Original Research Paper

Volume - 16 | Issue - 08 | August - 2026 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Paediatrics

EARLY-ONSET PYRIDOXINE-DEPENDENT EPILEPSY DUE TO A HOMOZYGOUS ALDH7A1 MUTATION PRESENTING AS REFRACTORY NEONATAL SEIZURES – A RARE CASE REPORT

Dr. Kambham Pavithra post graduate, Department of Pediatrics, PES Institute of Medical Sciences and Research (PESIMSR), Kuppam.

Dr. Dhurva Sandeep Assistant Professor & Paediatric Neurologist,Department of Pediatrics, PES Institute of Medical Sciences and Research (PESIMSR), Kuppam.

Dr. Deepthi Shalma Associate Professor,Department of Pediatrics, PES Institute of Medical Sciences and Research (PESIMSR), Kuppam.

ABSTRACT Pyridoxine-dependent epilepsy (PDE) is a rare autosomal recessive neurometabolic disorder characterized by neonatal-onset seizures that are resistant to conventional antiseizure medications but respond dramatically to pyridoxine (vitamin B6). The condition is most commonly caused by pathogenic variants in the ALDH7A1 gene, resulting in impaired lysine metabolism and functional deficiency of pyridoxal-5-phosphate, an essential cofactor for neurotransmitter synthesis. Early diagnosis is crucial because delayed recognition may lead to persistent seizures and irreversible neurodevelopmental impairment.We report a term male neonate born at 38+4 weeks of gestation who developed recurrent seizures within 12 hours of birth. Despite treatment with phenobarbitone and levetiracetam, seizures persisted. Intravenous pyridoxine administration resulted in immediate cessation of seizures. Recurrence of seizures following withdrawal of pyridoxine and subsequent resolution after reintroduction strongly suggested pyridoxine-dependent epilepsy. Magnetic resonance imaging demonstrated Grade II hypoxic-ischemic encephalopathy, initially masking the diagnosis. Whole exome sequencing confirmed a homozygous pathogenic ALDH7A1 c.328C>T (p.Arg110Ter) mutation, establishing the diagnosis of early-onset vitamin B6-dependent epilepsy. The infant showed sustained clinical improvement on oral pyridoxine therapy and was discharged with regular neurological follow-up.This case highlights the importance of considering pyridoxine-dependent epilepsy in all neonates with refractory seizures, even when an alternative diagnosis such as hypoxic-ischemic encephalopathy appears likely. Early therapeutic administration of pyridoxine and timely genetic confirmation are essential for optimizing neurological outcomes and facilitating genetic counseling.

KEYWORDS : Pyridoxine-dependent epilepsy; ALDH7A1; Vitamin B6; Neonatal seizures; Whole exome sequencing.

INTRODUCTION

Neonatal seizures are among the most common neurological emergencies encountered in neonatal intensive care units and are associated with significant mortality and long-term neurodeve lopmental sequelae. Hypoxic-ischemic encephalopathy, intracranial hemorrhage, metabolic disturbances, central nervous system infections, and structural brain abnormalities account for the majority of cases. However, a small proportion of neonates have inherited metabolic epilepsies that are potentially treatable if recognized early.

Pyridoxine-dependent epilepsy (PDE) is a rare autosomal recessive disorder caused predominantly by pathogenic variants in the ALDH7A1 gene encoding antiquitin, an enzyme involved in lysine degradation.[2,3] Deficiency of antiquitin leads to accumulation of α-aminoadipic semialdehyde and piperideine-6-carboxylate, resulting in functional depletion of pyridoxal-5-phosphate, the active form of vitamin B6.[5] Since pyridoxal-5-phosphate is an essential cofactor for several enzymes involved in neurotransmitter synthesis, its deficiency results in neuronal hyperexcitability and recurrent seizures.

The clinical presentation is highly variable, although most patients develop seizures during the neonatal period.[7,8] Affected infants frequently present with seizures that are refractory to conventional antiseizure medications but show a dramatic response to pyridoxine administration.[1,3] The diagnosis may be overlooked because the presentation often mimics more common neonatal conditions, particularly hypoxic-ischemic encephalopathy and neonatal sepsis. Molecular confirmation by identification of pathogenic variants in ALDH7A1 has become the gold standard for diagnosis.[4]

We report a genetically confirmed case of early-onset pyridoxine-dependent epilepsy in a term neonate presenting with refractory seizures initially managed as hypoxic-ischemic encephalopathy. The case emphasizes the importance of early pyridoxine administration in unexplained neonatal seizures and highlights the role of whole exome sequencing in establishing the diagnosis and guiding long-term management.

CASE REPORT

A term appropriate-for-gestational-age male neonate weighing 3.3 kg was born at 38 weeks and 4 days of gestation by emergency lower segment caesarean section for grade III meconium-stained liquor with pathological cardiotocography. The infant cried after initial stimulation with Apgar scores of 6 and 9 at one and five minutes, respectively. Respiratory distress developed soon after birth, requiring admission to the Neonatal Intensive Care Unit (NICU). The baby was started on Continuous Positive Airway Pressure (CPAP), intravenous fluids, empirical antibiotics, and supportive care.

At approximately 12 hours of life, the neonate developed recurrent episodes of generalized myoclonic jerks associated with lip smacking and oxygen desaturation. Considering the history of perinatal distress, hypoxic-ischemic encephalopathy (HIE) with neonatal seizures was suspected. Intravenous phenobarbitone was administered as a loading dose followed by maintenance therapy. As seizures persisted, additional loading doses of phenobarbitone and intravenous levetiracetam were administered; however, seizure control could not be achieved.

Because of persistent drug-resistant seizures, a therapeutic trial of intravenous pyridoxine (100 mg) was administered. Following pyridoxine administration, seizures stopped completely without cardiorespiratory compromise. However, the infant experienced recurrence of seizures after pyridoxine withdrawal. Re-administration of intravenous pyridoxine again resulted in immediate cessation of seizures, strongly suggesting pyridoxine-dependent epilepsy (PDE). Oral pyridoxine was subsequently initiated at 18 mg/kg/day, and no further clinical seizures were observed.

Routine investigations demonstrated leukocytosis with elevated inflammatory markers. Blood culture grew Enterobacter species, for which appropriate intravenous antibiotics were administered according to culture sensitivity. Cerebrospinal fluid analysis showed mildly elevated protein without evidence of bacterial meningitis. Metabolic investigations including serum glucose, calcium, magnesium, renal function tests, liver function tests, and serum ammonia did not reveal an alternative metabolic cause for seizures.

Magnetic resonance imaging of the brain demonstrated diffusion restriction involving the bilateral frontal periventricular white matter and corona radiata with absent posterior limb sign, suggestive of Grade

II hypoxic-ischemic encephalopathy.

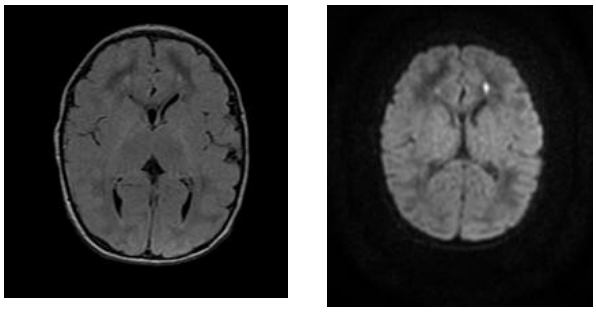

FIG 1: Magnetic resonance imaging (MRI) of the brain showing features suggestive of hypoxic-ischemic encephalopathy grade II with bilateral periventricular diffuse restriction.

Further history revealed consanguinity and the death of a previous sibling during the neonatal period following recurrent seizures requiring NICU admission, raising suspicion of an inherited epileptic disorder. Whole exome sequencing identified a homozygous pathogenic nonsense variant in exon 4 of the ALDH7A1 gene (c.328C>T; p.Arg110Ter), confirming the diagnosis of early-onset pyridoxine-dependent epilepsy (OMIM #266100).

Gene[#] (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification[$]
ALDH7A1 **(-)** (ENST00000409134.8)	Exon 4	c.328C>T **(p.Arg110Ter)**	Homozygous	Epilepsy, early-onset, 4, vitamin B6-dependent (OMIM#266100)	Autosomal recessive	Pathogenic (PVS1, PM2, PP5)

FIG 2: Whole exome sequencing revealing a homozygous pathogenic variant in the ALDH7A1 gene mutation, confirming the diagnosis of Pyridoxine-dependent epilepsy (PDE).

The infant gradually improved with pyridoxine therapy. Respiratory support was discontinued, enteral feeds were well tolerated, and no further seizure episodes occurred during hospitalization. The baby was discharged on the 35th postnatal day with oral pyridoxine, and vitamin D supplementation. The parents were counseled regarding the genetic nature of the disease, the importance of lifelong pyridoxine therapy, and the need for regular neurological and developmental follow-up.

DISCUSSION

Pyridoxine-dependent epilepsy (PDE) is a rare autosomal recessive neurometabolic disorder that usually presents during the neonatal period with seizures refractory to conventional antiseizure medications. The majority of cases result from pathogenic variants in the ALDH7A1 gene, leading to deficiency of antiquitin, an enzyme involved in lysine metabolism.[2] Accumulation of α-aminoadipic semialdehyde and piperideine-6-carboxylate causes inactivation of pyridoxal-5-phosphate, resulting in impaired synthesis of inhibitory neurotransmitters and recurrent seizures.[5]

The present case initially posed a diagnostic challenge because the infant had significant perinatal distress, metabolic acidosis, and MRI findings suggestive of Grade II hypoxic-ischemic encephalopathy (HIE). Consequently, seizures were initially attributed to HIE. However, persistence of seizures despite adequate doses of phenobarbitone and levetiracetam prompted consideration of an alternative diagnosis. The dramatic cessation of seizures following intravenous pyridoxine administration, recurrence after withdrawal, and subsequent response following reintroduction strongly suggested pyridoxine-dependent epilepsy. Similar observations have been reported in previous studies and remain one of the most important clinical clues for diagnosis.[1,3,9]

The presence of consanguinity and a previous sibling with neonatal seizures further increased suspicion of an inherited metabolic disorder. Whole exome sequencing demonstrated a homozygous pathogenic ALDH7A1 c.328C>T (p.Arg110Ter) mutation, confirming the diagnosis. Molecular diagnosis is currently considered the gold standard because it confirms the disease, facilitates genetic counselling, and enables prenatal diagnosis in future pregnancies.[4,6]

Although seizure control is usually excellent with lifelong pyridoxine supplementation, delayed diagnosis has been associated with developmental delay, intellectual disability, and language impairment.[9,10] Therefore, early therapeutic administration of pyridoxine should be considered in every neonate with unexplained or drug-resistant seizures, irrespective of neuroimaging findings or suspected perinatal asphyxia.[11,12] Our patient responded well to pyridoxine therapy with complete seizure control before discharge, emphasizing the importance of early recognition of this treatable condition.

CONCLUSION

Pyridoxine-dependent epilepsy should be included in the differential diagnosis of all neonates presenting with refractory seizures. Persistence of seizures despite appropriate anticonvulsant therapy should prompt an immediate therapeutic trial of pyridoxine. Early diagnosis, molecular confirmation, and lifelong pyridoxine supplementation significantly improve seizure control, neurodevelopmental outcome, and allow appropriate genetic counselling for affected families.[4,10] This case emphasizes that the coexistence of hypoxic-ischemic encephalopathy should not exclude the possibility of an underlying metabolic epilepsy.

REFERENCES

1. Hunt AD Jr, Stokes J Jr, McCrory WW, Stroud HH. Pyridoxine dependency: report of a case of intractable convulsions in an infant controlled by pyridoxine. Pediatrics. 1954;13:140-145.
2. Mills PB, Struys E, Jakobs C, et al. Mutations in ALDH7A1 cause pyridoxine-dependent epilepsy. Nat Genet. 2006;38:1113-1118.
3. Baxter P. Pyridoxine-dependent and pyridoxine-responsive seizures. Dev Med Child Neurol. 2001;43:416-420.
4. Coughlin CR II, van Karnebeek CDM, Al-Hertani W, et al. Consensus guidelines for the diagnosis and management of pyridoxine-dependent epilepsy due to ALDH7A1 deficiency. J Inherit Metab Dis. 2021;44:178-192.
5. Plecko B, Paul K, Mills PB, et al. Biochemical and molecular characterization of pyridoxine-dependent epilepsy. Neurology. 2007;69:1921-1928.
6. Stockler S, Plecko B, Gospe SM Jr, et al. Pyridoxine-dependent epilepsy. GeneReviews. University of Washington; 2023.
7. van Karnebeek CDM, Tiebout SA, Niermeijer J, et al. Pyridoxine-dependent epilepsy: review of clinical spectrum and treatment. Mol Genet Metab. 2016;118:1-9.
8. Gospe SM Jr. Pyridoxine-dependent epilepsy. Semin Pediatr Neurol. 2020;35:100820.
9. asura GJ, Hagland SP, Wiltse AM, Gospe SM Jr. Clinical features and long-term outcomes of pyridoxine-dependent epilepsy. Dev Med Child Neurol. 2009;51:498-502.
10. Bok LA, Halbertsma FJ, Houterman S, et al. Long-term outcome in pyridoxine-dependent epilepsy. Dev Med Child Neurol. 2012;54:849-854.
11. Pearl PL, Hyland K, Chiles J, et al. Pyridoxal phosphate-responsive epilepsy. Epilepsia. 2013;54:123-129.
12. Rahman S, Footitt EJ, Varadkar S, Clayton PT. Vitamin-responsive epilepsies. Dev Med Child Neurol. 2013;55:307-314.