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Case Report

A Newborn with Hypotonia, Facial Dysmorphism, Microcephaly and Stridor due to Pathogenic Mutations in VARS2 and MARS2 Genes

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Abstract

Mitochondrial disease (MD) are a heterogeneous group of diseases associated with multisystemic disorders, frequently presenting as encephalo- and/or cardiomyopathies.

We report here the identification by mitochondrial nuclear gene panel by next generation sequencing (NGS), the pathogenic mutations in VARS2 and MARS2 genes. The patient showed hypotonia, seizures, exotropia, oftalmoplegia, facial dysmorphism, acquired microcephaly and stridor. Blood test revealed high levels of alanine, glycine and lactic acid, common indicators of OXPHOS deficiency. The skin biopsy for biochemical study revealed reduced citrate synthase activity with no deficiency observed in Electron Transport Chain Activities.

Keywords: *Hypotonia; Dysmorphism; MARS2; VARS2; Mitochondrial*

Introduction

Mitochondrial disease (MD) are a heterogeneous group of diseases associated with multisystemic disorders, frequently presenting as encephalo- and/or cardiomyopathies, associated with a broad range of causative genes. The incidence is 1/10,000 live births.

The diagnosis relies on the clinical presentation, biochemical markers, histological, enzymatic and molecular results.

Their biochemical signature is the presence of defective activity in the mitochondrial respiratory chain (MRC) complexes, resulting in faulty oxidative phosphorylation (OXPHOS).

Mutations in several genes associated with defects of mitochondrial protein synthesis, affecting either mitochondrial DNA (mtDNA) or nucleus-encoded genes, have been reported in a range of mitochondrial syndromes.

We report here the identification by mitochondrial nuclear gene panel by next generation sequencing (NGS), the association mutation in VARS2 and MARS2 genes in patients with clinical presentations compatible with mitochondrial disorders and OXPHOS deficiency [1-3].

Patients and Methods

We described an Asian female newborn, born at the 38th week of gestation by cesarean section due to rupture of membrane > 24 hours. Birth weight: 2.6 kg (percentile 3 - 10), length: 45 cm (percentile < 3) and head circumference: 34 cm (percentile 25). Apgar score 10/10/10. Clear amniotic fluid.

The parents are young and unrelated. G1P1, with transient oligohydrammio found in the second trimester with mild decrease of fetal weight. At 20 hours of life, after taken formula milk for 3 times, vomited one time, and the mother found that the baby was not breathing. He was floppy with cyanosis. Intubation was done in the maternity and transferred to the Neonatal intensive care unit (NICU). Desaturation and bradicardia were found with start of cardiopulmonary resuscitation. He was ventilated with high flow oxygen and FiO2, 30%. Later start fever and we associated Penicillin G and Netilmycin for prevention of risk of infection. The blood culture was negative. On the first day at NICU, one episode of suction movement and tonic-clonic seizures were registered. Later we found stridor while wake up and crying. By endoscopy, we found vocal cord symmetric but opening of glottis is limited. We found exotropia with oftalmoplegia and optic

nerve mild pale in ophalmology fundus. No heart murmur and hepatosplenomegaly were found. The newborn showed facial dysmorphism. The growth velocity of the head circumference decreased after birth and at 2 months of life showed microcephaly. The newborn still need nasogastric tube for feeding. At 5 months of age, during an episode of respiratory infection, died with heart failure.

Brain MRI, heart echo, EEG, ECG and abdominal ultrasound were all normal. The blood test revealed lactic acid above normal range: 2.55 mmol/L (0.50 - 2.20), plasma amino acids with high alanine: 467 mmol/L (108 - 448) and glycine: 466 mmol/L (101 - 307), organic acids in urine with increased excretion of lactate, pyruvate and 2-ketoglutarate. Pyruvic acid, amnonia, acylcarnitine, CDG were normal. Because we suspect of mitochondrial disease not only by the clinical presentation but also because showed increase levels of alanine, glycine, lactic acid, we check for mitochondrial nuclear gene panel of blood and mitochondrial full genome analysis of muscle by NGS. We also checked the biochemical study of respiratory chain disorder by skin biopsy. We started treatment with coenzyme Q10 and carnitine.

Results of Molecular and Biochemical Analysis

The MITON (mitochondrial nuclear gene panel by NGS) of blood, showed heterozygous variants of uncertain significance with two genes: MARS2, pA461G (Ala461Gly),c.1382C>G,Chr2:198571511/VARS2,p.T647M(Thr647Met),c.1940C>T,Chr6:30889936. Alterations in the MARS2 gene have been associated with autosomal recessive combined oxidative phosphorylation deficiency and autosomal recessive spastic ataxia. This alteration is not present in large, control population databases. The absence of this alteration in large control populations suggests that it is not a common benign polymorphism, but could be consistent with either a rare benign variant or a pathogenic mutation.

The significance of the c.1940C>T (p.T647M) alteration in the VARS2 gene is uncertain.

Alterations in the VARS2 gene have been associated with autosomal recessive combined oxidative phosphorylation deficiency. The overall minor allele frequency for this alteration is approximately 0.022% with a frequency up to 0.27% in certain Asian subpopulations.

The MITOP (mitochondrial full genone analysis by NGS) of muscle was negative. The skin biopsy for biochemical study revealed reduced citrate synthase activity. Citrate synthase is used as a marker for mitochondrial content. However, no deficiency was observed in any Electron Transport Chain Activities (ETC). These normal activities in skin fibroblast cultures do not exclude the presence of tissue specific ETC defects.

Discussion

Mutations in genes coding for mitochondrial aminoacyl-tRNA synthetases have been associated with diverse clinical presentations, usually inherited as early-onset autosomal recessive traits.

The MITOP (mitochondrial full genone analysis by NGS) of muscle was negative. These results do not rule out the diagnosis of a mitochondrial DNA (mt DNA) disease. Some individuals who have mitochondrial genome involvement may have a mutation that is not identified by the methods performed (e.g. mutations present at a low heteroplasmy level or confined to tissues that were not tested). Small deletions and insertions greater than 50 nucleotides in length are not detected by NGS.

The molecular results of blood using MITON panel, although the results showed variants of uncertain significance identified, should be interpreted in the context of clinical findings and other laboratory testing. MARS2 were described in a cohort of patients with autosomal recessive spastic ataxia with leukoencephalopathy [4,5]. Patients with VARS2 presented with hypotonia, seizures, ptosis, ophtalmoplagia, liver dysfunction, facial dysmorphism, cardiomyopathy and early-onset encephalopathy. In the literature, we find association of VARS2 and TARS2 mutations with the 8-year-old patient presenting with of encephalomyopathy, psychomotor delay, facial dysmorphisms, seizures and microcephaly and in two siblings with axial hypotonia, limb hypertonia, and psychomotor delay [6].

In our case, how we prove if we identified a polymorphism or a pathogenic mutations in VARS2 and MARS2 genes?

The patient showed several symptoms that support a pathogenic mutations: hypotonia, seizures, oftalmoplegia, facial dysmorphism and acquired microcephaly, very common in mitochondrial disease. On the other hand, the blood test revealed high levels of alanine, glycine and lactic acid, reduced citrate synthase activity in the skin fibroblasts, common indicators of OXPHOS deficiency.

Conclusion

We concluded that we identified novel mutations in two genes encoding mitochondrial aminoacyl-tRNA synthetases (VARS2 and MARS2), which have not been appreciated previously as causing mitochondrial disease.

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