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Case Report

A compound heterozygous EARS2 mutation associated with mild leukoencephalopathy with thalamus and brainstem involvement and high lactate (LTBL)

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Abstract

Mitochondrial glutamyl-tRNA synthetase is a major component of protein biosynthesis that loads tRNAs with cognate amino acids. Mutations in the gene encoding this enzyme have been associated with a variety of disorders related to oxidative phosphorylation. Here, we present a case of leukoencephalopathy with thalamus and brainstem involvement and high lactate (LTBL) presenting a biphasic clinical course characterized by delayed psychomotor development and seizure. High-throughput sequencing revealed a novel compound heterozygous mutation in mitochondrial glutamyl-tRNA synthetase 2 (EARS2), which appears to be causative of disease symptoms.
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1. Introduction

Mitochondrial aminoacyl tRNA synthetase mutations exhibit a high level of tissue specificity, with the central nervous system being the organ system most commonly affected [1,2]. Leukoencephalopathy with thalamus and brainstem involvement and high lactate (LTBL) occurs as a result of autosomal recessive mutations in mitochondrial glutamyl-tRNA synthetase 2 (EARS2) [3], an enzyme that plays an important role in the mtDNA translation by promoting the joining of glutamate into nascent mtDNA-encoded proteins [1]. Patients with EARS2 mutations display a wide spectrum of symptoms, ranging from severe disease, characterized by delayed psychomotor development, seizures, and early-onset hypotonia, to a mild form that manifests as irritability and psychomotor regression; however,

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since both clinical and biochemical improvements are observed beginning at the age of 2, the condition is not associated with further clinical deterioration [1,4]. In this report, we describe a pediatric patient harboring a novel EARS2 mutation whose clinical and magnetic resonance imaging (MRI) characteristics differed from those of the normal LTBL spectrum.

2. Case report

A 42-month-old female patient, the only child of healthy non-consanguineous parents, was born at full-term through normal delivery following a pregnancy without complications. Her weight at birth was 4,300 g. She had a normal perinatal period, with an APGAR score of 9/10. At 7 months of age, the patient first presented a self-limiting episode of generalized tonic–clonic seizure that lasted 2 min and was characterized by eye rolling, and her seizure did not recur. Physical examination revealed mild axial hypotonia and brisk deep tendon reflexes at all extremities. She could not sit without support. Her head control and eye-tracking were normal. Laboratory tests revealed a significant increase in plasma lactate levels (12 mEq/L; normal range < 2 mEq/L). Her liver function tests, hemogram, urine and blood amino acid levels, and lysosomal enzyme profiles were all normal. Electroencephalogram readings were normal; therefore antiepileptic treatment was not initiated. Cranial MRI revealed symmetrical T2 hyperintensities in the cerebral deep white matter, midbrain, thalami, dorsal pons, dentate nuclei, and cerebellar white matter. The periventricular rim was not affected, exhibiting a normal T2 signal. The posterior part of the corpus callosum was abnormally thin (Fig. 1). Magnetic resonance spectroscopy (MRS) could not be performed due to a lack of parental consent, while genetic analyses for LTBL were not possible due to technical challenges. The patient was started on a treatment of riboflavin (10 mg/day), thiamine (100 mg/day), and CoQ10 (100 mg/day). At 12 months of age, the patient's deep tendon reflexes were brisk at all extremities, her muscle tonus mildly increased, and she had begun sitting without support; however, she still could not stand up on her own. Her clinical course significantly improved, as she became capable of walking with support by 18 months, and without support by 22 months. The second cranial MRI performed when she was 36 months old revealed apparent improvement in the deep white matter, cerebellar white matter, and thalamus. However, there was still mild T2 hyperintensity in the pons, mesencephalon, and dentate nucleus. MRS did not show any lactate peaks in any of the affected regions. Diffusion MR was normal (Fig. 2).

In the light of clinical and radiologic findings, we decided to study only EARS2 gene. Genetic analysis was performed using the MiSeq next generation sequencing (NGS) platform (Illumina, San Diego, CA, USA) and analyzed with MiSeq Reporter software (Illumina Inc.) using the hg 19 genome for sequence alignment. Visualization was performed using IGV 2.3 (Broad Institute, Cambridge, MA, USA) software (Fig. 3). Sequencing revealed a novel compound heterozygous mutation, p.R412C (c.1234C>T)/p.K471Nfs*14 (c.1413delG), in EARS2 gene. She inherited the p.R412C (c.1234C>T) mutation from her unaffected mother and the p.K471Nfs*14 (c.1413delG) mutation from her unaffected father, both in heterezygous state (Fig. 3).

Neuromotor development showed significant improvement at follow-up, with no reported episodes of seizure. The patient exhibited mild generalized muscle weakness, but was able to walk with a wide-based gait without support. Her lactate blood levels had decreased from 12 mEq/L at admission to <2 mEq/L at 3 years of age. All cardiac, fundoscopic, and hearing tests indicated no abnormalities. The Development Screening Test DENVER-II (TSDD-II), performed when the patient was 42 months old, revealed the following results: personal social (94%), language (70%), fine motor-adaptive (88%), and gross motor (96%) [5].

3. Discussion

LTBL is known to exhibit a biphasic clinical course. The severe form of the disease is characterized by delayed psychomotor development, seizures, early-onset hypotonia, and persistently increased lactate levels. In contrast, the mild form of the disease typically manifests as irritability and psychomotor regression after the age of 6 months; however, since clinical and biochemical improvements are observed starting from the age of 2, the condition is not associated with further clinical deterioration [1,4]. The distinctive features of LTBL are extensive symmetrical deep white matter abnormalities, signal changes of the thalami, brain stem, and cerebellar white matter, as well as lactate elevation on MRS; however, the mild form has been associated with significant improvement due to the absence of new lesions and MRS normalization, while the affected structures show progressive atrophy in the severe type [1,4].

Our patient presented with seizure and delayed psychomotor development beginning at 7 months of age, with the severity of the clinical course strongly correlated with the presence of generalized lesions on MRI. When the initial and final MRIs were compared, we were able to see significant improvement in radiographical lesions, which was reflected in the clinical findings. The MRI findings and clinical improvement of presented case is remarkable similar to a patient reported by Biancheri et al. [4]. At the age of 3 months, the patient presented with feeding difficulties and muscle hypotonia. His brain MRI revealed hyperintensity of

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