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CASE REPORT

Pyridoxamine 5'-Phosphate Oxidase Deficiency: A Potentially Treatable Epileptic Encephalopathy

Lateefa Almutawea[1*], Ayman Khalil[2]

[1]Pediatric Resident, Pediatrics and Neonatology Department, King Hamad University Hospital, Bahrain; Tel.: (+973) 36306290; Email: latifa.almutawea@gmail.com

[2]Consultant, Pediatric Neurology, Department of Clinical Neurosciences, Salmaniya Medical Complex, Bahrain; Tel.: (+973) 39900075; Email: aymanali131@gmail.com

***Corresponding author:**
Dr. Lateefa Almutawea, Pediatric Resident, Pediatrics and Neonatology Department, King Hamad University Hospital, Bahrain; Tel.: (+973) 36306290; Email: latifa.almutawea@gmail.com

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Abstract

Pyridoxal phosphate-responsive neonatal epileptic encephalopathy due to pyridoxamine-5-prime-phosphate oxidase deficiency is a rare cause of epileptic encephalopathy. A neonate with this condition presents early in life with refractory seizures which does not respond to conventional anti-epileptic medications, depressed level of consciousness, and severe psychomotor retardation if left untreated. Early initiation of active cofactor pyridoxal-5'-phophate can be curative. We are describing a rare neurometabolic condition; the first case in the Kingdom of Bahrain to the best of our knowledge.

Keywords: Pyridoxal-5'-phosphate, pyridoxamine 5'-phosphate oxidase, pyridoxine dependent epilepsy, epileptic encephalopathy, neonatal seizure

Introduction

Kuo and Wang were the first to present a female infant with seizures responsive to pyridoxal phosphate, but resistant to pyridoxine. They suggested pyridoxal-5'-phospahte (PLP) was superior to pyridoxine in treating patients suspected of pyridoxine-dependent epilepsy.[1]

Pyridoxine and its active form pyridoxal-5'-phosphate are involved in more than 100 biochemical pathways including synthesis of sphingolipids, nucleic acid, neurotransmitters, glycogen, hemoglobin, and some amino acids.[2]

There are four main inborn errors of metabolism that are known to affect vitamin B6 concentrations in the brain: hyperprolinemia type 2, antiquitin, pyridoxine phosphate oxidase deficiency and hypophosphatasia with congenital rickets. All the above conditions are associated with refractory epilepsy, which does not respond to classic anti-epileptic medications except vitamin B6 and its cofactor pyridoxal phosphate.[3]

Inherited metabolic epilepsies can cause neonatal epileptic encephalopathy which can be a dreadful condition leading to severe epilepsy and psychomotor arrest. Early recognition and prompt treatment with pyridoxal-5'-phosphate in all neonates and infants with epileptic encephalopathy should bemandatory, permitting normal development in at least some of those affected with pyridoxamine 5'-phosphate oxidase deficiency.[4]

Case presentation

The patient was a Bahraini male, born at thirty-six weeks of gestation through emergency lower segment cesarean section due to breech presentation and fetal distress with a thin meconium-stained liquor. His birth weight was 2020 grams (3rd centile), head circumference 31 cm (10th centile) with Apgar scores of 9, 10 at 1 and 5 minutes respectively.

The patient's mother was primigravida and the pregnancy was uneventful except at the time of delivery. The parents are first cousins with no family history of significant neurological conditions.

Within a few hours of delivery, the patient developed abnormal spells of subtle seizures in the form of chewing, smacking of the lips, and pedaling associated with the state of encephalopathy, reduced activity, and alertness. The patient was initially given: Phenobarbital and Phenytoin loading and maintenance. Despite achieving good therapeutic levels, he continued to have a flurry of seizures.

Eventually, intubation was done due to poor respiratory effort secondary to the side effects of medication, and he was started on Midazolam intravenously .

Investigations

The patients basic blood work including complete blood count, calcium, magnesium, renal and hepatic profiles were unremarkable.

Cranial ultrasound did not show major brain anomalies except for a small germinolytic cyst at the caudothalamic groove.

Cerebral function monitoring (amplitude-integrated EEG) was started to monitor his seizures.

Other anti-epileptic medications including Levetiracetam and Clonazepam drops were given, but response.

During the period of hospitalization, the patient was treated on several occasions for sepsis. He developed transient renal impairment which did not require dialysis. Further investigations were done, and CSF amino acid showed elevated threonine 122 µmol/l (22.2-52.6) while normal in serum; increased urinary lactic acid and vanillacetic acid were detected.

The patient was given a trial of pyridoxine, folinic acid and biotin but did not show adequate effect. He developed another type of seizure in the form of multi focal erratic myoclonic jerks involving the facial muscles and extremities.

Conventional neonatal EEG was done at six weeks while awake, depicting discontinuous activity with variable interburst interval (IBI) 5-10 seconds (Figure 1).

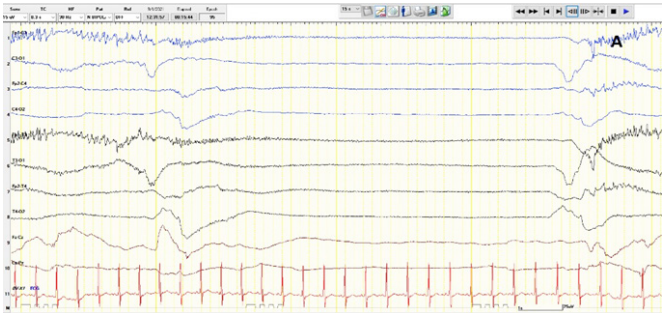

Figure 1: EEG at six weeks

At this stage, his condition refined more toward early myoclonic encephalopathy (EME); this electroclinical pattern frequently associated with underlying inborn error of metabolism.

Brain MRI revealed atrophy with secondary ventriculomegaly and impaired myelination (Figure 2); while a single voxel magnetic resonance spectrum (long echo time: 256ms) obtained from the right basal ganglia showed low N-acetyl aspartate (NAA) peak at 2.02 ppm with low N-acetyl aspartate to creatine ratio (NAA/Cr) (Figure 3).

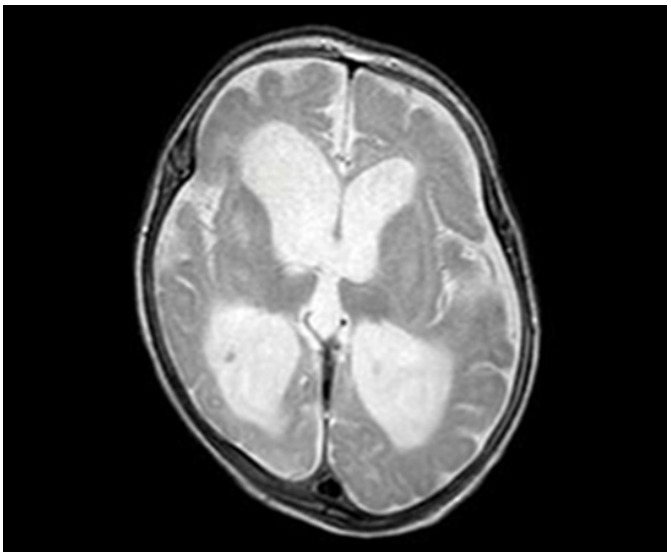

Figure 2: Brain MRI showing atrophy with secondary ventriculomegaly and impaired myelination

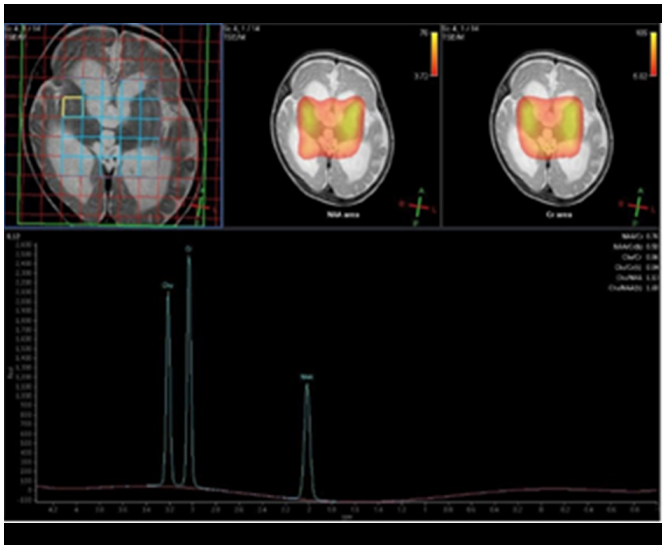

Figure 3: Single voxel magnetic resonance spectrum showing low N-acetyl aspartate

Genetic testing for epilepsy panel was consistent with the diagnosis of pyridoxamine-5-prime-phosphate oxidase deficiency (PNPO) inherited as an autosomal recessive pattern. PNPO variant c.686G>A p.(Arg228Gln) causes an amino acid change from Arginine to Glutamine at position 229.

Treatment

Accordingly, the patient was started on pyridoxal-5'-phosphate (PLP). He showed fair response to medication (PLP), and we were able to wean him from Midazolam drip and other parental anti-epileptic medications and did not require ventilator anymore.

Outcome and follow up

The patients' level of alertness improved, and he was able to open his eyes and look around, but his visual attention was limited. He was able to move all limbs with good antigravity movement and symmetrical bilateral deep tendon reflexes; he started gaining weight as well. Although, he continued to have occasional seizures of different semiology in the form of focal motor seizures and head version. Oxcarbazepine was added. An EEG report at twelve weeks showed significant improvement in background activity: continuous, reactive, and symmetrical bilateral intermixed with occasional multi regional sharp waves mainly in the central and occipital head regions (Figure 4).

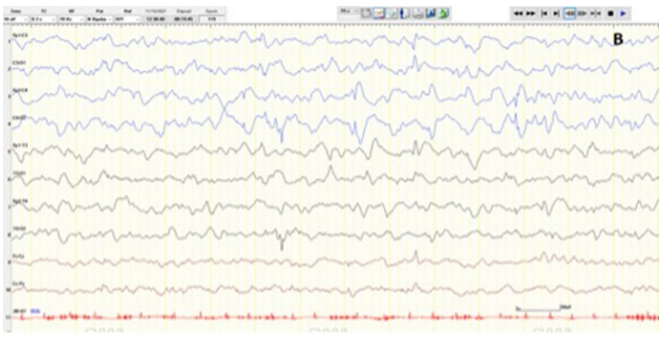

Figure 4: EEG at 12 weeks

Discussion

Neonatal and infantile epileptic encephalopathies are wide and various in etiology. Proper diagnosis and prompt intervention is challenging but essential as this directly effects cognition and neurodevelopmental outcomes. Identifying metabolic causes should be a priority as these might fail in fully responding to conventional seizure management protocols, leading to high mortality rates with delayed disease-specific treatment.[5]

In order to achieve complete control of seizures in pyridoxine unresponsive epileptic encephalopathies in the neonates and infants, such as in the case of PNPO deficiency, it is of importance to understand the related metabolic pathways. Formulating management strategies is possible by understanding the genetic attributions behind these pathways.

Pyridoxal-N-phosphate oxidase (PNPO) is a mononucleotide that is dependent on riboflavin as co factor to transform pyridoxine and pyridoxamine to pyridoxal phosphate (PLP). PLP is the active form of pyridoxine and pyridoxamine obtained from dietary sources.[5] Enzymes dependent on PNPO as catalyst account for approximately 4% of all enzyme-catalyzed reactions in the human body.[6] These include the synthesis and metabolism of various neurotransmitters, hemoglobin, sphingomyelin, amino acids, and glycogen. This explains why other cases reported in literature also presented with retinopathy, anemia, phosphate imbalance, and movement disorders of variable severity alongside epileptic encephalopathy.[7] The presence and reversibility of these systemic symptoms with specific treatment aid in the differentiation

from pyridoxine-dependent epilepsies. Our case had isolated early-onset neonatal seizures refractory to seizure management protocols and vitamins supplementation in absence of systemic manifestations at the time of presentation.

Seizure semiology in previously reported patients with PNPO deficiency were similar to cases of pyridoxine responsive epilepsy including irritability, inconsolable cry, myoclonic movements, tonic seizures, facial grimacing, and abnormal eye movements and twitching.[8] Seizure characteristics in our patient were notably similar.

While genetic testing is a good diagnostic tool, it is not always feasible. Cerebrospinal fluid (CSF) pyridoxal 5′-phosphate (PLP) level testing is possible, but false-negative results have been observed in some patients with them being symptomatic despite normal PLP levels in CSF even without pretreatment with pyridoxine phosphate.[9] This is thought to be attributed to a channeling mechanism that transfers newly formed PLP from both PNPO and pyridoxine kinase to other multiple enzymes that require it as a cofactor.[9] This is observed in some PNPO mutations where this transfer step is affected and the normal CSF PLP level would be insufficient for cofactor delivery to PLP-dependent enzymes.[10] CSF samples in our patient were not tested for pretreatment PLP level, but CSF amino acid revealed high threonine levels consistent with threonine dehydratase disturbance, and elevated urinary vanillacetic acid pointing toward aromatic amino acid decarboxylase abnormalities all of which are PLP-dependent enzymes. A combination diagnostic approach for suspected cases in the future can yield best results.

Magnetic resonance spectroscopy is a complementary imaging modality that has the ability to study various metabolites in the region of interest (ROI) and thereby helps in the understanding brain abnormalities and may correlate with brain pathology; for example, N-acetyl aspartate is a neuronal marker and reflects neuronal integrity while phosphocreatine is a cellular bioenergetic maker. In our case, low levels of N-acetylaspartate may indicate neuronal dysfunction or loss that would correlate with long-term outcomes.

Supplementation with pyridoxine phosphate is found to improve EEG background activity within hours in some patients to weeks in others, the clinical response however is observed to be within days in most PNPO deficiency cases.[8] Few patients required prolonged durations of treatment to reduce seizures, with EEG changes lagging behind further. This was dependent on the level of the deficiency, with the more severely affected patients who had lower levels of PLP requiring longer duration of supplementation in order to show response.[7]

The natural history of PNPO deficiency is known to be catastrophic, but satisfactory outcomes in this treatable inborn error of metabolism are observed with prompt diagnosis and management. The outcomes of patients diagnosed with PNPO deficiency can vary from death if left untreated to different stages of developmental delay and psychomotor retardation with proper timely treatment.[11]

Unfortunately, PLP is not included in many hospital formularies and not readily available which makes starting this treatment as a trial limited. Genetic counseling is paramount as PNPO deficiency is an autosomal recessive disorder with a 25% recurrence risk.

Conclusion

Our patient had pyridoxal-N-phosphate oxidase (PNPO) deficiency on genetic testing with mal-response to conventional seizure treatments similar to the other cases reported in literature. The patient responded to treatment with pyridoxal-5'-phosphate (PLP) supplements, stressing on the importance of relating the phenotypical picture with the genetic diagnosis. Follow-ups are needed to identify long-term developmental outcomes.

Authors contribution

Both authors drafted the initial manuscript and did multiple editions to finalize the final case report.

Conflict of interest

None declared.

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