Pediatric Neurotransmitter Disorders

By Stephen R. Deputy, MD, FAAP, pediatric neurologist at Children’s Hospital and associate professor of neurology at LSU Health New Orleans. This issue of Pediatric Review is intended for pediatricians, family physicians and all other interested medical professionals. For CME purposes, the author has no relevant financial relationships to disclose.

Objectives

At the end of this activity, the participant should be able to:
1. Describe the biochemical changes that accompany pediatric neurotransmitter disorders
2. Describe some of the more common phenotypic features of children with neurotransmitter disorders
3. Consider specific treatment options for patients with neurotransmitter disorders

Introduction

The pediatric neurotransmitter disorders represent a challenging group of rare neurometabolic disorders classified on the basis of alterations in neurotransmitter metabolic pathways. The disorders are currently classified into disturbances of monoamine (dopamine, serotonin and norepinephrine) and gamma-aminobutyric acid (GABA) metabolism. Most of the monoamine disorders are at least partially responsive to L-dopa administration, and several of the GABA disorders respond to pyridoxine or pyridoxal-5-phosphate. One of the challenging aspects of these disorders is their varied clinical presentations ranging from mental retardation to epilepsy to movement disorders. Another challenging aspect is their diagnosis, which often relies on measuring neurotransmitter metabolites in the cerebrospinal fluid (CSF), as analysis of amino acids in the plasma and organic acids in the urine are uninformative.

Disorders of monoamine metabolism include guanosine triphosphate (GTP)-cyclohydrolase I deficiency, tyrosine hydroxylase deficiency, aromatic L-amino acid decarboxylase deficiency and sepiapterin reductase deficiency. Disorders that fall under the spectrum of GABA metabolism include succinic semialdehyde dehydrogenase deficiency, pyridoxine-dependent epilepsy and GABA-transaminase deficiency. One disorder from each category—GTP-cyclohydrolase I deficiency and pyridoxine dependent epilepsy—is discussed below.

Disorders of Monoamine Metabolism

GTP-cyclohydrolase I deficiency (GCH-1 deficiency, Segawa disease) is an autosomal dominant form of DOPA-responsive dystonia. It was first described by Masaya Segawa in 1971 as a hereditary progressive basal ganglia disease with marked diurnal fluctuation. This disorder is caused by mutations of the GCH1 gene located on 14q22.1–q22.2. The worldwide prevalence is estimated to be at least 1:1,000,000, as the disorder may often go undiagnosed.

GTP-cyclohydrolase I catalyzes the first step of tetrahydrobiopterin synthesis from GTP. Tetrahydrobiopterin is an essential cofactor for tyrosine hydroxylase, tryptophan hydroxylase and phenylalanine hydroxylase (Figure 1). These enzymes are responsible for the synthesis of dopamine (phenylalanine hydroxylase and tyrosine hydroxylase) as well as for serotonin (tryptophan hydroxylase). Reduced enzymatic activity of GTP-cyclohydrolase I also results in reduced formation of neopterin.

Clinical symptoms usually start with monomelic postural dystonia (often pes equinovarus) beginning in early school age, which then gradually progresses to affect all extremities over the next 10 to 15 years. There is a marked diurnal fluctuation of the dystonia severity at the onset of the disease, which diminishes over time. GTP-cyclohydrolase I deficiency is often mistaken for cerebral palsy, which should not be progressive or show diurnal fluctuation of symptoms. On physical examination, deep tendon reflexes are exaggerated with flexor plantar responses. Linear growth is often impaired whereas cognitive function is usually spared. Clinically, there is a marked, sustained improvement of all neurological deficits to low doses of orally administered L-dopa. Neuroimaging studies are generally normal.

The pathophysiology of GTP-cyclohydrolase I deficiency is caused by reduced levels of tyrosine hydroxylase activity as well as of dopamine itself within the caudate and putamen nuclei of the basal ganglia. The diagnosis of GTP-
cyclohydrolase I deficiency is strongly suggested by reduced levels of tetrahydrobiopterin, neopterin, homovanillic acid and 5-hydroxyindolacetic acid in the CSF. The disease can also be confirmed in 60 percent of patients by finding mutations in the GCH-I gene. This intervention usually results in significant and sustained improvement of the dystonia. As such, this may be a simpler and more affordable approach to making the diagnosis rather than by gene sequencing or CSF analysis of neurotransmitter metabolites.

**Disorders of GABA metabolism**

Most children with Pyridoxine-dependent epilepsy (PDE) present in the neonatal period with frequent seizures and an epileptic encephalopathy unresponsive to traditional anticonvulsant medications. PDE is an autosomal recessive disorder with a point prevalence that ranges from 1:20,000 in Germany (where pyridoxine challenges in neonatal seizures are quite common) to 1:687,000 in the United Kingdom and Ireland for definite and probable cases. The diagnosis of definitive PDE has been suggested by the complete cessation of seizures within seven days of pyridoxine administration, the recurrence of seizures following withdrawal of pyridoxine, and the subsequent remission of seizures when pyridoxine is re-administered. While most children present in the newborn period, convincing cases with epilepsy onset as late as 7 years of age have been reported. While the full spectrum of clinical symptomatology has not been fully elucidated, some children with PDE appear to be cognitively normal whereas others have been reported to have autism or intellectual disabilities. Seizure types vary from infantile spasms, recurrent partial motor seizures, generalized convulsive seizures and/or myoclonus.

Diagnosis of PDE is suggested by normalization of the interictal electroencephalogram (EEG) and cessation of seizures following a 50–100mg injection of intravenous pyridoxine. If there is not an immediate clinical and electrical response to this dose, additional dosages of 100mg of pyridoxine given every 10 to 15 minutes may be administered up to a total 500mg to determine if a response exists. Pyridoxine is an essential cofactor for glutamic acid decarboxylase and is necessary for the conversion of glutamic acid into GABA. Patients with PDE who are treated with intravenous pyridoxine may become hypotonic and apneic due to the sudden increase in CSF GABA concentrations, and artificial ventilation may be required. There are, however, reported cases of PDE that do not immediately respond to intravenous pyridoxine but that do gradually but completely respond to ongoing oral pyridoxine administration at dosages of 30/mg/kg/day.

Most patients with PDE have been found to have point mutations in the antiquitin gene (ALDH7A1) on chromosome 5q31. This gene encodes the enzyme alpha-aminoadipic semialdehyde dehydrogenase, which is part of the cerebral lysine degradation pathway (Figure 2). Dysfunction of this enzyme leads to accumulations of alpha-aminoadipic semialdehyde (AASA) as well as delta-1-piperidine-6-carboxylate (P6C) and L-pipeolic acid in serum, urine and CSF. P6C inactivates pyridoxal-5-phosphate, which is the active form of pyridoxine.

Several children with PDE have been found to have significant elevations of pipeolic acid in the serum prior to administration of pyridoxine treatment and milder elevations that have persisted once treatment began. Likewise, significant elevations of serum and urine AASA have been reported in PDE even after treatment.

Once a diagnosis of PDE is confirmed (either through pyridoxine treatment criteria or by documenting elevated levels of serum pipeolic acid or AASA), ongoing maintenance therapy with oral pyridoxine at dosages ranging from 50 to 200mg/day or more should be instituted. The dosage should be titrated upwards until all seizures stop or until there is normalization of CSF glutamate levels, which has also been suggested.

**References**

FIGURE 1
Monoamine metabolism

FIGURE 2
Pyridoxal-5-phosphate and cerebral lysine metabolism
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Please circle the best possible answer. CME offer is good until September 30, 2016.

1. Monoamines include all of the following neurotransmitters except:
   a. Gamma-Aminobutyric Acid
   b. Serotonin
   c. Dopamine
   d. Norepinephrine

2. Which of the following compounds inactivates Pyridoxal-5-Phosphate (the active form of vitamin B-6) in patients with pyridoxine-dependent epilepsy (PDE)?
   a. Pipecolic Acid
   b. Pyridoxamine
   c. Delta-1-Piperidine-6-Carboxylate
   d. α-aminoadipic Acid

3. Patients with GTP-cyclohydrolase I deficiency have lower levels of each of the following metabolites in their CSF except:
   a. Tetrohydrobiopterin
   b. Neopterin
   c. Phenyalaline
   d. Homovanillic Acid
   e. 5-Hydroxyindolacetic Acid

4. Clinical features of GTP-cyclohydrolase I deficiency have all of the following characteristics except:
   a. Patients are frequently misdiagnosed as having cerebral palsy.
   b. Treatment with low-dose levodopa-carbidopa results in a significant amelioration of their motor symptoms.
   c. Intelligence is usually severely impaired.
   d. Dystonia usually starts in one extremity (usually in the legs) before progressing to involve the trunk and all four extremities over 10 to 15 years.

5. Which of the following statements is least correct concerning patients with pyridoxine-dependent epilepsy (PDE)?
   a. Clinical response with cessation of seizures and normalization of the EEG following intravenous injection of 50-100mg of pyridoxine is suggestive of a diagnosis of PDE.
   b. Point mutations within the antiquitin gene (ALDH7A1), which encodes alpha-aminoadipic semialdehyde dehydrogenase, are responsible for causing PDE.
   c. Dysfunction of alpha-aminoadipic semialdehyde dehydrogenase results in significantly reduced levels of delta-1-piperidine-6-carboxylate (P6C) and pipecolic acid within the urine, serum and CSF.
   d. Maintenance dosing of pyridoxine ranging from 50 to 200mg per day should be continued once a diagnosis of PDE has been made.

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