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## Pearls & Oysters: Delayed Response to Pyridoxine in Pyridoxine-Dependent Epilepsy

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**Abstract**

Inborn errors of metabolism are a diverse group of genetic disorders including many that cause neonatal-onset epilepsy such as pyridoxine-dependent epilepsy (PDE). PDE occurs secondary to biallelic pathogenic variants in *ALDH7A1* and can present with refractory neonatal seizures and status epilepticus. Neonatal seizures and encephalopathy are modifiable with pyridoxine (vitamin B6) supplementation. However, the clinical response to pyridoxine supplementation can be delayed. We present the case of a full-term neonate with PDE in which seizure cessation was seen a few hours after intravenous pyridoxine load, but the improvement in EEG background and level of clinical encephalopathy occurred five days later. We share this case to provide an example in which clinical improvement in PDE was gradual and required continuation of treatment for several days illustrating the necessity of continuing vitamin B6 supplementation in suspected cases until confirmatory genetic testing is obtained or an alternate cause is found.

## Pearls

- *ALDH7A1*-related pyridoxine-dependent epilepsy (PDE-*ALDH7A1*) is a rare cause of neonatal encephalopathy and seizures.
- PDE-*ALDH7A1* should be considered in the differential of neonatal epileptic encephalopathy because it is one of few treatable neonatal epilepsies.
- Pyridoxine supplementation can control neonatal seizures and improve the level of neonatal encephalopathy.

## Oy-sters

- Since clinical and EEG improvement can be delayed following initiation of supplementation, pyridoxine should be continued until PDE-*ALDH7A1* is ruled out by confirmatory testing.
- Brain imaging abnormalities in neonates with PDE-*ALDH7A1* can be nonspecific.
- Genetic neonatal epilepsies, including PDE-*ALDH7A1*, should be considered if seizure burden is out of proportion to imaging findings.

## Case Report

The neurology team was consulted for suspected seizures in a 1-day-old male. Pregnancy was reported as unremarkable. The patient was born at 40 weeks gestation via uncomplicated vaginal delivery, with normal Apgar scores (8 and 9 at 1 and 5 minutes, respectively) and no need for resuscitation. Around 5 hours of age, he was noted to have respiratory distress and episodes of rhythmic multifocal limb movements, concerning for seizures. Venous blood gas showed a pH of 6.95, pCO<sub>2</sub> of 70.4 mmHg, HCO<sub>3</sub> of 16.1 mmol/L, and base deficit of 16.9. He was intubated and transferred to our center from the birth hospital. An elevated lactate (10 mmol/L) was noted on admission. Basic cerebrospinal fluid (CSF) analysis was negative for signs of infection. Plasma amino acids and CSF amino acids were unremarkable. Conventional EEG was initiated shortly after presentation and confirmed frequent multifocal electrographic seizures, arising from the bilateral centrotemporal regions and evolving to bilateral rhythmic discharges (Figure 1A-B). Status epilepticus lasting up to 70 minutes was noted. Loading intravenous (IV) doses of phenobarbital, fosphenytoin, and levetiracetam were given in close succession over the first 24 hours of presentation, with improvement in seizure burden but not complete cessation. EEG background rapidly evolved to severe encephalopathy in the form of a burst-suppression pattern (Figure 1C-D). Clinical examination also showed severe encephalopathy with absent response to stimulation, diffuse hypotonia, and ventilator dependence with high respiratory support settings. Hypoxic-ischemic encephalopathy was thought to be unlikely; therapeutic hypothermia was thus not considered.

Given suspicion for a genetic-metabolic epilepsy, a single IV dose of pyridoxine [100 mg] was added at 52 hours of age in addition to maintenance doses of the other antiseizure medications (ASM). No seizures were recorded after the pyridoxine loading dose. However, the EEG background continued to show a burst-suppression pattern over the following two days (Figure 1E-F), at which point the EEG was discontinued. The neurological examination continued to show a severe encephalopathy and ongoing mechanical ventilation was required due to a lack of respiratory drive. Brain MRI at 3 days of age showed multiple small areas of periventricular

white matter injury, a small cerebellum, a thin corpus callosum, and normal spectroscopy values in the basal ganglia (Figure 2). These non-specific MRI findings did not explain the severity of encephalopathy and extensive seizure burden. Given the questionable response to the IV load of pyridoxine, maintenance dosing of pyridoxine was initiated at five days of age. Because of the concern for partial response to pyridoxine, raising the possibility of pyridoxamine-5'-phosphate oxidase (PNPO) deficiency, pyridoxal-5'-phosphate (PLP) was also added a few days later as part of the local protocol for refractory neonatal seizures. Phenobarbital and fosphenytoin doses were discontinued at six days of age because of suprathreshold levels; levetiracetam was continued. Seizures did not recur.

A repeat EEG at seven days of age showed significant improvement in background activity (only mild excess discontinuity in sleep for age) and no seizures (Figure 1G-H). Neurological examination mirrored these drastic improvements, with spontaneous limb movements and normal resting tone by nine days of age. He was extubated to room air at 10 days of age. Repeat EEG at 21 days of age remained stable, and the neurological examination was then normal for age. Repeat brain MRI at 22 days of age showed mildly decreased white matter volume, mild thinning of the corpus callosum, mild pontine atrophy, and mega cisterna magna. He was discharged home at 30 days of age on levetiracetam, pyridoxine, and PLP maintenance; both pyridoxine and PLP were continued until the genetic diagnosis was obtained. At 6 months of age, the patient remained seizure-free, although showed mild gross motor delay.

An epilepsy gene panel identified a homozygous missense variant in *ALDH7A1* (c.1559C>T; p.Ser520Phe), inherited from both parents. This was reported by the laboratory as a variant of uncertain significance. However, given his clinical phenotype, allelic homozygosity, and the pathogenic features of the variant, including multiple streams of *in silico* testing (SIFT, PROVEAN, Mutation assessor, LIST-S2, PolyPhen-2) that predicted a deleterious effect, we concluded the variant was disease-causing and consistent with pyridoxine-dependent epilepsy (PDE). Once the diagnosis was established, we discontinued PLP, and the infant was continued on pyridoxine and levetiracetam.

## Discussion

Genetic disorders are rare but important causes of neonatal seizures that often lead to a complex clinical picture that may be difficult to diagnose and treat.<sup>1</sup> In the Neonatal Seizure Registry, 13% (79/611) of neonates with seizures were diagnosed with neonatal epilepsy, 30% (24/79) of which were found to have a genetic cause.<sup>2</sup> PDE-*ALDH7A1* is a rare genetic cause of refractory neonatal seizures that is well described in the literature, characterized by a remarkable response to pyridoxine supplementation.<sup>3-5</sup> This disorder is caused by biallelic pathogenic variants in *ALDH7A1*, a gene that encodes for alpha-aminoacidic semialdehyde ( $\alpha$ -AASA) dehydrogenase – also known as antiquitin.<sup>4-10</sup> Antiquitin deficiency leads to an abnormality in lysine catabolism and accumulation of intermediate metabolites, including delta-1-piperidine-6-carboxylate, which binds to and deactivates pyridoxal-5'-phosphate (PLP).<sup>4,5</sup> PLP is an active B6 vitamer that acts as a cofactor for multiple essential enzymes; downstream dysregulation of these enzymatic pathways through PLP deficiency causes neonatal epileptic encephalopathy which is salvaged by pyridoxine supplementation.<sup>3-5,10</sup>

Although atypical cases are described,<sup>4,8,10</sup> PDE-ALDH7A1 classically presents in the neonatal period with prolonged and drug-refractory seizures, status epilepticus, and encephalopathy.<sup>6,7,9</sup> Various seizure types are described, including clonic, tonic, myoclonic, autonomic, sequential, and electrographic only.<sup>11</sup> Poor feeding, respiratory distress, apneas, lactic acidosis, and electrolyte disturbances have been described.<sup>10</sup> Typical EEG patterns include high voltage delta activity, multifocal epileptiform discharges, and a burst-suppression pattern.<sup>4,7,9,12</sup> Seizures are usually unresponsive to common ASM, although reports of partial or temporary response to initial therapy are described. Refractory seizures, EEG background, and clinical encephalopathy usually respond rapidly to pyridoxine loading and supplementation.<sup>9,10,13</sup> Delayed response of a few days to weeks have been reported, but this is thought to be infrequent.<sup>5</sup> Thus, in the appropriate clinical setting, we recommend initiating a pyridoxine trial even with a partial response to ASM and continuing pyridoxine maintenance therapy even if the clinical impact is not immediately striking.<sup>5,13</sup> Repeat EEG monitoring and serial neurological examinations are indicated to assess for this possible delayed response.

Given that pyridoxamine-5'-phosphate oxidase (PNPO) deficiency is on the differential diagnosis of refractory neonatal epileptic encephalopathy,<sup>3,4,6,9</sup> the addition of enteral PLP should be considered when there is an incomplete response to pyridoxine, as discussed in published protocols.<sup>5</sup> Caused by biallelic pathogenic variants in the *PNPO* gene, PNPO deficiency also ultimately leads to a decrease in PLP, causing downstream effects on PLP-dependent enzymes.<sup>5</sup> Some newborns with PNPO deficiency will respond to pyridoxine therapy, whereas many have a better response to specific PLP supplementation.<sup>5,9</sup>

Recommendations for investigation of suspected PDE-ALDH7A1 include urine  $\alpha$ -AASA, plasma pipercolic acid, and sequencing of *ALDH7A1*, as well as other genes of interest.<sup>3,12</sup> Brain MRI is done to assess for structural causes of neonatal seizures,<sup>12</sup> although non-specific imaging findings have been described in PDE-ALDH7A1: corpus callosum abnormalities, white matter lesions, parenchymal atrophy, small cerebellum, and mega cisterna magna.<sup>4,8,14</sup> PDE-ALDH7A1 should be considered even when the brain MRI is abnormal, especially if seizures are out of proportion to the imaging findings. These neonates may also have a history of low tone, poor Apgar scores, and abnormal blood gas, which may be misdiagnosed as hypoxic-ischemic encephalopathy. Lack of a clear perinatal event, drug-resistant seizures, and discordance between the degree of MRI abnormalities and the level of encephalopathy should raise suspicion for PDE-ALDH7A1.

In confirmed cases of PDE-ALDH7A1, enteral supplementation with pyridoxine should continue lifelong; the specifics of therapy and monitoring are well described.<sup>3,4,6,9</sup> Neurological outcomes in treated patients are variable. Most patients have developmental delays and intellectual disability, although some are reported to be cognitively normal.<sup>9,15</sup> There may be a correlation between early onset of seizures or delayed initiation of pyridoxine and poorer outcomes, although this finding has not been consistent in the literature.<sup>4,9</sup>

## References

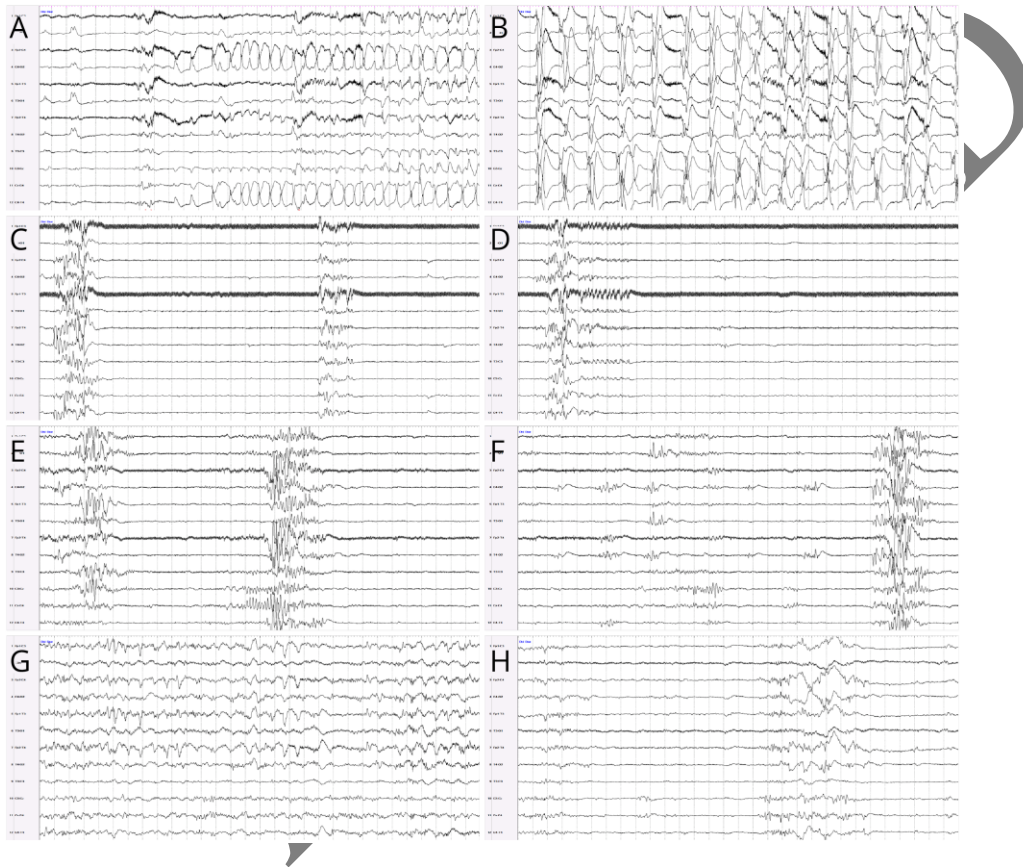
1. Yamamoto H, Okumura A, Fukuda M. Epilepsies and epileptic syndromes starting in the neonatal period. *Brain Dev.* 2011;33:213–220.
2. Shellhaas RA, Wusthoff CJ, Tsuchida TN, et al. Profile of neonatal epilepsies: Characteristics of a prospective US cohort. *Neurology*. Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology; 2017;89:893–899.
3. Coughlin II CR, Tseng LA, Abdenur JE, et al. Consensus guidelines for the diagnosis and management of pyridoxine-dependent epilepsy due to  $\alpha$ -aminoadipic semialdehyde dehydrogenase deficiency. *J Inherit Metab Dis.* 2021;44:178–192.
4. Coughlin II CR, Gospe Jr. SM. Pyridoxine-dependent epilepsy: Current perspectives and questions for future research. *Ann Child Neurol Soc.* 2023;1:24–37.
5. Wilson MP, Plecko B, Mills PB, Clayton PT. Disorders affecting vitamin B6 metabolism. *J Inherit Metab Dis.* 2019;42:629–646.
6. Gospe SM. Pyridoxine-Dependent Epilepsy – ALDH7A1. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. *GeneReviews*<sup>®</sup> [online]. Seattle (WA): University of Washington, Seattle; 1993. Accessed at: <http://www.ncbi.nlm.nih.gov/books/NBK1486/>. Accessed January 16, 2023.
7. Kaminiów K, Pająk M, Pająk R, Paprocka J. Pyridoxine-Dependent Epilepsy and Antiquitin Deficiency Resulting in Neonatal-Onset Refractory Seizures. *Brain Sci. Multidisciplinary Digital Publishing Institute;* 2022;12:65.
8. Mills PB, Footitt EJ, Mills KA, et al. Genotypic and phenotypic spectrum of pyridoxine-dependent epilepsy (ALDH7A1 deficiency). *Brain.* 2010;133:2148–2159.
9. Stockler S, Plecko B, Gospe SM, et al. Pyridoxine dependent epilepsy and antiquitin deficiency: Clinical and molecular characteristics and recommendations for diagnosis, treatment and follow-up. *Mol Genet Metab.* 2011;104:48–60.
10. van Karnebeek CDM, Tiebout SA, Niermeijer J, et al. Pyridoxine-Dependent Epilepsy: An Expanding Clinical Spectrum. *Pediatr Neurol.* Elsevier; 2016;59:6–12.
11. Pressler RM, Cilio MR, Mizrahi EM, et al. The ILAE classification of seizures and the epilepsies: Modification for seizures in the neonate. Position paper by the ILAE Task Force on Neonatal Seizures. *Epilepsia.* 2021;62:615–628.
12. Mastrangelo M, Celato A, Leuzzi V. A diagnostic algorithm for the evaluation of early onset genetic-metabolic epileptic encephalopathies. *Eur J Paediatr Neurol.* 2012;16:179–191.
13. Bok LA, Maurits NM, Willemsen MA, et al. The EEG response to pyridoxine-IV neither identifies nor excludes pyridoxine-dependent epilepsy. *Epilepsia.* 2010;51:2406–2411.

14. Friedman SD, Ishak GE, Poliachik SL, et al. Callosal alterations in pyridoxine-dependent epilepsy. *Dev Med Child Neurol*. 2014;56:1106–1110.
15. Basura GJ, Hagland SP, Wiltse AM, Gospe SM. Clinical features and the management of pyridoxine-dependent and pyridoxine-responsive seizures: review of 63 North American cases submitted to a patient registry. *Eur J Pediatr*. 2009;168:697–704.

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### Figure 1 – Evolution of EEG findings

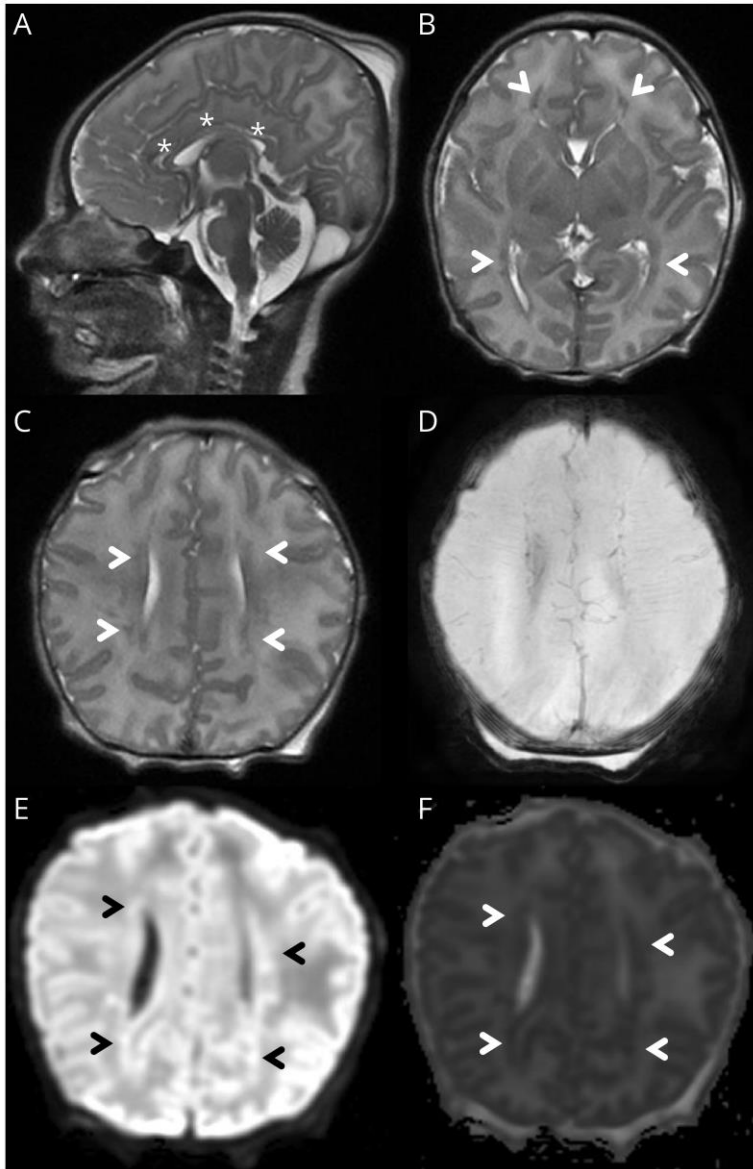
Modified neonatal double distance montage, read at 15 uV for panels A-B and at 7 uV for panels D-H, with 30 seconds per page in all panels. Electrographic seizures with right centrotemporal onset (A) and evolution to rhythmic bilateral large amplitude spike-and-wave discharges (B); Background activity prior to the pyridoxine load, showing a severely abnormal burst-suppression pattern for 60 consecutive seconds (C,D); Background activity 48 hours after the pyridoxine load, showing an ongoing abnormal burst-suppression pattern (E), although some activity is rarely seen within the inter-burst interval (\*, F); Background activity five days after the pyridoxine load, showing normal activity with typical neonatal electrographic elements during wakefulness (G), and mildly excessive discontinuity during quiet sleep (H).





**Figure 2 – Brain MRI Findings**

Sagittal T2 sequence showing diffusely thin corpus callosum (\*, A); Axial T2 sequence showing areas of abnormal signal in the periventricular white matter anterior to the frontal horns and postero-lateral to the occipital horns (arrowheads, B); Axial T2 sequence (rostral to B) showing small multifocal areas of abnormal signal in the periventricular white matter (arrowheads, C); Corresponding SWI sequence showing absence of hemorrhage (D); Corresponding DWI (E) and ADC (F) sequencing showing areas of restricted diffusion in the periventricular white matter, consistent with acute injury (arrowheads).



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