A novel combined heterozygous mutation in the PLA2G6 gene associated with early-onset Parkinson's disease

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

INTRODUCTION

PLA2G6-associated neurodegeneration (PLAN) is a rare, heterogeneous group of neurodegenerative disorders caused by homozygous mutations in the PLA2G6 gene. Infantile neuroaxonal dystrophy (INAD), atypical neuroaxonal dystrophy (ANAD), autosomal recessive early-onset Parkinson's disease (AREP) and adult onset dystonia parkinsonism (DP) are the subtypes of PLAN according to the age of onset and clinical features.

OBJECTIVES

Herein, we report a Turkish case of possible AREP associated with a two novel heterozygous mutation of PLA2G6 gene to draw the attention to the fact that the spectrum of PLA2G6-related disease can be variable and genotype-phenotype association can not be made clearly for every cases.

CASE

7-year-old, female

Complaint:

- Tremor in hands
- Gait abnormality
- Posture balance disturbance
- Speech disorder for 3 months

History:

- Family history was unremarkable

Examination:

- Postural tremor, dystonia and gait ataxia

CASE

Investigations:

- Metabolic screening: Normal
- Cranial MRI: Iron accumulation in the mesencephalon and globus pallidus (Figure 1)
- SLC2A1, PANK2 gene analysis were negative
- WES: Two new, previously unidentified,*c.1630A>G p.M544V* and *c.1748T>C p.M583T heterozygous mutations in the PLA2G6 gene*
- Insilico analyzes shows that mutations are pathogenic and the mother was heterozygous for c.1630A>G p.M544V and the father was heterozygous for c.1748T>C p.M583T.

DISCUSSION

The PLA2G6 gene encodes a protein called Ca^{+2}-independent phospholipase A2 (iPLA2) which plays an important role in phospholipid remodeling, signal transduction, cell proliferation, endoplasmic reticulum stress-mediated apoptosis and ferroptosis. As a result, mitochondrial abnormalities occur due to the disruption of membrane permeability, fluidity and ion homeostasis.

Since extrapyramidal symptoms (parkinsonism/dystonia) in PLAN are a clinical finding shared by all subtypes, it is defined as disease in the movement disorders group. The most common features of ANAD are iron deposition in the globus pallidus (86%), cerebellar atrophy (71%), pyramidal manifestations (67%), and parkinsonism (62%). However PLA2G6-AREP patients have pyramidal signs (76%), cerebellar atrophy (38%), and globus pallidus iron deposition (26%). Therefore, PLAN can be occur with some intermediate phenotypes other than the classical disease pattern and, genotype-phenotype association can not be made clearly for every cases.

Although PLAN has been reported worldwide, it is still a relatively rare disease. Only 25 ANAD and 87 PLA2G6-related parkinsonism patients have been reported so far. In addition, three PLA2G6 related cases from Turkey have been reported so far. Ozes et al. reported two affected Turkish siblings with PLA2G6 mutation presenting as HSP and broadened the clinical spectrum of PLAN. The age of onset of these siblings were 9 and 21. Giri et al. reported PLA2G6-related dystonia-parkinsonism in 33-year-old Turkish patient. Our patient is only seven year old and extrapyramidal symptoms are most prominent clinical features. The present case has combined heterozygous mutation of PLA2G6 gene which both are novel.

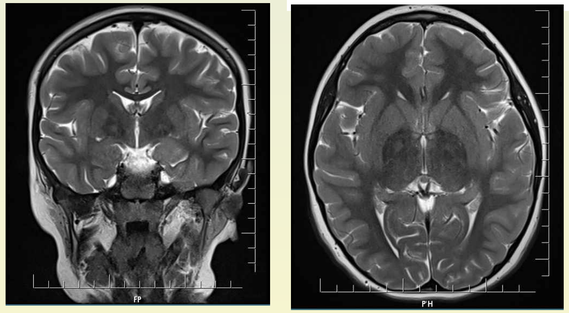

Figure 1: Iron accumulation in the mesencephalon and globus pallidus

CONCLUSION

The spectrum of PLA2G6-related disease can be variable and genotype-phenotype association can not be made clearly for every cases. **To our knowledge, this is the first child of PLA2G6 variant associated AREP from Tukey. In addition, two novel pathogenic variants identified by this study expanded the mutational spectrum of PLA2G6-associated neurodegeneration.**

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