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Case Report

PNPO Deficiency Following a Novel Mutation, Intriguingly Turned Out to be Pyridoxine Responsive Neonatal Epilepsy: A Case Report

Chandima Roshani Gunaratne[1]* and Deva Thusitha Sameera Kumarasiri[2]

[1]*Acting Consultant Neonatologist, Teaching Hospital, Batticaloa, Sri Lanka*

[2]*Senior Registrar in Emergency Medicine, Lady Ridgeway Hospital for Children, Colombo, Sri Lanka*

***Corresponding Author:** Chandima Roshani Gunaratne, Acting Consultant Neonatologist, Teaching Hospital, Batticaloa, Sri Lanka.

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Abstract

Pyridoxine-5'-phosphate oxidase (PNPO) deficiency is a rare, autosomal-recessive, treatable neuro-metabolic neonatal epileptic encephalopathy disorder, characterised by recurrent intractable seizures in the prenatal, neonatal and postnatal period, that are resistant to antiepileptic drugs, but classically responsive to pyridoxal-5'phosphate (PLP).

PNPO enzyme is a key factor for the conversion of pyridoxine to PLP, which is the co-factor especially for the synthesis of neurotransmitter (NT) GABA, the major inhibitory NT of the CNS, from glutamate (major excitatory NT). PNPO deficiency is caused by the mutations in PNPO gene in Chromosome 17.

As of today, 24 disease causing mutations were identified in PNPO gene, mostly been missense and nonsense mutations. We report, a novel frameshift mutation owing to a deletion in PNPO gene, leading to pyridoxine responsive neonatal epilepsy.

Clinically, a great variety of intermixed seizures are seen, the most common seizure being the generalised tonic clonic convulsions with recurrent episodes of status epilepticus. However, other seizure types such as, recurrent self-limiting partial, atonic, clonic, myoclonic seizures or spasms could also be seen. In 20% of cases, a retrospective history of intra-uterine convulsions.

could be reported. Foetal loss along with preterm labour and foetal distress during labour and meconium at birth may present, that might lead to the misdiagnosis as perinatal asphyxia as flaccidity and early neonatal seizures are commonly seen in both conditions.

No lab test is available to confirm the diagnosis including EEG, apart from the genetic studies, thus delay in the diagnosis, especially in sporadic cases is common.

Management includes: maternal supplementation of PLP during antenatal period and subsequent lifelong supplementation of PLP to the patient. Prognosis varies based on many factors and could lead to neuro-developmental disabilities ranging from mild to severe and sometimes death.

Keywords: *Neonatal Epilepsy; PNPO Deficiency; Pyridoxine-5'phosphate (PLP); Pyridoxine; Novel Mutation*

Introduction

Pyridoxine-5'-phosphate oxidase (PNPO) deficiency is a rare, autosomal-recessive, treatable neuro-metabolic neonatal epileptic encephalopathy disorder, characterised by recurrent intractable seizures in the prenatal, neonatal and postnatal period, that are resistant to antiepileptic drugs, but classically responsive to pyridoxal-5'phosphate (PLP-active form of Vitamin B6/pyridoxine) [1-4].

PNPO deficiency is caused by the mutations in PNPO gene in Chromosome 17 [2,5]. PNPO enzyme is a key factor for the conversion of pyridoxine to PLP, which is the co-factor especially for the synthesis of neurotransmitter (NT) GABA, the major inhibitory NT of the CNS, from glutamate (major excitatory NT). Glutamate leads to marked increment in excitatory status, precipitating seizures [2].

So far, 24 disease causing mutations were identified in PNPO gene, mostly been missense and nonsense mutations [2]. We report, a novel frameshift mutation owing to a deletion in PNPO gene, leading to pyridoxine responsive neonatal epilepsy.

Case History

27 year old $G_3P_2C_0$ mother (blood group B+), with a POA of 36 wks+3 days, delivered a baby boy by an elective lower segment caesarian section (LSCS) due to oligohydroamnios and past section. Mother had not felt increased foetal movements antenatally. The baby had cried after stimulation and had no meconium at delivery and the APGAR score was 1^9, 5^{10} and 10^{10}. Cord blood gas revealed metabolic acidosis (pH-7.136, PCO_2-43.2 mmHg, PO_2-55.7 mmHg, HCO_3-16.2 mmol/L, Base excess-12.5 mmol/L and lactate-7.mmol/L), which was corrected by a normal saline bolus-10 ml/kg. Initial blood sugar was 32 mg/dL for which, 10% dextrose IV drip was commenced following a 10% dextrose bolus-2 ml/kg. He was haemo-dynamically stable with no respiratory distress.

The parents had 2nd degree consanguinity and the first pregnancy was a 1st trimester miscarriage and the second was a late neonatal death of a baby boy (delivered late preterm (POA- 36+2) with a good birth weight of 2.94 kg, following an emergency LSCS owing to delayed second stage of labour) at 14 days of life following intractable status epilepticus, following which the parents were undergone genetic studies revealing that, both parents are heterozygous carriers of frameshift variant in the PNPO gene[(c.365del;p.(As122Alafs*25));heterozygous]. Both parents were genetically counseled as 25% risk in the next pregnancy, of having a baby with a similar picture. Unfortunately, the mother was not supplemented with PLP during this pregnancy.

After 30 minutes of birth, the baby was noted to have generalized tonic-clonic seizure lasting ≥ 5 minutes, needing IV phenobarbitone 20 mg/kg bolus. Since baby had recurrent generalized as well as myoclonic convulsions, phenobarbitone 20 mg/kg was repeated and paediatric neurologist opinion was taken. Prophylactic anti-meningitis treatment with crystalline-penicillin and cefotaxime were commenced and considering the previous history and genetic defects of parents, lifelong daily supplementation of pyridoxine-5'phosphate were suggested. However, owing to the unavailability oral pyridoxine-5'phosphate, oral pyridoxine 100 mg stat dose was commenced at 6 hours of delivery along with IV folinic acid 2.5 mg twice a day (bd), after which the fits were temporarily controlled. However, since recurrent brief convulsions appeared soon, IV midazolam infusion was started and titrated up to the maximum dose-24 µg/kg/min over next 2 days along with mechanical ventilation. Since the seizures were poorly controlled, oral pyridoxine-100 mg given twice.

The baby's blood group was B+ and his basic full blood count, liver enzymes and bilirubin levels, renal functions including calcium and magnesium levels, prothrombin (PT) and activated partial thromboplastin time (APTT) were normal. The CPK (creatinine phosphokinase) was elevated-3096 U/L (normal value male = 39-308U/L), which was explainable due to recurrent convulsions.

Oral levetiracetam (due to the unavailability of IV form) 10 mg/kg was started for seizure control on day 03 and increased to the maximum of 40 mg/kg by 5th day. On day 08, oral topiramate 3.25 mg/d was also commenced and reasonable seizure control was achieved by day 11 with oral pyridoxine 100 mg/d, oral folinic acid 2.5 mg/d, along with 4 other anticonvulsant drugs including phenobarbitone maintenance (2.5 mg/kg/bd). On day 12, oral supplementation of pyridoxine was changed to 25 mg/6 hourly along with the commencement of phenobarbitone and midazolam tailing off. Midazolam was omitted on Day 15 and the baby was extubated the following day. On day 17 and 24, two brief focal fits were noted, following which the topiramate dose was increased to 3.25 mg/bd. The post treatment EEG on Day 26 showed a near normal background activity with few multifocal spikes and sharp waves in bilateral fronto-central regions. Subsequently, the baby was noted to have mild generalised hypertonia with poor sucking and swallowing along with inspiratory stridor.

Micro Laryngoscopy and Bronchoscopy (MLB) was performed by the ENT surgeon and excluded structural causes. Evolving cerebral palsy as a cause of above symptoms were suggested and the baby was discharged on Day 47 with NG feeding, 2 anticonvulsants, pyridoxine and folinic acid supplementation. Currently the baby is 2 months of age and has a fair control of seizures with neurological deficit, with pyridoxine along with tailing off doses of levetiracetam and topiramate.

Discussion

Though a great variety of intermixed seizures are seen[2], the most common seizure type is prolonged generalized tonic clonic convulsions with recurrent episodes of status epilepticus [1], which was so in our baby as well. Other seizure types include, recurrent self-limiting partial, atonic, clonic, myoclonic seizures or spasms [1,2].

There could be a retrospective history of intra-uterine convulsions, only in 20% of cases, reported as; sustained hammering sensation, lasting 15 - 20 minutes, usually starting at 5 months of POA [2]. Foetal loss along with preterm labour is also reported [1,2]. Foetal distress during labour and meconium at birth may present in 1/3 of patients [3] and these symptoms along with flaccidity and early neonatal seizures frequently lead to the misdiagnosis as perinatal asphyxia [1,2]. Nevertheless, none of the above features were present in our case. However, other rare features of PNPO deficiency such as: oligohydramnios, metabolic acidosis and hypoglycaemia[1] were present in our baby.

As no lab test is available to confirm the diagnosis, delay in diagnosis and treatment is common in all sporadic cases except familial ones [1,2]. Nevertheless, the low PLP levels in plasma and CSF could be of value [2].

Though, no pathognomonic EEG features, the suggestive pattern, before treatment, is usually the bursts of spike and wave discharges [2,3]. In our case, no EEG was done before treatment due to the unavailability of portable EEG facility.

Management should include supplementary PLP to the mother during last half of gestation [1]. It has been suggested that antenatal supplementation may be effective in preventing intrauterine seizures, decreasing the risk of complicated birth and improving neuro-developmental outcomes[1]. Usually there is no response to IV pyridoxine, but to oral PLP 10 mg/kg, thus named pyridoxal phosphate responsive or PLP dependent seizures [3]. Subsequent treatment of lifelong supplementation of PLP 30 - 50 mg/kg/d should be instituted [1-3]. However, owing to the unavailability of PLP, we had to commence pyridoxine, which showed a fair response in our patient. This was explained by Mills., *et al*. as: "pyridoxine responsiveness is also noted especially with certain influential factors like; prematurity, the time of the therapeutic trial, maternal pyridoxine supplementation, neonatal riboflavin status and the genetic mutation involved" [1,6].

Prognosis of PNPO deficiency is variable and depends in part on genotype, associated abnormalities in brain development and response to pyridoxine or PLP treatment [1,5,6]. Nevertheless, most patients will achieve seizure control along with generally good prognosis especially with prompt treatment [1-6]. However, it may lead to neuro-developmental disabilities ranging from mild to severe, intellectual disability and sometimes death especially in untreated patients [1,2,5]. Our patient also shows early features of neuro-developmental delay, with generalized hypertonia along with severe palato-pharyngeal in-coordination.

Conclusion

Even though PNPO deficiency classically responds to PLP, the active form of pyridoxine, depends on the genetic mutation; there could be a response to exogenous supplementation of pyridoxine as well. However, which genetic mutation of PNPO deficiency responds to pyridoxine should be researched comprehensively, before any further conclusion is made.

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