The first case of spastic ataxia type 4 associated with heterozygous mutations in MTPAP gene

İlknur Erol[1] , Ruken Tekdemir[2] **Elif Perihan Öncel**[1] , Şeyda Besen[1] , Leman Tekin Orgun[1] , Atıl Bişgin[3]

[1]Baskent University Faculty of Medicine, Adana Dr. Turgut Noyan Application and Research Center, Department of Pediatric Neurology, Adana, Turkey
[2]Baskent University Hospital Ankara, Faculty of Medicine, Department of Pediatrics, Adana, Turkey
[3]Cukurova University AGENTEM (Adana Genetic Diseases Diagnosis and Treatment Center) and Medical Genetics Department of Medical Faculty, Adana, Turkey

ICNC 2022
17th INTERNATIONAL CHILD NEUROLOGY CONGRESS
ANTALYA, TURKEY | OCTOBER 3-7, 2022

INTRODUCTION

MTPAP is a nuclear-encoded polymerase that synthesizes homopolymeric poly (A) tails on mitochondrial mRNAs which is important to maintain mitochondrial gene expression. MTPAP gene mutations are related with spastic ataxia type 4 which is first described in Old Amish family members who have homozygous MTPAP mutation. This is a neurodegenerative condition with cerebral ataxia (limb and truncal), spastic paraparesis, cerebellar and spastic dysarthria, learning difficulties and optic atrophy. Autosomal recessive perinatal encephalopathy with lethality in the first year of life related with homozygous MTPAP mutation was also described, recently.

OBJECTIVES

Here, we describe the first case of a child who is carrying heterozygous mutation in MTPAP gene and presenting with only spastic paraparesis.

CASE

7-year-old male patient

Complaint:

- Tip toe walking
- Pain and fatigue in legs with movement

History:

- No medical and familial history

Examination:

- Mild pes cavus deformity
- Spasticity and hyperreflexia in lower limb

Investigations:

- CK: Normal
- Brain and spinal MRI: Normal
- Vitamine E and metabolic analysis : Normal
- ENMG: Normal
- WES: a heterozygous *p.L285fs*4(c.853delC)* mutation in *MTPAP gene*
- Mother has *a heterozygous p.L285fs*4(c.853delC) mutation in MTPAP gene*

DISCUSSION

Hereditary cerebellar ataxias and hereditary spastic paraplegias (HSPs) are clinically and genetically heterogeneous and often overlapping neurological disorders. Both HSP and hereditary ataxias can be associated with other neurologic and non-neurologic features, resulting in complex phenotypes with frequent intra- and interfamilial variability. Significantly, cerebellar ataxias are very often associated with pyramidal involvement, leading to more than 50% of recessive ataxias manifesting as spastic ataxias. Because spastic ataxias are rare and genetically heterogeneous, their molecular diagnosis is challenging and time-consuming.

Crosby et al., described an autosomal-recessive spastic ataxia with optic atrophy due to homozygous MTPAP mutation in the Old Order Amish in 2010. The MTPAP mutation results in a lack of polyadenylation in mitochondrial mRNA that results in dysfunction of mitochondrial complexes I and IV.

Wilson et al., shown that the p.N478D mutation in MTPAP is pathogenic. The defect prevents the enzyme from efficiently polyadenylating mt-mRNA. The resultant loss of polyadenylation causes a differential modulation of steady-state levels of specific mt-mRNAs and perturbs mitochondrial protein synthesis leading to profound depletion of complexes I and IV of the respiratory chain, resulting in a form of spastic ataxia and optic atrophy. Eyck et al., described an autosomal recessive perinatal encephalopathy with lethality in the first year of life associated with novel MTPAP mutations. In three individuals from two unrelated families, inherited either in the compound heterozygous or homozygous state, and provide evidence that these variants affect mitochondrial transcript polyadenylation and subsequent expression of mitochondrially encoded proteins.

Hiramatsu et al., performed whole-exome sequencing on 247 patients with autosomal recessive or sporadic inheritance for further analysis of 167 mitochondrial-related nuclear genes. They detected novel bi-allelic pathogenic MTPAP mutation in one male patient. This patient had gait disturbance at the age of 1 year and 6 months. At 28 years, scoliosis, equinus foot, and paresthesia were present, and he could not walk. His ENMG was consistent with sensory-dominant axonal polyneuropathy and brain MRI was characterized by patchy T2 hyperintensities in the white matter of the temporal and occipital lobes.

Homozygous MTPAP mutations have been observed to cause different mitochondrial disorder in different individuals. It is not yet clear why a particular MTPAP mutations can cause different patterns of signs and symptoms.

DISCUSSION

The clinical findings of our case were characterized by lower extremity weakness and spasticity. All genes associated with hereditary HSP and ataxia were analyzed in detail by WES, and no mutations were detected other than heterozygous MTPAP mutation. Therefore, he was diagnosed as spastic ataxia possibly associated with heterozygous MTPAP mutation.

CONCLUSIONS

Up-to-date all reported cases with MTPAP mutations related with spastic ataxia are always seen as a homozygous form but, in this case, heterozygous MTPAP gene mutation caused mild form of spastic ataxia. We thought that heterozygous MTPAP mutation may cause autosomal dominant form of spastic ataxia type 4 with mild clinical findings including spasticity is more prominent. However the mother has also the same variant in heterozygous state, there has been still an unclarified genetic situations such as incomplete penetrance or variable expression patterns.

Diseases associated with MTPAP are newly defined, and as more cases and mutations are defined, the relationship between inheritance pattern and genotype phenotype will be understood more clearly.

REFERNCES

1. Hiramatsu, Y., *et al. J Neurol* **269**, 4129–4140 (2022). https://doi.org/10.1007/s00415-022-11026-w
2. Van Eyck L,. et al. Neuropediatrics. 2020 Jun;51(3):178-184. doi: 10.1055/s-0039-3400979.
3. Martin NT., et al. Cell Death Dis. 2014 Mar 20;5(3):e1130. doi: 10.1038/cddis.2014.99.
4. Wilson WC., et a Hum Mol Genet. 2014 Dec 1;23(23):6345-55. doi: 10.1093/hmg/ddu352.
5. Crosby AH,. et al. Am J Hum Genet. 2010 Nov 12;87(5):655-60. doi: 10.1016/j.ajhg.2010.09.013.
6. Lapkouski M, Hällberg BM. Nucleic Acids Res. 2015 Oct 15;43(18):9065-75. doi: 10.1093/nar/gkv861.

CONTACT

Prof. Dr. İlknur EROL
e-mail: ilknur_erol@yahoo.com
Phone: +905053837661