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## Review Article

## Pyridoxine-Dependent Epilepsy: An Expanding Clinical Spectrum

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## ABSTRACT

**BACKGROUND:** Pyridoxine-dependent epilepsy is a rare autosomal recessive epileptic encephalopathy caused by antiquitin (*ALDH7A1*) deficiency. In spite of adequate seizure control, 75% of patients suffer intellectual developmental disability. Antiquitin deficiency affects lysine catabolism resulting in accumulation of  $\alpha$ -aminoadipic semialdehyde/pyrroline 6' carboxylate and pipercolic acid. Beside neonatal refractory epileptic encephalopathy, numerous neurological manifestations and metabolic/biochemical findings have been reported. **METHODS AND RESULTS:** We present a phenotypic spectrum of antiquitin deficiency based on a literature review (2006 to 2015) of reports ( $n = 49$ ) describing the clinical presentation of confirmed patients ( $n > 200$ ) and a further six case vignettes. Possible presentations include perinatal asphyxia; neonatal withdrawal syndrome; sepsis; enterocolitis; hypoglycemia; neuroimaging abnormalities (corpus callosum and cerebellar abnormalities, hemorrhage, white matter lesions); biochemical abnormalities (lactic acidosis, electrolyte disturbances, neurotransmitter abnormalities); and seizure response to pyridoxine, pyridoxal-phosphate, and folinic acid dietary interventions. **DISCUSSION:** The phenotypic spectrum of pyridoxine-dependent epilepsy is wide, including a myriad of neurological and systemic symptoms. Its hallmark feature is refractory seizures during the first year of life. Given its amenability to treatment with lysine-lowering strategies in addition to pyridoxine supplementation for optimal seizure control and developmental outcomes, early diagnosis of pyridoxine-dependent epilepsy is essential. All infants presenting with unexplained seizures should be screened for antiquitin deficiency by determination of  $\alpha$ -aminoadipic semialdehyde/pyrroline 6' carboxylate (in urine, plasma or cerebrospinal fluid) and *ALDH7A1* molecular analysis.

**Keywords:** metabolic epilepsy, neonatal encephalopathy, seizures, B6 vitamers, lysine catabolism, treatment

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## Introduction

Pyridoxine-dependent epilepsy is a rare autosomal recessive disorder, classically presenting with neonatal seizures that can be controlled with pharmacologic doses of pyridoxine.<sup>1,2</sup> Since the 1950s, pyridoxine-dependent epilepsy was diagnosed clinically with vitamin B6 as a diagnostic trial.<sup>3</sup> The reported incidence varies from 1:20,000<sup>4</sup> to 1:276,000<sup>5</sup> and 1:783,000.<sup>3</sup> In 2006 a defect in the lysine degradation pathway (*ALDH7A1* encoding  $\alpha$ -amino adipic semialdehyde dehydrogenase, also known as antiquitin [ATQ]) was identified as the genetic basis of this rare epilepsy.<sup>6</sup> Accumulation of  $\alpha$ -amino adipic semialdehyde ( $\alpha$ -AASA)/L- $\Delta$ 1-piperidine-6 carboxylate (P6C) results in chemical inactivation of pyridoxal phosphate (PLP).<sup>6</sup> These insights unveiled novel diagnostic biomarkers and the lysine degradation pathway as adjunct treatment targets<sup>7-10</sup> (Fig 1). To compile an overview of possible clinical presentations,<sup>11</sup> we performed a literature review to collect data on reported pyridoxine-dependent epilepsy patients. Case vignettes are presented to illustrate the clinical spectrum.

## Materials and Methods

This study was approved by the Ethics Boards at British Columbia Children's and Women's Hospital, University of British Columbia (Canada) and the University of Colorado (United States of America). Parents provided informed consent for publication of the case vignettes.

For the literature review, we searched PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>; 2006 to October 2015) using a combination of the following terms (restricted to humans): pyridoxine-dependent epilepsy (PDE), pyridoxine-dependent seizures, Antiquitin, ATQ,  $\alpha$ -amino adipic semialdehyde dehydrogenase, *ALDH7A1*,  $\alpha$ -amino adipic semialdehyde, and  $\alpha$ -AASA. For the selection of articles, we applied the following criteria: (1) publication date after the discovery of *ALDH7A1* mutations as the cause of pyridoxine-dependent epilepsy in 2006<sup>6</sup>; (2)

publication language English; and (3) reporting one or more pyridoxine-dependent epilepsy patient(s) with confirmed ATQ deficiency, including a description of the clinical symptoms.

We subsequently extracted clinical, biochemical, and neuroimaging data/symptoms from the selected articles. For each of the reported symptoms, the following classification was made (Fig 2): either "classical," defined as the typical or core phenotypic presentation (reported in the vast majority of patients) or "spectrum," defined as less common or atypical (reported in minority of patients). The "spectrum symptoms" were organized into different categories: neurologic, biochemical, neuroimaging findings; seizure onset; seizure type; and response to medication other than pyridoxine, behavioral/psychiatric, and "other" symptoms. We indicated the ultrarare symptoms, i.e., those reported in less than five patients in the literature. To overcome the limitations of our PubMed search and subsequent potential "reporting bias" (i.e., that only a selection of pyridoxine-dependent epilepsy patients is published as a case report), we also asked clinicians (all nine coauthors) with expertise and experience in ATQ deficiency to review and edit the clinical spectrum generated by the literature review, i.e., whether any symptoms were missing or unjustified and provide illustrative case vignettes.

## Results

Of the 246 articles generated by the PubMed search, 49 met the outlined criteria, including 266 descriptions of patients with confirmed ATQ deficiency.<sup>5,7,8,11-55</sup> Figure 2 provides a comprehensive visual overview of the presenting clinical and biochemical features of patients reported in the literature.

### Patient vignettes

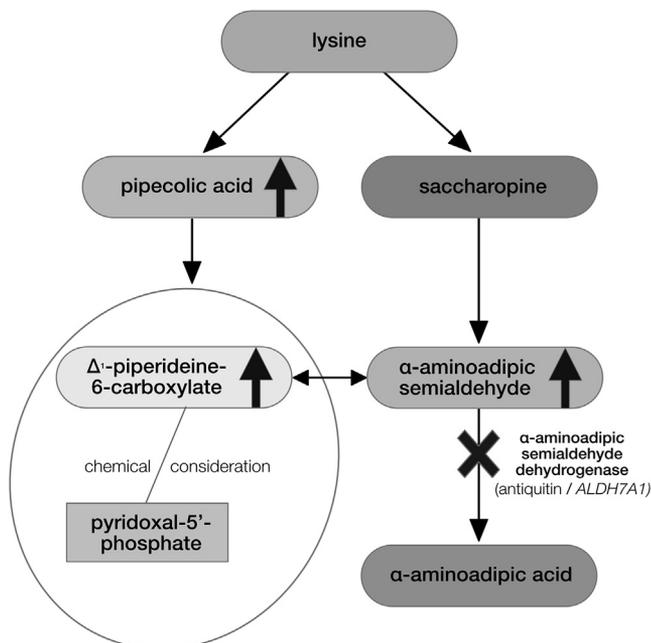
One or more of the authors follow each of the patients described below. Although Patients 2 and 4 are novel, i.e., have not previously been reported in the literature, we have expanded on the remaining published reports to include more recent information.

#### Patient #1: lactic acidosis and cardiomyopathy mimicking mitochondrial disease

This girl was born at 33 weeks, then developed recurrent apnea; distended abdomen; feeding intolerance; lactic acidosis; hyponatremia; and increased urinary excretion of lactate, ketone bodies, and dicarboxylic acids on day one.<sup>12</sup> On day ten, choreoathetoid movements of arms and legs, orofacial twitches, and burst suppression pattern on electroencephalograph (EEG) were unresponsive to phenobarbital but improved after the administration of 100 mg of pyridoxine intravenously. A magnetic resonance imaging (MRI) revealed bilateral temporal lobe hemorrhages and thalamic changes. ATQ deficiency was confirmed by homozygosity for a known pathogenic sequence change (c.1279G>C; p.E427Q) in *ALDH7A1*. During the first year of life, she remained seizure free on oral pyridoxine (15 to 30 mg/kg/day). At age 11 months, a lysine-restricted diet was initiated with addition of arginine at age 6.3 years. This regimen has been well tolerated, with pipercolic acid normalizing and  $\alpha$ -AASA dropping below the detection limit; at age seven years of age, aside from mild motor delay, she demonstrates normal psychomotor development.<sup>7,8</sup>

#### Patient #2: recurrent burst suppression on oral pyridoxine and periventricular leukomalacia

This girl was born spontaneously at 34 weeks gestation, then exhibited generalized myoclonus, particularly



**FIGURE 1.** Role of antiquitin (*ALDH7A1*) in the catabolic pathway of lysine.

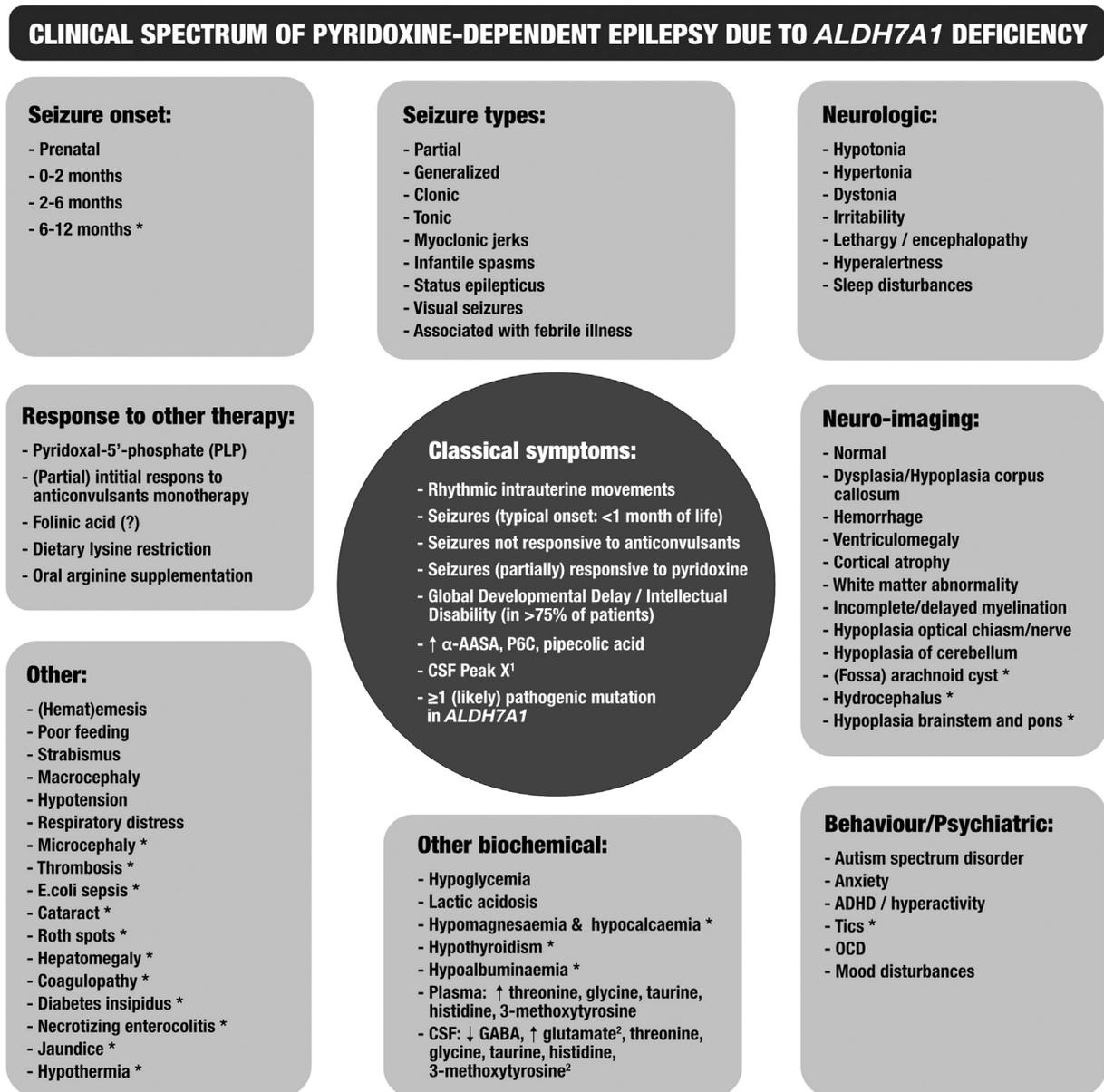


FIGURE 2.

Overview of the symptoms reported in the literature for patients with ATQ deficiency. Classical symptoms (center circle): clinical and biochemical symptoms observed in the vast majority patients. Spectrum symptoms (boxes): symptoms present in the minority of patients. \*Ultrarare symptoms, reported in less than five literature cases. <sup>1</sup>Unidentified peak in the HPLC chromatogram for CSF monoamine neurotransmitter analysis in ATQ deficiency patients. <sup>2</sup>Potentially normalize on pyridoxine therapy.  $\alpha$ -AASA,  $\alpha$ -amino adipic semialdehyde; ADHD, attention deficit hyperactivity disorder; ATQ, anti-quitin; CSF, cerebrospinal fluid; HPLC, high performance liquid chromatography; GABA, *gamma*-aminobutyric acid; OCD, obsessive–compulsive disorder; P6C, L- $\Delta$ 1-piperidine-6 carboxylate.

of the diaphragm, lactic acidosis (9.8 mmol/L, reference range < 2.1), and an EEG illustrating a high-voltage burst suppression pattern on day one. Therapy with IV phenobarbital and lidocaine was ineffective, whereas one dosage of intravenous pyridoxine 100 mg resulted in immediate cessation of myoclonus on day two. An MRI brain scan on day eight indicated a small subependymal hemorrhage in the right hemisphere and diffuse punctate bleeding in the periventricular white matter. ATQ deficiency was confirmed by increased pipercolic acid in cerebrospinal fluid (CSF; 11.6  $\mu$ mol/L, reference range = 0.00

to 0.10) and in plasma (32.7  $\mu$ mol/L, reference range = 0.1 to 7.0), and homozygous mutations (c.1286G>T; p.S429L) in *ALDH7A1*.

While on pyridoxine (30 mg/kg/day) and folinic acid (3 to 5 mg/kg/day), breakthrough seizures occurred during febrile episodes at nine and 21 months of age. An MRI at age 14 months indicated widened extracellular spaces and periventricular leukomalacia with diffuse white matter loss, a more severe than the usual evolution observed in ex-premature patients. At age three years, she has mild delay in gross and fine motor skills.

*Patient #3: myoclonia with onset beyond the neonatal period and folinic acid-responsive seizures*

This boy with an unremarkable perinatal history had episodes of eye deviation, jerking movements of arms and legs accompanied by irritability, and crying at age 2.5 months. In retrospect, episodic jerking of the eyes and legs had been noticed since birth. The results of EEG, performed for the first time after an initial phenytoin and phenobarbital load, was normal, whereas abnormal movements disappeared only after a dose of oral pyridoxine (100 mg twice daily). At 4.5 months, he was diagnosed with “folinic acid-responsive seizures,” based on the presence of “peak X” in his CSF.<sup>13</sup> At age 12 months, breakthrough seizures occurred after he missed several dosages of pyridoxine. ATQ deficiency was diagnosed based on elevated plasma pipercolic acid (7.9  $\mu\text{mol/L}$ , normal < 3), elevated urinary  $\alpha$ -AASA (32.7  $\mu\text{mol/L}$ ; reference range < 1), and compound heterozygous mutations in *ALDH7A1* (c.750G>A, p.V250V/c.1195G>C, p.E399Q).<sup>11</sup> Dietary lysine restriction and oral arginine supplementation as adjunct to pyridoxine and folinic acid, began at three and eight years, resulted in decreased CSF  $\alpha$ -AASA and significant improvements in behaviors and language skills.<sup>7,8</sup>

*Patient #4: insomnia and continuous choreoathetotic movements mimicking neonatal drug withdrawal*

This boy was born at 38 weeks (Apgar scores 6 and 8; cord blood pH = 7.09), developed tachypnea, motor hyperexcitability, choreoathetotic movements, and oral stereotypies within the first hours of life. He was hyperalert and manifested insomnia for the first 48 hours of life. Based on a preliminary diagnosis of neonatal substance withdrawal syndrome, he received morphine, which was ineffective. Lactic acidosis (pH 7.11; BE = -17 mmol/L; lactate = 10.8 mmol/L) and subsequent pyridoxine-responsive status epilepticus prompted the diagnosis of ATQ deficiency, which was demonstrated by elevated plasma pipercolic acid (52.3  $\mu\text{mol/L}$ , reference range < 2.5) and a homozygous mutation in *ALDH7A1* (c.1195G>C; p.E399Q).

Numerous breakthrough seizures occurred on oral pyridoxine (30 to 35 mg/kg/day). Dietary lysine restriction was initiated at age 40 months. At six years of age, he has a squint, poor oral motor coordination with drooling, and attention deficit disorder.

*Patient #5: early-onset myoclonia and delayed response to pyridoxine*

This boy was born at 39 weeks with normal Apgar scores. He developed myoclonia during the first two days of life but had no evidence of epileptic activity on EEG. Cranial computed tomography and MRI revealed a small hemorrhage in the left and right occipital and temporal regions. From day 11 onwards, on treatment with phenobarbital, he demonstrated hypertonia of the lower extremities, sunset phenomenon of the eye, hyperalertness, insomnia, poor oral intake, and burst suppression EEG and was unresponsive to 100-mg pyridoxine intravenously. The myoclonia resolved, and his EEG improved on oral topiramate, folinic acid (5 mg/day), and pyridoxine (15 mg/kg/day). Insomnia, jitteriness, and myoclonus recurred one week after discontinuation of pyridoxine and folinic acid. No improvement was observed after

reinstitution of folinic acid, but a single, oral dose of pyridoxine 50 mg was followed by a marked decrease in tone, decrease in startle, and absence of myoclonus. ATQ deficiency was confirmed by elevated plasma pipercolic acid levels (14.4  $\mu\text{mol/L}$ , reference = 0.1 to 3.9) and compound heterozygous mutations in *ALDH7A1* (c.248G>A/c.1208C>T; p.G83E/p.P403L). At six months, he exhibited mild motor delay and hypotonia.<sup>14</sup>

*Patient #6: infantile epileptic encephalopathy responsive to pharmacologic monotherapy and cerebral folate deficiency*

This girl developed seizures at age five days of age which were initially responsive to conventional pharmacotherapy. At 12 months of age, she experienced status epilepticus. Seizure control was achieved with levetiracetam. At the age of 11 years, she had intellectual disability and expressive language delay. Her MRI showed left mesial temporal sclerosis, mild periventricular leukomalacia, and bilateral cerebellar volume loss.<sup>8</sup>

Her younger sister, who had a similar presentation of neonatal seizures, was diagnosed with ATQ deficiency (p.G274E/p.S317L) through an epilepsy gene panel<sup>8</sup> (Patient 2) at age 9 months. Elevated plasma  $\alpha$ -AASA confirmed the same diagnosis in this patient. Treatment with pyridoxine 100 mg by mouth three times per day (10 mg/kg/day) was initiated. She was not compliant on lysine-restricted diet. CSF studies obtained while on this regimen showed elevated  $\alpha$ -AASA levels at 0.42  $\mu\text{mol/L}$  (reference range < 0.1) and reduced 5-methyltetrahydrofolate at 29 nmol/L (reference range = 40 to 210). Notably, neither this CSF sample nor the CSF sample investigated nine years earlier for monoamine neurotransmitter metabolites identified peak(s) X, characteristically associated with ATQ deficiency.<sup>13</sup> Conversely, 5-methyltetrahydrofolate was normal (61 nmol/L).

## Discussion

More than 200 patients with genetically confirmed pyridoxine-dependent epilepsy have been described in the literature since the identification of *ALDH7A1* as a causative gene, although many more patients are diagnosed in clinical practice. Our review highlights pyridoxine-dependent epilepsy/ATQ deficiency as an epileptic encephalopathy with a complex clinical and biochemical presentation. Classical symptoms such as intractable neonatal seizures responsive to pyridoxine are well known to neonatologists and neurologists, whereas numerous neuroradiologic, systemic, and biochemical features might provide rise to different differential diagnoses and thus delay the final diagnosis. Mills et al.<sup>11</sup> provide comprehensive data on symptom frequency in patients diagnosed in their institution. Our goal was to provide an overview of the type of symptoms so as to depict the phenotypic spectrum of this rare condition. We were unable to provide reliable information on the true frequency of the various symptoms, reasons for which include the following (1) reporting bias (i.e., not all those diagnosed are reported, often only patients with rare or unusual phenotypes); (2) incomplete data on patient phenotypes in the literature (i.e., not all cases are comprehensively described and some symptoms might not have been reported); and (3) diagnostic bias (i.e., we only screen for this condition in patients with the classic presentation and thus

miss the diagnosis in atypical presentations). The latter may change now that epilepsy gene panels and genome-wide sequencing are frequently ordered in the clinical setting.

Neonatal onset of seizures unresponsive to pharmacologic treatment is the most common denominator for pyridoxine-dependent epilepsy/ATQ deficiency. More specific associations include myoclonia, hyperalertness, sleeplessness, poor feeding, and vomiting. As illustrated by Patient 4, symptoms can mimic substance withdrawal. Because PLP acts as a cofactor for more than 140 enzymatic reactions,<sup>56</sup> its reduced availability explains the numerous metabolic derangements, associated with pyridoxine-dependent epilepsy/ATQ deficiency. Aside from hypoglycemia and lactic acidosis, electrolyte disturbances, coagulopathy, abnormal plasma, and CSF amino acid concentrations have been observed, which clearly assigns pyridoxine-dependent epilepsy/ATQ deficiency to the group of metabolic epileptic encephalopathies.

Seizure types vary as illustrated in Fig 2, and onset beyond the neonatal period is uncommon although does occur exemplified by Patient 3. No literature reports were identified describing patients who developed seizures for the first time at age 12 months or older. Such atypical forms may well have been missed due to testing bias; with the advent of genome-wide sequencing, late-onset patients of ATQ deficiency might well be diagnosed in the future.

ATQ deficiency presents with a variety of neurologic symptoms and neuroimaging abnormalities varying from neonatal intracerebral hemorrhage, congenital hydrocephalus and subependymal cysts, to ventriculomegaly, hydrocephalus, and hypoplasia of the corpus callosum.<sup>12,15–17</sup> In some patients, cerebral heterotopia and cortical malformation may explain the intractable nature of the epilepsy.<sup>11,18</sup> As demonstrated in Patient 2, loss of white matter after an initial insult in the neonatal period may be progressive, to a degree that exceeds the usual evolution of periventricular malacia observed in prematurity/perinatal asphyxia. Behavioral abnormalities become apparent during early childhood only but were included in Fig 1 because these were prominent in patients who were diagnosed later in life, i.e., missed on initial presentation with the classical early-onset seizures.

Furthermore, as exemplified by Patient #1,<sup>12</sup> the diagnosis of ATQ deficiency can be challenged by the many other biochemical/metabolic abnormalities that can be present during the acute phase.

Response to folinic acid and identification of a characteristic yet unidentified metabolite (Peak X) in the CSF, previously led to the assumption that folinic acid-responsive seizures are a separate clinical entity.<sup>13</sup> Only recently has it been shown that folinic acid-responsive seizures and ATQ deficiency are allelic.<sup>14</sup> The results of Patient #6 indicate that the peak(s) observed on monoamine neurotransmitter analysis are not fully sensitive for ATQ deficiency and that  $\alpha$ -AASA in blood, urine, or CSF and/or molecular analysis are essential. The identification of low 5-methyltetrahydrofolate in CSF suggests that this might be assessed in patients with pyridoxine-dependent epilepsy, and supplementation with folinic acid could be considered if the value is low, although clear evidence of benefit for this patient population is currently lacking.

As illustrated by Patient #5 and 14% of patients reported by Mills et al.,<sup>11</sup> not all children respond immediately to

pyridoxine. Thus clinical diagnosis should be focused on biochemical metabolites and not solely on response to pyridoxine, which has incomplete sensitivity and specificity.

In spite of effective treatment of seizures with pyridoxine, approximately 70% of affected individuals with pyridoxine-dependent epilepsy suffer developmental delay/intellectual disability. New treatments targeting the metabolic defect in lysine degradation,<sup>7,8</sup> potentially improve long-term developmental and cognitive outcomes, and the preliminary data are promising. This review of clinical manifestations may help the clinician to identify patients at risk, particularly if they present with atypical/rare manifestations. Collaborative, observational studies are underway with the PDE Patient Registry ([www.pdeonline.org](http://www.pdeonline.org)), an active data collection study, to better understand the clinical spectrum and long-term outcomes associated with the various available treatment modalities.

Overall, pyridoxine-dependent epilepsy due to ATQ deficiency is a treatable cause of epilepsy and intellectual disability.<sup>57</sup> Diagnosis of ATQ deficiency is established by determination of  $\alpha$ -AASA/P6C in blood or urine (see <https://www.genetests.org/> for an overview of clinical laboratories providing this test). Elevation of  $\alpha$ -AASA/P6C persists on treatment with pyridoxine. Thus patients at risk should immediately be treated with pyridoxine orally or intravenously, and diagnostic urine and blood samples can be taken any time after initiation of treatment.<sup>1</sup> Pipecolic acid is another diagnostic marker.<sup>58</sup> However, although analysis of this marker is widely available, its specificity for the diagnosis of ATQ deficiency is limited. Molecular analysis of the ATQ gene (*ALDH7A1*) is performed for diagnostic confirmation. If sequencing does not reveal point mutations, molecular testing for insertions, copy number variants, and intronic variants should be performed.<sup>59</sup> To date, more than 80 mutations have been reported within the 18 exons of *ALDH7A1* on the Human Gene Mutation Database web site. The missense mutation, p.E399Q in exon 14, occurs in various populations and accounts for about 30% of published alleles.<sup>11,23,60</sup> If biochemical/molecular analyses are negative, then other genetic causes of pyridoxine-responsive seizures should be considered, including (but not limited to) pyridoxamine 5'-phosphate oxidase deficiency (MIM# 610090)<sup>61</sup> and hypophosphatasia due to alkaline phosphatase deficiency (MIM #241500).<sup>62</sup>

The wide range of clinical presentations of pyridoxine-dependent epilepsy that hamper diagnostic recognition of this treatable neurometabolic disorder supports further development of a reliable and affordable method of newborn screening (e.g., via determination of  $\alpha$ -AASA/P6C in blood spots<sup>63</sup>), followed by a pilot study to enable timely identification and immediate initiation of treatment to optimize patient outcomes. We propose that all infants presenting with unexplained seizures should be screened for ATQ deficiency by determination of  $\alpha$ -AASA/P6C in urine/plasma and, if abnormal, subsequent *ALDH7A1* molecular analysis (or *vice versa*). A vitamin B6 trial should be provided at a low threshold. Given its amenability to adjunct nutritional therapy and the potential positive impact on seizure control and development, even, when initiated at an older age, this rare metabolic epilepsy could be considered in the older children with intractable seizures as well.

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