REVIEW ARTICLE

Movement Disorders in Children

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ABSTRACT

PURPOSE OF REVIEW: **This article provides an overview of the clinical features and disorders associated with movement disorders in childhood. This article discusses movement disorder phenomena and their clinical presentation in infants and children and presents a diagnostic approach to suspected genetic disorders with a focus on treatable conditions.**

RECENT FINDINGS: **Technologic advances in molecular genetic testing over the past decade continue to lead to the discovery of new diseases. This article discusses the clinical presentation and early experience with treatment for several recently described genetic forms of infantile-onset and childhood-onset dystonia and chorea.**

SUMMARY: **The clinical spectrum of pediatric movement disorders is broad and heterogeneous, ranging from acute or transient self-limited conditions to conditions that cause profound lifelong motor disability. Most movement disorders in childhood are chronic, and the large number of rare, genetic conditions associated with pediatric movement disorders can pose a significant diagnostic challenge. Recognition of distinctive diagnostic clues in the history and examination can facilitate the diagnosis of potentially treatable disorders.**

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INTRODUCTION

Movement disorders in childhood encompass a range of neurologic syndromes that are characterized by abnormalities of tone, posture, the initiation or control of voluntary movements, or unwanted involuntary movements. Movement disorders are conventionally divided into two main categories: hyperkinetic (involuntary movements such as dystonia, chorea, myoclonus, and tremor) and hypokinetic (parkinsonism). In contrast to adults, children often present with mixed movement disorders rather than pure syndromes. Also, symptoms may evolve over time as brain development interacts with the underlying disease process so that different motor symptoms emerge at different ages along the course of a given disease.

This article describes the approach to clinical evaluation and diagnosis of movement disorders that cause dystonia, chorea, ataxia, myoclonus, and parkinsonism in infancy and childhood. This article focuses on genetic disorders and highlights rare, treatable disorders that present in infancy. For information

on tics and stereotypies, refer to the article "Tics and Tourette Syndrome" by Harvey S. Singer, MD, FAAN,[1] in this issue of *Continuum*.

MOVEMENT DISORDER PHENOMENOLOGY IN CHILDREN

The terminology used to describe movement disorder phenomena in childhood is the same as that used in adults, but some specific features relevant to the manifestation of each type of movement disorder in children are considered briefly here.

Dystonia

Dystonia is one of the most common movement disorders in children and is defined as abnormal often repetitive movements or postures that are caused by sustained or intermittent involuntary muscle contractions. Numerous conditions are associated with dystonia in children. Dystonic cerebral palsy associated with brain injury due to complications of prematurity, stroke, or hypoxic ischemic encephalopathy is the most common cause. Dystonia is also a feature of many genetic disorders and may occur either in isolation or as part of a complex neurologic syndrome. In contrast to dystonia in adults, isolated dystonia in children is more likely to progress to generalized or multifocal dystonia than remain focal.

Chorea

Chorea, ballism, and athetosis are hyperkinetic movement disorders that often coexist in the same patients and are viewed as part of a continuum. Chorea is characterized by an ongoing random-appearing sequence of one or more discrete involuntary movements or movement fragments.[2] Chorea is frequently associated with athetosis (choreoathetosis), which is characterized by slow, continuous, involuntary distally predominant writhing movements that prevent maintenance of a stable posture. Ballism is defined as chorea that affects proximal joints such as shoulder or hip joints and leads to large-amplitude movements of the limbs. In children, acute chorea due to postinfectious/autoimmune conditions is the most frequent cause of chorea, while dyskinetic cerebral palsy is the most frequent cause of chronic chorea. In general, genetic chorea is chronic, develops gradually, and tends to be generalized and symmetric, whereas acquired chorea often manifests acutely or subacutely and, when related to brain injury, can be asymmetric or unilateral.

Ataxia

Ataxia refers to impaired muscle control or coordination of voluntary movements that cannot be attributed to weakness or involuntary movements (eg, dystonia, chorea, or myoclonus).[3] On examination, children with ataxia may exhibit a variety of clinical signs, depending on the underlying pathology. Signs include eye movement abnormalities (saccade dysmetria, nystagmus, oculomotor apraxia), slow speech with impaired articulation (cerebellar dysarthria), poor accuracy and coordination of voluntary reaching movements (dysmetria, intention tremor), poor stability of head and trunk position during sitting (titubation), and an unsteady, broad-based, or veering gait (gait ataxia). Young children with ataxia may habitually walk quickly or run to compensate for their balance difficulties and minimize falls.

Acute or subacute ataxia usually has an underlying toxic, autoimmune, traumatic, or neoplastic etiology. Intermittent ataxia may be a feature of inborn errors of metabolism or a genetic episodic ataxia. Chronic nonprogressive ataxia may be a manifestation of congenital cerebellar malformations or genetic neurodevelopmental disorders, while chronic progressive ataxia usually occurs in the context of a genetic, neurodegenerative disease process.

Some practical points are worth bearing in mind when evaluating a child who has been referred with suspected ataxia. The first is to question whether ataxia is in fact the main motor disturbance. For example, a young child with clumsiness and balance problems caused by chorea or dystonia may sometimes be mischaracterized as ataxic. Similarly, multifocal myoclonus can produce the appearance of action tremor, leading to a mislabel of dysmetria during reaching movements. Careful observation for involuntary movements and specific characterization of the ataxic features will help to ensure accurate characterization of the motor syndrome. A second point is that ataxia in children often occurs in combination with other motor abnormalities, such as spasticity and dystonia. A child with a spastic-ataxic gait may have a normal or narrow base, rather than a wide base, walk on his or her toes, and have leg stiffness in addition to gait unsteadiness.

KEY POINTS

- Many causes of childhood ataxia exist that may be broadly divided into acute, intermittent, and chronic categories.
- Myoclonus can be physiologic (hypnic myoclonus), or it can be the manifestation of a broad range of systemic disorders and metabolic derangements.
- Parkinsonism in infants and young children differs from parkinsonism in adults, often manifesting as bradykinesia/hypokinesia, dystonia, and axial hypotonia; tremor is often absent.

Myoclonus

Myoclonus is defined as the "sequence of repeated, often nonrhythmic, brief shock-like jerks due to sudden involuntary contraction or relaxation of one or more muscles."[2] Myoclonus is associated with abnormal neuronal excitability of cortical or subcortical gray matter; it can be classified based on distribution of the movements (focal, multifocal, segmental, generalized) or on the etiologic location (cortical, subcortical, spinal). While myoclonus in adults is often a benign sign associated with metabolic disturbances, myoclonus in children is often an ominous manifestation that can be caused by tumors, metabolic diseases, neurodegenerative disease, or encephalitis and is often associated with seizures and encephalopathy. Benign forms of myoclonus can occur in children as well.[2] Myoclonus can be physiologic (hypnic myoclonus) or it can be the manifestation of a broad range of systemic disorders and metabolic derangements, the adverse effect of multiple drugs, and the symptom of a broad range of neurologic disorders. In pediatric patients, neurologic conditions manifesting with myoclonus include inflammatory/autoimmune disorders (ie, opsoclonus-myoclonus-ataxia syndrome), severe hypoxic injury, encephalitis, and focal mass lesions or dysplasias (often manifesting as epilepsia partialis continua).[4,5]

Parkinsonism

Parkinsonism is characterized by the combination of bradykinesia and one or more of the following cardinal signs: rigidity, resting tremor, and postural instability. Parkinsonism is rare in children, especially in infancy, and the clinical manifestations in children differ from adults in several important ways. First, tremor is often, but not always, absent. Second, dystonia is a common accompanying feature; hence, childhood-onset parkinsonism is frequently referred to as *parkinsonism-dystonia*.[6] Third, infants with parkinsonism typically have marked hypotonia as the primary baseline disturbance of tone.

Tremor

Tremor refers to oscillating, rhythmic movements about a fixed point, usually a joint, producing a regular back-and-forth movement. Common causes of acute tremor in children include drug-induced tremor and psychogenic tremor. Essential tremor, characterized by a chronic, slowly progressive, isolated postural and action tremor, may begin in childhood. Many secondary tremors occur in conjunction with other movement disorders, such as dystonia and ataxia. Parkinsonian resting tremor is uncommon in children.

BENIGN TRANSIENT DEVELOPMENTAL MOVEMENT DISORDERS OF INFANCY

Neonates, infants, and toddlers may manifest with a number of abnormal movements that are benign and typically display complete resolution over time. The abnormal movements may appear as myoclonus, dystonia, or tremor and are often paroxysmal. They are thought to be a manifestation of central nervous system immaturity and disappear with brain maturation. Typically, psychomotor development and neurologic function are normal.

TABLE 10-1 **Common Acute Movement Disorder Presentations in the Previously Healthy Child**

Movement Disorder	Etiologies	Comments
Chorea	Poststreptococcal (Sydenham chorea), other autoimmune encephalitis	Movement disorder often mixed (dystonia, stereotypies) in anti-*N*-methyl-D-aspartate (NMDA) receptor and other autoimmune encephalitis; treatment: immunomodulatory therapy for autoimmune encephalitis
	Drug induced	Anticholinergics, dopaminergic medications (acute chorea); dopamine receptor blockers (tardive: often mixed syndrome with akathisia, dystonia; withdrawal-emergent dyskinesia: hyperkinetic movement disorder with ataxia)
Dystonia	Acute dystonic reaction	Caused by dopamine receptor–blocking medications, including antipsychotics and antiemetics (eg, metoclopramide); treatment of acute episode: anticholinergic medication
Myoclonus	Opsoclonus-myoclonus-ataxia syndrome	May be accompanied by ataxia, sleep disruption, irritability; often associated with neuroblastoma; treatment: immunosuppression with goal of inducing remission of symptoms, limiting long-term motor and intellectual disability
Ataxia	Postinfectious cerebellar ataxia	May follow infectious illness or vaccination; onset is usually very acute, 90% recover completely over period of 2 to 3 months
	Drug ingestion	For example, antiepileptics, benzodiazepines, antihistamines; typically accompanied by mental status changes
Parkinsonism	Drug induced	Caused by dopamine receptor–blocking medications
	Autoimmune encephalitis	Rare; associated with inflammatory lesions of the basal ganglia
Tremor, dystonia, gait disturbance	Psychogenic movement disorder	Clinical clues: sudden onset of dystonia with fixed posture, episodic tremor; treatment may include physical therapy and management of comorbid mood symptoms with medication or psychotherapy

Benign transient conditions with myoclonic appearance include benign neonatal sleep myoclonus, which occurs during sleep and disappears by waking up the baby, and benign myoclonus of infancy, which resembles the infantile spasms of West syndrome. Tremor appearance includes jitteriness, a generalized tremor that is highly stimulus sensitive and occurs in neonates; shuddering that resembles shivering and occurs during infancy or early childhood; and spasmus nutans, which occurs in late infancy and is characterized by the triad of head nodding, nystagmus, and head tilt. In the case of spasmus nutans, neuroimaging is indicated because it has occasionally been associated with optic pathway gliomas.[7,8]

Benign transient conditions with dystonic appearance include benign paroxysmal torticollis of infancy, which is a putative infantile migraine variant that manifests with periodic episodes of head tilt and may be associated with pallor, vomiting, irritability, or ataxia. Benign idiopathic dystonia of infancy is characterized by segmental dystonia at rest, usually of one arm, that disappears with volitional movement. Sandifer syndrome is characterized by torticollis or opisthotonic posturing associated with gastroesophageal reflux, and infantile masturbation manifests by stereotyped posturing of the lower limbs. Finally, paroxysmal tonic upgaze of infancy is characterized by episodes of sustained conjugate upward deviation of the eyes resembling ocular dystonia and is often accompanied by neck flexion.[7,8]

Treatment for these benign transient infantile conditions is not required, but it is important to recognize them so that parental anxiety and unnecessary investigations can be avoided.

KEY POINTS

- Neonates, infants, and toddlers may manifest with a number of benign and transient movement disorders such as myoclonus, dystonia, or tremor; development is normal, and treatment is not required.
- The most common etiologies underlying acute movement disorders in a previously healthy child are autoimmune, drug-induced, and psychogenic.

ACUTE MOVEMENT DISORDERS

The acute onset of movement disorder symptoms in a previously healthy, developmentally normal child will often prompt a request for urgent neurologic evaluation, either in the office or in the emergency department. It is helpful to be familiar with the conditions that typically present in an acute fashion (TABLE 10-1). Autoimmune, drug-induced, and psychogenic etiologies are the predominant conditions in this context.[9] Accurate diagnosis is important as many of these are treatable conditions. Treatment is directed at the underlying cause.

Acute-on-chronic movement disorder presentations may also occur in children with a preexisting neurologic disorder. A common example is the acute worsening of dystonia (status dystonicus) in a child with dystonic cerebral palsy due to a documented history of brain injury. Another example is the acute onset of severe chorea and ballismus in a child with *GNAO1* encephalopathy, a genetic disorder that may initially manifest nonspecifically with hypotonia and developmental delay. In both of these situations, management in an intensive care setting is frequently required.

CHRONIC MOVEMENT DISORDERS

Most movement disorders in childhood are chronic and may be either acquired or genetic.

Dyskinetic Cerebral Palsy

Cerebral palsy is the single most prevalent cause of childhood movement disorders. Cerebral palsy is an umbrella term that describes a motor disorder resulting from a nonprogressive lesion or dysfunction of the developing brain.

While no single etiology is specified, the term cerebral palsy usually implies an underlying acquired etiology, such as brain lesions associated with complications of prematurity, neonatal hypoxic ischemic encephalopathy, perinatal stroke, or chronic sequelae of meningoencephalitis. Dyskinetic cerebral palsy is the phenotypic classification applied to the 10% to 15% of children with cerebral palsy whose motor syndrome is predominated by involuntary movements. Children with dyskinetic cerebral palsy typically have a combination of dystonia and athetosis, often accompanied by axial hypotonia with or without spasticity in the limbs.

Dyskinetic cerebral palsy is classically associated with injury to the basal ganglia. In practice, dystonia is a relatively common finding in children with other cerebral palsy phenotypes, including spastic hemiplegia, diplegia, and quadriplegia, who have injury to brain structures other than the basal ganglia. Normal brain imaging has been reported in approximately one-third of patients with a diagnosis of dyskinetic cerebral palsy,[10] suggesting that etiologies other than brain injury may underlie the diagnosis of cerebral palsy in a significant proportion of children with a diagnosis of dyskinetic cerebral palsy.

Approach to Clinical Evaluation and Diagnosis

When evaluating a young child with motor developmental delay and abnormal movements, a frequent diagnostic question is whether the child has a syndrome compatible with a diagnosis of cerebral palsy or whether the child may have an underlying genetic disorder. The diagnosis of a genetic disorder has important implications for genetic counseling for the family. In some cases, the diagnosis also has important treatment implications because some metabolic diseases have available treatment that targets the primary disease process rather than control of symptoms, and early initiation of the disease-specific treatment may dramatically improve the long-term outcome (eg, the disorders of monoamine neurotransmitter synthesis and glucose transporter type 1 [GLUT1] deficiency syndrome). In older children who present with progressive symptoms suggesting a neurodegenerative disease, the identification of a rare treatable disorder, such as Wilson disease or ataxia with vitamin E deficiency, is similarly important.

Diagnostic Approach for a Suspected Genetic Disorder

The rarity, phenotypic diversity, and large number of genetic disorders that may cause movement disorders pose a diagnostic challenge even for experienced specialists. On occasion, distinctive features in the history and neurologic examination strongly suggest a well-defined disease. In many cases, however, the clinical features may be nonspecific or atypical, making definitive clinical diagnosis difficult.

As a first step, the clinical evaluation aims to capture key features of the history and construct an accurate characterization of the neurologic and systemic features of the clinical syndrome. Factors of particular importance in the history include the presence of possible perinatal risk factors for brain injury (prematurity, complicated delivery, neonatal intensive care admission), age of onset of symptoms, family history, and developmental history (developmental delay or regression). With regard to the motor symptoms themselves, it is important to inquire specifically about the time course of symptoms: are they persistent, intermittent, or fluctuating (eg, diurnal variation, worsened by stress,

illness, or exercise); or are they stable or progressive? In addition to the general and neurologic examination, ophthalmologic evaluation should be strongly considered. Eye findings, such as Kayser-Fleischer rings (associated with Wilson disease), or pigmentary retinopathy or optic atrophy (both associated with some forms of neurodegeneration with brain iron accumulation, for example) may provide important diagnostic clues. An accurate and complete characterization of the clinical syndrome both informs the choice of genetic testing and is likely, at a later stage, to aid in the interpretation of genetic test results.

Brain imaging with MRI is usually indicated early in the course of investigation. Brain imaging may detect an acquired structural lesion as the cause of a cerebral palsy sydrome. Alternatively, the finding of specific brain lesions or structural abnormalities may narrow the differential diagnosis of potential genetic disorders. Imaging may be considered an important component of the phenotype.

In the past decade, the advent of next-generation sequencing technology for molecular genetic analysis has had a huge impact on the approach to diagnostic testing and the yield of genetic testing in child neurology. In this context, what is the current role of biochemical laboratory investigations in the workup of children with suspected genetic or metabolic disease? The authors of this article argue that there remains a role for screening biochemical investigations, although lengthy and exhaustive metabolic testing procedures prior to genetic testing are now rarely performed. Biochemical markers can provide rapid and unequivocal evidence for some treatable metabolic conditions, facilitating prompt initiation of treatment (TABLE 10-2). Even for disorders without a disease-specific treatment, the finding of a positive biomarker may narrow the differential diagnosis so that a more focused (and therefore time-saving and cost-saving) genetic testing strategy can be pursued. Analysis of selected biochemical markers may also be performed after genetic testing to evaluate the pathogenicity of genetic variants of unknown significance that are detected using next-generation sequencing methods.

The appropriate genetic testing strategy will depend on the diagnostic impression of the clinician based on clinical, radiological, and biochemical findings as outlined above. If a clear and specific syndrome emerges, confirmatory molecular genetic testing may be directed at a small number of genes. In many cases, however, a more comprehensive testing approach is appropriate. Comparative genomic hybridization microarray analysis to detect copy number variants should always be considered, particularly if the syndrome includes intellectual disability, dysmorphism, or multiple systemic abnormalities suggesting a contiguous gene syndrome. Next-generation sequencing techniques, including multigene panels and whole exome sequencing, should then be pursued if available. The diagnostic accuracy of next-generation sequencing tests depends upon the interpretation of findings in relation to the patient's syndrome, so thoughtful clinical characterization remains vital.

GENETIC MOVEMENT DISORDERS THAT USUALLY PRESENT IN INFANCY

Many of the genetic movement disorder syndromes that present in infancy or early childhood are nonprogressive disorders that impair motor development and may be accompanied by other neurologic symptoms including seizures and intellectual disability. It is common for these disorders to manifest with mixed

movement disorders (eg, dystonia in combination with chorea, ataxia, or myoclonus). These patients may be misdiagnosed with dyskinetic cerebral palsy because of the early age of onset and nonprogressive course of their motor symptoms.

Neurodevelopmental disorders often present initially with fairly nonspecific motor features such as hypotonia and developmental delay. It is common for motor symptoms to evolve with age as the brain develops, even when the underlying pathology is nonprogressive. Involuntary movements and ataxia often become more apparent as the child begins to attempt to sit, stand, walk,

TABLE 10-2 **Treatable Metabolic Disorders Associated With Movement Disorders in Infancy or Childhood**

Condition	Gene(s)	Age of Onset	Key Clinical Features
Monoamine neurotransmitter disorders	*GCH, TH, PTS, QDPR, SPR, DDC, DNAJC12*	Infancy, childhood	Hypotonia, dystonia, oculogyric crises, ptosis, autonomic dysfunction (dopa-responsive dystonia: dystonia, spastic paraplegia with diurnal variation)
Glucose transporter type 1 (GLUT1) deficiency syndrome	*SLC2A1*	Infancy, childhood	Ataxia, spasticity, dystonia, paroxysmal exertional dyskinesia, seizures, intellectual disability
Cerebral folate deficiency	*FOLR1*[a]	Infancy, childhood	Hypotonia, developmental delay, irritability, ataxia, spasticity, chorea, dystonia, seizures
Thiamine deficiency syndromes	*SLC19A3*	Infancy, childhood	Recurrent acute encephalopathy, dystonia, spasticity, ataxia, seizures
Pyruvate dehydrogenase complex deficiency	*PDHA1, DLAT,* others	Infancy, childhood	Ataxia (may be intermittent in milder cases), hypotonia, intellectual disability, seizures, paroxysmal exertional dyskinesia (rare)
Biotinidase deficiency	*BTD*	Infancy, childhood	Ataxia, hypotonia, seizures, eczematous skin rash, alopecia
Coenzyme Q_{10} deficiency	*COQ8A, PDSS2,* others	Infancy to adulthood	Ataxia, may have encephalopathy, spasticity, seizures, myopathy, intellectual disability, sensorineural deafness
Creatine deficiency	*GAMT*	Childhood, adolescence	Dystonia, chorea, ataxia, intellectual disability, hyperactivity, self-injurious behavior
Ataxia with vitamin E deficiency	*TTPA*	Childhood, adolescence	Ataxia, dystonia, head tremor, may have peripheral neuropathy, decreased vibration sense
Wilson disease	*ATP7B*	Childhood, adolescence	Dystonia, parkinsonism, tremor, liver disease
Hypermanganesemia	*SLC30A10*	Childhood, adulthood	Dystonia, parkinsonism, polycythemia, liver disease

CSF = cerebrospinal fluid; GAA = guanidinoacetate; MRI = magnetic resonance imaging.
[a] Note that *FOLR1* mutations are a rare cause of cerebral folate deficiency. The most common cause is blocking autoantibodies against the folate receptor.

and make purposeful arm movements. Some neurodegenerative diseases may also present in infancy or early childhood. In these cases, a history of significant developmental regression (not only of developmental delay) is a red flag that should alert the clinician to this possibility.

Treatable metabolic conditions that may present during infancy include the primary monoamine neurotransmitter disorders, GLUT1 deficiency syndrome, organic acidurias, thiamine deficiency syndromes, pyruvate dehydrogenase deficiency, coenzyme Q_{10} deficiency, cerebral folate deficiency, creatine deficiency syndromes, and biotinidase deficiency. Therefore, metabolic

Brain MRI Findings	Laboratory Investigations	Treatment
Usually normal	Disease-specific abnormalities of CSF monoamine neurotransmitter metabolites and pterins (some disorders: elevated blood phenylalanine on newborn screening)	Neurotransmitter precursor replacement, may have tetrahydrobiopterin, folinic acid (selected disorders)
Usually normal	Low CSF glucose, normal serum glucose, low-normal CSF lactate	Ketogenic diet
Frontotemporal atrophy, periventricular white matter T2 hyperintensity; may be normal	Low CSF 5-methyltetrahydrofolate	Folinic acid
T2 hyperintensity in basal ganglia, brainstem	High CSF lactate, abnormal urine organic acids profile	Thiamine, biotin supplementation
Ventriculomegaly, corpus callosum dysgenesis, T2 hyperintensity in basal ganglia, brainstem	High lactate, pyruvate (plasma, CSF) normal lactate to pyruvate ratio	Ketogenic diet, thiamine
Cerebral volume loss, white matter T2-hyperintensity	High serum ammonia, high lactate, may have abnormal urine organic acids profile; low serum biotinidase activity	Biotin
May have cerebellar atrophy	High plasma lactate, low coenzyme Q_{10}	Coenzyme Q_{10} (ubiquinone)
T2 hyperintensity in globus pallidus; may be normal	High GAA, low creatine (urine and plasma)	Arginine restriction, creatine and ornithine supplements
May have cerebellar atrophy (half of reported patients)	Low plasma vitamin E	Vitamin E
T2 hyperintense lesions in basal ganglia, midbrain, pons, may have T1 hyperintensity in globus pallidus	Low or normal serum copper, ceruloplasmin; high urine copper	Zinc, tetrathiomolybdate
T1 hyperintensity of basal ganglia, sparing thalamus	High whole-blood manganese	Chelation with disodium calcium edetate; iron

screening investigations, including CSF analysis, should be strongly considered in this age group (TABLE 10-2), particularly if the clinical history reveals marked fluctuation of motor symptoms, symptom exacerbation in the context of illness or other catabolic stress, or encephalopathy. Some of the treatable and more common disorders are highlighted below.

Primary Monoamine Neurotransmitter Disorders

The primary monoamine neurotransmitter disorders comprise defects of enzymes, cofactors, and transporters that are involved in the metabolism and homeostasis of the catecholamines (dopamine, norepinephrine, and epinephrine) and serotonin. The majority of these disorders are inherited in an autosomal recessive fashion. These disorders manifest clinically with infantile dystonia-parkinsonism (CASE 10-1). Onset is usually within the first months of life with

CASE 10-1

A 6-month-old girl was brought by her parents for evaluation of hypotonia and developmental delay. She had been born full term after an uneventful pregnancy, delivery, and neonatal period. Her parents had begun to be concerned at around the age of 4 months because of the lack of motor development and the occurrence of daily episodes of tonic upward eye deviation of several minutes duration that resolved with sleeping. She often had nasal congestion and sweated profusely.

On examination she was alert and interactive but was easily distressed. She showed poor facial expression and minimal spontaneous movements. She had dystonic posturing of all limbs and dystonic tremor of the upper limbs. She had prominent axial hypotonia. Appendicular tone was decreased when relaxed and increased when manipulated or distressed. Tendon reflexes were brisk, and her toes were spontaneously up (striatal toes).

Brain MRI was normal. CSF analysis of biogenic amines disclosed decreased concentration of the dopamine metabolite homovanillic acid. Molecular analysis of the gene encoding tyrosine hydroxylase revealed a homozygous pathogenic mutation (c.707T>C). These findings were consistent with tyrosine hydroxylase deficiency.

She was started on treatment with levodopa 0.5 mg/kg/d that was followed by gradual psychomotor development. The oculogyric crises decreased in frequency and gradually disappeared. Her hyperhidrosis and nasal congestion resolved completely.

COMMENT

This case illustrates the typical motor and autonomic symptoms of infantile dystonia-parkinsonism associated with congenital disorders of monoamine neurotransmitter synthesis: oculogyric crises, hypokinesia, hypotonia, and dystonia, in conjunction with excessive sweating and nasal congestion. CSF examination readily detected a low concentration of the dopamine metabolite homovanillic acid, and diagnosis was confirmed with molecular genetic testing. The patient had an excellent response to treatment with levodopa.

hypotonia, developmental delay, decreased spontaneous movements, rigidity, and dystonia. Oculogyric crises are a common feature and are characterized by sustained, tonic conjugate, typically upward deviation of the eyes lasting from seconds to hours that may also be associated with axial or appendicular dystonic posturing.[11] In addition, approximately half of patients may have tremor.[12] As a result of the deficiency of dopamine and other catecholamines, patients often manifest signs of autonomic dysfunction (ptosis, sweating, nasal congestion), sleep disturbance, and prominent dysphoric mood. The findings of profound hypotonia, hypokinesia, and ptosis may lead to misdiagnosis of a neuromuscular disease. The important distinguishing features to recognize are the associated oculogyric crises and dystonia, which will lead to accurate clinical diagnosis of a neurotransmitter disorder. Neuroimaging is usually normal, and diagnosis is confirmed with molecular analysis and with the analysis of monoamine neurotransmitter metabolites and pterins in CSF.[11,12]

Glucose Transporter Type 1 Deficiency Syndrome

GLUT1 deficiency syndrome is a neurodevelopmental disorder that usually presents in infancy and has both persistent and paroxysmal neurologic symptoms. The two most common initial symptoms reported in infants with GLUT1 deficiency syndrome are seizures and characteristic episodes of repetitive eye-head movements consisting of apparently involuntary multidirectional shifts of gaze. Ataxia is often a prominent component and usually becomes evident as the child begins to stand and walk. In this disorder, a typical feature is the fluctuating severity of ataxia with worsening in the context of exercise, illness, or fasting (eg, ataxia first thing in the morning upon waking). The full neurologic syndrome consists of variable combinations of ataxia, spasticity, dystonia, seizures, and intellectual disability. A variety of episodic neurologic phenomena may also occur, including paroxysmal exertional dyskinesia, migraines, dysphoria, and hemiparesis or quadriparesis (refer to the section on paroxysmal dyskinesia). CSF analysis can provide a rapid diagnostic clue with the finding of a low CSF glucose concentration in the setting of normoglycemia. The majority of patients have a heterozygous variant in *SLC2A1,* which encodes the GLUT1 transporter. Treatment with the ketogenic diet typically leads to a dramatic improvement in the paroxysmal and fluctuating symptoms (including ataxia, seizures, and paroxysmal dyskinesia) and may improve long-term developmental outcome. (CASE 10-2)

NKX2-1–Related Disorders (Brain-Thyroid-Lung Syndrome)

NKX2-1–related disorders are autosomal dominant movement disorders that result from mutations of the NK2 homeobox 1 gene (*NKX2-1*), encoding a transcription factor that is essential for the development of lung, thyroid, and basal ganglia. In *NKX2-1*–related disorders, chorea occurs in association with variable thyroid and respiratory involvement (brain-thyroid-lung syndrome). Thyroid involvement may range from subclinical elevation of thyroid-stimulating hormone (TSH) to severe congenital hypothyroidism causing failure to thrive in early infancy, while lung involvement may manifest with neonatal respiratory distress, recurrent pulmonary infections, asthma, and lung cancer.

Patients usually present with hypotonia, delayed walking, and generalized chorea. Chorea improves in adolescence and stabilizes or resolves completely in

KEY POINTS

- In a child with a dyskinetic cerebral palsy phenotype, absent risk factors for perinatal brain injury, and normal brain MRI, investigation for an underlying genetic disorder should be considered. Some genetic disorders have disease-specific treatment that improves symptoms and developmental outcome.
- The primary monoamine neurotransmitter disorders comprise defects of enzymes, cofactors, and transporters involved in the metabolism and homeostasis of the catecholamines and serotonin.
- In biogenic amine disorders, neuroimaging is usually normal, and diagnosis is confirmed with the analysis of monoamine neurotransmitter metabolites and pterins in CSF and with molecular analysis.

CASE 10-2

A 5-year-old boy presented for evaluation following his first seizure. He had a history of unsteady gait. He had been a healthy neonate and had been born at term without perinatal complications. His parents had become concerned about his motor development when he was 12 months old. He often fell when trying to stand. He walked independently at age 16 months, but his gait always appeared unsteady. His parents noticed that he was much stiffer and less steady in the mornings immediately after waking, with subsequent improvement by midmorning after eating breakfast. His balance also worsened whenever he was sick.

At 4 years of age he had several brief episodes, typically 10 to 15 minutes in duration, of involuntary stiffening and jerking movements of both legs following periods of running or active play. At age 5 years, he presented to the hospital following a single, brief generalized tonic-clonic seizure.

On examination, he was observed to be alert and cooperative but distractible. His speech was dysarthric. He had moderate lower limb spasticity and abnormally brisk lower limb reflexes with several beats of bilateral ankle clonus. He had mild upper limb dysmetria and a spastic-ataxic gait pattern characterized by a narrow but variable base, toe walking, veering, unsteadiness, and multiple falls.

His brain MRI was normal. A lumbar puncture was performed, and his CSF glucose was 35 mg/dL (serum glucose 92 mg/dL, with a CSF to serum ratio of 0.38). A diagnosis of glucose transporter type 1 (GLUT1) deficiency syndrome was confirmed with the finding of a heterozygous pathogenic missense variant in *SLC2A1*.

He was started on the ketogenic diet, and on follow-up 6 months later, he had had no further seizures or episodes of involuntary leg movements, showed marked improvement in his ataxia, and had improved attention at school.

COMMENT

This case illustrates the typical constellation of neurologic symptoms found in patients with GLUT1 deficiency syndrome: developmental delay, spasticity, fluctuating ataxia that worsens during fasting and illness, paroxysmal dyskinesia provoked by sustained physical activity, and seizures. The CSF glucose concentration was approximately half the value expected for the given serum glucose concentration (ratio of approximately 1:3, instead of 2:3). Treatment with the ketogenic diet provides an alternative brain fuel source to glucose, with resulting dramatic symptom improvement.

early adulthood. Approximately half of patients develop other movement disorders such as dystonia, ataxia, or intention tremor. Cognition is relatively preserved, and neuroimaging is normal.[13]

ADCY5-Related Dyskinesia

ADCY5-related dyskinesia is due to heterozygous mutations in the *ADCY5* gene. Patients manifest with infantile-onset or early childhood hypotonia, motor delay, and dyskinesia (chorea, ballismus, choreoathetosis). Episodic exacerbation of baseline dyskinesia during drowsiness upon awakening, when falling asleep, or during intercurrent illnesses, lasting minutes to hours, is characteristic. Generalized dystonic spasms can also occur.[13]

Another gene associated with generalized childhood-onset chorea is *PDE10A*, which may follow either dominant or recessive inheritance.[13]

Epileptic-Dyskinetic Encephalopathies

A recently described group of complex neurologic disorders that may manifest with a hyperkinetic movement disorder early in life are the epileptic-dyskinetic encephalopathies. They are a genetically and clinically heterogeneous group of disorders characterized by a spectrum of manifestations ranging from isolated movement disorders (most frequently chorea, but also dystonia and stereotypies) to severe infantile epileptic encephalopathy.[13] Mutations in *FOXG1* cause a developmental encephalopathy manifesting in infancy or early childhood with severe developmental delay, acquired microcephaly, profound intellectual disability, epilepsy, and a hyperkinetic movement disorder emerging within the first year of life that includes various combinations of chorea, orolingual/facial dyskinesias, dystonia, myoclonus, and hand stereotypies. Neuroimaging may show corpus callosum hypoplasia or aplasia, delayed myelination, simplified gyration, and frontotemporal abnormalities.[14] Mutations in *GNAO1* can cause a severe infantile epileptic encephalopathy or a static encephalopathy with associated hyperkinetic movement disorder (chorea, ballismus, dystonia, and orofaciolingual dyskinesia) (CASE 10-3). The initial motor phenotype is often nonspecific with hypotonia, dystonia, and motor developmental delay. Characteristic episodes of severe chorea and ballismus in combination with autonomic dysfunction, triggered by infections or other stressors, can last hours or days.[13] Other genes associated with epileptic-dyskinetic encephalopathies include *GRIN1*, *SCN8A*, *FRRS1L*, *GPR88*, *UNC13A*, and *SYT1*.[15] The list is likely to expand further with the discovery of new genes.

KEY POINT

- The epileptic-dyskinetic encephalopathies are a heterogeneous group of disorders that are associated with a spectrum of movement disorders, most frequently chorea, but also dystonia and stereotypies.

GENETIC MOVEMENT DISORDERS THAT USUALLY PRESENT IN CHILDHOOD

A diverse range of movement disorder syndromes may present with symptom onset in childhood or adolescence, typically after a period of normal motor development in infancy.

Dystonia

Dystonia is a feature of many childhood-onset genetic conditions, divided into three main categories: (1) isolated (pure dystonia), (2) combined (dystonia accompanied by myoclonus or parkinsonism), and (3) complex (dystonia as one feature of a complex neurologic syndrome).

ISOLATED AND COMBINED DYSTONIAS. In the isolated and combined genetic dystonia syndromes, symptoms usually appear after a period of normal infantile motor development. These are non-neurodegenerative diseases, but the dystonia is typically progressive. The age of onset varies widely, from as young as 1 year of age, to adulthood. The distribution of dystonia helps to distinguish between the different genetic forms of isolated dystonia. Prominent cranial and bulbar involvement is typical in DYT6-*THAP1* and DYT28-*KMT2B*, while it is rare in DYT1-*TOR1A*. Limb involvement is common to all of the disorders and usually occurs early in the course. Progression to generalized or multifocal dystonia occurs in more than half of patients with childhood-onset isolated genetic dystonia, and as a general rule, the earlier the age of onset, the higher the risk of generalization. Brain imaging is normal in DYT1 and *THAP1*–related dystonia, but *KMT2B*-related dystonia may be associated with subtle T2 hypointensity of the globus pallidus.

CASE 10-3

An 11-year-old girl presented to the emergency department with acute, severe chorea and ballismus. She had been born at term following an uncomplicated pregnancy and delivery. As a neonate she had hypotonia and feeding difficulties, and at age 9 months she was diagnosed with developmental delay when she was unable to sit independently. She eventually sat at 18 months and walked with a walker at age 3 years.

On examination at age 3 years she had generalized hypotonia, bradykinesia, dystonia in the upper and lower limbs, and slightly brisk lower limb reflexes. Her brain imaging was normal, and a diagnosis of atypical cerebral palsy was made.

At age 9 years she had an episode of mild chorea in the context of an acute viral respiratory illness, which resolved spontaneously within a few weeks.

At age 11, in the setting of another viral upper respiratory tract illness, she developed severe acute chorea complicated by rhabdomyolysis. This led to a prolonged intensive care unit admission. Whole exome sequencing performed during this admission revealed a de novo heterozygous pathogenic missense variant mutation in *GNAO1*.

Treatment with tetrabenazine 400 mg/d controlled the involuntary movements. Six months later, bilateral globus pallidus internus deep brain stimulation leads were placed, and over the next 18 months, the tetrabenazine was tapered off without any recurrence of chorea. Her motor function remained significantly impaired compared to baseline; she could no longer sit independently or walk and was very hypokinetic.

COMMENT

This case illustrates the characteristic clinical features of the predominant motor phenotype of *GNAO1* encephalopathy: a static neurodevelopmental disorder consisting of hypotonia and developmental delay, with recurrent episodes of acute chorea triggered by illness that can be severe and life-threatening. As in this case, the hyperkinetic movement disorder has been reported to be responsive to deep brain stimulation in several patients.

Dopa-responsive dystonia (DYT5) is an important diagnosis to consider in the differential diagnosis of childhood-onset dystonia as symptoms have a dramatic and sustained response to treatment with low-dose levodopa (2 mg/kg/d to 7 mg/kg/d). Children typically present between 5 and 9 years of age with focal limb dystonia, involving the leg more than the arm, which has a characteristic diurnal fluctuation of severity. Symptoms worsen in the afternoon and evening and improve following sleep. Diurnal fluctuation is a key diagnostic clue for a dopa-responsive dystonia and is particularly helpful in patients with atypical presentations such as spastic paraparesis or a nonspecific gait disturbance, rather than clear dystonia. In adulthood, patients may proceed to develop signs of parkinsonism, including bradykinesia and postural instability.[16]

Dopa-responsive dystonia is most often caused by a heterozygous mutation in *GCH*, the gene encoding guanosine triphosphate cyclohydrolase, resulting in deficient brain dopamine synthesis. More complex forms of dopa-responsive dystonia that present in infancy were discussed in the previous section on monoamine neurotransmitter disorders.

DYT1 dystonia is the most common form of isolated genetic dystonia and is inherited in an autosomal dominant manner with 30% penetrance. A three base-pair deletion in *TOR1A* explains up to 90% of the generalized dystonias in the Ashkenazi Jewish population and approximately 40% to 60% of cases of generalized dystonia in the non–Ashkenazi Jewish population.[17] DYT1 dystonia often starts in childhood as a focal lower limb dystonia, usually involving the leg. The average age of onset is 13 years but varies widely. More than 60% of patients will progress to generalized or multifocal dystonia. DYT1 dystonia has a robust response to globus pallidus internus deep brain stimulation (DBS), which should be considered early if symptoms are severe.

DYT6-*THAP1*–related dystonia is an autosomal dominant disorder with 60% penetrance. Half of patients initially present with cranial or cervical dystonia and have prominent laryngeal involvement. DBS seems to be less effective for DYT6 than for DYT1 dystonia. It has been hypothesized that cranial and cervical symptoms may be less responsive to DBS.

The *KMT2B* gene was identified in 2016 by two independent groups and is the most recently described genetic cause of childhood-onset dystonia.[18,19] More than 40 patients have been reported to date.[20] It is an autosomal dominant disorder and may be associated with either heterozygous intragenic *KMT2B* variants or a chromosome 19 microdeletion syndrome involving the *KMT2B* gene. Patients with contiguous deletions are more likely to present with a complex syndrome, including additional neurologic and systemic findings (eye movement abnormalities, developmental delay, microcephaly, short stature, and mild facial dysmorphism), while those with intragenic variants typically present with isolated dystonia.[20] Dystonia usually begins in the lower limbs before 10 years and becomes generalized over time, with prominent involvement of cervical, oromandibular, and laryngeal regions. Patients with chromosomal microdeletions tend to have an earlier age of onset than those with intragenic variants. Brain MRI in many, but not all, patients demonstrates subtle globus pallidus externus hypointensities on susceptibility-weighted imaging (SWI).[18] Reported patient response to treatment so far indicates limited benefit from antidystonia medications such as trihexyphenidyl but showed substantial improvement following bilateral globus pallidus internus stimulation in 13 patients.[20]

Rapid-onset dystonia-parkinsonism (DYT12) is associated with heterozygous mutations in *ATP1A3*. In contrast to the slow and gradual symptom progression typically observed in the genetic dystonias, the distinctive feature of rapid-onset dystonia-parkinsonism is the acute onset of dystonia over a period of days to months, often triggered by an emotional or physical stress. Prominent involvement of the lower cranial and bulbar region, in addition to the limbs, is common. Dystonia in rapid-onset dystonia-parkinsonism typically has limited responsiveness to levodopa, antidystonia medications, or DBS, making this a challenging condition to treat.

COMPLEX DYSTONIA SYNDROMES. Dystonia may be a component of numerous genetic neurodegenerative diseases. In these cases, dystonia is progressive and is typically accompanied by other neurologic abnormalities. Clinical red flags include cranial-onset or cervical-onset dystonia, rapid dystonia progression, eye movement abnormalities such as supranuclear gaze palsy, associated hearing or vision loss, associated parkinsonism, and progressive cognitive decline or behavioral symptoms. A review of these conditions may be found in other sources.[21–23]

Importantly, treatable neurodegenerative conditions that may present in childhood or adolescence with dystonia include disorders of heavy metal accumulation (eg, Wilson disease, manganese transporter deficiency) and ataxia with vitamin E deficiency (**TABLE 10-2**).

Chorea

The prototype neurodegenerative condition manifesting with chorea is Huntington disease, which is the most frequent form of genetic chorea in adulthood. It is dominantly inherited and is secondary to an expansion in the number of CAG repeats in the huntingtin (*HTT*) gene. Younger age at onset and more rapid disease progression is associated with longer CAG repeats in *HTT*. Huntington disease in childhood often presents with an akinetic-rigid syndrome rather than chorea, while adolescents are more likely to present with the typical clinical triad seen in adults: chorea, cognitive decline, and psychiatric or behavioral disturbance.[15]

Neuroacanthocytosis syndromes are progressive neurodegenerative conditions that resemble Huntington disease. Two forms may present earlier in life with prominent facial involvement: *VPS13A* gene mutations (chorea-acanthocytosis, autosomal recessive) and *XK* gene mutation (McLeod syndrome, X-linked recessive).[14]

Chorea may be a prominent feature of conditions that typically present with other movement disorder abnormalities, including neurodegenerative disorders with metal ion accumulation (Wilson disease and pantothenate kinase–associated neurodegeneration), and cerebellar ataxias such as ataxia-telangiectasia and, more rarely, ataxia with oculomotor apraxia type 1, 2, and 4, and Friedreich ataxia.[14]

Ataxia

Numerous genes are associated with chronic progressive ataxia, which is usually subdivided broadly into autosomal dominant, autosomal recessive, and spastic-ataxia subgroups.[24] The autosomal recessive ataxias are collectively the most common in childhood and include Friedreich ataxia (the most prevalent inherited ataxia), ataxia-telangiectasia, ataxia with oculomotor apraxia types 1 and 2, and ataxia with vitamin E deficiency.[25] Several genes that are more commonly associated with complex dystonia syndromes may also present with a predominantly ataxic phenotype, including *PLA2G6* and *ATP1A3*. The autosomal

dominant ataxias include a number of the spinocerebellar ataxias (SCAs), as well as dentatorubral-pallidoluysian atrophy, which manifests with seizures, myoclonus, and dementia in addition to ataxia.

Most chronic progressive ataxias present later in childhood or adolescence after a period of normal development in infancy and early childhood. One exception is ataxia-telangiectasia, which classically presents between the ages of 1 and 4 years, but may rarely present in the first year of life. Clinical diagnosis can be challenging in the initial stages because young children with ataxia-telangiectasia may have prominent dystonia and chorea in addition to ataxia, ataxia may appear static in the first 1 to 2 years before progression becomes evident, and oculocutaneous telangiectasia may emerge months or years after neurologic symptom onset (usually by 6 years of age). Ataxia-telangiectasia is a multisystem disorder that also includes immunodeficiency and increased susceptibility to malignancy. The immunodeficiency is characterized by low numbers of circulating T lymphocytes and B lymphocytes, and decreased serum immunoglobulin levels, particularly IgA, IgG_2, and IgG_4.[26] A history of recurrent sinopulmonary infections may precede the onset of neurologic symptoms in some children.

Friedreich ataxia is the most common autosomal recessive ataxia in white populations. The clinical syndrome is characterized by progressive ataxia, dysarthria, limb weakness, impaired proprioception and vibration sense, areflexia, and extensor plantar responses. Homozygous GAA triplet repeat expansions in exon 1 of the frataxin gene (*FXN*) are detected in more than 95% of patients. The remaining patients have an abnormal GAA expansion on one allele coupled with another pathogenic variant on the other allele.

The following general approach is a suggested guide to the evaluation of a child with a suspected progressive genetic ataxia:

- **Delineate the clinical syndrome, including any accompanying involuntary movements, and associated neurologic features and systemic features. If a distinctive clinical syndrome, such as Friedreich ataxia, is apparent, consider proceeding directly to single-gene genetic testing.**
- **Examine the brain MRI to determine whether cerebellar atrophy is present (eg, ataxia-telangiectasia, ataxia with oculomotor apraxia types 1 and 2) or absent (eg, Friedreich ataxia, ataxia with vitamin E deficiency) and search for associated abnormalities including cerebral or brainstem volume loss, white matter lesions, or basal ganglia lesions.**
- **Perform selected routine laboratory investigations to screen for treatable disorders (plasma vitamin E, coenzyme Q10), and identify abnormal biochemical markers that may assist in the diagnosis of a nontreatable ataxia syndrome (ataxia-telangiectasia and ataxia with oculomotor apraxia types 1 and 2), including serum α-fetoprotein, IgG subclasses, albumin, creatine kinase, and cholesterol panel.**
- **Perform molecular genetic testing: In cases where the clinical, biochemical, and radiologic phenotype suggests a specific syndrome, single-gene testing may be appropriate. Increasingly, multigene next-generation sequencing panels or whole exome sequencing are used early in the testing process. It is important to be aware that next-generation sequencing methods will not detect triplet repeat expansions, which is an important consideration for a number of the genetic ataxias (selected SCAs, dentatorubral-pallidoluysian atrophy, and Friedreich ataxia).**

KEY POINT

- **Huntington disease in childhood often presents with an akinetic-rigid syndrome rather than chorea.**

Myoclonus

Genetic conditions manifesting with nonprogressive myoclonus include hereditary hyperekplexia and myoclonus-dystonia, while progressive myoclonus is characteristic of the progressive myoclonic epilepsies. Other neurodegenerative

disorders, such as ataxia-telangiectasia, may feature myoclonus as part of a complex syndrome.

Myoclonus-dystonia is a rare movement disorder characterized by a combination of nonepileptic myoclonic jerks and dystonia. The disorder usually begins in childhood, with symptom onset at a mean age of 6 years. Myoclonus is usually the presenting symptom, while dystonia may be present initially or develop later. Both symptoms may affect any part of the body but are usually most prominent in the upper limbs and neck. The myoclonus in myoclonus-dystonia is present at rest; precipitated or aggravated by posture, action, and stress; and is stimulus insensitive. Most older patients notice significant reduction of their myoclonus in response to alcohol ingestion, but this information is not typically available in pediatric patients. Patients have normal cognition and often have psychiatric comorbidities including depression, anxiety, and obsessive-compulsive disorder. Neuroimaging is normal. Severity and clinical course vary widely and cannot be predicted. Myoclonus-dystonia is not a degenerative disorder and is compatible with an active life and a normal life span. In some cases, however, myoclonus-dystonia may be progressive and may lead to considerable functional disability. Symptomatic drug therapy is usually disappointing. Some patients benefit from anticholinergic drugs and benzodiazepines, which are occasionally effective for both myoclonus and dystonia. Botulinum toxin can be used to treat focal dystonia. In patients with severe and disabling myoclonus-dystonia, DBS of the globus pallidus internus is safe and can be effective.[27]

The syndrome of myoclonus-dystonia is genetically heterogeneous. *SGCE* mutations are detected in 30% to 50% of cases. Inheritance is autosomal dominant with reduced penetrance because of imprinting and subsequent silencing of the maternal allele. Transmission is therefore paternal.[28] Myoclonus-dystonia has also been reported to be associated with mutations in other genes including *ADCY5, KCTD17, CACNA1B,* and *RELN*. However, in these cases, the clinical phenotype is distinct from the phenotype usually observed in myoclonus-dystonia due to *SGCE* mutations.[27]

Progressive Myoclonic Epilepsies

The progressive myoclonic epilepsies are a clinically and genetically heterogeneous group of disorders characterized by the core features of action myoclonus, epileptic seizures, and progressive neurologic decline (ataxia, dementia).[29] Typically, myoclonus is in a focal or segmental distribution and is arrhythmic, asynchronous, and asymmetric. Progressive myoclonic epilepsies typically present during childhood and are often fatal. The majority of genes involved encode lysosomal proteins, and the disorders are inherited in an autosomal recessive pattern, including the neuronal ceroid lipofuscinoses, Unverricht-Lundborg disease (cystatin B [*CSTB*]), Lafora disease (*NHLRCI*), and sialidosis. Children with juvenile neuronal ceroid lipofuscinoses typically experience progressive loss of vision due to pigmentary retinopathy. Mitochondrial disorders including myoclonic epilepsy with ragged red fibers (MERRF), mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes (MELAS), and *POLG*-related disorders can also manifest with progressive myoclonus.

Parkinsonism

Several degenerative conditions resemble Parkinson disease with recessive modes of inheritance and onset of symptoms before 21 years of age.[30] In these

cases, the term *juvenile parkinsonism*, rather than juvenile Parkinson disease, is preferred, since the histopathologic characteristics differ.[31] The genes involved, in order of frequency, are *PRKN* (parkin), *PINK1,* and *DJ1*. Age of onset is variable with the youngest reported patient being 5 years old.[32] Dystonia is frequently observed at onset, while tremor is less common than in adult-onset idiopathic Parkinson disease. Patients with parkin mutations often experience marked sleep benefit. Disease progression is slower than in idiopathic Parkinson disease. Patients have a marked response to levodopa, although dyskinesia and motor fluctuations occur early.

A number of genetic neurodegenerative disorders manifest with juvenile parkinsonism as one component of a complex neurologic syndrome that may feature dystonia, chorea, ataxia, gaze abnormalities, neuropsychiatric symptoms, dementia, and other neurologic abnormalities. These conditions include Wilson disease, early-onset Huntington disease (Westphal variant), SCA2 and SCA3, neurodegeneration with brain iron accumulation (*PKAN*, *PLA2G6*, *ATP13A2*), juvenile neuronal ceroid lipofuscinoses, and Niemann-Pick disease type C, among others.[22,30,31]

Enhancement of dopamine transmission is the mainstay of parkinsonism treatment. This can be achieved with levodopa, dopamine agonists, and monoamine oxidase inhibitors. The type of drug, response to treatment, and prognosis depend on the etiology. Most of the congenital disorders of monoamine neurotransmitter synthesis, but not all, respond well to treatment. Levodopa should be started at a low dose (0.5 mg/kg/d to 1 mg/kg/d) and titrated slowly until complete benefit or dose-limiting side effects occur[33] due to the high prevalence of dyskinesia in all patients with pediatric parkinsonism, regardless of the underlying cause. In children who have congenital dopamine deficiency due to a metabolic defect of dopamine synthesis, dyskinesia is expected to gradually improve over time so that larger doses eventually become well tolerated. In children with neurodegenerative diseases, dyskinesia and the behavioral side effects of levodopa are frequently dose limiting. In acquired parkinsonism (ie, ischemic lesions, tumors, encephalitis), response to treatment is variable. While presynaptic dopaminergic transmission failure can respond to dopaminergic drugs, the effect is limited in postsynaptic failure where there is injury to the striatal targets.[31]

PAROXYSMAL MOVEMENT DISORDERS

A number of genetic conditions that cause episodic involuntary movements or ataxia typically present during childhood or adolescence. The paroxysmal dyskinesias and episodic ataxias have traditionally been considered distinct phenotypes, but it is increasingly recognized that there is considerable phenotypic overlap associated with these genetic disorders that encompasses movement disorders and other episodic neurologic symptoms such as migraine and epilepsy.

Paroxysmal Dyskinesias

The paroxysmal dyskinesia syndromes are a group of childhood-onset genetic conditions that are characterized by discrete episodes of involuntary movements (dystonia, chorea, ballism, myoclonus, or a combination) lasting from seconds to hours depending on the specific disorder. The most important clinical features that distinguish the disorders from each other are the episode trigger, duration, and the presence or absence of interictal neurologic abnormalities, rather than

KEY POINTS

- **Myoclonus-dystonia is a rare genetic movement disorder characterized by a combination of nonepileptic myoclonic jerks and dystonia.**
- **Myoclonus-dystonia is compatible with an active and normal life span; however, some patients have a progressive course leading to considerable disability. Treatment is usually disappointing.**
- **Progressive myoclonic epilepsy is characterized by action myoclonus, epileptic seizures, and progressive neurologic decline. The majority of genes involved in progressive myoclonic epilepsy encode lysosomal proteins and are inherited in an autosomal recessive pattern. The largest group of progressive myoclonic epilepsies are the neuronal ceroid lipofuscinoses.**
- **Juvenile parkinsonism refers to hereditary conditions with onset before the age of 21 years that clinically resemble Parkinson disease but with different histopathologic characteristics.**
- **In juvenile parkinsonism, progression is slower than in idiopathic Parkinson disease. Patients have a marked response to levodopa, although dyskinesias and motor fluctuations occur early.**
- **The classic genetic paroxysmal dyskinesias may be clinically distinguished from one another by the episode triggers, episode duration, and the presence or absence of interictal neurologic features.**

the precise motor phenomena that occur during the episode itself. Review of the episodes on home video remains a valuable tool to distinguish the attacks from seizures or another episode type. The three classic paroxysmal dyskinesia syndromes are paroxysmal kinesigenic dyskinesia, paroxysmal exertional dyskinesia, and paroxysmal nonkinesigenic dyskinesia.

Children with paroxysmal kinesigenic dyskinesia and paroxysmal nonkinesigenic dyskinesia typically have a normal interictal neurologic examination. Paroxysmal kinesigenic dyskinesia episodes are usually seconds in duration, while paroxysmal nonkinesigenic dyskinesia episodes typically last minutes to hours. Paroxysmal kinesigenic dyskinesia episodes are often triggered by sudden movement or the intent to move, while paroxysmal nonkinesigenic dyskinesia episodes may be triggered by caffeine, alcohol, and stress. Both disorders are caused by monoallelic mutations in their respective genes, *PRRT2* (for paroxysmal kinesigenic dyskinesia) and *PNKD* (for paroxysmal nonkinesigenic dyskinesia), and may be either sporadic or inherited in an autosomal dominant pattern. Paroxysmal kinesigenic dyskinesia episodes are typically well controlled with low-dose anticonvulsant medication, most commonly carbamazepine, while paroxysmal nonkinesigenic dyskinesia is treated with benzodiazepines.

Episodes of paroxysmal exertional dyskinesia are triggered by sustained exercise. Disorders that cause paroxysmal exertional dyskinesia usually have other interictal neurologic features, including intellectual disability and persistent motor abnormalities such as ataxia or dystonia. GLUT1 deficiency syndrome, the prototypical cause of paroxysmal exertional dyskinesia, is one example and is an important diagnosis to recognize as it is treatable with the ketogenic diet (discussed in the section on GLUT1 deficiency syndrome). Paroxysmal exertional dyskinesia has also been rarely reported as a manifestation of pyruvate dehydrogenase deficiency, which may respond to treatment with thiamine.[34]

Other genetic disorders in which paroxysmal dyskinesia occurs in the context of a complex neurologic syndrome include *ADCY5*-related dyskinesia (as previously discussed) and alternating hemiplegia of childhood due to mutations in *ATP1A3*. In *ADCY5*-related dyskinesia, a distinctive feature of the paroxysmal attacks is that they may occur at night during drowsiness.[35] Infants with *ATP1A3*-related alternating hemiplegia of childhood may have episodes of paroxysmal dystonia, typically accompanied by other classic signs including monocular nystagmus, episodic hemiplegia or quadriplegia, and persistent neurologic deficits, including hypotonia, ataxia, dystonia, chorea, and bulbar dysfunction.[36]

Intermittent and Episodic Ataxias

The episodic ataxias are a group of autosomal dominant disorders characterized by intermittent discrete attacks of ataxia, usually with accompanying mild interictal neurologic findings. Age of onset ranges from 2 to 20 years. Patients with episodic ataxia type 1 (caused by a mutation in the potassium channel gene *KCNA1*) typically experience brief attacks, seconds to minutes in duration, that may be triggered by startle or exercise, and have myokymia on examination between attacks. Patients with episodic ataxia type 2 (the most common type of episodic ataxia, caused by a mutation in the calcium channel subunit gene *CACNA1*), have attacks lasting minutes to hours and have gaze-evoked nystagmus between episodes. Some patients with episodic ataxia type 2 ultimately develop persistent progressive ataxia. There are other rare episodic

ataxia subtypes, each described in one or two families so far. Treatment with acetazolamide can be effective in preventing attacks, particularly in episodic ataxia type 2.[37]

Some conditions that present with recurrent acute ataxia are treatable metabolic disorders. These often present in infancy or early childhood, and episodes may be accompanied by encephalopathy. Examples are organic acidurias (eg, methylmalonic aciduria, propionic acidemia), urea cycle enzyme defects (eg, ornithine transcarbamylase deficiency), mild forms of pyruvate dehydrogenase deficiency, and biotinidase deficiency.

CONCLUSION

Movement disorders in infants and children are associated with a large number of acquired and genetic disorders. Clinical characterization of (1) the course and timing of neurologic symptoms in the context of the child's development, and (2) the movement disorder phenomena and associated neurologic and systemic findings on examination are the key to accurate diagnosis. Disease-modifying treatments exist for many movement disorders that present acutely and for selected genetic, metabolic conditions that present with chronic symptoms. In the current context of technologic advances in relation to genetic diagnosis and to treatment, such as neuromodulation and gene therapy, the diagnosis and treatment of childhood movement disorders is poised to evolve rapidly.

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