Brain & Development 37 (2015) 442–445

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Case Report

Seizure recurrence following pyridoxine withdrawal in a patient with pyridoxine-dependent epilepsy

Moe Tamaura [a], Hiroko Shimbo [a], Mizue Iai [a], Sumimasa Yamashita [a], Hitoshi Osaka [a,b,*]

[a] *Division of Neurology, Kanagawa Children's Medical Center, Yokohama, Japan*
[b] *Department of Pediatrics, Jichi Medical School, Shimotsuke, Tochigi, Japan*

Received 8 March 2014; received in revised form 11 July 2014; accepted 19 July 2014

Abstract

Pyridoxine-dependent epilepsy (PDE) is an autosomal recessive disorder characterized by early onset and recurrent seizures that can be controlled by a high dose of pyridoxine. PDE is caused by mutations in *ALDH7A1*, which encodes antiquitin. Antiquitin converts α-aminoadipic semialdehyde to α-aminoadipic acid. Seizure recurrence after pyridoxine withdrawal is a criterion for diagnosis, but PDE can be diagnosed conclusively by genetic testing for mutations in the *ALDH7A1* gene. In this case study, we report the long-term follow-up of a patient suspected with PDE. She experienced prolonged generalized tonic seizures and was hospitalized in an intensive care unit following pyridoxine withdrawal. Later, we identified a compound heterozygous mutation, c.1216G>A, p.Gly406Arg, and a novel splice donor site mutation, IVS9+5G>A. Confirmation of these mutations would have prevented an unsafe withdrawal test. This case suggests the importance of the genetic determination of PDE to avoid the diagnostic withdrawal of pyridoxine.

Keywords: Pyridoxine-dependent epilepsy; Pyridoxine; *ALDH7A1* gene

1. Introduction

Pyridoxine-dependent epilepsy (PDE; OMIM 266100) is an autosomal recessive disorder characterized by recurrent seizures in the neonatal or early infantile period [1]. Patients with PDE cannot be controlled with conventional anticonvulsants; instead, they respond clinically and electroencephalographically to high doses of pyridoxine [2]. PDE is caused by the deficient enzymatic activity of α-aminoadipic semialdehyde dehydrogenase (antiquitin), which is encoded by the *ALDH7A1* [3], with the accumulation of α-aminoadipic semialdehyde (α-AASA) and Δ^1-piperideine 6-carboxylate (P6C; Supplemental Fig. 1). Approximately 90 mutations of the *ALDH7A1* gene have been reported (Human Gene Mutation Database (HGMD) Professional release 2013.12), most of which are missense, nonsense, and splice site mutations, and 5 patients have been diagnosed in Japan [4]. PDE can be diagnosed conclusively by molecular genetic testing of the *ALDH7A1* gene; however, the diagnosis of PDE can also be established by a good response to pyridoxine and seizure recurrence after pyridoxine withdrawal [5].

Here, we report the long-term follow-up of an individual with PDE. She experienced prolonged

* Corresponding author at: Department of Pediatrics, Jichi Medical School, 3311-1 Yakushiji, Shimotsuke-shi, Tochigi 329-0498, Japan. Tel.: +81 285 58 7366; fax: +81 285 44 6123.
E-mail address: hosaka@jichi.ac.jp (H. Osaka).

http://dx.doi.org/10.1016/j.braindev.2014.07.008
0387-7604/

generalized tonic seizures that recurred following pyridoxine withdrawal, implying the importance of the genetic confirmation of PDE.

2. Case report

The patient was a 23-year-old female born at term to healthy non-consanguineous Japanese parents. She was born at 41 weeks gestation, with Apgar scores of 5 and 9 at 1 and 5 min, respectively. At birth, her body weight was 2600 g. Limb clonic seizures occurred at 5 h after birth. Laboratory data, including plasma ammonia and amino acids, were all normal. Electroencephalographic recordings (EEGs) showed a burst-suppression pattern. Cerebral ultrasound and brain imaging by computed tomography were unremarkable. She was treated unsuccessfully with phenobarbital, valproic acid (VPA), and phenytoin, and required mechanical ventilation. At day 24 after birth, an intravenous injection of pyridoxine (70 mg) stopped the seizures and normalized the EEGs (Fig. 1A and B). We diagnosed her as PDE from the clinical course and started with oral pyridoxine of 10 mg/kg daily in two divided doses.

The patient displayed developmental delay with rolling over at 8 months of age and walking at 16 months. At 21 months of age, she started to show complex partial seizures, especially in association with febrile events. VPA, carbamazepine, and zonisamide were started, in addition to pyridoxine. A neuropsychological evaluation at 5 years of age revealed mental retardation with an IQ of 55 with Tanaka-Binet Intelligence Scale. She has not had a seizure since 6 years of age with VPA and pyridoxine treatment.

At 16 years of age, when she was living outside of Japan, VPA was reduced to 100 mg/day without seizures. Pyridoxine was discontinued, and generalized tonic-clonic seizures occurred at 1 month after cessation. She was hospitalized to an intensive care unit and intravenous diazepam and phenytoin were used to terminate status convultics. Pyridoxine and VPA were restarted. Currently, she is 23 years old and seizure-free with 480 mg/day pyridoxine and 800 mg/day VPA.

3. Materials and methods

Genomic DNA was extracted from peripheral white blood cells using a QuickGene DNA Whole Blood Kit S (Fujifilm, Tokyo, Japan) according to the manufacturer's instructions. PCR of all exons and exon–intron boundaries of the *ALDH7A1* gene was performed with specific primers using an Ex Taq PCR Version 1.0 Kit (Takara, Shiga, Japan) according to the manufacturer's instructions (Supplemental Table 1). Total RNA was extracted from leukocytes using the ISOGEN reagent

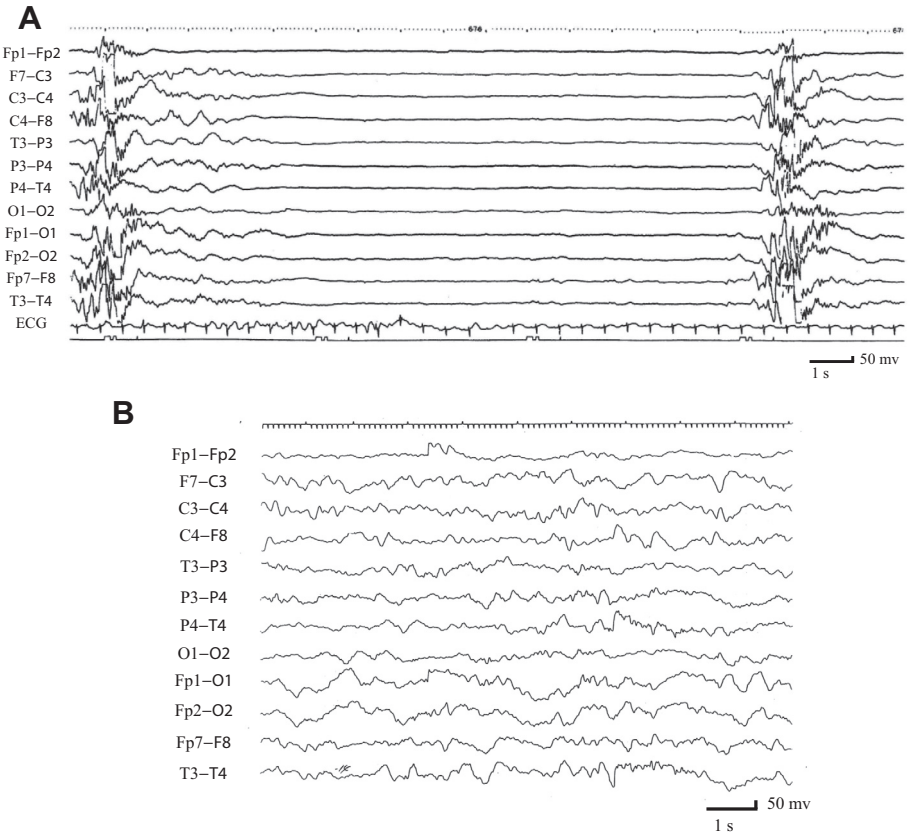

Fig. 1. EEGs of the patient before (A) and after intravenous pyridoxine injection, showing rapid EEG normalization (B).