Pyridoxine dependent epilepsy (PDE) is caused by mutations in the ALDH7A1 gene encoding α-aminoadipic semialdehyde dehydrogenase. The classic clinical presentation is neonatal seizures responsive only to pyridoxine therapy. White matter abnormalities, corpus callosum agenesis or hypoplasia, megacisterna magna, cortical dysplasia, neuronal heterotopias, intracerebral hemorrhage, and hydrocephalus in neuroimaging have been reported in patients with PDE. We report a new patient with asymmetric progressive ventriculomegaly noted on fetal sonography at 22 weeks’ gestation. Postnatal brain sonography on day 1 and MRI on day 5 confirmed bilateral asymmetric ventriculomegaly caused by bilateral subependymal cysts. Intractable seizures at age 7 days initially responded to phenobarbital. Markedly elevated urinary α-aminoadipic acid semialdehyde levels and compound heterozygous mutations in the ALDH7A1 gene (c.446C>A/c.919C>T) confirmed the diagnosis of PDE caused by ALDH7A1 genetic defect. Despite the presence of structural brain malformations and subependymal cysts, PDE should always be included in the differential diagnosis of neonatal seizures that are refractory to treatment with antiepileptic drugs. Pediatrics 2014;133:e1092–e1096
Pyridoxine dependent epilepsy (PDE) is an autosomal recessively inherited disease and was first described by Hunt et al in 1954. In 2006, Mills et al identified mutations in the ALDH7A1 gene encoding α-aminoadipic semialdehyde dehydrogenase enzyme in the lysine catabolic pathway. α-Aminoadipic semialdehyde dehydrogenase deficiency leads to accumulation of α-aminoadipic acid semialdehyde (α-AASA) and piperidine 6-carboxylic acid; the later inactivates pyridoxal-5-phosphate. Pipelicolic acid (PA) elevations in body fluids were reported in patients with PDE as a secondary biomarker.

Clinical phenotypes include (1) neonatal onset intractable seizures with a dramatic response to pyridoxine and (2) later onset seizures (up to 3 years of age) initially responsive but then refractory to antiepileptic drugs and with a slower response to pyridoxine. Abnormal brain imaging findings including white matter abnormalities, corpus callosum agenesis or hypoplasia, megacisterna magna, cortical dysplasia, neuronal heterotopias, intracerebral hemorrhage, and hydrocephalus have been previously reported. None of these were found to be pathognomonic for PDE.

We report a new patient with PDE caused by ALDH7A1 genetic defect (PDE-ALDH7A1) with prenatal progressive ventriculomegaly secondary to bilateral subependymal cysts (SECs) and neonatal seizures initially responsive to phenobarbital.

**CASE REPORT AND RESULTS**

This boy was born at 38 weeks' gestation via caesarean delivery to non-consanguineous parents. Apgar scores were 8 and 9, at 1 and 5 minutes, respectively. Birth weight was at 25th, length at third, and head circumference at 50th percentiles. Pregnancy was remarkable for a left lateral ventriculomegaly identified at 22 weeks' gestation on fetal ultrasound. Serial fetal ultrasounds at 30 and 36 weeks' gestation revealed progression of unilateral mild ventriculomegaly to asymmetric bilateral severe ventriculomegaly. Head ultrasound confirmed bilateral ventriculomegaly and bilateral SECs at birth (Fig 1A). Cranial MRI revealed bilateral asymmetric dilation of the lateral ventricles with bilateral large SECs at 4 days of age (Fig 1 B–D).

He developed poor feeding, vomiting, and hyponatremia (127, normal 133–142 mmol/L) at age 4 days and multifocal clonic seizures (10–15 clustering) at age 7 days. He was given lorazepam and phenobarbital and became transiently seizure free until 16 days of age on phenobarbital. EEG revealed discontinuous background activity with frequent sharp-wave transients over the bilateral centro-temporal head regions. At age 17 days, while on phenobarbital, he had 4 generalized tonic-clonic seizures lasting 5 to 10 seconds each and was given lorazepam and his seizures stopped. Next day, he developed lip smacking, posturing, and eye rolling, which resolved without addition of other antiepileptic medications. At age 19 days, he had multiple generalized tonic-clonic seizures lasting 15 to 30 seconds, which then progressed to status epilepticus. He was loaded with phenytoin and lorazepam and midazolam infusion (5 μg/kg per minute) was started in the ICU. Levetiracetam and pyridoxine (14 mg/kg per day intravenous) were added at age 21 days. Midazolam was gradually...
discontinued at age 24 days, and pyridoxine was switched to oral (14 mg/kg per day) therapy. There were no further seizures.

Investigations were normal for infectious and metabolic causes. Due to neonatal onset intractable epilepsy, α-AASA and plasma PA for PDE-ALDH7A1 were performed at age 3 weeks. He was discharged from the hospital at age 30 days on phenobarbital, levetiracetam, and pyridoxine. At age 2 months, neonatal seizures were attributed to SECs and ventriculomegaly, and pyridoxine was discontinued. He re-presented with generalized tonic-clonic seizures lasting 20 to 30 seconds in 1 week. He was treated with levetiracetam dose increase, lorazepam, and phenytoin. Overnight video EEG revealed multiple cortical epileptiform discharges. Clinical seizures continued 1 to 2 per day lasting up to 10 minutes. Laboratory results revealed markedly elevated urinary α-AASA (39.6 mmol/mol creatinine; reference range 0.0–2) and plasma PA (31.2 μmol/L; reference range 0.1–5.3 μmol/L) levels. Pyridoxine was restarted at 30 mg/kg per day, and his seizures ceased the following day. Mutation analysis revealed compound heterozygosity for a novel missense variant, c.446C>T;p.Arg307Cys (alanine 149 moderately conserved in evolution; not detected in 210 control alleles; maternally inherited) and another pathogenic missense mutation (c.919C>T;p.Arg307X); paternally inherited) in the ALDH7A1 gene. Additionally, cerebrospinal fluid (CSF) PA (8.39 μmol/L; reference range 0.009–0.12) was markedly elevated in the neonatal period, but mild to moderately elevated at age 8 months (0.88 μmol/L).

At age 7 months, he remained seizure free on pyridoxine of 200 mg/day (29 mg/kg per day). He was age appropriate for gross motor, fine motor, and receptive and expressive language domains by Mullen’s Scale of Early Learning. His neurologic examination was unremarkable. His EEG was normal at age 6 months. SECs were resolved at age 4 months, and ventriculomegaly was resolved at age 7 months on head ultrasound.

**DISCUSSION**

Our patient with PDE-ALDH7A1 presented with progressive severe prenatal onset ventriculomegaly associated with SECs and atypical features of PDE including moderate hyponatremia and late onset neonatal seizures initially and transiently responsive to phenobarbital for 2 weeks. Due to SECs and ventriculomegaly, pyridoxine was discontinued at age 2 months resulting in seizure recurrence. Markedly elevated urinary α-AASA and plasma PA levels at age 2.5 months and compound heterozygous mutations in the ALDH7A1 gene confirmed the diagnosis of PDE-ALDH7A1. Hyponatremia and hypomagnesemia have been reported in 2 patients with PDE.8 Hyponatremia identified in our patient expands the biochemical phenotype in patients with PDE. The majority of patients with PDE present within the first few days after birth with seizures nonresponsive to antiepileptic medications. Only 5 patients (4 with neonatal onset9–12 and 1 with late onset12) have been reported with initial response to phenobarbital up to 9 months. Our patient adds to these patients with PDE who were reported with transient initial good seizure control on phenobarbital therapy.

SECs are reported in 1% to 5% of newborns in cranial ultrasounds as a common finding.13–15 They likely occur due to cellular destruction of the ventricular ependymal cells and residual cavity formation.14 Bilateral SECs have also been reported in patients with hypoxic-ischemic insult, prematurity-related complications, congenital infections, and chromosomal disorders.15–18 It has been shown that SECs were resolved spontaneously within 1 to 12 months of age in 93.5% of cases independent of underlying etiology.17 SECs have been found in patients with inherited metabolic disorders including mitochondrial depletion syndrome,19 glutaric aciduria type 1,19 holocarboxylase synthetase deficiency,20 pyruvate dehydrogenase deficiency,21 D-2-hydroxy glutaric aciduria,22 and Zellweger syndrome.23,24 Unfortunately, there are no reports of neuroimaging studies for the outcome of cysts in these patients, except 1 patient with holocarboxylase synthetase deficiency, who had resolution of SECs at age 6 months on biotin therapy.20 Independent of underlying etiology, the mechanism for the resolution of SECs is not well known. In our patient, SECs were also resolved at the age of 4 months. We do not know if pyridoxine therapy has a role in this process. Because PDE-ALDH7A1 is a treatable neuronal metabolic disorder, this should be included in the differential diagnosis of SECs.

PA is elevated in Zellweger syndrome,25 other peroxisomal biogenesis defects,25 and hyperpippecolic acidemia.26 CSF PA levels were 17.8 to 65 times elevated within the first 6 months of life in 8 patients and 2.6 to 5.6 times elevated after 2 years of age in 3 patients with PDE-ALDH7A1.4,27 In our patient, CSF PA level was 70 times elevated in the neonatal period, but it was only 7 times elevated at age 8 months on pyridoxine therapy alone. Age-related decrease in CSF PA levels and pyridoxine therapy might be an explanation for the resolution of SECs in our patient. The common denominator in peroxisomal disorders and PDE-ALDH7A1 is elevated PA levels. There could be a relationship between elevated PA levels and SECs.
because they have been reported in peroxisomal disorders and in our patient with PDE-ALDH7A1 in this report. Additionally, it has been shown that human ALDH7A1 protein encoded by the ALDH7A1 gene has osmoprotective28 (against hyperosmotic stress induced) and cytoprotective28 (against reactive oxygen species induced) functions and attenuates apoptotic cell death in Chinese hamster ovary cells.

Structural brain malformations including focal cortical dysplasia, polymicrogyria, periventricular nodular and subcortical band heterotopia, hydrocephalus, benign cysts, and lissencephaly are associated with seizures.29,30 Various abnormalities in cranial MRI have been reported in patients with PDE including thinning of the corpus callosum, white matter abnormalities, ventriculomegaly, gray matter heterotopia, cortical dysplasia, gray and white matter atrophy, and megacisterna magna.8–12 One patient with PDE was reported with mild ventriculomegaly on prenatal ultrasound, resolved on neonatal cranial MRI. Neonatal MRI in that patient revealed petechial hemorrhage in periventricular white matter.8 There was only 1 patient with PDE reported with bilateral SECs in a neonatal head ultrasound, but neonatal cranial computed tomography scan revealed delayed myelination but did not confirm SECs.32 To the best of our knowledge, our patient is the first patient presenting with fetal onset of asymmetric progressive ventriculomegaly, confirmed on neonatal cranial MRI to be caused by bilateral SECs obstructing the foramen of Monro.

CONCLUSIONS

We report a new patient with PDE-ALDH7A1. Our patient had new biochemical (hyponatremia) and neuroradiographic findings (ventriculomegaly due to SECs) expanding the spectrum of PDE. We think that PDE should be included in the differential diagnosis of intractable neonatal or infantile seizures even in the presence of structural brain malformations (in our case ventriculomegaly due to SECs). Initial transient seizure response to phenobarbital therapy should not discourage consideration of PDE. Pyridoxine should be continued until investigations exclude the diagnosis of PDE-ALDH7A1.

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