ORIGINAL RESEARCH PAPER
Volume - 14 | Issue - 05 | May - 2025 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

RECURRENT SEIZURES IN A NEONATE WITH PYRIDOXAMINE-5-PHOSPHATE OXIDASE DEFICIENCY: A COMPREHENSIVE CASE REPORT AND REVIEW OF LITERATURE

Neonatology

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ABSTRACT

Pyridoxamine-5-phosphate oxidase (PNPO) deficiency is a rare autosomal recessive disorder characterized by intractable neonatal seizures that are unresponsive to conventional antiepileptic drugs with varied responsive to pyridoxine or pyridoxal phosphate. Till date less than 100 genetically proven cases have been reported worldwide. This report describes a neonate with recurrent seizures successfully managed with Pyridoxal phosphate after multiple failed antiepileptic regimens. A detailed clinical presentation, including MRI and EEG findings, is provided, along with a comprehensive metabolic workup. Genetic testing confirmed PNPO deficiency. This report underscores the importance of early diagnosis and management of vitamin B6-dependent epilepsies in neonates presenting with refractory seizures. The case is supplemented with relevant literature, highlighting clinical and genetic aspects.

KEYWORDS

Pyridoxamine-5-phosphate Oxidase; Recurrent Seizures; Pyridoxal Phosphate

INTRODUCTION

Pyridoxine-dependent epilepsy (PDE) and related disorders, such as PNPO deficiency, are characterized by seizures that are resistant to common antiepileptic medications either respond dramatically or varied responsive to pyridoxine or pyridoxal phosphate.[1] PNPO deficiency, however, results from mutations in the PNPO gene that impair the synthesis of pyridoxal phosphate (PLP), active form of vitamin B6, necessary for normal neurotransmitter metabolism.[2] These conditions are rare, with an estimated incidence of 1 in 400,000 to 1 in 700,000 live births.[3] Seizure develops typically within 24 hours and in the most of cases, refractory seizures start within first week of life. Despite being treatable, diagnostic delays often occur due to their nonspecific presentation and resemblance to other neonatal conditions like hypoxic-ischemic encephalopathy, sepsis, or metabolic encephalopathies.[4]

Case Report

Thirty-seven weeks term female baby was born to consanguineous parents on 14 July 2024 via caesarean section due to fetal distress. Birth weight was 2.6 kg, with Apgar scores of 7 and 8 at 1 and 5 minutes, respectively. There were no complications during pregnancy, and the initial postnatal period was uneventful for the first 24 hours of life.

On the second day of life, the infant exhibited sudden onset of multiple myoclonic jerks involving both upper and lower limbs, which lasted for several seconds and recurred every few minutes. These were accompanied by subtle tonic posturing of the extremities. Given the concern for neonatal seizures, an urgent neurological assessment was conducted. Initial management included a loading dose of phenobarbital (20 mg/kg) which was increased to (40mg/kg/day) followed by maintenance therapy (5 mg/kg/day). Despite this intervention, the seizures persisted with minimal reduction in frequency and duration. After that we initiated levetiracetam at a dose of 20 mg/kg/day which was increased to 60 mg/kg/day. Over the next 24 hours, there was a transient reduction in seizure frequency; however, by day 5, the seizures returned with increased frequency and intensity. The baby began to exhibit clustering of seizures, with each episode lasting longer than before and involving more pronounced multiple myoclonic jerk. This prompted the administration of phenytoin, given as a loading dose of 20 mg/kg intravenously and maintenance dose of 5mg/kg/day, in an attempt to control the escalating seizure activity. Unfortunately, the seizures persisted, and the baby's clinical condition continued to deteriorate by the start of 6th day of life.

On day 6, EEG monitoring showed multiple electrographic seizures (>20) characterized by bursts of spike and wave discharges, predominantly over the left posterior quadrant, with spread to the bilateral hemispheres. The EEG demonstrated a burst suppression pattern indicative of severe encephalopathy and non-convulsive status epilepticus. Intravenous pyridoxine (100 mg) didn't show any improvement in the EEG with persistent background abnormality amounting to severe encephalopathy and non-convulsive status epilepticus. At this point, likely differentials for the above refractory seizures were either an inborn of metabolism or pyridoxamine 5-phodphatase deficiency (PNP0) or folinic acid deficiency or rare epilepsy syndrome

A detailed family history revealed that the parents were consanguineous and had experienced the loss of a previous child under similar circumstances. The older sibling had reportedly died at 3 months of age following an unexplained illness characterized by recurrent seizures and subsequent respiratory failure. Cause of death had not been determined, but this history raised significant concern for an underlying genetic or metabolic disorder contributing to the presentation in this infant. Given the familial history of early neonatal death and the current clinical scenario, a broad metabolic and genetic workup was initiated to identify a potential etiology. Blood and cerebrospinal fluid (CSF) samples were obtained for a comprehensive metabolic screen, including measurements of ammonia, lactate, glycine, and glutamate levels, as well as genetic testing to evaluate for inborn errors of metabolism.

An MRI performed on day 7 showed multiple areas of restricted diffusion in the bilateral frontal, parietal, and occipital lobes with associated haemorrhage in the posterior cortical region. No structural malformations or congenital anomalies were noted. An echocardiogram performed showed normal cardiac structure and function, with no evidence of congenital heart disease or cardiomyopathy. The ejection fraction was within normal limits, and there were no signs of pulmonary hypertension. On day 6, EEG monitoring showed multiple electrographic seizures (>20) characterized by bursts of spike and wave discharges, predominantly over the left posterior quadrant, with spread to the bilateral hemispheres. The EEG demonstrated a burst suppression pattern indicative of severe encephalopathy and non-convulsive status epilepticus.

Preliminary results showed elevated serum ammonia levels (250 µmol/L, normal range <50 µmol/L), suggesting a potential urea cycle disorder or another metabolic derangement contributing to the refractory seizures. CSF analysis revealed mildly increased glycine levels (4 µmol/L, normal range 0.5-2 µmol/L), while glutamate levels were within the normal range. These findings prompted further genetic testing to explore potential metabolic etiologies, including pyridoxine-dependent epilepsy or pyridoxamine-5-phosphate oxidase deficiency, given their association with intractable neonatal seizures and similar biochemical profiles.

Whole-exome sequencing identified compound heterozygous mutations in the PNPO gene, consistent with pyridoxamine-5-phosphate oxidase deficiency (Figure 1). This diagnosis provided a unifying explanation for the clinical presentation and the sibling's history of unexplained early death.

Figure 1: Whole-exome sequencing identified compound heterozygous mutations in the PNPO gene, consistent with pyridoxine-5-phosphate oxidase deficiency

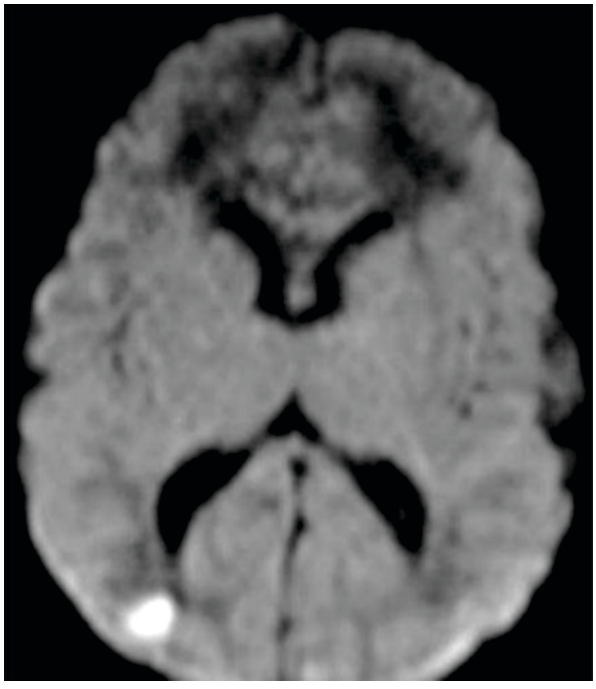

Figure 2: Axial Diffusion Weighted Image MRI

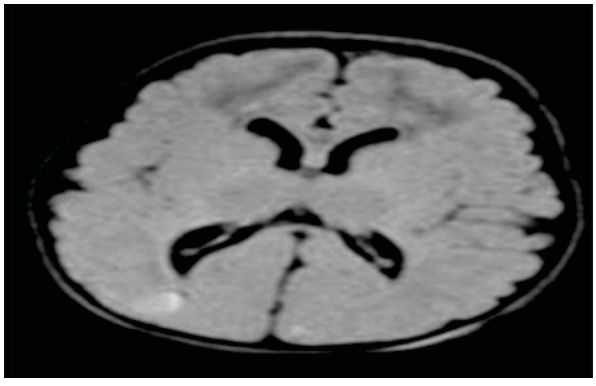

Figure 3: Axial Diffusion Weighted Image Flair MRI

Figure 2,3: Axial diffusion weighted image MRI and FLAIR MRI on day of life 7 show multiple areas of restricted diffusion in bilateral frontal, parietal, occipital lobes

Upon confirmation of the diagnosis, the patient was started on Pyridoxal phosphate at a dose of 30 mg/kg/day, which resulted in a rapid cessation of seizures and marked clinical improvement. The infant was subsequently stabilized, and sedative infusions were gradually weaned. She was successfully extubated to non-invasive ventilation and eventually transitioned to room air over the next two weeks. The family was provided with extensive genetic counselling and instructed on need for lifelong Pyridoxal phosphate supplementation and regular follow-up for monitoring neurological development. This extended case highlights the critical need for early recognition and intervention in neonates with refractory seizures, especially in the context of a concerning family history.

DISCUSSION

PNPO deficiency is a rare inborn error of metabolism that affects the conversion of pyridoxine phosphate and pyridoxamine 5phosphate to pyridoxal phosphate.[5] Pyridoxal phosphate is crucial coenzyme for various enzymes involved in neurotransmitter metabolism, including those that synthesize gamma-aminobutyric acid (GABA) and dopamine. Deficiency of pyridoxal phosphate results in a buildup of neurotoxic metabolites and decreased synthesis of inhibitory neurotransmitters, contributing to the development of seizures.[6]

The genetic mutations identified in this case disrupt normal splicing and function of the PNPO enzyme, resulting in a severe clinical phenotype characterized by early-onset, intractable seizures. The clinical presentation often overlaps with other causes of neonatal encephalopathy, making early diagnosis challenging.[7,8]

The clinical presentation of PNPO deficiency is often indistinguishable from other causes of neonatal seizures, leading to diagnostic delays. Typical features include intractable seizures unresponsive to standard AEDs and a dramatic response to pyridoxine.[9,10] However, not all cases respond to pyridoxine alone; some may require pyridoxal phosphate due to the specific enzymatic block in the pyridoxal phosphate pathway.

In this case, the rapid response to pyridoxine was a key diagnostic clue that prompted early genetic testing. The early administration of pyridoxine prevented further neurological damage and stabilized the patient's clinical condition.[11] Several case reports and series have described the clinical features, genetic mutations, and management of PDE and PNPO deficiency. The largest cohort study by Mills et al. (2010) reviewed 59 cases of PDE, highlighting the genetic spectrum and clinical variability.[12] The study emphasized the importance of early recognition and treatment in preventing long-term neurological squeale. Recent advances in genetic testing, including whole-exome and whole-genome sequencing, have facilitated early diagnosis and improved outcomes.[13]

The primary treatment for PNPO deficiency is lifelong supplementation with pyridoxine or pyridoxal phosphate. The dose of pyridoxine varies but typically ranges from 30 to 50 mg/kg/day.[14] In patients with confirmed PNPO deficiency, pyridoxal phosphate may be more effective. Early and continuous treatment is crucial to prevent neurodevelopmental sequelae. Prognosis is generally favourable if treatment is initiated early. However, even with optimal management, some patients may experience developmental delays or cognitive impairments. This case demonstrated a favourable outcome, with child remaining seizure-free. However, baby requires to be under close follow up for attainment of developmental milestones and may require early cognitive and behavioural therapy.

This case highlights the importance of including vitamin B6-dependent epilepsies in the differential diagnosis of neonatal seizures. Early recognition and treatment with pyridoxine or pyridoxal phosphate can significantly alter the clinical course and prevent long-term neurological damage. Genetic testing plays a pivotal role in confirming the diagnosis and guiding therapy. Increased awareness among clinicians and the availability of rapid genetic testing can improve outcomes for affected infants and their families.

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