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Original Article

Clinical and Genetic Profile of a Cohort of Pyridoxamine 5-Phosphate Oxidase Deficiency – A Single-Center Experience

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Abstract

Background: Pyridoxamine 5-phosphate oxidase deficiency (PNPOD) is a rare treatable neonatal epileptic encephalopathy. It is important to raise awareness about this condition to enable early treatment. **Methodology:** This is a retrospective chart review of PNPOD cases followed at Mafraq Hospital during 2011–September 2017. The inclusion criteria include confirmed homozygous or compound heterozygous mutation in pyridox(am)ine-5-phosphate oxidase (PNPO) gene. **Results:** Seven cases were identified, all Emiratis from two tribes. Six cases from Tribe A had homozygous genetic variant C.674G>T: P. Arg255 Leu (one is presumed to have the same mutation based on confirmed proband sibling and carrier state of the parents of this sibship). One patient from Tribe B was tested abroad and has a confirmed homozygous pathogenic variant in PNPO gene (details not available). All six patients with the identical mutation are from one Emirati tribe suggest a founder effect. Two neonates treated in the first few days of life had the best clinical outcome of seizure control and neurodevelopment. One mortality (the deceased sibling of a normally developing child with this disease) highlights the great importance of early treatment. The remaining four patients had incomplete seizure control with neurobehavioral delay. Patients with intractable epilepsy and poor neurodevelopment never received pyridoxal 5-phosphate in the 1st days of life, although they received pyridoxine and other anti-seizure medications. **Conclusion:** PNPOD is a treatable neonatal epileptic encephalopathy; however, early treatment is essential for optimal outcomes. A management algorithm for intractable neonatal seizures emphasizing the crucial "treat before you diagnose" approach is critical for such cases.

Keywords: Neonatal seizures, pyridoxal 5-phosphate, pyridoxamine 5-phosphate oxidase deficiency

Introduction

Seizures occur in approximately 1–5/1000 live births, and are frequently manifested in neonates with acute encephalopathy,[1,2] and are associated with increased risk of infant morbidity and mortality.[2] Identifying treatable underlying etiologies in addition to controlling the seizures is an important modifiable variable that helps lower the risk for infant morbidity and mortality. When neonatal seizures are refractory to conventional anti-seizure medications, rare inborn errors of metabolism, such as vitamin responsive seizures, should be considered.[3] Since Hunt *et al*. first reported a case of pyridoxine (B6) responsive refractory infantile epilepsy in 1954,[4] and Mills *et al*. showed that mutations in ALDH7A1 gene are present in children with pyridoxine-responsive epilepsy,[5] the spectrum of B6-responsive epilepsy have continued to expand, with recognition of another metabolic pathway involving the active cofactor of the B6 pathway, namely pyridoxal 5-phosphate (PLP) that leads to an intractable neonatal epileptic encephalopathy that is partially or completely unresponsive to pyridoxine alone. Even more recently, Darin *et al*. reported seven patients with early onset B 6-dependent epilepsy due to mutations in PROSC gene which encodes a PLP binding protein, and hypothesized that this protein may have a role in intracellular PLP homeostasis.[6] PLP responsive epilepsy represents an important example of such rare vitamin responsive neonatal seizures, and is caused by Pyridoxamine 5-prime-phosphate oxidase deficiency (PNPOD) (OMIM 610090), a rare autosomal recessive inborn error of metabolism caused by homozygous or compound heterozygous

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mutations in the pyridox(am)ine 5 phosphate oxidase (PNPO) gene on chromosome 17q21.32.[7] The phenotypic expression of PNPOD is very early on in the 1st day of life, with what is basically a neonatal epileptic encephalopathy, as described by Mills *et al*.[8]

The aim of this review is to examine the genotype and phenotype profile of our patients with a confirmed diagnosis of PNPOD, to help raise awareness and implement timely empiric treatment of neonates with early intractable seizures and neonatal epileptic encephalopathy, since the outcomes of delayed treatment or lack of treatment of babies affected by PNPOD is very poor and is associated with high morbidity and mortality. Moreover, PLP is not readily available in hospital pharmacies or standard hospital formularies, and physicians may not be aware of or familiar with the use of this life-saving treatment. Hence, increasing knowledge, awareness, and incorporating PLP in the standard emergency treatments in the formularies of hospitals that deal with newborn babies is a crucial outcome the authors hope to achieve by this study. The authors also suggest an algorithm for emergency treatment of neonatal seizures that take into account the most important vitamin responsive neonatal epilepsies.

Methodology

This is a noninterventional retrospective chart review that is an electronic health record system. All cases of PNPO deficiency followed at Mafraq Hospital during January 2011–September 2017 were identified. A chart review was conducted and every patient was given a unique identifying code to maintain each individual patient's privacy, no personal identifiers are present in this study. The patients' tribe was coded by alphanumeric code (i.e., Tribe A and Tribe B) to assure cultural sensitivity. Every chart was reviewed to confirm a documented molecular genetic diagnosis, and characterize the genotype/phenotype profile of all identified cases. The phenotype profile included patient's sex, nationality, tribe, seizure onset, and response to pyridoxine (vitamin B6), age at the time of the study, documented comorbidities, and current treatment.

Genetic testing for PNPOD is not readily available in the United Arab Emirate (UAE), so all these patients had their genetic confirmation done either by request of the treating physician in our division through send out testing to genetic laboratories abroad, or by genetic testing ordered in referral centers were some of the patients had been referred for second opinion for intractable epilepsy (these patients were not initially seen by any of the authors but were cared for by previous physicians at our hospital).

Results

Characteristics of the study population

There were seven identified cases of PNPOD during the study [Table 1]. There was a near equal sex distribution (4 males: 3 females). All the patients were Emirati from in UAE, and they all belonged to one of two large tribes; Tribe A and Tribe B.

Genotype of the study population

All the patients had a documented genetic diagnosis. We had details of the genotype for all but one patient (patients from Tribe B), this patient had his genetic test done abroad and was confirmed as having a "homozygous pathogenic variant in PNPO gene;" however, we could not gain access to the specific mutation he had. We had details of all remaining six patients; they were all from one tribe (Tribe A) had a homozygous genetic variant C.674G>T: P. Arg255 Leu (one of the six cases is presumed to have the same mutation based on his confirmed proband sibling and confirmed carrier state of the both their parents).

Age at presentation with seizures and response to anti-seizure therapy

There were two neonates that were treated very early in the first few days of life had the best clinical outcome of seizure control and neurodevelopment. There was one mortality (patient 4b) in a previously undiagnosed sibling of a normally developing patient (patient 3b) with genetically confirmed PNPOD. The remaining four patients had incomplete seizure control and moderate-to-severe neurobehavioral delay. None of the patients with intractable epilepsy and poor neurodevelopment were treated with PLP in the 1st days of life, although they received pyridoxine and other anti-seizure medications.

Comorbidities and outcomes

There were four patients with prematurity between 32 and 35 weeks' gestational age (57% of this cohort), all patients had seizures at birth (i.e., day 1 of life). Lactate, ammonia, and acid-base state, were within normal range for age. Liver enzymes were mildly elevated (up to 8 folds normal range) in patients 1a, 2b, 3, and 5. All patients were hemodynamically normal. Urine pipecolic acid and cerebral-spinal-fluid neurotransmitters were not performed. Seizures were refractory to conventional anti-seizure medications requiring empiric treatment with vitamin B6 (pyridoxine) at variable time from seizure onset and with variable response. Of interest, 2/7 patients had full seizure control with pyridoxine alone; patient 3b responded to moderate dose (200 mg/day) and patient 7 later requiring as high as 800 mg/day of pyridoxine. Both patients were started early on pyridoxine and have normal for age development (patient 3b) and mild developmental delay (patient 7: Attending regular school with learning difficulty, no formal psychoeducational testing done), respectively. Patients 1a, 2a who were diagnosed and treated late (beyond the neonatal period) and patient 4b (died before diagnosis) had very poor neurobehavioral and developmental outcomes and are both in special needs center, despite seizures being controlled in patients 1a, 2a with a combination of pyridoxine, PLP, and conventional anti-seizure medications.

Discussion

The human receives dietary pyridoxine and pyridoxamine from vegetable and meat sources, respectively. Both vitamins need

Table 1: Demographic, phenotypic, and genetic profile of our centers cohort of patients with pyridoxamine 5-phosphate oxidase deficiency

Patient number/sex	Nationality/tribe	Seizure onset	Response to B6	Current age	Comorbidities	Current TX	PNPO gene
1a*/female	UAE/tribe A	Birth	Partial response	9 years	GDD Behavioral disorder	PLP, B6, anti-seizure drugs	Homozygous variant C.674G>T: P.Arg255Leu
2a*/female	UAE/tribe A	Birth	Partial response	7 years	GDD Behavioral disorder	PLP, B6, anti-seizure drugs	Homozygous variant C.674G>T: P.Arg255Leu
3b*/male	UAE/tribe A	Birth	Full response	3 years	35 week premature Normal development	PLP, B6	Homozygous variant C.674G>T; Arg225Leu
4b*/male	UAE/tribe A	Birth	Unknown	Died age 19 months	Intractable epilepsy, global developmental delay	N/A	Presumed identical to proband
5/male	UAE/tribe A	Birth	Partial response	13 months	32 week premature Mild GDD	PLP, B6, anti-seizure drugs	Homozygous variant C.674G>T: P.Arg255Leu
6/female	UAE/tribe A	Birth	Partial response	13 months	35 week premature (infantile spasms)	PLP, B6, anti-seizure drugs	Homozygous variant C.674G>T: P.Arg255Leu
7/male	UAE/tribe B	Neonatal period	Full response	9 years	32 week premature Mild delay	B6 high dose	Homozygous variant (record not accessible)

*Patients sharing the same small alphabet are sibships. B6: Pyridoxine, PLP: Pyridoxal 5 phosphate, PNPO gene: Pyridoxamine 5-phosphate oxidase deficiency, GDD: Global developmental delay, TX: Treatment

to be converted to the active cofactor, PLP, in a 2-step pathway involving a kinase, and then the enzyme PNPO.[9] Expression studies in mammalian cells have clearly demonstrated that homozygous mutations in PNPO gene result in reduced activity in PNPO.[8,10] Although reduced activity in PNPO oxidase results in reduced levels of the active cofactor PLP, the role of PNPO in biochemical homeostasis and prevention of seizures is rather complex, as evident in part by the PNPOD patients who are B6 responsive, and those who may actually worsen with PLP replacement.[8,11] Nevertheless, the phenotype of babies with PNPOD has become well recognized; these neonates are typically premature, present with seizures on day 1 that are intractable and quickly develop a neonatal epileptic encephalopathy.

As demonstrated in our cohort, very early treatment is linked to normal or near normal outcome; defined as seizure control and age-appropriate neurobehavioral development. Conversely, late or no treatment with PLP with or without pyridoxine is universally related to poor outcome with severe neurobehavioral disorder, intractable seizures, and death. This observation is in keeping with the phenotypic features and neurological outcomes of babies with PNPOD described in the literature.[8,10] It should be noted, however, that treatment with pyridoxine as early as day 2 and day 4 of life in neonates with genetically confirmed ALDH7A1-related B6-dependent epilepsy[5] and as early as 40 h of age in a neonate with genetically confirmed PNPO deficiency[12] was still associated with variable degrees of developmental delay as reported by Mills *et al*., and Hatch *et al*.[8,12]

There are several important points observed in our cohort. First, 2 out of 7 patients had full response to pyridoxine alone. This observation has previously been published by others,[13,14] but is worth reiterating so that physicians facing patients will neonatal seizures fully responsive to pyridoxine but test negative for ALDH7A1 (Aldehyde Dehydrogenase 7 Family, Member A1), the genetic cause for pyridoxine responsive seizures will pursue genetic testing for PNPOD, since this will have great implication on follow-up, genetic counseling and timely treatment for future offspring. Second, our sibship in which there was one mortality (in the previously undiagnosed sibling of a normally developing patient with genetically confirmed PNPOD) and one completely normally developing a child with full seizure control highlights the great importance of early diagnosis and treatment and the possibility of achieving good neurologically preserved survival in patients with PNPOD. Interestingly, this was a child who also was fully responsive to pyridoxine alone early in the neonatal period. Third, patients 1a, 2a who were diagnosed and treated late, beyond the neonatal period, had very poor neurobehavioral and developmental outcomes, despite seizures being controlled with a combination of pyridoxine, PLP, and conventional anti-seizure medications. This is very important to motivate physicians to early empiric treatment with pyridoxine and PLP as early as possible, typically within the first few days of life, to prevent such poor neurobehavioral outcomes. Finally, the fact that all six patients with the same mutation are Emirati and belong to the same large tribe (Tribe A) suggest it is highly likely that there is a founder effect. This is an important observation that should alert the treating physicians in our region to consider this disease in pregnancies with such a family history and proactively question the pregnant about abnormal fetal movements and plan timely detection and treatment of seizures once born.

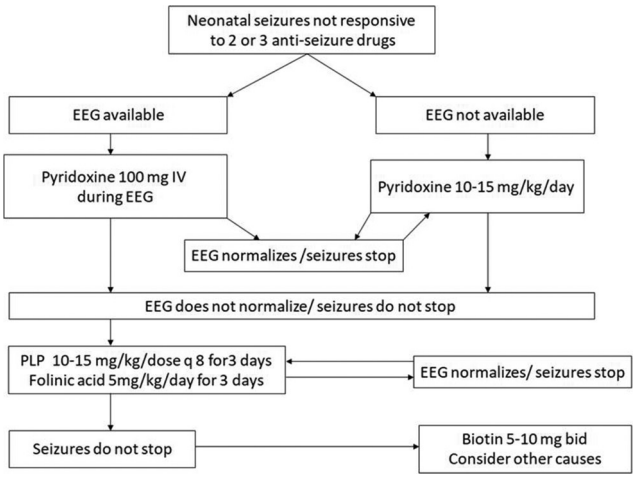

Figure 1: Neonatal seizures management algorithm

Conclusion

It is of paramount importance that treatable etiologies of neonatal seizures are considered proactively and that timely initiation of safe yet very effective vitamin therapy with pyridoxine and PLP is part of the management algorithm of neonatal seizures. The authors have established a neonatal seizures management algorithm [Figure 1] aiming to increase awareness among our treating physicians, and shorten the time to empiric treatment with vitamin B6 and PLP in neonates with intractable seizures and neonatal epileptic encephalopathies. This algorithm, however, has not been validated yet and cannot be formally recommended. The recognition of a founder effect in one of our large tribes should also heighten alertness to suspect PNPO deficiency in high risk populations based on family history and tribal origin.

Disclosures

All authors contributed to the care of the patient, drafting of the case report, revision, and approval of its final version.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Compliance with ethical principles

No prior ethical approval is required for single case reports or small case series based on retrospective review of de-identified charts.

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