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Case Report

PNPLA 8 Mutation in Mitochondrial Disease: Second Case Worldwide

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Abstract

Mitochondrial myopathies are a group of neuromuscular diseases caused by an altered function of the mitochondrial oxidative phosphorylation with an onset starting before the age of 20. Herein, we report a case of a 6 months old girl with a remarkable neonatal history of microcephaly and seizures refractory to antiepileptic drugs who presented to our clinic for abnormal right-side tonic and clonic movements with focal mouth twitching and global neurologic delay. An electroencephalogram showed left sharp waves and generalized spikes; brain.

Magnetic resonance imaging (MRI) was significant for lissencephaly and incomplete left temporal lobe. Whole exome sequencing showed a homozygous pathogenic variant in the PNPLA8 gene and this finding was consistent with the genetic diagnosis of an autosomal recessive mitochondrial myopathy with lactic acidosis.

Keywords: Mitochondrial Myopathies; Magnetic Resonance Imaging (MRI); PNPLA 8 Mutation

Abbreviations

ATP: Adenosine Triphosphate; DNA: Deoxyribonucleic Acid; EEG: Electro-Encephalography; iPLA2: Independent Phospholipase A2; MCPs: Mitochondriopathies; MRI: Magnetic Resonance Imaging; nDNA: Nuclear DNA; NICU: Neonatal Intensive Care Unit

Introduction

Mitochondrial myopathies also called "mitochondriopathies", defined as the diseases due to a defect of the mitochondrial oxidative phosphorylation cover a wide range of conditions caused by genetic mutations. Mitochondriopathies (MCPs) are categorized into two types: primary MCPs and secondary MCPs. The primary MCPs occur as a result of sporadic or inherited mutations in nuclear or mitochondrial DNA located genes, whereas secondary MCPs occur due to exogenous factors [3]. Mitochondrial myopathy is the disease of the muscle which is usually caused by a malfunction in the oxidative phosphorylation [1]. The enzyme Phospholipase A2 is essential for maintenance of normal mitochondrial function and any mutation in the genetic code can lead to decrease in mitochondrial respiration [7]. When the PNPLA8 gene is mutated mitochondrial related neurodegeneration can be observed.

We performed whole exome sequencing on a female infant with a suspected mitochondrial myopathy who manifested with hypotonia, seizures and spasticity. She was found to have a homozygous variant in the PNPLA8 gene that has been confirmed by parental testing.

Case Presentation

We present a case of a 6 months old girl presenting to our clinic for abnormal right-side tonic and clonic movements that have become recently continuous associated with focal mouth twitching and global neurologic delay. The patient was a full-term baby girl, born to first-degree consanguineous parents who previously had a healthy 3 year old girl; the baby was delivered at home by normal

vaginal delivery, birth weight was 3500g, head circumference was 28 cm (microcephalic), with stimulation because of cyanosis, hypoactivity and hypothermia (34.5 degree Celsius).

Neonatal history was remarkable for a girl with a poor suck who was exclusively on a high caloric formula and bilateral arm tonic and clonic movements since day 1 of life. She was hospitalized at day 14 of life for dehydration in neonatal intensive care unit for 7 days. The baby did not achieve normal developmental milestones, she could not roll over at 4 months of age and could not sit unsupported at 6 months of age.

On her Physical examination, she was not alert, pupils symmetric and reactive to light, she had a head circumference of 31 cm, central hypotonia plus peripheral spasticity, deep tendon reflexes were present and symmetric.

An electroencephalogram (EEG) was performed and showed left sharp waves and generalized spikes; the magnetic resonance imaging of the brain was significant for lissencephaly and incomplete left temporal lobe.

Treatment was started, however seizures were refractory to antiepileptic drugs: clonazepam, topiramate, levetiracetam, phenytoin and oxcarbazepine.

For better evaluation, the whole exome genetic testing was performed and showed homozygous likely pathogenic variant in the PNPLA8 gene located on the chromosome 7 classified as a nonsense or a stop codon mutation in the DNA sequence.

Discussion

The mitochondrion found in the human body is an important organelle typically used for bio-energetics and cellular signaling, and in this cell many chemical mechanisms occur. These chemical mechanisms usually occur in response to certain physiological and pathophysiological disturbances. However, these mechanisms are still not understood fully [4].

During the DNA replication, several mutations can happen in the genetic code. The DNA of the mitochondria is susceptible to these mutations which can either happen in the mitochondrial DNA or nuclear DNA coding for mitochondrial proteins; causing several mild or severe diseases. One of these diseases is known as mitochondrial myopathy; which presents as prominent muscular problems. However, mitochondrial myopathy can vary according to the symptoms presented by a patient, such as muscle weakness, heart failure, seizures, and many more [2].

For a disease to be caused by an autosomal recessive disorder, two alleles of the gene in nDNA need to be mutated. Furthermore, if both parents are carriers of the mutated gene, there is a 25% chance that any child they conceive will inherit this disorder according to the Punnett square [2].

Mammalian independent phospholipase A2 is an enzyme which cleaves phospholipids and is in charge of cell signaling, lipid homeostasis, second messenger generation and ion channel function [6].

The PNPLA8 gene is located on the long arm of chromosome 7 (7q31), which is part of the group VI family of iPLA2s [5].

A study has been conducted on mice to test the mutation of the PNPLA8 gene. This predominant enzyme - typically found in mammalian mitochondria - has been characterized using genetic loss and gain of function in mouse models. This led to the assumption that the PNPLA8 may cause disturbances in the lipid metabolism that is associated with neurodegenerative diseases [6].

Further histopathological analysis and studies regarding skeletal muscles in iPLA2-related diseases showed slightly similar findings. In *PLA2G6*-related diseases, a primary pathogenic mechanism is the cause of the degeneration of the mitochondrial inner membrane. Similar to the PLA2G6, the PNPLA8- related diseases are caused by a disturbance in the mitochondrial inner membrane, where the proteins in charge of electron transportation and synthesis of adenosine triphosphate (ATP) are affected by altered membrane homeostasis. however, they are not caused by a primary pathogenic mechanism as seen with the PLA2G6-related diseases [6].

The mouse with the mutated PNPLA8 gene showed multiple dysfunctions including: impaired learning, mitochondrial dysfunction, low endurance during exercise, boost of insulin sensitivity, a thin body habitus, and an intolerance to cold temperatures [6].

The differential diagnosis is any metabolic disease, muscular dystrophy and neuropathies.

Similarly, the first case reported about mitochondrial myopathy was in 2016 by Saunders., *et al*. of a 7 year old girl presenting for

dystonia and abnormal gait with suspicion of mitochondrial myopathy who was found to have a homozygous mutation in the PNPLA8 gene.

Conclusion

PNPLA8 gene null mutation is an extremely rare mutation with only one single reported case in the literature by Saunders., *et al*. and it coded for mitochondrial myopathy. It is responsible for the clinical form of the disease manifested as neuromuscular dysfunction and cognitive defects. Our case represents the second case to be ever reported and demonstrates the useful role of the new generation genetic tests, including whole genome sequencing.

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