Movement Disorders in Inherited Metabolic Diseases in Children

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Abstract

Movement disorders are one of the important neurological manifestations of inherited metabolic disorders. Important clues to the presence of an underlying inborn error of metabolism are early onset, presence of neuroregression or degeneration, parental consanguinity, sibling affection, paroxysmal events, waxing and waning course, skin or hair changes, absence of a perinatal insult or any structural cause, and presence of identifiable triggers. It is particularly important to recognize this class of movement disorders as several of them are eminently treatable and may often need disease-specific therapy besides symptomatic treatment. The current review focusses on the movement disorders associated with inherited metabolic defects in children, with emphasis on treatable disorders.

Keywords: Chorea, dystonias, genetic, tremor

Introduction

Movement disorders are important and one of the most common neurological manifestations of metabolic disorders. Both acquired and inherited disorders of metabolism contribute to the etiology of movement disorders. These metabolic disorders are often associated with other neurological manifestations such as alteration of consciousness, headache, vomiting, seizures, and raised intracranial pressure or organ-specific functional derangement that help the clinician suspect the underlying problem. It is particularly important to recognize movement disorders associated with metabolic defects as some of them are eminently treatable or at least, available treatment options help in the reduction of symptoms and improvement in the quality of life.[1] The current review focusses on the treatable movement disorders associated with inherited metabolic defects in children and their pragmatic management options.

Burden of movement disorders associated with IEMs

The expression of movement disorders in IEMs depends on the age of presentation, pattern of injury in the brain, and the course of illness. The exact burden of movement disorders may be underestimated in developing countries as the diagnostic facilities are not routinely available and a variety of central nervous system infections including viral encephalitis mimic the acute presentations. In addition, as the movement disorders may evolve or have an adult-onset, there is a chance that their true estimation may be missed. In a prospective study of 170 patients with confirmed or probable IEMs with neurological manifestations, nearly one-third (29%, $N = 50$) had one or more types of movement disorder.[2] The most common types were dystonia (54%) and myoclonus (28%) followed by stereotypies (14%).[2] Of these cases with movement abnormalities, 38% cases were contributed by disorders of complex molecules and neurotransmitters, followed by disorders of intermediate metabolism (34%) and disorders of energy metabolism (28%).[2] In a study of 24 children with IEMs and movement disorders, dystonia, myoclonus, and ataxia were most commonly seen and significantly impacted the health-related quality of life.[3] On the contrary, nearly one-tenth (9.3%) patients of any age and nearly one-fifth (22%) pediatric patients with a movement disorder have been estimated to suffer from a metabolic etiology.[4,5]

Clinical Presentation

Inborn errors of metabolism (IEMs) can be broadly classified as *small-molecule diseases* (such as amino-acidopathies, urea cycle disorders, organic acidemias, fatty acid oxidation disorders, purine and pyrimidine disorders, and disorders of metal metabolism) and *large-molecule diseases* (such as lysosomal storage disorders, peroxisomal disorders, and congenital disorders of glycosylation).[6,7] In turn, the small-molecule diseases can be classified into *intoxication* disorders (such as organic acidemias, urea cycle disorders, or

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aminoacidopathies) associated with accumulation of a toxic substrate or a byproduct or disorders of *energy deficiency* (such as fatty acid oxidation disorders, disorders of pyruvate metabolism and gluconeogenesis, and mitochondrial disorders).[8,9] With this backdrop, the typical presentations of movement abnormalities in IEMs can be divided into 3 forms:

- *Acute form:* Commonly seen as acute-onset chorea and/or dystonia with encephalopathy, seizures, vomiting, and precipitation with a triggering event such as minor febrile illness or infection. Common examples of IEMS in this category are urea cycle defects, organic acidemia, and aminoacidopathies
- *Intermittent or paroxysmal forms:* Often present with ataxia, chorea, dystonia with or without encephalopathy. Common examples of IEMs in this group are urea cycle defects, organic acidemias, and glucose transporter defects.
- *Chronic neurodegenerative disorders:* This group of disorders present predominantly with cognitive and neuropsychiatric impairment, seizures, vision and/or hearing impairment, retinopathy, and spasticity besides movement abnormalities such as ataxia or slowly progressive dystonia. Common examples include disorders of lysosomal storage, purine metabolism, mitochondrial energy pathways, and metal transport.

Table 1 presents the characteristic features of movement disorders in children that are associated with IEMs. Some of the common red-flag signs suggesting an underlying IEM in a movement disorder include an early age of onset of movement abnormality, additional neurological signs and symptoms or a multisystem involvement, progressive neuroregression or degeneration, parental consanguinity, sibling affection/unexplained deaths in the family, paroxysmal events, waxing and waning course, skin or hair changes, absence of a perinatal insult or any structural cause, and presence of identifiable triggers such as infection, trauma, fever, fasting, and high protein intake.[10,11] The list can be longer for an experienced clinician and, hence, one should always be on a lookout for underlying IEMs.

Types of movement disorders and causes

Movement disorders in children are broadly classified into hyperkinetic and hypokinetic disorders. The common hyperkinetic disorders include chorea, dystonia, tremors, myoclonus, tics, stereotypies, and athetosis, whereas common hypokinetic disorders include Parkinsonism and hypokinetic-rigid syndromes. A recent review summarized the most common symptoms in 207 inherited metabolic disorders as ataxia (73%), dystonia (47%), chorea/athetosis (24%), hypokinetic-rigid syndrome (17%), tremor (15%), and myoclonus (14%).[10] The description of each type of movement disorder is beyond the scope of this review and the reader is referred to specific reviews on the subject.[12,13] The broad categories of inborn errors of metabolism (IEMs) that cause movement disorders include organic acidemias, mitochondrial disorders, metal transport defects, neurotransmitter disorders, creatine deficiency disorders, and lipid storage abnormalities. Table 2 provides a list of common causes of various movement abnormalities associated with IEMs.

Treatable IEMs with movement disorders [Table 3]

Dopa responsive dystonia

Dopa-responsive dystonia (DRD) is a prototypical inherited metabolic movement disorder in children that is easy to recognize and is eminently treatable with the sustained use of L-dopa. The disorder should be suspected in any child who presents with subacute-onset, mild-to-severe severity, progressive, fluctuating and spreading dystonia from lower limbs to upper limbs, and spared cognition.[14] Gait impairment secondary to the onset of

Table 1: Characteristic features of movement disorders associated with IEMs[11,33]

An individual IEM may be associated with more than one type of movement disorder or may evolve over time
Specific movement disorder does not predict an IEM
Can be seen in acute, intermittent, and chronic progressive forms of IEM
All patient may not show a corresponding anatomical defect on MRI
Complex phenotype—movement disorder can be a dominating or a minor feature, and associated with additional neurological features such as spasticity, epilepsy, psychomotor retardation, contractures or other movement disorders resulting in a complex clinical picture
Recognition important for diagnosis and to plan appropriate management
Besides symptomatic therapy, underlying disease-specific therapy is often needed

Table 2: Common IEMS presenting as different types of movement disorders[34,35]

Newborn period
Branched-chain organic acidurias
Nonketotic hyperglycinemia
Neurotransmitter disorders, e.g., very severe forms of tyrosine hydroxylase deficiency
Infant
Glutaric aciduria type I
Leigh syndrome
Propionic acidemia, methylmalonic acidemia
Lesch-Nyhan disease
Adenosine deaminase deficiency
Neurodegeneration with brain iron accumulation
Disorders of creatine metabolism
Glucose transport disorder
Neurotransmitter diseases
Manganese transporter defects
Children and adolescents
Lysosomal storage disorders: GM1 and GM2 gangliosidosis, Niemann-Pick disease type C
Pantothenate-kinase-associated neurodegeneration
Wilson disease
Lesch-Nyhan disease
Neurodegeneration with brain iron accumulation
Disorders of creatine metabolism
Glucose transport disorder
Neurotransmitter diseases
Intermittent forms of urea cycle defects
Neuronal ceroid lipofuscinosis

Table 3: Treatable Metabolic Disorders Associated With Movement Disorders in Infancy or Childhood[11,12]

Disorder	Treatment of choice
Metal disorders	
Wilson disease	D-penicillamine, zinc, trientine, molybdenum
Hypermanganesemia	Disodium calcium edetate, iron
Neurotransmitter disorders	
GTP cyclohydrolase 1 deficiency	Levodopa, anticholinergic drugs, dopamine agonists
Tyrosine hydroxylase deficiency	Levodopa, anticholinergic drugs, dopamine agonists
PTP synthase deficiency	BH4, levodopa, 5-hydroxytryptophan, diet low in phenylalanine
Sepiapterinreductase deficiency	Levodopa, 5-hydroxytryptophan
Dihydropteridinereductase deficiency	Levodopa, 5-hydroxytryptophan, diet low in phenylalanine
Cerebral folate deficiency	Folinic acid
Energy Metabolism Disorders	
Coenzyme Q10 deficiency	Coenzyme Q10 supplementation
Glucose transporter type 1 deficiency	Ketogenic diet
Biotin thiamine responsive basal ganglia disease	Thiamine and high dose biotin
Pyruvate dehydrogenase complex deficiency	Ketogenic diet, thiamine
Creatine deficiency	Arginine restriction, creatine and ornithine supplements
Lysosomal Diseases	
Gaucher disease	Enzyme replacement therapy with glucocerebrosidase
gangliosidoses	Miglustat substrate reduction therapy
Disorders of Intermediary Metabolism	
Propionic aciduria	Diet low in branchedchain amino acids
Glutaric aciduria type I	Carnitine supplementation, Lysine restriction
CBS deficiency (classical homocystinuria)	Vitamin B6, methionine restriction, folic acid, hydroxycobalamin, vitamin C, betaine
Hyperphenylalaninaemia	Low-phenylalanine diet
Nonketotic hyperglycinemia	Sodium benzoate, dextromethorphan, ketamine
Biotinidase deficiency	Biotin
Others	
Cerebrotendinous xanthomatosis	Chenodeoxycholic acid
Ataxia with vitamin E deficiency	Vitamin E

dystonia in the lower limbs is often the first neurological symptom. A characteristic feature of DRD is the presence of diurnal fluctuation with worsening dystonia toward the end of the day. If it is untreated, the disorder may progress to a more severe Parkinsonian phenotype with unusually slow movement (bradykinesia), rigidity, tremors, and postural instability. The disorder is most commonly associated with pathogenic variations in the *GCH1* gene (GTP cyclohydrolase 1-deficient dopa-responsive dystonia); *TH* and *SPR* genes are also associated with this condition. Management includes 1–10 mg/kg of oral levodopa daily with slow dose titration and small increments. Motor problems start improving within a few days of starting levodopa therapy and treatment is generally lifelong.

Tyrosine hydroxylase (TH) deficiency in humans is an autosomal-recessive disorder associated with mutations in the tyrosine hydroxylase *TH* gene that presents with early-onset progressive L-dopa-responsive dystonia/encephalopathy. The disorder presents as 2 major types: Early-onset (within the first year of life, 2 months–5 years range) progressive hypokinetic-rigid dystonic syndrome, and the early-onset (0–3 months of age) complex encephalopathy associated with complicated perinatal history and followed by significant hypokinesia, bradykinesia, and hypotonia soon after birth and supplemented dystonia, jerky involuntary movements, bilateral ptosis, and oculogyric crises.[15,16] While the first type is exquisitely responsive to L-dopa in combination with a decarboxylase inhibitor and responds dramatically to low doses (3 to 10 mg/kg per day in three doses) with good cognitive and neurological outcomes,[17] the second type is often hypersensitive to these does and an extremely low dose initially (<0.5 mg/kg per day in 4–6 divided doses) or no treatment may have to be followed, with comparatively poorer motor and cognitive outcomes.[15]

Other disorders that present with similar phenotype include early-onset parkinsonism and primary deficiencies of CSF neurotransmitters such as tetrahydrobiopterin-related enzymes deficiencies and sepiapterin reductase deficiency. Secondary neurotransmitter deficiencies in the brain can also occur in association with pediatric neurodegenerative disorders such as spinocerebellar ataxia type 2, neuronal ceroid lipofuscinosis, Menkes disease, and hypoxic-ischemic encephalopathy.

Wilson's disease

Wilson disease is an autosomal recessive, inherited disorder of copper metabolism that presents between 3 and 50 years of age and may have a hepatic, neurological, psychiatric or a combination of these presentations at the onset. The neurological presentation commonly begins with gradually progressive dementia and/or behavioral problems, prominent movement disorders including coarse tremors (wing-beating type), loss of fine-motor control, choreoathetosis, and rigid dystonia, mark-like facies, abnormal giggle, gait impairment, micrographia, dysphagia, and dysarthria. The typical clinical picture, demonstration of Kayser–Fleischer corneal rings and bilateral basal ganglia involvement [Figure 1], especially in the putamen nucleus and head of the caudate nucleus in the setting of low serum ceruloplasmin and cupriuria typically clinches the diagnosis. Detection of biallelic pathogenic variations in *ATP7B* gene encoding a copper transporting P-type ATPase required for copper excretion into the bile confirms the diagnosis. Treatment with copper chelating agents (D-penicillamine 10–20 mg/kg/day given in 2–3 divided doses, or trientine 20 mg/kg/day in 2–3 divided doses) and inhibition of gut absorption by zinc (acetate or sulphate,

25 mg twice daily of elemental zinc in children < 5 years of age, 75–150 mg/day in 3 divided doses in children > 5 years of age) synergistically is the standard therapy. Initiation of therapy in presymptomatic patients may prevent the development of neurological, hepatic, and/or psychiatric manifestations. Treatment is lifelong and is supplemented with avoidance of copper-rich foods (liver, chocolate, mushrooms, shellfish, and nuts) and vitamin E. Common differential diagnosis of the movement disorders' phenotype with dementia include Huntington disease, Dentatorubro-pallidoluysian atrophy, Juvenile Parkinson disease, inherited dystonias, and neurodegenerative disorders.

Manganese transporter defect

Manganese transportopathies are a newly described group of inherited metabolic movement disorders that are potentially treatable. The homeostasis of the heavy metal "manganese" in the body is largely maintained by the efflux transporter SLC30A10 and the uptake transporter SLC39A14 (both together help in reducing Mn load in the body), and uptake facilitator SLC39A8.[18] Biallelic pathogenic variations in *SLC39A14* or *SLC30A10* transporter genes result in a spectrum of neurological disorders with prominent movement disorders:

- Hypermanganesaemia with dystonia 1 (SLC30A10 deficiency): Systemic hypermanganesemia in childhood results in polycythaemia, chronic liver disease, progressive dystonia, spasticity, high-stepping "cock-walk" gait, and spared cognition. Neurotoxicity manifests as Mn deposition in bilateral globuspallidus giving rise to T1-hyperintesen and T2-hypontense signal [Figure 2]. Late-onset forms may mimic adult Parkinsonism.
- Hypermanganesaemia with dystonia 2 (SLC39A14 deficiency): Neurological hypermanganesemia in younger children results in rapidly progressive dystonia, parkinsonism, dysarthria, bulbar dysfunction, and T1 hyperintensity in globuspallidi.

Mn blood level is a simple and cost-effective bedside screening test for Mn transportopathies. Management consists of lifelong regular chelation therapy with intravenous disodium calcium edetate as a 5 to 8 day course every 4 weeks (20 mg/kg/dose twice a day), iron supplementation (as iron competes with and displaces Mn at several binding and uptake sites in the body), regular monitoring of whole blood Mn levels, avoidance of foods high in Mn (cloves, saffron, nuts, dark chocolate, pumpkin, sesame, and sunflower seeds), and rehabilitation. Mn levels should be checked as a part of routine neurological work-up in individuals with developmental delay and/or movement disorder.

Glutaric aciduria type 1 (GA1)

GA type 1 is a common, autosomal recessive, inherited organic aciduria that results from pathogenic variations in the glutaryl-CoA dehydrogenase (*GCDH*) gene. The affected protein is a flavin adenine dinucleotide-dependent mitochondrial matrix protein involved in the metabolism of lysine, hydroxylysine, and tryptophan. Accumulation of these substrates in GCDH-deficient children causes an acute encephalopathic crises (pseudo encephalitic presentation) with bilateral striatal injury following a minor infection, intercurrent illness, or immunization. The commonest age of presentation for metabolic crisis is 3 months to 3 years. The characteristic neurological sequelae include generalized dystonia, axial hypotonia, and developmental delay. The disorder should be suspected in any infant with progressive macrocephaly or secondary generalized dystonia following an encephalitis-like illness and a characteristic neuroimaging showing bilateral basal ganglia hyperintensities, open opercula giving a bat-wing appearance, white matter abnormalities, and bilateral subdural hemorrhage [Figure 3].[19] The diagnosis can be easily corroborated at the bedside by detection of glutaric acid, 3-hydroxy glutaric acid, and glutarylcarnitine in body fluids by gas chromatography/mass spectrometry. Treatment consists of lysine restriction in the diet, carnitine supplementation, intense crisis management during catabolic states, and supportive treatment for dystonia and spasticity.[20] The manifestations are preventable if the condition is diagnosed

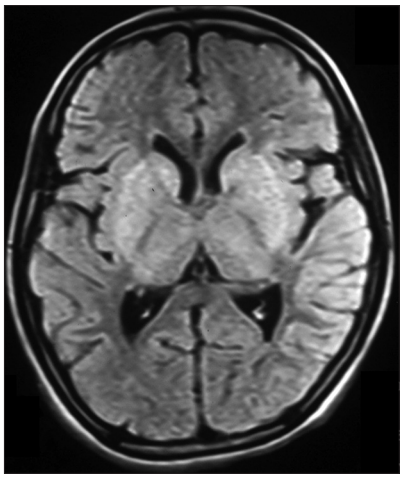

Figure 1: MRI brain T2-weighted section showing bilateral striatal changes in a child with KF rings and dementia suggestive of Wilson disease

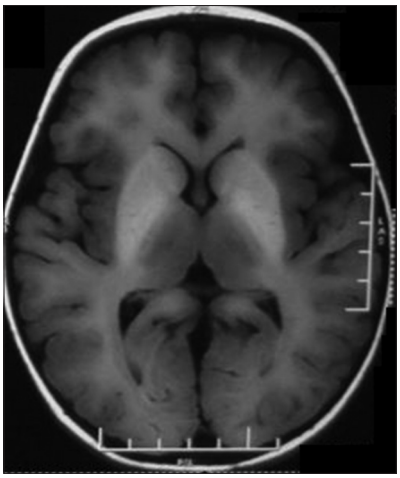

Figure 2: MRI brain T1-weighted axial scan showing hyperintensities in bilateral globuspallidi suggestive of mineral deposition

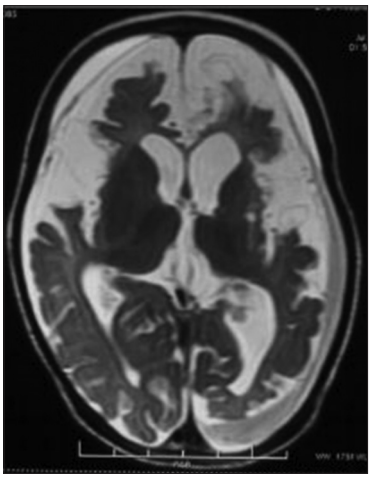

Figure 3: MRI brain T2-weighted axial scan showing open opercula giving a bat-wing appearance, white matter abnormalities, and bilateral subdural hemorrhage suggestive of glutaric aciduria 1

early before the striatal injury sets in; hence, newborn screening is recommended in all children.[21]

Biotin and thiamine responsive basal ganglia disease

Biotin-responsive basal ganglia disease, or thiamine metabolism dysfunction syndrome-2, or biotin-thiamine responsive basal ganglia disease is a rare, autosomal recessive, inherited defect of metabolism that results in recurrent acute/subacute encephalopathy, seizures, dysphagia, dysarthria, and external ophthalmoplegia following a minor febrile illness and may progress to severe rigidity, dystonia, spastic quadriparesis, and even death.[22] It commonly presents in children between 3 and 10 years of age, although infants may also be affected. The underlying genetic basis has been mapped to pathogenic variations in *SLC19A3* gene that encodes a second thiamine transporter hTHTR2. The disorder should be considered in any infant or child presenting with unexplained acute or recurrent encephalopathy, with or without a preceding febrile illness, and bilateral striatal swelling and signal change. Biochemical metabolic screening may only show lactic acidosis. Emergency treatment should include administration of high dose of biotin (5–10 mg/kg/day) and thiamine (300–900 mg orally; for younger patients, 20 mg/kg/day may be used). It is important to control fever in these patients as elevated temperature downregulates *SLC19A3* and may exacerbate the disease. Symptoms typically resolve within days. Long-term management includes lifelong biotin and thiamine, avoidance of triggers such as infection, trauma, and advice to parents to double the regular dose of thiamine during acute decompensation.[23] Common differential diagnoses include infectious and toxic encephalopathies, acquired demyelination syndromes, other neurometabolic disorders such as organic acidemias, Leigh's syndrome, urea cycle defects, and CNS vasculitis in acute states.[24]

Glucose transporter type 1 (GLUT-1) deficiency syndrome

GLUT1 deficiency disorder, also known as De Vivo Disease, is a rare, autosomal dominant, inherited metabolic disorder associated with pathogenic variations in the *SLC2A1* gene. This results in diminished levels of functional glucose transporter 1 protein, causing restriction of facilitated movement of glucose across the blood-brain barrier via this transporter. The classic presentation includes seizures with onset before 2 years of age, eye movement abnormalities (eye-rolling, fluttering, opsoclonus, oculogyric movements, and repetitive eye blinks), apneic episodes, developmental delay, acquired microcephaly, and complex paroxysmal movement disorders such as ataxia with/without spasticity, action limb dystonia, mild chorea, cerebellar action tremor, dyspraxia, or myoclonus.[25] The extended spectrum of GLUT1 deficiency disorders now also includes paroxysmal exercise-induced dyskinesia, paroxysmal choreoathetosis with spasticity, atypical childhood absence epilepsy, myoclonic astatic epilepsy, and alternating hemiplegia.[26] Diagnosis can be established at the bedside by a simple lumbar puncture after 4 h of fasting, which typically shows hypoglycorrhachia (<60 mg/dL, range 16.2–52 mg/dL) with normal blood glucose (sample drawn at the same time as CSF) and CSF/blood glucose ratio <0.4.[27] In a systematic review on cerebrospinal fluid analysis in the workup of GLUT1 deficiency syndrome, the authors concluded that if age-specific reference values were applied (CSF glucose 16.2 to 50.5 mg/dL, CSF to blood glucose ratios 0.19 to 0.59, CSF lactate 5.4 to 13.5 mg/dL), CSF glucose and lactate levels are adequate biomarkers in the diagnostic workup of GLUT1 deficiency syndrome.[27] The mainstay of therapy is ketogenic diet which provides ketone bodies as an alternative brain fuel via monocarboxylic transporter 1 in the brain. Adjunct modalities include use of alpha lipoic acid which facilitates glucose transportation in the body, and avoidance of drugs that inhibit the function of GLUT1 such as phenobarbital and caffeine, or drugs that interfere with ketogenic diet (valproic acid, topiramaate, zonisamide, and acetazolamide).[28] Epilepsy response is often dramatic and treatment is lifelong.

Ataxia with vitamin E deficiency (AVED)

AVED, also known as familial isolated vitamin E deficiency, is a rare, autosomal recessive, inherited multisystem metabolic disorder which, if untreated, manifests as progressive cerebellar ataxia, peripheral neuropathy, spasticity with absent deep tendon reflexes, posterior column involvement, dysarthria, retinitis pigmentosa, xanthomas, cardiomyopathy, and scoliosis. The disorder commonly manifests between 5 and 15 years of age. Clinically, when a child presents with Friedreich ataxia-like neurologic phenotype with significantly reduced vitamin E (α-tocopherol) levels in plasma and a normal lipoprotein and lipid profile, and absence of fat malabsorption, a diagnosis of AVED should be considered. Common differential diagnoses include Friedreich's ataxia, Refsum syndrome, and abetalipoproteinemia. Confirmation is by detection of biallelic *TTPA* pathogenic variations that result in deficient hepatic alpha-tocopherol transfer protein.[29] Treatment consists of lifelong oral vitamin E supplementation in high doses (800 mg to 1500 mg, or 40 mg/kg body weight in children) and maintaining the plasma vitamin E concentration

in a high-normal which may reverse ataxia and intellectual impairment.[30,31] Treatment of other presymptomatic children in the family prevents the development of symptoms. Hence, vitamin E levels should be checked in all patients with young onset progressive cerebellar ataxia.[32]

Conclusion

Movement disorders frequently occur in both inherited as well as acquired metabolic disorders. Children commonly present with acute, intermittent, and chronic movement abnormalities associated with inherited metabolic disorders. Clues to the presence of an underlying inborn error of metabolism include the presence of developmental delay or regression, encephalopathy, seizures, and/or tone abnormalities. Early recognition is important both for diagnostic and therapeutic purposes as several of these disorders are treatable.

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Conflicts of interest

There are no conflicts of interest.

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