Isolated Neonatal Seizures: When to Suspect Inborn Errors of Metabolism

Can Ficicioglu MD, PhD a,*, David Bearden MD b

a Section of Biochemical Genetics, Department of Pediatrics, Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

b Division of Neurology, Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

Introduction

Neonatal seizures occur during the first 28 days of age, and often comprise the first clinical indicator of central nervous system dysfunction. Ninety percent of seizures in full-term newborns are indicative of an identifiable cause. The more common disorders that present with neonatal seizures include hypoxic-ischemic encephalopathy, cerebrovascular disorders, infections, cerebral dysgenesis, and transient metabolic disturbances such as hypocalcaemia, hyponatraemia, hypomagnesaemia, and hypoglycaemia. However, neonatal seizures sometimes constitute the first sign of inborn errors of metabolism that are much more difficult to diagnose and are therefore often overlooked or misdiagnosed. After neonatal seizures are confirmed and no structural or infectious cause is apparent, inborn errors of metabolism should always be considered in the differential diagnosis. An early diagnosis of inborn errors of metabolism is crucial to long-term outcomes, because some can be treated effectively with dietary restriction or supplementation. In addition, all are inherited disorders that may recur in future pregnancies, and therefore their diagnosis allows for appropriate genetic counseling.

The goals of this review include: (1) an emphasis on the importance of considering inborn errors of metabolism in the differential diagnosis of neonatal seizures; (2) a discussion of warning signs for inborn errors of metabolism as a cause of neonatal seizures; and (3) an overview of the signs, diagnosis, and treatment of inborn errors of metabolism.

When to suspect inborn errors of metabolism

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isolated seizures period. This review will mainly focus on inborn errors of metabolism in neonatal seizures to consider them in the differential diagnosis and perform specific targeted testing. This review will mainly focus on inborn errors of metabolism presenting with isolated seizures in the newborn period.

**Signs of inborn errors of metabolism that cause isolated seizures**

Several inborn errors of metabolism that may present with seizures during the newborn period are, in general, poorly responsive to antiepileptic drugs. Seizures usually constitute the only sign, but some patients may also manifest microcephaly, hypotonia, or hypertonia. Routine biochemical tests such as comprehensive metabolic panels, urinalysis, or the determination of ammonia levels do not lead physicians to suspect these disorders. Electroencephalographic findings are nonspecific, although many of these disorders will manifest severe disorganization with multifocal spike and wave discharges or burst suppression. In most inborn errors of metabolism, magnetic resonance imaging imaging findings indicative of hypoxic-ischemic injury, without an obvious hypoxic insult at delivery.

| Table 1. Warning signs for inborn errors of metabolism as a cause of isolated neonatal seizures |
| Seizures beginning prepartum |
| Seizures refractory to conventional antiepileptic drugs |
| Progressive worsening of clinical and electroencephalographic abnormalities |
| Magnetic resonance imaging imaging findings indicative of prominent brain atrophy |
| Magnetic resonance imaging imaging findings indicative of hypoxic-ischemic injury, without an obvious hypoxic insult at delivery |

**Approach to diagnostic testing**

An overview of diagnostic findings in inborn errors of metabolism in conjunction with isolated neonatal seizures is presented in Table 2. The key to the diagnosis of most inborn errors of metabolism involves the detection of characteristic metabolites accumulating in body fluids. Certain inborn errors of metabolism cannot be detected easily because their metabolites are normal in blood and urine. An analysis of cerebrospinal fluid is almost always essential in rendering the diagnosis. Demonstrating the accumulation or absence of a specific metabolite in cerebrospinal fluid may be diagnostic in and of itself, or may suggest the need for specific genetic testing or tissue biopsy. A diagnostic approach to the

| Table 2. Overview of diagnostic findings in inborn errors of metabolism presenting with isolated neonatal seizures |
| Disorder | MRI and MRS Findings | CSF Findings | Further Diagnostic Testing |
| Pyridoxine-dependent seizures | Normal or hypoplasia of corpus callosum and cerebellum | Increased levels of α-AASA, pипocleic acid, and neurotransmitter markers | Urinary and serum α-AASA or pipocleic acid, ALDH7A1 gene testing |
| Pyridoxal-phosphate-dependent seizures | Generalized atrophy | May be normal, or nonspecific changes | Pyridoxamine-5-phosphate oxidase gene testing |
| Defects of serine biogenesis | Initially normal, progressing to profound hypomyelination | Low levels of serine; may also have low levels of glycine or 5-MTHF | Skin biopsy for 3-phosphoglycerate dehydrogenase activity |
| GLUT-1 deficiency | Normal or generalized atrophy | CSF glucose <40 mg/dL or <1/2 of serum glucose | FDG-PET; 3-OMG uptake in red blood cells; gene testing for SNCA |
| Nonketotic hyperglycinemia | Normal, or agenesis or thinning of the corpus callosum | Increased levels of glycine, and increased CSF/plasma glycine ratio | Liver glycine cleavage complex enzyme activity; gene testing for nonketotic hyperglycinemia |
| Sulfite oxidase/molybdenum cofactor deficiency | MRI findings can mimic those of hypoxic-ischemic injury; MRS reveals increased levels of lactate, myoinositol, and choline, with decreased levels of NAA | Normal or nonspecific changes in amino acid profile | Plasma homocysteine and uric acid; urine sulfites, sulfocystine, and thiosulfates; sulfite oxidase enzyme activity in skin or liver biopsy |
| Congenital neuronal ceroid-lipofuscinosis | Generalized cerebral hypoplasia | Normal | Cathepsin D gene testing |
| γ-aminobutyric acid transferase deficiency | MRI indicates leukodystrophy and agenesis of the corpus callosum; MRS indicates elevated levels of γ-aminobutyric acid in the basal ganglia | Increased levels of homocarnosine | Enzyme activity in lymphocytes |
| Dihydropyrimidine dehydrogenase deficiency | Diffuse atrophy | Increased levels of uracil and thymine | Dihydropyrimidine dehydrogenase gene testing |
| Creatine deficiency syndromes | MRI indicates delayed myelination | Normal | Serum creatine and guanidinoacetate; urinary creatine, creatinine, and guanidinoacetate; fibroblast enzyme activity; specific genetic testing |

Abbreviations:

- 3-OMG = 3-O-methyl-D-glucose
- 5-MTHF = 5-methyltetrahydrofolate
- α-AASA = α-aminoadipic semialdehyde
- CSF = Cerebrospinal fluid
- FDG-PET = Fluorodeoxyglucose-posittion emission tomography
- MRI = Magnetic resonance imaging
- MRS = Magnetic resonance spectroscopy
- NAA = N-acetylaspartate

* For current information on the best locations to perform biochemical and genetic testing, see genereviews.org.
evaluation of suspected inborn errors of metabolism is summarized in Fig 1.

**Treatment**

Although treatable metabolic causes of isolated neonatal seizures are uncommon, a prompt diagnosis is important in order to initiate treatment and prevent irreversible neurologic and cognitive damage. Thus, upon suspicion of an inborn error of metabolism, performing appropriate metabolic testing while initiating treatment and observing the response is important (Table 3 and Fig 2). If no option to send laboratory tests first exists, treatment should not be delayed.

**Specific disorders**

**Pyridoxine-dependent seizures**

**Overview**

Although several causes of neonatal seizures may be responsive to pyridoxine, pyridoxine-dependent seizures are attributable to a deficiency of $\alpha$-amino adipic semialdehyde dehydrogenase, also known as anti-qui- tin [1]. This enzyme in the lysine degradation pathway converts $\alpha$-amino adipic semialdehyde to $\gamma$-2-amino adipic acid. The deficiency of $\alpha$-amino adipic semialdehyde dehydrogenase results in an accumulation of $\alpha$-amino adipic semialdehyde and piperoc acid in body fluids, resulting in severe secondary pyridoxal-5 phosphate deficiency. Pyridoxal-5 phosphate is a cofactor of various enzymes in the central nervous system, and its deficiency causes seizures attributable to a perturbation of the metabolism of cerebral amino acids and neurotransmitters [2].

**Presentation**

Patients generally present with seizures very shortly after birth or during the prenatal period, although atypical cases with late-onset seizures were also described. Almost all seizure types, both generalized and partial, have been described. Some seizures may be completely or partially responsive to standard antiepileptic drugs at first, but become more difficult to control as the child ages. Mothers of patients with early-onset pyridoxine-dependent seizures may describe abnormal intrauterine movements (e.g., episodic, recurrent hammering movements) during pregnancy.

**Diagnosis**

Testing for serum, urine, and cerebrospinal fluid $\alpha$-amino adipic semialdehyde levels and specific genetic testing for ALDH7A1 are commercially available, and thus a trial of pyridoxine withdrawal is no longer necessary to render a diagnosis of pyridoxine-dependent seizures [3]. If a therapeutic trial with pyridoxine is performed, plasma and urine samples for $\alpha$-amino adipic semialdehyde should always be collected before the trial. In pyridoxine-dependent seizures, the level of piperoc acid increases in urine, blood, and cerebrospinal fluid, and this level can be measured if testing for $\alpha$-amino adipic semialdehyde is unavailable. Although $\alpha$-amino adipic semialdehyde is a specific marker for pyridoxine-dependent seizures, levels of piperoc acid can be elevated in liver disease or in defects of peroxisomal biogenesis, and thus are less specific. Finally, a marker in cerebrospinal fluid neurotransmitter testing corresponds with elevated levels of $\alpha$-amino adipic semialdehyde [4]. Although specific diagnostic testing strategies can vary according to the regional availability of specific tests, one approach entails sending serum and cerebrospinal fluid $\alpha$-amino adipic semialdehyde (or piperoc acid) samples, in addition to neurotransmitter testing, if the patient is not receiving pyridoxine supplementation. If the patient is already receiving pyridoxine, genetic testing for ALDH7A1 can be performed.

**Treatment**

All patients with unexplained treatment-refractory neonatal seizures should undergo a pyridoxine trial of 100 mg (about 30 mg/kg) intravenously, during electroencephalographic monitoring if possible. An initial electroencephalogram response may not occur, so continuing the same dose at least 3 more days to assess the response is important. If a clinical or electroencephalographic response to pyridoxine occurs, the pyridoxine should be continued while diagnostic testing is pending. With the availability of specific genetic testing, a trial withdrawal of pyridoxine is generally unnecessary, and in fact should be avoided, if possible, to prevent potential harm to the patient. If the diagnosis is confirmed, pyridoxine supplementation should be continued indefinitely. Gallagher et al. recommended considering treatment with both pyridoxine and folic acid in patients with

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<tr>
<td>Pyridoxal phosphate-dependent seizures</td>
<td>Pyridoxal-5-phosphate (50-100 mg/kg/day)</td>
</tr>
<tr>
<td>Folic acid-responsive seizures</td>
<td>Folic acid (3-5 mg/kg/day) ± pyridoxine</td>
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<tr>
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$^*$ The dose should be adjusted according to the response.

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### Table 3. Treatment of metabolic causes of isolated neonatal seizures

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**α-aminoadipic semialdehyde dehydrogenase deficiency** [4]. Pyridoxal phosphate may be used as the first-line drug instead of pyridoxine in the United States upon its approval and licensing from the Food and Drug Administration.

**Folinic acid-responsive seizures**

Recent evidence suggests that most, if not all, cases of folinic acid-responsive seizures are genetically and biochemically indistinguishable from pyridoxine-dependent seizures, because both are associated with elevations of α-aminoadipic semialdehyde and mutations in ALDH7A1 [4]. A marker for this disorder in neurotransmitter testing was previously described. However, this marker is also present in pyridoxine-responsive seizures, and seems to correspond with elevated levels of α-aminoadipic semialdehyde, rather than predicting a response to folinic acid [4]. Thus, patients with a clinical response to folinic acid should undergo diagnostic testing as already described for pyridoxine-dependent seizures, and should be treated simultaneously with folinic acid and pyridoxine [4,5].

A biochemically and genetically distinct disorder of cerebral folate deficiency may be secondary to a variety of causes, because both are mutations in ALDH7A1 [4]. A marker for this disorder in neurotransmitter testing was previously described. However, this marker is also present in pyridoxine-responsive seizures, and seems to correspond with elevated levels of α-aminoadipic semialdehyde, rather than predicting a response to folinic acid [4]. Thus, patients with a clinical response to folinic acid should undergo diagnostic testing as already described for pyridoxine-dependent seizures, and should be treated simultaneously with folinic acid and pyridoxine [4,5].

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**Pyridoxal phosphate-dependent seizures**

**Overview**

Pyridoxamine-5-phosphate oxidase enzyme converts pyridoxine and pyridoxamine into pyridoxal-5-phosphate, which is a cofactor for many enzymes involved in the synthesis of dopamine, serotonin, glutamate, serine, γ-aminobutyric acid, quinolinic acid, and kynurenic acid, and in the catabolism of γ-aminobutyric acid. Pyridoxamine-5-phosphate oxidase deficiency results in treatment-refractory neonatal seizures that respond to treatment with pyridoxal-5-phosphate, but not to conventional antiepileptic drugs or pyridoxine [7].

**Presentation**

Most patients reported in the literature were born prematurely, and presented with seizures within their first weeks of age. The clinical findings are nonspecific, and some cases may be misdiagnosed as hypoxic-ischemic encephalopathy. An electroencephalogram usually indicates a pattern of severe disorganization or burst suppression. Magnetic resonance imaging may indicate hypomyelination or cerebral atrophy.

**Diagnosis**

Although several metabolite levels may change in urine and cerebrospinal fluid because of the reduced activity of several pyridoxal-5-phosphate-dependent enzymes, many patients exhibit normal or inconclusive biochemical findings. Plasma amino acid analysis may demonstrate elevated levels of glycine or threonine. Analyses of urine organic acids may reveal increased levels of vanillactic acid. Decreased concentrations of homovanillic acid, 5-hydroxytryptophan-acetic acid, and 3-methoxy-4-hydroxyphenylglycol, and increased levels of L-dopa, 5-hydroxytryptophan, and 3-O-methyl-L-dopa are evident in cerebrospinal fluid analysis. Levels of threonine, glycine, and histidine can be elevated in cerebrospinal fluid. Some patients may manifest lactic acidemia and hypoglycemia. The diagnosis is confirmed by mutation analysis.

**Treatment**

A therapeutic trial dose of pyridoxal-5-phosphate, 30 mg/kg/day, in three divided doses for at least 1 day should be administered to newborns with seizures of unknown etiology (Fig 2) who do not respond to pyridoxine. The recommended dose of pyridoxal-5-
phosphate is 50-100 mg/kg/day in patients with known pyridox-amine-5-phosphate oxidase deficiency. Some patients may require higher doses.

**Defects of serine biogenesis**

**Overview**

The enzymes 3-phosphoglycerate dehydrogenase and 3-phosphoserine phosphatase are important in the biosynthesis of L-serine, a nonessential amino acid that plays a role in cellular proliferation and serves as a precursor for the neurotransmitter glycine. The L-serine-derived phospholipids may also play a role in the development of myelin. A deficiency of these enzymes results in low levels of cerebrospinal fluid serine, and produces severe neurologic sequelae and intractable neonatal seizures [8,9]. The majority of serine biosynthesis defects are secondary to 3-phosphoglycerate dehydrogenase deficiency. A single case of 3-phosphoserine phosphatase deficiency was described with a similar presentation [10].

**Presentation**

In the majority of patients, the signs begin before birth, and patients are born with congenital microcephaly. Seizures usually begin during the newborn period, and severe psychomotor retardation develops during the first months of age. Seizures begin either as generalized tonic-clonic seizures or as infantile spasms. Patients gradually develop neurologic abnormalities such as generalized hypertonat, hyperexcitability, nystagmus, or spastic quadriplegia. In some patients, adducted thumbs, cataracts, hypogonadism, or megaloblastic anemia were reported. Electroencephalographic findings include hypsarrhythmia or severe multifocal epileptic abnormalities with poor background. No abnormal findings of magnetic resonance imaging occur during the newborn period, but may develop during the first year of age. Losses of brain volume, attenuated white matter, and hypomyelination were reported.

**Diagnosis**

The hallmark of the disease is a low level of serine in cerebrospinal fluid and plasma. However, plasma serine levels can be normal in postprandial samples, and thus plasma amino acid analysis should be performed after overnight fasting. Urinary amino acid analysis is not informative. The analysis of cerebrospinal fluid amino acid is a more reliable diagnostic test, because a low level of serine in cerebrospinal fluid is always present and is unrelated to feeds. Low levels of cerebrospinal fluid glycine and 5-methyltetrahydrofolate were also reported. The activity of the 3-phosphoglycerate dehydrogenase enzyme can be measured in cultured skin fibroblasts for confirmation.

**Treatment**

Oral supplementation of serine can be effective in the treatment of seizures [11]. The recommended dose range is between 400-600 mg/kg/day. If the seizures are not controlled with serine, glycine can be added at a dose of 200-300 mg/kg/day. A clinical response to treatment usually occurs within 1-2 weeks after the initiation of treatment. Some patients develop vomiting, nystagmus, and myoclonic jerks after the introduction of serine. Doses higher than 600 mg/kg/day are not recommended. Long-term follow-up indicates that not all patients remain seizure-free on serine therapy. In some patients, the progression of disease was evident despite therapy.

**Glucose transporter type 1 deficiency**

**Overview**

Glucose transporter type 1 is the major glucose transporter, and is responsible for the entry of glucose into the brain. Thus, a deficiency of glucose transporter type 1 results in severe central hypoglycemia, despite normal levels of peripheral glucose. However, glucose transporter type 1 is important not only for glucose transport, but also for galactose, water, and glycopeptide transport, and a deficiency of these substrates may contribute to the pathology of this syndrome.

**Presentation**

Signs of glucose transporter type 1 deficiency usually begin during infancy, and seizures may constitute the first finding during the newborn period [12]. The phenotype of glucose transporter type 1 deficiency is heterogeneous, and patients can present with different seizure types, developmental delay, ataxia, hypotonia, acquired microcephaly, and abnormal movements ranging from restlessness to dystonia. Electroencephalographic findings include generalized slowing, focal and multifocal spike and wave discharges, and generalized high-amplitude spike and wave discharges. A marked improvement in electroencephalographic abnormalities after eating was described [13]. The findings of magnetic resonance imaging are normal or else reveal nonspecific abnormalities or generalized atrophy. Fluorodeoxyglucose-postion emission tomography was reported to demonstrate diminished cortical uptake with more severe areas of hypometabolism in the mesial temporal lobes and thalami [14].

**Diagnosis**

The laboratory hallmarks of glucose transporter type 1 deficiency include a reduced concentration of cerebrospinal fluid glucose (<40 mg/dL) and a decreased cerebrospinal fluid/blood glucose ratio of <0.5. Specific genetic testing can confirm the diagnosis. A blood test indicating decreased uptake of 3-O-methyl-D-glucose in erythrocytes can also be diagnostic.

**Treatment**

Seizures are usually poorly controlled by antiepileptic medications. In many cases, a ketogenic diet can control the seizures and improve cognition by providing ketones as an alternate source of energy in the brain, while exerting a secondary effect on cerebral glucose transport [12]. However, some patients may not respond well to a ketogenic diet. Antioxidants may also be beneficial. Medications and substances that inhibit glucose transporter type 1, such as phenobarbital, diazepam, methylxanthine, and green tea, should be avoided.

**Nonketotic hyperglycinemia**

**Overview**

Nonketotic hyperglycinemia is attributable to a defect in the glycine cleavage complex. Glycine functions as a neurotransmitter that exerts an inhibitory effect in the brainstem and spinal cord, but an excitatory effect in the cerebral cortex.

**Presentation**

Historically, nonketotic hyperglycinemia is divided into several forms according to its severity and the progression of signs. Viewing nonketotic hyperglycinemia as a spectrum may be more appropriate. The majority of patients are at the severe end of the spectrum, and manifest in the first hours to days of age with lethargy, hypotonia, apnea, and seizures (neonatal-onset form) [15]. Patients usually die during the newborn period. If they survive,
they develop severe mental retardation and continue to manifest intractable seizures.

A transient form of nonketotic hyperglycinemia is characterized by clinical findings similar to those of the neonatal form. However, signs of the disease partly or completely resolve over days to months, and a normal outcome is possible. A delay in the maturation of the glycine cleavage system, which is active at 8–16 weeks of gestation, may cause the transient hyperglycinemia. Electroencephalograms indicate a burst suppression pattern that may evolve into multifocal spikes and hypsarrhythmia. Magnetic resonance imaging may produce normal results or reveal agenesis or thinning of the corpus callosum. Patients may later develop cerebral atrophy and decreased myelination.

**Diagnosis**

Patients manifest elevated levels of glycine in their blood, urine, and cerebrospinal fluid. Simultaneous samples of cerebrospinal fluid and plasma are necessary to calculate the cerebrospinal fluid/plasma glycine ratio. An increased cerebrospinal fluid/plasma glycine ratio (i.e., >0.08; normal, <0.02) is suggestive of nonketotic hyperglycinemia. Urinary organic acids are normal in nonketotic hyperglycinemia.

Glycine cleavage enzyme activity can be measured in the liver. More than 80% of patients with nonketotic hyperglycinemia exhibit defects in the P protein of the glycine cleavage complex. Approximately 10–15% of patients with nonketotic hyperglycinemia manifest defects in the T protein of the glycine cleavage complex. Most reported genes are rare or unique. No reliable genotype-phenotype correlations are available, with the exception of the S564F mutation found in Finnish patients with severe neonatal-onset nonketotic hyperglycinemia.

**Treatment**

No effective treatment exists for nonketotic hyperglycinemia [16]. Sodium benzoate at 250–750 mg/kg/day can reduce levels of plasma and cerebrospinal fluid glycine. It may decrease seizure activity and improve behavior in some patients. Phenobarbital, benzodiazepines, or phenytoin may decrease seizure activity in some patients. Valproate increases the concentration of serum glycine, and is contraindicated in nonketotic hyperglycinemia.

**Sulfite oxidase and molybdenum cofactor deficiency**

**Overview**

The catabolism of the sulfur-containing amino acids methionine and cysteine contributes to the bulk of the sulfite load that requires the sulfite oxidase enzyme and molybdenum cofactor for oxidation to sulfates. In sulfite oxidase deficiency, sulfites cannot be converted to sulfates, and the accumulation of toxic sulfites leads to neurologic disease [17]. Sulfite oxidase is one of the three enzymes that require molybdenum as a cofactor, along with xanthine oxidase and aldehyde oxidase. Xanthine oxidase catalyzes the hydroxylation of hypoxanthine to xanthine, and then to uric acid. Aldehyde oxidase is involved in the hydroxylation of hypoxanthine to xanthine, but not to uric acid. In both disorders, the accumulation of sulfites inhibits glutamate dehydrogenase, leading to decreases in the production of α-ketoglutarate and other Krebs cycle intermediates. An overall decrease in nicotinamide adenine dinucleotide flux to the electron transport chain and a decrease in the biosynthesis of adenosine triphosphate cause an energy crisis, which explains why these patients may exhibit a pathology similar to that seen in hypoxic-ischemic injury. The inhibition of mitochondrial glutamate dehydrogenase by sulfites and possible accumulation of glutamate or glutamine result in further neurotoxicity.

These metabolites may be detected by magnetic resonance spectroscopy.

**Presentation**

Patients with sulfite oxidase deficiency usually present with intractable seizures during the newborn period. In infants who survive, lens dislocation may occur after 8 weeks of age. Sulfite oxidase deficiency should be considered in all newborns with intractable seizures and findings suggestive of hypoxic-ischemic encephalopathy on magnetic resonance imaging, but without an obvious hypoxic insult at delivery. Molybdenum cofactor deficiency, which is more common than isolated sulfite oxidase deficiency, manifests with a similar presentation, including intractable seizures, hypotonia, feeding difficulties, developmental delay, lens subluxation, and low levels of uric acid [18]. Facial dysmorphism is common in both disorders. Milder cases attributable to partial molybdenum cofactor deficiency may present with less severe signs later in life.

An electroencephalogram may initially produce normal results, but rapid progress to burst suppression occurs [19]. The findings of magnetic resonance imaging include periventricular white matter changes involving central and U fibers, and gray matter signal changes with a rapid progression to cystic lesions of a symmetric pattern in the frontal, parietal, and temporal lobes. In sulfite oxidase deficiency, the findings of magnetic resonance imaging can mimic those of hypoxic-ischemic encephalopathy [20], although these findings are usually more severe than in hypoxic-ischemic encephalopathy, and demonstrate no subsequent recovery. Magnetic resonance spectroscopy indicates an energetic and metabolic imbalance, with elevations of lactate and myoinositol and a reduction of N-acetylaspartate [21]. In contrast to hypoxic-ischemic encephalopathy, an increased choline peak occurs, probably attributable to undeveloped myelination and the breakdown of membranes as part of the process of atrophy.

**Diagnosis**

The biochemical findings of sulfite oxidase deficiency and molybdenum cofactor deficiency include the presence of urinary sulfites, an elevation of urinary thiosulfate levels, increased levels of plasma and urinary S-sulfocysteine, and reduced levels of plasma total homocysteine and cysteine. In molybdenum cofactor deficiency, levels of serum and urinary uric acid are reduced, and levels of urinary xanthine and hypoxanthine are increased, because of the secondary deficiency in xanthine oxidase activity.

Because urinary sulfites are very unstable, urine samples should be collected on ice and tested for sulfites as soon as possible. False-negative results may occur if the urinary pH is measured at less than 6. False-positive results may occur in the presence of drugs containing the aliphatic sulfhydryl group, such as dimercaprol and N-acetylcysteine.

The determination of plasma total homocysteine levels and uric acid may constitute the best initial test, because these can be performed in any clinical chemistry laboratory. If the degree of suspicion is high, levels of urinary sulfites (in fresh urine) and of urinary thiosulfate and sulfocysteine should be measured. Urinary thiosulfate and sulfocysteine are more stable. Antibiotics such as cefotaxime, cefuroxime, ampicillin, and benzylpenicillin may produce false-positive results in the measurement of urinary thiosulfates. Sulfite oxidase enzyme activity can be measured in liver and skin fibroblasts for a confirmation of the diagnosis.

**Treatment**

Treatment is largely supportive. Unfortunately, the instability of molybdenum cofactor precludes its clinical use at this point. A
single case of the successful treatment of molybdenum cofactor deficiency with purified cyclic pyranoceptor monophosphate was described [22]. Dietary supplementation of thiamine, sulfate, and uric acid, the restriction of dietary cysteine and methionine, chelation, and treatment with betaine were all proposed, but no clear benefit has been demonstrated. Most patients with a neonatal onset of signs die within weeks to months of diagnosis.

**Congenital neuronal ceroid-lipofuscinosis**

**Overview**
Congenital neuronal ceroid-lipofuscinosis is a disorder of cathepsin D deficiency [23]. Cathepsin D hydrolyzes certain peptide bonds of target proteins, and is the predominant lysosomal aspartic acid protease. Congenital neuronal ceroid-lipofuscinosis constitutes the earliest onset and most aggressive form of neuronal ceroid-lipofuscinosis [24].

**Presentation**
Congenital neuronal ceroid-lipofuscinosis should be considered in newborns with microcephaly and seizures at or before birth. Patients can also manifest respiratory failure and hypertonia. Neuropathologic changes are characterized by the complete disorganization of neurons in the cerebral cortex, a loss of Purkinje cells and inner granule cells in the cerebellum, and extreme glial activation. Periodic acid-Schiff-positive storage material with a granular ultrastructure and immunoreactivity against sphingolipid activator protein D is also evident in brain. Magnetic resonance imaging indicates generalized hypoplasia of the cerebral hemispheres and cerebellum.

**Diagnosis**
A diagnosis of congenital neuronal ceroid-lipofuscinosis can be confirmed with a mutation analysis of the cathepsin D gene.

**Treatment**
No effective treatment exists for congenital neuronal ceroid-lipofuscinosis, and patients usually die within hours to weeks of birth.

**4-Aminobutyrate aminotransferase (γ-aminobutyric acid transferase) deficiency**

**Overview**
This deficiency involves a rare inborn error of γ-aminobutyric acid metabolism. The enzyme catalyzes the conversion of γ-aminobutyric acid to succinic acid.

**Presentation**
Three patients were reported in the literature [25–27]. In 1984, Jaeken et al. [25] reported on the first patient, who presented with seizures, hypotonia, hyperreflexia, and mental retardation. An older sibling had manifested the same findings and died at age 1 year. Medina-Kauwe et al. reported on a second patient who presented with seizures at 10 minutes of age [26]. That patient also manifested hypertonia and dysmorphic features, e.g., downsloping eyes and mild retrognathia. Tsuji et al. [27] reported on a third patient with intractable seizures and psychomotor retardation. Electroencephalograms indicated a burst suppression pattern. Published findings of magnetic resonance imaging include leukodystrophy, agenesis of the corpus callosum, abnormal gyration of the hemispheres, and cerebellar hypoplasia. Magnetic resonance spectroscopy revealed an elevated concentration of γ-aminobutyric acid in the basal ganglia in the third case, and this finding could indicate a useful tool in the diagnosis of 4-aminobutyrate aminotransferase (γ-aminobutyric acid transferase) deficiency [27].

**Diagnosis**
All reported cases demonstrated elevated levels of γ-aminobutyric acid in plasma, and levels of homocarnosine were also elevated in the cerebrospinal fluid and urine. The level of β-alanine was elevated in the first but not the second reported patient. If a diagnosis of this deficiency is suspected, the activity of γ-aminobutyric acid transferase can be measured in lymphocytes or lymphoblasts.

**Treatment**
No effective treatment is known.

**Dihydropyrimidine dehydrogenase deficiency**

**Overview**
Dihydropyrimidine dehydrogenase is the initial and rate-limiting enzyme that catalyzes the reduction of thymine and uracil to 5,6-dihydrothymine and 5,6-dihydrouracil, respectively [28]. In this rare disease of pyrimidine metabolism, deficiency of the enzyme leads to thymine-uraciluria with possible secondary deficiency of β-alanine.

**Presentation**
The clinical presentation varies among patients. Seizures and developmental delay in the first year of age comprise the most common manifestations, but some patients presented with isolated neonatal seizures [29]. Microcephaly, growth retardation, autism, and dysmorphic features may also be evident. Although severe dihydropyrimidine dehydrogenase deficiency will lead to the features already described, a partial deficiency puts patients at risk of severe toxicity when exposed to the chemotherapeutic agent 5-fluorouracil.

The findings of magnetic resonance imaging include diffuse cerebral atrophy and white-matter hyperintensity. Magnetic resonance spectroscopy indicates diffuse neuronal loss, as indicated by a relative decrease of N-acetylaspartate and an increase in levels of choline.

**Diagnosis**
Increased levels of uracil and thymine can be detected in urine, blood, and cerebrospinal fluid. The activity of dihydroxyimididine dehydrogenase can be measured in fibroblasts or mononuclear cells [30]. The dihydroxyimididine dehydrogenase gene was mapped to chromosome 1p22, and several mutations, including deletion and splice-site mutations, were reported in patients. The most common mutation involves the G->A splice site. A clear relationship between phenotype and genotype has not been observed.

**Treatment**
No effective treatment exists.

**Creatine deficiency syndromes**

**Overview**
Three closely related syndromes are attributed to a deficiency of the enzyme guanidinoacetate methyltransferase or γ-arginine glycine amidinotransferase in the creatine biosynthesis pathway or the creatine transporter defect, SLC6A8 deficiency [31]. The creatine and phosphocreatine system play important roles in the energy metabolism of brain, muscle, and nerve tissue.

**Presentation**
Seizures, developmental and speech delay, hypotonia, and mental retardation developing during the first year of age comprise
the most common signs of creatine deficiency syndromes. Neonatal seizures were not previously described, but excluding these defects in patients with isolated neonatal seizures is important, because deficiencies of guanidinoacetate methyltransferase and l-arginine glycine amidotransferase may be treated with creatine supplementation, and early diagnosis and treatment improve long-term outcomes.

Cranial magnetic resonance imaging indicates delayed myelination or increased T2 signal intensity in the globus pallidus in some patients. Cranial magnetic resonance spectroscopy indicates a complete absence of the creatine peak, along with normal choline and N-acetylaspartate peaks in patients with creatine deficiency syndromes.

Diagnosis

Levels of urinary and serum guanidinoacetate and creatine and levels of urinary creatinine are helpful in rendering a diagnosis of creatine deficiency syndromes. In guanidinoacetate methyltransferase deficiency, the levels of guanidinoacetate are increased, and the levels of creatine in urine and serum are low. In l-arginine glycine amidotransferase deficiency, levels of guanidinoacetate and creatine are both lower than normal. The creatine/creatinine ratio is normal in both enzyme deficiencies. In creatine transporter defects (SLC6A8 deficiency), the level of guanidinoacetate is normal, but the level of creatine and the urinary creatine/creatinine ratio are elevated. For confirmation of the diagnosis, activities of guanidinoacetate methyltransferase and the l-arginine glycine amidotransferase enzyme can be measured in fibroblasts or lymphoblasts, and creatine uptake studies in fibroblasts can be performed to confirm the diagnosis of creatine transport defects. Mutation analysis is available for all three gene defects.

Treatment

Creatine supplementation (0.35-2 g/kg/day) may restore depleted creatine in the brain and improve seizures and developmental outcomes [32,33]. All patients benefit from creatine supplementation to a certain degree, but developmental and speech delays often persist. In one patient with arginine glycine amidotransferase deficiency, early diagnosis and treatment prevented the occurrence of clinical manifestations [34]. Whether early treatment with creatine supplementation can prevent the development of signs in all asymptomatic patients remains unknown. Creatine supplementation therapy was unsuccessful in patients with a creatine transport defect (SLC6A8 deficiency) [35].

Conclusion

All neonates with suspected inborn errors of metabolism should be promptly evaluated with a stepwise diagnostic workup (Fig 1). However, because establishing a definitive diagnosis may take weeks or months, a therapeutic trial should always be considered in the interim. We recommend starting with electrolytes, a hepatic function panel, an ammonia screen, and a standard newborn screen to exclude common alternative diagnoses and as an initial screen for amino acidopathies, organic acidemias, and defects of the urea cycle. The next step involves the measurement of urinary organic acids and serum amino acids to exclude amino acidopathies, organic acidemias, and defects of the urea cycle. An acylcarnitine profile as a screen for disorders of β-oxidation, an evaluation of serum lactate/pyruvate as a screen for mitochondrial disease, and cranial magnetic resonance imaging and magnetic resonance spectroscopy should also be performed. In all patients for whom no diagnosis has been reached at this point, a lumbar puncture should be performed, because it is essential in the diagnosis of the potentially treatable disorder of glucose transporter type 1 deficiency, and of pyridoxine-dependent seizures/folinic-acid responsive seizures, defects of serine biogenesis, and nonketotic hyperglycinemia. The next step in the diagnostic workup is highly individualized, and may include further biochemical testing (e.g., for sulfite oxidase deficiency or creatine deficiency syndromes), specific genetic testing, or tissue biopsy.

Although individual inborn errors of metabolism are rare, as a group they are probably undiagnosed. They are important to consider in the differential diagnosis of neonatal seizures of unknown etiology, because some respond to specific treatments, without which a catastrophic deterioration of the affected infant is almost certain. Even in disorders without specific treatment, the diagnosis allows for appropriate counseling regarding the prognosis and planning for future pregnancies. In this review, we hope to raise awareness of metabolic disorders that cause isolated seizures, and to provide a framework for their evaluation and treatment.

References


