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Case Report

A treatable early onset epileptic encephalopathy: pyridoxamine 5'-phosphate oxidase deficiency

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ABSTRACT

Pyridox (am) ine 5'-phosphate oxidase (PNPO) deficiency is a rare epileptic encephalopathy condition due to mutations in PNPO gene. It is one of treatable metabolic epilepsies. It is unresponsive to antiseizure medications, but respond to pyridoxal-5-phosphate (PLP), active form of vitamin B6. It is characterized by refractory seizures from newborn or in utero, developmental delay. Based on refractory seizures, age of onset, negative biochemical profile and response to PLP, suspect PNPO deficiency. Next generation sequencing will help in the diagnosis. Early diagnosis and early initiation of PLP will help to cessation of seizures and better neurological outcome. Here we present a case of PNPO deficiency, which is diagnosed early and noticed good response with PLP.

Keywords: PNPO deficiency, Epileptic encephalopathy, Pyridoxine, Vitamin responsive epilepsy

INTRODUCTION

Although inborn errors of metabolism (IEM) are an uncommon cause of epilepsy, individuals who have IEM regularly experience seizures and epilepsy. These epilepsies are characterized by co-morbid developmental delay/regression, intellectual disability, and behavioral abnormalities. They can manifest at any stage of life and share the trait of being resistant to anti-epileptic medications. Since some of these conditions respond well to particular treatment approaches, prompt and accurate diagnosis is essential to achieving better results.[1] Pyridox (am) ine 5'-phosphate oxidase (PNPO) deficiency is an inborn error of vitamin B6 metabolism, which causes an epileptic encephalopathy responsive to pyridoxal-5-phosphate (PLP). This deficiency is caused by mutations in the PNPO gene encoding this enzyme. PNPO deficiency causes severe epileptic encephalopathy.[2] Early diagnosis and treatment improve the prognosis and quality of life of patients. Here, we report a child with PNPO deficiency which was recognized early and had good response with PLP.

CASE REPORT

A 6 months old female child, 2nd child of consanguineous parents, delivered by normal vaginal delivery. Child had mild developmental delay. Child had recurrent febrile and afebrile seizures within four months, even with three antiepileptic medications. Elder sibling had epilepsy since 5 months of age with severe developmental delay. Magnetic resonance imaging (MRI) brain and metabolic screening were normal and no definitive diagnosis was not identified in sibling. This sibling died at the age of two years with status epilepticus and pneumonia. On examination, no dysmorphic features, mild hypotonia with normal head circumference. Based on early onset epilepsy, family history, early onset infantile epilepsy with genetic etiology was considered. Serum electrolytes, calcium, magnesium, blood glucose, tandem mass spectroscopy, lactate, serum biotinidase were normal. Electroencephalogram (EEG) showed no abnormality. MRI brain was normal. Child was suspected to have familial febrile seizures or developmental epileptic encephalopathy. DNA analysis with next-generation

sequencing showed a novel missense mutation of variant c.413G>A, p.Arg138His in exon 4 of the PNPO gene in a homozygous state, which is constant with PNPO deficiency. Child was started on PLP 200 mg/day. After initiation of PLP, child had only one episode of seizures. On one year follow up, now child is seizures free and not taking any antiepileptic medications. Motor milestones are normal, but child had mild autistic features. Child was improving with behavioral therapy and regular PLP.

DISCUSSION

Epileptic encephalopathy refers to a group of disorders in which the unremitting epileptic activity contributes to progressive cerebral dysfunction which cannot be explained by the underlying etiology alone.[3] These are due to variable etiologies. Some of the epileptic encephalopathies are due to IEM. In these, some are treatable with some simple drugs like pyridoxine, biotin, PLP, folinic acid. PNPO deficiency also such type of treatable epileptic encephalopathy condition due to metabolic derangements in vitamin B6 metabolism.[4]

Pyridoxal 5'-phosphate (PLP) is the active form of vitamin B6 and cofactor of so many enzymatic reactions in the body, many of them involved in the synthesis and degradation of amino acids and amines, which serve as neurotransmitters or neuromodulators in the brain. PLP is derived from pyridoxine and pyridoxamine by PNPO enzyme.[5] Due to PNPO deficiency, unable to metabolize pyridoxine and pyridoxamine, leading to deficiency of PLP. PNPO deficiency occurs due to mutations in the PNPO gene on chromosome 17q21, which is transmitted with an autosomal recessive inheritance.[2]

The first case was reported by Brautigam et al in twins as neonatal epileptic encephalopathy mimicking aromatic L-amino acid decarboxylase deficiency.[6] Miller et al find out that this condition is due to PNPO deficiency.[6] As of now approximately 90 cases have been identified with PNPO deficiency.[7] PLP is a cofactor for over 140 enzymes, hence PLP deficiency have diverse clinical presentations. However, neurological phenotype is predominant phenotype of PNPO deficiency.[8] Neurological manifestations of PNPO deficiency are early onset of refractory seizures. These seizures beginning soon after birth, or in some cases before birth. Abnormal movements and signs of intrauterine fetal distress have also been described in some patients. In this case report, both siblings had seizures since 5 months of age. In first child, seizures were unresponsive to antiseizure drugs and child died at the age of 2 years. Based upon family history, early onset epilepsy, suspected genetic epilepsy and next generation sequencing was done. Genetic testing revealed PNPO mutation and child was treated with PLP. Mills et al reported a patient had seizures at 5 months of age with hypsarrhytmia on EEG.[6] Xue et al reported that a child with afebrile seizure at age five months and gradually developed resistant epilepsy.[9] Alghamdi et al provided a comprehensive review of clinical, biochemical and molecular profile for PNPO deficiency.[8]

Antiseizure medications are ineffective in PNPO deficiency patients and they are well responding with daily doses of PLP. Most of the patients have seizure free after treatment with PLP, they will suffer from intellectual disability, autism and developmental delay. 60% of patients show cessation of seizures in one to three days of PLP treatment and showed improvement of abnormal EEG findings.[7] Alghamdi et al reported that 61% of patients had complete cessation of seizures. Among this, 56% of patients suffer developmental delay or intellectual disability.[8] In this case report, child was seizures free since last 18 months, but child had mild autistic features. Child was regularly monitored with liver function test and up to now no adverse effects noted.

CONCLUSION

Epileptic encephalopathies are severe neurological condition with variable etiologies. Some are due to treatable metabolic derangements. Early detection and early initiation of therapy will give good prognosis. PNPO deficiency is unable to diagnosed by clinical and biochemical testing, genetic testing will help.

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