Current Treatment and Management of Pyridoxine-Dependent Epilepsy

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Opinion statement

Pyridoxine-dependent epilepsy (PDE) is a rare autosomal recessive disorder and is considered as a prototypical form of metabolic epilepsy. Characterized by recurrent seizures in the prenatal, neonatal, and/or postnatal periods that are resistant to conventional anti-epileptic drugs, PDE is responsive to pharmacological dosages of pyridoxine. Presently, however, there are no clear dose recommendations for long-term treatment. While pyridoxine supplementation is the first line of treatment and should be initiated in all confirmed PDE patients at an early age, various other treatment strategies are emerging. These include a lysine-restricted diet and arginine fortification. These will be discussed in light of current evidence, together with recommendations for best management of patients with this rare but treatable metabolic epilepsy, and future research and collaborative efforts, including the International PDE Consortium.

Introduction

Pyridoxine-dependent epilepsy (PDE, MIM #266100) is a rare autosomal recessive disorder and is considered as a prototypical form of metabolic epilepsy. It is characterized by recurrent seizures in the prenatal, neonatal, and/or postnatal periods that are resistant to conventional anti-epileptic drugs (AED), but responsive to

pharmacological dosages of pyridoxine [1••, 2]. Hunt et al. first described PDE in 1954 in a newborn with pharmaco-resistant seizures that were controlled immediately after parenteral administration of a multivitamin cocktail containing vitamin B6 [3]. In the more than six decades since, over 200 cases of PDE have been reported [4–8]. The point prevalence of PDE may vary from 1:20,000 to 1:600,000, based on the degree of systematic ascertainment via a therapeutic trial with pyridoxine [9–11]. The underlying genetic defect was identified in 2006 as mutations in *ALDH7A1* resulting in the deficiency of α–aminoadipic semialdehyde dehydrogenase (antiquitin), which is involved in cerebral lysine catabolism (MIM #107323) [12]. Folinic acid-responsive seizures are caused by mutations in the same gene [13]. Antiquitin (ATQ) deficiency results in the accumulation of intermediate substrates arising from lysine degradation proximal to the deficient enzyme activity, including α –aminoadiphic semialdehyde (AASA), Δ-1-piperidine-6-carboxylate (P6C) and pipecolic acid (Fig. 1). Inactivation of pyridoxal 5′ phosphate (PLP) via chemical reaction with P6C is the pathophysiological mechanism of pyridoxine dependency [14••].

PDE typically presents within hours or days of birth with seizures that are refractory to AEDs. In some instances, seizures have been reported to occur intrauterine, with onset at the end of the last trimester. Late onset and other atypical forms of PDE, including infants whose seizures first respond to AEDs but relapse weeks to months later with refractory seizures, and patients whose seizures are not controlled by initial large doses of pyridoxine but which respond at a later time to a second trial, have also been reported in the literature [4, 15–18].

PDE patients have a heterogeneous clinical phenotype. The neonatal epileptic encephalopathy presentation may include gastrointestinal symptoms such as emesis and abdominal distention, sleeplessness, hyper-alertness, irritability, paroxysmal facial grimacing and abnormal eye movements. These striking findings are associated with recurrent partial motor seizures, generalized tonic seizures or myoclonus. Depending upon the phenotype, response (if any) to AEDs and timing of the initiation of pyridoxine supplementation, complex partial seizures, infantile spasms and other myoclonic seizures, as well as a mixed seizure pattern and recurrent status epilepticus, may develop [8, 19–22, 11]. Brain activity on EEG is non-specific, and can remain abnormal even with pyridoxine therapy [23]. PDE patients also have associated neurodevelopmental disabilities, ranging from mild to severe developmental delay/intellectual disability commonly affecting the domains of expressive language, along with a low-normal motor/performance IQ [4, 19, 20, 24]. Magnetic resonance imaging studies show different patterns, from white matter lesions, general cerebral atrophy, corpus
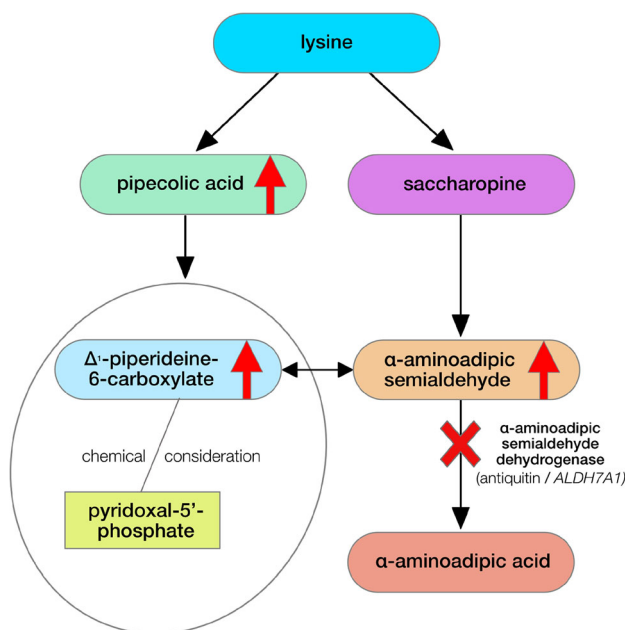

Fig. 1. Treatment with pyridoxine compensates for chemical PLP inactivation, but the accumulation of substrates from lysine degradation is not sufficiently reduced.

callosum hypoplasia or dysplasia, to a structurally normal brain [25•, 26].

Clinical phenotypes of PDE can be classified into three groups: Group 1 consists of patients with complete seizure control, with pyridoxine and normal development; Group 2 consists of patients with complete seizure control with pyridoxine, but with developmental delay; and Group 3 consists of patients with persistent seizures and developmental delay despite pyridoxine. Despite extensive studies, correlations between the genotype and these phenotypic categories have not yet been established [1••, 27].

Patients presenting with unexplained early onset epilepsy and poor response to AEDs should be assessed for PDE. Situations under which PDE screening should be considered are clearly outlined by Stockler et al. [14••]. PDE diagnosis is based upon determination of AASA/P6C in urine, plasma and/or cerebral spinal fluid (CSF). Over time, pipecolic acid has proven less reliable than AASA for diagnosis, given its limited sensitivity and specificity. Thus, pipecolic acid is a secondary marker, and should only be used in conjunction with AASA. *ALDH7A1* molecular analysis should be performed for diagnostic confirmation. If sequencing does not reveal point mutations, testing for insertions/deletions is indicated.

The differential diagnosis of neonatal epileptic encephalopathy is quite diverse and includes not only inborn errors of metabolism such as PDE, but also an array of other genetic conditions (single gene defects and chromosomal copy number variants), along with acquired disorders such as fetal or neonatal brain injury from maternal or postnatal infection, exposure to teratogens, pre-/perinatal hypoxia and/or ischemia, and intracerebral hemorrhage. High AASA is not only a distinctive characteristic for PDE. Elevated levels are also seen in patients with molybdenum cofactor deficiency and isolated sulfite oxidase deficiency, particularly in children with epileptic encephalopathy and atypical response to pyridoxine [28, 29]. Other forms of vitamin B6 responsive epilepsy include pyridoxamine 5′-phosphate oxidase (PNPO) deficiency, hyperprolinemia II (*ALH4A1*), and tissue non-specific alkaline phosphatase (TNSALP) deficiency. As patients with PNPO deficiency may present with a similar clinical phenotype, this rare metabolic disorder must also be kept in mind, and for patients with medically intractable neonatal seizures who do not respond to pyridoxine, a trial of pyridoxal phosphate (PLP) should also be instituted. Similarly, tissue non-specific alkaline phosphatase (TNSALP) deficiency must be considered in young patients with medically refractory neonatal or infantile seizures, particularly when signs of abnormal bone mineralization with or without low serum alkaline phosphatase are present; seizures in this condition improve on pyridoxine treatment [14••].

Treatment

For an overview of currently available treatments for PDE, the reader is referred to Table 1.

Pharmacological treatments

Pyridoxine

The standard treatment of PDE includes lifelong pyridoxine supplementation in pharmacologic doses. In an acutely seizing infant, an initial single—or more—100 mg dose of pyridoxine should be given intravenously without delay; given the risk of apneas, this should be administered in a controlled environment. Treatment with oral pyridoxine (15–30 mg/kg/day, divided in two to three doses) should be continued until negative biochemical or genetic testing excludes PDE.

Table 1. Overview of currently practiced treatments for PDE

Medication	Dosage	Indication	Monitoring	Pitfalls / Managment
Pyridoxine *IV*	100 mg *(single dose)*	Interruption of initial status epilepticus, or of prolonged break through seizures	EEG if available	May result in respiratory arrest. Administer only with readiness of respiratory support
Pyridoxine *Oral / Enteral*	15-30 mg / kg/d *(divided in 3 doses)* Up to 200 mg/d in neonates, and 500 mg/d in adults	Long term treatment	Clinical and electrophysiological signs of neuropathy	Continue with dosages above the range only if high dosage has proven essential for effective seizure control
Pyridoxine *Oral Prenatal / Maternal*	100 mg/d	Prevention of intrauterine seizures and irreversible brain damage Start in early pregnancy, continue throughout pregnancy in case of positive prenatal diagnosis or if no prenatal diagnosis has been performed	Monitor for seizures and encephalopathy after delivery in NICU / SCN setting.	Continue oral / enteral pyridoxine supplementation at 30 mg / kg / d immediately after birth and immediately initiate biochemical and molecular genetic investigations to prove or rule out ATQ / PNPO deficiency.
Pyridoxal-phosphate *Oral / Enteral*	30 mg/kg/d *(divided in 3 doses)*	Interruption of initial status epilepticus if pyridoxine has failed Long term treatment: Alternative to pyridoxine	Liver dysfunction No neuropathy reported upon PNP thus far	Continue treatment or switch to pyridoxine in confirmed ATQ deficiency.
Folinic acid *Oral / Enteral*	3-5 mg/kg/d *(divided in 3 doses)*	Additional therapy if pyridoxine or PLP failed to control seizures	No particular monitoring	May cause / exacerbate seizures
Lysine restricted diet	Should always be given as adjunct to pyridoxine Daily lysine intake at an amount that maintains the plasma lysine level within the lower normal age-dependent reference range, preferably in the lower quartile [van Karnebeek et al. 2014].	In ATQ deficient patients except those with normal development and seizure control. Goal: reduction of AASA/P6C accumulation; improvement of neurodevelopmental outcomes and seizure control.	AASA/P6C (U, CSF) Aminoacids (P) Pre-albumin, albumin, plasma amino acids; complete blood count; micronutrients Weight/Height	Lysine deficiency Tryptophan deficiency if lysine free aminoacid formulas for GAI are used (also low in tryptophan)
Arginine	150 mg/kg/day if administered as adjunct to lysine restricted diet and pyridoxine 400 mg/kg/day if administered as adjunct to pyridoxine only	In ATQ deficient patients except those with normal development and seizure control. Goal: reduction of AASA/P6C accumulation; improvement of neurodevelopmental outcomes and seizure control.	AASA/P6C (U, CSF) Aminoacids (P) Pre-albumin, albumin, plasma amino acids; complete blood count; micronutrients Weight/Height	Lysine deficiency Tryptophane deficiency if lysine free aminoacid formulas for GAI are used (also low in tryptophan) Hyperargininemia and Liver toxicity

At present, there are no clear dose recommendations for long-term treatment. In a regular diet, the recommended daily allowance for pyridoxine is 0.5 mg for infants and 2 mg for adults. In most patients with PDE, therapeutic pyridoxine dosages vary between 15 and 30 mg/kg/day in infants, or up to 200 mg/day in neonates and 500 mg/day in adults. Some patients respond to small doses. These oral dosages seem to be safe in long-term treatment. Higher pyridoxine doses may cause sensory, and rarely, motor neuropathy, which may be reversible [30, 31]. Nerve conduction studies are performed to exclude sensory neuropathy as an adverse effect of pyridoxine treatment. This test is performed either upon clinical evidence of neuropathy or as a regular monitoring (e.g., annually), in particular if high doses (>500 mg/day or >30 mg/kg/day) are used. Some patients experience breakthrough seizures during febrile illness. In these cases, higher (e.g., double) dosages may be given during the first 3 days of febrile illnesses. Despite sufficient seizure control with oral pyridoxine, in most cases (80 %), long-term patient outcome with PDE remains poor, especially with respect to neurodevelopment [19, 27].

Prophylactic prenatal and postnatal treatment

Prenatal treatment of an at-risk or confirmed PDE fetus with supplemental pyridoxine given during pregnancy may prevent intrauterine seizures and improve neurodevelopmental outcome [32]. Prenatal treatment with high-dose pyridoxine followed by postnatal treatment was shown to be effective in preventing seizures, but failed to mitigate poor cognitive outcomes in two affected offspring in a family with a homozygous stop codon in exon 14 of *ATQ* (Y380X) [31]. In contrast, Bok et al. reported good developmental outcomes after prenatal treatment in three patients homozygous for the missense mutation in the same gene (E399Q) [33] when oral pyridoxine was given to pregnant women at a dosage of 100 mg/day from early pregnancy. The dosage of 100 mg pyridoxine/day seems to be safe, as it has been used for the treatment of hyperemesis gravidarum without fetal side effects [32].

Adverse effects, including increased seizure activity, have been seen in children with high pyridoxine or PLP intake [34, 35]. A neonate with a positive family history was on prophylactic intrauterine treatment with pyridoxine, and treatment was continued postnatally until PDE was ruled out. On day 15, while on treatment, the patient developed status epilepticus and encephalopathy. Upon receiving the final biochemical results, pyridoxine treatment was discontinued and his condition improved [36]. Thus, biochemical and genetic testing should be done as soon as possible, in order to limit unnecessary (high-dose) treatment with pyridoxine.

Pyridoxal phosphate

Some patients with medically refractory seizures and unresponsiveness to pyridoxine may respond to PLP. In most, PNPO deficiency has been identified as the underlying genetic condition [37, 38], but idiopathic PLP response can occur as well [39]. As PLP has the potential to treat both PNPO deficiency [40, 41] and PDE, some centers advocate its use

(30 mg/kg/day divided into three doses) as the first line form of vitamin B6, while other centers advocate its consecutive use when pyridoxine, given over 3 consecutive days, has failed to control seizures [37]. In any case, treatment should be continued until results from metabolic investigations in urine, blood and CSF are available, as well as confirmation via molecular analysis of *PNPO*. As shown in animal experiments and communicated via anecdotal reports in humans, high PLP concentrations in the brain can lead to convulsions and liver damage [42].

Both vitamers (pyridoxine and PLP) are relatively inexpensive. However, PLP tablets cost six to ten times more than pyridoxine products and are less readily available in North America and the rest of the world [43]. Therefore, from a practical standpoint, local availability of PLP may determine how this particular vitamer is used and studied.

Folinic acid

Response to folinic acid was seen in patients who initially did not respond well to pyridoxine, but who later received a confirmed PDE diagnosis. However, the underlying mechanism for this has yet to be established. Folinic acid (3–5 mg/kg/day) may have a potential benefit as an add-on treatment in neonates, especially in the presence of incomplete pyridoxine responsiveness or breakthrough seizures. In older patients, 10–30 mg/day is recommended [13]. Whether long-term folinic acid provides benefit once the seizures are stabilized remains to be determined. High-dose folinic acid therapy can also exacerbate a seizure disorder and the clinical benefit must be closely monitored.

Diet intervention

Lysine-restricted diet

While treatment with pyridoxine compensates for chemical PLP inactivation, the accumulation of substrates from lysine degradation is not sufficiently reduced (Fig. 1). The presence of these potentially neurotoxic compounds could explain the partial efficacy of pyridoxine, as 75–80 % of patients suffer from developmental delay or intellectual disability (IQ < 70), despite excellent seizure control in the majority of patients [25•]. Standard treatment for inborn errors of metabolism affecting catabolic pathways of essential amino acids consists of substrate reduction for the deficient enzyme through dietary modification. Thus, for ATQ deficiency, dietary lysine restriction can reduce the accumulation of lysine-derived substrates and possibly contribute to the improvement of cerebral function (neurodevelopment, cognition, behavior, and seizure control).

Based on this rationale, an open-label observational study was conducted to test the effectiveness and safety of dietary lysine restriction as an adjunct to pyridoxine therapy on chemical biomarkers, seizure control, and developmental outcome in seven children with confirmed ATQ deficiency [44•]. The results from the study show that dietary lysine restriction (evidence

level IV): 1) is tolerated without adverse events; 2) leads to significant decreases of potentially neurotoxic biomarkers in different body compartments; and 3) has potential benefit for seizure control and neurodevelopmental outcomes. The lysine-restricted diet is thus a promising add-on therapy for ATQ deficiency, with the potential to improve short-term and long-term clinical outcomes.

The evidence, however, remains limited, and as with any diet, lysine restriction poses a burden on patients and families, often in conflict with social and cultural traditions [45]. Also, such dietary treatment cannot be taken lightly: it requires monitoring by a specialist and metabolic dietician, with regular clinical follow-up, dietary protocols, and laboratory testing. Different effects can be expected based on the patient's prenatal history, associated congenital brain abnormalities, genotype and other factors, and further study is required.

Based on the positive outcomes of this study, including the limited evidence level and experience with this burdensome diet, an international PDE Consortium developed and published consensus recommendations for implementation of lysine restriction along with monitoring and follow-up [46••]. Such standardization allows a systematic evaluation of the safety and effectiveness of this novel therapy, and helps to generate more solid evidence to substantiate its potential benefits.

In summary, every patient with confirmed ATQ deficiency treated with pyridoxine 15-30 mg/kg/day whose seizures are not well controlled and/or whose neurodevelopment is abnormal, is eligible for dietary lysine restriction, which can be initiated after baseline investigations. Its use is recommended throughout life. Lysine intake is based on the guidelines for Glutaric Aciduria type I by Kölker et al. [47], using both the World Health Organization (WHO) guidelines [48] and a paper by Yannicelli et al. [49] as additional references. These recommendations for age-dependent lysine restriction are detailed in the Consortium Recommendations paper [46••]. To allow for more precise and consistent lysine intake, a lysine prescription, rather than a simpler protein restriction, is recommended (at least during the initiation of the diet in the first year of life). Daily lysine intake should be managed to maintain the plasma lysine level within the lower normal reference range. In order to meet the recommended daily protein intake [48, 50], the diet may include commercially available, lysine-free amino acid formulas approved for use in conditions affecting lysine metabolism. Lysine-free amino acid formulas are often supplemented with vitamins and minerals in order to provide adequate or significant intake of these nutrients, and adequate supply of iron, minerals and vitamins must be confirmed by regular laboratory testing. Where lysine-free amino acid formulas are not used, vitamin and mineral supplement preparations must be added. Because limited amounts of high protein from the meat, fish and dairy food groups will be consumed, the use of fats and oils, carbohydrates and special low protein sources are often necessary to provide adequate caloric intake. Safety monitoring at baseline and every 1–6 months thereafter (frequency depending on age and duration of treatment) includes measurement of lysine and branched-chain amino acids in plasma, albumin, pre-albumin, iron parameters, calcium, phosphate, 25-OH-vitamin D3, zinc, selenium, complete blood count, folic acid, and vitamin B12 in serum or plasma.

Main outcomes include the biochemical parameters (PA and α-AASA levels in body fluids), seizure control and neurodevelopmental parameters.
In order to reduce the burden of the diet for patients and family/caregivers, an App has been developed to calculate lysine content, and to facilitate the management and monitoring the lysine-restricted diet, including documentation of food records. The App will be launched, free of charge, at the end of 2014 (www.pdeonline.org). The designers, in collaboration with Genetic Metabolic Dietitians International, Inc. (GMDI), aim to support patient families, and improve therapeutic adherence and thereby their experience, and ultimately disease outcomes.

Arginine fortification

Cerebral lysine influx and oxidation can be modulated by arginine, which competes with lysine for transport at the blood–brain barrier (cationic amino acid transporter 1, CAT1, which is one of three CATs that are called system y+) and the inner mitochondrial membrane (mitochondrial ornithine carriers, ORNT1 and ORNT2) [51]. It is hypothesized that arginine supplementation will compete with lysine, thereby reducing the excess lysine influx into the brain, which can lead to accumulation of the neurotoxic substrates caused by ATQ deficiency. The relationship between arginine fortification and plasma lysine has been proven in GA1 treatment, indicating that transport competition exists at both cerebrovascular and gastrointestinal barriers, suggesting that their co-administration is key to their efficacy.
Arginine fortification has proven safe as an add-on treatment to lysine restriction, as well as effective in improving outcomes in GA1 over the past 10 years [47, 52]. Following 12 months of arginine supplementation at 400 mg/kg/day, together with pyridoxine 200 mg/kg/day, a decrease in CSF α-AASA and improvement in general abilities, as well as verbal and motor functions, were reported [53]. These patients did not receive a lysine-restricted diet. In order to further restrict cerebral lysine influx, arginine supplementation of 150 mg/kg/day was initiated as triple therapy adjunct to the lysine-restricted diet and pyridoxine. This resulted in near normalization of urine AASA and plasma pipecolic acid, and improvement in developmental and cognitive domains, specifically in motor skills and speech. Furthermore, a decrease in brain lysine influx after arginine supplementation was noted [54].

Emerging therapies

Perez et al. provided proof-of-concept in cells for antisense therapy in PDE [2]. They reported the clinical, biochemical and genetic analysis of 12 unrelated patients with ATQ deficiency, including seven novel mutations changes. Transcriptional profile analysis showed the silent nucleotide change c.75C>T to be a novel splicing mutation creating a new donor splice site in exon 1. Antisense therapy of the aberrant mRNA splicing in a lymphoblast cell line harboring this mutation was

successful, suggesting that this strategy may be a means of rescuing splice site changes in *ALDH7A1* and preventing neurologic damage.

Conclusion and future directions

In conclusion, a therapeutic trial with pyridoxine should be performed in all patients with pharmaco-resistant epilepsies, until negative biochemical or genetic testing excludes PDE. Pyridoxine supplementation is the first line of treatment and should be initiated in all PDE patients at an early age. Therapeutic pyridoxine should be administered for life at dosages between15 and 30 mg/kg/day in infants, or up to 200 mg /day in neonates and 500 mg /day in adults, together with adequate safety monitoring. Prophylactic intrauterine treatment with supplemental pyridoxine in fetuses and neonates at risk of PDE can be considered for better outcomes; however, treatment exposure should be limited to the shortest possible interval so as to prevent any potential problems related to toxicity. Recently developed novel therapies based on the pathophysiology of PDE—i.e., lysine-restricted diet and arginine fortification—also provide potential treatment options.

Future research should focus on a better understanding of the phenotypic spectrum of PDE, its natural history, determination of the appropriate dose of pyridoxine supplementation (by both age and genotype-phenotype); the utility of the longitudinal measurements of levels of α-AASA and other biomarkers for disease management; the role of folinic acid in the treatment of PDE; and the effectiveness and long-term outcomes of a lysine-restricted diet and arginine fortification, along with optimal dosing of the different treatment regimens.

PDE, being a rare disease, poses some inherent challenges to research, which include small patient numbers spread around the world; under-diagnosis due to insufficient awareness; clinical heterogeneity; incomplete insight into the clinical spectrum and genotype–phenotype correlation; limited financial resources; and diverse specialists treating this metabolic epilepsy [55]. Suggested methods to overcome these roadblocks include establishment of a task force, the International PDE Consortium (www.pdeonline.org), to develop recommendations for treatment; use of digital tools and databases to unite patients and families, scientists and clinicians, and to facilitate knowledge dissemination; and novel trial methodologies with the simultaneous use of different study designs allowing inclusion of all patients, irrespective of age, severity, symptoms, and interventions.

Collaboration and sharing of data is of primary importance. To that end, we have established a longitudinal prospective 'PDE patient registry' (accessible viawww.pdeonline.org) that enables investigators to evaluate the utility of genotype, levels of biochemical markers, clinical neuropsychological studies and imaging modalities, thereby providing valuable insights into the natural history of PDE and improving the evidence for treatments.

Finally, novel approaches to early detection, and ultimately newborn screening, are being developed, such as the P6C measurement via dried bloodspot analysis [56]. Once implemented, this analysis will be instrumental in effectively determining the frequency of this treatable condition, while also

providing an opportunity to initiate treatment immediately after birth, so as to prevent and control seizures, and ultimately limit brain damage in affected individuals.

Compliance with Ethics Guidelines

Conflict of Interest
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Sravan Jaggumantri reports no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by the authors.

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