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Clinical Observations

A Prospective Case Study of the Safety and Efficacy of Lysine-Restricted Diet and Arginine Supplementation Therapy in a Patient With Pyridoxine-Dependent Epilepsy Caused by Mutations in *ALDH7A1*

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ABSTRACT

BACKGROUND: Pyridoxine-dependent epilepsy (PDE) is caused by mutations in *ALDH7A1* (PDE-*ALDH7A1*), which encodes α-aminoadipic semialdehyde dehydrogenase in the lysine catabolic pathway, resulting in accumulation of α-aminoadipic-acid-semialdehyde. **PATIENT DESCRIPTION AND RESULTS:** We present a three-year treatment outcome of a child with PDE-*ALDH7A1* on pyridoxine (started at age three weeks of age), lysine-restricted diet (started at age seven months), and arginine supplementation therapy (started at age 26 months). He had a markedly elevated urinary α-aminoadipic-acid-semialdehyde (39.6 mmol/mol of creatinine; reference range = 0 to 2) and compound heterozygous mutations in *ALDH7A1* (c.446C>A and c.919C>T). He has been seizure free since the age three weeks. He achieved normal cognitive function at age 3.5 years. He exhibited gross motor delay after the age 13 months. Tryptophan supplementation was added for the mild cerebral serotonin deficiency at the thirteenth month of therapy. Arginine supplementation was added to achieve further decrease in the cerebrospinal fluid α-aminoadipic-acid-semialdehyde levels at the 26th month of therapy. His cerebrospinal fluid α-aminoadipic-acid-semialdehyde levels were markedly decreased on this combined therapy. **CONCLUSIONS:** This treatment was well tolerated. Mild cerebral serotonin deficiency was the only biochemical effect with no clinical features. Despite excellent compliance and strict treatment regimen, cerebrospinal fluid α-aminoadipic-acid-semialdehyde levels did not normalize.

Keywords: pyridoxine-dependent epilepsy, lysine-restricted diet, ALDHA71 gene, arginine supplementation

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Introduction

Pyridoxine-dependent epilepsy (PDE) (Online Mendelian Inheritance in Man #266100) was first described in 1954.[1] The underlying genetic defect in *ALDH7A1* (PDE-*ALDH7A1*) was identified in 2006.[2] The *ALDH7A1* encodes α-aminoadipic semialdehyde dehydrogenase (Enzyme Commission 1.2.1.31) in the lysine catabolic pathway.[2] α-aminoadipic semialdehyde dehydrogenase deficiency leads to the

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accumulation of α-aminoadipic-acid-semialdehyde (α-AASA) and piperidine-6-carboxylic-acid (P6C), which is in equilibrium with α-AASA. P6C inactivates pyridoxal-5-phosphate.[2]

Neonatal onset intractable seizures are the classical presentation with a dramatic response to pyridoxine. An initial response to antiepileptic drugs has been also reported.[3] Pyridoxine supplementation alone neither prevents developmental delays nor normalizes the accumulation of α-AASA and pipecolic acid (PA) levels in the central nervous system (CNS).[3,4] The outcome of lysine-restricted diet has been reported in 11 patients with PDE-*ALDH7A1*.[5-7] In one patient, cerebrospinal fluid (CSF) α-AASA was decreased 82%, and CSF PA was decreased 87%. Developmental milestones were improved in four of five patients, and seizures were stabilized or improved in six of seven patients reported in 2012.[5] Successful outcome of short-term arginine supplementation monotherapy (competitive inhibition of lysine and ornithine transport into CNS[8]) was reported in a single patient with PDE-*ALDH7A1* as an alternative therapy to the lysine-restricted diet.[9] Triple therapy with pyridoxine, arginine supplementation, and dietary lysine restriction was given to six patients with PDE-*ALDH7A1* with improvements in seizure control and neurodevelopmental outcomes.[7]

We describe a three-year clinical, neurodevelopmental, and biochemical treatment outcome of a child with PDE-*ALDH7A1* on a lysine-restricted diet and arginine supplementation therapy in addition to pyridoxine as a prospective case study and a stepwise treatment approach. A one-year treatment outcome of this patient on lysine-restricted diet was reported previously as a prospective case study.[6]

Patient and Methods

This 44-month-old boy presented with neonatal-onset intractable epilepsy and was diagnosed with PDE-*ALDH7A1* at three months of age based on his markedly elevated urinary α-AASA (39.6 mmol/mol of creatinine; reference range = 0.0 to 2) and plasma PA (31.2 μmol/L; reference range = 0.1 to 5.3 μmol/L). Compound heterozygous mutations in *ALDH7A1* (c.446C>A; p.Ala149Glu and c.919C>T; p.Arg307X) confirmed the diagnosis.[6] For the clinical, biochemical, and molecular genetic features reported previously, please refer to both references for details.[6,10]

He continued the same dose of pyridoxine (200 mg/day; started with 44 mg/kg/day with the current dose of 13 mg/kg/day) throughout therapy. The lysine-restricted diet was started at age seven months, and a one-year treatment outcome was reported previously.[6] PDE Consortium Consensus Recommendations were employed as guidelines[5,10] but modified according to the patient's tolerance to the medical formula in order to prevent diet-related complications such as growth failure.

TABLE 1.
Growth Parameters, Total and Natural Protein Intake, and lysine and Tryptophan Intake Throughout the Treatment

Treatment Duration (Age of Treatment)	Weight/Length–Height Percentiles	Total Protein*/Natural Protein Intakes g/kg/day	Lysine/Tryptophan† Intakes mg/kg/day (Tryptophan Supplementation)	PDE Consortium Consensus Recommendations for Lysine Restriction According to Age[10]
Baseline (7 mo; pyridoxine monotherapy)	10th/20th	1.53/1.3	81/23	55-70 mg/kg/day
Third month of therapy (10 mo; pyridoxine and lysine-restricted diet)	<3rd/15th	1.7/1.44	109/NA	55-70 mg/kg/day
Sixth month of therapy (13 mo; pyridoxine and lysine-restricted diet)	6th/32nd	1.6/1.34	94/NA	50-80 mg/kg/day
Ninth month of therapy (16 mo; pyridoxine and lysine-restricted diet)	18th/55th	1.76/1.56	102/NA	50-80 mg/kg/day
12th month of therapy (19 mo; pyridoxine and lysine-restricted diet)	40th/75th	1.7/1.35	93/NA	50-80 mg/kg/day
15th month of therapy (22 mo; pyridoxine and lysine-restricted diet)	40th/55th	1.9/1.4	82/17 (+21)‡	50-80 mg/kg/day
17th month of therapy (24 mo; pyridoxine and lysine-restricted diet)	32nd/50th	1.77/1.3	68/16 (+21)‡	50-80 mg/kg/day
21st month of therapy (28 mo; pyridoxine and lysine-restricted diet)	20th/40th	1.9/1.4	61.5/15 (+21)‡	50-80 mg/kg/day
25th month of therapy (32 mo; pyridoxine and lysine-restricted diet)	50th/32nd	1.66/1.12	48.5/12 (+18)‡	50-80 mg/kg/day
28th month of therapy (35 mo; pyridoxine, lysine-restricted diet and arginine)	65th/45th	1.4/0.9	39/NA (+16)‡	50-80 mg/kg/day
34th month of therapy (41 mo; pyridoxine, lysine-restricted diet and arginine)	50th/50th	1.68/1.2	50/14 (+16)‡	50-80 mg/kg/day

Abbreviations:
NA = Not available
PDE = Pyridoxine-dependent epilepsy

* Total protein intake (g/kg) recommendations according to age from the 2014 PDE Consortium Consensus Recommendations: 1-6 months 2.75-3.5 g/kg/day; <1 year of age 2.5-3.25 g/kg/day; and 1 to <4 years of age 1.8-2.6 g/kg/day.

† Tryptophan requirements (mg/kg) for the general population, from a publication in the British Journal of Nutrition (2012): <1 year 9 mg/kg/day; 1-3 years 6 mg/kg/day; and >3 years 5 mg/kg/day.

‡ Tryptophan supplementation was added.