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Topical Review

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 α-aminoadipic semialdehyde/pyrroline 6′ carboxylate and pipecolic 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 patient 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 α-aminoadipic semialdehyde/pyrroline 6′ carboxylate (in urine, plasma or cerebrospinal fluid) and *ALDH7A1* molecular analysis.

Keywords: metabolic epilepsy, neonatal encephalopathy, seizures, B6 vitamer, 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.[1,2] Since the 1950s, pyridoxine-dependent epilepsy was diagnosed clinically with vitamin B6 as a diagnostic trial.[3] The reported incidence varies from 1:20,000[4] to 1:276,000[5] and 1:783,000.[3] In 2006 a defect in the lysine degradation pathway (*ALDH7A1* encoding α-aminoadipic semialdehyde dehydrogenase, also known as antiquitin [ATQ]) was identified as the genetic basis of this rare epilepsy.[6] Accumulation of α-aminoadipic semialdehyde (α-AASA)/L-Δ1-piperidine-6 carboxylate (P6C) results in chemical inactivation of pyridoxal phosphate (PLP).[6] These insights unveiled novel diagnostic biomarkers and the lysine degradation pathway as adjunct treatment targets[7-10] (Fig 1). To compile an overview of possible clinical presentations,[11] we performed a literature review to collect data on reported pyridoxine-dependent epilepsy patients. Patient vignettes are presented to illustrate the clinical spectrum of the disorder.

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 patient 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, α-aminoadipic semialdehyde dehydrogenase, ALDH7A1, α-aminoadipic semialdehyde, and α-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[6]; (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 noted the ultra-rare 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.

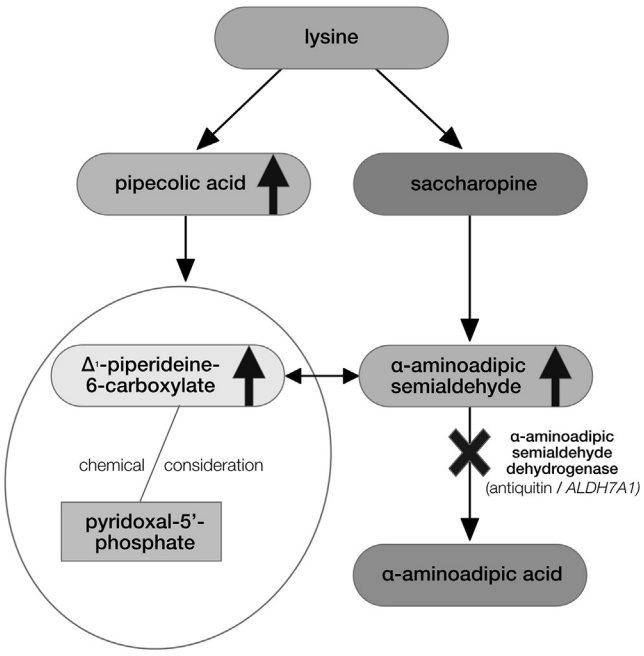

FIGURE 1.
Role of antiquitin (ALDH7A1) in the catabolic pathway of lysine.

Results

Of the 246 articles generated by the PubMed search, 49 met the outlined criteria, including 266 descriptions of patients with confirmed ATQ deficiency.[5,7,8,11-55] 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.[12] 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 pipecolic acid normalizing and α-AASA dropping below the detection limit; at age seven years of age, aside from mild motor delay, she demonstrates normal psychomotor development.[7,8]

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