Pyridoxine-dependent early onset seizures associated with rare gene mutations: A case series

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Abstract

Pyridoxine dependent epilepsy (PDE) is a rare autosomal recessive disorder. Several genes involved in Pyridoxine (B6) metabolism have been implicated in the pathogenesis of PDE, two such genes are Aldehyde Dehydrogenase 7 Family Member A1 (ALDH7A1) and Pyridox(am)ine 5'-phosphate oxidase (PNPO). To add to the limited data on PDE, three cases of Vitamin B6 dependent neonatal epilepsy caused by pathogenic variation in the ALDH7A1 and PNPO genes are reported. PDE is a rare, but potentially debilitating, cause of neonatal-onset epilepsy. Keeping in view the variable presentations of this condition, patients with a clinical picture suggestive of PDE must be carefully evaluated and treatment initiated as early as possible to achieve the best outcomes.

Keywords: Pyridoxine, Epilepsy, ALDH7A1 and PNPO.

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Introduction

Pyridoxine dependent epilepsy (PDE), a rare autosomal recessive disorder, is characterised by the onset of severe seizures in the neonatal period or early infancy.[1] Diagnosis traditionally includes seizures refractory to conventional anticonvulsants, a good response to Pyridoxine, complete seizure control on Pyridoxine monotherapy, and seizure recurrence after Pyridoxine withdrawal. Biomarkers and genetic testing have eliminated the need for Pyridoxine withdrawal to confirm PDE diagnosis.[2]

PDE classically presents with the onset of intractable seizures in the first month of life, often within hours of birth, but unresponsiveness to conventional treatment is the most common presentation of classical PDE.[3]

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Mutations in genes involved in B6 metabolism, such as Aldehyde Dehydrogenase 7 Family Member A1 (ALDH7A1) and Pyridox(am)ine 5'-phosphate oxidase (PNPO), are implicated in PDE. ALDH7A1 mutations reduce α-aminoadipic semialdehyde dehydrogenase activity, causing accumulation of α-aminoadipic semialdehyde (α-AASA), piperideine-6-carboxylate (P6C), and pipecolic acid, inactivating pyridoxal phosphate (PLP). PLP is a cofactor for glutamic acid decarboxylase, so its deficiency leads to excess glutamate and seizures.4 PNPO mutations reduce PNPO activity, causing a deficiency in active PLP.1 This deficiency leads to an accumulation of lysine degradation intermediates, inactivating PLP and causing seizures.[4]

Here, we report three cases of PDE caused by pathogenic variation in the ALDH7A1 and the PNPO genes.

Case Series

Case 1: This was a case of a nine-month-old girl, born to consanguineous parents at 38 weeks' gestation via spontaneous vaginal delivery. She had an immediate cry and APGAR scores of (8/1 and 9/5). There is no family history of epilepsy or developmental delay. Her birthweight was (2.9 kg) (25th percentile), length (50 cm) (50th to 75th percentile), and head circumference (31.5 cm) (< 3rd percentile). At three hours of life, she developed respiratory distress, desaturation, posturing, and grunting, leading to treatment with IV antibiotics (Gentamycin and Ampicillin) and transfer to a neonatal intensive care unit (NICU) at the Aga Khan University Hospital (AKUH), Karachi, on June 29, 2023. Her older brother had seizures on the second day of life, treated with Phenobarbital for two years.

Upon arrival at the tertiary care hospital's emergency, the baby appeared dusky with increased tone, brisk reflexes, and poor sucking. She experienced multiple seizures and metabolic acidosis, necessitating intubation. The neonate received a loading dose of Levetiracetam (20mg/kg/day) and antibiotics were escalated to meningitis doses of Meropenem and Vancomycin due to her worsening condition. Intravenous Phenobarbitone (5mg/kg/day) was added to address persisting posturing before the baby was transferred to the NICU.

Cranial ultrasound on the first day of life revealed bilateral Grade 1 intraventricular haemorrhages (IVH). EEG showed intermittent bilateral fronto-centro-temporal sharp waves and several electro-graphical seizures without clinical manifestation. Magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), and magnetic resonance venography (MRV) of the brain indicated a small subgaleal collection along the right parieto-occipital region. Biochemical workup showed elevated plasma sodium, lactate, ammonia, Lactate dehydrogenase (LDH), creatine phosphokinase (CPK), and a positive urine ketones test. Initial diagnosis of meningitis and hypoxic ischaemic encephalopathy was made. Cerebrospinal fluid (CSF) analysis showed high neutrophils, proteins, and low glucose, with negative cultures. Her antiepileptic drugs (AEDs) were optimised as follows: Levetiracetam (45mg/kg/day), Phenobarbitone (5mg/kg/day) and Phenytoin (7.5mg/kg/day). She remained seizure free for over 24 hours, therefore, was extubated on the sixth day of admission. Examination revealed persistence of weak reflexes despite clinical improvement and subtle facial features, like depressed nasal bridge and prominent ears that did not fit into any epilepsy syndrome. As the baby remained haemodynamically stable, her level of care was de-escalated to special care ward bed, and antibiotics were discontinued. The parents were asked to stay for further care, but they requested discharge on the ninth day of admission.

Following discharge, she had two breakthrough seizures at 23rd and 48th day of life, leading to readmission. Genetic testing confirmed a diagnosis of autosomal recessive Pyridoxine-dependent epilepsy due to a pathogenic homozygous mutation in the ALDH7A1 gene (c.312+1G>A (Splice donor)). Family testing showed carrier status in the father, mother, and brother. Her anti-seizure medications were gradually tapered off, and oral Pyridoxine was maximised.

The follow-up at nine months of age, showed her to be seizure-free on Pyridoxine alone (30mg/kg/day). She had acquired microcephaly (head circumference <3rd centile). Her weight and length continued to track normally. Her hearing, vision, speech, and social development were age appropriate; however, her motor development milestones were mildly delayed for her age, as she achieved neck holding but could only sit with support.

Case 2: A baby girl who was delivered via caesarean section due to stalled labour experienced a seizure at 30 minutes of life, which included eye up rolling and frothing from the mouth. She was subsequently admitted to the neonatal intensive care unit due to respiratory distress. Another seizure occurred on day six of life, lasting two minutes. Her family history was unremarkable. At three months of age, the child was having one to two seizures daily, despite being on multiple AEDs (Clonazepam, Topiramate, Phenobarbital, and Levetiracetam). She displayed global developmental delay and had no eye contact, neck holding, or recognition of her mother at three months of age. She achieved neck holding at six months of age.

On December 9, 2022, at the age of two years, the child was admitted at AKUH with frequent seizure episodes, and an electroencephalogram (EEG) was conducted to rule out status epilepticus. However, it revealed focal seizures and mild cerebral encephalopathy. Genetic testing on the recommendation of the Geneticist at the AKUH confirmed a PNPO gene variant (c.674G>A, p.Arg225His), which is consistent with pyridoxal 5'-phosphate-dependent epilepsy. Vitamin B6 supplementation three times a day (25 mg per kg per day) was added to the child's medication regimen. The seizure frequency reduced to zero, and the child's other AEDs were tapered off. Regular physiotherapy was started, with the help of which, the child has started walking at the age of four years. The child is currently developing well in terms of cognition, social, and physical milestones, and has been advised to start schooling at four years of age.

Case 3: A baby boy, born via elective C-section to consanguineous parents, had an uneventful birth but developed frequent seizures on the seventh day of life on December 2, 2022, lasting 35-40 minutes, with accompanying hypoxia. Seizures were focal and tonic-clonic. Family history revealed paternal uncle having prolonged seizures until three years of age. Initial treatment in AKUH emergency room (ER) with Phenobarbitone and Levetiracetam was ineffective, and Clonazepam drops were added. Initially, the baby had elevated ammonia and lactate levels, which normalised within 10 days. After discharge, he experienced recurring seizures every 15-20 days, characterised by eye up rolling, increased body tone, and unresponsiveness lasting one to one and a half minutes.

At four months of age, Biotin and Pyridoxine were added at suboptimal doses at another hospital. At five months, the baby presented to the emergency department of AKUH with active seizures lasting one hour. Lab tests showed normal complete blood count (CBC), lactic acid, and blood glucose, with calcium, magnesium, C- reactive protein (CRP), and ammonia levels in normal range. Seizures were controlled with Levetiracetam and Phenobarbital. Brain MRI reported the patient undergoing myelination and asymmetric prominence of the left ventricle as compared to the right with undulating margins of the left lateral ventricle. Subsequent EEG was reported to be normal with

Table: Similar and distinguishing features of cases reported.

	Age at first seizure	Family history of seizures	Genetic mutation	Breakthrough seizures on AEDs	Betterment on Pyridoxine optimal dose
Case 1	14 hours	Yes (brother)	ALDH7A1 (c.312+1G>A)	Yes	Seizure-free Mild developmental delay
Case 2	30 minutes	None	PNPO (c.674G>A)	Yes	Seizure-free Development milestones appropriate
Case 3	7 Days	Yes (Uncle)	ALDH7A1 (c.1556G>A)	Yes	Seizure-free Mild developmental delay

no epileptiform discharges. Genetic testing confirmed Pyridoxine-dependent Epilepsy with a homozygous strong variant in the ALDH7A1 gene. Medication adjustments included optimising Pyridoxine to (25-30mg/kg/day) and tapering off Levetiracetam.

The family received counselling regarding the condition and the risk in future pregnancies. Currently, at 10 months of age, the baby remains seizure-free with optimised Pyridoxine dosage, but developmental milestones are delayed. Dietary recommendations were provided, and consultations with a geneticist and nutritionist are ongoing.

Discussion

The atypical phenotype of PDE is highly variable, with seizures starting as late as two years of age. Infants may present with multiple seizure types, along with additional neurological and behavioural symptoms such as irritability, abnormal cry, trembling, and exaggerated startle response. Abnormal biochemical findings, including lactic acidosis and hyperammonaemia, as well as gastrointestinal manifestations, like abdominal distension, emesis, and hepatomegaly, can also occur.[3] Febrile illness and respiratory distress may be present, and some infants with PDE have features consistent with birth asphyxia or suspected hypoxic ischaemic encephalopathy[5] as was in Case 1. The first patient in this case series had suspected meningitis due to suggestive CSF and systemic findings, hence, antibiotics were started but seizures were refractory. Moreover, the incidental finding of IVH could not have been the cause of seizures due to the mild nature and lack of any cause. No apparent association was noted between PDE and IVH. Neuroimaging findings in PDE can vary widely, from minimal findings to hydrocephalus, ventriculomegaly, cortical dysplasia, callosal dysgenesis, and subependymal cysts.[6] There is no defined pathognomonic EEG pattern for PDE, making its clinical diagnosis challenging. The present case series highlights the variability in PDE presentations, including onset as early as the neonatal period with refractory seizures unresponsive to conventional AEDs.

Initial protocol when encountering AED resistant, possible cofactor-responsive seizures is to start a Pyridoxine trial at an initial dose of 100mg IV Pyridoxine followed by an oral maintenance dose, ranging between 15 and 30 mg/kg per day in infants and 200 mg/day in neonates.[7] Based on clinical and EEG response, trials of PLP (60 mg/kg/day), Folinic acid (Leucovorin 2.5 mg IV), and Biotin (10 mg PO) can be conducted along with screening urine for metabolites.[8] These trials and continuous monitoring are often a challenge in resource limited settings in low- and middle-income countries (LMICs). The family of Case 1 patient decided to leave against medical advice because of financial constraints and further workup could not be done while the baby was in the NICU. Unfortunately, the kid presented several days later with breakthrough seizures.

Genetic testing (Epilepsy panel) remains the gold standard for diagnosing PDE and helping parents take informed decisions pertaining to future pregnancies. However, due to unavailability in Pakistan, blood samples were couriered with appropriate preparation and technique to INVITAE™ and ARCENSUS™ genetic testing services with the assistance of the hospital geneticist. In the present series, the parents of Case 1 patient underwent the testing and were noted to be carriers for PDE. Parents of the other two patients refused testing.

The impact of PDE on neurological development is variable. Most studies report significant delays in developmental milestones. Long-term outcomes indicate that 75% of PDE patients have cognitive impairment and developmental delay, despite seizure control with Pyridoxine.[9] Cases 1 and 3 demonstrate mild delay in developmental milestones despite treatment. Lysine-restricted diet and Arginine supplementation have been associated with better neurological outcomes in PDE patients on Pyridoxine.[10] All three patients were counselled, however, parents of Case 1 and 2 were reluctant to adopt this diet.

Conclusion

PDE is a rare but debilitating cause of neonatal-onset epilepsy. Diagnosis relies on genetic testing, currently not available in Pakistan. Therefore, patients with AED resistant epilepsy should be considered for and started on treatment of PDE as early as possible. Limited reported cases from Pakistan and variable nature of cases underscore the novelty and importance of our contribution to the literature.

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Dissemination to participants and related patient and public communities: To disseminate our results, we will share this information within our professional societies and networks at conferences and webinars. We will use social media to share the key messages and produce a plain language summary to be used for wider dissemination to patient advocacy groups, and patient organisations.

Ethics Statement: ERC (Ethical Review Committee) Exemption was taken for the study since it involved the collection of existing data or records. The exemption was taken by Ethical review board (ERB) Aga Khan University, Karachi, with the ERC exemption ID: 2023-9025-27377.

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