Thinning of the corpus callosum prominent in the splenium and colpocephaly: the AP-4 deficiency syndrome

Aydan Değerliyurt, Özlem Yayıcı Köken, Hanife Saat, Tülin Hakan Demirkan

[1]Akdeniz University Medical Faculty, [2]Ankara City Hospital

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

INTRODUCTION

The *AP4M1* gene encodes a subunit of the heterotetrameric adaptor protein (AP) complex, a component of intracellular transport of proteins that is thought to have a unique role in neurons. This gene encodes a subunit of the heterotetrameric AP-4 complex. The encoded protein belongs to the adaptor complexes medium subunits family. This AP-4 complex is involved in the recognition and sorting of cargo proteins with tyrosine-based motifs from the trans-golgi network to the endosomal-lysosomal system. Autosomal recessive defects of either the B1, E1, M1 or S1 subunit of the Adaptor Protein complex-4 (AP4) are characterized by developmental delay, severe intellectual disability, spasticity, and occasionally mild to moderate microcephaly of essentially postnatal onset. Autosomal recessive spastic paraplegia-50 (SPG50) is caused by homozygous mutation in the *AP4M1* gene on chromosome 7q22. And also, the gene mutations were referred as Severe Intellectual Disability And Progressive Spastic Paraplegia on Orphanet. Spastic paraplegia-50 (SPG50) is an autosomal recessive neurodevelopmental disorder characterized by neonatal hypotonia that progresses to hypertonia and spasticity and severely impaired intellectual development with poor or absent speech development. Adaptor protein-4 (AP-4) complex mutations result in an autophagy disorder and cause a hereditary spastic paraplegia phenotype called the 'AP-4 deficiency syndrome, which mimics cerebral palsy'

OBJECTIVES

We here report on a patient with an *AP4M1* mutation, progressive spastic paraplegia, stereotypic laughing and typical MRI findings.

METHODS

A CES analysis was performed by using xGen Exome Research Panel v2. VCF files were annotated using Qiagen Ingenuity Variant Analysis and Clinical Insight Interpret (QIAGEN GmbH).

RESULTS

An intracerebral cyst was detected during the intrauterine period of our patient who was born following an uneventful birth from consanguineous parents. Epileptic seizures were started at the age of 4 months. Myoclonic seziures as epilepsy recurrence were observed at the age of 8 after the withdrawal of antiepileptic treatments. Refractory seizures started at the age 4 months was being confused by the clinician as thought to be he is an epileptic encephalopathy. The patient could only walk with support and then lost the walking ability at the age of 8 years. The examination revealed drooling, intermittent stereotypical laughing, and marked pyramidal tract involvement. Despite the literature, microcephaly, cerebellar and cortical atrophy were not observed in our patient. Table 1 summaries the HPO terms related with *AP4M1* mutations and observed features in our patient was colored with pink. Neuroimaging findings were shown in Figure-1. Clinical exome sequencing revealed the c.952 C>T (p.Arg318Ter) homozygous mutation in exon 12 of the *AP4M1* gene (Figure-2).

CONCLUSION

Adaptor protein-4 (AP-4) complex mutations result in an autophagy disorder and cause a hereditary spastic paraplegia phenotype called the 'AP-4 deficiency syndrome, which mimics cerebral palsy' (1,2). MRI shows thin corpus callosum (prominent posteriorly) and ventriculomegaly/colpocephaly (2).

Table 1 shows the reported HPO terms related with SPG50 (data avaible:https://hpo.jax.org/app/)

Everted upper lip vermilion	Ventriculomegaly	Neonatal hypotonia	Cerebellar atrophy	Acetabular dysplasia
Seizure	Waddling gait	High palate	Wide nasal ridge	Abnormal facial shape
Microcephaly	Babinski sign	Bulbous nose	Spastic tetraplegia (progressive)	Strabismus
Shyness	Wide mouth	Drooling	Motor stereotypy	Mandibular prognathia
Genu recurvatum	Babinski sign	Poor speech	Hypotonia	Difficulty walking
Narrow forehead	Amblyopia	Short stature	Intellectuel disability	Talipes equinovarus
Pseudobulbar signs	Wide mouth	Short philtrum	Pes planus	Glosis
Facial hypotonia	Dysartria	Abnormal periventricular white matter morphology	Hypereflexia	Autosomal recessive inheritance
Global developmental delay	Cerebellar cortical atrophy	Adducted thumb	Generalized joint laxity	Overweight

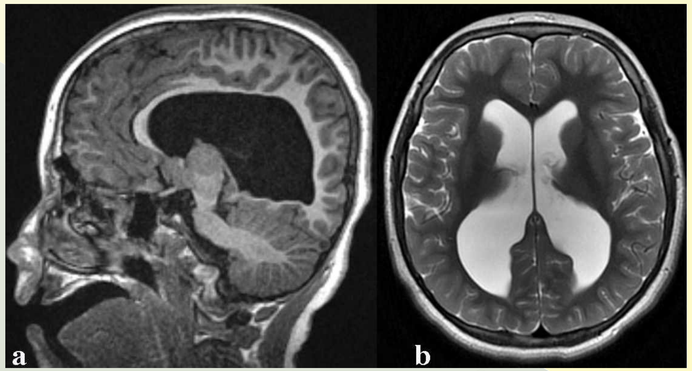

Figure 1

1a. Thinning of the corpus callosum is prominent in the splenium on the sagittal T1 image.

1b. Ventriculomegaly (asymmetric colpocephaly) on the axial T2 image.

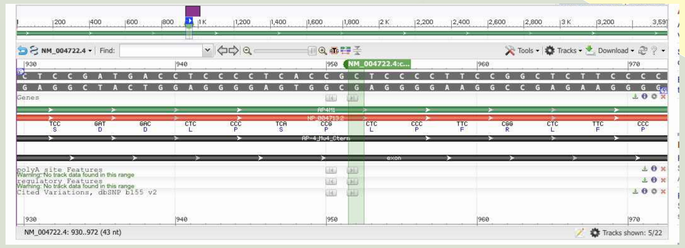

Figure 2 shows the molecular map of the position of the mutation

REFERENCES

1. Mattera R, De Pace R, Bonifacino JS. The role of AP-4 in cargo export from the trans-Golgi network and hereditary spastic paraplegia. Biochem Soc Trans. 2020;48(5):1877-1888.

2. Ebrahimi-Fakhari D, Teinert J, Behne R, et al. Defining the clinical, molecular and imaging spectrum of adaptor protein complex 4-associated hereditary spastic paraplegia. Brain. 2020;143(10):2929-2944.

ACKNOWLEDGEMENT

'Özlem Yayıcı Köken was supported by an MRC strategic award to establish an International Centre for Genomic Medicine in Neuromuscular Diseases (ICGNMD) MR/S005021/1'