Profound Neonatal Hypoglycemia and Lactic Acidosis Caused by Pyridoxine-Dependent Epilepsy

abstract

Pyridoxine-dependent epilepsy (PDE) was first described in 1954. The ALDH7A1 gene mutations resulting in α-aminoadipic semialdehyde dehydrogenase deficiency as a cause of PDE was identified only in 2005. Neonatal epileptic encephalopathy is the presenting feature in >50% of patients with classic PDE. We report the case of a 13-month-old girl with profound neonatal hypoglycemia (0.8 mmol/L; reference range >2.4), lactic acidosis (11 mmol/L; reference range <2), and bilateral symmetrical temporal lobe hemorrhages and thalamic changes on cranial MRI. She developed multifocal and myoclonic seizures refractory to multiple antiepileptic drugs that responded to pyridoxine. The diagnosis of α-aminoadipic semialdehyde dehydrogenase deficiency was confirmed based on the elevated urinary α-aminoadipic semialdehyde excretion, compound heterozygosity for a known splice mutation c.834G>A (p.Val278Val), and a novel putative pathogenic missense mutation c.1192G>C (p.Gly398Arg) in the ALDH7A1 gene. She has been seizure-free since 1.5 months of age on treatment with pyridoxine alone. She has motor delay and central hypotonia but normal language and social development at the age of 13 months. This case is the first description of a patient with PDE due to mutations in the ALDH7A1 gene who presented with profound neonatal hypoglycemia and lactic acidosis masquerading as a neonatal-onset gluconeogenesis defect. PDE should be included in the differential diagnosis of hypoglycemia and lactic acidosis in addition to medically refractory neonatal seizures. Pediatrics 2012;129:e1368–e1372

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KEY WORDS
pyridoxine-dependent epilepsy, myoclonic epilepsy, hypoxic ischemic encephalopathy, neonatal hypoglycemia, lactic acidosis, ALDH7A1 deficiency

ABBREVIATIONS
α-AASA—α-aminoadipic semialdehyde
α-AASDH—α-aminoadipic semialdehyde dehydrogenase
CSF—cerebrospinal fluid
IV—intravenous
PDE—pyridoxine-dependent epilepsy
PNPO—pyridoxamine phosphate oxidase

Dr Mercimek-Mahmutoglu diagnosed the patient and performed conception and design, acquisition of data, interpretation of data, drafting and revision of the article for intellectual content, and final approval of the version to be published; Dr Horvath contributed to diagnostic work-up, revising the article for intellectual content, and final approval of the version to be published; Dr Coulter-Mackie contributed to revising the article for intellectual content and final approval of the version to be published; Dr Nelson provided interpretation of mutation analysis and pathogenicity of the mutations, interpretation of different nomenclature, revision of the article for intellectual content, and final approval of the version to be published; Dr Waters contributed to the biochemical parameters, revision of the article for intellectual content, and final approval of the version to be published; Dr Sargent provided MRI results and figures and contributed to revision of the article for intellectual content, providing final approval of the version to be published; Dr Straus and Jakobs performed biochemical measurements for pyridoxine-dependent epilepsy, revised the article for intellectual content, and provided final approval of the version to be published; Dr Stockler-Ipsiroglu supported mutation analysis and provided final approval of the version to be published; and Dr Connolly made substantial contributions to conception and design, acquisition of data or analysis and interpretation of data, analysis of EEGs (epilepsy part), and critical revision of the article for important intellectual content.

(Continued on last page)
Pyridoxine-dependent epilepsy (PDE) (Online Mendelian Inheritance in Man: 266100) is an autosomal-recessive disorder caused by mutations in the \(ALDH7A1\) gene causing \(\alpha\)-aminoadipic semialdehyde dehydrogenase (\(\alpha\)-AASADH) enzyme deficiency (Online Mendelian Inheritance in Man: 107323) (Enzyme Commission or Enzyme number: 1.2.1.31) in the lysine catabolic pathway.\(^1\) The pathophysiology of \(\alpha\)-AASADH deficiency is determined by accumulation of \(\alpha\)-aminoadipic semialdehyde (\(\alpha\)-AASA) and piperidine-6-carboxylate. The piperidine-6-carboxylate undergoes a chemical condensation with pyridoxal phosphate, the active form of pyridoxine, resulting in functional pyridoxal phosphate deficiency.\(^2\)

Neonatal encephalopathy is the presenting feature in >50% of patients, characterized by hyperalertness, irritability, tremulousness, and excessive startle response. Abnormal cord blood gases and low Apgar scores mimicking hypoxic ischemic encephalopathy have been described in one-third of patients.\(^3\)\(^,\)\(^4\) We report the case of a 13-month-old girl with PDE caused by mutations in the \(ALDH7A1\) gene who presented with profound neonatal hypoglycemia and lactic acidosis, suggestive of gluconeogenesis defects.

**PATIENT PRESENTATION**

This patient is a 13-month-old girl of unrelated white parents. She was born at 41 weeks' gestation by spontaneous vaginal delivery after an uneventful pregnancy. Her Apgar scores were 4, 9, and 9 at 1, 5, and 10 minutes, respectively. Her birth weight was at the 50th percentile, her length was at the 95th percentile, and her head circumference was at the 75th percentile. She was discharged from the hospital at 1 day of age. Parents reported her being hyperalert and sleepless in the first 3 days of life. She had multiple emeses on the third day of life, culminating in hematemesis, frequent episodes of mouthing movements, eye rolling, and generalized stiffening of the limbs at the time of presentation to the local pediatric emergency department at the age of 4 days. Her blood glucose level was 0.6 mmol/L (10.8 mg/dL; reference range >2.4 mmol/L; ie, >43.2 mg/dL), her lactate level was 11 mmol/L (99 mg/dL; reference range <2.2; ie, <19.8 mg/dL), and metabolic acidosis was present (pH: 7.23; bicarbonate, 6; and anion gap, 29). The hypoglycemia and lactic acidosis resolved by continuous intravenous (IV) glucose infusion (4.2 mg/kg/minute) within 6 hours of her admission. She had 4 seizures characterized by mouthing and bilateral tonic clonic movements lasting from 1 minute to 1 hour in the first 2 days despite IV administration of phenobarbital, midazolam, and phenytoin. There was no further hypoglycemia on IV glucose infusion. According to hospital policy for continuing seizures, pyridoxine (50 mg IV) was given on the second day of admission and was continued with 50 mg/day throughout her hospitalization. She became seizure-free after the first dose. Her cranial MRI revealed bilateral symmetrical inferior temporal lobe hemorrhages, petechial hemorrhages in the cerebellum and supratentorial brain, small amounts of intraventricular blood, and restricted diffusion in bilateral ventrolateral thalami, in midbrain, and, to a lesser extent, in the dorsal pons (Figs 1 and 2). EEG examination on the day of presentation showed marked suppression and discontinuity of the background and multifocal sharp waves (longitudinal bipolar and coronal bipolar montage). She had electrographic seizures lasting 8 to 13 minutes arising from the left occipital and right occipital temporal area, correlating with clinical seizures. Investigations were initiated for gluconeogenesis defects (fructose-1, 6-bisphosphatase; pyruvate carboxylase; and phosphoenolpyruvate carboxykinase deficiencies) because of profound hypoglycemia and lactic acidosis and excellent response to IV glucose infusion. She was discharged from the hospital in a good clinical condition with oral feeding on phenobarbital at age 2 weeks, and treatment with pyridoxine was discontinued.

She developed irritability and recurrence of seizures 1 week after discontinuation of pyridoxine and presented to the local pediatric emergency department again. Her blood glucose level was normal, and her lactate level was elevated mildly at 3.3 mmol/L (29.7 mg/dL). She was transferred to our hospital for management. She had myoclonic seizures with diffuse spike and wave on EEG (longitudinal bipolar and coronal bipolar montage) and focal seizures of the left temporal and bilateral parietal lobe origin. Her seizures were treated with administration of high-dose midazolam (IV infusion), phenobarbital, clobazam, clonazepam, topiramate, levetiracetam, and piracetam. She required intubation and assisted ventilation in the ICU.
Her lactate levels were elevated mildly (up to 2.9 mmol/L; i.e., 26.1 mg/dL) during her second admission. The mildly elevated lactate levels were likely due to frequent seizures. Her blood glucose levels were between 2.4 mmol/L (43.2 mg/dL) and 4.4 mmol/L (79.3 mg/dL) throughout the admission. On the 18th day of her second admission, administration of pyridoxine (200 mg/day) was restarted, and urine α-AASA testing was requested. She became seizure-free the next day.

Urinary α-AASA level (21.3 mmol/mol creatinine; reference range <1) was elevated markedly (measured by using a previously reported method).

Sequencing of the ALDH7A1 gene, as described previously, detected compound heterozygosity for a paternally inherited novel missense mutation in exon 13, c.1192G>C (p.Gly398Arg) and a maternally inherited mutation in exon 9, c.834G>A (p.Val278Val) (in the literature referred to as c.750G>A; p.V250V), previously demonstrated to interfere with normal splicing. Mutations are described relative to RefSeq NM_001182.3 (consensus coding sequences [CDS] identification number consensus coding sequences [CCDS] 4137) by using Human Genome Variation Society (HGVS) recommendations for the description of sequence variants, version 2.0, and differ from legacy nomenclature used extensively throughout the literature pertaining to ALDH7A1. Protein prediction programs PolyPhen-2® (Polymorphism Phenotyping v2, Available at: http://genetics.bwh.harvard.edu/pph2/) and Align (International Agency for Research on Cancer; World Health Organization, Lyon, Cedex, France; Available at: http://agvgd.iarc.fr/index.php) predict, respectively, that this change will be probably damaging (1.00) and most likely will affect function (C65). This mutation was not identified in 100 normal control chromosomes. Fructose 1,6 bisphosphatase by FBP1 gene-sequencing mutation analysis, pyruvate carboxylase, and phosphoenolpyruvate carboxykinase deficiencies by normal enzyme activities in the cultured fibroblasts were excluded. Cerebrospinal fluid (CSF) collected at age 1 month, before diagnosis, revealed normal results for monoamine neurotransmitter metabolites, including 3-O-methyltyrosine and 5-methyltetrahydrofolate. Two unknown peaks on monoamine metabolite analysis, which are characteristic for α-AASADH, also were identified in the CSF. Her pyridoxal phosphate was markedly low in the CSF (3.6 nmol/L; reference range: 30–80) before pyridoxine treatment.

She has been seizure-free on a regimen of 200 mg/day of pyridoxine since 1.5 months of age; her current age is 13 months. Piracetam and phenobarbital usage was decreased gradually and discontinued in the first year of life. Her EEG demonstrated mild background suppression and multifocal spikes at the age of 1.5 months, after pyridoxine therapy. At the age of 6 months, the EEG was normal in drowsy and sleep states (data not shown). At a chronological age of 12 months using the Gesell assessment, her developmental milestones were as follows: gross motor; 7 months; fine motor; 8 months; cognitive/adaptive functions, 11 to 12 months; language, 9 months; and personal/social skills, 12 months. Her neurologic examination showed normal head growth, truncal hypotonia, mildly increased peripheral tone in the upper extremities, and normal muscle stretch reflexes at age 13 months.

DISCUSSION

We report the case of a patient with PDE caused by mutations in the ALDH7A1 gene with profound neonatal hypoglycemia and lactic acidosis. The effect of low-dose pyridoxine was overlooked in the neonatal period because hypoglycemia and lactic acidosis are not typical biochemical features of PDE. Owing to recurrence of intractable seizures within 1 week of discontinuation of pyridoxine in the late neonatal period and no response to multiple antiepileptic drugs, we included PDE in the differential diagnosis. Good clinical response to pyridoxine, markedly elevated α-AASA levels in urine samples, and compound heterozygous mutations in the ALDH7A1 gene confirmed the diagnosis of α-AASADH deficiency in this patient.

A direct relationship between neuronal glutamate metabolism (main excitatory neurotransmitter) and cerebral oxidative glucose metabolism in the central nervous system was reported previously. Excitatory neurotransmitter circuitry is localized mainly in basal ganglia, thalamus, and the perirolandic cerebral cortex. Energy failure caused by hypoglycemia disrupts the neuronal glutamate metabolism and causes excitotoxicity, resulting in neuronal injury. Severe white matter, basal ganglia, and thalamic hemorrhagic insult have been reported in 35 term infants with symptomatic
neonatal hypoglycemia. Asymmetric small foci of intracranial hemorrhage and sinus venous thrombosis have been described previously in patients with PDE. We report the first patient with PDE with bilateral, symmetrical temporal lobe hemorrhages.

The presence of low levels of CSF pyridoxal phosphate was another interesting finding in our patient. This finding typically occurs in pyridoxamine phosphate oxidase (PNPO) deficiency and also has been reported recently in 2 patients with PDE caused by mutations in the ALDH7A1 gene. In our patient, based on the normal monoaminergic neurotransmitter metabolites, including 3-0-methylpore, normal threonine, and glycine in the CSF and detection of compound heterozygosity for presumed pathogenic mutations in the ALDH7A1 gene, PNPO deficiency was unlikely. We did not perform sequencing of the PNPO gene.

Metabolic acidosis without measured lactate levels has been reported in patients with PDE (26%). Only 1 patient with PDE caused by mutations in the ALDH7A1 gene has been reported with an episode of unexplained collapse, sweating, and profound lactic acidosis at age 3 weeks associated with hyperglycemia but not hypoglycemia. Mild, nonpersistent hypoglycemia responsive to IV glucose infusion was reported in 4 of 32 patients with PDE. Severe hypoglycemia in combination with severe lactic acidosis has not been reported in >100 patients with PDE-caused mutations in the ALDH7A1 gene. To our knowledge, our patient is the first with profound neonatal hypoglycemia and lactic acidosis in addition to intractable multifocal and myoclonic seizures and neonatal encephalopathy mimicking hypoxic ischemic encephalopathy due to PDE caused by mutations in the ALDH7A1 gene. Despite our center’s experience with pediatric metabolic disorders and familiarity with PDE, the atypical biochemical features caused delays in the diagnosis and treatment of our patient. Pyridoxal phosphate is the cofactor for >140 enzymes, as shown in the Expasy Enzyme Database (http://enzyme.expasy.org/cgi-bin/enzyme/enzyme-search-cf?Pyridoxal_5'-phosphate) and its deficiency could cause various, previously not described biochemical disturbances in affected neonates and infants. More atypical cases with PDE presenting with various manifestations accompanied by intractable seizures should be expected, and PDE should be included in the differential diagnosis of neonatal and infantile-onset hypoglycemia and lactic acidosis in addition to intractable seizures.

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