Late Diagnosis of Pyridoxine-Dependent Epilepsy in Two Adolescent Siblings

Pyridoxine-dependent epilepsy (PDE) is a rare autosomal recessive disorder that typically presents with intractable seizures in the neonatal period that are unresponsive to conventional anti-epileptic treatments.[1] It is caused by a deficiency of aldehyde dehydrogenase 7 family member A1 (*ALDH7A1*) and generally affects neonates or infants.[2] A wide range of mutations has been described in patients with PDE.[3] Herein, we will describe two siblings, who were diagnosed with PDE in adolescence. We believe that this is an interesting condition, emphasizing that PDE should also be kept in mind in older children.

A 13-year-old girl was diagnosed with epilepsy about 3 years ago. She was also having a mild intellectual disability. Her physical and neurological examinations and routine laboratory tests were unremarkable. She had episodes of focal seizures and was treated with carbamazepine, levetiracetam, lamotrigine, and topiramate. She was never treated with pyridoxine. Routine electroencephalography (EEG) showed generalized epileptic activity [Figure 1]. Brain magnetic resonance imaging (MRI) was also normal.

Her 14-year-old brother was also being followed by pediatric neurology division with seizures. His seizures had started at the age of 12 years. He was unresponsive to carbamazepine, levetiracetam and, clobazam and still having seizures. A mild intellectual disability was also determined during his physical examination but all other findings were normal. Laboratory tests and brain MRI were also normal. EEG showed epileptic activity on the bitemporo-occipital regions. Their parents were first-degree relatives (cousins). After obtaining informed parental consent, an epilepsy gene panel was sent for sequencing and deletion, and duplication analysis of 70 genes. Both patients' gene analysis revealed a homozygous missense mutation in the *ALDH7A1* gene causing (NM_001182: c.A571G; p.I191V) amino acid change. After initiation of high dose oral vitamin B6 (15 mg/kg/day) treatment, seizures stopped in both siblings. In their first-year follow-up, they did not have any seizures without any anti-epileptic treatments. After the treatment, the patients' findings completely improved [Figure 2]. Psychomotor evaluation with the Standford-Binet test showed a full-scale IQ of 65 points. Both were in the range of mild intellectual disability.

In this paper, we reported two siblings diagnosed with PDE in their teenage years. PDE is a rare disorder but generally affects infants or young children. In that point, our cases are interesting that this rare disease was diagnosed in their adolescence and they did not have any seizures before. Due to the mutations in the ALDH7A1 gene, a deficiency in the α-amino adipic semialdehyde dehydrogenase enzyme takes place; causing accumulation of α-amino adipic semialdehyde piperideine-6-carboxylate, and pipecolic acid.[4] These accumulated products inactivate pyridoxal phosphate which is an important cofactor for many enzymes in the brain.[5] For that reason, daily vitamin B6 administration can overcome cofactor deficiency and prevent seizures.

In general, PDE is diagnosed in the neonatal period or rarely in infancy. Recently, Srinivasaraghavan *et al*.[6] reported a juvenile-onset PDE in a 17-year-old Indian female who was having the most prevalent *ALDH7A1* missense mutation in exon 1. She was also completely seizure-free with pyridoxine treatment. We believe both of these mutations are causing hypomorphic alleles, thus making the phenotype less severe. Although PDE is a treatable disease, the patients are highly prone to misdiagnoses or delayed diagnosis owing to the rarity of the disease. Clinical suspicion is highly important for prompt diagnosis. In general, the outcome of patients with PDE is defined as poor.[7] Even if there is not large case series, late-onset was suggested as a predictor of a favorable outcome.[8] In this report, also two siblings had favorable outcomes with vitamin B6 treatment. This condition may be associated with different presentations of different genotypes of the disease.

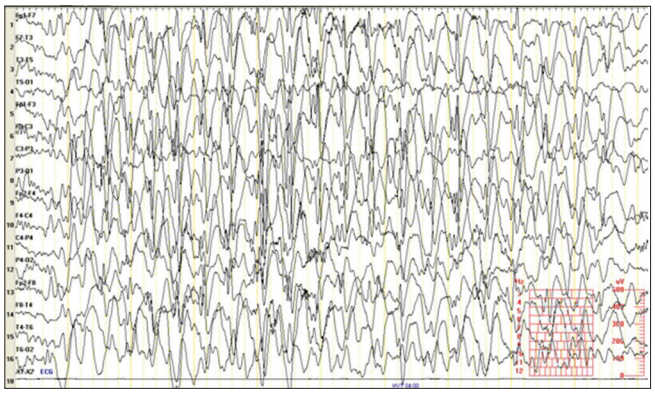

Figure 1: Interictal EEG revealed generalized spike and slow-wave activity, occurring intermittently in wakefulness

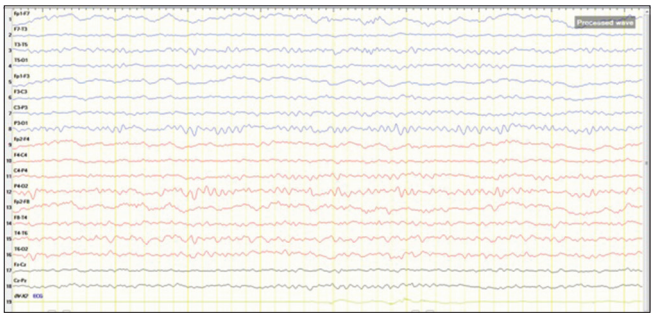

Figure 2: Post-treatment index patient's interictal electroencephalogram was normal

In conclusion, although PDE is a rare genetic disorder mainly affecting neonates or infants, it also should be kept in mind in the differential diagnosis of patients with seizures resistant to conventional treatments. PDE in adolescents should be suspected when there is mild intellectual disability, refractory epilepsy, and consanguinity. Further studies are mandatory to standardize diagnostic and therapeutic protocols for PDE and to determine short- and long-term outcomes of patients.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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