Case Report: Intravenous and Oral Pyridoxine Trial for Diagnosis of Pyridoxine-Dependent Epilepsy

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Abstract

Pyridoxine-dependent epilepsy is a rare, autosomal recessive, treatable cause of neonatal seizures. Genetic testing can confirm mutations in the ALDH7A1 gene, which encodes antiquitin. To avoid delays in initiating treatment while awaiting confirmatory genetic testing, it is recommended that all neonates with unexplained seizures should receive trial of intravenous (IV) pyridoxine to assess for responsiveness. However, oral pyridoxine is not commonly continued in the absence of the typical EEG changes. Two cases are presented that highlight the potential inadequacy of this single-step approach. One neonate ultimately diagnosed with pyridoxine-dependent seizures had no EEG changes after administration of IV pyridoxine. In contrast, another neonate who did not have this diagnosis had profound EEG changes after pyridoxine administration. We present 2 cases that highlight the difficulties in using initial EEG response to IV pyridoxine in establishing a diagnosis of pyridoxine-dependent seizures in the neonate. Given the availability of biochemical markers and gene testing, we suggest that oral pyridoxine treatment should be continued until biochemical and/or genetic testing has confirmed the presence or absence of pyridoxine-dependent epilepsy.

Pyridoxine-dependent epilepsy (PDE) is rare and has a reported incidence of 1:400,000 to 1:750,000.1 Mutations in ALDH7A1, which encodes antiquitin, were established as the cause of PDE in 2006.2 Since then, more than 60 different mutations have been identified within the ALDH7A1 gene.2-6 This genetic defect causes a deficiency in the enzyme a-amino adipic semialdehyde dehydrogenase, part of the lysine catabolic pathway, resulting in accumulation of a-amino adipic semialdehyde (AASA), piperideine-6-carboxylate (P6C), and pipecolic acid (PA).4 P6C inactivates pyridoxal phosphate, which is the active form of pyridoxine. Pyridoxal phosphate is a cofactor for glutamic acid decarboxylase, which converts glutamate into the inhibitory neurotransmitter γ-amino butyric acid. Pyridoxal phosphate is also a cofactor for many other enzymes in the brain.7 The seizures and encephalopathy in PDE are likely secondary to cofactor deficiency and consequent decreased γ-amino butyric acid function and effects on other neurotransmitters. Daily administration of adequate amounts of oral pyridoxine cannot overcome antiquitin deficiency, but can significantly improve seizure control and neurodevelopmental outcome, highlighting the importance of early recognition, diagnosis, and treatment of this condition.1

Biochemical testing for PDE is characterized by elevated PA and AASA in urine, plasma, and cerebrospinal fluid (CSF).4 Genetic testing can confirm mutations in the ALDH7A1 gene. To avoid delays in initiating treatment while awaiting confirmatory testing, neonates with unexplained seizures usually receive a trial of oral pyridoxine. Two cases are presented that highlight the potential inadequacy of this single-step approach. One neonate ultimately diagnosed with pyridoxine-dependent seizures had no EEG changes after administration of IV pyridoxine. In contrast, another neonate who did not have this diagnosis had profound EEG changes after pyridoxine administration. We present 2 cases that highlight the difficulties in using initial EEG response to IV pyridoxine in establishing a diagnosis of pyridoxine-dependent seizures in the neonate. Given the availability of biochemical markers and gene testing, we suggest that oral pyridoxine treatment should be continued until biochemical and/or genetic testing has confirmed the presence or absence of pyridoxine-dependent epilepsy.
intravenous (IV) pyridoxine. Responsiveness has typically been assessed by changes in the EEG, notably immediate resolution of epileptiform discharges after administration of pyridoxine. However, there have been case reports of EEG changes in neonates without PDE after IV pyridoxine administration, as well as lack of EEG response in PDE acutely postpyridoxine. We present 2 cases that highlight the difficulties in using initial EEG response to IV pyridoxine in establishing a diagnosis of pyridoxine-dependent seizures in the neonate. Given these difficulties, we recommend (1) testing all neonates with refractory seizures for PDE, and (2) continuing pyridoxine supplementation until all testing confirms the presence or absence of PDE.

**CLINICAL CASE 1**

Patient 1 was born via spontaneous vaginal delivery at 38 weeks' gestation. Birth, family, and social histories were unremarkable. General and neurologic examinations were unremarkable. On the fifth day of life, she had events concerning for seizures, characterized by nonsuppressible rhythmic movements of her extremities with associated eye deviation and oxygen desaturation. Continuous video EEG monitoring was performed and confirmed that these events were myoclonic-tonic and brief tonic seizures. The EEG background showed excessive multifocal sharp-wave discharges and discontinuity for the stated postconceptual age. She received IV pyridoxine (100 mg × 2 doses) with no appreciable change in the EEG background. She was continued on maintenance phenobarbital and oral pyridoxine as other diagnostic testing was performed.

MRI of the brain was unremarkable. Serum and CSF studies for infectious (complete blood count, blood culture, urinalysis, urine culture, CSF culture) and metabolic (comprehensive metabolic panel, ammonia, urine organic acids, serum amino acids, serum lactate, serum pyruvate, CSF amino acids) disorders were unrevealing. CSF testing for monoamine metabolites showed a profile suggestive of pyridoxine-dependent seizures. Subsequent ALDH7A1 sequencing was positive for 1 known heterozygous deleterious mutation (c.328C>T; p.R110×) and 1 novel heterozygous missense mutation (c.869T>C; p.F290S). Each parent was found to carry 1 of each of the mutations. Pyridoxine dose was increased to 150 mg once daily and she was successfully weaned off phenobarbital. Neurologic development has been normal and she has had no seizure recurrence. Urine AASA was 1.76 mmol/mol creatinine (range <0.5 mmol/mol creatinine). Serial follow-up EEGs (last one at 28 months of age) have been normal. Her clinical course, response to pyridoxine, and genetic testing results confirmed the diagnosis of pyridoxine-dependent seizures.

**CLINICAL CASE 2**

Patient 2 was born via spontaneous vaginal delivery at 37 4/7 weeks' gestation. Birth, family, and social histories were unremarkable. At 21 days of age, she presented with new-onset seizures characterized by myoclonic jerks of upper and lower extremities and head deviation. Clinical seizures resolved after administration of phenobarbital, but encephalopathy persisted. Initial EEG was abnormal due to almost continuous epileptiform discharges from sites in both hemispheres that were invariant and not responsive to state or stimulation (Fig 1A). After administration of IV pyridoxine (100 mg × 2 doses), the EEG improved rapidly to a normal pattern for age (Fig 1B). General and neurologic examinations were otherwise unremarkable. Seizures were controlled with phenobarbital and oral pyridoxine as other diagnostic testing was performed.

Initial MRI of the brain showed symmetric areas of restricted diffusion and parenchymal signal abnormality involving the periventricular and deep white matter, dorsal thalami, internal capsules, corticospinal tracts, and corpus callosum. Serum and CSF studies for infectious (complete blood count, blood culture, urinalysis, urine culture, CSF culture) and metabolic (comprehensive metabolic panel, ammonia, urine organic acids, serum amino acids, serum lactate, serum pyruvate, CSF amino acids, urine sulfocysteine) disorders were unrevealing. Testing for PDE, which included serum PA, urine AASA (0.43 mmol/mol creatinine [range <0.5]), and ALDH7A1 sequencing were normal. She was discharged from the hospital 3 days after admission on phenobarbital and pyridoxine. Pyridoxine and phenobarbital were discontinued at 4 and 6 months of age, respectively. Her development was normal and she had no deficits on physical or neurologic examinations at 15 months of age. Follow-up EEG done at 2 and 5 months of age were mildly abnormal, showing rare focal epileptiform discharges. Follow-up brain MRI done at 6 months of age showed subtle T2 signal changes in the deep supratentorial white matter and mild thinning of the corpus callosum. Despite the initial dramatic “positive” EEG response to pyridoxine, the subsequent clinical course and negative biochemical and genetic test results were not consistent with PDE.

**DISCUSSION**

PDE is a rare, autosomal recessive, cause of neonatal seizures and encephalopathy of likely underestimated incidence. Pediatricians and neonatologists
should be aware of this potentially treatable cause of neonatal-onset epilepsy. The clinical diagnosis is challenging for a variety of reasons. Infants with this disorder can have multiple seizure types that include focal, clonic, tonic, and myoclonic seizures.\textsuperscript{6,8,12} Neonates can have additional symptoms, such as tremulousness, hyperalertness, abdominal distension, emesis, and irritability that can precede seizure and obscure the diagnosis.\textsuperscript{7,8,13} One study noted that approximately one-third of infants with PDE present with birth asphyxia or suspected hypoxic ischemic injury.\textsuperscript{8} Hypoglycemia and lactic acidosis accompanying PDE also have been reported.\textsuperscript{14} MRI findings are variable and include callosal dysgenesis (hypoplastic or dysplastic corpus callosum), cortical dysplasia, hydrocephalus, ventriculomegaly, and subependymal

FIGURE 1
EEG from patient without PDE (clinical case 2) showing response to IV pyridoxine. A, Wake epoch before treatment shows an abnormal and invariant background with almost continuous epileptiform discharges. B, Wake epoch after treatment with IV pyridoxine showing normal background for age.
cysts. In these cases, epilepsy is often attributed to structural brain lesions and no further investigations are carried out. Some neonates with PDE can respond initially to conventional anticonvulsants and later are found to have seizures that are responsive to pyridoxine. Furthermore, there is no single pathognomonic EEG pattern in PDE. Typical EEG patterns include abnormal sleep patterns, focal or multifocal epileptiform discharges, rhythmic slowing, or burst suppression. In neonates with unexplained seizures refractory to conventional antiepileptic medications, a trial of IV pyridoxine with continuous EEG monitoring is commonly performed. If no clinical or EEG change is noted, pyridoxine administration may not always be continued after the negative response to the IV trial in current practice paradigms.

These 2 cases highlight the potential pitfalls of this single-step approach with IV pyridoxine. It is important to recognize that this approach is outdated given that the affected pathway has been identified and biochemical markers and DNA sequencing of the gene are available as sensitive and specific tests. The neonate who was ultimately diagnosed with PDE had no EEG changes after administration of IV pyridoxine, whereas the infant without PDE did have profound EEG changes. These findings are consistent with other studies that show that IV pyridoxine can be associated with nonspecific EEG changes that are not diagnostic or exclusionary of the disorder. These and previous reported cases emphasize that oral pyridoxine treatment should be continued while waiting for further testing results. Evidence-based protocols for acute or maintenance therapy are not available, but an initial dose of 100 mg IV pyridoxine followed by oral maintenance dosing ranging between 15 and 30 mg/kg per day is suggested. The evaluation can include serum or urine AASA, serum and CSP PA, and plasma P6C, all of which accumulate due to deficiencies of aldehyde dehydrogenase in the lysine degradation pathway. However, it is important to recognize that PA also can be elevated secondary to liver disease and in peroxisomal disorders. Similarly, elevated AASA is not specific and can be associated with isolated sulfite oxidase deficiency and the related condition, molybdenum cofactor deficiency. CSF monoamine metabolite analysis shows specific peaks (of yet undetermined compounds) and elevated AASA specific to PDE. Genetic testing with sequencing of ALDH7A1 is available, but it should be noted that PDE is inherited in an autosomal recessive manner and the diagnosis is definitive only when 2 pathogenic mutations are identified. Ideally, each parent is confirmed as a carrier of 1 mutation (demonstrating each mutation is on a different chromosome in the affected child). Pyridoxal 5′-phosphate oxidase deficiency is a related cause of neonatal seizures that can present like PDE. This condition usually requires supplementation with pyridoxal phosphate, but also may be responsive to pyridoxine in some cases. Therefore, diagnostic evaluation via CSF determination of pyridoxal 5′-phosphate (low in this condition) is recommended as well. If abnormal, DNA sequencing of the pyridoxal 5′-phosphate oxidase gene can be performed. Although PDE is rare, it is a potentially treatable cause of neonatal-onset epilepsy that should be aggressively and systematically evaluated for the best possible outcome. PDE also can have later-onset presentation (beyond neonatal and infancy periods) and testing for this condition should be considered in older children with intractable epilepsy.

**ABBREVIATIONS**

AASA: α-aminoadipic semialdehyde
CSF: cerebrospinal fluid
IV: intravenous
PA: pipecolic acid
PDE: pyridoxine-dependent epilepsy
P6C: piperideine-6-carboxylate

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