A Patient with Pyridoxine-Dependent Epilepsy Who Was Treated with Triple Therapy

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Pyridoxine-dependent epilepsy (PDE) is a type of developmental and epileptic encephalopathy manifesting as seizures that are resistant to anti-seizure medication (ASM) but responsive to pharmacologic doses of pyridoxine [1]. PDE caused by bi-allelic mutations in the aldehyde dehydrogenase 7 family member A1 (ALDH7A1) gene on chromosome 5q32.2 is designated PDE-ALDH7A1 [1,2]. Mutations at this locus are associated with decreased activity of α-aminoadipic semialdehyde (α-AASA) dehydrogenase in lysine metabolism [3]. PDE-ALDH7A1 is a rare disease with an estimated incidence of 1:65,000 to 1:250,000 live births [2]. Refractory neonatal seizures are the most common presentation; however, 25% to 30% of patients were found to present with seizures outside of the neonatal period, and varying intellectual disabilities and developmental delays were found in 75% of patients [4].

We report the case of a 9-year-old boy with intractable seizures related to homozygous ALDH7A1 mutations, who improved after triple therapy. The patient had neonatal seizures on his 12th day of life. He was started on multiple ASMs, including phenobarbital, phenytoin, levetiracetam, topiramate, vigabatrin, and clonazepam; however, his seizures and the related epileptiform discharges on electroencephalography (EEG) persisted. He received empiric high-dose vitamin therapy, which included pyridoxine, inconsistently. For the next 7 years, he was admitted repeatedly for recurrent status epilepticus whenever his medications were discontinued.

When the patient was 7 years old, his father stopped giving him the prescribed vigabatrin and pyridoxine. Ten days after therapy interruption, he was admitted to the intensive care unit (ICU) for seizures, vomiting, and poor general condition. Doctors resumed vigabatrin and pyridoxine. However, the recurrence of vomiting prevented oral intake of these medications, and he had seizures again. He was readmitted to the ICU and was administered pyridoxine at 50 mg/day (2 mg/kg body weight), after which the seizures stopped.

Prompted by this clinical information, whole-exome sequencing was performed in the proband, mother, and father for an accurate diagnosis. Compound heterozygous mutations were identified in the ALDH7A1 genes: NM_001182.4:c.210C > A (p.Cys70Ter) and c.871+5G > A. The variants confirmed by Sanger sequencing were classified as pathogenic according to the guidelines of the American College of Medical Genetics and Genomics [5]. A segregation study showed both parents as carriers of the variants (Fig. 1). We diagnosed the patient with PDE and increased the pyridoxine dose to 300 mg/day (10 mg/kg). Since pyridoxine supplementation, he became sei-
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Fig. 1. Findings of genetic testing of the patient. The patient and his relatives underwent genetic testing. Both copies of the patient’s aldehyde dehydrogenase 7 family member A1 (ALDH7A1) gene had mutations, albeit different ones. Each of these mutations was found in his father and mother, who were asymptomatic carriers. A deceased elder brother presented similarly and is assumed to have had the mutations. An elder sister showed no clinical or genetic evidence of the disease.

Não há padrões específicos de convulsão ou EEG com esse desencadeador [6]; portanto, PDE precisa ser testada em qualquer caso de epilepsia com etiologia desconhecida [2]. Testes bioquímicos adicionais para a-aASA e Δ1-piperideine-6-carboxilato em sérum, urina, e líquido cefalorraquidiano devem ser realizados quando uma única variante patogênica ou uma variante de significância incerta é identificada em testes genéticos [1,2].

Triple therapy consists of pyridoxine and arginine supplementation, as well as lysine restriction, and is effective in PDE-ALDH7A1 [7]. PDE-ALDH7A1 should be treated with pyridoxine supplementation of 100 mg/day in newborns, 30 mg/kg/day (maximum of 300 mg/day) in infants, and 5 to 30 mg/kg/day (maximum of 500 mg/day) in children and adolescents [2]. All patients on pyridoxine supplementation must undergo clinical screening for peripheral neuropathy (PN) [2]. Initially, only patients treated with > 500 mg/day of pyridoxine were considered at risk for PN [8]. However, Ghavanini and Kimpinski [9] suggested that even pyridoxine doses as low as 50 mg/day, if used for greater than 6 months, may increase the risk of neuropathy. Lysine reduction therapies have been associated with improved long-term neurologic outcomes [2]. The use of a lysine-free formula with amino acid supplementation permits the limitation of lysine intake while ensuring adequate intake of the other amino acids [10]. Lysine is an essential amino acid and over-restriction of lysine could lead to malnutrition [8]. Thus, patients on a lysine-restricted diet should have plasma amino acids measured at least every 3 (< 3 years of age) to 6 months (> 3 years of age) [2]. Pharmacologic doses of arginine compete with lysine for intestinal absorption, transport across the blood-brain barrier, and entry into the mitochondria [2].

In summary, we report the case of a boy with intractable seizures and sepsis (Fig. 1). This boy first had seizures at 2 months of age and was treated with ASMs and pyridoxine at 12.5 mg/day. When he was 7 years old, he was unable to take oral medications and supplements due to vomiting, and he eventually died. He did not undergo next-generation sequencing, but he is presumed to have had the ALDH7A1 mutations. Because the discontinuation of pyridoxine coincided with that of the ASMs, physicians failed to relate the seizures with the withdrawal of pyridoxine.

This study was approved by the Institutional Review Board of the Gangnam Severance Hospital, Yonsei University College of Medicine (3-2017-0168). The requirement for informed consent for this retrospective study was waived by the board.
Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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