Case Report

Treatable Cause of Refractory Seizures in an Infant with a Novel Mutation

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Pyridoxine-dependent epilepsy is a treatable cause of epilepsy, which is very well known. It is most commonly caused by mutations in ALDH7A1 and PNPO genes. A 5-month-old infant presented with refractory seizures. Magnetic resonance imaging (MRI) brain was normal. Clinical exome sequencing showed a novel mutation in PROSC gene. He responded very well to pyridoxine and has been seizure free since the beginning of the treatment. PROSC gene mutations have been recently described as a cause for pyridoxine-dependent epilepsy. Here, we describe a first case report of PROSC mutation from India with a rare genetic variant presenting as pyridoxine-dependent epilepsy.

**Keywords:** PROSC, pyridoxine-dependent epilepsy, refractory epilepsy

**INTRODUCTION**

Pyridoxine deficiency is a well-known cause of treatable metabolic epilepsy.[1] Treatment is with either pyridoxine and/or pyridoxal 5'-phosphate (PLP). Most common mutations that are found to be related with B6-dependent epilepsies are ALDH7A1 and PNPO.[2,3] PROSC mutations were recently found to have an association with pyridoxine-dependent epilepsy.[4] We hereby report a case of pyridoxine-dependent epilepsy with a homozygous variant in exon 1 of PROSC gene with a complete response to oral pyridoxine.

**CASE DESCRIPTION**

A 5-month-old male infant first born to a third-degree consanguineous parentage, developmentally appropriate for age, presented to our hospital with refractory seizures. Child was delivered by a spontaneous vaginal delivery and cried at birth. Child was apparently asymptomatic till 40 days of life after which he had three episodes of generalized seizures, each lasting for less than 1 min. Child was admitted in a tertiary care hospital, treated with intravenous phenobarbitone, and discharged on oral phenobarbitone. Despite good drug compliance, child had another episode of seizures per day. Capillary blood glucose and serum electrolytes were normal. Serum calcium was 9.1 mg/dL and serum magnesium was 2.2 mEq/L. Magnetic resonance imaging (MRI) brain was normal. Electroencephalogram (EEG) showed generalized epileptiform activity with intermittent burst suppression pattern. The doses of phenytoin and phenobarbitone were increased to the maximum dosage permitted in children. Child was also loaded with levetiracetam and sodium valproate. However, he continued to have seizures.

Metabolic causes of seizures were considered. Preliminary metabolic workup was done. Blood glucose was 98 mg/dL, pH was 7.34, arterial lactate was 0.8 mmol/L, serum ammonia was 40 mcg/dL, and urine ketones were negative. In view of refractory seizures with normal MRI brain, child was started on oral pyridoxine hydrochloride. Child has been completely seizure free since then. Oral phenobarbitone was tapered and stopped 1 month later. Due to unaffordability of the family, extended metabolic evaluation could not be done. Clinical exome sequencing

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was done which showed a PROSC gene mutation with a rare variant c.38T>A (p.Val13Asp). This novel variant has been validated by Sanger sequencing. This variant has not been reported in the literature till now. The last follow-up was at 1 year of age. The child was developmentally normal and seizure free.

**DISCUSSION**

PLP, the active form of vitamin B6, functions as a cofactor in humans for more than 100 enzymes, many of which are involved in neurotransmitter synthesis and degradation. A deficiency of PLP can present, therefore, as seizures and other symptoms that are treatable with PLP and/or pyridoxine.[3] Pyridoxine-dependent epilepsy is most often caused due to mutation in PNPO and ALDH7A1 genes. PROSC mutations were recently found to be a cause of vitamin B6-dependent epilepsy. PROSC encodes for PLP-binding protein, which is important for maintaining the intracellular homeostasis of free PLP. Pyridoxal enters the cell and is phosphorylated by pyridoxal kinase. PLP is transferred to the binding site within the barrel of PROSC thereby maintaining low levels of low free PLP in the cell. PROSC then presents the PLP required by B6-dependent apoenzymes. When PROSC is dysfunctional, it cannot protect PLP resulting in PLP being dephosphorylated by cellular phosphatases. Although the levels of free PLP in the cells are high, the levels available for B6-dependent apoenzymes are not sufficient, resulting in a state of neurotransmitter imbalance leading to seizures.[4]

In a study by Darin et al.[4] sequencing of PROSC in a cohort of 29 children with B6-responsive epilepsy (for whom ALDH7A1 and PNPO mutations had been excluded via genetic and/or biochemical evidence) identified potential pathogenic variants in four subjects. The mutations in PROSC in the children with B6-dependent epilepsy include nonsense, missense, and splice-site mutations. In a case series by Plecko et al.[6] four unrelated patients were identified with mutations in PROSC gene. They found a total of six different mutations, including four novel disease mutations. Of the four patients, one responded well to pyridoxine monotherapy, whereas the others required additional anti-epileptics. The variant found in our study has not been reported in literature before. It is a homozygous missense variation in exon 1 of the PROSC gene that results in the amino acid substitution of Aspartic acid for Valine at codon 13. This is the first report of PROSC mutation causing pyridoxine-dependent epilepsy from India. This case report adds to the existing literature about the novel genes causing pyridoxine-dependent seizures other than ALDH7A1 and PNPO.

**Informed Consent**

Written informed consent was obtained from the parents for publishing the case report along with genetics.

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**Conflicts of interest**

There are no conflicts of interest.

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