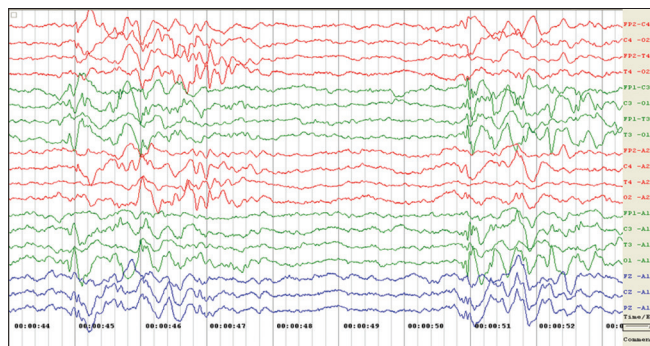


## Pyridoxine Trial in Early Infantile Epileptic Encephalopathy: Never Forget!

Sir,

A 75-day-old male infant presented with complaints of seizures for the past 1 month. He was a term-born first child of a third-degree consanguineous couple. Mother had a history of oligohydramnios during an otherwise uneventful antenatal and perinatal period. During the third week of life, he developed recurrent episodes of vomiting and abdominal distention. At the age of 6 weeks, he developed seizures with left eyelid twitching and jerky movements of the left half of the body. He received intravenous antibiotics, calcium, phenobarbitone, and antiemetics. His cerebrospinal fluid (CSF) examination, sepsis screen, electrolytes, and magnetic resonance imaging (MRI) of the brain were normal. At 8 weeks of age, seizure semiology changed to frequent abnormal jerky eye movements, fragmented limb myoclonus, generalized myoclonic seizures, and rapidly progressive myoclonic status unresponsive to conventional antiepileptics.

On examination, anthropometry was age appropriate. He was lethargic, with poor state to state variability and central hypotonia. He had repetitive, irregular, jerky eye movements, fragmented limb myoclonus, and generalized myoclonic seizures. A possibility of early myoclonic encephalopathy (EME) secondary to genetic or metabolic etiology was considered. Seizures remained unresponsive to antiepileptics (phenobarbitone, levetiracetam) and he remained in myoclonic status epilepticus. Electroencephalogram (EEG) showed burst suppression pattern [Figure 1]. Intravenous pyridoxine (100 mg) was given, and immediate cessation of all forms of seizures noted, however he was apneic, developed coma and hypotensive shock. He was managed with intubation, mechanical ventilation, and inotropes. Gradually, hemodynamics stabilized, respiratory support



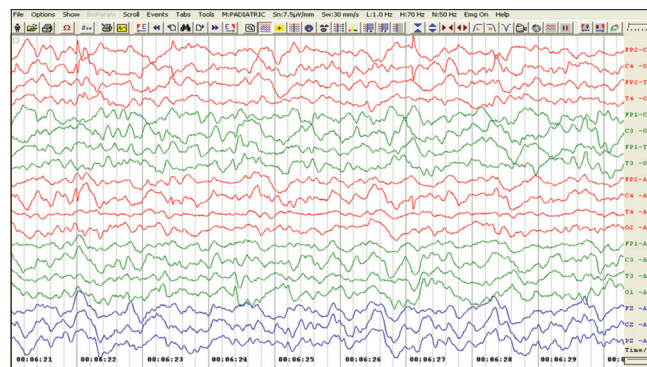
**Figure 1:** Electroencephalogram before pyridoxine trial. Sedated EEG (neonatal montage, sensitivity- 7.5  $\mu\text{V}/\text{mm}$ , sweep speed- 30 mm/s, HPF- 70 Hz, and LPF- 1 Hz) at 11 weeks of age showing bursts of slow waves with sharps and spikes lasting for 2 s followed by attenuation of background activity lasting for 4 s

was withdrawn, and he remained seizure free and had improvement in encephalopathy. He was continued on oral pyridoxine, along with folinic acid. MRI of the brain was unremarkable, and an inter-ictal EEG post IV pyridoxine showed marked improvement with continuous and reactive background activity with occasional central discharges [Figure 2].

His blood spots for acylcarnitines by tandem mass spectrometry, urinary organic acids by gas chromatography mass spectrophotometry, ammonia, lactate, CSF glycine, CSF/plasma glycine ratio, biotinidase assay, CSF pipercolic acid levels were unremarkable. Next-generation sequencing revealed a homozygous variation (c.323C > Ap.Pro108Gln) in Exon 4 of the *ALDH7A1* gene, confirming the diagnosis of pyridoxine-dependent epilepsy (PDE). Parents were heterozygous carriers for the same variant.

At 5 years of follow-up, he was maintained on oral pyridoxine 400 mg/day, folinic acid 15 mg/day, levetiracetam, and oxcarbazepine. He continued to have infrequent fever-triggered seizures (1--2 episodes/year) and afebrile dyscognitive seizures. Developmental milestones were delayed, especially in the language sector, with features of autism and intellectual impairment (intelligence quotient with Vineland social maturity scale-56). The follow-up EEG was unremarkable.

The underlying etiology of EME include several inborn errors of metabolism such as PDE, pyridoxamine 5'-phosphate oxidase (PNPO) deficiency, folinic acid responsive seizures (FARS), biotinidase deficiency, glucose transporter defect, nonketotic hyperglycinemia (NKH), mitochondrial disorders, and genetic disorders (STXBP1, KCNQ2, KCNQ3, KCNT1, GRIN2B, ARX, and CDKL5).<sup>[1]</sup>



**Figure 2:** Electroencephalogram after pyridoxine trial. Sedated EEG (neonatal montage, sensitivity- 7.5  $\mu\text{V}/\text{mm}$ , sweep speed- 30 mm/s, HPF- 70 Hz and LPF- 1 Hz) after pyridoxine trial showed marked improvement with continuous and reactive background record and occasional spikes and slow waves from right central region

PDE is a rare autosomal recessive disorder, first described by Hunt and colleagues in 1954.<sup>[2]</sup> The prevalence of PDE ranges from 1 in 100,000 to 1 in 600,000.<sup>[3]</sup> Mutation in the  $\alpha$ -amino adipic-semialdehyde ( $\alpha$ -AASA) dehydrogenase (also known as antiquitin, ATQ) encoded by the ALDH7A1 or ATQ gene is responsible for PDE. Antiquitin is involved in brain lysine metabolism and its deficiency causes accumulation of  $\alpha$ -AASA, piperidine-6-carboxylic acid (P6C), pipercolic acid, and inactivation of pyridoxal 5'-phosphate (PLP). PLP, the active form of pyridoxine, is an essential cofactor for cerebral amino acid and neurotransmitter metabolism resulting in glutamate excitation and inhibition of GABAergic neurons.<sup>[4,5]</sup>

The classical presentation of PDE is the neonatal onset of pharmacoresistant seizures within few hours to days after birth with sleeplessness, hyperalertness, recurrent vomiting, and feed regurgitation. The predominant seizure types are myoclonic seizures, focal motor, generalized tonic, and epileptic spasms.<sup>[3]</sup> Seizures are usually refractory to anticonvulsants but have a rapid response to pyridoxine therapy.

Intravenous (IV) pyridoxine 100 mg leads to an immediate cessation of all types of seizures in an acutely seizing patient. Immediate complication of IV pyridoxine is apnea in neonates with PDE, so it should be used with EEG monitoring and in the intensive care areas. A transient coma concomitant with seizure cessation is characteristic for PDE, but does not always occur. Facilities for intubation and ventilation should be available and it should be infused slowly over 10 min. Repeat doses of IV pyridoxine can be used in 30 min with partial response. Outside intensive care areas oral pyridoxine (30 mg/kg) can be used.

Oral/enteral pyridoxine needs careful monitoring, respiratory depression has been reported occasionally. Response to oral pyridoxine may be gradual, delayed, or masked by concomitant medications, so oral pyridoxine should be given for longer duration. Decision to stop pyridoxine should be taken after negative genetic testing results. Response to IV or oral pyridoxine supports the diagnosis of PDE, however, lack of clinical or EEG response does not rule out the diagnosis and it should be confirmed with genetic testing.

Up to one-third of cases with PDE have the atypical presentation, such as late-onset seizures up to 3 years of age, autism, an initial response to antiepileptic drugs but later unresponsiveness, and infants whose seizures are unresponsive to pyridoxine trial initially but later response.<sup>[6]</sup> There are unique patterns of paroxysmal events in addition to seizures that can prompt clinical suspicion including abnormal eye movements, facial grimacing, frightened facial expression, inconsolable crying, and sleeplessness.<sup>[7]</sup> Low Apgar score labeled as hypoxic-ischemic encephalopathy (HIE) and, neonatal sepsis-like presentation with lactic acidosis, hypoglycemia, profound electrolyte disturbances have been reported in patients with PDE. An initial label of HIE or neonatal sepsis may delay future pyridoxine trial and diagnostic workup.

PDE is diagnosed by estimation of intermediate metabolite ( $\alpha$ -AASA) in urine, plasma, CSF, electroclinical response to pyridoxine treatment and confirmed by mutation analysis in the ALDH7A1 gene. Diagnosis of PNPO deficiency should be considered in infants with the clinical features of PDE, who are not fully responsive to pyridoxine, lack the confirmatory biochemical markers, and respond to PLP. MRI brain may be normal or may show ventriculomegaly, corpus callosum thinning, hypoplasia or dysplasia, cerebral atrophy, multifocal white matter changes, delayed myelination, hypoplastic cerebellum, brain stem, optic chiasm, and optic nerves, arachnoid cysts, and enlarged cisterna magna.<sup>[3,8,9]</sup>

Treatment includes lifelong supplementation of pyridoxine (15--30 mg/kg/day in 2--3 divided doses) along with other rehabilitative measures. Pyridoxine supplementation does not correct the accumulation of intermediate metabolites (AASA and pipercolic acid), and dietary lysine restriction and arginine supplementation are recommended for better neurodevelopmental outcomes.<sup>[10]</sup> Accidental or diagnostic withdrawal of pyridoxine is associated with seizure recurrence.

Around 75% of children with PDE have neurocognitive impairment of varying severity and length of delay in diagnosis and initiation of pyridoxine correlate with severity of neurocognitive impairment.<sup>[3]</sup> Behavioral or psychiatric abnormalities including autism, anxiety, hyperactivity, mood disturbance, tics, and obsessive-compulsive disorders are noted in the majority of the children.

To conclude PDE, although rare, but is a treatable vitamin responsive epileptic encephalopathy. PDE should be suspected in all children with neonatal, early infantile-onset, drug-refractory epilepsy, and also in infants with abnormal ocular movements, feeding problems, facial grimacing, choreo-athetoid movements in addition to the seizures.

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### Conflicts of interest

There are no conflicts of interest.

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