1] Athetosis is characterized by slow writhing movements typically involving distal extremities, although other body parts, such as the face, can be involved. When dystonia, such as dystonic hand posturing, coexists with flowing movements, it is sometimes difficult to separate athetosis from dystonia, resulting in the so-called dystonic-choreoathetoid movements seen in cerebral palsy.

The velocity of chorea can vary. The flowing component of chorea is usually faster than that of dystonia but not as fast as the jerking component of myoclonus. However, when chorea has a quick velocity along with low amplitude, it may appear quite jerky and can be mistaken as myoclonic jerks. Chorea has a wide variation of severity; patients with a mild degree can appear fidgety, and thus chorea may be overlooked. Therefore, it is important to observe patients with their socks off and legs hanging from the examination table to examine small choreic movements in the feet and toes.

DIFFERENTIATING CHOREA FROM OTHER ABNORMAL MOVEMENTS

Dystonia can have motor overflow mimicking the flowing movements of chorea, but an abnormal posturing typically coexists. In addition, dystonia produces patterned movements that are predictable, in contrast to the randomness of chorea. Sensory tricks, a null point, and mirror movements are supportive features of dystonia. Dystonic tremor that is usually irregular and jerky, when present, is clinically distinct from the flowing quality of chorea.

As mentioned earlier, chorea with a quick velocity may resemble myoclonic jerks, but the randomness of chorea distinguishes the two. In addition, the jerks in chorea are not as brief as those in myoclonus, which are "lightninglike"

because of typical burst durations of less than 200 milliseconds. Stimulus sensitivity, if present, also supports the identification of myoclonus. However, when the jerks are frequent, stimulus sensitivity may be difficult to assess, and spontaneous jerks should not be mistaken as stimulus sensitive.

Common movement patterns and body distribution, such as eye blinking or shoulder shrugging, help identify tics. However, with uncommon patterns of tics, the presence of a premonitory urge and suppressibility will help distinguish them from chorea.

Stereotypies, as seen in anti–*N*-methyl-D-aspartate (NMDA) receptor encephalitis or tardive syndrome with orobuccolingual involvement, can have a flowing quality similar to chorea. However, its stereotypic pattern, as if the same video is running in a repetitive loop, distinguishes it from chorea.

Large-amplitude cerebellar outflow tremor with proximal extremity involvement may look similar to chorea. However, regular oscillation around the axis and activation of the tremor with movements (postural and kinetic components) distinguish it from chorea.

KEY POINTS

- **Randomness is the key phenomenologic feature of chorea.**
- **Chorea with quick velocities may look jerky, resembling myoclonic jerks.**

APPROACH TO CHOREA

Given an extensive differential diagnosis, chorea can be challenging to many clinicians. Nevertheless, there are some important clinical features that can serve as diagnostic clues to the specific diagnosis. These include three body distributions and other crucial features.

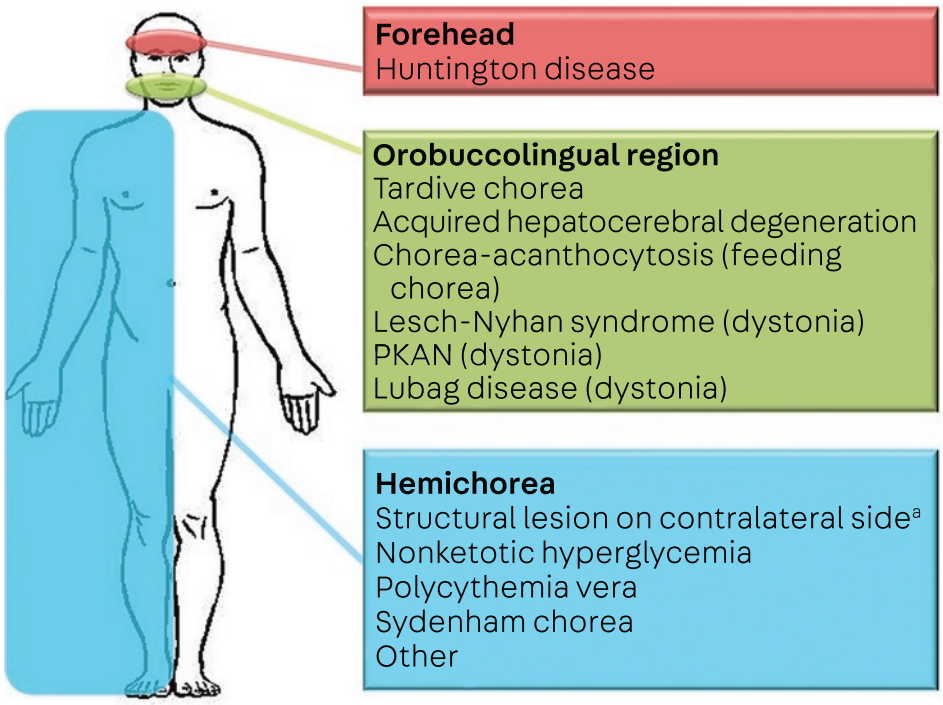

FIGURE 6-1

Body distribution as a phenomenologic clue in chorea. The differential diagnoses are demonstrated in each distribution.

PKAN = pantothenate kinase–associated neurodegeneration.

[a] Locations outside the subthalamic nucleus can also be involved.

Body Distribution as a Clue

While the list of disorders presenting with generalized chorea is extensive, three body distributions carry a more limited number of possible diagnoses and serve as useful diagnostic clues (FIGURE 6-1). These include hemichorea, orobuccolingual, and forehead distributions.

HEMICHOREA. Lesions leading to hemichorea are classically localized to the contralateral subthalamic nucleus. However, the lesions are not restricted to the subthalamic nucleus and can be located in other anatomic locations, such as the contralateral basal ganglia or corona radiata.[2] Systemic disorders, such as nonketotic hyperglycemia and polycythemia vera, can also present with hemichorea or very asymmetric involvement.[3,4] Sydenham chorea can also have a very asymmetric presentation or even hemichorea. Therefore, systemic

CASE 6-1

A 77-year-old woman presented with abnormal movements of her left arm, left leg, and left face. She had a history of type 2 diabetes mellitus and poor compliance. She had run out of her medications and not taken them for 2 weeks before developing abnormal flinging movements of her left arm upon waking up in the morning, followed a few days later by movements in her left leg and left face. The movements had gradually become worse over the week, prompting her to seek medical attention.

On presentation to the hospital, examination revealed left hemichorea/hemiballism involving her left arm, left leg, and left face (VIDEO 6-2, *links.lww.com/CONT/A352*). The chorea abated during sleep. Blood testing on presentation showed a glucose level of 445 mg/dL and hemoglobin A_{1c} of 12%. She had no ketosis.

The diagnosis of left hemichorea/hemiballism secondary to nonketotic hyperglycemia was made, which was initially managed by IV and subcutaneous insulin. Her oral diabetic medications were resumed, with improvement in her blood glucose level. MRI of the brain revealed a hyperintense signal on T1-weighted images in the right (contralateral) putamen (FIGURE 6-2A). A faint hyperdense signal could also be seen on a CT scan without contrast in the same region (FIGURE 6-2B).

Her chorea was not adequately improved with blood glucose control alone, and haloperidol was started at 0.5 mg/d with about 50% improvement in her hemichorea. The dose was then increased to 0.5 mg 2 times a day with further improvement. She required low-dose haloperidol for several weeks before the chorea subsided.

COMMENT

The acute temporal profile in this patient is suggestive of an acquired cause of chorea. Hemichorea/hemiballism can be a manifestation of systemic disorders such as nonketotic hyperglycemia or polycythemia vera. Nonketotic hyperglycemia is common among Asian populations, especially women (this patient was from Thailand). Blood glucose control serves as a specific treatment, but most patients will also need symptomatic therapies, as chorea may take several weeks or months to resolve.

etiologies should always be kept in the differential diagnosis, especially when neuroimaging does not reveal any structural lesions.

Nonketotic hyperglycemia–induced hemichorea is common in Asians, especially women. With a high index of suspicion, diagnosis can easily be made by blood glucose testing, even in patients with no previous history of diabetes mellitus.[5] MRI of the brain typically demonstrates a hyperintense signal in the putamen and caudate nuclei on T1-weighted images, usually more prominent on the side contralateral to hemichorea. While blood sugar control is the therapeutic mainstay, symptomatic treatment of chorea for at least several weeks or a few months is also often needed (CASE 6-1).

OROBUCCOLINGUAL INVOLVEMENT. Choreic movements in the orobuccolingual or lower cranial region are classically seen in tardive syndrome and acquired

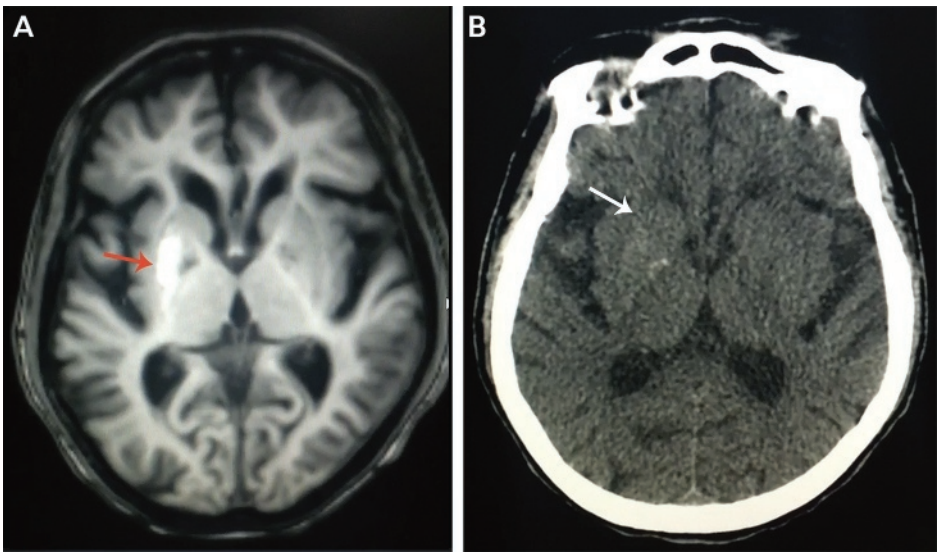

FIGURE 6-2
Imaging of the patient in CASE 6-1 with nonketotic hyperglycemia. *A*, Axial T1-weighted MRI shows hyperintense signal in the right putamen (*red arrow*), contralateral to the side of hemichorea. *B*, CT scan of the same patient demonstrates mild hyperdensity in the same region (*white arrow*).

hepatocerebral degeneration. Of note, in tardive syndrome with orobuccolingual involvement, stereotypy may be a more precise phenomenologic term, since the movements are often repetitive. Lateral lingual movements, as if the patient has candy in his or her cheek (called the *bonbon sign*), can be seen in patients with orobuccolingual involvement in tardive syndrome. Levodopa-induced dyskinesia in multiple system atrophy tends to involve the orobuccolingual region, as opposed to limb dyskinesia in classic Parkinson disease.

In some choreic disorders, dystonia (not chorea) in the orobuccolingual region can coexist. These include neuroacanthocytosis syndromes, neurodegeneration with brain iron accumulation disorders such as pantothenate kinase–associated neurodegeneration and neuroferritinopathy, X-linked dystonia-parkinsonism (also known as Lubag disease), Wilson disease, and Lesch-Nyhan syndrome.

Neuroacanthocytosis syndromes are a group of disorders in which progressive neurodegeneration is associated with acanthocytes.[6] The two main disorders are chorea-acanthocytosis (autosomal recessive inheritance) and McLeod syndrome (X-linked inheritance). Chorea-acanthocytosis can present with severe tongue protrusion dystonia, especially when eating, or feeding dystonia, which can interfere with appropriate oral intake and cause lip and tongue biting. In contrast, orobuccolingual involvement, including feeding dystonia, is much less commonly seen in McLeod syndrome. Of note, when considering disorders that can present with oromandibular dystonia and self-mutilating behavior, Lesch-Nyhan syndrome is also in the differential diagnosis, in addition to chorea-acanthocytosis. Lesch-Nyhan syndrome is an X-linked recessive disorder that typically has an onset within the first few years of life, whereas onset of chorea-acanthocytosis is usually in early adulthood.

FOREHEAD CHOREA. Forehead muscles are often involved in HD, in which wiggling of the eyebrows or activation of the frontalis muscle can be seen.[7] Forehead involvement can be a useful supportive clinical feature to distinguish HD from tardive dyskinesia, in which the forehead is usually spared. However, cases of HD without forehead chorea and cases of tardive dyskinesia with forehead involvement can sometimes be seen.

DIAGNOSTIC APPROACH

Useful diagnostic clues include demographic data (eg, age, gender, and ethnicity); family history; coexisting movement phenomenology such as dystonia, myoclonus, or tics; and associated clinical features, such as seizures, neuropathy, and myopathy. Given the broad differential diagnosis of chorea, the clinical approach can be challenging to clinicians. A proposed practical clinical approach is illustrated in FIGURE 6-3. The three most crucial features are time course, age group, and known prevalence.

As a general rule, acquired or sporadic causes of chorea usually present with an acute or subacute temporal profile, whereas genetic causes are chronic (longer than 1 year in duration). It is crucial to identify acquired causes, as many of them are treatable. Autoimmune etiologies should always be included in the differential diagnosis, especially in subacute presentations; these disorders typically respond to immunotherapies, including IV immunoglobulin (IVIg), steroids, other immunosuppressive agents, and plasma exchange. In recent years, the number of autoimmune neurologic disorders has been expanding with advances in neuroimmunology and identification of novel autoantibodies.

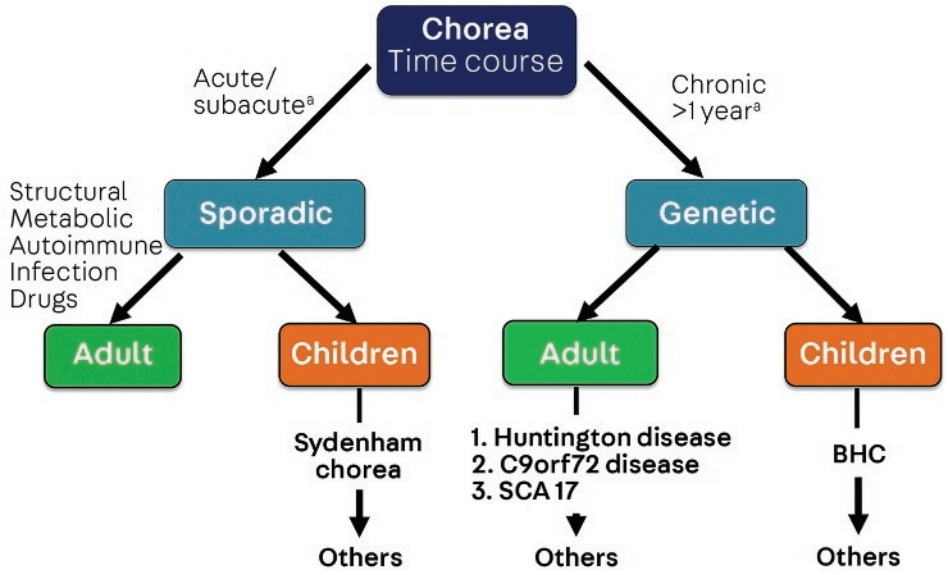

FIGURE 6-3

Diagnostic approach to chorea.

BHC = benign hereditary chorea; SCA17 = spinocerebellar ataxia type 17.

[a] The association between the temporal profile and sporadic versus genetic causes of chorea is only a general rule. In clinical practice, overlaps (ie, genetic chorea with temporal profile of less than 1 year) can occur, but these are not common.

Age group and known prevalence are also crucial diagnostic clues in chorea. In the pediatric population, Sydenham chorea is the most common cause of acquired chorea and the most common among all choreic disorders, excluding choreoathetoid cerebral palsy. In adults, HD is by far the most common genetic cause, whereas C9orf72 disease is the second most common according to studies in the European population[8] and spinocerebellar ataxia type 17 (SCA17) is the third. Before the discovery of the *C9orf72* gene, SCA17 was thought to be the second most common genetic cause of chorea. In 2011, *C9orf72* gene mutations with the GGGGCC hexanucleotide repeat expansion were discovered in familial frontotemporal dementia with amyotrophic lateral sclerosis. Subsequently, the clinical spectrum has broadened, and studies in HD phenocopies (patients with negative HD gene testing) revealed that C9orf72 disease is even more common than SCA17. The most common genetic cause of chorea in children is benign hereditary chorea. It is important to note that when a child presents with chorea, the diagnosis is very unlikely to be HD, since juvenile HD typically presents with parkinsonism (also known as the Westphal variant), dystonia, and seizures, rather than chorea.

While family history can be a helpful diagnostic clue, a negative family history does not exclude the possibility of having a genetic chorea. This can be due to nonpaternity, incomplete penetrance, de novo mutations, or undiagnosed affected parents with symptoms, such as depression or suicidality, incorrectly attributed to other causes. Common genetic causes of chorea, including HD, C9orf72 disease, SCA17, and benign hereditary chorea, are autosomal dominant. In most repeat expansion disorders such as HD, larger numbers of repeats occur in successive generations and are associated with earlier age at onset. This phenomenon is called *anticipation* and has been reported in C9orf72 disease[9] but much less frequently in SCA17. Absence of male-to-male transmission is a

KEY POINTS

- Chorea in one of three body distributions (hemichorea, orobuccolingual involvement, and forehead chorea) can serve as a clue to narrow down the differential diagnoses.
- Structural lesions and systemic disorders (such as nonketotic hyperglycemia and polycythemia vera) can cause hemichorea.
- Sydenham chorea can present with hemichorea or very asymmetric involvement.
- The time course can help classify chorea into acquired and genetic etiologies.
- Age group and known prevalence are very important diagnostic clues in chorea.
- The most common acquired chorea in children is Sydenham chorea.
- The most common genetic chorea in adults is Huntington disease, followed by C9orf72 disease and spinocerebellar ataxia type 17.
- The most common genetic chorea in children is benign hereditary chorea.
- A negative family history does not exclude genetic causes of chorea.

TABLE 6-1

Acquired Causes of Chorea[a]

Category	Examples
Structural lesion	Vascular causes: ischemic and hemorrhagic strokes, vascular malformation (eg, Moyamoya syndrome)
	Tumors
	Demyelinating lesions
Metabolic/endocrine	Nonketotic hyperglycemia
	Hypoglycemia
	Hypocalcemia
	Hyponatremia/hypernatremia
	Uremia
	Acquired hepatocerebral degeneration
	Hyperthyroidism
	Hypoparathyroidism/hyperparathyroidism
Infectious	Toxoplasmosis
	HIV encephalopathy
	Prion diseases
Drug-induced	Levodopa
	Cocaine ("crack-dancing")
	Amphetamine
	Anticonvulsants
	Lithium
	Anticholinergics
	Neuroleptic withdrawal
Autoimmune/paraneoplastic	Sydenham chorea
	Rheumatologic diseases: systemic lupus erythematosus, antiphospholipid antibody syndrome, systemic sclerosis
	Autoimmune neurologic syndromes: anti–CRMP-5, anti-NMDA, anti-Hu (ANNA-1), anti-Yo, anti-LGI1, anti-CASPR2, anti-GAD65, anti-IgLON5
Other	Polycythemia vera
	Postpump chorea

ANNA-1 = antineuronal nuclear antibody type 1; CASPR2 = contactin-associated proteinlike 2; CRMP-5 = collapsin response mediator protein-5; GAD65 = glutamic acid decarboxylase 65; HIV = human immunodeficiency virus; LGI1 = leucine-rich glioma inactivated 1; NMDA = *N*-methyl-D-aspartate.

[a] Modified with permission from Termsarasab P.[11] © 2017 American Academy of Neurology.

hallmark of X-linked disorders, examples of which include McLeod syndrome and Lesch-Nyhan syndrome. Notably, while much more common in males, females can also be affected because of skewed inactivation of X chromosomes.

Ethnicity can be an important diagnostic clue. For example, Huntington disease–like 2 (HDL2) is almost exclusively seen in patients with African ancestry and has been reported to be a common cause of HD phenocopies in South African patients with African ancestry.[10]

ACQUIRED CAUSES OF CHOREA

The list of acquired causes of chorea is extensive but can be grouped into at least six categories, including structural, metabolic/endocrine, infectious, drug-induced, autoimmune/paraneoplastic, and others (TABLE 6-1[11]). Among these, levodopa-induced chorea (or *dyskinesia*) is the most common acquired cause encountered in movement disorders clinics.

Chorea can be an initial presentation in several disorders, such as polycythemia vera, systemic lupus erythematosus (VIDEO 6-3, *links.lww.com/CONT/A353*), antiphospholipid antibody syndrome, and diabetes mellitus (with nonketotic hyperglycemia). Therefore, an absence of a known underlying medical problem should not dissuade clinicians from considering that particular etiology.

Autoimmune and paraneoplastic etiologies are considered "don't miss," diagnoses, especially when a patient presents with a subacute time course, since they can be treated with immunotherapies. In adults, autoimmune etiologies include anti-Hu, anti–collapsin response mediator protein-5 (CRMP-5), anti-NMDA receptor encephalitis, anti–leucine-rich glioma inactivated 1 (LGI1), anti–contactin-associated proteinlike 2 (CASPR2), and antistriational antibody diseases.[12] With more clinical recognition of anti-NMDA receptor encephalitis in the past decade, a variety of associated movement disorders, including chorea, dystonia, and myoclonus, have been reported. Stereotypic movements in orobuccolingual muscles, arms, and legs are characteristic. A 2018 study found that dystonia, chorea, and stereotypies are the most common abnormal movements in this disorder.[13] Some patients may have been misdiagnosed with tardive dyskinesia, but important clues are an encephalopathic clinical picture and no previous history of neuroleptic use. It is crucial to search for an underlying tumor or malignancy in some of these autoimmune/paraneoplastic disorders (eg, ovarian teratoma in women with anti-NMDA receptor encephalitis).

Anti-IgLON5 disease has recently been described.[14,15] Clinical features include obstructive sleep apnea, rapid eye movement (REM) and non-REM parasomnias, dementia, chorea, and vertical supranuclear gaze palsy. Parasomnia can manifest as finalistic behaviors during sleep in which a patient acts as if he or she is performing work activities, such as installing an antenna or threading electrical wires. Despite being an autoimmune disorder, most patients with anti-IgLON5 disease have a chronic temporal profile longer than 1 year. Earlier detection may be possible when the disorder is better recognized. Interestingly, neuropathologic studies of anti-IgLON5 disease also demonstrated neurodegeneration with mixed 3-repeat and 4-repeat tauopathy.[16] Further studies may provide insight on the link between autoimmunity and neurodegeneration and determine which is primary in the pathogenesis.

In children, Sydenham chorea (VIDEO 6-4, *links.lww.com/CONT/A354*[17]) is the most common autoimmune chorea. When considering rheumatic heart disease in the era of antibiotics, it remains a health care burden worldwide with higher prevalence in some geographic distributions. In the United States,

KEY POINTS

- **Huntington disease–like 2 is almost exclusively seen in patients with African ancestry.**
- **Autoimmune chorea should be included in the differential diagnoses of chorea with a subacute temporal profile.**

Sydenham chorea is still the most common cause of chorea in the pediatric population, after choreoathetoid cerebral palsy. Patients typically develop chorea 2 to 3 months after group A β-hemolytic streptococcal throat infection. Therefore, when chorea is already present, throat culture is usually negative and not helpful. Furthermore, antibody testing usually performed in clinical practice (including antistreptolysin O [ASO] and antideoxyribonuclease B [anti-DNase B]), although having higher diagnostic yields than throat culture, does not have high sensitivity. In addition to chorea, patients may have tics and neurobehavioral features, such as anxiety, irritability, attention deficit hyperactivity disorder, and obsessive-compulsive behaviors, that can sometimes be disruptive. Thus, the term *Sydenham disease* has been proposed to cover the entire spectrum of its clinical features. Some patients have severe hypotonia along with florid chorea, called *chorea paralytica*.

Recognition of Sydenham chorea is important, since patients will require a cardiac workup, particularly echocardiography, and secondary antibiotic prophylaxis with long-term penicillin, the duration of which depends on the severity of carditis. Treatment of Sydenham chorea is discussed further in the treatment section of this article. Sydenham chorea can recur in 20% to 50% of patients, and persistent symptoms after 2-year follow-up have been reported in up to 50%.[18]

Chorea gravidarum refers to chorea that initially emerges, reemerges, or exacerbates during pregnancy. It is a descriptive terminology rather than specific diagnostic entity, as underlying etiologies such as HD, systemic lupus erythematosus, antiphospholipid antibody syndrome, and hyperthyroidism should always be sought. Patients with a history of Sydenham chorea in childhood can have reemergence of chorea during pregnancy. However, thorough investigations for other potential underlying causes of chorea in these patients should not be neglected. Another hormonal-related chorea is chorea that may emerge or reemerge during the use of oral contraceptive pills, and the same principles should be applied. Chorea gravidarum can improve spontaneously in the third trimester or shortly after the patient gives birth,[19] and treatment may not be required. Nevertheless, the most crucial "don't-miss" step is searching for an underlying etiology.

The workup for acquired causes of chorea can be extensive. If diagnostic clues are present, a targeted approach can be pursued. In clinical practice, if no diagnostic clues are present, the first-tier testing includes complete blood cell count, thyroid function tests, liver function tests, serum electrolytes, serum calcium, antinuclear antibody, anti–double-stranded DNA antibody, lupus anticoagulant, and antiphospholipid antibody syndrome workup. When patients present with a subacute temporal profile, antibody testing in both serum and CSF should be considered in addition to routine CSF studies.

GENETIC CAUSES OF CHOREA

The most common genetic cause of chorea in adults is HD. Other genetic disorders that can mimic HD (ie, HD phenocopies) will subsequently be discussed. Benign hereditary chorea is the most common genetic chorea in children.

Huntington Disease

HD is by far the most common genetic chorea in adults (TABLE 6-2). Geographic variability is seen, with higher prevalence in some regions because of founder effects, such as in Venezuela around Lake Maracaibo. Clinical features can be grouped into three major categories: movement disorders, cognitive impairment,

and neuropsychiatric features. It is important not to overlook the latter two domains, which can be more debilitating than chorea itself. Regarding motor symptoms, chorea is the main phenomenology in adults but not in children. The forehead is usually involved, and forehead chorea can be useful to distinguish HD from tardive dyskinesia. In addition to chorea, other abnormal movements, including dystonia, myoclonus, and ataxia, can coexist. While dystonic components such as pelvic tilting can be apparent during walking, the gait pattern is quite complex and probably attributed to more than just a combination of chorea and dystonia.[20] During the natural course of the disease, the severity of chorea increases and then plateaus. Subsequently, in later stages, chorea gradually subsides and parkinsonian features become more prominent.[21] Hyperkinetic movements transition into an akinetic-rigid syndrome in the later stages. One implication of this evolution is that symptomatic treatment of chorea in HD requires periodic revision over the course of the disease (CASE 6-2).

Cognitive dysfunction in HD includes subcortical dementia, impaired frontal executive function, disinhibition, difficulty with multitasking, and short-term memory impairment. Neuropsychiatric features include depression, suicidal ideation, anxiety, irritability, apathy, aggression, psychosis, obsessive-compulsive behaviors, and reduced awareness of deficit.[22]

Another important diagnostic clue is eye movement abnormalities. Delayed initiation of saccades is a hallmark oculomotor abnormality in HD.[23] Other choreic disorders with delayed initiation of saccades include ataxia-telangiectasia and oculomotor apraxia types 1 and 2. However, these disorders typically present at a younger age, and coexisting neuropsychiatric features are uncommon. Another eye movement abnormality in HD is an impaired antisaccade task. This can be seen by asking the patient to look to the side contralateral to the side on which the examiner is holding up a finger. Patients with HD tend to look to the ipsilateral side, reflecting frontal disinhibition.

HD is an autosomal dominant disorder due to CAG repeat expansion in the *HTT* (also known as *IT15*) gene on chromosome 4p encoding the huntingtin protein. Individuals with 40 or more CAG repeats have complete penetrance (FIGURE 6-4), with an inverse correlation between the number of repeats and the age at onset. Individuals with between 36 and 39 CAG repeats are manifesting carriers with incomplete penetrance; not all individuals with CAG repeats in this range will develop HD manifestations during their lifetime. Patients with lower numbers of repeats tend to have presentation of chorea in late life, which has been called *senile chorea*. However, this term is considered obsolete and should not be used as a diagnosis. A careful search for underlying etiologies, including HD, should be conducted. Generally, individuals with fewer than 36 CAG repeats (35 or fewer) will not manifest the symptoms or signs of HD. Nevertheless, rare case reports exist of manifest HD with an intermediate number (27 to 35) of CAG repeats. Anticipation tends to occur when unstable CAG repeats are inherited from the father, because of CAG-repeat instability during spermatogenesis. Children with manifest HD typically have 50 to 60 CAG repeats or more. In contrast to the adult-onset form, juvenile HD (onset at younger than 20 years of age) typically presents with parkinsonism (also known as the Westphal variant) and dystonia rather than chorea, as well as seizures. Nevertheless, not only the number of CAG repeats but also genetic modifiers and environmental factors contribute to the age at onset[24]; therefore, the age at onset in an individual cannot be accurately predicted exclusively from the number of CAG repeats.

KEY POINTS

- Neuropsychiatric features such as irritability, attention deficit hyperactivity disorder, and obsessive-compulsive behavior can be seen in Sydenham chorea.
- It is important to search for an underlying etiology in hormonal-related chorea, including chorea gravidarum and estrogen-induced chorea.
- Nonmotor features in Huntington disease are often more debilitating than chorea itself.
- Chorea is gradually replaced by parkinsonian features in later stages of Huntington disease; thus, the treatment regimen requires revision periodically.
- Delayed initiation of saccades is a hallmark eye movement abnormality in Huntington disease.
- Senile chorea should not be used as a diagnosis, and an underlying etiology should be sought.
- Children with Huntington disease typically do not present with chorea but rather parkinsonism, dystonia, and seizures.
- Age at onset in Huntington disease is determined by the number of CAG repeats, genetic modifiers, and environmental factors.

TABLE 6-2 **Genetic Causes of Chorea That Primarily Present in Adulthood**[a]

Disorder	Pattern of Inheritance	Gene (Protein Encoded)	Selected Clinical Clues (Other Than Chorea)	Remarks/Caveats
Huntington disease	Autosomal dominant	CAG repeat expansion in *HTT* (also known as *IT15*) gene (huntingtin) 36–39 repeats: reduced penetrance ≥40: full penetrance >60: juvenile Huntington disease (Westphal variant)	Chorea (forehead involvement common), psychiatric (anxiety, depression, obsessive-compulsive disorder) and cognitive features Delayed initiation of saccades, abnormal antisaccade task Motor impersistence (tongue and milkmaid's grip) Hung-up and pendular knee jerks Patients can have dystonia and parkinsonism Parkinsonism becomes more prominent upon progression (when chorea "dies out") Gait can be complex Children: parkinsonism (Westphal variant) and seizures; typically no chorea	Founder effect in some regions (eg, Venezuela around Lake Maracaibo) but found worldwide Consider genetic counseling before genetic testing, especially predictive testing
C9orf72 disease	Autosomal dominant	GGGGCC repeat expansion in *C9orf72* gene (C9orf72)	Phenotypic variability: some patients have frontotemporal dementia-amyotrophic lateral sclerosis Pyramidal features (hyperreflexia)	Recently found to be the most common cause of Huntington disease phenocopies
SCA17 (HDL-4)	Autosomal dominant	*TBP* (TATA-box binding protein)	Ataxia, dystonia Cognitive impairment, neuropsychiatric features	The second most common cause of Huntington disease phenocopies after C9orf72 disease
Huntington disease–like 2 (HDL-2)	Autosomal dominant	CTG/CAG repeat expansion in *JPH3* (junctophilin 3)	African ancestry Can also present with parkinsonism without chorea Neuropsychiatric features	Acanthocytes can be present in 10% of patients

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Disorder	Pattern of Inheritance	Gene (Protein Encoded)	Selected Clinical Clues (Other Than Chorea)	Remarks/Caveats
Neuroacanthocytosis syndromes				Special technique required to detect acanthocytes in peripheral blood smear Acanthocytes not specific to these disorders (refer to TABLE 6-3)
Chorea-acanthocytosis	Autosomal recessive	*VPS13A* (chorein)	Dystonia with predilection to lower cranial region Characteristic "feeding" (tongue protrusion) dystonia Self-mutilation: lip and tongue biting (mimicking Lesch-Nyhan syndrome) Myopathy (with elevated creatine kinase), neuropathy, seizure Psychiatric features (depression, anxiety, obsessive-compulsive disorder) Head drop, rubber man gait Compared to Huntington disease (anecdotally), delayed saccade initiation is less impaired at the same stage of neuropsychiatric abnormalities MRI: atrophy of caudate nuclei, similar to Huntington disease	
McLeod syndrome	X-linked	*XK* (Kx antigen)	Cardiomyopathy in two-thirds Seizure, neuropathy, myopathy Feeding dystonia rare	Patients can benefit from autologous blood banking because of the risk of transfusion reaction

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Disorder	Pattern of Inheritance	Gene (Protein Encoded)	Selected Clinical Clues (Other Than Chorea)	Remarks/Caveats
Dentatorubral-pallidoluysian atrophy	Autosomal dominant	*ATN1* (atrophin 1)	Generally manifests with choreoathetosis if age at onset >20 years Adult-onset: ataxia, dystonia, parkinsonism, dementia Childhood-onset: epilepsy, myoclonus MRI: pontocerebellar atrophy, white matter T2 hyperintensities	High prevalence in Japan but can also be seen in other populations Reported as "Haw River syndrome" in an African American family in North Carolina
Neurodegeneration with brain iron accumulation				Pantothenate kinase–associated neurodegeneration is rarely reported to cause chorea
Neuroferritinopathy	Autosomal dominant	*FTL* (ferritin light chain)	Dystonia with predilection to lower cranial region Low serum ferritin (not all cases) MRI gradient recalled echo (GRE), or susceptibility-weighted imaging (SWI): cystic degeneration in caudate and putamen; "pencil sign" (cortical lining of iron) has also been reported	
Aceruloplasminemia	Autosomal recessive	*CP* (ceruloplasmin)	Dystonia, ataxia, diabetes mellitus, retinal degeneration, anemia Absent serum ceruloplasmin (as opposed to low level in Wilson disease) Iron accumulation on GRE or SWI MRI sequences in the striatum, thalami, and dentate nuclei	

HDL = Huntington disease–like; MRI = magnetic resonance imaging; SCA17 = spinocerebellar ataxia type 17.
[a] Modified with permission from Termsarasab P.[11] © 2017 American Academy of Neurology.

Genetic testing in HD is a complex and sensitive issue. Genetic results can impact not only a patient but also an entire family; therefore, great caution should be exercised before ordering genetic testing. Appropriate counseling should be performed by geneticists or genetic counselors, especially for predictive genetic testing in asymptomatic individuals.[25,26]

The current clinical and research diagnostic criteria of HD are based on the presence of unequivocal motor symptoms and signs including chorea, not solely on the number of CAG repeats. However, attempts have been made to incorporate cognitive and more subtle motor features to identify patients with HD at a prodromal stage.[27] Identification of individuals at premanifest and prodromal stages may be useful for subject recruitment into natural history

CASE 6-2

An 83-year-old woman presented with an 18-month history of abnormal movements. The movements initially started in both her hands and feet, later spreading to the proximal arms and legs. The movements were absent during sleep. In addition, in the past 8 months, her family members noted she had developed irritability and inappropriate jocularity. She denied memory problems, depression, or suicidal ideation. She had no significant family history.

Examination revealed moderate generalized chorea with choreic gait (VIDEO 6-5, *links.lww.com/CONT/A355*). Upper facial chorea, seen as activation of the frontalis muscle and eyebrow wiggling, was also present. She demonstrated impulsivity and frontal disinhibition, including making inappropriate jokes during the examination. She had delayed initiation of saccades, more prominent in the horizontal than vertical directions, and blinked her eyes or thrust her head to generate saccades. Antisaccade tasks were also abnormal. She also had motor impersistence including inability to maintain tongue protrusion and milkmaid's grip. Hung-up jerks, demonstrated as prolonged knee extension upon quadriceps reflex testing, were present.

She was initially diagnosed with "senile chorea." Complete blood cell count, thyroid function tests, serum calcium, and parathyroid hormone were normal. CT of the brain revealed mild to moderate bilateral caudate atrophy. After appropriate genetic counseling, genetic testing was performed, revealing 40 CAG repeats in the *HTT* gene. Risperidone 0.5 mg/d was initiated for symptomatic control of chorea.

COMMENT

A chronic course (longer than 1 year) is suggestive of a genetic etiology of chorea, the most common of which in adults is Huntington disease (HD). HD manifests not only with chorea but also cognitive and neuropsychiatric features that can sometimes be more debilitating than the chorea itself. Senile chorea, which she had previously been diagnosed with, should not be used as a diagnosis, and an underlying etiology, such as HD, hyperthyroidism, or autoimmune causes should be sought. An individual with a low number of expanded CAG repeats in the *HTT* gene typically has a late-onset presentation, as in this patient.

studies and clinical trials for disease-modifying therapies; however, ethical issues and impact on patients and families should be taken into consideration.

Huntington Disease Phenocopies

HD phenocopies refers to a group of disorders with clinical features like HD. Given the much higher prevalence of HD compared to HD phenocopies, HD is often excluded by genetic testing in these patients before HD phenocopies are considered.

C9ORF72 DISEASE. According to studies in Europe, the most common HD phenocopy is C9orf72 disease, followed by SCA17.[8,28] However, these data cannot be simply applied to other populations since the prevalence of these choreic disorders may differ among various ethnic groups. In addition to chorea, other movement disorders in C9orf72 disease include ataxia and myoclonus. One important diagnostic clue is upper motor neuron signs or pyramidal features. Pathologic studies revealed transactive response DNA-binding protein 43 (TDP-43) pathologies in this disorder. Of note, these repeat expansion disorders can be missed in next-generation sequencing techniques. Therefore, when suspecting these disorders, clinicians should ensure that the test panels and genetic techniques used cover these disorders appropriately.

SPINOCEREBELLAR ATAXIA TYPE 17. SCA17 (also known as Huntington disease–like 4 [HDL4]) is due to CAG/CAA repeat expansion in the *TBP* gene encoding TATA-box binding protein. In addition to ataxia and chorea, patients can also have psychiatric features or cognitive impairment. Of note, chorea can also be a presentation in SCA1, SCA2, SCA3, SCA8, and SCA12. However, these SCAs are less common than SCA17 among HD phenocopies.

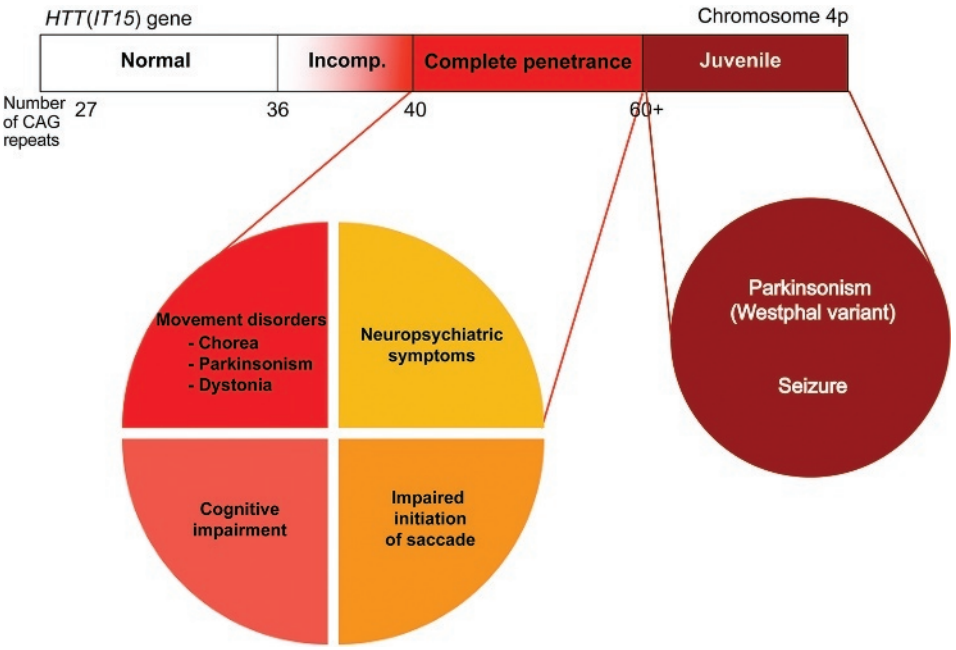

FIGURE 6-4
Relationship between CAG repeat length and Huntington disease phenotype.
Figure courtesy of Thananan Thammongkolchai, MD.

DENTATORUBRAL-PALLIDOLUYSIAN ATROPHY. Dentatorubral-pallidoluysian atrophy (DRPLA), an autosomal dominant disorder due to CAG repeat expansion in the *ATN1* gene encoding atrophin 1, can also present with chorea. The prevalence is high in Japan, but it has also been reported in other populations. In the United States, DRPLA was initially reported in an African American family in North Carolina and was called *Haw River syndrome*[29]; it has almost exclusively been seen in patients with African ancestry. In an early-onset form (younger than 20 years of age), patients with DRPLA usually have epilepsy and myoclonus, whereas chorea, ataxia, dystonia, parkinsonism, and dementia are features of the late-onset form.

AUTOSOMAL RECESSIVE ATAXIA SYNDROMES. In addition to the autosomal dominant SCAs mentioned above, several autosomal recessive ataxia syndromes with typical onset in childhood can present with a variety of hyperkinetic movement disorders, including chorea, dystonia, and myoclonus.[30] Examples include Friedreich ataxia, ataxia-telangiectasia, ataxia with oculomotor apraxia types 1 and 2, abetalipoproteinemia, and ataxia with vitamin E deficiency.

HUNTINGTON DISEASE–LIKE 2. HDL2 (VIDEO 6-6, *links.lww.com/CONT/A356*) is an autosomal dominant disorder due to CTG/CAG repeat expansion in the *JPH3* gene encoding junctophilin 3. Clinical features, including neuropsychiatric features and cognitive impairment, can be similar to HD. Ethnicity is an important diagnostic clue, as it is almost exclusively seen in patients with African ancestry. Parkinsonism can be a presentation in some patients. Interestingly, acanthocytes can be found in about 10% of patients with HDL2. Of note, HDL1 and HDL3 are even rarer than HDL2. HDL1 is a prion disease, and HDL3 has been reported in only a few families.

NEUROFERRITINOPATHY AND ACERULOPLASMINEMIA. Among all neurodegeneration with brain iron accumulation disorders, chorea is more commonly seen in neuroferritinopathy and aceruloplasminemia. Chorea is, in fact, rare in pantothenate kinase–associated neurodegeneration, the most common neurodegeneration with brain iron accumulation disorder, which typically presents with pure dystonia without chorea. Serum ferritin (reduced in neuroferritinopathy) and ceruloplasmin (absent, not just reduced, in aceruloplasminemia) can be helpful in the diagnosis. MRI can also be a useful diagnostic clue (eg, bilateral symmetric cystic change in the basal ganglia or "cortical pencil lining" in neuroferritinopathy [FIGURE 6-5[32–34]]).

NEUROACANTHOCYTOSIS SYNDROMES. Acanthocytes can be present in a number of movement disorders[35]:

- Chorea-acanthocytosis
- McLeod syndrome
- HDL2 (in approximately 10% of patients)
- Pantothenate kinase–associated neurodegeneration (in approximately 10% of patients)
- Abetalipoproteinemia (Bassen-Kornzweig syndrome)
- Aceruloplasminemia

The two main disorders in this group are chorea-acanthocytosis and McLeod syndrome. Chorea-acanthocytosis is due to mutations in the *VPS13A* gene

KEY POINTS

- Genetic counseling should be considered before ordering genetic testing for Huntington disease.
- Autosomal recessive ataxia syndromes can present with a variety of hyperkinetic movement disorders, including chorea.

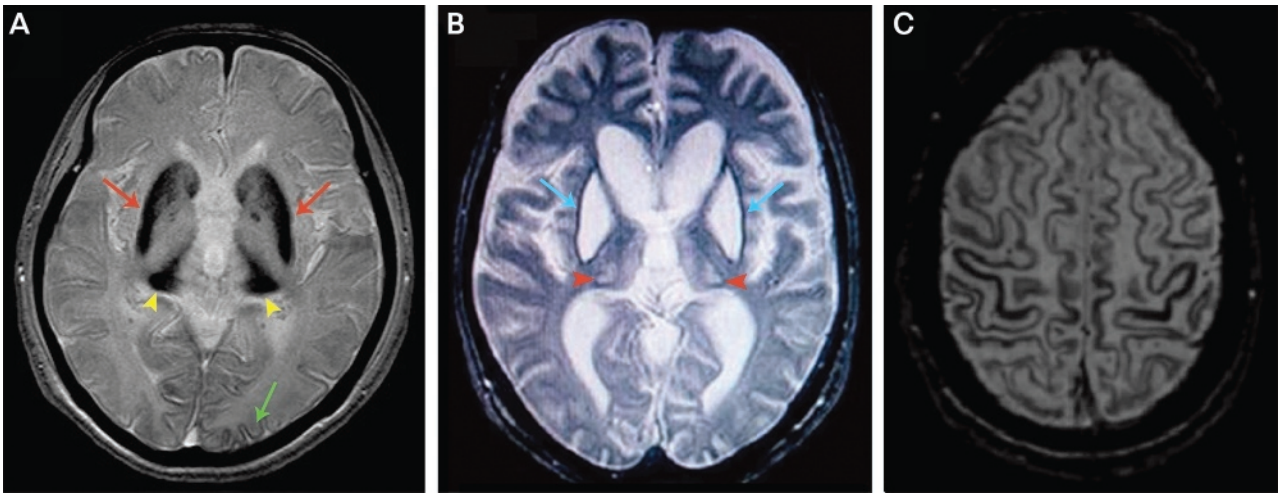

FIGURE 6-5

Neuroimaging in choreic disorders. *A*, Axial T2* MRI shows hypointensity in the bilateral striatum (*red arrows*), thalami (*yellow arrowheads*), and cortical surface (*green arrow*), representing iron accumulation in a patient with aceruloplasminemia. *B*, Axial T2-weighted MRI shows cystic degeneration of the bilateral basal ganglia (*blue arrows*) and hyperintense signal with a hypointense rim at the bilateral thalami (*red arrowheads*) in a patient with neuroferritinopathy. *C*, Axial susceptibility-weighted imaging (SWI) shows "cortical pencil lining" representing superficial iron accumulation in a patient with neuroferritinopathy.

Panel A reprinted with permission from Fujita K, et al, Neurology.[32] © 2013 American Academy of Neurology. Panel B reprinted with permission from Ohta E, Takiyama Y, Neurol Res Int.[33] © 2012 The Authors. Panel C reprinted with permission from Batla A, et al, Neurology.[34] © 2015 American Academy of Neurology.

encoding for chorein. However, because of the large size of the gene with 76 exons, gene sequencing is not feasible. Using Western blot to detect chorein deficiency is another diagnostic method. McLeod syndrome is due to mutations in the *XK* gene on the X chromosome encoding for the Kx antigen on the surface of red blood cells. The mutations lead to absent Kx antigen and reduced Kell antigen. Kx is not a part of the Kell antigen system, but molecular structural interaction between these two proteins leads to reduction of Kell protein when Kx antigen is absent. The McLeod phenotype can be discovered in blood banks during blood screening and can be detected by using anti-Kx and anti-Kell antibodies.

While acanthocytes are a hallmark of these disorders, three caveats are important to note here. First, acanthocytes are not specific to these two disorders and can also be seen in others as noted above. These disorders have also been included under the umbrella of neuroacanthocytosis syndromes.[36] Second, a special technique using a wet unfixed preparation of an isotonically diluted blood sample, as described in detail by Storch and colleagues,[37] is required for higher sensitivity of acanthocyte detection in peripheral blood smear. Although the yield of acanthocyte detection from routine peripheral blood smear is lower, it should still be examined, with an understanding of its limitations. Third, even with the appropriate technique, acanthocytes can be absent in neuroacanthocytosis syndromes; thus, the absence of acanthocytes on peripheral blood smear does not exclude these disorders.

In chorea-acanthocytosis, dystonia has a predilection to involve the lower cranial region, and feeding dystonia is one of the characteristic features. This can lead to poor nutritional status. Lip and tongue biting can be due to feeding dystonia and possibly coexisting obsessive-compulsive behaviors. Intermittent

head drop has been observed.[31] Delayed saccade initiation, similar to HD, can be a feature of chorea-acanthocytosis but anecdotally appears or becomes more obvious in the later stages as compared to HD.[23] The classic "rubber man" gait is characterized by intermittent truncal flexion, extension spasms, and, sometimes, knee flexion during walking. The phenomenology of this gait appearance remains unclear, but dystonia has been proposed.[38,39] Similar to HD, chorea can gradually be replaced by parkinsonian features in the later stages of the disease (CASE 6-3).

Clinical features of chorea-acanthocytosis and McLeod syndrome include not only motor features but also neuropsychiatric features similar to HD, including depression, anxiety, and obsessive-compulsive behaviors.

Associated medical and neurologic features can be helpful diagnostic clues in neuroacanthocytosis syndromes. Coexisting neuropathy, myopathy, and seizures can be seen in both chorea-acanthocytosis and McLeod syndrome. Serum creatine kinase and nerve conduction studies and EMG are useful investigations. Elevated serum creatine kinase is suggestive of coexisting myopathy, and nerve conduction studies and EMG may show evidence of neuropathy or myopathy, or both.

One of the major clinical differences between chorea-acanthocytosis and McLeod syndrome is that in the latter, cardiomyopathy can be present in more than 70% of patients but feeding dystonia is rare. Recognition of McLeod syndrome is of particular importance, since patients can benefit from cardiac surveillance and autologous blood transfusion. Allogeneic blood transfusion can potentially lead to severe life-threatening blood transfusion reaction, since antibodies to Kx and Kell antigens are produced after the first exposure of these antigens to blood without the McLeod phenotype.

Atrophy of the caudate nuclei on neuroimaging is not specific to HD and can also be seen in other disorders, including chorea-acanthocytosis and HDL2 (FIGURE 6-6[31]).

Benign Hereditary Chorea Syndromes

Benign hereditary chorea is the most common genetic cause of chorea in children (TABLE 6-3). The "classic" benign hereditary chorea is an autosomal dominant disorder due to mutations in the *NKX2-1* (formerly known as *TITF-1*) gene encoding thyroid transcription factor-1. Chorea usually begins in infancy or early childhood, and usually no or minimal progression occurs, with plateauing in adulthood; rare remission is seen. Other associated clinical features include ataxia, dystonia, hypotonia, and delayed motor milestones. Cognitive function is usually normal, but intellectual disability can occur. Given that the *NKX2-1* gene also has a role in lung and thyroid development, neonatal respiratory distress, interstitial lung disease, congenital hypothyroidism, or thyroid agenesis can coexist and serve as useful diagnostic clues. *NKX2-1*–related benign hereditary chorea is also called *brain-lung-thyroid syndrome*; however, involvement of all three organs is seen in only 30% to 40% of the patients (CASE 6-4).[40,41]

Although indicated in the name as "benign," it is not always benign. Some patients may have learning disabilities, attention deficit hyperactivity disorder, pituitary cysts, recurrent pulmonary infection, pulmonary fibrosis, and malignancies, such as lung cancer, bladder cancer, or leukemia.[42]

In addition to the *NKX2-1* gene, benign hereditary chorea or benign hereditary chorea–like phenotypes have been reported in other genes,

KEY POINTS

- In addition to chorea-acanthocytosis and McLeod syndrome, acanthocytes can also be seen in 10% of Huntington disease–like 2 and pantothenate kinase–associated neurodegeneration as well as abetalipoproteinemia and aceruloplasminemia.
- Patients with McLeod syndrome can benefit from cardiac surveillance and autologous blood transfusion.
- Caudate atrophy is not specific to Huntington disease and can also be seen in other disorders, such as chorea-acanthocytosis and Huntington disease–like 2.
- Benign hereditary chorea syndromes can be due to multiple mutations; the classic benign hereditary chorea is due to *NKX2-1* (*TITF*) mutations. Some patients with *NKX2-1*–related benign hereditary chorea can paradoxically respond to levodopa.

CASE 6-3

A 36-year-old woman presented for an evaluation of her progressive neurologic symptoms. At age 22, she had developed generalized tonic-clonic seizures that required multiple antiepileptic medications to control, including lamotrigine, gabapentin, and zonisamide. During one episode, she spilled boiling water on herself and required a burn unit admission and skin graft placement. At age 32, she developed speech and swallowing problems. She said that her tongue involuntarily pushed food out when eating, and she also had frequent choking, once requiring the Heimlich maneuver. She bit her lips and tongue and wore a bite block 24 hours per day. Her family had difficulty understanding her speech over the phone. At age 35, she developed flinging movements of her arms, trunk, and legs. She had difficulty walking and experienced multiple falls. She had developed depression, memory loss, and irritability around age 22 but denied obsessive-compulsive behavior. Family history was negative.

Examination revealed a mild parkinsonian appearance with facial dystonia, especially in the lower facial region (VIDEO 6-7, *links.lww.com/CONT/A357*). She had moderate dysarthria. Eye examination revealed delayed initiation of vertical saccades with more limited range of downgaze than upgaze. She had mild intermittent chorea in her extremities and trunk as well as some dystonic posturing of the left arm. Her gait was complex and partially composed of choreic and dystonic components. She had some hyperextension and circumduction of the left leg when walking. Deep tendon reflexes were absent throughout.

Acanthocytes were found on a routine peripheral blood smear. Her creatine kinase was 790 U/L. A previous MRI brain reportedly showed no caudate atrophy but was not available for review. Western blot of her blood sample revealed absence of chorein protein. The diagnosis of chorea-acanthocytosis was confirmed. Her care was managed by a multidisciplinary team, including physical, occupational, and speech therapists.

COMMENT

Chorea, along with feeding dystonia, seizures, and coexisting neuropathy or myopathy (evidenced by absent or reduced deep tendon reflexes and elevated creatine kinase) are very suggestive of chorea-acanthocytosis, an autosomal recessive form of neuroacanthocytosis syndromes. Although present in this patient, acanthocytes in the peripheral blood smear are not always seen even with a special technique using a wet unfixed preparation of an isotonically diluted blood sample. Delayed initiation of saccades, similar to that seen in Huntington disease, can be seen in chorea-acanthocytosis; however, it usually comes in the later stages compared to Huntington disease. Vertical supranuclear gaze palsy is an unusual feature in chorea-acanthocytosis. Therapies for choreic disorders are not restricted to the treatments of chorea. Although specific therapies are not yet available, and symptomatic treatment is not required if chorea is mild and nonbothersome, patients such as this one could benefit from multidisciplinary care by a physical medicine and rehabilitation specialist and physical, occupational, and speech therapists.

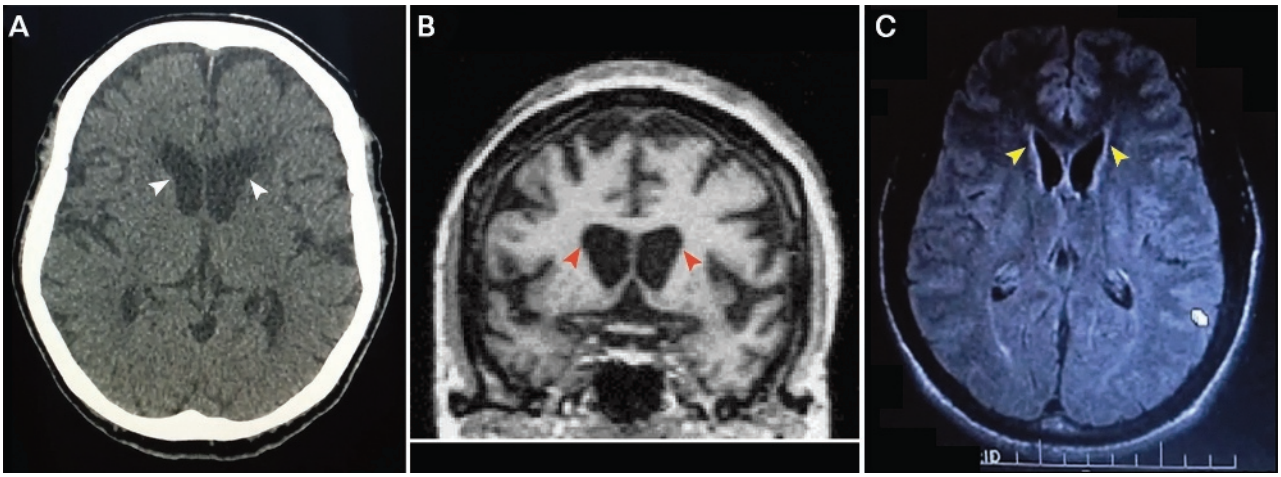

FIGURE 6-6

Choreic disorders with bilateral caudate atrophy on neuroimaging. *A*, CT scan showing bilateral caudate atrophy in Huntington disease (*white arrowheads*). *B*, Coronal T1-weighted MRI in a patient with Huntington disease–like 2 (*red arrowheads*). *C*, Axial fluid-attenuated inversion recovery (FLAIR) MRI in a patient with chorea-acanthocytosis (*yellow arrowheads*).

Panel B reprinted with permission from Margolis RL, Holmes SE, Clin Neurosci Res.[31] © 2001 Nature Press.

including *ADCY5*,[43,44] *PDE10A*,[45,46] *GNAO1*,[47] and *SLC16A2* (associated with Allan-Herndon-Dudley syndrome).[48] Therefore, benign hereditary chorea represents the clinical syndromes, rather than one specific disorder. The term *benign hereditary chorea syndromes* has been used to represent the entire group of patients with clinical features compatible with or similar to benign hereditary chorea as described above regardless of the underlying genetic defects, whereas the term *classic benign hereditary chorea* specifically denotes *NKX2-1*–related benign hereditary chorea. While no consensus definition or distinct clinical boundary of benign hereditary chorea syndromes exists, this term may be useful for searching for other underlying genetic defects when encountering patients with clinical pictures similar to or mimicking *NKX2-1*–related benign hereditary chorea. Unfortunately, this terminology has not been consistently used in the literature or clinical practice; thus, whether *benign hereditary chorea* represents only the classic form or the benign hereditary chorea syndromes should always be clarified.

In addition to general symptomatic therapies for chorea, patients with *NKX2-1*–related benign hereditary chorea can paradoxically respond to levodopa for unknown reasons. In the author's experience, this responsiveness can be seen in some, but not all, patients.

ADCY5-related dyskinesia, previously known as *familial dyskinesia with facial myokymia*,[49] is an autosomal dominant disorder due to mutations in the *ADCY5* gene encoding adenylate cyclase 5. Patients may have clinical features mimicking *NKX2-1*–related benign hereditary chorea, but mixed movement disorders, including chorea, dystonia, and myoclonus, often occur.[43,44] One diagnostic clue is facial dyskinesia, which cannot be perfectly categorized into any previously described movement disorder phenomenology. Facial myokymia was a misnomer, since subsequent electrophysiologic studies did not reveal evidence of myokymia.[50] Other clinical features include hypotonia, delayed motor milestones, and exacerbation of dyskinesia during transitions between wakefulness and sleep including drowsiness and sleep arousal.[51] In some patients, the movements may be paroxysmal.

TABLE 6-3 Genetic Causes of Chorea That Primarily Present in Childhood[a]

Disorder	Pattern of Inheritance	Gene (Protein Encoded)	Selected Clinical Clues (Other Than Chorea)	Remarks/Caveats
Choreoathetoid cerebral palsy	NA	NA	Dystonia often coexists with chorea Flowing component may sometimes be difficult to differentiate between dystonia and choreoathetosis Dystonic hand posturing typically not painful; it is unique and difficult for healthy person to mimic	Included in this table as it is likely composed of a mixed bag of genetic/neurometabolic disorders, in addition to hypoxic brain injury, which have to be ruled out carefully before making this diagnosis
Benign hereditary chorea syndromes				Can be due to mutations in several genes, including *NKX2-1, ADCY5, PDE10A, GNAO1, SLC16A2* (Allan-Herndon-Dudley syndrome)
Classic benign hereditary chorea syndrome or *NKX2-1*–related benign hereditary chorea	Autosomal dominant	*NKX2-1* (formerly known as *TITF-1*) gene (thyroid transcription factor-1)	Also called *brain-lung-thyroid syndrome* (or *BLT syndrome*) Hypothyroidism and pulmonary disease (eg, respiratory distress or interstitial lung disease) can coexist Typically nonprogressive, but not always benign (considered relatively more benign, compared to Huntington disease) Patients may have developmental delay or short stature	Some may have paradoxical response to levodopa

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Disorder	Pattern of Inheritance	Gene (Protein Encoded)	Selected Clinical Clues (Other Than Chorea)	Remarks/Caveats
ADCY5-related dyskinesia	Autosomal dominant	*ADCY5* (adenylate cyclase 5)	Phenotypic variability Mixed movement disorders, including chorea, dystonia, myoclonus Movements can be paroxysmal	Previously called *familial dyskinesia with facial myokymia*, but the facial movements are, in fact, not myokymia, based on EMG studies
Lesch-Nyhan syndrome	X-linked recessive	*HPRT1* (hypoxanthine-guanine phosphoribosyltransferase)	Often associated with dystonia with predominant lower cranial involvement Self-mutilation May resemble chorea-acanthocytosis, but age group is typically younger in Lesch-Nyhan syndrome Hyperuricemia	Females can less commonly be affected because of skewed inactivation of X chromosome
Wilson disease	Autosomal recessive	*ATP7B* (ATP7B)	Varieties of movement disorders, including dystonia, parkinsonism, ataxia, tremor (including classic wing-beating tremor, a form of cerebellar tremor but not common) Kayser-Fleischer rings (pay attention to upper and lower corneal limbi); when in doubt, refer for slit-lamp examination Low serum ceruloplasmin, low serum copper, high 24-hour urine copper	

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Disorder	Pattern of Inheritance	Gene (Protein Encoded)	Selected Clinical Clues (Other Than Chorea)	Remarks/Caveats
Autosomal recessive ataxia				Most autosomal recessive ataxias with onset in childhood can present with hyperkinetic movement disorders, including dystonia, chorea, and myoclonus
Friedreich ataxia	Autosomal recessive	*FXN* due to GAA repeat expansion and/or mutations (frataxin)	Dystonia, ataxia, pes cavus, hyporeflexia, diabetes mellitus, cardiomyopathy, scoliosis Eye movement examination: macrosaccadic oscillations, hypermetric saccades Relatively preserved cerebellar size on MRI until late stages Variants (these two overlap): Friedreich ataxia with retained reflex or hyperreflexia, often late onset Late-onset Friedreich ataxia	
Ataxia with oculomotor apraxia type 1 (AOA1)	Autosomal recessive	*APTX* (aprataxin)	Oculomotor apraxia (delayed initiation of saccades) Neuropathy Low serum albumin, high cholesterol	Differential diagnoses of oculomotor apraxia associated with ataxia include ataxia-telangiectasia, AOA1 and AOA2
Ataxia with oculomotor apraxia type 2 (AOA2)	Autosomal recessive	*SETX* (senataxin)	Age group is typically older than AOA1 Oculomotor apraxia Neuropathy High α-fetoprotein in almost all cases	α-Fetoprotein can also be elevated in ataxia-telangiectasia (almost all cases)

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Disorder	Pattern of Inheritance	Gene (Protein Encoded)	Selected Clinical Clues (Other Than Chorea)	Remarks/Caveats
Metabolic disorders (eg, organic acidemia)	Autosomal recessive	Multiple	Can also present with dystonia Hyperintense signals at bilateral lentiform nuclei on T2-weighted MRI	Differential diagnoses include methylmalonic acidemia and glutaric aciduria type I, among others Check plasma amino acids and urine organic acids
Mitochondrial disorders (eg, Leigh syndrome or MELAS)	Mitochondrial or autosomal recessive (if attributed to nuclear mutations)	Mitochondrial/nuclear gene mutations	May also present with dystonia MRI in Leigh syndrome: hyperintense signal at bilateral basal ganglia and/or brainstem on T2-weighted sequences MELAS can have basal ganglia calcification (CT is useful to demonstrate)	Start by checking for high lactate level in serum and CSF

CSF = cerebrospinal fluid; CT = computed tomography; EMG = electromyography; MELAS = mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes; MRI = magnetic resonance imaging; NA = not applicable.
[a] Modified with permission from Termsarasab P.[11] © 2017 American Academy of Neurology.

Other rarer genes related to benign hereditary chorea syndromes are discussed here only briefly. *PDE10A* mutations can be either autosomal dominant or recessive. The dominant forms or de novo mutations typically present with chorea at around 5 to 10 years of age and show bilateral striatal hyperintense signals on MRI (hence, also called childhood-onset bilateral striatal necrosis), but no intellectual impairment is seen.[45] The recessive forms are more severe. Clinical features include infantile-onset chorea and motor and language developmental delay but, interestingly, no striatal hyperintensity on MRI.[46]

Gain-of-function mutations in the *GNAO1* gene can present with chorea,[47] whereas loss-of-function mutations cause Ohtahara syndrome, a form of early infantile epileptic encephalopathy. Relatively new genes reported in chorea associated with epilepsy include *FOXG1* (in which patients can have prominent orofacial chorea/dyskinesia),[52] *GRIN1*[53,54] and *FRRS1L*.[55]

CASE 6-4

A 6-year-old boy came to the clinic for follow-up of his choreic disorder. He was born full term without any prenatal and perinatal complications. However, during the first 2 years of life, he was diagnosed with hypothyroidism and "asthma." Around 4.5 years of age, he was evaluated in the movement disorder clinic because of abnormal movements compatible with generalized chorea, which had gradually become more noticeable in the past 1.5 years. Multiple family members on his maternal side had thyroid problems and asthma; however, no abnormal movement was reported in these family members. The diagnosis of benign hereditary chorea was suspected, and it was confirmed by the mutation in the *NKX2-1* (formerly known as *TITF-1*) gene. He had mild intellectual disability and had participated in a special school program. His chorea had been stable in the past 2 years. He was trialed on levodopa at the age of 6 years up to 5 mg/kg/d for symptomatic control of chorea. However, because no improvement was seen, it was subsequently discontinued.

Examination revealed mild to moderate generalized chorea involving all extremities, trunk, neck, and lower facial region, as well as mild bilateral foot dystonia demonstrated as mild foot inversion when walking. The dystonic component was much less prominent than chorea. Treatment options, including tetrabenazine, were discussed with his parents.

COMMENT

This patient's chronic temporal profile is suggestive of a genetic cause of chorea, the most common of which in children is benign hereditary chorea. Benign hereditary chorea syndrome can be due to several mutations. The "classic" benign hereditary chorea syndrome is due to *NKX2-1 (TITF-1)* mutations, which can also cause lung and thyroid problems (hence the term *brain-lung-thyroid syndrome*), as in this patient. While seen in this patient, involvement of all three organs is present in only 30% to 40% of patients. Benign hereditary chorea is not always "benign"; for example, this patient has intellectual disability. Some, but not all, patients with this disorder can respond to levodopa.

CHOREA IN PAROXYSMAL MOVEMENT DISORDERS

This special group of disorders can be divided into two main categories: primary and secondary paroxysmal dyskinesias. Based on the triggers, primary paroxysmal dyskinesias can be further classified into paroxysmal kinesigenic dyskinesia, paroxysmal nonkinesigenic dyskinesia, and paroxysmal exercise-induced dyskinesia. Although dystonia is common during the paroxysmal attacks, chorea can also be seen. When encountering patients with paroxysmal chorea, these disorders should be considered. Paroxysmal kinesigenic dyskinesia typically has exquisite response to low-dose antiepileptic medications, especially carbamazepine. In patients with paroxysmal exercise-induced dyskinesia, glucose transporter 1 deficiency syndrome, which is treatable, should be excluded. With advances in genetics, the number of genes associated with each phenotype has been expanding.[56–58] A detailed discussion about paroxysmal movement disorders is beyond the scope of this article.

TREATMENT

The first question before initiating treatment is "Does chorea need to be treated?" (TABLE 6-4). When chorea is mild and nonbothersome and does not interfere with a patient's daily activities, symptomatic treatment is not required. In some choreic disorders, such as HD, lack of awareness of the deficit by patients as a possible coexisting neuropsychiatric feature may limit evaluation of chorea severity solely from patients' reports. Thus, the clinician's and family's evaluation of chorea severity should also be incorporated into clinical decisions. When clinicians decide to treat, two main categories of therapies should be considered: specific therapies and symptomatic therapies (TABLE 6-5).

Specific Therapies

Many acquired choreas are treatable, so correct diagnosis of these "don't-miss" disorders is a crucial step before using corresponding specific therapies. Examples include blood sugar control in nonketotic hyperglycemia, phlebotomy and hydroxyurea in polycythemia vera, antibiotics in central nervous system (CNS) infection such as CNS toxoplasmosis, and immunotherapies in autoimmune choreas, including systemic lupus erythematosus.

Symptomatic Therapies

Symptomatic therapies include pharmacologic treatment and deep brain stimulation (DBS).

Principles of Chorea Treatment TABLE 6-4

Step 1: Does chorea need to be treated? When it is mild and nonbothersome, treatment is not required.

Step 2: Is specific treatment available?

Step 3: If chorea is not controlled by specific treatment or specific treatment is not available, what symptomatic therapies should be selected?

Step 4: Are there any other symptoms than chorea that require treatment or surveillance? Patients can benefit from multidisciplinary approach.

Step 5: Does any family member need further evaluation or genetic counseling?

TABLE 6-5

Therapeutic Options in Chorea

Specific Therapies

- **Blood sugar control in nonketotic hyperglycemia**
- **Phlebotomy and hydroxyurea in polycythemia vera**
- **Treatment for hyperthyroidism**
- **Immunotherapies in autoimmune choreas**

Symptomatic Therapies

- **Pharmacologic therapies**
  - ◇ Presynaptic dopamine depletors
    - → Tetrabenazine and reserpine
    - → New-generation vesicular monoamine transporter 2 inhibitors
      - – Deutetrabenazine
      - – Valbenazine
  - ◇ Postsynaptic dopamine receptor blockers (dopamine receptor blocking agents, neuroleptics or antipsychotics)
    - → Typical antipsychotics
      - – Haloperidol
    - → Atypical antipsychotics
      - – Olanzapine
      - – Risperidone
      - – Quetiapine
      - – Clozapine
  - ◇ Others
    - → Antiepileptics
      - – Valproic acid
      - – Carbamazepine

Deep Brain Stimulation

- **Reported in Huntington disease, chorea-acanthocytosis, and some acquired choreas**

Multidisciplinary Approach

- **Psychiatrist; physical medicine and rehabilitation specialist; physical, occupational, and speech therapists**
- **Geneticist, genetic counselor**
- **Social worker**

PHARMACOLOGIC THERAPIES. As a general principle, the "start low, go slow" strategy should be followed. Medications should be started at a low dose and gradually titrated over time to reach the effective dose to avoid side effects. If side effects occur, tapering the medications and monitoring are required. If medications need to be discontinued for any reason, slow tapering should be considered to avoid withdrawal side effects.

Given a hyperdopaminergic state as a general hypothesis of the pathophysiology of chorea, the strategy for symptomatic therapies is to reduce the amount of dopamine or its effect within the CNS. The main pharmacologic targets are dopaminergic synapses, either at presynaptic or postsynaptic sites (FIGURE 6-7).

MEDICATIONS TARGETING THE PRESYNAPTIC SITE (PRESYNAPTIC DOPAMINE-DEPLETING AGENTS). Presynaptic dopamine-depleting agents include tetrabenazine and reserpine. Both drugs inhibit vesicular monoamine transporter (VMAT) 2 in the CNS, thereby preventing packaging of dopamine into presynaptic vesicles. Dopamine is then degraded by a monoamine oxidase B enzyme. Tetrabenazine is a selective VMAT2 inhibitor, whereas reserpine also inhibits VMAT1 in the peripheral nervous system and can lead to hypotension. Tetrabenazine is widely used in clinical practice and was approved by the US Food and Drug Administration (FDA) for chorea associated with HD in 2008, based on the TETRA-HD (Efficacy, Safety, and Dose Tolerability of

KEY POINTS

- Patients with choreic disorders can benefit from a multidisciplinary approach. Associated features and comorbidities, such as cognitive and neuropsychiatric features, should be taken into consideration when treating chorea. Mild and nonbothersome chorea does not require treatment. Immunotherapies are treatment options in Sydenham chorea.
- The main pharmacologic targets of chorea are dopaminergic synapses, either at presynaptic or postsynaptic sites

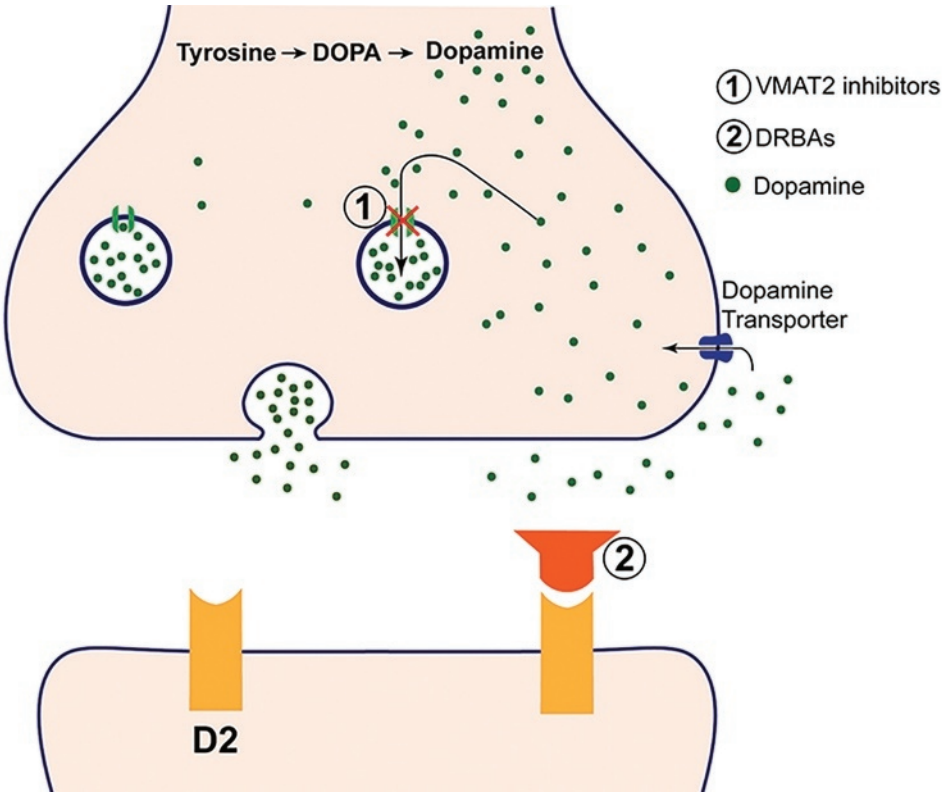

FIGURE 6-7
Sites of action of the main pharmacologic therapies in chorea. *1*, Presynaptic dopamine-depleting agents are vesicular monoamine transporter 2 (VMAT2) inhibitors. *2*, Postsynaptic dopamine receptor blocking agents (DRBAs) act by blocking mainly D_2 receptors.
Figure courtesy of Thananan Thammongkolchai, MD.

Tetrabenazine for Chorea in Huntington Disease) study.[59] In addition to HD, tetrabenazine has been used off-label for other indications, including chorea from other etiologies and various hyperkinetic movement disorders such as tics and Tourette syndrome.[60,61] Because of presynaptic monoamine depletion, side effects include parkinsonism, depression, and akathisia. Because of the potential risks of depression and suicidality, tetrabenazine carries an FDA boxed warning. Its active metabolites are degraded by the CYP2D6 enzyme. When the dose is greater than 50 mg/d, CYP2D6 enzyme testing is currently recommended to determine whether patients are poor, intermediate, or extensive metabolizers. Extensive metabolizers may require higher doses.

The new-generation selective VMAT2 inhibitors include deutetrabenazine and valbenazine. Deutetrabenazine was approved by the FDA for chorea associated with HD in April 2017 and for tardive dyskinesia in August 2017, based on the FIRST-HD (First Time Use of SD-809 in Huntington Disease)[62] and AIM-TD (Addressing Involuntary Movements in Tardive Dyskinesia)[63] studies, respectively. Six hydrogen atoms in tetrabenazine are replaced by deuterium or "heavy hydrogen" atoms in deutetrabenazine. This leads to pharmacokinetic advantages, including longer plasma half-life (9 to 10 hours for deutetrabenazine compared to 5 to 7 hours for tetrabenazine) and less plasma level fluctuation of the drug, and thus fewer side effects, especially sedation. In addition, deutetrabenazine can be administered 2 times a day, instead of 3 times a day as with tetrabenazine. Despite no statistical difference in depression and suicidality between the treatment and control groups in the FIRST-HD study, deutetrabenazine carries an FDA boxed warning for depression and suicidality in patients with HD.

Valbenazine is a prodrug of one of the isomeric metabolites of tetrabenazine. It is slowly metabolized into (+)-α-dihydrotetrabenazine. The pharmacokinetic advantage of valbenazine and its metabolite is long plasma half-life (16 to 22 hours), so the medication can be administered once daily. It was approved for tardive dyskinesia in adults in April 2017, based on the KINECT-3 (A Phase 3 Study of NBI-98854 for the Treatment of Tardive Dyskinesia) study.[64] Valbenazine has not been studied in chorea associated with HD. Side effects of valbenazine include sedation, headache, and QTc prolongation. It is contraindicated in patients with underlying congenital prolonged QT syndrome or arrhythmias with prolonged QT interval.

α-Methyl-p-tyrosine (metyrosine) depletes presynaptic dopamine by inhibiting tyrosine hydroxylase, the rate-limiting enzyme in dopamine synthesis. However, this drug is not available in the United States and most other countries.

MEDICATIONS TARGETING THE POSTSYNAPTIC DOPAMINERGIC SITES. Medications that target the postsynaptic dopaminergic sites are mainly dopamine receptor blocking agents (also called antipsychotics or neuroleptics). The dopamine receptor blocking agents effective for treatment of chorea typically have a mechanism of action at the D_2 receptor, which also contributes to the risk of developing tardive dyskinesia. The "cleaner" dopamine receptor blocking agents, such as clozapine and quetiapine, have also been used but may not be as effective as dopamine receptor blocking agents with higher affinity to D_2 receptors, such as the typical antipsychotics, in particular, haloperidol, and atypical antipsychotics such as olanzapine and risperidone While clozapine is relatively the "cleanest" with regard to the risk of tardive dyskinesia, the need for frequent blood monitoring limits its use, especially in the setting of

coexisting cognitive impairment or poor compliance, which may not be uncommon in patients with chorea. Because of the risks of tardive dyskinesia, many clinicians, especially clinicians in the United States, prefer the presynaptic dopamine-depleting agents to dopamine receptor blocking agents. According to a 2011 international survey,[65] treatment preferences for chorea in HD differed between Europe and America. In Europe, clinicians preferred antipsychotics to tetrabenazine, whereas in the United States, preferences were roughly equally split between antipsychotics and tetrabenazine. However, there may be a trend to use more presynaptic dopamine-depleting agents in current clinical practice.[66]

Other associated clinical features or comorbidities should be taken into consideration when selecting treatment for chorea. Antipsychotics may be preferable to presynaptic dopamine-depleting agents when one or more of the following exists: (1) coexisting psychosis or aggression, which can be seen in some choreic disorders such as HD and chorea-acanthocytosis; (2) coexisting depression and suicidal risks that preclude the use of presynaptic dopamine-depleting agents; and (3) noncompliance.[65] Given the higher cost of presynaptic dopamine-depleting agents and their limited availability, antipsychotics remain the only or more preferable choice in many regions of the world.

Dopamine receptor blocking agents, especially olanzapine and risperidone, can cause metabolic syndromes, including weight gain, which can be a beneficial effect in patients with significant weight loss and poor nutritional status. Blood chemistries, including lipid profile and glucose, should be monitored periodically. Other symptomatic therapies for chorea include antiepileptic drugs such as valproic acid and carbamazepine (eg, in Sydenham chorea), and levodopa (in benign hereditary chorea).

Treatment of Sydenham chorea deserves some specific discussion here. For symptomatic treatment of the chorea, antiepileptic drugs, including valproic acid and carbamazepine, have been found to be effective.[67] Antipsychotics can pose risks of drug-induced parkinsonism in Sydenham chorea and thus have to be used with caution, typically as second-line treatment.[68] Immunomodulatory therapies (which serve as specific rather than symptomatic therapies), including IVIg, IV steroids, and plasma exchange, have been increasingly employed in Sydenham chorea,[69] although more evidence from clinical trials is needed. This option can be considered in patients with severe Sydenham chorea such as chorea paralytica or as second-line treatment in patients with inadequate response to conventional symptomatic therapies.

DEEP BRAIN STIMULATION. DBS in chorea remains a moving target. Most studies have been done in HD[70] and chorea-acanthocytosis.[71] These are mostly case reports or small case series,[72] which can pose some biases, as cases with poor outcome are unlikely to be reported. The most common target is the globus pallidus internus (GPi), and stimulation at the ventral GPi is known to have an antidyskinetic effect from extensive DBS experience in Parkinson disease. Further clarification on DBS efficacy, candidacy, and appropriate targets can be elucidated from future studies and randomized controlled trials.

Factors other than chorea also should be considered when selecting DBS as a treatment. First, coexisting cognitive and neuropsychiatric features can even be more debilitating than chorea and other motor features and are unlikely to be responsive to DBS. Secondly, chorea in HD and chorea-acanthocytosis can gradually be replaced by parkinsonism in the later stages of the diseases. Thus, the

natural history of the disease can contribute to chorea reduction, and different stimulation or programming strategies may be required in different stages (eg, more dorsal electrodes in GPi to control parkinsonism). Experimental genetic therapies, especially huntingtin-lowering treatment, are under active investigation,[73,74] and more data will be required before application to clinical practice.

A holistic approach is also crucial in the care of patients with chorea. Many patients with chorea experience not only motor symptoms but also cognitive and neuropsychiatric features as well as psychosocial issues. A multidisciplinary team approach that includes psychiatrists, physical medicine and rehabilitation specialists, physical therapists, occupational therapists, speech therapists, social workers, and geneticists and genetic counselors can be beneficial. Furthermore, in some disorders, especially HD, the unit of treatment is an entire family rather than an individual patient. Caregiver burden and the stress of at-risk family members should also be supported.

CONCLUSION

The etiology of chorea can be categorized into acquired and genetic causes. Among the most useful features in the diagnostic approach are time course, age group, and known prevalence in the population. Other clinical diagnostic clues can help guide the investigation. Genetic counseling should be considered before sending genetic testing in chorea. Management should include not only symptomatic treatment of chorea but also other associated medical, neurologic, and psychiatric aspects. Family and caregiver support should be also taken into consideration when caring for patients with chorea.

VIDEO LEGENDS

VIDEO 6-1
Hemiballism secondary to central nervous system toxoplasmosis. Video shows a 54-year-old man with left hemiballism exhibiting large-amplitude movements involving the predominantly proximal arm and leg. On MRI, fluid-attenuated inversion recovery (FLAIR) images show numerous multifocal hyperintense lesions that also involve the basal ganglia.
links.lww.com/CONT/A351

Courtesy of Steven Frucht, MD.

VIDEO 6-2
Hemichorea secondary to nonketotic hyperglycemia. Video shows the 77-year-old woman described in CASE 6-1. She has hemichorea secondary to nonketotic hyperglycemia and demonstrates left hemichorea involving the face, arm, and leg as well as hemichoreic gait.
links.lww.com/CONT/A352

VIDEO 6-3
Lupus chorea. Video shows a 29-year-old woman with acute generalized chorea and encephalopathy as her first presentation of systemic lupus erythematosus. Both chorea and her mental status improved after 3 days of treatment with IV steroids and tetrabenazine 75 mg/d.
links.lww.com/CONT/A353

Courtesy of Steven Frucht, MD.

VIDEO 6-4
Sydenham chorea. Video shows an 8-year-old boy with Sydenham chorea who presented with an acute temporal profile of severe generalized chorea. He also displays hypotonia and milkmaid's grip. He is unable to stand unassisted.
links.lww.com/CONT/A354

Reproduced with permission from Frucht SJ.[17]

VIDEO 6-5
Huntington disease. Video shows the 83-year-old woman described in CASE 6-2. She has Huntington disease and exhibits generalized chorea including upper and lower facial involvement, parakinesia, motor impersistence involving the tongue, milkmaid's grip, and choreic gait. Hung-up knee jerk is also shown.
links.lww.com/CONT/A355

VIDEO 6-6
Huntington disease–like 2. Video shows a 56-year-old woman exhibiting generalized chorea and tongue impersistence. She is originally from Barbados with African ancestry. Genetic testing for Huntington disease is negative, and she is genetically confirmed to have mutations in *JPH3* diagnostic of Huntington disease–like 2.
links.lww.com/CONT/A356

Courtesy of Steven Frucht, MD.

VIDEO 6-7
Chorea-acanthocytosis. Video shows the 36-year-old woman with chorea-acanthocytosis described in CASE 6-3. The first video segment demonstrates severe tongue protrusion and feeding dystonia. In the second segment, she exhibits a mild parkinsonian appearance and lower facial and left arm dystonia, but only mild truncal chorea. She walks with stutter steps and has circumduction of the left leg.
links.lww.com/CONT/A357

REFERENCES

1 Morris JGL, Jankelowitz SK, Fung VSC, et al. Athetosis I: historical considerations. Mov Dis 2002;17:1278–1280. doi:10.1002/mds.10267.

2 Postuma RB, Lang AE. Hemiballism: revisiting a classic disorder. Lancet Neurol 2003;2:661–668. doi:10.1016/S1474-4422(03)00554-4.

3 Cosentino C, Torres L, Nunez Y, Suarez R, Velez M, Flores M. Hemichorea/hemiballism associated with hyperglycemia: report of 20 cases. Tremor Other Hyperkinet Mov (N Y) 2016;6:402. doi:10.7916/D8DN454P.

4 Lew J, Frucht SJ, Kremyanskaya M, et al. Hemichorea in a patient with JAK2V617F blood cells. Blood 2013;121(7):1239–1240. doi:10.1182/blood-2012-12-468751.

5 Ryan C, Ahlskog JE, Savica R. Hyperglycemic chorea/ballism ascertained over 15 years at a referral medical center. Parkinsonism Relat Disord 2018;48:97–100. doi:10.1016/j.parkreldis.2017.12.032.

6 Walker RH. Untangling the thorns: advances in the neuroacanthocytosis syndromes. J Mov Disord 2015;8(2):41–54. doi:10.14802/jmd.15009.

7 Fekete R, Jankovic J. Upper facial chorea in Huntington disease. J Clin Mov Disord 2014;1:7. doi:10.1186/2054-7072-1-7.

8 Hensman Moss DJ, Poulter M, Beck J, et al. C9orf72 expansions are the most common genetic cause of Huntington disease phenocopies. Neurology 2014;82(4):292–299. doi:10.1212/WNL.0000000000000061.

9 Van Mossevelde S, van der Zee J, Gijselinck I, et al. Clinical evidence of disease anticipation in families segregating a C9orf72 repeat expansion. JAMA Neurol 2017;74(4):445–452. doi:10.1001/jamaneurol.2016.4847.

10 Krause A, Mitchell C, Essop F, et al. Junctophilin 3 (JPH3) expansion mutations causing Huntington disease like 2 (HDL2) are common in South African patients with African ancestry and a Huntington disease phenotype. Am J Med Genet B Neuropsychiatr Genet 2015;168(7):573–585. doi:10.1002/ajmg.b.32332.

11 Termsarasab P. Hyperkinetic movement disorders: videodiagnosis and treatment. Presented at: 69th Annual Meeting of the American Academy of Neurology; April 22–28, 2017; Boston, MA.

12 Damato V, Balint B, Kienzler AK, Irani SR. The clinical features, underlying immunology, and treatment of autoantibody-mediated movement disorders. Mov Disord 2018;33(9):1376–1389. doi:10.1002/mds.27446.

13 Varley JA, Webb AJS, Balint B, et al. The movement disorder associated with NMDAR antibody-encephalitis is complex and characteristic: an expert video-rating study. J Neurol Neurosurg Psychiatry 2018;pii:jnnp-2018-318584. doi:10.1136/jnnp-2018-318584.

14 Sabater L, Gaig C, Gelpi E, et al. A novel non-rapid-eye movement and rapid-eye-movement parasomnia with sleep breathing disorder associated with antibodies to IgLON5: a case series, characterisation of the antigen, and post-mortem study. Lancet Neurol 2014;13(6):575–586. doi:10.1016/S1474-4422(14)70051-1.

15 Gaig C, Graus F, Compta Y, et al. Clinical manifestations of the anti-IgLON5 disease. Neurology 2017;88(18):1736–1743. doi:10.1212/WNL.0000000000003887.

16 Gelpi E, Höftberger R, Graus F, et al. Neuropathological criteria of anti-IgLON5-related tauopathy. Acta Neuropathol 2016;132(4):531–543. doi:10.1007/s00401-016-1591-8.

17 Frucht SJ, editor. Movement disorder emergencies. 2nd edition. New York, NY: Humana Press, 2013.

18 Cardoso F, Vargas AP, Oliveira LD, et al. Persistent Sydenham's chorea. Mov Disord 1999;14(5):805–807. doi:10.1002/1531-8257(199909)14:5<805::AID-MDS1013>3.0.CO;2-P.

19 Robottom BJ, Weiner WJ. Chorea gravidarum. Handb Clin Neurol 2011;100:231–235. doi:10.1016/B978-0-444-52014-2.00015-X.

20 Termsarasab P, Frucht SJ. The "stutter-step": a peculiar gait feature in advanced Huntington's disease and chorea-acanthocytosis. Mov Disord Clin Pract 2018;5:223–224. doi:10.1002/mdc3.12586.

21 Bates GP, Dorsey R, Gusella JF, et al. Huntington disease. Nat Rev Dis Primers 2015;1:15005. doi:10.1038/nrdp.2015.5.

22 McColgan P, Tabrizi SJ. Huntington's disease: a clinical review. Eur J Neurol 2018;25(1):24–34. doi:10.1111/ene.13413.

23 Termsarasab P, Thammongkolchai T, Rucker JC, Frucht SJ. The diagnostic value of saccades in movement disorder patients: a practical guide and review. J Clin Mov Disord 2015;2:14. doi: 10.1186/s40734-015-0025-4.

24 Gusella JF, MacDonald ME, Lee JM. Genetic modifiers of Huntington's disease. Mov Disord 2014;29(11):1359–1365. doi:10.1002/mds.26001.

25 MacLeod R, Tibben A, Frontali M, et al. Recommendations for the predictive genetic test in Huntington's disease. Clin Genet 2013; 83(3):221–231. doi:10.1111/j.1399-0004.2012.01900.x.

26 Nance MA. Genetic counseling and testing for Huntington's disease: a historical review. Am J Med Genet B Neuropsychiatr Genet 2017;174(1): 75–92. doi:10.1002/ajmg.b.32453.

27 Reilmann R, Leavitt BR, Ross CA. Diagnostic criteria for Huntington's disease based on natural history. Mov Disord 2014;29(11):1335–1341. doi: 10.1002/mds.26011.

28 Schneider SA, Bird T. Huntington's disease, Huntington's disease look-alikes, and benign hereditary chorea: what's new? Mov Disord Clin Pract 2016;3:342–354. doi:10.1002/mdc3.12312.

29 Burke JR, Wingfield MS, Lewis KE, et al. The Haw river syndrome: dentatorubropallidoluysian atrophy (DRPLA) in an African-American family. Nat Genet 1994;7(4):521–524. doi:10.1038/ ng0894-521.

30 Pearson TS. More than ataxia: hyperkinetic movement disorders in childhood autosomal recessive ataxia syndromes. Tremor Other Hyperkinet Mov (N Y) 2016;6:368. doi:10.7916/ D8H70FSS.

31 Margolis RL, Holmes SE. Huntington's disease-like 2: a clinical, pathological, and molecular comparison to Huntington's disease. Clin Neurosci Res 2003;3(3):187–196. doi.org/10.1016/S1566-2772(03)00061-6.

32 Fujita K, Osaki Y, Harada M, et al. Brain and liver iron accumulation in aceruloplasminemia. Neurology 2013;81(24):2145–2146. doi: 10.1212/01. wnl.0000437304.30227.bd.

33 Ohta E, Takiyama Y. MRI findings in neuroferritinopathy. Neurol Res Int 2012;2012: 197438. doi: 10.1155/2012/197438.

34 Batla A, Adams ME, Erro R, et al. Cortical pencil lining in neuroferritinopathy: a diagnostic cluc. Neurology 2015;84(17):1816–1818. doi: 10.1212/ WNL.0000000000001511.

35 Jung HH, Danek A, Walker RH. Neuroacanthocytosis syndromes. Orphanet J Rare Dis 2011;6:68. doi:10.1186/1750-1172-6-68.

36 Peikert K, Danek A, Hermann A. Current state of knowledge in chorea-acanthocytosis as core neuroacanthocytosis syndrome. Eur J Med Genet 2017;61(11):699–705. doi:10.1016/j.ejmg.2017.12.007.

37 Storch A, Kornhass M, Schwarz J. Testing for acanthocytosis: a prospective reader-blinded study in movement disorder patients. J Neurol 2005;252(1)84–90. doi:10.1007/s00415-005-0616-3.

38 Schneider SA, Lang AE, Moro E, et al. Characteristic head drops and axial extension in advanced chorea-acanthocytosis. Mov Disord 2010;25(10):1487–1491. doi:10.1002/mds.23052.

39 Bhidayasiri R, Jitkritsadakul O, Walker RH. Axial sensory tricks in chorea-acanthocytosis: insights into phenomenology. Tremor Other Hyperkinet Mov (N Y) 2017;7:475. doi:10.7916/D8PV6RWW.

40 Gras D, Jonard L, Roze E, et al. Benign hereditary chorea: phenotype, prognosis, therapeutic outcome and long term follow-up in a large series with new mutations in the TITF1/NKX2-1 gene. J Neurol Neurosurg Psychiatry 2012;83(10): 956–962. doi:10.1136/jnnp-2012-302505.

41 Peall KJ, Lumsden D, Kneen R, et al. Benign hereditary chorea related to NKX2.1: expansion of the genotypic and phenotypic spectrum. Dev Med Child Neurol 2014;56(7):642–648. doi:10.1111/dmcn.12323.

42 Peall KJ, Kurian MA. Benign hereditary chorea: an update. Tremor Other Hyperkinet Mov (N Y) 2015; 5:314. doi:10.7916/D8RJ4HM5.

43 Mencacci NE, Erro R, Wiethoff S, et al. ADCY5 mutations are another cause of benign hereditary chorea. Neurology 2015;85(1):80–88. doi:10.1212/WNL.0000000000001720.

44 Chen DH, Méneret A, Friedman JR, et al. ADCY5-related dyskinesia: broader spectrum and genotype-phenotype correlations. Neurology 2015;85(23): 2026–2035. doi:10.1212/WNL.0000000000002058.

45 Mencacci NE, Kamsteeg EJ, Nakashima K, et al. De novo mutations in PDE10A cause childhood-onset chorea with bilateral striatal lesions. Am J Hum Genet 2016;98(4):763–771. doi:10.1016/j.ajhg.2016.02.015.

46 Diggle CP, Sukoff Rizzo SJ, Popiolek M, et al. Biallelic mutations in PDE10A lead to loss of striatal PDE10A and a hyperkinetic movement disorder with onset in infancy. Am J Hum Genet 2016;98(4):735–743. doi:10.1016/j.ajhg.2016.03.015.

47 Saitsu H, Fukai R, Ben-Zeev B, et al. Phenotypic spectrum of GNAO1 variants: epileptic encephalopathy to involuntary movements with severe developmental delay. Eur J Hum Genet 2016;24(1):129–134. doi:10.1038/ejhg.2015.92.

48 Kurian MA, Jungbluth H. Genetic disorders of thyroid metabolism and brain development. Dev Med Child Neurol 2014;56(7):627–634. doi:10.1111/dmcn.12445.

49 Fernandez M, Raskind W, Wolff J, et al. Familial dyskinesia and facial myokymia (FDFM): a novel movement disorder. Ann Neurol 2001;49(4): 486–492. doi:10.1002/ana.98.

50 Tunc S, Brüggemann N, Baaske MK, et al. Facial twitches in ADCY5-associated disease - Myokymia or myoclonus? An electromyography study. Parkinsonism Relat Disord 2017;40:73–75. doi:10.1016/j.parkreldis.2017.04.013.

51 Chang FC, Westenberger A, Dale RC, et al. Phenotypic insights into ADCY5-associated disease. Mov Disord 2016;31(7):1033–1040. doi:10.1002/mds.26598.

52 Papandreou A, Schneider RB, Augustine EF, et al. Delineation of the movement disorders associated with FOXG1 mutations. Neurology 2016;86(19):1794–1800. doi:10.1212/WNL.0000000000002585.

53 Lemke JR, Geider K, Helbig KL, et al. Delineating the GRIN1 phenotypic spectrum: a distinct genetic NMDA receptor encephalopathy. Neurology 2016;86(23):2171–2178. doi:10.1212/WNL.0000000000002740.

54 Zehavi Y, Mandel H, Zehavi A, et al. De novo GRIN1 mutations: an emerging cause of severe early infantile encephalopathy. Eur J Med Genet 2017;60(6):317–320. doi:10.1016/j.ejmg.2017.04.001.

55 Madeo M, Stewart M, Sun Y, et al. Loss-of-function mutations in FRRS1L lead to an epileptic-dyskinetic encephalopathy. Am J Hum Genet 2016;98(6):1249–1255. doi:10.1016/j.ajhg.2016.04.008.

56 Erro R, Sheerin UM, Bhatia KP. Paroxysmal dyskinesias revisited: a review of 500 genetically proven cases and a new classification. Mov Disord 2014;29(9):1108–1116. doi:10.1002/mds.25933.

57 Erro R, Bhatia KP, Espay AJ, Striano P. The epileptic and nonepileptic spectrum of paroxysmal dyskinesias: channelopathies, synaptopathies, and transportopathies. Mov Disord 2017;32(3):310–318. doi:10.1002/mds.26901.

58 Erro R, Bhatia KP. Unravelling of the paroxysmal dyskinesias. J Neurol Neurosurg Psychiatry 2018; pii:jnnp-2018-318932. doi:10.1136/jnnp-2018-318932.

59 Huntington Study Group. Tetrabenazine as antichorea therapy in Huntington disease: a randomized controlled trial. Neurology 2006;66(3):366–372. doi:10.1212/01.wnl.0000198586.85250.13.

60 Chen JJ, Ondo WG, Dashtipour K, Swope DM. Tetrabenazine for the treatment of hyperkinetic movement disorders: a review of the literature. Clin Ther 2012;34(7):1487–1504. doi:10.1016/j.clinthera.2012.06.010.

61 Jankovic J. Dopamine depleters in the treatment of hyperkinetic movement disorders. Expert Opin Pharmacother 2016;17(18):2461–2470. doi:10.1080/14656566.2016.1258063.

62 Huntington Study Group, Frank S, Testa CM, et al. Effect of deutetrabenazine on chorea among patients with Huntington disease: a randomized clinical trial. JAMA 2016;316(1):40–50. doi:10.1001/jama.2016.8655.

63 Anderson KE, Stamler D, Davis MD, et al. Deutetrabenazine for treatment of involuntary movements in patients with tardive dyskinesia (AIM-TD): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Psychiatry 2017;4(8):595–604. doi:10.1016/S2215-0366(17)30236-5.

64 Hauser RA, Factor SA, Marder SR, et al. KINECT 3: a phase 3 randomized, double-blind, placebo-controlled trial of valbenazine for tardive dyskinesia. Am J Psychiatry 2017;174(5):476–484. doi:10.1176/appi.ajp.2017.16091037.

65 Burgunder JM, Guttman M, Perlman S, et al. An international survey-based algorithm for the pharmacologic treatment of chorea in Huntington's disease. PLoS Curr 2011;3:RRN1260. doi:10.1371/currents.RRN1260.

66 Bashir H, Jankovic J. Treatment options for chorea. Expert Rev Neurother 2018;18(1):51–63. doi:10.1080/14737175.2018.1403899.

67 Genel F, Arslanoglu S, Uran N, Saylan B. Sydenham's chorea: clinical findings and comparison of the efficacies of sodium valproate and carbamazepine regimens. Brain Dev 2002;24(2):73–76. doi:10.1016/S0387-7604(01)00404-1.

68 Cardoso F. Sydenham's chorea. Curr Treat Options Neurol 2008;10(3):230–235. doi:10.1007/s11940-008-0025-x.

69 Dean SL, Singer HS. Treatment of Sydenham's chorea: a review of the current evidence. Tremor Other Hyperkinet Mov (N Y) 2017;7:456. doi:10.7916/D8W95GJ2.

70 Wojtecki L, Groiss SJ, Hartmann CJ, et al. Deep brain stimulation in Huntington's disease—preliminary evidence on pathophysiology, efficacy and safety. Brain Sci 2016;6(3); pii: E38. doi:10.3390/brainsci6030038.

71 Liu Z, Liu Y, Wan X, et al. Pallidal deep brain stimulation in patients with chorea-acanthocytosis. Neuromodulation 2018;21(8):741–747. doi:10.1111/ner.12763.

72 Smith KM, Spindler MA. Uncommon applications of deep brain stimulation in hyperkinetic movement disorders. Tremor Other Hyperkinet Mov (N Y) 2015;5:278. doi:10.7916/D84X56HP.

73 Wild EJ, Tabrizi SJ. Therapies targeting DNA and RNA in Huntington's disease. Lancet Neurol 2017;16(10):837–847. doi:10.1016/S1474-4422(17)30280-6.

74 Tabrizi SJ, Leavitt BR, Landwehrmeyer GB, et al. Targeting Huntington expression in patients with Huntington's Disease [published online May 6, 2019]. N Engl J Med 2019. doi:10.1056/NEJMoa1900907.