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CASE REPORT

Normal Neurodevelopmental Outcomes in PNPO Deficiency: A Case Series and Literature Review

J. Hatch · D. Coman · P. Clayton · P. Mills · S. Calvert · R.I. Webster · Kate Riney

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Abstract Pyridox(am)ine 5′-phosphate oxidase deficiency results in an early-onset neonatal encephalopathy that can be fatal if not detected and treated early. The condition is rare, can result in preterm delivery, and can mimic hypoxic ischemic encephalopathy. Thus, suspicion of the diagnosis, appropriate investigations, and therapeutic trials with pyridoxal-5′-phosphate are often delayed. In this paper we report four cases of pyridox(am)ine 5′-phosphate oxidase deficiency, two of whom are siblings. Three were treated with pyridoxal-5′-phosphate in the first few days of life and the fourth within the first month. One of the siblings was electively treated from birth until a diagnosis was secured. Our cases demonstrate that early diagnosis and treatment can be associated with normal neurodevelopment in childhood. We suggest that a low threshold for investigating for pyridox(am)ine 5′-phosphate oxidase deficiency and electively treating with pyridoxal-5′-phosphate is considered in any neonate with encephalopathy, including those with presumed hypoxic ischemic encephalopathy in whom the degree of encephalopathy is not expected from perinatal history, cord gases and/or neuroimaging.

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J. Hatch · D. Coman · K. Riney
Uniting Care Health Clinical School, The Wesley Hospital, Brisbane, QLD, Australia

D. Coman
Department of Metabolic Medicine, The Lady Cilento Children's Hospital, Brisbane, QLD, Australia

D. Coman · S. Calvert · K. Riney
The School of Medicine, The University of Queensland, Brisbane, QLD, Australia

D. Coman
The School of Medicine, Griffith University, Gold Coast, QLD, Australia

P. Clayton · P. Mills
UCL Institute of Child Health, London, UK

S. Calvert · K. Riney (✉)
Neurosciences Unit, The Lady Cilento Children's Hospital, 501 Stanley Street, South Brisbane 4101, QLD, Australia
e-mail: kate.riney@health.qld.gov.au

R.I. Webster
Department of Neurology, The Children's Hospital Westmead, Sydney, NSW, Australia

R.I. Webster
Sydney Medical School, The University of Sydney, Sydney, NSW, Australia

Introduction

Pyridoxal-5′-phosphate (PLP), the active form of vitamin B6, is a cofactor for over 100 different metabolic reactions integral to normal cellular health and maintenance (Hoffmann et al. 2007; Clayton 2006). Examples of metabolic processes requiring PLP as a cofactor include the synthesis of nucleic acids, haemoglobin, sphingomyelin and other sphingolipids; synthesis of neurotransmitters such as dopamine, norepinephrine and gamma-aminobutyric acid (Clayton 2006); and the metabolism of some amino acids and glycogen (Clayton 2006).

Evidence to support the protean importance of PLP is demonstrated in clinically and biochemically significant manifestations of the B6 deficiency disease states. The classic examples are the inborn errors of metabolism (IEM) associated with B6 synthesis, pyridoxine-dependent epilepsy (PDE, OMIM 266100) and pyridox(am)ine 5′-phosphate oxidase (PNPO) deficiency (OMIM 610090). The role of PLP depletion in these disease processes occurs

via varied mechanisms. PDE is caused by mutations in the *ALDH7A1* gene that encodes the enzyme antiquitin, which is involved in cerebral lysine catabolism (Stockler et al. 2011). A block at the level of antiquitin leads to the accumulation of piperideine-6-carboxylic acid (P6C), which inactivates PLP via a Knoevenagel condensation.

PNPO deficiency is a rare autosomal recessive IEM. To date there have been <40 cases reported in the medical literature (Mills et al. 2005, 2014; Hoffmann et al. 2007; Bagci et al. 2008; Ruiz et al. 2008; Schmitt et al. 2010; Veerapandiyan et al. 2011; Ware et al. 2014; Plecko et al. 2014; Porri et al. 2014). The initial clinical reported phenotype of PNPO deficiency included prematurity, early-onset neonatal encephalopathy and seizures that are resistant to conventional anticonvulsants and pyridoxine. Those who have survived the neonatal period have had significant neurodevelopmental disorders in the form of ongoing seizures, developmental delay and microcephaly (Mills et al. 2005; Hoffmann et al. 2007; Bagci et al. 2008; Ruiz et al. 2008). As is often the case with rare diseases, the clinical phenotype expands as more cases are diagnosed with time. Three subgroups of patients have recently been proposed: (1) patients with neonatal onset seizures responding to PLP, (2) patients with infantile spasms responsive to PLP and (3) patients with seizures starting under 3 months of age responding to pyridoxine (Mills et al. 2014). In this paper we report four cases of PNPO deficiency, two of whom are siblings, who all demonstrate normal neurodevelopmental outcomes. We discuss the importance of distinguishing PNPO deficiency from other more common neonatal encephalopathies, such as hypoxic ischaemic encephalopathy (HIE).

Case Reports

Table 1 provides a summary of the four cases while salient features of the four are expanded in the reports below.

Case 1

Cases 1 and 2 are siblings and have been reported previously with respect to genotype-phenotype correlation (Mills et al. 2014). By 1.5 h of age, case 1 had developed status epilepticus and severe encephalopathy was recognised. He required intubation and ventilation and received loading doses of phenobarbitone, phenytoin and midazolam without seizure control being established. A trial of oral PLP 100 mg TDS was commenced at 40 h of age, after iv pyridoxine failed to result in clinical or EEG change. Prior to PLP administration, the EEG demonstrated a burst suppression pattern; in the 12 h following PLP administration, the EEG showed ongoing ictal events, the majority of which manifested clinically as multifocal erratic myoclonic jerks. EEG improvement was seen by 3 days of treatment with PLP; seizures and neonatal encephalopathy progressively resolved. A withdrawal of PLP was attempted at 4 months of age; however, seizures recurred when PLP was weaned to a dose of 50 mg once daily. Subsequently a PNPO gene mutation was confirmed, and PLP was continued at doses of up to 50 mg/kg/day. Seizures occurred only infrequently, typically at trough times in PLP dosing (usually in the early morning or if delays in dose administration). On follow-up at 4.5 years of age, case 1 is developing normally. A formal Bayley Scale of Infant and Toddler Development (Bayley-III) and Preschool Language Scale (Fourth Edition) were administered at 2.6 years of age. Low average range scores were obtained on the cognitive and adaptive behaviour scales; average scores were obtained for language, gross and fine motor scales; and high average scores were obtained for social-emotional scales. Formal clinical neurological and developmental examination is normal.

Case 2

Case 2 is the younger sibling of case 1. Her mother had taken pyridoxine as part of a pregnancy multivitamin during the pregnancy (2.6 mg/day pyridoxine) and PLP during the last 3 days of the pregnancy. The infant was administered PLP from birth as a precaution given her sibling's diagnosis. No seizures or abnormal neurological behaviour was noted. An EEG, done at 24 h of age, was normal.

Initial PLP dosing was 25 mg TDS (30 mg/kg/day). This dose was changed to four times a day at 3 months of age to facilitate administration of PLP at the same times as her sibling. An EEG at this time showed periods of focal slowing with sharp waves overlaid, in a posterior distribution. Case 2 has had two seizures to date, the first at 10 months corrected age and the second at 11 months corrected age. Formal clinical neurodevelopmental assessment at 2.5 years of age shows her progress to be within age-appropriate parameters and her neurological examination is normal.

Case 3

Case 3 has been reported previously with respect to genotype-phenotype correlation (Mills et al. 2014). Her mother had taken pyridoxine during the pregnancy as part of a multivitamin supplement. Seizures were first diagnosed at 4 weeks of age, although more subtle events may have occurred prior to this. Trials of pyridoxine at 4 weeks and phenobarbitone, phenytoin and oxcarbazepine failed to control seizures. An EEG at 4 weeks of age was normal;

Table 1 Summary of clinical features and investigations

	Case 1[a]	Case 2[a]	Case 3	Case 4
Current age	4.5	2.5	7.5	11
Heritage	Caucasian	Caucasian	Caucasian	Caucasian
Neonatal				
Gestation	37/40	34/40	38/40	38/40
Mode of delivery	emLUSCS	emLUSCS	SVD	SVD
Foetal distress	Nil	Reduced foetal movement and non-reassuring CTG	Nil	Nil
APGAR	5^1, 8^5	9^1, 9^5	7^1, 9^5	8^1, 9^5
Irritability	Extreme	Nil	Nil	Nil
Neonatal encephalopathy	Yes	No[b]	No	Yes
Neurological examination	Hypotonic	Normal	Normal	Normal
Growth parameters	BW 3.4 kg	BW 2.4 kg	BW 2.6 kg	BW 3.4 kg
	L 50 cm	L 46 cm	L 48 cm	L 53.5 cm
	HC 34 cm	HC 30.2 cm	HC 31.5 cm	HC 33 cm
Seizure semiology				
Age of seizure onset	1.5 h of age	10 months[b]	4 weeks	24 h of age
Myoclonus	Yes	No	No	Yes
Status epilepticus	Yes	No	Yes	Yes
Ictal eye movements	Yes (from infancy)	No	Yes	Yes
Focal clonic	No	No	Yes	Yes
Initial EEG pattern	Burst suppression	Normal	Rhythmic slowing in posterior regions, with frequent focal seizures	Normal
MRI	Normal	NP	Normal	Normal
Pretreatment CSF studies[c]				
Homovanillic acid	343	NP	576	1,063
	RR 330–1,300 nmol/L		RR 330–1,300 nmol/L	RR 310–1,100 nmol/L
3-*O* methyl DOPA	438 RR <300 nmol/L	NP	111 RR <300 nmol/L	NP
5-HIAA	395	NP	362	838
	RR 200–1,160 nmol/L		RR 200–1,160 nmol/L	RR 150–800 nmol/L
HVA/5-HIAA ratio	0.9 RR 1.5–3.5	NP	1.6 RR 1.5–3.5	1.2
Tetrahydrobiopterin	57 RR 40–110 nmol/L	NP	55 RR 40–110 nmol/L	NP
Total neopterin	8 RR 7–65 nmol/L	NP	7 RR 7–65 nmol/L	NP
Folate	153 RR 50–180 nmol/L	NP	63 50–180 nmol/L	NP
Glycine	9	NP	1.9	9
	RR 4.7–8.1 μmol/L		RR 4.7–8.1 μmol/L	RR 0.7–14.7 μmol/L
Threonine	60	NP	49.6	51
	RR 12.6–18.6 μmol/L		RR 12.6–18.6 μmol/L	RR 22.5–52.6 μmol/L
Phenylalanine	12 RR 5.8–7.6 μmol/L	NP	2.8 5.8–7.6 μmol/L	NP
Urine VMA	11.1	NP	4.2	Not detected

(continued)

Table 1 (continued)

	Case 1[a]	Case 2[a]	Case 3	Case 4
	RR <10 mmol/mol creatinine		RR <10 mmol/mol creatinine	
Response to B6	No	No treatment	No	No
PLP				
Age at first treatment	40 h	At birth	8 weeks	28 days
Initial dose	−30 mg/kg/day in three divided doses	−30 mg/kg/day in three divided doses	40 mg TDS	100 mg/kg/day
Current dose	50 mg/kg/day	50 mg/kg/day	~45 mg/kg/day	50–60 mg/kg/day
Current dose interval	Q6H	Q6H	Q6H	4 hourly with no dose overnight
***PNPO* sequencing**	c.737 C>T/c.737 C>T (p.P213S/p.P213S)	c.737 C>T/c.737 C>T (p.P213S/p.P213S)	c.98A>T/c.98A>T (p.D33V/p.D33V)	c.98A>T/c.246delT (p.D33V/p.(Leu83Trpfs*17))
Development				
Gross motor skills	Age appropriate	Age appropriate	Age appropriate	Age Appropriate
Fine motor skills	Age appropriate	Age appropriate	Age appropriate	Age appropriate
Speech and language	Mild delay in expressive language (clarity)	Age appropriate	Mild delay in expressive language (clarity)	Age appropriate
Social skills	Age appropriate	Age appropriate	Age appropriate	Age appropriate
Formal Psychometric testing				
Age of assessment	Bailey-III, 3 years	[d]	[d]	[d]
Cognition	Low average	[d]	[d]	[d]
Language	Average	[d]	[d]	[d]
Motor	Average	[d]	[d]	[d]
Social-emotional	High average	[d]	[d]	[d]

[a] Siblings
[b] Was treated with PLP from birth
[c] Cases 1, 2, 3 and 4 performed in different laboratories, hence variant reference ranges
[d] Formal psychometric testing not performed but normal developmental assessments by paediatric neurologist
BW birth weight, *L* length, *HC* head circumference, *NP* not performed, *RR* reference ranges. *LUSCS* lower uterine segment caesarean section, *CTG* cardiotocogram, *SVD* spontaneous vaginal delivery

however, by 6 weeks of age, the EEG demonstrated periods of slowing and frequent intermixed multifocal sharp waves. A further EEG at 8 weeks of age, when seizures had changed to include tonic events with vocalisation, showed periods of electrodecrement with ongoing multifocal epileptiform discharges.

PLP (40 mg TDS) was commenced at 8 weeks of age with cessation of seizures and normalisation of the EEG. Occasional break through seizures occurred, related to periods of febrile illness, vomiting or medication refusal. At 20 months of age, a trial of PLP withdrawal for 24 h resulted in a significant increase in seizures and deterioration in the EEG. The current dose of PLP is 100 mg five times a day (~45 mg/kg/day). Neurodevelopmental assessments were normal throughout, with the exception of minor delays in expressive language development, affecting clarity of speech. Case 3 is now school age (7.5 years), is progressing well with no concerns in relation to her learning and is considered advanced in her reading ability for her age.

Case 4

Details of the initial presentation of case 4 have been reported previously (Hoffmann et al. 2007; Schmitt et al. 2010; Sudarsanam et al. 2014). Intractable neonatal seizures occurred, with a number of different seizure types seen – abnormal eye movements, abnormal smiling, multifocal myoclonic jerks, focal clonic seizures and spasms associated with screaming and irritability. He was treated with multiple different anticonvulsants and pyridoxine, before being treated with PLP at 28 days of age. This was associated

with immediate resolution of seizures. A trial of withdrawal of PLP at 8 months of age was associated with recurrence of encephalopathy, and PLP has subsequently been continued (doses ranging from 50 to 100 mg/kg/day in divided doses). However, at age 2 years, as a result of concerns about hepatotoxicity (Sudarsanam et al. 2014), lower PLP doses were given more frequently (on a 4 hourly basis including an overnight dose) and the total daily dose was decreased to 50–60 mg/kg/day. During infancy, episodes of encephalopathy were relatively frequent and often associated with febrile illnesses, but after 18 months of age these became less frequent and abated with careful management of PLP dosage and timing of administration. He currently receives frequent doses of PLP (4 hourly during the day); however, the overnight dose has been able to be omitted. At 11 years of age, he is academically advanced in school, particularly in mathematics and music. His neurological examination is normal.

Discussion

Neonatal encephalopathies are uncommon, with an incidence of 9 in 1,000 live births worldwide (Graham et al. 2008). While HIE is the most common cause of a neonatal encephalopathy, numerous genetic conditions can masquerade as HIE; prime examples are the IEM associated with vitamin B6 responsiveness. Other IEM that can masquerade as HIE in the newborn period broadly include (a) disorders of neurotransmitter metabolism, e.g. nonketotic hyperglycinaemia (OMIM 605899); (b) disorders of energy metabolism, e.g. biotinidase deficiency (OMIM 253260); and (c) biosynthetic defects, e.g. the congenital disorders of glycosylation (Van Hove and Lohr 2011).

Early reports have suggested that the common clinical features in the reported PNPO cases thus far include (1) neonatal encephalopathy, seizures resistant to multiple anticonvulsants (Mills et al. 2005; Schmitt et al. 2010), (2) burst suppression EEG pattern (Veerapandiyan et al. 2011), (3) non-responsiveness to pyridoxine (Clayton 2006), (4) complete or partial responsiveness to PLP (Pearl et al. 2013), (5) prematurity (Veerapandiyan et al. 2011) and (6) neonatal lethality if the diagnosis is not suspected and PLP administered (Khayat et al. 2008). Early diagnosis and treatment with PLP have been linked with improved neurodevelopmental outcomes (Hoffmann et al. 2007; Plecko et al. 2014) with more recent reports supporting that normal neurodevelopmental outcomes can occur (Khayat et al. 2008; Mills et al. 2014; Plecko et al. 2014). The four cases reported in this paper reinforce these observations, with case 2 being the only known patient to have been treated as a preventative measure from birth, until it was confirmed by genetic testing whether she had PNPO deficiency or otherwise.

Mothers of cases 2, 3 and 4 took multivitamins containing pyridoxine during the pregnancy. Maternal supply of B6 has been postulated to modify the clinical phenotype in infants with PNPO deficiency (Mills et al. 2014). It is likely, in the four current cases, that maternal treatment in pregnancy, prompt early consideration of PNPO deficiency in the differential diagnosis, early administration of PLP and excellent tertiary level supportive neonatal care have all contributed to the normal developmental and neurological outcomes that occurred. Expression studies involving the D33V and the R225H/C mutations demonstrate sufficient residual enzyme activity to allow synthesis of PLP from pyridoxine (Mills et al. 2014), which may result in higher foetal levels of PLP with maternal pyridoxine supplementation in pregnancy. Case 2 is unique in the literature; her elder brother presented with a neonatal encephalopathy in the first few hours of life. Case 2 was treated in utero with maternal supplementation of pyridoxine containing multivitamins and electively supplemented with PLP immediately after her premature delivery, in the delivery suite. She was identified as having an abnormal interictal EEG at 3 months of age, but did not have any neurological or developmental signs or symptoms until she experienced a seizure at 10 months of age. She is the first case, to the best of our knowledge, that has been treated presymptomatically in utero, with this likely modifying her age of presentation.

In the presence of clinical suspicion of PNPO deficiency, the results of molecular and/or biochemical investigation should not defer a therapeutic trail of PLP. Elevated urinary vanillyllactate can serve as a marker for PNPO deficiency, but the sensitivity and specificity of this test in neonates with seizures are unclear at this stage (Clayton 2006). Cerebrospinal fluid (CSF) studies, collected via lumbar puncture, may demonstrate aberrations in amino acids and neurotransmitters reflecting the role of PLP as a cofactor for their respective enzymatic metabolism, e.g. elevated serine, glycine (consequent of defective glycine cleavage system) and threonine (threonine dehydratase) and decreased 5-hydroxyindoleacetic acid and homovanillic acids with elevated 3-methoxytyrosine (due to decreased L-AADC function) (Goyal et al. 2013; Clayton 2006). However, normality in these biochemical parameters cannot completely exclude PNPO deficiency, as patients have been reported with normal CSF amino acids and neurotransmitter values (Hoffmann et al. 2007; Bagci et al. 2008). Case 1 in our cohort supports this observation and highlights the importance of a clinical trial of PLP in neonates with

encephalopathy. It is possible to measure CSF concentrations of PLP; however, low levels are not diagnostic for B6-related seizure disorders and there are age-related variations (Footitt et al. 2011; Albersen et al. 2012; Ormazabal et al. 2008). The evolution of next-generation sequencing (NGS) over recent years has proven beneficial for clinicians dealing with clinical phenotypes with genetic heterogeneity. NGS is a valuable diagnostic tool for disorders with encephalopathy; however, if PNPO deficiency is suspected, early treatment trial with pyridoxine and/or PLP is an important practical approach while awaiting NGS results to become available.

The treatment of PNPO deficiency requires frequent administration of PLP. Our patients demonstrate exquisite sensitivity to PLP dose and timing of administration in preventing seizures. The dosage required to achieve this varied with age and body weight. PLP dosages of 10 mg/kg every 6 h have been utilised to control seizures (Clayton 2006). A consistent feature within our cohort is breakthrough seizures occurring at times of dosage interruption/delay. This was most commonly observed at times of intercurrent vomiting illnesses. Case 1 in particular has demonstrated remarkable dosage sensitivity; a delay in the delivery of any dose through the day by even 20 minutes can lead to a seizure, which often is associated with apnoea. A similar time-sensitive requirement for PLP dose administration has been reported once before (Hoffmann et al. 2007). The requirement for 4–6 hourly medication delivery, with the ever-present fear of breakthrough seizures and encephalopathy, results in a significant burden for the families. Cases 1 and 4 have utilised rectal delivered PLP in cases of seizure emergencies and at times of reduced oral intake, e.g. fasting for a surgical procedure or during an intercurrent vomiting illness.

The normal neurodevelopmental outcomes in the cases reported here emphasise the importance of early consideration of PNPO deficiency in the assessment of any neonate presenting with seizures and/or encephalopathy. Infants with PNPO deficiency can be born preterm and may have foetal distress with lactic acidosis, factors that are also associated with HIE. It is important that clinicians have a low threshold for investigating for PNPO deficiency and electively treating with PLP, in any case of presumed HIE in whom the degree of encephalopathy is not fully explained by perinatal history, cord gases and/or neuroimaging.

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Compliance with Ethics Guidelines

Conflict of Interest

Joshua Hatch, David Coman, Peter Clayton, Philippa Mills, Sophie Calvert, Richard Webster and Kate Riney declare that they have no conflicts of interest.

Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

Author Contributions

Dr Joshua Hatch has driven the manuscript development.

Professor David Coman is a metabolic physician involved in the care of patients 1–3 and has coordinated the manuscript development and design.

Professor Peter Clayton is a metabolic physician who has provided invaluable clinical advice on all four patients and has been involved in the manuscript development.

Dr Philippa Mills has provided valuable advice regarding the molecular pathogenicity of the mutations identified and has been involved in the manuscript development.

Dr Sophie Calvert is a paediatric neurologist, providing neurology care for case 3, and has been involved in the manuscript development.

Dr Richard Webster is a paediatric neurologist, providing neurology care for case 4, and has been involved in the manuscript development.

Dr Kate Riney is a paediatric neurologist, providing neurology care for cases 1 and 2, and has been involved in the manuscript development.

References

Albersen M, Groenendaal F, van der Ham M, de Koning TJ et al (2012) Vitamin B6 vitamer concentrations in cerebrospinal fluid differ between preterm and term newborn infants. Pediatrics 130 (1):e191–e198

Bagci S, Zschocke J, Hoffmann GF et al (2008) Pyridoxal phosphate-dependent neonatal epileptic encephalopathy. Arch Dis Child Fetal Neonatal Ed 93(2):F151–F152

Clayton PT (2006) B6-responsive disorders: a model of vitamin dependency. J Inherit Metab Dis 29(2–3):317–326

Footitt EJ, Heales SJ, Mills PB, Allen GF, Oppenheim M, Clayton PT (2011) Pyridoxal 5′-phosphate in cerebrospinal fluid; factors affecting concentration. J Inherit Metab Dis 34(2):529–538

Goyal M, Fequiere PR, McGrath TM, Hyland K (2013) Seizures with decreased levels of pyridoxal phosphate in cerebrospinal fluid. Pediatr Neurol 48(3):227–231

Graham EM, Ruis KA, Hartman AL, Northington FJ, Fox HE (2008) A systematic review of the role of intrapartum hypoxia-ischemia in the causation of neonatal encephalopathy. Am J Obstet Gynecol 199(6):587–595

Hoffmann GF, Schmitt B, Windfuhr M et al (2007) Pyridoxal 5′-phosphate may be curative in early-onset epileptic encephalopathy. J Inherit Metab Dis 30(1):96–99

Khayat M, Korman SH, Frankel P et al (2008) PNPO deficiency: an under diagnosed inborn error of pyridoxine metabolism. Mol Genet Metab 94(4):431–434

Mills PB, Surtees RA, Champion MP et al (2005) Neonatal epileptic encephalopathy caused by mutations in the PNPO gene encoding pyridox(am)ine 5′-phosphate oxidase. Hum Mol Genet 14(8):1077–1086

Mills PB, Camuzeaux SS, Footitt EJ et al (2014) Epilepsy due to PNPO mutations: genotype, environment and treatment affect presentation and outcome. Brain 137:1350–1360

Ormazabal A, Oppenheim M, Serrano M et al (2008) Pyridoxal 5′-phosphate values in cerebrospinal fluid: reference values and diagnosis of PNPO deficiency in paediatric patients. Mol Genet Metab 94(2):173–177

Pearl PL, Hyland K, Chiles J, McGavin CL, Yu Y, Taylor D (2013) Partial pyridoxine responsiveness in PNPO deficiency. JIMD Rep 9:139–142

Plecko B, Paul K, Mills P et al (2014) Pyridoxine responsiveness in novel mutations of the PNPO gene. Neurology 82(16):1425–1433

Porri S, Fluss J, Plecko B, Paschke E, Korff CM, Kern I (2014) Positive outcome following early diagnosis and treatment of pyridoxal-5′-phosphate oxidase deficiency: a case report. Neuropediatrics 45(1):64–68

Ruiz A, García-Villoria J, Ormazabal A et al (2008) A new fatal case of pyridox(am)ine 5′-phosphate oxidase (PNPO) deficiency. Mol Genet Metab 93(2):216–218

Schmitt B, Baumgartner M, Mills PB, Clayton PT, Jakobs C, Keller E, Wohlrab G (2010) Seizures and paroxysmal events: symptoms pointing to the diagnosis of pyridoxine-dependent epilepsy and pyridoxine phosphate oxidase deficiency. Dev Med Child Neurol 52(7):e133–e142

Stockler S, Plecko B, Gospe SM Jr et al (2011) Pyridoxine dependent epilepsy and antiquitin deficiency: clinical and molecular characteristics and recommendations for diagnosis, treatment and follow-up. Mol Genet Metab 104(1–2):48–60

Sudarsanam A, Singh H, Wilcken B et al (2014) Cirrhosis associated with pyridoxal 5′-phosphate treatment of pyridoxamine 5′-phosphate oxidase deficiency. JIMD Rep 17:67–70

Van Hove J, Lohr N (2011) Metabolic and monogenic causes of seizures in neonates and young infants. Mol Genet Metab 104:214–230

Veerapandiyan A, Winchester SA, Gallentine WB, Smith EC, Kansagra S, Hyland K, Mikati MA (2011) Electroencephalographic and seizure manifestations of pyridoxal 5′-phosphate-dependent epilepsy. Epilepsy Behav 20(3):494–501

Ware TL, Earl J, Salomons GS, Struys EA, Peters HL, Howell KB, Pitt JJ, Freeman JL (2014) Typical and atypical phenotypes of PNPO deficiency with elevated CSF and plasma pyridoxamine on treatment. Dev Med Child Neurol 56(5):498–502