Vitamin B6-dependent epilepsy due to pyridoxal phosphate-binding protein (PLPBP) defect – First case report from Pakistan and review of literature

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ABSTRACT

Introduction: The Vitamin B6-dependent epilepsies are a heterogeneous group of autosomal recessive disorders usually characterized by neonatal onset seizures responsive to treatment with vitamin B6 available as pyridoxine (PN) or as the biologically active form pyridoxal 5-phosphate (PLP). The vitamin B6–dependent epilepsies are caused by mutations in at least five different genes involved in B6 metabolism. A literature review revealed that only 30 patients with vitamin B6-dependent epilepsy caused by PLPBP mutation have been reported worldwide.

Presentation of case: We report a case of baby boy born to first-cousin Pakistani parents who presented with generalized as well as focal seizures starting a few hours after birth and responsive to PLP. Whole exome sequencing revealed a homozygous pathogenic variant NM_007198.4:c.46_47insCA, NP_009129.1:p.Leu17Hisfs, causing a CA duplication resulting in a frameshift in the PLPBP gene.

Discussion: Vitamin B6-Dependent Epilepsy due to PLPBP defect is a rare disorder. The developmental outcomes are variable even with early therapy. Few patients are reported to achieve optimal developmental milestones with therapy. PLP has been advocated as the treatment of choice for PLPBP defect, but oral PN has also demonstrated good seizure control in some patients, including ours.

Conclusion: Vitamin B6-dependent epilepsy due to PLPBP defect is an important differential diagnosis to consider in patients with biochemical features suggestive of pyridoxamine 5'-phosphate Oxidase (PNPO) defect and gene testing can facilitate in reaching the correct diagnosis. Prompt diagnosis and treatment led to excellent seizure control in most patients.

1. Introduction

The Vitamin B6-dependent epilepsies are a heterogeneous group of autosomal recessive disorders usually characterized by neonatal onset seizures responsive to treatment with vitamin B6 available as pyridoxine (PN) or as the biologically active form of vitamin B6, pyridoxal 5-phosphate (PLP) [1]. PLP serves an essential role for the development of nervous system, owing to its role in neurotransmitter synthesis and as a co-factor for over 160 catalytic enzymes involved in lipid and amino acid metabolism [2].

The vitamin B6–dependent epilepsies are caused by mutations in five genes involved in B6 metabolism. Accumulation of toxic metabolites resulting in inactivation of PLP is caused by Aldehyde Dehydrogenase 7 Family Member A1 (ALDH7A1) (MIM#266100) and Aldehyde Dehydrogenase 4 Family Member A1 (ALDH4A1) (MIM#239510) gene defects, Mutations in pyridoxamine 5'-phosphate Oxidase (PNPO) (MIM#610090) and tissue-nonspecific alkaline phosphatase (TNSALP) (MIM#171760) result in impaired interconversion of B6 vitamers. PLP homeostasis is impaired by defects in pyridoxal phosphate-binding protein (PLPBP) (MIM#604436), previously termed PROSC [2–4]. PLPBP encodes a PLP homeostasis protein (PLPHP) located in both mitochondria and cytoplasm [5]. PLPHP has a PLP-binding domain and serves as an active transporter of PLP to apo-enzymes, preventing its side reactivity and degradation by intracellular phosphates [4].

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The hallmark of pyridoxine-dependent epilepsy is onset of intractable seizures within the first few months of life that are not controlled with antiepileptic drugs but respond both clinically and electrophysiologically to large daily supplements of PN [5]. In the PLPBP defect, neonatal onset seizures are the predominant feature. These seizures do not show much response to treatment with PN, but respond dramatically to PLP. Movement disorders, encephalopathy and hyperglycinemia have also been described in few patients with PLPBP defect [6].

Vitamin B6-dependent epilepsies can be detected by their respective biomarkers and confirmed by molecular testing. Increased levels of threonine and glycine in the cerebrospinal fluid (CSF) suggest a general defect of B6-dependent enzymes [4]. In ALDH7A1 and ALDH4A1 defects, elevated alpha-amino adipic semialdehyde (also been described in few patients with PNPO defect), oral PLP was not immediately available. Oral pyridoxine, 50 mg twice daily, was started on the 11th day of life, and this was replaced with oral PLP 30mg thrice daily when this became available at 1 month of age. The patient showed significant clinical improvement in terms of overall activity, spontaneous eye opening, limb movement, normal crying and active suckling on feeding, all of which were noted even on early oral PN therapy. A repeat EEG was normal.

PNPO gene sequencing did not show any sequence change leading us to further explore other genes. Whole exome sequencing revealed a homozygous pathogenic variant NM_001984.4:c.-46_47insCA, NP_009129.1:p.Leu17Hisfs, causing a CA duplication resulting into a frameshift in PLPBP. Only one heterozygote for this mutation is present in gnomAD, yielding an allele frequency of 4.81 × 10⁻⁶.

The baby continued to experience occasional seizures with fever. The oral PLP therapy was interrupted for few weeks at 3.5 years of age due to non-availability of the medicine and he experienced significantly increased seizure frequency without fever, including an admission for status epilepticus. When oral PLP was re-started his seizures were controlled within few hours. At 4 years of age due to the COVID-19 pandemic, the PLP supply chain was interrupted and he was again started on oral pyridoxine 50 mg four times a day. He is also on oral Levetiracetam 100 mg twice daily. At present he is 4 years 5 months old and his seizures are controlled except for occasional brief seizures associated with fever for the last 5 months. His motor and fine motor milestones are age appropriate, but his speech, cognitive functions and social skills are delayed for his age and has an acquired microcephaly, OFC being 48.2 cm (<0.2 percentile).

3. Discussion

Vitamin B6-Dependent Epilepsy due to PLPBP defect is a rare disorder. A comparison of the age of symptoms onset, clinical manifestations, neuro-imaging findings, treatment regimens, response to therapy and outcome in all thirty-one reported patients with PLPBP defect including our patient is summarized in Tables 1 and 2.

The PLPBP defect is pan-ethnic as it has been reported from Europe, United States of America, Canada, South East Asia, Western Asia, South Asia, Africa, United Arab Emirates, Syria and India [2,4,6–10]. Both males 19 (61.2%) and females 11 (35.5%) are reported. Gender is not reported for patient number 16. Consanguinity of parents is reported in 21 (68%) patients including ours. The median age of presentation was 2 (IQR: 1–7) days. At the time of these publications, five (16%) patients were deceased, with the age of death ranging from 2 weeks to 4.5 months with a median of 56 days (IQR: 31.5–96.5).

PN has to pass through a conversion to PLP to serve as a coenzyme, but PLP is the active coenzyme form of vitamin B6, with better bioavailability as it is able to protect itself from hydrolysis [9]. Responses to therapy in patients with PLPBP defects vary in the literature. Darin et al. reported better responses to PLP than PN, whereas Plecko et al. reported that 75% of the patients responded well to PN with prompt cessation of seizures [4,8]. In 24 (80%) reported patients, PN was used as the first treatment modality, with seizure control achieved in 19 (63%). Six patients (20%) experienced seizure recurrence after PN withdrawal and cessation of seizure after PN reintroduction. In 7 patients (23%), PN was switched to PLP and this resulted in improved seizure control. Two reported patients (12 and 19) received PLP as the initial treatment [2,9]. In patient 19, whose initial therapy was PLP and adjuvant anti-epileptic drugs, switching PLP to PN did not improve seizure control. This patient subsequently received PN and midazolam.
Table 1
Demographics, clinical presentation, treatment initiated and neuroimaging findings of cases with PLPB defect including our case (n = 31).

| Patient No. | Ethnicity            | Age at presentation /Gender | Clinical Presentation                                                                 | Neuro Imaging                                                                 | Treatment  | Consanguinity |
|-------------|----------------------|----------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|------------|---------------|
| 1 [4]       | Syrian               | 1 DOL/M                    | Seizures, Anemia, Abdominal distension, vomiting, or feed intolerance, microcephaly   | Brain MRI (Age:2 Months): Global Underdevelopment of brain with broad gyri and shallow sulci, Periventricular cyst | Pyridoxine | Yes           |
| 2 [4]       | Syrian               | 1 DOL/M                    | Seizures, hypertonia, microcephaly                                                  | Not mentioned                                                                   | AEDs, Pyridoxine | Yes           |
| 3 [4]       | Syrian               | 1 DOL/F                    | Seizures, microcephaly                                                              | Brain MRI (Age: 10 days): Global Underdevelopment of brain with broad gyri and shallow sulci, Periventricular cyst | AEDs, Pyridoxine | Yes           |
| 4 [4]       | Indian               | 1 DOL/F                    | Seizures, Anemia, hypertonia, Abdominal distension, vomiting, or feed intolerance, Irritability, microcephaly, Respiratory distress | Brain MRI (Age:10 days): Global Underdevelopment of brain with broad gyri and shallow sulci, White matter edema, deep white matter petechial hemorrhages | AEDs, Pyridoxine, PLP | Yes           |
| 5 [4]       | German               | 1 DOL/F                    | Seizures, hypotonia, Abdominal distension, vomiting, or feed intolerance, Irritability, microcephaly, Respiratory distress | Brain MRI (Age:16 days): Global Underdevelopment of brain with broad gyri and shallow sulci, Periventricular cyst | AEDs, Pyridoxine, PLP | No            |
| 6 [4]       | Indian               | 1 DOL/M                    | Seizures, hypertonia, Irritability, microcephaly, Respiratory distress               | Not reviewed                                                                    | AEDs, Pyridoxine, PLP | Yes           |
| 7 [4]       | Italian              | 1 Month/M                  | Seizures                                                                            | Not reviewed                                                                    | AEDs, Pyridoxine | No            |
| 8 [8]       | Swiss Italian        | 7 DOL/F                    | Irritability, sleeplessness, seizures with grimacing, roving eye movements and tremor| Brain MRI: normal                                                               | AEDs, Pyridoxine | No            |
| 9 [8]       | German               | 5 DOL/F                    | Seizures, poor feeding, irritability, sleeplessness and tremor                       | Brain MRI: normal                                                               | AEDs, Pyridoxine | No            |
| 10 [8]      | Arabic               | 3 DOL/M                    | Seizures                                                                            | Brain MRI: normal                                                               | AEDs, PYPYDoxine | Yes           |
| 11 [8]      | Italian              | 9 DOL/M                    | Seizures                                                                            | Brain MRI: normal                                                               | AEDs, Pyridoxine | Yes           |
| 12 [5]      | Japanese             | 10 DOL/M                   | Seizures                                                                            | Brain MRI (Age 12 days): normal                                                 | AEDs, PYPYDoxine | No            |
| 13 [5]      | Japanese             | 3 months/M                 | Seizures                                                                            | Brain MRI (Age 13 years): normal                                                | AEDs, Pyridoxine | No            |
| 14 [5]      | Malaysian            | 1 DOL/M                    | Seizures                                                                            | Brain MRI (Age 1 year): normal                                                  | AEDs, Pyridoxine | Yes           |
| 15 [5]      | Malaysian            | 34 DOL/M                   | Seizures                                                                            | Brain MRI (Age 17 days): normal                                                 | AEDs, Pyridoxine | No            |
| 16 [10]     | Canada               | Not mentioned              | Seizures, renal failure, anemia                                                     | Not mentioned                                                                   | AEDs, pyridoxine | Not mentioned |
| 17 [2]      | Arab (Oman)          | 5 DOL/M                    | Seizures, developmental delay, speech delay                                          | Brain MRI (Age:6 weeks): mild white matter changes                              | AEDs, Pyridoxine, PYPYDoxine | Yes           |
| 18 [2]      | Arab (Oman)          | 7 DOL/M                    | Seizures                                                                            | Not done                                                                        | AEDs, Pyridoxine | Yes           |
| 19 [2]      | African/Creole (Curacao) | 2 DOL/F                | Seizures, developmental delay, speech delay, hypertonia, strabismus                   | Brain MRI (Age 10 Days): white matter changes, large para ventricular pseudocysts | AEDs, Pyridoxine | Yes           |
| 20 [2]      | Dutch                | 1 DOL/F                    | Seizures                                                                            | Brain MRI (Age 1 Day): white matter changes, large para ventricular pseudocysts | AEDs, Pyridoxine | No            |
| 21 [2]      | Canada               | 1 DOL/F                    | Seizures, developmental delay, speech delay, hypotonia                               | Brain MRI (Age 6 Days): cystic leukoencephalopathy                               | AEDs, Pyridoxine | Yes           |
| 22 [2]      | Arab (UEA)           | 4 DOL/M                    | Seizures, developmental delay, speech delay, hypotonia                               | Brain MRI (Age 8 months): Normal                                                | AEDs, Pyridoxine | Yes           |
| 23 [2]      | Hispanic (Guatemala) | 2 months/M                 | Seizures                                                                            | Brain MRI (Age 2 months): Normal                                                | AEDs, PYPYDoxine | No            |
| 24 [2]      | Arab (Oman)          | 1 week/M                   | Seizures                                                                            | Brain MRI (Age 4 weeks): Normal                                                | AEDs, PYPYDoxine | Yes           |
| 25 [2]      | Arab (Oman)          | 5 DOL/M                    | Seizures, hyperreflexia                                                            | Brain MRI (Age 10 months): Normal                                               | AEDs, PYPYDoxine | Yes           |
| 26 [2]      | Kurdish              | 1 DOL/F                    | Seizures, hypotonia, mild dysmetria, wide based gait                               | Brain MRI (Age 2 days): underdeveloped frontal gyri                             | AEDs, Pyridoxine | Yes           |
| 27 [2]      | Kurdish              | 1 DOL/F                    | Seizures, hypotonia, mild dysmetria, wide based ataxic gait                        | Brain MRI (Age Not mentioned): Normal                                           | AEDs, Pyridoxine | Yes           |
| 28 [2]      | African American     | 1 DOL/F                    | Seizures, hypotonia                                                                | Brain MRI (Age 2 days): white matter changes, mild dilatation of lateral and third ventricles | AEDs, Pyridoxine | Yes           |
| 29 [6]      | Turkish (Denmark)    | 1 DOL/M                    | Seizures                                                                            | Brain MRI (Age 3 days): global developmental delay with broad gyri, shallow sulci, dysmature cerebral hemispheres, delayed myelination, delayed cortical folding, sub cortical and deep white matter edema | AEDs, Pyridoxine | Yes           |
| 30 [6]      | Indian (Sweden)      | 1 DOL/M                    | Seizures,                                                                            | Brain CT (4 Days): broad gyri, shallow sulci, decreased attenuation of the white matter | AEDs, Pyridoxine, PYPYDoxine | Yes           |
| 31 [6]      | Pakistani            | 2 DOL/M                    | Seizures, dullness, lethargy, absent neonatal reflexes, severe hypotonia, hypo-reflexia | Brain MRI: differential myelination of the white matter, hyper intensity in subcortical white matter in frontal lobes. A well-defined cystic area adjacent to the frontal horns of the left ventricle was noted | Pyridoxine | Yes           |

DOL: Day of Life; MRI: Magnetic Resonance Imaging; CT: Computed Tomography; AEDs: anti-epileptic drugs.
Table 2
Outcome and genetic analysis of cases with PLPB defect including our case (n = 31).

| Patient No. | Outcome | Seizure Control achieved | Motor Development Delay | Cognitive Development Delay | Acquired Microcephaly | Age | Seizure Control at the time of Publication | Motor Development | Zygosity | Consequence | Gene Variant | Variant classification |
|------------|---------|--------------------------|-------------------------|---------------------------|-----------------------|-----|--------------------------------------|-------------------|----------|-------------|--------------|-----------------------|
| 1 [4]      | Yes     | Yes                      | Not applicable          | Not applicable            | Yes                   | 4.5 months | Not applicable                       | Not applicable    | Homozygous | nonsense    | c.233C > G (M)  | pathogenic            |
| 2 [4]      | Yes     | Yes                      | Yes                     | Not applicable            | Yes                   | 9 years    | breakthrough seizures with fever     | Not mentioned     | Homozygous | nonsense    | c.233C > G (P)  | pathogenic            |
| 3 [4]      | Yes     | Yes                      | Yes                     | No                        | Yes                   | 6 years    | breakthrough seizures with fever     | Not mentioned     | Homozygous | nonsense    | c.233C > G (P)  | pathogenic            |
| 4 [4]      | Yes     | Yes                      | Yes                     | No                        | No                    | 3 years, 6 months | Seizures Controlled                 | Not mentioned     | Homozygous | missense    | c.524T > C (M)  | pathogenic            |
| 5 [4]      | Yes     | Yes                      | Yes                     | Yes                       | Yes                   | 5 years, 6 months | breakthrough seizures with fever     | Not mentioned     | Compound heterozygous | missense    | c.207Y > E; A | pathogenic            |
| 6 [4]      | Yes     | No                       | Yes                     | Yes                       | Yes                   | 3 years, 2 months | breakthrough seizures with fever     | Not mentioned     | Homozygous | nonsense    | c.211C > Tp; Gln71Ter | pathogenic            |
| 7 [4]      | Yes     | No                       | Yes                     | No                        | Not applicable        | 16 years   | breakthrough seizures with fever     | Attends normal school and leads a normal life | Compound heterozygous | missense    | c.260C > T p.; Pro67Leu; Arg241Gln | pathogenic            |
| 8 [8]      | Yes     | No                       | No                      | Not mentioned             | No                    | 12.5 years | stayed seizure-free                 | At age 12 years she performs well at her sixth class | Compound heterozygous | missense    | c.119C > T p.; Pro40Leu; Arg241Gln | pathogenically probably damaging |
| 9 [8]      | Yes     | Yes                      | No                      | Not mentioned             | No                    | 15.5 years | stayed seizure-free                 | She attends the ninth class of grammar school with good performance | Compound heterozygous | Truncating and missense | c.249.Ser84Cysfs*21; Arg205Gln | pathogenically probably damaging |
| 10 [8]     | Yes     | Yes                      | No                      | Not mentioned             | No                    | 2 years 3 months | occasional tonic clonic seizures | At age 27 months he is not able to walk independently and speech development is absent | Homozygous | missense    | c.260C > Tp; Pro67Leu | pathogenic            |
| 11 [8]     | Yes No  | Yes                      | Not mentioned           | No                        | 30 years              | stayed seizure-free                  | At age 30 years he has a driving license and is working in a supermarket. | Homozygous | missense    | c.206A > Gp; Tyr69Cys | probably damaging |
| 12 [5]     | Yes     | Yes                      | No                      | Yes                       | 3 years, 6 months     | stayed seizure-free                  | Not mentioned                  | Compound heterozygous | missense    | c.122G > A, Arg41Gln | likely pathogenic     |
| Patient No. | Outcome | Outcome at the time of Publication | Molecular analyses |
|------------|---------|-----------------------------------|-------------------|
| 13 [5]     | Yes     | No                                | Not mentioned     |
| 14 [5]     | Yes     | No                                | Not mentioned     |
| 15 [5]     | Yes     | No                                | Not mentioned     |
| 16 [10]    | No      | Not mentioned                     | Not mentioned     |
| 17 [2]     | Yes     | No                                | Not mentioned     |
| 18 [2]     | Yes     | No                                | Not mentioned     |
| 19 [2]     | Yes     | Yes                               | Not mentioned     |
| 20 [2]     | Yes     | No                                | Not mentioned     |
| 21 [2]     | No      | Not applicable                     | Not applicable    |
| 22 [2]     | Yes     | Yes                               | Not mentioned     |
| 23 [2]     | Yes     | No                                | Not mentioned     |
| 24 [2]     | Yes     | No                                | Not mentioned     |
| 25 [2]     | Yes     | No                                | Not mentioned     |
| 26 [2]     | Yes     | Yes                               | Not mentioned     |
| 27 [2]     | Yes     | Yes                               | Not mentioned     |
| 28 [2]     | No      | No                                | Not mentioned     |
| 29 [6]     | Yes     | Not mentioned                     | Not mentioned     |

(continued on next page)
(used during acute episodes only) [2]. Our patient experienced breakthrough seizures when treatment was switched from PLP to PN for a few weeks at 3.4 years of age, and this resolved upon re-introduction of PLP. However, a subsequent therapy change to PN at 4 years of age was well tolerated and the child remained seizure free.

All of the patients presented with characteristic early neonatal seizures. The median age of treatment initiation with any form of vitamin B6 ranged from an earliest of 4 days to a maximum of 2920 days with a median of 29 days (IQR: 14–65). Of the five deceased patients, only two were treated with PN, but the age of treatment initiation was not mentioned in these patients [4,8]. The patient reported by Darin et al. developed respiratory depression due to PN and expired at 4.5 months of age [4]. Both motor and cognitive developmental delay (DD) was evident in 14 patients, motor DD alone in 3 cases, and cognitive DD alone in 3 cases. Five patients had age-appropriate developmental milestones and adequate information was not available for the remaining patients. For the patients with age appropriate developmental milestones and optimum seizure control, the age of treatment initiation with PN ranged from 14 to 75 days with a median of 28 days (IQR: 19.5–52). The three cases started on PN within 1 month of age showed good school performances. In our patient treatment with PN was initiated at 11th day of life, despite such early initiation of therapy seizure control was achieved but cognitive development remains sub-optimal.

In our patient, elevated plasma glycine and marked excretion of vanillactic acid in UOA impelled a diagnosis of PNPO defect. As the biochemical markers of PNPO, Aromatic L-amino acid decarboxylase deficiency (AADC) and PLPBP defects often overlap and no specific biomarkers have been identified for patients with PLPBP defects, genetic analysis is essential to distinguish it from other causes [6].

The spectrum of the variants in the patients with PLPBP defect is heterogeneous and missense, nonsense, frameshift and deletions are reported. There is no genotype-phenotype correlation evident from the reported patients as shown in Table 2. Most of the patients had private familial variant in PLPBP gene.

4. Conclusions

Vitamin B6-dependent epilepsy due to PLPBP defect is an important differential diagnosis to consider in patients with biochemical features suggestive of PNPO defect and gene testing can facilitate in reaching the correct diagnosis. Prompt diagnosis and treatment led to excellent seizure control in most patients. However, the developmental outcomes are variable even with early therapy. Few patients are reported to achieve optimal developmental milestones with therapy. PLP has been advocated as the treatment of choice for PLPBP defect, but oral PN has also demonstrated good seizure control in some patients, including ours.

Ethics approval and consent to participate

The study was approved by the Institutional Ethics Committee (ERC #2020-4941-10686) written informed consent was obtained from the parents of the patient.

Consent for publication

Written informed consent was obtained from the parents of the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Declaration of competing interest

The authors declare that they have no competing interests.

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