Pyridoxine Dependent Epilepsy with ALDH7A1 Mutation: Clinical Spectrum and Outcome in A Multicenter Study Cohort From Turkey

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INTRODUCTION

Pyridoxine-dependent epilepsy which is caused by homozygous or compounds heterozygous mutation in the ALDH7A1 (PDE-ALDH7A1) gene is a rare condition with a frequency of 1/100000-1/700000 characterized by seizures that started in intrauterine life, in infancy or early childhood. Early diagnosis of PDE and treatment with appropriate dosage of pyridoxine is important not only to control of the seizures but also improve the prognosis of long-term outcomes including behavioral and cognitive impairments.

OBJECTIVES

The purpose of the study is to describe the clinical characteristics of Turkish children with PDE-*ALDH7A1* as well as possible genotype–phenotype correlation.

MATERIALS & METHODS

The study design was a multicentric, retrospective data-recording research. Demographic, clinical, and genetics data of 41 patients with PDE-*ALDH7A1* obtained from 15 Pediatric Neurology Centers in Turkey.

RESULTS

The demographic, clinical and laboratory findings of the patients are given on Table 1. The median age at the onset of first seizure was the 4th day of life and the range is from birth to 15 months. The time from seizure onset to first pyridoxine administration ranged from first seizure to 24 months. Different types of seizures were observed and focal motor and myoclonic seizures were dominant. The pyridoxine dosage that succeeded in seizure control was changed from 50 to 250 mg, and intravenous administration could make only in 7 patients. Four patients needed to repeat the dose of pyridoxin for seizure control.

24 of 41 patients were diagnosed with a single gene study for ALD7A1. Homozygous mutations were detected in 37 patients. 19 different ALDH7A1 variants which four were novel were identified. 23 of 41 patients had homozygous c.1597_1597delG mutation in ALDH7A1gene (Table 2).

Table 1. The demographic, clinic and laboratory features of the patients

Features of 41 patient		Values
Gender		18 female/23 male
Birth weight(gr), mean ±STD (min-max)		3181±407(2300-4000)
Gestational age(week), mean ±STD (min-max)		38±2.12(32-40)
Positive consanguinity history, n (%)		22 (53.6)
Family history of neurological disease/seizure		18(43)
Seizure onset age,median (min-max)		4 days (at birth- 15 months)
Seizure onset day, n (%)	0-7 day	34(82)
	8-29 days	4
	1-6 months	1
	≥6 months	2
Seizure onset age, median (min-max)		4 days (at birth- 15 months)
The first administration time of pyridoxine from the seizure, median (min-max)		24 day(at onset-24 months)
Age at the genetic diagnosis, median (min-max)		25.3 months (15 day-156 months)
Seizure type at onset, n		Focal motor :25, generalized :7, IS:3,dialeptic:1, unknown:5
EEG features before the B6 treatment, n		Abnormal :26 (focal: 12, Multifocal:7, BS:5, hypsarrhythmia: 2), normal :6, unknown/absent: 9
EEG features after the B6 treatment		Abnormal:28 , normal :13
Brain MRI, n		Abnormal:21, normal :20

n: Number of patiens, IS:Infantile spasm, BS : Burst-supresion

Table 2. The features of ALDH7A1 mutations

Number of the patients	Mutations	Mutation type/ Mutation effects	Known /Novel
23	c.1597delG (p.Ala533ProfsTer18)	H,F	K
1	c.1279G>C (p.Glu427Gln)	H,M	K
1	c.1384delG(p.Ala490LeufsTer28)	H,F	K
1	c.1072C>T(p.Arg358Ter)	H,S	K
1	c.781 A>G (p.Met261Val)	H,M	K
1	IVS16+5G>A (c.1489+5G>A)	H,IV	K
1	c.1292C>T (p.Ala431Val)	H,M	K
1	c.1292C>T (p.Pro431Leu)	H,M	K
1	c.328C>T (p.Arg110Ter)	H,S	K
1	c.1556G>A (p.Arg519Lys)	H,M	K
1	c.1232C>T (p.Pro411Leu)	H,M	K
1	c.297del (p.Trp99Ter) / c.1292C>T (p.Pro431Leu)	CH,F/del	K
1	p.Arg110Ter (c.328C>T)/ IVS17-1G>T(c.1566-1G>T)	CH,S/I	K/K
1	c.328C>T (p. Arg110Ter)/ IVS17-1G>T(c.1566-1G>T)	CH,S/I	K/K
1	c.296G>A(p.Trp99Ter)/ c.1292C>T (p.Pro431Leu)	CH,S/M	K/K
1	c.656C>G (p.Gly219Ala)/ c.1519G>C(p.Glu507Gln)	CH,M	K/**N**
1	c.588C>A (p.Phe196Leu)	H,M	**N**
1	c.1427C>T (p.Ser476Leu)	H,M	**N**
1	c.1427C>T (p.Ser476Leu)	H,M	**N**

H: Homozygous, CH: Compound heterozygous, F: Frameshift, M: Missense, IV:Intronic Variant, S:Stop kodon; K: Known, N: Novel

The follow-up time changed from 15 to 221 months (mean: 84,73 ± 61,25 months). Twenty of the 41 patients (54%) were seizure-free after only pyridoxine or pyridoxal phosphate treatment. However 18 (44%) patients continued to take additional antiepileptic treatment and eight of them continued to have EEG abnormality. Two patients were on a lysine restricted diet as an adjunctive therapy. The pyridoxine therapy was disrupted at least once in 19 patients and all of them had seizure recurrence. Mild to moderate psychomotor retardation was detected in 25(60%) of the cases. The patient, who was followed up with the diagnosis of refractory epilepsy in the neonatal period, died at the age of 6 months, despite the addition of appropriate dosage of pyridoxine when she presented with resistant status epilepticus. A homozygous c.1292C>T p.(Pro431Leu) variant on ALDH7A1gene was detected in this patient.

DISCUSSION

Pyridoxine dependent epilepsy was first recognized in the 1950s and pathogenic variants within the ALDH7A1 gene have been identified to cause PDE in 2011. The number of cases with PDE-ALDH7A1 reported from different ethnicity is less than one hundred until now. We present 41 children with PDE-ALDH7A1 from Turkey. To best of the our knowledge, this is the largest study about patients with PDE-ALDH7A1 reported from a single country. It can be thought that PDE-ALDH7A1 is more common than expected in countries where consanguineous marriages are common like our country.

PDE patients treated with pyridoxine generally have complete resolution of clinical seizures, however, in some patients, PDE may be associated with intellectual disability. The cognitive and behavioral prognosis of PDE patients is multifactorial which includes the lag time from clinical seizure onset until treatment, with pyridoxine, ALDH7A1 genotype, and associated central nervous system structural abnormalities. Cognitive impairment was detected in 60 % of the our cases, and one of our patients who had c.1292C>T p.(Pro431Leu) variant possibly died due to delay in diagnosis or related with variant type. In our study, most of the patients(82%) had seizure onset in the first week of their life, however, the age at the genetic diagnosis changed from 15 days to 156 months (median:25.3 months).

CONCLUSIONS

The present multicentric study is the first study of Turkish children with PDE-ALDH7A1 with a large sample and detailed clinical information. The most common ALDH7A1 mutation in Turkey was found to be homozygous c.1597_1597delG. The present study supports the literature that Turkish children with ALDH7A1 pathogenic variants usually had classical phenotypes. However, it is difficult to know whether this is because PDE-ALDH7A1 is considered more frequently in neonatal seizures or because the atypical form is less common. Every clinician should be aware of the significant phenotypic heterogeneity in this disease.