A CASE OF MITOCHONDRIAL DEPLETION SYNDROME TYPE 13 DUE TO A FBXL4 VARIANT

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INTRODUCTION

Mitochondrial DNA depletion syndromes comprise multystemic disorders caused by variants of nuclear genes that are responsible for the stabilization of mitochondria.

Mutations in FBXL4 are known to cause mitochondrial DNA depletion syndrome type 13 that lead to early-onset lactic acidosis hypotonia, and developmental delay. Approximately a 100 cases and 54 pathogenic variants have been reported to date. We present a case of mtDNA depletion syndrome type 13 that was diagnosed by clinical exome analysis.

OBJECTIVE

Here, we present a case with hypotonia, dysmorphic facial appearance, developmental delay and lactic acidosis and identified mtDNA depletion syndrome type 13.

METHODS

Karyotyping and Array-CGH Analyses

Cytogenetic analysis was performed on GTG-banded chromosomes from circulating leukocytes using a standard protocol. Array-CGH was performed using a 60 K whole-genome oligonucleotide microarray following the manufacturer's protocol (Human Genom CGH Microarray, 60K, Agilent Inc.).

Whole-exome sequencing (WES) Studies

WES was performed to diagnosis

Sanger Sequencing

Parental segregation of the homozygous mutation in the case was confirmed by sanger sequencing.

RESULTS

One-year old girl presented due to hypotonia. She was the 8th child of consanguinous parents, with a historiy of a sibling death in the neonatal peiod due to unknown etiology. She was born after an uncomplicated pregnancy

Her developmental milestones were delayed (head control at 6 months, supported sitting at 9 months). She was not able to walk an was non-verbal.

Physical examination revealed dysmorphic findings including a prominent forehead, thich eyebrows, short palpebral fissures, epicanthic folds and a small chin. She had severe axial hypotonia and titubation on head and body.

Laboratory examination revealed increased lactate (63 mg/dl) without metabolic acidosis Metabolic tests including urine and blood aminoacids, tandem MS+acylcarnitine levels, urine organic acids, very long chain fatty acids were normal.

Echocardiography (ECHO) showed abnormal right subclavian arteria. Abdominal USG showed hyperechogenity on liver and kidney.

Cranial MRI showed hypomyelinisation and restricted diffusion on cerebral white matter and the cerebellum(Fig.1)

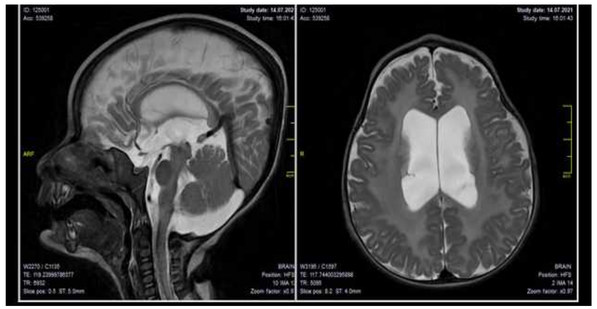

Fig.-1: Cranial MRI showing hypomyelinizattion, restricted diffusion of the white matter, corticospinal tracts, tegmentum and cerebellum. Ventricular dilatation and retrocerebellar cystic enlargement, aracnoid cyst .

A homozygous missense c.617G>A (p.R206Q) (p.Arg206Gln) rs1018430772variant in FBXL4 gene which is detected by means of whole exome sequencing study of the proband. Sanger analyses of parents confirmed the heterozygous mutation in this region.

CONCLUSION

Variants of FBXL4 account for a significant proportion of mitochondrial depletion syndromes. The clinical consequences of FBXL4 should be kept in mind especially in patients with congenital lactic acidosis hypotinia and multisystemic tissue involvements. Our case has a new mutation. Expanding phenotype with novel pathogenic varians in the FBXL4 gene will help associate specific mutations with the range of disease phenotypes.

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