Two Different Phenotypes Caused by Mutation in the EARS2 Gene in Two Siblings

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INTRODUCTION

Glutamyl-tRNA synthetase 2 (encoded by *EARS2 gene*) mutations are one of the newest members of nuclear mitochondrial disorders characterized by disturbed mitochondrial translation. Pathogenic *EARS2* variants have been related to a rare mitochondrial disease known as leukoencephalopathy with thalamus and brainstem involvement and high lactate (LTBL). Two distinct clinical courses are described: severe and moderate. Neurological clinical presentations contain early-onset encephalopathy, seizures, leukodystrophy, and sensorineural hearing loss.

CASE ONE

A two-and-a-half-year-old male from two siblings with a history of parental consanguinity was admitted due to psychomotor delay that started at one year. After an uneventful pregnancy, he was born by section as a twin, birth weight of 1850 gr, at 33 weeks of gestation. He received mechanical ventilator support for three days due to postpartum respiratory distress. He achieved head control at nine months and succeeded in sitting without support at 15 months. He could speak five or six words.

Lactate level (3,25 mmol/L, reference range 0.4–1,4) was high. Blood ammonia and other biochemical measurements were within normal limits. His cranial Magnetic Resonance Imaging (MRI) revealed symmetrical T2 hyperintensities in the cerebral hemispheres, subcortical and deep white matter, corpus callosum. There was no regression in his developmental milestones. MRI lesions in subcortical white matter taken at the 26th month showed some regression (Figure 1).

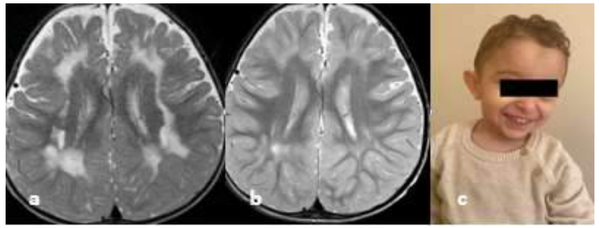

Figure 1. a-Cranial Magnetic Resonance Imaging (MRI) at 14 months (Axial T2), b-cranial MRI at 26 months (Axial T2), MRI lesions had regressed over time, c-Patient's photograph.

CASE TWO

His two-month-old brother presented with hypoglycemia-related seizure and acute metabolic crisis. He received phototherapy due to hyperbilirubinemia on the postnatal 12th day. On physical examination, body weight was 3.6kg (50.P), height 51cm (75.P), and head circumference 36.5cm (75.P). He was pale and sluggish. Hepatomegaly was found. Deep tendon reflexes were hypoactive. Laboratory evaluation was significant for abnormal liver function tests: AST 478U/L (0-40), ALT 322U/L (0-41), alkaline phosphatase 586U/L (122-469), GGT 174U/L (0-60), total bilirubin 11.55mg/dl (0–1.2), direct bilirubin 10.55mg/dl (0–0.3), and prothrombin time 25.5s (9.4-12.5). Blood ammonia was normal. In addition, the lactate level was (14.4mmol/L (0.4–1.4)) high. Cranial MRI showed symmetrical restricted diffusion in the cerebral deep white matter, including both cerebral crus, mesencephalon, cerebellar peduncles, dentate nuclei, medulla oblongata, and along the corticospinal tract. MRI spectroscopy revealed abnormal lactate peaks in the basal ganglia and both thalamus (Figure 2). Whole-exome sequencing analysis of two siblings was compound heterozygous for pathogenic variants c.319C>T;p.Arg107Cys/c.1005_1006del;p.Leu336Aspfs (Combined Oxidative Phosphorylation Deficiency 12, OMIM#614924) in *the ERS2* gene and their parents were carriers for these mutations. The younger brother died when he was three months old, while the older can currently walk unassisted.

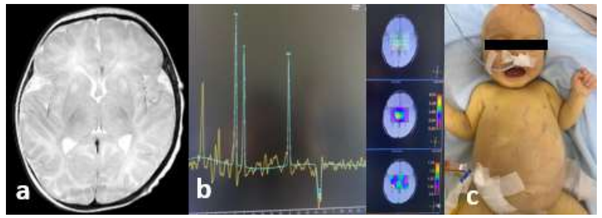

Figure 2. a-Cranial Magnetic Resonance (MR) Imaging at two months (Axial T2), b-Multivoxel proton MR spectroscopy shows a lactate peak at the basal ganglia and both thalamus , c- Patient's photograph.

CONCLUSION

Clinical findings of LTBL show variable phenotypic features, including neonatal death, acquisition of developmental milestones and improvement of MRI abnormalities. The severe form is characterized by early-onset time, seizures, hypotonia, and persistently elevated lactate levels. The mild form usually manifests clinically after six months of age with irritability and psychomotor regression. Here, we present two siblings with identical heterozygous *EARS2* mutations and different clinical phenotypes. The clinical spectrum of disease associated with *EARS2* mutations is very broad. It is essential to consider this phenotypic variability in mitochondrial diseases during the diagnosis process.

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