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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 electrographically 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 (α-AASA), piperideine-6-carboxylate (P6C), and pipecolic acid concentrations can be detected in the CSF, urine and plasma. In *PNPO* defect, accumulation of vanillactate in urine and low PLP in CSF are present. *TNSALP* defect is accompanied by hypophosphatasia. In *PLPBP* defects, the biochemical phenotype is similar to *PNPO* defect, making genetic analysis essential to distinguish it from other causes [6].

We searched the MEDLINE and Google Scholar databases for studies with the search terms "vitamin B6-dependent epilepsy" and "PLPBP" or "PLPHP" or "PROSC", without date and language restrictions. The title, abstract and full text of all documents identified according to these search criteria were scrutinized by the authors. Additionally, all references found in the published articles were reviewed for case report ascertainment. The search revealed 6 case reports and case series, including 30 patients with confirmed vitamin B6-dependent epilepsy caused by *PLPBP* gene defects on molecular analysis [2,4,6–10]. Here we report the first Pakistani patient with *PLPBP* defect with four years of follow-up. We have also compared the clinical outcome of our patient with thirty reported patients with *PLPBP*, including their treatment and clinical outcomes. The study was approved by the Institutional Ethics Committee (ERC #2020-4941-10686) and written informed consent was obtained from the parents of the patient for publication of this case report. This work has been reported in line with the Case Report (CARE) guidelines [11].

2. Case report

A baby boy was born to first-cousin Pakistani parents after a term, uncomplicated pregnancy through spontaneous vaginal delivery (SVD). A few hours after birth he was noted to be dull and lethargic. Thirteen hours after birth he began to have both generalized and focal seizures, which were clonic in nature. His dullness persisted and he was referred for a genetics evaluation on the ninth day of life. Family history revealed the death of two siblings with similar presentation during the neonatal period. On examination, the baby was comatose, with no response even upon maximal physical stimulation. The examination was also notable for an absence of neonatal reflexes, severe hypotonia, hyporeflexia of the deep tendon reflexes and a normal anterior fontanalle. The birth length and weight were 49 cm (<25th percentile) and 2.7 kg (10th percentile), respectively. The occipitofrontal circumference (OFC) was recorded as 33.5 cm (between 4th and 0.2nd percentile).

A biochemical workup revealed plasma lactate of 5.1 mmol/L (normal 0.5–1.6); ammonia of 22.3 μmol/L (normal < 99.8); and anion gap 17.7. A random blood glucose was 4.7 mmol/L (normal < 11.1). The urine was negative for ketones. Plasma amino acid (PAA) quantification revealed an elevated threonine of 295 μmol/L (normal 55–187) and glycine of 476 μmol/L (normal 20–356) with normal serine of 145 μmol/L (normal 60–240). Marked excretion of vanillactic acid was evident on the urine organic acid analysis (UOA). Cellularity and cultures of the CSF were inconsistent with meningitis. Blood cultures were also negative.

An electroencephalogram (EEG) showed epileptic discharges, myoclonic jerks and continuous low voltage activity with generalized bursts of sharp transients. Magnetic Resonance Imaging (MRI) of the brain showed differential myelination of the white matter with hyperintensity in subcortical white matter in the frontal lobes. A well-defined cystic area adjacent to the frontal horn of the left ventricle was also noted. MR spectroscopy showed an increased lactate peak with decreased N-acetyl aspartate (NAA).

The elevated plasma glycine and marked excretion of vanillactic acid suggested the diagnosis of *PNPO* defect. Although this disorder is reported to respond to PLP, 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_007198.4: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 *PLPB* defect including our patient is summarized in Tables 1 and 2.

The *PLPBP* defect is pan-ethinic 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 *PLPB* 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, PLP	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, microcephaly	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, Pyridoxine	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, PLP	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, PLP	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, PLP	Yes
20 [2]	Dutch	1 DOL/F	Seizures	Brain MRI (Age 1 Day): white matter changes, large para ventricular pseudocysts	AEDs	No
21 [2]	Canada	1 DOL/F	Seizures	Brain MRI (Age 6 Days): cystic leukoencephalopathy	AEDs	Yes
22 [2]	Arab (UAE)	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, Pyridoxine,	No
24 [2]	Arab (Oman)	1 week/M	Seizures	Brain MRI (Age 4 weeks): Normal	AEDs, Pyridoxine,	Yes
25 [2]	Arab (Oman)	5 DOL/M	Seizures, hyperreflexia	Brain MRI (Age 10 months): Normal	AEDs, Pyridoxine	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, PLP	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, PLP	Yes
30 [6]	Indian (Sweden)	1 DOL/M	Seizures,	Brain CT (4 Days): broad gyri, shallow sulci, decreased attenuation of the white matter	AEDs	Yes
31	Pakistani	2 DOL/M	Seizures, dullness, lethargy, absent neonatal reflexes, sever 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 horn of the left ventricle was noted	Pyridoxine, PLP	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				Vitamin B6 withdrawal (recurrence of seizures)	Outcome at the time of Publication			Molecular analyses			
	Seizure Control achieved	Motor Developmental Delay	Cognitive Developmental Delay	Acquired Microcephaly		Age	Seizure Control	Motor Development	Zygosity	Consequence	Gene Variant	Variant classification
1 [4]	Yes	Not applicable	Not applicable	Yes	Not applicable	Expired at 4.5 months	Not applicable	Not applicable	Homozygous	nonsense	c.233C > G (M) + c.233C > G (P) p.Ser78Ter	pathogenic
2 [4]	Yes	Yes	Yes	Yes	Not applicable	9 years	breakthrough seizures with fever	Not mentioned	Homozygous	nonsense	c.233C > G (M) + c.233C > G (P) p.Ser78Ter	pathogenic
3 [4]	Yes	Yes	Yes	Yes	No	6 years	breakthrough seizures with fever	Not mentioned	Homozygous	nonsense	c.233C > G (M) + c.233C > G (P) p.Ser78Ter	pathogenic
4 [4]	Yes	Yes	Yes	Yes	No	3 years, 6 months	Seizures Controlled	Not mentioned	Homozygous	missense	c.524T > C (M) + c.524T > C (P) p.Leu175Pro	pathogenic
5 [4]	Yes	Yes	Yes	Yes	Yes	5 years, 6 months	breakthrough seizures with fever	Not mentioned	Compound heterozygous	missense	c.207Yes1G > A; splicing effect c.320–2A > G; splicing effect	pathogenic
6 [4]	Yes	No	Yes	Yes	Yes	3 years, 2months	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. Pro87Leu; c.722G > A p. 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; c.722G > A p. Arg241Gln	predominantly probably damaging 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_252del p. Ser84Cysfs*21; c.614G > Ap. Arg205Gln	predominantly 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. Pro87Leu	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	Yes	No	Yes	3 years, 6 months	stayed seizure-free	Not mentioned	Compound Heterozygous	missense	c.122G > Ap. Arg41Gln;	likely pathogenic

(*continued on next page*)

Table 2 (*continued*)

Patient No.	Outcome				Vitamin B6 withdrawal (recurrence of seizures)	Outcome at the time of Publication			Molecular analyses			
											c.134T > Ap. Val45Asp	
13 [5]	Yes	Yes	Yes	No	No	8 years	stayed seizure-free	Not mentioned	Homozygous	missense	c.122G > Ap. Arg41Gln	likely pathogenic
14 [5]	Yes	Yes	Yes	Yes	No	3 years	Tonic–clonic seizure once a month	Not mentioned	Homozygous	missense	c.199G > Ap. Glu67Lys	likely pathogenic
15 [5]	Yes	Yes	Yes	Yes	No	5 years, 5 months	Only 1 febrile seizure after administration of Pyridoxine	Not mentioned	Homozygous	missense	c.614G > Ap. Arg205Gln	likely pathogenic
16 [10]	No	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Expired at 58 days	Not mentioned	Not mentioned	Homozygous	deletion	c.370_373del; p. Asp124Lysfs*	pathogenic
17 [2]	Yes	Yes	Yes	Not mentioned	No	12 years	breakthrough seizures with fever	Not mentioned	Homozygous Homozygous	missense	c.347C > Tp. Thr116Ile; c.823C > Gp. His275Asp	likely pathogenic VUS
18 [2]	Yes	No	No	Not mentioned	No	14 years	breakthrough seizures with fever	Average School performance	Homozygous	missense	c.122G > Ap. Arg41Gln	likely pathogenic
19 [2]	Yes	Yes	Yes	Not mentioned	Yes	12 years	breakthrough seizures with fever	Not mentioned	Homozygous	missense	c.199G > Ap. Glu67Lys	likely pathogenic
20 [2]	Yes	Not applicable	Not applicable	Not mentioned	Not applicable	Expired at 2 weeks	Not applicable	Not applicable	Compound heterozygous	nonsense and missense	c.320–2A > G; splicing; c.671G > Cp. Gly224Ala	pathogenic
21 [2]	Yes	Not applicable	Not applicable	Not mentioned	Not applicable	Expired at 8 weeks	Not applicable	Not applicable	Homozygous	nonsense	c.370–373del p.Asp124Lys fs*2	pathogenic
22 [2]	Yes	Yes	Yes	Not mentioned	Yes	12 years	breakthrough seizures with fever	Developmental quotient = 70, 2nd percentile (Bayley-III Cognitive Composite score)	Homozygous	missense	c.347C > Tp. Thr116Ile	likely pathogenic
23 [2]	Yes	No	No	Not mentioned	No	23 months	Seizures Controlled	Not mentioned	Homozygous	missense	c.280A > Tp. Ile94Phe	likely pathogenic
24 [2]	Yes	No	No	Not mentioned	No	12 years	breakthrough seizures with fever	Excellent school performance	Homozygous	missense	c.122G > Ap. Arg41Gln	likely pathogenic
25 [2]	Yes	No	Not applicable	Not mentioned	No	14 months	Seizures Controlled	Not mentioned	Homozygous	missense	c.122G > Ap. Arg41Gln	likely pathogenic
26 [2]	Yes	Yes	Yes	Not mentioned	Yes	12 years	breakthrough seizures with fever	Not mentioned	Homozygous	missense	c.199G > Ap. Glu67Lys	likely pathogenic
27 [2]	Yes	Yes	Yes	Not mentioned	Yes	12 years	breakthrough seizures with fever	Not mentioned	Homozygous	missense	c.199G > Ap. Glu67Lys	likely pathogenic
28 [2]	Yes	No	Not applicable	Not mentioned	No	5 months	Seizures Controlled	Not mentioned	Homozygous	deletion	c.370–373del p.Asp124Lys fs*2	pathogenic
29 [6]	Yes	Yes	Not mentioned		Yes				Homozygous	Splice site		pathogenic

(*continued on next page*)

Table 2 (*continued*)

Patient No.	Outcome			Vitamin B6 withdrawal (recurrence of seizures)	Outcome at the time of Publication			Molecular analyses				
			Not mentioned		23 months	Rare breakthrough seizure	Bayley Scales of Infant and Toddler Development at the age of 18 months revealed gross and fine motor skills at a developmental age of 9 and 7 months, respectively				c.207Yes1G > A splicing effect	
30 [6]	No	Not applicable	Not mentioned	Not applicable	Expired at 7 weeks	Seizures continued, not given B6	Not applicable	Homozygous	missense		c.121C > T p. Arg41Trp	likely pathogenic
31	Yes	Yes	Yes	Not applicable	4 years	Seizures Controlled	At present he is at age appropriate motor and fine motor mile stones but speech, cognitive functions and social skills are delayed for his age	Homozygous	frameshift		c.46_47InsCA p.Leu17Hisfs	pathogenic

(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, nonsenses, 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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References

[1] R. Percudani, A. Peracchi, The B6 database: a tool for the description and classification of vitamin B6-dependent enzymatic activities and of the corresponding protein families, BMC Bioinf. 10 (2009) 273.
[2] D.L. Johnstone, H.H. Al-Shekaili, M. Tarailo-Graovac, et al., PLPHP deficiency: clinical, genetic, biochemical, and mechanistic insights, Brain 142 (3) (2019) 542–559.
[3] J. Campistol, B. Plecko, Treatable newborn and infant seizures due to inborn errors of metabolism, Epileptic Disord. 17 (3) (2015) 229–242.
[4] N. Darin, E. Reid, L. Prunetti, et al., Mutations in PROSC disrupt cellular pyridoxal phosphate homeostasis and cause vitamin-B6-dependent epilepsy, Am. J. Hum. Genet. 99 (6) (2016) 1325–1337.
[5] S.M. Gospe Jr., Pyridoxine-dependent epilepsy, in: M.P. Adam, H.H. Ardinger, R. A. Pagon, et al. (Eds.), GeneReviews((R)). Seattle (WA), 1993.
[6] K.V. Jensen, M. Frid, T. Stodberg, et al., Diagnostic pitfalls in vitamin B6-dependent epilepsy caused by mutations in the PLPBP gene, JIMD Rep 50 (1) (2019) 1–8.
[7] S. Ikegawa, M. Isomura, Y. Koshizuka, Y. Nakamura, Cloning and characterization of human and mouse PROSC (proline synthetase co-transcribed) genes, J. Hum. Genet. 44 (5) (1999) 337–342.
[8] B. Plecko, M. Zweier, A. Begemann, et al., Confirmation of mutations in PROSC as a novel cause of vitamin B 6 -dependent epilepsy, J. Med. Genet. 54 (12) (2017) 809–814.
[9] H. Shiraku, M. Nakashima, S. Takeshita, et al., PLPBP mutations cause variable phenotypes of developmental and epileptic encephalopathy, Epilepsia Open 3 (4) (2018) 495–502.
[10] K.D. Kernohan, T. Hartley, S. Naumenko, et al., Diagnostic clarity of exome sequencing following negative comprehensive panel testing in the neonatal intensive care unit, Am J Med Genet A 176 (7) (2018) 1688–1691.
[11] J.J. Gagnier, G. Kienle, D.G. Altman, D. Moher, H. Sox, D. Riley, CARE Group, The CARE guidelines: consensus-based clinical case reporting guideline development, J. Med. Case Rep. 7 (1) (2013 Dec 1) 223.