Child Neurology: Late-Onset Vitamin B₆-Dependent Epilepsy Identified by Rapid Genome Sequencing

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Hundreds of distinct epilepsy-causing genes have been identified.¹ The vitamin B₆-dependent epilepsies are a heterogeneous group of genetic disorders due to incomplete formation, transport, or inactivation of pyridoxal 5'-phosphate (PLP).² The *ALDH7A1*, *PNPO*, *ALPL*, *ALDH4A1*, and more recently *PLPBP* genes have been implicated.³ Characteristic presentation of vitamin B₆-dependent epilepsies includes neonatal onset of encephalopathy and seizures refractory to first-line antiseizure medications (ASMs) followed by cessation or dramatic improvement of seizures after administration of pyridoxine or PLP. Because initiation of proper treatment is essential for seizure control, timely diagnosis is critical to optimizing clinical outcome. We describe the case of a 3-year-old boy who presented with progressively worsening refractory seizures starting at 14 months of age and was subsequently diagnosed with pyridoxal phosphate homeostasis protein (PLPHP) deficiency via rapid genome sequencing during a critical care hospitalization for status epilepticus. He was started on pyridoxine with immediate cessation of seizure activity and has remained seizure-free. We review the diagnosis, management, and outcome of PLPHP deficiency, as well as implications for use of rapid genetic testing in the acute care setting.

Clinical Case

The patient was born at 39 weeks' gestational age via an uncomplicated pregnancy and delivery. He was developmentally appropriate for age without significant medical or family history prior to his initial presentation at 14 months of age, when he presented with new, prolonged, and recurrent emotional and myoclonic seizures. On EEG, the interictal background was diffusely slow and disorganized with superimposed, high-amplitude, synchronous bi-occipital, as well as generalized, sharp and spike discharges. Ictal recordings showed insidious increase in frequency of epileptiform discharges (1–2 Hz frequency), waxing and waning for prolonged periods of time (10–30 minutes), with unclear onset/offset (figure 1A) and occasional myoclonic jerks (figure 1B). Clinically, the patient ran to his parents and appeared frightened, then became still with decreased responsiveness, occasionally followed by intermittent generalized myoclonic twitching, corresponding to generalized epileptiform discharges on EEG. After seizure onset, his speech regressed. At his initial presentation, he had a normal brain MRI. Laboratory diagnostic testing, including evaluation of routine CSF studies, metabolic studies (urine organic acids, plasma and CSF amino acids, CSF homovanillic acid, 3-O-methyldopa, and 5-hydroxyindoleacetic acid), paraneoplastic studies (urine vanillylmandelic/homovanillic acid), and CSF and serum autoimmune encephalitis antibody panels were normal, with exception of mild hyperlactatemia. A comprehensive epilepsy gene panel showed variants of unknown significance in *SCN2A*, *IQSEC2*, and *ABAT* genes. Levetiracetam, fosphenytoin, zonisamide, and benzodiazepines were trialed with continued breakthrough seizure clusters. His prolonged seizures resolved with phenobarbital loads and seizures stopped after initiation of topiramate and IV immunoglobulin (IVIg). He experienced seizure freedom for 6 months prior to returning with another period of frequent seizure clustering and onset of tonic-clonic seizures as

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well. Repeat brain MRI at 22 months demonstrated bilateral mesial temporal sclerosis (figure 2). He had frequent pediatric intensive care unit (PICU) admissions for super-refractory status epilepticus responsive to phenobarbital and propofol. He was transitioned to valproic acid, clobazam, and lacosamide, with resolution of his seizures. He was seizure-free until 3 years of age, when he had 4 PICU admissions for super-refractory status epilepticus, despite escalation in ASM dosing, over a 3-month period. His parents noted more prominent regressions with each seizure cluster. With his most recent admission, he underwent multiple rounds of anesthetic drips including propofol, ketamine, and pentobarbital burst suppression. Rapid induction of the ketogenic diet was trialed, but stopped due to development of pancreatitis. IVIg and high-dose IV steroid courses were trialed with unclear efficacy. Rapid whole genome sequencing (rWGS) was obtained and revealed a compound heterozygous pathogenic variation of the *PLPBP* gene, formerly known as *PROSC*⁴ (maternal inheritance of c260C>T variant and paternal inheritance of c.320-2A>G variant). α -Aminoadipic semialdehyde (AASA) and pipercolic acid in serum and urine were normal. He was given a pyridoxine 100 mg IV trial and has remained seizure-free since then. Concurrent EEG monitoring with pyridoxine administration showed subtle increased amplitude and greater prominence of diffuse beta activity. At time of diagnosis, he was treated with 5 ASMs and at discharge successfully weaned

PLPHP deficiency is the most recently discovered pathogenic gene variant responsible for vitamin B₆-dependent epilepsy, with approximately 30 cases published thus far, all with onset of symptoms prior to 3 months of age.⁷ PLPHP is responsible for intracellular homeostasis of PLP, an important enzymatic cofactor, particularly in the CNS. Enzyme activity of γ -aminobutyric acid (GABA) transaminase is reliant on PLP, thus disruptions in this pathway may be responsible for seizures.²

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Our patient had partial response to phenobarbital, a GABA-mediated antiseizure agent, which has been previously reported in PLPHP deficiency.^{4,7,8} Based on previously reported cases and our patient's experience, recurrent episodes of seizure clustering resistant to adjustments in ASMs and anesthetic drips separated by prolonged periods of seizure control may be a distinguishing hallmark of PLPHP deficiency. Focal seizures consisting of intense fear, hallucinations, and emotional lability are also unique features for PLPHP deficiency.^{2,8}

Diagnostics

Other vitamin B₆-dependent epilepsies such as PDE and pyridoxal-5'-phosphate dependent epilepsy have specific abnormal biomarkers (AASA and pipelicolic acid); however, these biomarkers are typically normal in PLPHP deficiency. Interestingly, hyperlactatemia is a consistently reported biochemical abnormality in PLPHP deficiency.⁷ EEG features in PLPHP deficiency vary from burst suppression pattern to normal. Nonspecific MRI abnormalities, such as microcephaly or underdeveloped white matter, are common, although a large portion of patients have no structural abnormalities.^{2,4,9} Normal metabolic screening and late onset of presentation were barriers to diagnosis in our patient.

Treatment

Our case illustrates the importance of a pyridoxine treatment trial in refractory epilepsy beyond the neonatal period. Typical pyridoxine trial dosage is 100 mg and if no response is seen, administration of up to 500 mg maximum may be trialed. EEG monitoring should also be obtained during pyridoxine challenge as abrupt resolution of seizures and depressed amplitudes can be indicative of treatment response. Our patient did not have electrocerebral depression with pyridoxine, although he has had complete resolution of seizures. Complications of high-dose IV pyridoxine include cardiorespiratory depression, although this has infrequently been observed in patients with PLPHP deficiency.^{2,8} Maintenance dosing of pyridoxine ranges from 15 to 30 mg/kg/d (divided in 2 to 3 doses) with maximum daily dose of 200 mg and 500 mg in neonates and adults, respectively. Long-term use of high-dose pyridoxine, especially at higher than recommended doses, may be complicated by sensory and rarely motor neuropathy.⁵ In PLPHP deficiency, complete seizure freedom with pyridoxine monotherapy is not the rule, and many patients require continued additional ASM therapy. If no response is seen with pyridoxine, a trial of PLP supplementation should be considered. Further studies are needed to determine whether pyridoxine or PLP supplementation is more efficacious for PLPHP deficiency.

Prognosis

In vitamin B₆-dependent epilepsies, breakthrough seizures are seen, particularly in setting of febrile illnesses, and some authors suggest management with transient increases in maintenance pyridoxine dosing.⁵ Despite early treatment with pyridoxine or

PLP, developmental delay and cognitive impairment appear to be a common feature for PLPHP deficiency.⁶

Rapid Whole Genome Sequencing

rWGS is widely used in neonatal intensive care units and has been shown to be useful for timely clinical management and decision making. In addition to decreased morbidity and mortality, rWGS has been shown to reduce hospital cost.¹⁰ Sanford et al¹⁰ recently demonstrated use of rWGS in yielding clinically relevant diagnostic information, which altered decision making in PICU settings as well. rWGS identified pathogenic variants with a turnaround time of 10 days in our patient. Use of rWGS allowed for targeted clinical management for our patient, avoidance of invasive neurosurgical procedures, and direct improvement in acute and long-term seizure control. In PLPHP deficiency, rWGS may be particularly advantageous as this disorder lacks conventional biomarkers for vitamin B₆-dependent epilepsies and is not present on most commercial epilepsy gene panels.

Our case demonstrates that PLPHP deficiency is a rare but treatable epileptic encephalopathy that may be missed via typical metabolic and genetic workups. Although typical presentation of vitamin B₆-dependent epilepsies is in the neonatal period, pyridoxine challenge should be considered in refractory epilepsy even if a patient's initial presentation occurs beyond the neonatal or infancy periods. There is growing evidence that rWGS is a useful clinical tool in evaluating previously undiagnosed children in hospital and pediatric critical care settings.

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Appendix Authors

Name	Location	Contribution
A. Chris Espinoza, MD	University of Utah, Salt Lake City	Patient management, literature review, initial draft of the manuscript, preparation and final approval of manuscript
Melissa A. Wright, MD	University of Utah, Salt Lake City	Patient management, critical review of the manuscript, final approval of manuscript

Continued

Appendix (continued)

Name	Location	Contribution
Meghan S. Candee, MD, MS	University of Utah, Salt Lake City	Patient management, critical review of the manuscript, final approval of manuscript
Cristina Trandafir, MD	University of Utah, Salt Lake City; Baylor College of Medicine, Houston, TX	Patient management, critical review of the manuscript, final approval of manuscript
Gary R. Nelson, MD	University of Utah, Salt Lake City	Patient management, critical review of the manuscript, final approval of manuscript

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