Movement Disorders and Neurometabolic Diseases.

Celanie K. Christensen, MS MD[1, 2,] Laurence Walsh, MD[1, 2, 3]

[1]Department of Neurology, Section of Child Neurology, Indiana University School of Medicine, Indianapolis, IN

[2]Department of Pediatrics, Section of Developmental Pediatrics, Indiana University School of Medicine, Indianapolis, IN

[3]Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, IN

From: Riley Hospital for Children at Indiana University Health and Indiana University School of Medicine

Address reprint requests to:

Celanie K. Christensen, MS MD

Section of Developmental Pediatrics

RI1601

705 Riley Hospital Drive

Indianapolis, IN 46202

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Abstract

Many inherited metabolic disorders cause movement disorders in children. This review focuses on chorea, dystonia, myoclonus, tremor, and parkinsonism. Broad categories commonly responsible for pediatric movement disorders include mitochondrial disorders, organic acidemias, mineral metabolism and transport disorders, neurotransmitter diseases, purine metabolism disorders, lipid storage disorders, and disorders of creatine metabolism. Each movement disorder can be caused by many different inherited metabolic disorders and several of the inherited metabolic disorders can cause multiple movement abnormalities. Dietary modifications, medications, and increasingly specific therapy can improve outcomes in children with movement disorders caused by metabolic disorders. Recognition and characterization of secondary movement disorders in children facilitate management of the abnormal movements and diagnosis, and possible treatment, of an underlying metabolic disorder.

Introduction

Many inborn errors of metabolism (IEM) cause movement disorders in children. [1, 2] Movement is a complex task that requires proper functioning of many areas of the nervous system. Any disturbance in the motor pathway from the central nervous system to muscle fibers can lead to abnormal movements. IEM may cause localized or systemic dysfunction. If the nervous system is involved, movement disorders are common. An individual IEM may be associated with more than one type of movement disorder. Likewise, a specific movement disorder usually does not predict a particular IEM.[2] While chronic movement disorders are more common in children with IEM, acute presentation of movement abnormalities can occur such as abrupt onset dystonia.[3] Conversely, children with abnormal involuntary movements due to a

known IEM may experience acute worsening of symptoms such as potentially life-threatening status dystonicus with rhabdomyolysis.[4]

Movement disorders covered in this review will include hyperkinetic movements (chorea, dystonia, myoclonus, and tremor) as well as hypokinetic movements (parkinsonism or hypokinetic rigid syndrome). Broad categories under the umbrella of IEM commonly responsible for pediatric movement disorders include mitochondrial disorders, organic acidemias, mineral metabolism and transport disorders, neurotransmitter diseases, purine metabolism disorders, lipid storage disorders, and disorders of creatine metabolism. Such diagnoses require screening of specific metabolites in urine, serum, and/or cerebrospinal fluid (CSF). Results of this initial testing may lead to further biochemical analysis or genetic testing. Timely recognition of these underlying metabolic causes often allows disease-specific treatments and the best possible outcome for the affected child.[2] Even with treatment, however, movement disorders in patients with IEM rarely resolve completely and can cause life-long disability.

Both IEM and movement disorders impact children's quality of life (QOL).[1] This impact on quality of life has been suggested to be greater than that of other childhood chronic disorders.[1] As expected, increasing severity of movement disorder positively correlated with lower (QOL) scores. Lower adaptive abilities were also linked to lower scores. Unfortunately, few patients included in this QOL study received treatments for the abnormal movements.[1] While it is suspected treatment improves QOL, this has not been formally quantified for the movement disorders in patients with IEM as a large group.

Typically, treatment of underlying IEM consists of dietary modifications and possible addition of cofactors or supplements. Better medical management options are increasing but

remain both elusive and often invasive. Secondary therapy of the movement disorder may also benefit patients with IEM for both chronic movement abnormalities and acute presentations. Beyond lack of primary treatment, barriers to treating children with IEM-associated movement disorders include under-recognition of both pediatric movement disorders and individually rare IEM, delay in reaching a suspected IEM diagnosis, and inadequate access to secondary movement disorder treatment.[1, 5]

Movement Disorders

Chorea is characterized by brief random movements that are neither rhythmic nor stereotyped. It occurs in injury to the striatum and subthalamic nucleus as well as widespread brain injury.[6] Movements appear purposeless and affect any part of the body, including the face. They can migrate from one side of the body to the other side and between upper limbs and lower limbs. Motor impersistence can be observed with voluntary tongue protrusion. Chorea occurs during both voluntary movement and with the child at rest. Individuals with chorea may appear restless due to the constant movement. Chorea typically abates during sleep. As patients become older, they may attempt masking the abnormal movements by incorporating them into a voluntary movement.[7] Chorea is a prominent feature of glutaric aciduria type 1, glucose transporter type 1 (GLUT1) deficiency, Wilson disease, neuronal brain iron accumulation disorders (NBIA), neurotransmitter diseases, and Lesch-Nyhan disease.[7,8] A full list of disorders associated with chorea is in Table 1.

Dystonia is a manifestation of repetitive muscle contractions that are sustained at their peak. These contractions lead to torsional postural changes. Although classified as a

hyperkinetic movement disorder, dystonia often appears to be a postural abnormality than an involuntary movement, but both are possible. While dystonia is often provoked by voluntary movement, which can be specific, more severe dystonia may persist at rest. Dystonia is classified as focal (affecting a single body part), multifocal (affecting two or more noncontiguous regions) segmental (affecting two or more contiguous body parts), hemidystonia (affecting the arm and leg on one side of the body), and generalized (affecting one or both legs, the trunk, and another body part).[9, 10] Dystonia localizes to the globus pallidus and striatum, even though thalamic, cortical, and cerebellar injury likely contribute to the movement disorder.[11] Many metabolic diseases have dystonia as a feature at some point during their course. In children with IEM, dystonia is often a prelude to parkinsonism in later childhood and adolescence. Focal, slowly progressive, and isolated dystonia is most likely to be caused by primary dopaminergic deficiencies (guanosine triphosphate (GTP) cyclohydrolase 1 deficiency and tyrosine hydroxylase deficiency).[12] Abrupt onset, generalized dystonia can be caused by many different metabolic abnormalities. Some of the most frequent IEM causing dystonia are glutaric aciduria type 1 (GA1), Leigh syndrome, and other mitochondrial cytopathies. Rare, but very treatable genetic causes of childhood dystonia include autosomal dominant GTP cyclohydrolase 1 deficiency, tyrosine hydroxylase deficient dopa-responsive dystonia, and GLUT1 deficiency.[12] A more complete list of IEM associated with dystonia is found in Table 2.

Myoclonus appears as a very quick and abrupt movement often described as “shock-like” in nature. It can be rhythmic or non-rhythmic, and it is not incorporated into a voluntary movement. There is a pause between individual myoclonic jerks. Myoclonus can be generalized, focal, or multifocal. It can be spontaneous or in response to a movement or sensation.[13] Myoclonus is thought to be caused by injury to cortical, brainstem, or spinal cord

gray matter and can be either epileptic or nonepileptic.[14] Table 3 provides a list of IEM that can have myoclonus as a feature. Specific IEM that often cause myoclonus are mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), myoclonic epilepsy with ragged red fibers (MERRF), GM1 gangliosidosis, cerebral creatine deficiency syndrome 2 (guanidinoacetate methyltransferase deficiency), GLUT1 deficiency, and Wilson disease.

Tremor is rhythmic oscillation about a central point or position with a fixed frequency. The types of tremor are distinguished by timing and morphology. Tremor may be resting, postural, action, or intention, affecting the extremities, trunk, head, and/or voice.[13] It may be of small or large amplitude (e.g. so-called "wing-beating" tremor seen in Wilson disease). Tremor may be a manifestation of dystonia as well as cerebellar dysfunction. Although it is a primary neurologic manifestation of Wilson disease, tremor is generally not the overarching neurologic symptom in pediatric IEM.[2] See Table 4 for a compilation of conditions in which tremor can be seen.

Parkinsonism is defined by the presence of two or more of the following: resting tremor, bradykinesia, rigidity, and postural instability. Hypokinetic rigid syndrome (HRS) is the preferred term for parkinsonism in children.[15] HRS is caused by dopaminergic transmission failure in the substantia nigra or striatum. Compared to parkinsonism in adults, children with HRS rarely have resting tremor and more commonly have other forms of abnormal movements such as dystonia.[15] HRS more commonly occurs in older children and adolescents than in infants and toddlers where it is quite rare. It also frequently develops as a secondary movement disorder after dystonia has been present for a few years. Since HRS is rare in children, underlying metabolic disorders require exclusion regardless of age in the pediatric population. Table 5 contains a list of conditions that either present as or feature HRS in childhood. Within these,

Wilson disease, NBIA, and neuronal ceroid lipofuscinoses are the most common associated disorders.

The remainder of this review will focus on several metabolic conditions that have movement disorders as a primary feature. While several have movement disorders as a common presenting abnormality, all conditions discussed below have movement disorder as a major feature at some point in the disease course.

Glutaric Aciduria Type 1

Glutaric aciduria type 1 (GA1) is an autosomal recessive IEM caused by mutations in the glutaryl CoA dehydrogenase gene (*GCDH*). Pathogenic mutations lead to a deficiency of glutaryl CoA dehydrogenase resulting in impaired catabolism of lysine, hydroxylysine, and tryptophan with resulting accumulation of 3-hydroxyglutaric acid and glutaric acid. These metabolites, in excess, lead to neuronal death.[16] Typical clinical presentation includes early progressive macrocephaly and hypotonia after an initial normal period.[17] Affected children often have acute decompensation with encephalopathy by the age of two years.[18] Triggers of the decompensation are typically illness, though a trigger is not always identified. During or shortly after the acute encephalopathic crisis, abnormal movements abruptly start. Patients usually experience generalized dystonia, though focal and segmental dystonia are possible.[19] The dystonia is mobile in childhood but typically becomes fixed by adolescence. Orofacial dystonia is prominent and typically occurs early, leading to speech and feeding difficulties. Dystonia may co-exist with hypokinetic rigidity (parkinsonism) or chorea. The degree of disability is linked to the age and severity of acute decompensation.[19]

Treatments specific for patients with GA1 focus on normalizing metabolism and preventing recurrent acute encephalopathic episodes that can lead to further brain damage. Treatments include protein restriction and supplementation with carnitine and riboflavin.[20] Therapy does not reverse the neurologic damage causing the movement disorder, nor does it ameliorate an already existing movement disorder. Medications that target the abnormal movements can be used. Baclofen for dystonia, benzodiazepines for dystonia and chorea, trihexyphenidyl for dystonia, and botulism toxin injections for dystonia have all been used in patient with GA1. These treatments tend to have uncertain success.[21]

GLUT1 Deficiency Syndrome

Glucose transporter type 1 (GLUT1) deficiency syndrome classically has been characterized by infantile-onset epilepsy refractory to medication management, acquired microcephaly, developmental delays, hypotonia, spasticity, ataxia, and dystonia.[22] Glut1 facilitates the transport of glucose across the blood-brain barrier, and symptoms result from this insufficient energy source to the brain.[23]

Most patients with GLUT1 deficiency have a CSF to blood glucose ratio of <0.5. If GLUT1 deficiency syndrome is suspected, the appropriate first test is obtaining CSF glucose and serum glucose simultaneously so that a ratio can be calculated. Hypoglycorrhachia is the distinctive biomarker but can be present in other conditions such as infection. The cut-off value for hypoglycorrhachia seen in GLUT1 deficiency syndrome patients has liberalized over time, including higher values as the phenotype has expanded.[24] Diagnosis is confirmed by the presence of a heterozygous mutation in the *SLC2A1* gene, which is typically *de novo*.

Pathogenic mutations have not been found in all affected patients, so the lack of an identified mutation should not preclude a treatment trial.[25]

As this condition has become more widely recognized, more phenotypes have been described. GLUT1 deficiency syndrome clinical presentations now also include paroxysmal exertion-induced dyskinesia with or without seizures, choreoathetosis, alternating hemiplegia, intermittent ataxia, intermittent dystonia, and migraine.[25, 26] Cognitive impairment varies widely in affected patients. Language delays are also possible either from cognitive delay or dysarthria. Severity of intellectual disability often positively correlates with that of other symptoms.[26]

Movement disorders in GLUT1 deficiency syndrome patients often evolve in complexity and may include ataxia, dystonia, chorea, tremor, myoclonus, and HRS. Movement abnormalities can be continuous or paroxysmal. Acute presentation of dystonia has been reported.[3] While movement disorders may be present initially, epilepsy more frequently occurs early in the disease course then gradually recedes, only to be replaced by abnormal involuntary movements.[27]

Early diagnosis is important as treatment with the ketogenic diet or modified Atkins diet allows for an alternate energy source for the brain and subsequent improvement in seizures, abnormal movements, and other symptoms of the disease.[28] Certain medications should be avoided as they impair GLUT1 function, including phenobarbital, diazepam, chloral hydrate, tricyclic antidepressants, and caffeine.[29] Secondary treatment of movement disorders can be used in patients with GLUT1 deficiency with certain cautions. Valproic acid used to treat myoclonus needs to be avoided in patients with GLUT1 deficiency as it increases the likelihood of Reye-like illness in patients on the ketogenic diet and may impair glucose transport.[30]

Wilson Disease

Wilson disease, otherwise known as hepatolenticular degeneration, is a copper transport disorder that is inherited in an autosomal recessive pattern. Pathogenic variants in the *ATP7B* gene encoding copper transport ATPase-2 lead to disease.[31] While certain populations have common pathogenic variants such as p.His1069Gln in Europeans (an amino acid substitution in a highly conserved motif close to the ATP-binding region) and p.Arg778Leu in Asian populations (an amino acid substitution in exon 8), over 800 mutations have been reported.[32, 33, 34] Types of pathogenic variants include nonsense, missense, frameshift, splice site, and large deletions. The Wilson Disease Mutation Database, curated at the University of Alberta, (http://www.wilsondisease.med.ualberta.ca/database.asp) contains documentation of the reported pathogenic variants as well as non-disease causing variants reported in the literature. Copper transport ATPase-2 is involved in transporting copper from hepatocytes into bile.[31]

Copper accumulation leads to cellular injury in the central nervous system, liver, and cornea. Symptoms can be isolated to one of the affected organ systems or occur in any combination. Significant phenotypic variability can be seen within families, and patients can present over a large age range from 3 to 50 years.[35]

Young children typically present with hepatic failure and not neurologic symptoms. However, adolescents are more likely to present with neurologic symptoms and minimal signs of hepatic dysfunction. Thus, adolescent patients often present with complaints of gait problems or changes in speech. Over years, patients with Wilson disease develop various movement disorders, including chorea, dystonia, rigidity, tremor, and postural instability. Prominent

features of Wilson disease include dysarthria, risus sardonicus (fixed pseudosmile), and inspiratory stridor all of which are caused by bulbar muscle dystonia.[36] Status dystonicus has been reported in children with Wilson disease which can be life threatening.[4] Increased muscle contractions overtime may progress to rhabdomyolysis with myoglobinuria and acute renal failure. Infection, medications or medication withdrawal typically triggers this deterioration. Other causes of discomfort such as constipation and gastroesophageal reflux need to be addressed aggressively during the episode.[3] The nearly pathognomonic feature of Wilson disease is the Kayser-Fleischer ring, a yellow-brown coloration of the limbus of the cornea caused by copper deposits in the Descemet membrane.[37] This finding is almost always present in patients with neurologic symptoms. Psychiatric symptoms are also possible and may be present before neurologic abnormalities.

Testing recommendations include obtaining serum copper, serum ceruloplasmin, and urine copper. Most individuals with Wilson disease have low serum copper and ceruloplasmin with elevated urine copper. Occasionally, serum and urine biochemical testing is inconclusive, so liver biopsy may be necessary to confirm the diagnosis. Disease status can also be confirmed using molecular genetic testing, though delays in obtaining these results may lead to delay in treatment.[38]

Early detection of Wilson disease is critical since early treatment can prevent permanent neurologic disorders and cirrhosis.[39] The first-line treatment for individuals with Wilson disease is the copper chelating agents D-penicillamine and trientine.[38] Medical treatment increases urinary excretion of copper with goals of five to ten times the normal urinary copper levels. D-penicillamine is typically the first agent used and must be given with pyridoxine. However, it can have significant side effects that limit long-term use. Patients taking this drug must have

regular monitoring for thrombocytopenia, aplastic anemia, and leukopenia. Kidney injury can also occur leading to proteinuria, nephrotic syndrome, and Goodpasture syndrome. Severe skin reactions are also possible. While steroids can sometimes mitigate some side effect symptoms, D-penicillamine treatment must be stopped in a significant portion of patients.[39, 40] The second-line agent typically used is trientine. This drug tends to be better tolerated but may be unavailable.[41] Zinc supplementation interferes with copper absorption in the gastrointestinal tract and can be used as first-line therapy, but is more often given after initial treatment with a chelating agent; zinc should not be used in conjunction with chelating agents.[42] Other adjunctive therapies include vitamin E supplementation to protect tissues from free radical damage and limiting intake of copper rich foods.[43] Therapy needs to continue throughout the patient's lifespan, including during pregnancy.[38] For patients who fail treatment with copper chelating agents or zinc, liver transplantation is an option. Liver transplantation early in disease management remains a controversial issue.[44] Medical therapy for individual movement disorders can also be used and deep brain stimulation has been reported as beneficial for severe tremor and dystonia in patients with Wilson disease.[45]

Leigh Syndrome

Leigh syndrome, otherwise known as subacute necrotizing encephalomyelopathy, can be inherited in several patterns including autosomal recessive, X-linked, and maternal. There are more than 50 nuclear-encoded genes and 14 mitochondrial-encoded genes that have been linked to Leigh syndrome.[46, 47] The most common cause of nuclear-encoded Leigh syndrome is pathogenic variants in the *SURF1* gene, which accounts for approximately 10% of all cases.[48]

For maternally inherited forms of Leigh disease, the most common cause is pathogenic variants in the *MT-ATP6* gene which occurs in roughly 50% of cases.[49] Most of the other genetic etiologies are found in single family case reports and account for <5% of cases each. The genes associated with Leigh syndrome encode proteins important in energy metabolism, and tissues with high energy requirements including the brain, heart, and liver are most often affected.[46, 47]

Patients with Leigh syndrome typically present between 3 and 12 months, though adult presentations have also been reported. Many patients present during or immediately after an acute illness with neurologic decompensation. Acute presentation of dystonia is also possible.[3] The neurologic decompensation leads to developmental delays and regression in a step-wise fashion. In between illnesses children are often stable and some may make developmental progress. However, decline with eventual respiratory or cardiac failure is typical.[36] Common neurologic abnormalities include hypotonia, spasticity, peripheral neuropathy, ataxia, and movement disorders including chorea, dystonia, and cogwheel rigidity. Other manifestations of Leigh syndrome are cardiomyopathy, anemia, renal tubulopathy, liver dysfunction, ptosis, and myopathy.[46, 47] The original criteria published in 1996 required the presence of a progressive neurologic disease with motor and intellectual developmental delays, involvement of the brainstem and/or basal ganglia, and elevated blood or CSF lactate levels. These criteria also required individuals to have one of the following: characteristic neuroimaging findings, typical neuropathologic findings, or typical neuropathologic findings in a similarly affected sibling.[50]

The characteristic neuroimaging findings seen with Leigh syndrome are bilateral symmetrical hypodensities on computed tomography (CT) or hyperintensities on T2-weighted magnetic resonance imaging (MRI) involving the brainstem and/or basal ganglia. Cerebellar and cerebral atrophy can also be seen on MRI. Another useful imaging modality is proton magnetic

resonance spectroscopy (MRS) for detection of elevated brain lactate levels seen in the basal ganglia, white matter, and/or brainstem. Neuropathologic findings of Leigh syndrome are multiple symmetric necrotic lesions involving the basal ganglia, thalamus, brainstem, dentate nuclei, and optic nerves bilaterally. The necrotic lesions typically have a spongiform appearance with demyelination, gliosis, and vascular proliferation with relative neuronal sparing. Diagnostic criteria of Leigh syndrome have relaxed overtime with more recent diagnostic criteria no longer requiring elevated lactate levels as lactate levels can vary over time in a single patient. As the etiology of Leigh syndrome has become more well established, the focus of diagnostic criteria has transitioned to presence of symptoms related to mitochondrial dysfunction, abnormal enzyme activity in either oxidative phosphorylation or the pyruvate dehydrogenase complex, and pathogenic variants in genes related to mitochondrial function.[51]

Treatment of most causes of Leigh syndrome is largely supportive. However, there is specific treatment for biotin-thiamine-responsive basal ganglia disease (caused by pathogenic variants in the *SLC19A3* gene), biotinidase deficiency (caused by pathogenic variants in the *BTD* gene), and primary coenzyme Q10 deficiency (caused by pathogenic variants in the *COQ2*, *COQ6*, *COQ8B*, or *PDSS2* genes).[46] Biotin-thiamine-responsive basal ganglia disease is treated by supplementation with biotin and thiamine. If provided early in the disease course, biotin and thiamine can lead to partial or complete symptom resolution.[52] Biotinidase deficiency is treated by oral biotin replacement. Individuals detected on newborn screening with replacement started in the neonatal period and lifelong treatment can remain symptom free. Even patients treated after symptom onset often improve.[53]

The natural history of certain forms of primary coenzyme Q10 deficiency is modifiable with high-dose oral coenzyme Q10. Patients may not develop further neurologic symptoms after

supplementation is initiated.[54] Treatment of all patients with Leigh syndrome, with and without available primary treatments, focuses on adequate nutritional support, appropriate hydration, and avoidance of illness and other causes of stress.

During acute exacerbations of acidosis, sodium bicarbonate or sodium citrate can be used.[46, 47] Typical antiepileptic drugs are used to treat seizures with care to avoid valproic acid and, if possible, barbiturates since these treatments interfere with mitochondrial respiratory chain function.[55] Patients with Leigh syndrome should also avoid other drugs that interfere with mitochondrial respiratory chain function, although toxicity related to many agents is relative and must be weighed against the risk of withholding the agent in question.

Standard therapies are used to treat dystonia including baclofen, benzhexol, tetrabenazine, gabapentin, and botulinum toxin. Dichloroacetate reduces lactate and was considered as a possible treatment for patients with lactic acidosis such as that seen in individuals with Leigh syndrome. However, during the clinical trial, patients experienced no clinical benefit and some developed peripheral neuropathy. Current recommendation is to avoid dichloroacetate given the risk of peripheral neuropathy from either drug exposure or from exacerbation of the underlying risk of peripheral neuropathy.[56]

Exposure to anesthesia needs to be carefully considered as inhaled anesthetics variably inhibit mitochondrial complex I activity, and respiratory function can be compromised leading to failure, which is a common cause of death in patients with Leigh syndrome. Ultimately, however, surgical risks in individuals with Leigh syndrome is likely affected mostly by success in maintaining normal perfusion, oxygenation, temperature, and metabolic parameters, and providing adequate pain control peri-and post-operatively.[57]

Neurodegeneration with Brain Iron Accumulation

Neurodegeneration with brain iron accumulation (NBIA) is a group of neurodegenerative disorders characterized by the accumulation of iron in the basal ganglia and axonal spheroids in the central nervous system. Frequently, iron accumulates in the globus pallidus and substantia nigra. Currently, there are ten recognized forms of NBIA (see Table 6) The known genes associated with NBIA play a part in energy and lipid metabolism as well as oxidative stress. These ten conditions account for most cases of NBIA, though 35-40% of patients with NBIA cannot be diagnosed with a specific form based on clinical criteria or genetic testing.[58] All forms of NBIA are inherited in an autosomal recessive pattern except for BPAN, which is inherited in an X-linked dominant pattern with suspected male lethality, and neuroferritinopathy, which is inherited in an autosomal dominant pattern.[58, 59] PKAN, associated with about 50% of NBIA cases, is the most common form followed by PLAN, MPAN, and BPAN.[60, 61, 62] The other six forms occur rarely.[63, 64] NBIA can present over a wide age range from infancy to adulthood. Forms commonly presenting in childhood are classic PKAN, PLAN (infantile neuroaxonal dystrophy and atypical neuroaxonal dystrophy sub-types), MPAN, BPAN, FAHN, Kufor-Rakeb syndrome, Woodhouse-Sakati syndrome, and CoPAN.[60-64]

NBIA is characterized by progressive neurologic symptoms including dystonia, dysarthria, chorea, tremor, rigidity, and spasticity.[58, 59] Other typical findings in patients with NBIA include psychiatric abnormalities, optic atrophy, and retinal degeneration. Some forms of NBIA have cognitive decline, but overall cognition is relatively spared. Some forms have rapid progression while other forms have slow progression with periods of stability. Status dystonicus

can be seen in patients with NBIA as well. Complications and triggers of status dystonicus are discussed previously in this paper. NBIA needs to be considered in children presenting with abnormal gait, dystonia, and/or dysarthria.

A brain MRI is the most helpful test in determining the utility of further diagnostic testing for various forms of NBIA. MRI findings consistent with brain iron accumulation are hypointense lesions in the globus pallidus and substantia nigra on T2 weighted images. These lesions are isointense on T1 weighted images.[59] A central region of hyperintensity in the globus pallidus with surrounding hypointensity on T2 weighted images, the so-called eye-of-the-tiger sign, is highly specific for pathogenic variants in the *PANK2* gene.[65] Other brain MRI findings commonly seen are generalized cerebral and cerebellar atrophy. Clinical features and molecular genetic testing are used to give patients a specific diagnosis when possible. Molecular gene testing can be directed by MRI findings and clinical features pointing to a specific form of NBIA; however, multi-gene panels for NBIA are available and may be more cost effective when MRI findings and/or clinical features are not highly suggestive of a specific NBIA.[58, 59]

Treatment for NBIA is supportive and includes standard therapies for seizures and spasticity. Dietary support and management of dysphagia including gastrostomy tube placement is important for patients with NBIA. Aspiration pneumonia is a common issue. Baclofen (oral or intrathecal) and botulinum toxin are often used for dystonia treatment. Levodopa has been used and is beneficial in rare cases though it's efficacy decreases over time.[58, 59] DBS may be beneficial for severe dystonia.[66] Extreme episodes of dystonia can occur as the disease progresses and can be triggered by minor insults such as pain or infection. Occult fractures also need to be considered in non-ambulatory patients with significant dystonia.[58]

Pediatric Neurotransmitter Diseases (PNDs)

Neurotransmitter deficiency disorders presenting in childhood are a group of diseases caused by abnormalities in the production, transport, release, and reuptake of compounds that allow neurons to communicate effectively with other neurons or myocytes. These conditions can be subdivided into categories based on the affected metabolic pathway: tetrahydrobiopterin, catecholamine (dopamine, norepinephrine, and epinephrine), and serotonin metabolism (with and without hyperphenylalaninemia), serine and glycine metabolism, pyridoxine metabolism, glutamate and gamma-aminobutyric acid (GABA) metabolism, and disorders with folate deficiency.[67] Most of these conditions are inherited in an autosomal recessive pattern except for autosomal dominant GTP cyclohydrolase 1 deficiency (a form of dopa-responsive dystonia or Segawa disease).

Patients with PNDs typically present in infancy or early childhood, though presentation can occur at any age. Common symptoms seen in this group of conditions are encephalopathy, developmental delay, developmental regression, central hypotonia, peripheral hypertonia, autonomic dysfunction, diurnal variation in symptoms with severity worsening later in the day, seizures, and abnormal movements (unilateral or asymmetric limb dystonia, progressive gait dysfunction, hypokinesia, rigidity, postural tremor, involuntary tongue thrusting, oculogyric crises, myoclonus, and chorea). Although abnormal movements in young children often alert the clinician to the possibility of an underlying neurotransmitter deficiency disorder, there is significant variability in patient presentation and severity within these disorders.[67, 68]

PNDs are typically diagnosed based on biochemical abnormalities. While serum and urine testing should be completed first, CSF collection and analysis is necessary for definitive diagnosis. Initial biochemical testing should include plasma amino acids, urine organic acids, urine pterins, pipecolic acid, catecholamines, and serum prolactin. The lumbar puncture for neurotransmitter deficiency testing requires a specific technique. CSF needs to be collected in specialized tubes in a certain order so the appropriate fraction can be analyzed for each metabolite and immediately frozen. The following compounds can be analyzed: amino acids, catecholamine and serotonin metabolites (homovanillic acid, 5-hydroxyindoleacetic acid, 3-O-methyldopa), pterins (neopterin, biopterin, primapterin, tetrahydrobiopterin), pyridoxal 5-phosphate, 5-methyltetrahydrofolate, total and free GABA, gamma-hydroxybutyric acid, and homocarnosine. Enzyme analysis and molecular gene testing for specific neurotransmitter deficiencies are also available for many of these disorders.[69] It is anticipated that molecular genetic diagnosis will eventually supplant other diagnostic testing including CSF analysis.

Movement disorders are predominant features in the following neurotransmitter deficiency diseases: 6-pyrvuvoyl-tetrahydropterin (PTPS) deficiency caused by pathogenic variants in the *PTS* gene; dihydropteridine reductase (DHPR) deficiency caused by pathogenic variants in the *QDPR* gene; autosomal recessive guanosine triphosphate cyclohydrolase 1 (GTPCH1) deficiency caused by pathogenic variants in the *GCH1* gene; autosomal dominant GTPCH1 deficiency (dopa-responsive dystonia or Segawa syndrome) also caused by pathogenic variants in the *GCH1* gene; aromatic L-amino acid decarboxylase (AADC) deficiency caused by pathogenic variants in the *DDC* gene; sepiapterin reductase (SR) deficiency caused by pathogenic variants in the *SPR* gene; and tyrosine hydroxylase (TH) deficiency caused by pathogenic variants in the *TH* gene.[68-74]

It is important to recognize and quickly diagnose these conditions as several have specific treatments that can alter the disease course. PTPS deficiency responds well to treatment if initiated prior to six months of age. Still, there is evidence that even later treatment may provide benefit. Recommended treatments include tetrahydrobiopterin (BH4), levodopa, and 5-hydroxytryptophan (5-HT)., Selegiline and entacapone can also be helpful.[73] DHPR deficiency also has a much better outcome with regards to movement abnormalities if treatment is initiated in the first six months; the cognitive delays do not respond as well to therapy. 5-HT and levodopa are standard treatments. Selegiline, entacapone, and folinic acid may also be useful in combination with the standard treatments. Autosomal recessive GTP cyclohydrolase 1 deficiency patients are responsive to levodopa and BH4 replacement. Motor symptoms commonly improve though not as well as in patients with the autosomal dominant form. Autosomal dominant GTP cyclohydrolase 1 deficiency (dopa responsive dystonia or Segawa disease) patients are very sensitive to levodopa therapy. Typically, patients experience improvement within days of starting treatment and maximal improvement is achieved within a few months. Dyskinesias may occur during dose titration, but they are not typically a limiting factor in treatment with slow medication increases. AADC deficiency patients are typically treated with pyridoxine, dopamine agonists, and monoamine oxidase MAO inhibitors. Some patients may respond to levodopa. Overall, clinical improvements are limited despite available treatments for most patients.[74] SR deficiency patients can see movement abnormality improvement with levodopa therapy and 5-HT when used in combination with carbidopa. Second-line therapy includes monoamine oxidase inhibitors, serotonin reuptake inhibitors, melatonin, dopamine agonists, anticholinergics, and methylphenidate. While the movement disorder symptoms can be improved, the developmental and intellectual delays are resistant to

treatment.[72] TH deficiency patients respond completely to levodopa with a decarboxylase inhibitor such as carbidopa. However, severe dyskinesias are common even with very low doses, especially in patients with more severe forms of the disease. Selegiline or amantadine in combination with levodopa may help decrease dyskinesias.[70, 71]

Conclusion

Inborn errors of metabolism present with broadly recognizable phenotypes. However, as biochemical and molecular testing improves and becomes more widely available new phenotypes and increased variability in severity for classic conditions becomes apparent. Review of the literature reveals that many IEM cause movement disorders and each movement disorder alone has poor specificity for a given IEM. Early or mild cases of IEM with movement disorders can also mimic benign disorders such as Sandifer syndrome, benign hereditary chorea, and childhood tic disorders. These variables can lead to delay in diagnosis. Delayed diagnosis then prolongs time until the patient receives primary treatment for the underlying condition. Beyond the complexity of determining a specific metabolic abnormality in patients with movement disorders, decreased suspicion and under-recognition of both movement disorders and IEM also lead to patients developing severe movement disorders before primary treatment of their underlying condition is initiated.

Currently, worsening or persistent movement disorders typically leads the clinician away from conditions with etiologies apart from IEM. A movement disorder that behaves atypically also may point to an underlying IEM even without other signs and symptoms. Progressively abnormal movements and the failure to respond to standard treatment serve as red flags, alerting

one to the need for further diagnostic inquiry. Diagnostic evaluations for IEM-associated movement disorders are multifaceted. They variously include neuroimaging, CSF, blood, and urine substrate and enzymatic evaluations, sometimes other tissue testing, and molecular (DNA) testing. We expect that molecular testing will continue to supplant the other modalities over the next few years and lead to increasing broad phenotypes for individual disorders.

Finally, treatment of children with IEM-associated movement disorders often has two facets: symptomatic treatment of the abnormal movements and management of the underlying IEM or neurotransmitter disorder. The most successful treatment usually occurs with early recognition of an underlying IEM that itself is amenable to therapy. Even when that cannot be accomplished, early diagnosis and treatment of the IEM may still improve outcome. In either case, symptomatic treatment of the movement disorder often improves the child's functional abilities and quality of life. In the future, we hope for increased awareness of pediatric movement disorders and IEM that can cause movement disorders. Improved access to testing providing a specific diagnosis and knowledge of primary and secondary treatments will also hopefully improve patient outcomes.

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Table 1 Metabolic Disorders Causing Chorea[13, 36, 75]

Organic acidemias

- Propionic acidemia
- Methylmalonic acidemia
- Cobalamin C disease
- Glutaric aciduria, type 1
- Costeff syndrome (form of 3-methylglutaconic aciduria)
- D-2-hydroxyglutaric aciduria

Amino acid metabolism disorders

- Nonketotic hyperglycinemia
- Homocystinuria
- Phenylketonuria

Urea cycle disorders

- Argininemia

Mitochondrial disorders

- Pyruvate dehydrogenase complex deficiency
- Pyruvate carboxylase deficiency
- Leigh syndrome
- *POLG*-related disorders

Purine metabolism disorders

- Lesch-Nyhan disease
- Adenosine deaminase deficiency
- Purine nucleoside phosphorylase deficiency

Mineral metabolism and transport disorders

Wilson disease

Neurodegeneration with brain iron accumulation

Pantothenate kinase-associated neurodegeneration

Lipid storage disorders

GM1 gangliosidosis

GM2 gangliosidosis

Sandhoff disease (hexosaminidase A and B deficiency)

Gaucher disease, type 2

Metachromatic leukodystrophy

Niemann Pick disease type C

Disorders of creatine metabolism

Cerebral creatine deficiency syndrome 2 (GAMT deficiency)

Glucose transport disorder

GLUT1 deficiency

Neurotransmitter diseases

6-pyrvuvoyl-tetrahydropterin deficiency

Dihydropteridine reductase deficiency

Autosomal recessive guanosine-triphosphate cyclohydrolase 1 deficiency

Aromatic L-amino acid decarboxylase

Table 2 Metabolic Disorders Causing Dystonia[13, 36, 75]

Mitochondrial disorders

- Pyruvate dehydrogenase complex deficiency
- MELAS (mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes)
- NARP (neuropathy, ataxia, retinitis pigmentosa)
- Leigh syndrome
- Biotin-thiamine-responsive basal ganglia disease
- Primary coenzyme Q10 deficiency
- LHON-dystonia syndrome

Mineral metabolism and transport disorders

- Wilson disease
- Neurodegeneration with brain iron accumulation
  - Pantothenate kinase-associated neurodegeneration
  - PLA2G6-associated neurodegeneration
  - Mitochondrial-membrane protein-associated neurodegeneration
  - Beta-propeller protein-associated neurodegeneration
  - COASY protein-associated neurodegeneration
  - Fatty acid hydroxylase-associated neurodegeneration
  - Kufor-Rakeb syndrome
  - Woodhouse-Sakati syndrome

Organic acidemias

- Methylmalonic acidemia
- Propionic academia
- Glutaric aciduria, type 1

D-2-hydroxyglutaric aciduria

Homocystinuria

Amino Acid metabolism disorders

Tetrahydrobiopterin metabolism abnormalities

Maple syrup urine disease

Purine metabolism disorders

Lesch-Nyhan disease

Adenosine deaminase deficiency

Purine nucleoside phosphorylase deficiency

Lipid storage disorders

GM1 gangliosidosis

GM2 gangliosidosis (juvenile hexosaminidase A deficiency)

Sandhoff disease (hexosaminidase A and B deficiency)

Niemann Pick disease type C

Metachromatic leukodystrophy

Disorders of creatine metabolism

Cerebral creatine deficiency syndrome type 2 (GAMT deficiency)

Cerebral creatine deficiency syndrome type 1 (GATM deficiency)

Glucose transport disorder

GLUT1 deficiency

Neuronal ceroid lipofuscinosis

CLN1 (palmitoyl protein thioesterase 1 deficiency)

CLN2 (tripeptidyl peptidase 1 deficiency)

CLN3 (Batten disease)

Neurotransmitter diseases

Tyrosine hydroxylase deficiency

6-pyrvuvoyl-tetrahydropterin deficiency

Dihydropteridine reductase deficiency

Autosomal recessive guanosine-triphosphate cyclohydrolase 1 deficiency

Autosomal dominant guanosine-triphosphate cyclohydrolase 1 deficiency

Aromatic L-amino acid decarboxylase deficiency

Sepiapterin reductase deficiency

Table 3 Metabolic Disorders Causing Myoclonus[13, 36, 75]

Lipid storage disorders

- GM1 gangliosidosis
- GM2 gangliosidosis (Tay Sachs disease/hexosaminidase A deficiency)
- Gaucher disease, type III
- Galactosialidosis, juvenile

Amino acid metabolism disorders

- Nonketotic hyperglycinemia

Organic acidurias

- Biotinidase deficiency
- Cobalamin deficiency (infantile)

Urea cycle disorders

- Hyperornithinemia, hyperammonemia, homocitrullinuria syndrome

Mitochondrial disease

- MERRF
- MELAS
- Alpers syndrome (*POLG*-related)

Mineral metabolism and transport disorders

- Wilson disease
- Neurodegeneration with brain iron accumulation
    - Kufor-Rakeb syndrome

Disorders of creatine metabolism

- Cerebral creatine deficiency syndrome 2 (GAMT deficiency)

Glucose transport disorder

- GLUT1 deficiency

Neurotransmitter diseases

Tyrosine hydroxylase deficiency

Aromatic L-amino acid decarboxylase deficiency

Lysosomal storage disorders

Sialidosis type 1 (neuramidase deficiency)

Neuronal ceroid lipofuscinosis

CLN1 (palmitoyl protein thioesterase 1 deficiency)

CLN2 (tripeptidyl peptidase 1 deficiency)

CLN3 (Batten disease)

Table 4 Metabolic Disorders Causing Tremor[13, 36, 75]

Mineral metabolism and transport disorders

- Wilson disease
- Cystinosis
- Hartnup disease
- Neurodegeneration with brain iron accumulation
  - Pantothenate kinase-associated neurodegeneration (PKAN)
  - PLA2G6-associated neurodegeneration (PLAN)
  - Mitochondrial-membrane protein-associated neurodegeneration (MPAN)
  - Kufor-Rakeb syndrome

Organic acidemias

- Biotinidase deficiency/multiple carboxylase deficiency

Mitochondrial disease

- MELAS
- Kearns-Sayre syndrome

Lipid storage disorders

- Niemann Pick disease type C
- Fucosidosis

Glucose transport disorder

- GLUT1 deficiency

Neurotransmitter diseases

- 6-pyrvuvoyl-tetrahydropterin deficiency
- Dihydropteridine reductase deficiency
- Autosomal recessive guanosine-triphosphate cyclohydrolase 1 deficiency
- Autosomal dominant guanosine-triphosphate cyclohydrolase 1 deficiency

Sepiapterin reductase deficiency

Tyrosine hydroxylase deficiency

Table 5 Metabolic Disorders Causing Parkinsonism/Hypokinetic Rigid Syndrome[13, 36, 75]

Mineral metabolism and transport disorders

- Wilson disease
- Neurodegeneration with brain iron accumulation
  - Pantothenate kinase-associated neurodegeneration
  - PLA2G6-associated neurodegeneration
  - Mitochondrial-membrane protein-associated neurodegeneration
  - Beta-propeller protein-associated neurodegeneration
  - COASY protein-associated neurodegeneration
  - Kufor-Rakeb syndrome

Neurotransmitter disorders

- Tyrosine hydroxylase deficiency
- 6-pyrvuvoyl-tetrahydropterin deficiency
- Dihydropteridine reductase deficiency
- Autosomal recessive guanosine-triphosphate cyclohydrolase 1 deficiency
- Autosomal dominant guanosine-triphosphate cyclohydrolase 1 deficiency
- Aromatic L-amino acid decarboxylase deficiency
- Sepiapterin reductase deficiency

Lysosomal storage disorders

- GM1 gangliosidosis
- Niemann-Pick disease type C
- Gaucher disease

Neuronal ceroid lipofuscinosis

Mitochondrial diseases

Leigh syndrome

Biotin-thiamine-responsive basal ganglia disease

Primary coenzyme Q10 deficiency

Respiratory chain defects

Pyruvate carboxylase deficiency

Purine metabolism disorders

Lesch Nyhan disease

Glucose transport disorder

GLUT1 deficiency

Table 6 Neurodegeneration with Brain Iron Accumulation Forms[74]

Disease Name	**Associated Gene**
Pantothenate kinase-associated neurodegeneration (PKAN)	*PANK2*
PLA2G6-associated neurodegeneration (PLAN)	*PLA2G6*
Mitochondrial-membrane protein-associated neurodegeneration (MPAN)	*C19ORf12*
Beta-propeller protein-associated neurodegeneration (BPAN)	*WDR45*
COASY protein-associated neurodegeneration (CoPAN)	*COASY*
Fatty acid hydroxylase-associated neurodegeneration (FAHN)	*FA2H*
Kufor-Rakeb syndrome	*ATP13A2*
Woodhouse-Sakati syndrome	*DCAF17*
Aceruloplasminemia	*CP*
Neuroferritinopathy	*FTL*

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