Inborn Errors of Metabolism with Seizures

Defects of Glycine and Serine Metabolism and Cofactor-Related Disorders

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KEYWORDS

• Inborn errors of metabolism • Seizures • Epilepsy • Myoclonic epilepsy • Glycine • Serine • Pyridoxine

KEY POINTS

- Inborn errors of metabolism (IEM) are relatively uncommon causes for seizures in children; however, they should be considered in the differential diagnosis because several IEM are potentially treatable and seizures can be resolved when appropriate treatment is initiated.
- IEM should be particularly considered in neonatal seizures and in the context of refractory seizures. Other clues from clinical presentation, physical examination, laboratory tests, and brain imaging can increase the possibility of IEM.
- Several IEM can present with seizures, either as the main presenting finding or as a part of a more complex phenotype.
- IEM that cause seizures include cofactor-related disorders (eg, pyridoxine-dependent epilepsy, pyridoxal phosphate-responsive epilepsy, and cerebral folate deficiency), glycine and serine metabolism defects (eg, glycine encephalopathy and serine biosynthesis defects), and other disorders (eg, glucose transporter type 1 deficiency, adenylosuccinate lyase deficiency, and guanidinoacetate methyltransferase deficiency).
- When IEM are suspected, diagnosis and treatment should be simultaneous. Early treatment can prevent, or at least minimize, long-term sequelae.

INTRODUCTION

Seizures are frequently encountered in pediatric practice with an estimated prevalence of 1% in children.[1] The etiologic factors of seizures are many, including genetic diseases; structural brain abnormalities; or acquired conditions such as infections, tumors, and trauma. Alternatively, seizures can be secondary to provoking factors such

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as fever and hypoglycemia.[2] Inborn errors of metabolism (IEM) are relatively uncommon causes for seizures in children (**Box 1**). They still should be always considered in the differential diagnosis because several IEM that cause seizures are potentially treatable (**Box 2**) and seizures can be resolved when appropriate treatment is initiated. IEM often require specialized dietary and therapeutic interventions that should be initiated in a timely manner to prevent, or at least minimize, long-term sequelae. Even with

Box 1
Inborn errors of metabolism that can present with seizures

- Cofactor-related disorders
  - Pyridoxine-dependent epilepsy
  - Pyridoxal phosphate-responsive epilepsy
  - Cerebral folate deficiency
  - Biotinidase deficiency
  - Holocarboxylase synthetase deficiency
  - Molybdenum cofactor deficiency
  - Severe methylenetetrahydrofolate reductase (MTHFR) deficiency
- Amino acid disorders
  - Glycine encephalopathy
  - Serine biosynthesis defects
  - Sulfite oxidase deficiency
  - Urea cycle disorders
  - Phenylketonuria
  - Organic acidemias
  - Maple syrup urine disease
- Metal transport
  - Menkes disease
- Lysosomal disorders
  - Neuronal ceroid lipofuscinosis
  - Sialidosis type I and type II
  - Metachromatic leukodystrophy
  - GM1 gangliosidosis
  - GM2 gangliosidosis
  - Gaucher disease types 2 and 3
  - Niemann-Pick disease type C
- Disorders of energy metabolism
  - Mitochondrial disorders
  - Guanidinoacetate N-methyltransferase (GAMT) deficiency
  - Disorders of pyruvate metabolism
  - Glucose transporter type 1 (GLUT-1) deficiency
  - Fatty acid oxidation disorders[a]
  - Disorders of gluconeogenesis[a]
  - Glycogen storage disorders[a]
- Disorders of purine and pyrimidine nucleotides metabolism
  - Adenylosuccinate lyase (ADSL) deficiency
  - Lesch-Nyhan syndrome
  - Dihydropyrimidine dehydrogenase deficiency
- Peroxisomal disorders
  - Zellweger syndrome
  - X-linked adrenoleukodystrophy
- Congenital disorders of glycosylation

[a] In these disorders, seizures are secondary to hypoglycemia.

Box 2
Treatable inborn errors of metabolism that can present with seizures

- Phenylketonuria
- Urea cycle disorders
- Organic acidemias
- Maple syrup urine disease
- Pyridoxine-dependent epilepsy
- Pyridoxal phosphate-responsive epilepsy
- Cerebral folate deficiency
- Attenuated glycine encephalopathy
- Serine biosynthesis defects
- Biotinidase deficiency
- GLUT-1 deficiency
- GAMT deficiency
- Severe MTHFR deficiency
- Molybdenum cofactor deficiency type A

untreatable disorders, reaching a diagnosis is essential to direct plans of care and to provide counseling to the family in terms of prognosis and recurrence risk.[3–7]

IEM can cause seizures by different mechanisms, including accumulation of toxic metabolites, energy deficit, cofactor deficiency, abnormal neurotransmission, and brain malformations.[3,4] An example of toxic accumulation is hyperammonemia. Ammonia accumulates in several IEM, including urea cycle disorders and organic acidemias, and is known for its neurotoxicity. Elevated ammonia in the brain results in increased glutamine synthesis that, in turn, induces astrocyte swelling and brain edema.[8] Glucose is the principal source of energy in the brain and, therefore, disorders that cause hypoglycemia (eg, fatty acid oxidation defects) or interfere with glucose transport to the brain (eg, glucose transporter type 1 [GLUT-1] deficiency) can result in brain dysfunction and seizures. In mitochondrial disorders, seizures can also result from energy deficiency and impaired adenosine triphosphate (ATP) production, which is reqred to maintain transmembrane potential.[3] Examples of cofactor-related disorders are pyridoxine-dependent epilepsy and pyridoxal phosphate-responsive epilepsy; both are associated with pyridoxal phosphate deficiency. Pyridoxal phosphate, the active form of pyridoxine, is an important cofactor for many enzymatic reactions, including neurotransmitter metabolism.[9] An example of abnormal neurotransmission is glycine encephalopathy that is associated with elevation in glycine, which is an agonist of N-methyl D-aspartate (NMDA) glutamate receptors. Overstimulation of these excitatory receptors results in seizures. Finally, several IEM are associated with brain malformations that can predispose to seizures. For example, polymicrogyria, which is seen in infants with peroxisomal disorders, is a malformation of cortical development that disrupts the neuronal circuit and leads to epileptic seizures.[10] In fact, the pathophysiology of seizures in IEM is more complex, involving multiple, interrelated mechanisms. Delineating these mechanisms can result in more targeted therapeutic interventions in the future.

More than 200 different IEM are associated with seizures,[4] either as the main presenting finding or, more commonly, as part of a more complex neurologic and metabolic phenotype. Although this seems overwhelming, especially because most IEM

are rare, the key point is to maintain a high index of suspicion when working up a child presenting with seizures, particularly in unexplained neonatal seizures and in the context of seizures refractory to standard treatment (**Box 3**). Isolated epilepsy with no other systemic or neurologic features is less likely to be due to IEM.[5]

This article first discusses an approach to IEM that present with seizures, followed by a summary of IEM that cause seizures, including cofactor-related disorders, glycine and serine metabolism defects, and other disorders.

APPROACH TO INBORN ERRORS OF METABOLISM PRESENTING WITH SEIZURES

Approach to a newborn or a child presenting with seizures should include a detailed history and physical examination, followed by comprehensive evaluation, including laboratory work up, electroencephalogram (EEG), and brain imaging if indicated.

History and Physical Examination

Seizures associated with IEM can present at any age (**Table 1**). In general, it is uncommon to have seizures as an isolated presentation of IEM.[5] Usually, there is a variable combination of other manifestations involving different systems. In some disorders, the presentation is nonspecific, in the form of sepsis-like illness or hypoxic ischemic encephalopathy (HIE). In fact, IEM may be accompanied by HIE and this can be misleading and results in delayed diagnosis. Therefore, the possibility of IEM should be considered if a newborn with HIE develops refractory seizures.[6] While taking a history, it is imperative to pay attention to details such as diet history, growth, and development. Children with IEM can have a long-standing history of nonspecific, subtle symptoms, including failure to thrive, recurrent vomiting, aversion to a particular food, or developmental delay. Similarly, a history of unexplained episodes of encephalopathy is alarming. Family history is essential and might be overlooked, especially in acute settings such as emergency rooms and intensive care units. Red flags in family history include previous stillbirth, unexplained neonatal death, and consanguinity.

Different forms of seizures are seen in children with IEM (**Table 2**) with variable EEG abnormalities.[11] For example, early myoclonic epileptic encephalopathy with a burst suppression pattern on EEG is seen in disorders such as glycine encephalopathy, pyridoxine-dependent epilepsy, pyridoxal phosphate-responsive epilepsy,

Box 3
Clues raising the suspicion of inborn errors of metabolism in children presenting with seizures

- Refractory seizures
- Unexplained neonatal seizures
- Early myoclonic epileptic encephalopathy
- Unexplained hypoxic ischemic encephalopathy
- History of unexplained episodes of encephalopathy and/or developmental delay
- Seizures related to fasting, food intake, and/or stress
- Aversion or intolerance to particular food, particularly protein
- Recurrent episodes of vomiting and dehydration
- Parental consanguinity
- Positive family history of seizures
- History of unexplained neonatal death in the family

Table 1
Classification of inborn errors of metabolism associated with seizures based on age on onset

Age Group	Disorders
In utero	• Pyridoxine-dependent epilepsy • Pyridoxal phosphate-responsive epilepsy • Glycine encephalopathy • Congenital neuronal ceroid lipofuscinosis
Neonatal period	• Pyridoxine-dependent epilepsy[a] • Pyridoxal phosphate-responsive epilepsy • Holocarboxylase synthetase deficiency • Molybdenum cofactor deficiency • Sulfite oxidase deficiency • Glycine encephalopathy[b] • Urea cycle disorders[c] • Organic acidemias • Maple syrup urine disease[d] • Zellweger syndrome • Serine biosynthesis defects • Congenital neuronal ceroid lipofuscinosis • Disorders of pyruvate metabolism
Infancy	• Organic acidemias • Peroxisomal disorders • Biotinidase deficiency • Serine biosynthesis defects • Molybdenum cofactor deficiency (mild form) • Sulfite oxidase deficiency (mild form) • Phenylketonuria • Menkes disease • Infantile neuronal ceroid lipofuscinosis • Glucose transporter type 1 (GLUT-1) deficiency • Guanidinoacetate N-methyltransferase (GAMT) deficiency • Adenylosuccinate lyase (ADSL) deficiency type I (severe form) • Cerebral folate deficiency • Sialidosis type II • GM2 gangliosidosis (infantile form) • Congenital disorders of glycosylation • Disorders of pyruvate metabolism • GM1 gangliosidosis (infantile variants) • Gaucher disease type 2 • Methylenetetrahydrofolate reductase (MTHFR) deficiency
Early childhood	• Late infantile neuronal ceroid lipofuscinosis • Creatine deficiency syndromes • ADSL deficiency type II (mild-moderate forms) • Mitochondrial disorders • Cerebral folate deficiency • Lesch-Nyhan syndrome • Sialidosis type II • Congenital disorders of glycosylation • X-linked adrenoleukodystrophy • GM1 gangliosidosis (late infantile form) • Metachromatic leukodystrophy (late infantile form)

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Table 1
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Age Group	Disorders
Late childhood and adolescence	• Juvenile neuronal ceroid lipofuscinosis • X-linked adrenoleukodystrophy • Gaucher disease type 3 • Niemann-Pick disease type C • Mitochondrial disorders • GM2 gangliosidosis (juvenile form) • Metachromatic leukodystrophy (juvenile form)

[a] Atypical cases can present later (≤3 years).
[b] Atypical forms may have later age of onset.
[c] Later onset is possible. Onset is variable, from infancy to adulthood.
[d] Variable onset in intermediate and intermittent forms.

sulfite oxidase deficiency, and molybdenum cofactor deficiency. Hypsarrhythmia is seen in serine biosynthesis defects, Menkes disease, and untreated phenylketonuria. Epilepsia partialis continua is a common form of seizure in mitochondrial disorders, particularly in Alpers syndrome. In this disorder, an EEG pattern of rhythmic high-amplitude delta with superimposed spikes can help in diagnosis.[12]

On physical examination, findings that suggest IEM include microcephaly, dysmorphic or coarse facial features, abnormal eye examination, unusual odor, hair or skin abnormalities, and organomegaly (**Table 3**).[13]

Table 2
Seizure forms that can be seen in some of the inborn errors of metabolism

Seizure from	Disorders
Myoclonic seizures	• Pyridoxine-dependent epilepsy • Pyridoxal phosphate-responsive epilepsy • Glycine encephalopathy • Neuronal ceroid lipofuscinosis • Biotinidase deficiency • Sialidosis type I and type II • Mitochondrial disorders • Menkes disease (in childhood)
Infantile spasms	• Serine biosynthesis defects • Menkes disease (late infancy) • Mitochondrial disorders • Phenylketonuria • Biotinidase deficiency
Generalized tonic-clonic	• GLUT-1 deficiency • Creatine deficiency syndromes • Mitochondrial disorders • Biotinidase deficiency • Neuronal ceroid lipofuscinosis
Progressive myoclonic epilepsy	• Myoclonic epilepsy with ragged red fibers • Neuronal ceroid lipofuscinosis • Sialidosis type I and type II • Gaucher disease type 3
Epilepsia partialis continua	• Mitochondrial disorders (in particular, Alpers syndrome)
Partial motor seizures	• Zellweger Syndrome

Table 3
Clinical features associated with some metabolic epilepsies

Clinical Feature	Associated Disorders
Microcephaly	• GLUT-1 deficiency • ADSL deficiency • Serine biosynthesis defects • Phenylketonuria • Congenital disorders of glycosylation
Macrocephaly	• GM2 gangliosidosis
Dysmorphic features	• Zellweger syndrome
Coarse features	• GM1 gangliosidosis • Sialidosis type II
Cherry-red spot	• GM1 gangliosidosis • GM2 gangliosidosis • Sialidosis type I and type II • Metachromatic leukodystrophy
Lens dislocation	• Sulfite oxidase deficiency • Molybdenum cofactor deficiency
Supranuclear horizontal ophthalmoplegia	• Gaucher disease type 3
Retinitis pigmentosa	• Neuronal ceroid lipofuscinosis • Congenital disorders of glycosylation • Mitochondrial disorders • Peroxisomal disorders
Inverted nipples	• Congenital disorders of glycosylation
Hepato(spleno)megaly	• Gaucher disease type 2 and 3 • Sialidosis type II • GM1 gangliosidosis • Peroxisomal disorders • Congenital disorders of glycosylation
Dermatitis	• Biotinidase deficiency • Phenylketonuria
Sparse hair	• Biotinidase deficiency (alopecia) • Meknes disease (kinky hair)
Movement disorders	• Organic acidemias • GAMT deficiency • GLUT-1 deficiency
Stroke-like episodes	• Mitochondrial disorders (in particular, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes [MELAS] syndrome) • Congenital disorders of glycosylation
Bone abnormalities	• Sialidosis type II • Gaucher disease type 3 • GM1 gangliosidosis • Peroxisomal disorders (chondrodysplasia punctate)

Laboratory Workup

The aim is to rule out common causes first, such as hypoglycemia, electrolyte disturbances, and central nervous system infections.[14] Although some IEM require detailed testing before diagnosis is made, others can be diagnosed on a clinical basis; for example, by cessation of seizures following administration of pyridoxine in a newborn with pyridoxine-dependent epilepsy. Results of the initial workup can provide some

clues (eg, hypoglycemia in fatty acid oxidations defects, metabolic acidosis with organic acidemias, and hyperammonemia in urea cycle disorders). Plasma ammonia and lactate levels should be always considered in the initial workup. Hyperammonemia can be seen in several IEM, including urea cycle disorders and organic acidemias. Seizure by itself can result in significant elevation of lactate but this elevation is transient. Once the seizure has resolved, lactate is rapidly cleared. Therefore, persistently elevated lactate beyond 1 to 2 hours following a seizure should trigger looking for another cause.[15] In the context of IEM, mitochondrial disorders and organic acidemias are examples of disorders that can cause high lactate levels. When available, results of newborn screening can be helpful. Based on the clinical suspicion made from the presentation and initial workup, a second tier of biochemical testing should be ordered, including plasma amino acids, urine organic acids, and plasma acylcarnitine profile, among others. Several IEM can be diagnosed based on a specific pattern of abnormalities in these metabolites. Biochemical tests are of highest diagnostic yield when ordered during acute metabolic decompensations. When obtained, cerebrospinal fluid (CSF) studies should be paired with plasma samples to get informative CSF-to-plasma ratios of metabolites of interest (**Fig. 1**). In several situations, another layer of testing, such as enzyme activity, single gene testing, and functional assays in skin fibroblast samples, might be warranted. In situations in which diagnosis still remains unclear, more comprehensive evaluation with gene panels, global metabolomic profiling, or whole exome sequencing, should be considered.[16]

Neuroimaging

Although neuroimaging is usually nonspecific or normal in IEM presenting with seizures, it can be helpful in limiting diagnostic considerations.[17] For example, glycine encephalopathy and pyridoxine-dependent epilepsy can be associated with dysgenesis of the corpus callosum. Peroxisomal disorders, such as Zellweger syndrome, are associated with cortical gyral abnormalities. Different patterns of signal abnormalities are associated with different IEM.[17]

Magnetic resonance spectroscopy is another imaging modality that allows for noninvasive measurement of central nervous system metabolite levels that can show elevated lactate peak (pyruvate metabolism defects and mitochondrial disorders), elevated glycine peak (glycine encephalopathy), and diminished creatine peak (creatine deficiency syndromes).[18]

Management Considerations

Whenever there is suspicion for IEM, diagnostic workup and treatment should be simultaneous. Early treatment can prevent, or at least minimize, long-term sequelae. Relevant to management of seizures in the context of IEM, there are few principles worth mentioning here. The presentation of early myoclonic epileptic encephalopathy with burst suppression pattern on EEG should trigger a pyridoxine therapeutic trial with EEG monitoring.[7] Similarly, other vitamins and cofactors can be initiated based on the clinical scenario, including pyridoxal phosphate, folinic acid, and biotin.[5] Ketogenic diet can be helpful in children with pyruvate dehydrogenase deficiency and GLUT-1 deficiency. In these disorders, glucose cannot be used as source for energy and with ketogenic diet, energy can be obtained from ketone bodies. Ketogenic diet is also used in children with intractable epilepsy in general.[19] Finally, the underlying suspected diagnosis should be considered when choosing antiepileptic drugs. A good example is valproic acid, which should be avoided in individuals with mitochondrial disorders due to its toxic effects on the mitochondria.[20] Similarly, phenobarbitone inhibits glucose transport and should be avoided in children with GLUT-1 deficiency.[21]

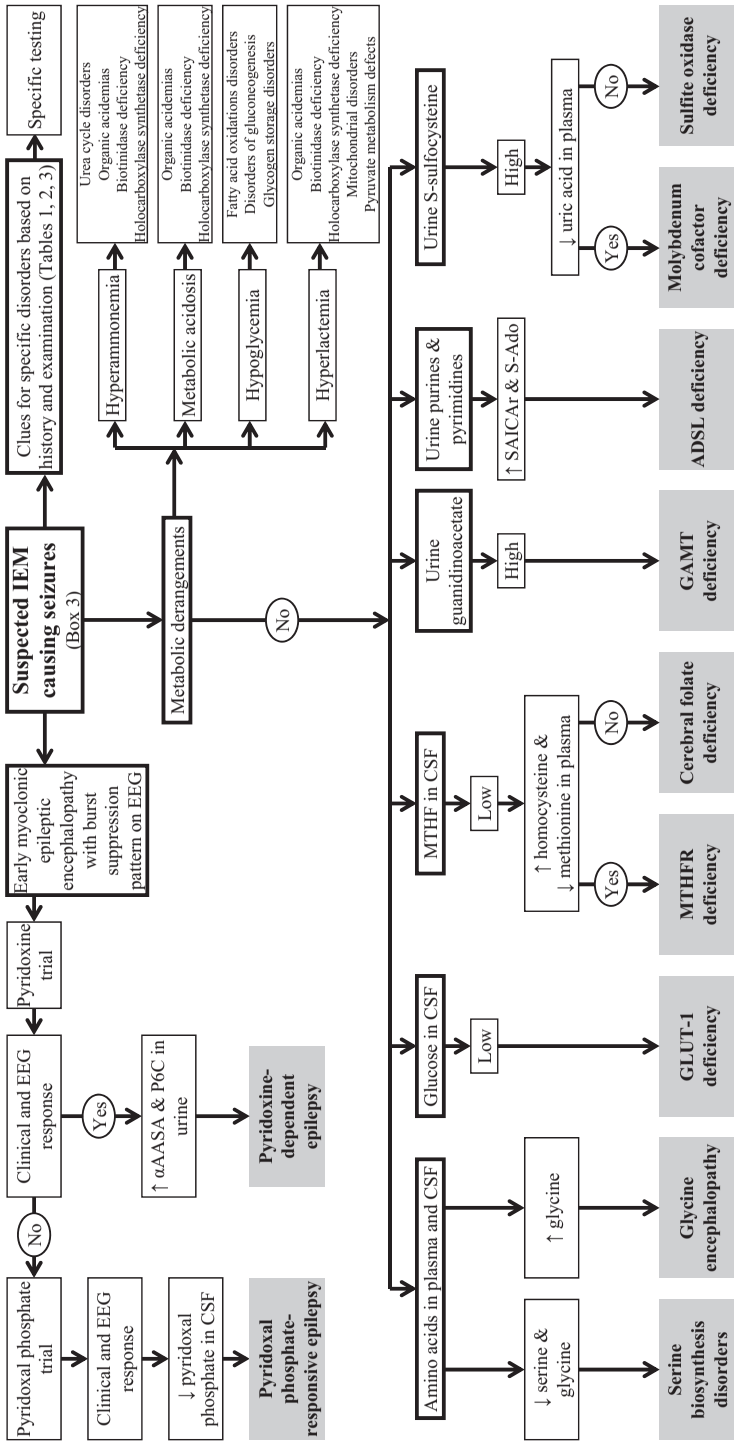

Fig. 1. Approach to IEM presenting with seizures. Decreased (*downward arrows*). Increased (*upward arrows*). ADSL, adenylosuccinate lyase; GAMT, guanidinoacetate N-methyltransferase; GLUT-1, glucose transporter type 1; MTHF, methyltetrahydrofolate; MTHFR, methylenetetrahydrofolate reductase; P6C, piperideine-6-carboxylate; S-Ado, succinyladenosine; SAICAr, succinylaminoimidazole carboxamide riboside; αAASA, α-aminoadipic semialdehyde.

All of these examples stress the importance of considering IEM in the differential diagnosis of seizures in children because they may influence the choice of antiepileptic drugs.

INBORN ERRORS OF METABOLISM THAT PRESENT WITH SEIZURES

The following IEM associated with seizures are discussed here: cofactor-related disorders (pyridoxine-dependent epilepsy, pyridoxal phosphate-responsive epilepsy, cerebral folate deficiency, methylenetetrahydrofolate reductase [MTHFR] deficiency, biotinidase deficiency, and molybdenum cofactor deficiency), glycine and serine metabolism defects (glycine encephalopathy and serine biosynthesis defects), and other disorders (GLUT-1 deficiency, adenylosuccinate lyase [ADSL] deficiency, and guanidinoacetate methyltransferase [GAMT] deficiency).

PYRIDOXINE-DEPENDENT EPILEPSY

Pyridoxine-dependent epilepsy is an autosomal recessive disorder with prevalence of 1 in 20,000 to 600,000.[9] It occurs due to deficiency of the enzyme antiquitin in the lysine metabolism pathway. Antiquitin functions as a piperideine-6-carboxylate (P6C) and α-aminoadipic semialdehyde (αAASA) dehydrogenase, therefore its deficiency results in the accumulation of αAASA and P6C. The latter binds and inactivates pyridoxal phosphate, which is a cofactor in neurotransmitters metabolism.[9]

Presentation

Pyridoxine-dependent epilepsy usually presents in the first few days of life with 70% of affected children presenting with neonatal seizures. Less commonly, atypical cases can present later, beyond the neonatal period but before the age of 3 years.[22] Seizures can be tonic, clonic, or myoclonic.[23] The hallmark is resistance to standard antiepileptic treatment. Associated clinical features include fetal distress at birth with a low Apgar score, respiratory distress, poor feeding, lethargy, or an encephalopathic picture with irritability and hypotonia.[23] Such presentation can be misinterpreted as HIE. Neuroimages are usually normal. However, some abnormalities may be seen, including hypoplasia or agenesis of the corpus callosum, enlarged ventricles, and mega cisterna magna.[17]

Diagnosis

Pyridoxine-dependent epilepsy should be suspected in a newborn presenting with early myoclonic epileptic encephalopathy with burst suppression pattern on EEG. EEG can evolve into hypsarrhythmia along with multifocal or focal discharges.[5] With such presentation, a trial with pyridoxine, which can be diagnostic and therapeutic, in addition biochemical evaluation is indicated.[7] The diagnosis is established clinically by showing a response to pyridoxine. Administering 100 mg of intravenous pyridoxine with EEG monitoring can result in cessation of the clinical seizures with corresponding EEG changes, generally over a period of several minutes. If a clinical response is not demonstrated, the dose can be repeated up to 500 mg. Oral pyridoxine (30 mg/kg/d) can result in cessation of the seizures within 3 to 5 days.[9] The treatment trial should be initiated in intensive care setting because cessation of seizures might be associated with transient isoelectric EEG along with coma and respiratory depression. Because of the possibility of delayed response to oral pyridoxine, treatment should be continued for at least 7 days[9] or, preferably, until the diagnosis of pyridoxine-dependent epilepsy is confirmed or excluded by biochemical and/or genetic testing.[9] Associated biochemical makers include elevated αAASA levels in

urine, plasma, and CSF. Pipecolic acid is another biomarker, but it is not specific. Urinary P6C is also increased.[24] Diagnosis can be confirmed by molecular testing of the *ALDH7A1* gene.

Treatment

Long-term treatment with pyridoxine (15–30 mg/kg/d) is required.[9] The daily dose should not exceed 500 mg because of the risk of peripheral neuropathy.[7]

PYRIDOXAL PHOSPHATE-RESPONSIVE EPILEPSY

Pyridoxal phosphate-responsive epilepsy is an autosomal recessive condition caused by deficiency of pyridox(am)ine phosphate oxidase, an enzyme that converts pyridoxine phosphate and pyridoxamine phosphate into pyridoxal phosphate, the active form of pyridoxine. It is rare condition with only 40 cases reported to date.[25]

Presentation

Presentation is similar to pyridoxine-dependent epilepsy with lethargy, hypotonia, and refractory seizures. Preterm delivery with fetal distress is seen in approximately 50% of affected neonates.[25] Seizures usually present in the first few days of life with more than 80% presenting in the first week.[25] Common forms of seizures are myoclonic, complex partial, and generalized motor.[26] Other forms can also be seen, including tonic-clonic, clonic, tonic, and spasms. EEG usually shows burst suppression.[26] Family history of infertility or fetal loss has been occasionally observed.[27]

Diagnosis

Diagnosis is established clinically by the demonstration of cessation of seizures with pyridoxal phosphate administration (50 mg orally) with corresponding EEG changes, usually within an hour. Some neonates respond to pyridoxine.[27,28] Pyridoxal phosphate in CSF is low. Because pyridoxal phosphate is cofactor for many enzymes, biochemical abnormalities reflecting decreased activity of these enzymes may be seen. These include elevations of glycine and threonine in CSF and plasma, elevation of 3-methoxytyrosine in CSF, and a decrease in the CSF concentrations of 5-hydroxyindolacetic acid and homovanillic acid.[5] Diagnosis can be confirmed by molecular testing of the *PNPO* gene.

Treatment

Seizures can usually be controlled with pyridoxal phosphate (30–50 mg/kg/d).[29] Due to case reports of deranged liver function and cirrhosis, liver function tests should be monitored in children treated with pyridoxal phosphate, especially when high doses are used.[27]

CEREBRAL FOLATE DEFICIENCY

Cerebral folate deficiency is associated with low levels of methyltetrahydrofolate (MTHF) in CSF due to defects in *FOLR1* gene that encodes the folate receptor alpha, a major folate transporter across the blood-brain barrier. This condition, which is inherited in an autosomal recessive manner, is rare and reported in a limited number of families. MTHF is a methyl donor involved in myelin formation and neurotransmitters synthesis.[30]

Presentation

Children with cerebral folate deficiency usually present in early childhood with developmental regression, seizures, movement disorders, and ataxia. Seizures are in the form of myoclonic, tonic, atonic, and generalized tonic-clonic, associated with slow background and multifocal epileptiform activity on EEG.[30] Neuroimaging can show hypomyelination and cerebral and cerebellar atrophy.[31]

Diagnosis

There are very low levels of MTHF in CSF with normal plasma folate levels. Diagnosis can be confirmed by molecular testing of the *FOLR1* gene.

Treatment

This condition should be treated with folinic acid (1–5 mg/kg/d), which can restore CSF folate concentrations and improve clinical symptoms.[30,31]

METHYLENETETRAHYDROFOLATE REDUCTASE DEFICIENCY

Severe MTHFR deficiency is a rare, autosomal recessive disorder with an estimated incidence of 1 in 200,000.[32] MTHFR catalyzes the reduction of methylenetetrahydrofolate to MTHF. Deficiency in MTHF, which is a methyl donor in the conversion of homocysteine to methionine, results in elevated total plasma homocysteine and low methionine. Low methionine in turn results in deficiency of S-adenosylmethionine, a methyl donor for several methylation reactions.

Presentation

Severe MTHFR deficiency presents in infancy with hypotonia, lethargy, feeding difficulties, and apnea. Myoclonic, tonic-clonic seizures, and infantile spasms can be seen in the first year of life. At a later age, seizures can evolve into Lennox-Gastaut syndrome.[33] If not identified, the disorder can progress into developmental regression, coma, and death. Later onset forms are seen in individuals with higher residual enzyme activity with features, including psychiatric disorders and gait disturbances.[34] Features on neuroimaging include brain atrophy, delayed myelination, and dilated ventricles.[34]

Diagnosis

Diagnosis can be suspected based on elevated total plasma homocysteine with low methionine. CSF MTHF is significantly low.[33] Blood folate level can be also decreased. Diagnosis can confirmed by measuring enzyme activity or by molecular testing of *MTHFR* gene.

Treatment

The mainstay of treatment is oral betaine (100–250 mg/kg/d), which is a substrate for betaine methyltransferase, an enzyme that converts homocysteine to methionine, therefore, betaine decreases homocysteine and increases methionine. Early treatment with betaine can improve the outcome.[35]

BIOTINIDASE DEFICIENCY AND HOLOCARBOXYLASE SYNTHETASE DEFICIENCY

Biotin is an essential cofactor for several carboxylase enzymes. Holocarboxylase synthetase is an enzyme that attaches biotin to the carboxylase enzymes, thereby activating them. Biotin is recycled through biotinidase enzyme. Holocarboxylase

synthetase and biotinidase deficiencies are autosomal recessive conditions associated with multiple carboxylase enzymes deficiencies. Estimated incidence of biotinidase deficiency is 1 in 60,000,[36] whereas holocarboxylase synthetase deficiency is rarer.

Presentation

Both conditions have overlapping symptoms. Holocarboxylase synthetase deficiency usually present early, before the age of 3 months, with metabolic decompensation in the form of lethargy, hypotonia, vomiting, and hypothermia. Tachypnea, due to acidosis and hyperammonemia is common. Biotinidase deficiency is characterized by more neurologic symptoms, including seizures, hypotonia, ataxia, developmental delay, and hearing and vision problems. The age of onset is variable, depending on the degree of enzyme activity. The average age of onset is 3.5 months in infants with profound deficiency (residual activity <10%).[37] In children with biotinidase deficiency, different forms of seizures can be seen, including myoclonic, generalized tonic-clonic seizures, and infantile spasms. EEG findings are also variable and can vary from normal to sharp, multifocal spikes, and hypsarrhythmia.[38] Both conditions are characterized by skin rash and alopecia, which can be important distinguishing features, although not always present.

Diagnosis

Suggestive findings include metabolic acidosis, elevated lactate, and hyperammonemia. Urine organic acids show a pattern consistent with multiple carboxylase enzymes deficiency with presence of 3-hydroxyisovalerate, 3-methylcrotonylglycine, methylcitrate, hydroxypropionate, and propionylglycine. Diagnosis of biotinidase deficiency can be confirmed by measuring enzyme activity or molecular testing of the *BTD* gene. Diagnosis of holocarboxylase synthetase deficiency can be confirmed by molecular testing of the *HLCS* gene.

Treatment

Both conditions respond to oral biotin with excellent results. In biotinidase deficiency, the dose is 5 to 10 mg/d.[36] Higher doses are usually required for holocarboxylase synthetase deficiency.[39]

MOLYBDENUM COFACTOR DEFICIENCY AND SULFITE OXIDASE DEFICIENCY

Molybdenum is a cofactor for 3 enzymes: xanthine oxidase, aldehyde oxidase, and sulfite oxidase. Deficiency of either molybdenum cofactor or sulfite oxidase results in accumulation of toxic sulfites. Both conditions are inherited in an autosomal recessive manner. More than 100 cases have been reported, although the conditions might be underdiagnosed.

Presentation

Both disorders are clinically indistinguishable. Affected newborns present shortly after birth with feeding difficulties, hypotonia, exaggerated startle response, and seizures.[40,41] Later on, significant developmental delay and spasticity evolve. Lens dislocation is seen in both disorders. Seizures are intractable with burst suppression pattern.[5] Findings on neuroimaging include extensive edema with evolution to encephalomalacia with cystic changes and cortical atrophy in older children.[17] Clinical and radiological presentation can mimic HIE.[17,42]

Diagnosis

Both conditions are associated with increased plasma and urinary *S*-sulfocysteine levels, and reduced plasma total homocysteine and cystine levels. Molybdenum cofactor deficiency can be differentiated by reduced serum uric acid levels and increased urinary xanthine and hypoxanthine levels because of a secondary deficiency in xanthine oxidase.[40] Diagnosis can be confirmed by molecular testing (*MOCS1*, *MOCS2*, and *GPHN* for molybdenum cofactor deficiency and *SUOX* for sulfite oxidase deficiency).

Treatment

Newborns with molybdenum cofactor deficiency type A (caused by defects in the *MOCS1* gene) can be treated with intravenous cyclic pyranopterin monophosphate, a biosynthetic precursor of the cofactor.[43] To be effective, treatment should be started very early before permanent neurologic damage ensues. There is no treatment for other forms of molybdenum cofactor deficiency. Similarly, the outcome is poor in isolated sulfite oxide deficiency with no effective treatment, although dietary therapy with low cysteine and methionine was reported to be beneficial in some children with the mild, late-onset form of the disease.[44]

GLYCINE ENCEPHALOPATHY

Glycine encephalopathy (nonketotic hyperglycinemia), caused by defects in glycine cleavage enzyme, is an autosomal recessive condition with an estimated incidence of 1 to 60,000.[45] Defects in glycine cleavage enzyme result in accumulation of glycine in body fluids, including the brain. Glycine is an inhibitory neurotransmitter in the brainstem and spinal cord, which can contribute to the apnea and decreased tone observed in affected neonates. Also, glycine is an agonist of NMDA glutamate receptors. Overstimulation of these excitatory receptors results in seizures.[46]

Presentation

Glycine encephalopathy can present in 4 overlapping phenotypes based on age of onset and developmental outcomes. Severe neonatal glycine encephalopathy has an onset during the first week of life and poor long-term outcome as measured by an IQ of less than 20. Attenuated neonatal glycine encephalopathy has an onset during the first week of life but a better long-term outcome (IQ >20). Severe infantile glycine encephalopathy has an onset after the neonatal period and a poor long-term outcome (IQ <20), whereas attenuated infantile glycine encephalopathy has an onset after the neonatal period and a better long-term outcome (IQ >20).[47] Most children (86%) present in the neonatal period, and most of them (92%) have poor outcomes. Presenting symptoms include hypotonia, which is seen in all affected children, seizures, coma, irregular breathing leading to apnea, and hiccups. Children with attenuated forms can have behavioral problems, hyperactivity, and movement disorders. Seizure forms in affected children include myoclonic and generalized seizures. These are often difficult to treat. Findings on EEG include early burst suppression with later progression to hypsarrhythmia or multifocal discharges by the end of first month.[5] Neuroimaging can show hypoplasia or agenesis of the corpus callosum, delayed myelination, brain atrophy, and enlarged ventricles.[17]

Diagnosis

Glycine encephalopathy is associated with elevated glycine in body fluids and this can be documented by measuring plasma and CSF glycine. Plasma levels can be normal

though.[45] A CSF-to-plasma glycine ratio of greater than 0.08 is seen in neonatal forms. Ratios less than or equal to 0.08 may predict attenuated outcomes.[48] Plasma and CSF samples should be drawn simultaneously for accurate calculation of the ratio. Diagnosis can be confirmed by molecular testing of the *GLDC*, *AMT*, and *GCSH* genes, which encode glycine cleavage enzyme subunits.[45]

Treatment

Outcomes are poor in children with severe glycine encephalopathy, even with early initiation of treatment.[49] On the other hand, in children with attenuated forms, early treatment can result in improved outcomes.[50] Treatment options include sodium benzoate (250–750 mg/kg/d), which can reduce plasma glycine concentrations, or an NMDA receptor antagonist, such as dextromethorphan, ketamine, or felbamate, which can result in better seizure control.[45]

SERINE BIOSYNTHESIS DEFECTS

Besides protein synthesis, L-serine is a precursor for several compounds, including phosphatidylserine, sphingomyelin, glycine, cysteine, and D-serine.[51] L-serine is synthesized through actions of phosphoglycerate dehydrogenase (PGDH), phosphoserine aminotransferase, and phosphoserine phosphatase. Impairment of any of these enzymes results in serine deficiency that has a broad phenotypic spectrum. At the severe end, infants present with Neu-Laxova syndrome, a lethal multiple malformations syndrome. Less severe forms present in infancy and childhood, mainly with neurologic manifestations, reflecting the important role for serine in neuronal function and development.[52] Serine biosynthesis defects are rare, with PGDH being the most commonly defective enzyme. All the forms are inherited in autosomal recessive manner.

Presentation

Children with infantile serine biosynthesis defects present with intrauterine growth retardation and microcephaly, which is congenital or early in onset. Early onset of seizures in the first few months of life is typical. Infantile spasms are common. Reported other forms of seizures include myoclonic, tonic-clonic, tonic, and atonic.[53] EEG can show hypsarrhythmia, multifocal seizure activity, and Lennox-Gastaut syndrome. Affected children have severe developmental delay. Other reported features include hypertonia, feeding difficulties, congenital cataracts, and hypogonadism.[54] Besides infantile presentation, a milder phenotype is described less frequently in older children with absence and tonic clonic seizures.[55] Neuroimaging can show hypomyelination or delayed myelination, brain atrophy, and ventriculomegaly.

Diagnosis

Serine and, to a lesser extent, glycine are low in CSF and plasma.[53] Plasma serine and glycine values can be normal if samples are drawn in nonfasting state. Therefore, CSF amino acid analysis is the preferred diagnostic test in children with suspected serine biosynthesis defects. Diagnosis can be confirmed by measuring enzyme activity in skin fibroblast or by molecular testing of the *PHGDH*, *PSAT1*, and *PSPH* genes.

Treatment

In the infantile PGDH deficiency, the use of L-serine (200–700 mg/kg/d) and glycine (200–300 mg/kg/d) had beneficial effects on the seizures, irritability, spasticity, and white matter volume and myelination.[54,56] However, there was little improvement of psychomotor development.[55,57] In childhood forms, a lower dose of L-serine

(100–150 mg/kg/d) can be used with improved control of seizures, behavior, and school performance.[55]

GLUCOSE TRANSPORTER TYPE 1 DEFICIENCY

GLUT-1 transports glucose to the brain through blood–brain barrier. Defects in this transporter impair brain energy supply because glucose is the major source of energy in the brain. This condition is inherited in an autosomal dominant pattern in most affected individuals, although recessive inheritance has been described. Incidence is estimated at 1 in 100,000.[58]

Presentation

The classic presentation is in the form of infantile refractory seizures along with developmental delay and movements disorders.[59] Acquired microcephaly can develop. The onset of the seizures is usually before 2 years of age.[59] Different forms of seizures reported include generalized tonic-clonic, absence, complex partial, myoclonic, drop attacks, tonic, simple partial seizures, and infantile spasms. Most affected individuals have mixed types.[60] EEG obtained while fasting can show slowing of background activity with multifocal or generalized high-amplitude irregular spikes and spike-and-waves. Significant difference may be seen between preprandial and postprandial EEG with a decrease in epileptic discharges following a carbohydrate meal.[61] Similarly, clinical symptoms can worse with fasting.

Diagnosis

GLUT-1 deficiency is associated with low CSF glucose, which is typically less than 2.5 mg/dL.[4] The CSF-to-blood glucose ratio is considered superior to the absolute glucose level in the CSF.[62] The normal ratio is greater than 0.6, whereas in GLUT-1 deficiency it is typically less than 0.5 (in the absence of CSF infection or hypoglycemia).[62] Ideally, CSF samples should be obtained while fasting. The diagnosis can be confirmed by molecular testing of the *SLC2A1* gene.

Management

Ketogenic diet is the first-line treatment in GLUT-1 deficiency.[63] Ketogenic diet provides an alternative source of energy to the brain in the form of ketone bodies. Initiation of a ketogenic diet leads to seizure control in most affected individuals with less prominent effect on development.[63]

ADENYLOSUCCINATE LYASE DEFICIENCY

ADSL enzyme catalyzes 2 steps in purine nucleotide synthesis. ADSL deficiency is an autosomal recessive disorder that results in the accumulation of succinylpurines that are believed to have toxic effects, particularly on the nervous system. The incidence of ADSL deficiency is not known. To date, fewer than 100 individuals have been reported.

Presentation

ADSL deficiency is associated with a broad clinical spectrum with 3 forms being described. Most affected individuals have type I (severe form), which is characterized by early-onset severe psychomotor retardation, hypotonia, feeding difficulty, growth failure, microcephaly, seizures, and autistic features. Children with the milder form (type II) can present with mild to moderate psychomotor retardation, hypotonia, ataxia, and autistic features.[64] A neonatal fatal form has been reported with intrauterine growth retardation, encephalopathy, severe hypotonia, respiratory

failure, intractable seizures, and early mortality.[65] In type I, refractory seizures start early in the first few months of life and are in the form of partial, simple partial motor, myoclonic, tonic seizures, and infantile spasms.[64] Neuroimaging often shows brain atrophy, hypomyelination, and atrophy of the cerebellum, particularly of the vermis.

Diagnosis

ADSL deficiency is characterized by the presence of succinylaminoimidazole carboxamide riboside and succinyladenosine in urine, CSF, and (to a minor extent) plasma. The diagnosis can be confirmed by measuring the ADSL enzyme activity in liver, kidney, blood lymphocytes, or cultured fibroblasts; or molecular sequencing of the *ADSL* gene.

Treatment

Currently, there is no effective treatment available. Seizures in ADSL deficiency are usually refractory and more than 1 antiepileptic agent is required.[64]

GUANIDINOACETATE METHYLTRANSFERASE DEFICIENCY

GAMT mediates the methylation of guanidinoacetate (GAA) that yields creatine. Defects in GAMT result in the deficiency of creatine, which is essential for brain function because of its role in energy storage and transmission, and as neurotransmitter or modulator. GAMT deficiency is an autosomal recessive condition with an estimated prevalence 1 in 500,000.[66]

Presentation

GAMT deficiency is characterized by developmental delay and intellectual disability. Speech and language development tends to be more severely affected. Other features include movement disorders, autism, hyperactivity, and other behavioral problems.[67,68] Onset is between early infancy to the third year of life.[68] Seizures are seen in more than two-thirds of children[67] and reported forms include myoclonic, generalized tonic-clonic, partial complex seizures, and drop attacks.[68]

Diagnosis

GAA is elevated in body fluids and magnetic resonance spectroscopy shows absent or severely reduced creatine peak. Diagnosis can be confirmed by molecular testing of the *GAMT* gene.

Treatment

Creatine deficiency is corrected with creatine-monohydrate (400–800 mg/kg/d) supplementation and GAA accumulation is reduced through L-ornithine supplementation (400–800 mg/kg/d) and arginine restriction, which is achieved through a protein-restricted diet together with arginine-free essential amino acid supplements.[67]

SUMMARY

IEM are relatively uncommon causes for seizures in children; however, they should be considered in the differential diagnosis because several IEM are potentially treatable and seizures can be resolved when appropriate treatment is initiated. Clues from clinical presentation, physical examination, laboratory tests, and neuroimaging can raise the possibility of IEM. Several IEM can present with seizures either as the main presenting finding or as a part of a more complex phenotype. When IEM are suspected,

diagnosis and treatment should be simultaneous because early treatment can prevent, or at least minimize, long-term sequelae.

REFERENCES

1. Russ SA, Larson K, Halfon N. A national profile of childhood epilepsy and seizure disorder. Pediatrics 2012;129:256–64.
2. Shorvon SD. The etiologic classification of epilepsy. Epilepsia 2011;52:1052–7.
3. Wolf NI, Bast T, Surtees R. Epilepsy in inborn errors of metabolism. Epileptic Disord 2005;7:67–81.
4. Rahman S, Footitt EJ, Varadkar S, et al. Inborn errors of metabolism causing epilepsy. Dev Med Child Neurol 2013;55:23–36.
5. Wolf NI, García-Cazorla A, Hoffmann GF. Epilepsy and inborn errors of metabolism in children. J Inherit Metab Dis 2009;32:609–17.
6. Campistol J, Plecko B. Treatable newborn and infant seizures due to inborn errors of metabolism. Epileptic Disord 2015;17:229–42.
7. Dulac O, Plecko B, Gataullina S, et al. Occasional seizures, epilepsy, and inborn errors of metabolism. Lancet Neurol 2014;13:727–39.
8. Brusilow SW, Koehler RC, Traystman RJ, et al. Astrocyte glutamine synthetase: Importance in hyperammonemic syndromes and potential target for therapy. Neurotherapeutics 2010;7:452–70.
9. Stockler S, Plecko B, Gospe S, et al. Pyridoxine dependent epilepsy and antiquitin deficiency: clinical and molecular characteristics and recommendations for diagnosis, treatment and follow-up. Mol Genet Metab 2011;104:48–60.
10. Leventer RJ, Guerrini R, Dobyns WB. Malformations of cortical development and epilepsy. Dialogues Clin Neurosci 2008;10:47–62.
11. Pearl PL, Bennett HD, Khademian Z. Seizures and metabolic disease. Curr Neurol Neurosci Rep 2005;5:127–33.
12. Wolf NI, Rahman S, Schmitt B, et al. Status epilepticus in children with Alpers disease caused by POLG1 mutations: EEG and MRI features. Epilepsia 2009;50:1596–607.
13. Enns GM, Packman S. Diagnosing inborn errors of metabolism in the newborn: clinical features. Neoreviews 2001;2:183–91.
14. Pearl PL. New treatment paradigms in neonatal seizures. J Inherit Metab Dis 2009;32:204–13.
15. Andersen LW, Mackenhauer J, Roberts JC, et al. Etiology and therapeutic approach to elevated lactate. Mayo Clin Proc 2013;88:1127–40.
16. Helbig KL, Farwell Hagman KD, Shinde DN, et al. Diagnostic exome sequencing provides a molecular diagnosis for a significant proportion of patients with epilepsy. Genet Med 2016;18:898–905.
17. Poretti A, Blaser SI, Lequin MH, et al. Neonatal neuroimaging findings in inborn errors of metabolism. J Magn Reson Imaging 2013;37:294–312.
18. Rincon SP, Blitstein MB, Caruso PA, et al. The use of magnetic resonance spectroscopy in the evaluation of pediatric patients with seizures. Pediatr Neurol 2016;58:57–66.
19. Barañano KW, Hartman AL. The ketogenic diet: uses in epilepsy and other neurologic illnesses. Curr Treat Options Neurol 2008;10:410–9.
20. Finsterer J, Zarrouk Mahjoub S. Mitochondrial toxicity of antiepileptic drugs and their tolerability in mitochondrial disorders. Expert Opin Drug Metab Toxicol 2012;8:71–9.

21. Gordon N, Newton RW. Glucose transporter type 1 (GLUT-1) deficiency. Brain Dev 2003;25:477–80.
22. Basura GJ, Hagland SP, Wiltse AM, et al. Clinical features and the management of pyridoxine-dependent and pyridoxine-responsive seizures: review of 63 North American cases submitted to a patient registry. Eur J Pediatr 2009;168:697–704.
23. Mills PB, Footitt EJ, Mills KA, et al. Genotypic and phenotypic spectrum of pyridoxine-dependent epilepsy (ALDH7A1 deficiency). Brain 2010;133:2148–59.
24. Struys EA, Bok LA, Emal D, et al. The measurement of urinary Δ^1-piperideine-6-carboxylate, the alter ego of α-aminoadipic semialdehyde, in Antiquitin deficiency. J Inherit Metab Dis 2012;35:909–16.
25. Guerin A, Aziz AS, Mutch C, et al. Pyridox(am)ine-5-Phosphate oxidase deficiency treatable cause of neonatal epileptic encephalopathy with burst suppression: case report and review of the literature. J Child Neurol 2015;30:1218–25.
26. Veerapandiyan A, Winchester S, Gallentine W, et al. Electroencephalographic and seizure manifestations of pyridoxal 5′-phosphate-dependent epilepsy. Epilepsy Behav 2011;20:494–501.
27. Mills PB, Camuzeaux SS, Footitt EJ, et al. Epilepsy due to PNPO mutations: genotype, environment and treatment affect presentation and outcome. Brain 2014;137:1350–60.
28. Plecko B, Paul K, Mills P, et al. Pyridoxine responsiveness in novel mutations of the PNPO gene. Neurology 2014;82:1425–33.
29. Hoffmann GF, Schmitt B, Windfuhr M, et al. Pyridoxal 5′phosphate may be curative in early onset epileptic encephalopathy. J Inherit Metab Dis 2007;30:96–9.
30. Steinfeld R, Grapp M, Kraetzner R, et al. Folate receptor alpha defect causes cerebral folate transport deficiency: a treatable neurodegenerative disorder associated with disturbed myelin metabolism. Am J Hum Genet 2009;85:354–63.
31. Grapp M, Just IA, Linnankivi T, et al. Molecular characterization of folate receptor 1 mutations delineates cerebral folate transport deficiency. Brain 2012;135:2022–31.
32. Tortorelli S, Turgeon CT, Lim JS, et al. Two-tier approach to the newborn screening of methylenetetrahydrofolate reductase deficiency and other remethylation disorders with tandem mass spectrometry. J Pediatr 2010;157:271–5.
33. Prasad AN, Rupar CA, Prasad C. Methylenetetrahydrofolate reductase (MTHFR) deficiency and infantile epilepsy. Brain Dev 2011;33:758–69.
34. Huemer M, Mulder-Bleile R, Burda P, et al. Clinical pattern, mutations and in vitro residual activity in 33 patients with severe 5, 10 methylenetetrahydrofolate reductase (MTHFR) deficiency. J Inherit Metab Dis 2016;39:115–24.
35. Huemer M, Diodato D, Schwahn B, et al. Guidelines for diagnosis and management of the cobalamin-related remethylation disorders cblC, cblD, cblE, cblF, cblG, cblJ and MTHFR deficiency. J Inherit Metab Dis 2017;40:21–48.
36. Wolf B. Biotinidase deficiency: if you have to have an inherited metabolic disease, this is the one to have. Genet Med 2012;14:565–75.
37. Wolf B. Biotinidase deficiency. In: Pagon RA, Adam MP, Ardinger HH, et al, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington; 2000. p. 1993–2017. Updated June 9, 2016.
38. Wolf B. The neurology of biotinidase deficiency. Mol Genet Metab 2011;104:27–34.
39. Baumgartner MR, Suormala T. Biotin responsive disorders. In: Saudubray JM, Baumgartner MR, Walter J, editors. Inborn metabolic diseases. 6th edition. Berlin: Springer; 2016. p. 375–83.

40. Tan WH, Eichler FS, Hoda S, et al. Isolated sulfite oxidase deficiency: a case report with a novel mutation and review of the literature. Pediatrics 2005;116:757–66.
41. Reiss J, Hahnewald R. Molybdenum cofactor deficiency: mutations in GPHN, MOCS1, and MOCS2. Hum Mutat 2011;32:10–8.
42. Topcu M, Coskun T, Haliloglu G, et al. Molybdenum cofactor deficiency: report of three cases presenting as hypoxic–ischemic encephalopathy. J Child Neurol 2001;16:264–70.
43. Schwahn BC, Van Spronsen FJ, Belaidi AA, et al. Efficacy and safety of cyclic pyranopterin monophosphate substitution in severe molybdenum cofactor deficiency type A: a prospective cohort study. Lancet 2015;386:1955–63.
44. Touati G, Rusthoven E, Depondt E, et al. Dietary therapy in two patients with a mild form of sulphite oxidase deficiency. Evidence for clinical and biological improvement. J Inherit Metab Dis 2000;23:45–53.
45. Van Hove J, Coughlin C II, Scharer G. Glycine encephalopathy. In: Pagon RA, Adam MP, Ardinger HH, et al, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington; 2002. p. 1993–2016. Updated July 11, 2013.
46. Van Hove J, Hennermann JB, Coughlin CR II. Noketotic hyperglycinemia (glycine encephalopathy) and lipoate deficiency disorders. In: Saudubray JM, Baumgartner MR, Walter J, editors. Inborn metabolic diseases. 6th edition. Berlin: Springer; 2016. p. 349–56.
47. Hennermann JB, Berger JM, Grieben U, et al. Predicition of long-term outcome in glycine encephalopathy: a clinical survey. J Inherit Metab Dis 2012;35:253–61.
48. Swanson MA, Coughlin CR, Scharer GH, et al. Biochemical and molecular predictors for prognosis in nonketotic hyperglycinemia. Ann Neurol 2015;78:606–18.
49. Korman SH, Wexler ID, Gutman A, et al. Treatment from birth of nonketotic hyperglycinemia due to a novel GLDC mutation. Ann Neurol 2006;59:411–5.
50. Korman SH, Boneh A, Ichinohe A, et al. Persistent NKH with transient or absent symptoms and a homozygous GLDC mutation. Ann Neurol 2004;56:139–43.
51. De Koning TJ, Snell K, Duran M, et al. L-serine in disease and development. Biochem J 2003;371:653–61.
52. El-Hattab AW, Shaheen R, Hertecant J, et al. On the phenotypic spectrum of serine biosynthesis defects. J Inherit Metab Dis 2016;39:373–81.
53. Van der Crabben SN, Verhoeven-Duif NM, Brilstra EH, et al. An update on serine deficiency disorders. J Inherit Metab Dis 2013;36:613–9.
54. El-Hattab AW. Serine biosynthesis and transport defects. Mol Genet Metab 2016;118:153–9.
55. Tabatabaie L, Klomp LWJ, Rubio-Gozalbo ME, et al. Expanding the clinical spectrum of 3-phosphoglycerate dehydrogenase deficiency. J Inherit Metab Dis 2011;34:181–4.
56. de Koning TJ, Jaeken J, Pineda M, et al. Hypomyelination and reversible white matter attenuation in 3-phosphoglycerate dehydrogenase deficiency. Neuropediatrics 2000;31:287–92.
57. de Koning TJ, Duran M, Van Maldergem L, et al. Congenital microcephaly and seizures due to 3-phosphoglycerate dehydrogenase deficiency: outcome of treatment with amino acids. J Inherit Metab Dis 2002;25:119–25.
58. Coman DJ, Sinclair KG, Burke CJ, et al. Seizures, ataxia, developmental delay and the general paediatrician: glucose transporter 1 deficiency syndrome. J Paediatr Child Health 2006;42:263–7.

59. Leen WG, Klepper J, Verbeek MM, et al. Glucose transporter-1 deficiency syndrome: the expanding clinical and genetic spectrum of a treatable disorder. Brain 2010;133:655–70.
60. Pong AW, Geary BR, Engelstad KM, et al. Glucose transporter type I deficiency syndrome: epilepsy phenotypes and outcomes. Epilepsia 2012;53:1503–10.
61. von Moers A, Brockmann K, Wang D, et al. EEG features of glut-1 deficiency syndrome. Epilepsia 2002;43:941–5.
62. De Giorgis V, Veggiotti P. GLUT1 deficiency syndrome 2013: current state of the art. Seizure 2013;22:803–11.
63. Klepper J. Glucose transporter deficiency syndrome (GLUT1DS) and the ketogenic diet. Epilepsia 2008;49(Suppl 8):46–9.
64. Jurecka A, Zikanova M, Kmoch S, et al. Adenylosuccinate lyase deficiency. J Inherit Metab Dis 2015;38:231–42.
65. Mouchegh K, Zikanova M, Hoffmann GF, et al. Lethal fetal and early neonatal presentation of adenylosuccinate lyase deficiency: observation of 6 patients in 4 families. J Pediatr 2007;150:57–61.
66. Desroches CL, Patel J, Wang P, et al. Carrier frequency of guanidinoacetate methyltransferase deficiency in the general population by functional characterization of missense variants in the GAMT gene. Mol Genet Genomics 2015; 290:2163–71.
67. Stockler-Ipsiroglu S, van Karnebeek C, Longo N, et al. Guanidinoacetate methyltransferase (GAMT) deficiency: outcomes in 48 individuals and recommendations for diagnosis, treatment and monitoring. Mol Genet Metab 2014;111:16–25.
68. Mercimek-Mahmutoglu S, Stoeckler-Ipsiroglu S, Adami A, et al. GAMT deficiency: features, treatment, and outcome in an inborn error of creatine synthesis. Neurology 2006;67:480–4.