Infantile Neuroaxonal Dystrophy in Two Cases: Siblings with Different Presentations

How to Cite This Article: Ansari B, Nasiri J, Namazi H, Sedghi M, Afzali M. Infantile Neuroaxonal Dystrophy in Two Cases: Siblings with Different Presentations. Iran J Child Neurol. summer 2022; 16(3): 193-198

Behnaz ANSARI MD[1], Jafar NASIRI MD [2], Hamide NAMAZI MD [3], Maryam SEDGHI PhD[3], Mahdieh AFZALI MD[4]

1. Neurologist, Isfahan Neuroscience Research Center, Al-Zahra Hospital Research Institute, Department of Pediatric Neurology, Isfahan University of Medical Science, Isfahan, Iran
2. Professor of Neurology, Department of Pediatric Neurology, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
3. Medical Genetics, Medical Genetics Laboratory, Al-Zahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran
4. Neurologist, Department of Neurologist, School of Medicine, Yas Hospital, Tehran University of Medical Sciences, Tehran, Iran

Abstract

Infantile neuroaxonal dystrophy (INAD) is a rare recessive neurodegenerative disorder manifested by symptoms like hypotonia, extrapyramidal signs, spastic tetraplegia, vision problems, cerebellar ataxia, cognitive complications, and dementia before the age of three. Various reports evaluated the relationship between the incidence of INAD and different mutations in the PLA2G6 gene. We described cases of two children with INAD whose diagnoses were challenging due to misleading findings and a mutation in the C.2370 T>G (p. Y790X) in the PLA2G6 gene based on NM_001349864, which has been reported previously.

Keywords: Group VI Phospholipases A2, Neurodegenerative Diseases, Glycerophospholipids; Muscle Hypotonia.

DOI: 10.22037/ijcn.v16i2.30864

Introduction

Phospholipase A2 Group VI (PLA2G6)-associated neurodegeneration (PLAN) includes a spectrum of neurodegenerative disorders, in which due to the mutation of the PLA2G2 gene and the subsequent defects in phospholipase A2 enzymes, neuroinflammation and oxidative stress in neurons occurs (1, 2). The iPLA2β protein encoded by the PLA2G6 gene is an important lipase in the human body that is widely distributed in the tissues of human organs. In the human brain, iPLA2β is highly expressed in the substantia nigra, cortex, and hippocampus. These disorders are divided into four groups of infantile neuroaxonal dystrophy (INAD), atypical neuroaxonal dystrophy (ANAD), adult-onset dystonia-parkinsonism (DP), and autosomal recessive-early-onset parkinsonism (AREP) (2). Previously known as Seitelberger's disease (Online Mendelian of Inheritance in Man ID 256600), INAD is a rare neurodegenerative disorder that was first described in 1952

Corresponding Author
Mahdieh Afzali M. MD
Assistant Professor of Neurology, Department of Neurology, School of Medicine, Yas Hospital, Tehran University of Medical Sciences, Tehran, Iran
Email: m.afzali2219@gmail.com

Received: 11-Jun-2020
Accepted: 10- May -2021
published:16- Jul-2022

by Franz Seitelberger, who described two siblings presenting with psychomotor delay in infancy followed by progressive neuroregression, leading to severe disability and death in the first decade of life (1, 2). This recessive neurodegenerative disorder is associated with several symptoms, including hypotonia, extrapyramidal signs, spastic tetraplegia, vision problems, cerebellar ataxia, cognitive complications, and dementia before the age of three (2-4). INAD may manifest with pathologic findings such as axonal inflammation, iron deposition in the brain, the appearance of spheroid bodies in different tissues, and cerebral changes in Magnetic resonance imaging (MRI). However, these findings are not specific to INAD (2, 3), and the diagnosis of INAD is difficult due to the frequency of atypical cases and lack of specific early signs (4). Various reports evaluated the relationship between the incidence of INAD and different mutations in the PLA2G2 gene (3, 5, and 6). We described cases of two children with INAD whose diagnoses were challenging due to misleading findings and a mutation of PLA2G6, which has been reported previously.

Case presentation

The study cases are two children (an older daughter, 8 years old, and a younger son, 7 years old) of a family who were referred to the Isfahan University Pediatric Neurology Clinic due to growth regression and weakness. Their parents were healthy and related, residing in Shahrekord city.

Pregnancy and delivery were unremarkable. Family history was positive, and their cousins had developmental regression and died. The older daughter and the younger son were born after a cesarean section, and both were born at term and were without specific problems. The older daughter had a birth weight of 3750 grams and a birth height of 45.5 cm. The younger son had a birth weight of 4350 grams and a birth height of 47.5 cm. The siblings had an age difference of approximately 18 months. Their developmental steps had been normal until 12 months of age in the older daughter and at the age of 15 months, the younger son, as they could sit, stand, and walk with the least support over time. Their mother mentioned that they were agitated at the age of 6 months and at the age of 18 months; both of them suffered from hypotonia and the inability to stand up and also hearing difficulties, which gradually progressed to the inability to walk and stand resulting in their referral to the Pediatric Neurology Clinic after demonstrating the symptoms as mentioned above. Initial medical examination revealed a reduction of muscle strength and deep tendon reflexes, which worsened in the subsequent examinations. The older daughter stopped producing sentences, and at examination, she had slurred speech and

also spasticity in four limbs from one year ago. Their parents had also noted progressive cognitive decline, with difficulty understand simple commands. No abnormal movements, seizures, and behavioral disturbances were observed. Before conducting further clinical and Para clinical evaluations and interventions, written informed consent of the patients' parents was obtained. At the last neurological examination, the patients did not have the ability to speak, make eye contact, and communicate in other ways. They were able to understand simple commands well. Cranial nerve examination, including the optic fundus, was normal. Motor examination revealed spasticity in the older daughter and hypotonia in all four limbs of the younger son, with the absence of tendon reflexes in both of them. The sensory examination was normal. Multiple deformities, such as elbow, knee, and Achilles contracture, were detected. According to the laboratory studies, metabolic diseases were not probable in the children. No abnormal findings were observed following the conduction of electroencephalography (EEG)). Following the electromyography (EMG) and nerve conduction velocity (NCV) study of the older daughter, the probability of the existence of Spinal muscular atrophy (SMA) was raised; however, DNA analysis by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique showed absence of any mutations in SMNt (exon 7 and 8), NAIP4, and NAIP5 genes, and as a result, SMA diagnosis seemed improbable. On the other hand, the deterioration of speech and motor activity, which occurred in the older daughter earlier than in the younger son, raised the suspicions about the Rett syndrome. However, the study of the MECP2 gene in the older daughter revealed the lack of mutation in this gene and, consequently, the little chance of Rett syndrome. MRI of the brain showed cerebellar atrophy with thin and vertical corpus callosum, chiasmal atrophy, and claval hypertrophy. Whole exome sequencing (WES) was performed on the DNA of the affected son.

Genomic DNA was extracted from the peripheral whole blood sample of the patients, and sequencing was done on the Illumina Hiseq4000 platform with 100X depth of coverage and 101 bp paired-end reads. Raw sequence data analysis was performed, including base calling, demultiplexing, alignment to the hg19 human reference genome (Genome Reference Consortium GRCh37), and variant calling. WES findings indicate a homozygous mutation in the position C.2370 T>G (p. Y790X) in the PLA2G6 gene based on NM_001349864.

Bidirectional sequencing was performed to confirm the result. Sanger sequencing study also identified the identical mutations in PLA2G6 genes of the affected daughter.

Discussion

The PLA2G6 gene is located on 22q13.11, consisting of 17 exons. The protein is encoded by PLA2G6, belonging to the A2 phospholipase family (PLA2), known as group VI calcium-independent phospholipase A2 (iPLA2β) that facilitates the hydrolysis of glycerophospholipids in the cell membranes and plays a significant role in moderating the process of arachidonic acid conversion to the pro-inflammatory agents (2). Any impairment in these processes might disturb the balance of pro-inflammatory agents and cause oxidative stress (7). The iPLA2β contains 806 amino acids; human iPLA2β is an 88 KDa. Functional domains in the PLA2G6 protein include an N-terminal region and the

ankyrin repeat domain (numbered regions between amino acids 150–382) that may be responsible for protein-protein interactions and a nucleotide-binding domain centered at amino acid 485. The GXSXG lipase domain with catalytic site (S519) could be located in regions between amino acids 517-521. A C-terminal region includes a calmodulin-binding region (amino acids 747–759) (7, 8, 9). This mutation occurs in the C-terminal of PLA2G6 protein in the position (p. Y790X) found in association with INAD that results in a premature stop codon, leading to truncation of the last 15 amino acids of the WT protein. This mutation results in a significant decline of PLA2G6 phospholipase activity compared to WT protein. Engel et al. indicated that mutations were associated with INAD/NBIA caused by loss of enzyme activity; for example, Y790X mutant proteins had less than 10% of the activity of WT protein (10). Loss of function mutations is usually associated with more severe forms of the disease, while a compound heterozygous variant usually has milder presentations. Mutation in each section of the PLA2G6 gene may be associated with different clinical signs and symptoms. On the other hand, similar mutations in the same sections of this gene may not necessarily demonstrate similar clinical signs and symptoms (2, 3, 11).

A PubMed search (http://www.ncbi.nlm.nih.gov/pubmed) using 'INAD and PLA2G6' phrase yielded 55 papers published from 2006 to 2020. In Iran, previous studies reported cases of PLA2G6 related Dystonia-Parkinson (11,12), and Dr. Rohani et al. noted a case with an oculogyric crisis with Dystonia-Parkinson (13). In this study, we presented two patients with PLA2G6-related infantile neuroaxonal dystrophy (INAD), which has not been reported before.

In a study on seven patients, of whom 4 had classic INAD, Paisán-Ruiz et al. revealed the presence of mutations by sequencing the PLA2G6 gene. Ten different PLA2G6 mutations were identified and confirmed by repeat sequencing. The mutations, including frameshift, missense, splice site, and stop mutations (p. Y790X), were reported in 2012 (14). In children suffering from the progressive disorder with motor and mental deterioration, cerebellar ataxia, hypotonia of the trunk with later pyramidal sign, and early visual impairment (15), particularly with typical MRI findings, INAD should be considered.

According to lower motor neuron sign, SMA was considered for the female patient but after negative genetic analysis and also developmental regression and language and movement abnormality, Rett syndrome was considered. It should be noted that this gene is on the X chromosome, and most boys suffering from this problem die shortly after birth (16), which is inconsistent with our patients who presented similar symptoms.

Our patients indicated hearing loss as well. Noteworthy, INAD associated with hearing loss has been rarely reported in previous studies (17, 18). Additionally, T2-weighted MRI typically showed cerebellar atrophy, thin corpus callosum (19), and hypertrophy of the calva (20), which have been reported in previous studies, and these pathological changes in our cases are consistent with INAD. Meanwhile, in some patients, MRI reveals different stages of cerebral atrophy and is challenging (1, 3, 21). EEG studies failed to demonstrate any pathological findings in our patients, while the investigation of brain waves in patients with INAD might confirm the discharge of epileptic waves (1). It is noteworthy that the different clinical presentations and paraclinical

studies of INAD in each individual make the diagnosis of this neurodegenerative disorder more complicated.

On the other hand, probably the impact of environmental factors on phenotypic differences is as significant as the effect of genotype in these patients (10). Our patients suffer from homozygous mutation of C. T2208G in the PLA2G6 gene in whom some clinical symptoms, such as absence of pyramidal sign, were not similar to the many typical clinical findings of previously reported INAD. Confusing clinical findings, along with the probable environmental factors, resulted in delayed diagnosis in our cases. The motor functions and cognitive symptoms were worsened over time in our patients. Regarding the disease progression, similar patterns have been evident in other similar reports. Therefore, when such symptoms progress over time, one should consider the strong possibility of genetic disorders as differential diagnoses. According to these differences, screening for INAD, with the help of biopsy and PLA2G6 gene mutation evaluation, is vital for early diagnosis, as no specific treatment has been confirmed for INAD yet.

Acknowledgement

We are grateful to Prof. Mohammad Reza Ghazavi, whose efforts in examination and evaluation of the cases made further diagnostic approaches more specific. We appreciate the efforts of Dr. Roham Nik Khah, who helped us prepare the final manuscript and collect relevant scientific papers. Also, our thanks go out to the patients and their family for participating in this study IR.UMSHA.REC.1397.459

Author's Contribution

Behnaz Ansari and Jafar Nasiri designed the study, revised the manuscript, and were the attending physicians for the patients. Hamideh Namazi and Maryam Sedqi gathered and interpreted the laboratory findings. Mahdieh Afzali wrote the manuscript. All authors read and approved the final manuscript. Mahdieh Afzali is the guarantor of this study.

Conflict of interest

The authors declare no conflicts of interest.

References

1. Gebril O, Uebe S, Reuter M, Schumacher J, Jamra RA, Reis A. A new missense mutation in PLA2G6 gene among a family with infantile neuroaxonal dystrophy INAD. Egyptian Pediatric Association Gazette. 2016;64(4):171-6.
2. Guo Y-P, Tang B-S, Guo J-F. PLA2G6-Associated Neurodegeneration (PLAN): Review of Clinical Phenotypes and Genotypes. Front Neurol. 2018; 9:1100.
3. Li H, Zou Y, Bao X, Wang H, Wang J, Jin H, et al. Monozygotic twins with infantile neuroaxonal dystrophy: A case report and literature review. Exp Ther Med. 2016;12(5):3387-9.
4. Iodice A, Spagnoli C, Salerno GG, Frattini D, Bertani G, Bergonzini P, Pisani F and Fusco C: Infantile neuroaxonal dystrophy and PLA2G6-associated neurodegeneration: An update for the diagnosis. Brain Dev 39: 93-100, 2017.
5. Zhang P, Gao Z, Jiang Y, Wang J, Zhang F, Wang S, et al. Follow-up study of 25 Chinese children with PLA2G6-associated neurodegeneration. European journal of neurology. 2013;20(2):322-30.
6. Frattini D, Nardocci N, Pascarella R, Panteghini C, Garavaglia B, Fusco C. Downbeat nystagmus as the presenting symptom of infantile neuroaxonal dystrophy: a case report. Brain & development. 2015; 37(2):270-2.

7. Babin PL, Rao SNR, Chacko A, Alvina FB, Panwala A, Panwala L, et al. Infantile Neuroaxonal Dystrophy: Diagnosis and Possible Treatments. Front Genet. 2018; 9:597.
8. Morgan NV, Westaway SK, Morton JE, Gregory A, Gissen P, Sonek S, Cangul H, Coryell J, Canham N, Nardocci N, Zorzi G. PLA2G6, encoding a phospholipase A 2, is mutated in neurodegenerative disorders with high brain iron. Nature genetics. 2006 Jul;38(7):752-4.
9. Gregory A, Westaway SK, Holm IE, Kotzbauer PT, Hogarth P, Sonek S, et al. Neurodegeneration associated with genetic defects in phospholipase A (2). Neurology. 2008;71(18):1402-9.
10. Engel LA, Jing Z, O'Brien DE, Sun M, Kotzbauer PT. Catalytic function of PLA2G6 is impaired by mutations associated with infantile neuroaxonal dystrophy but not dystonia-parkinsonism. PLoS One. 2010;5(9):e12897-e.
11. Sina F, Shojaee S, Elahi E, Paisan-Ruiz C. R632W mutation in PLA2G6 segregates with dystonia-parkinsonism in a consanguineous Iranian family. European journal of neurology. 2009; 16(1):101-4.
12. Karkheiran S, Shahidi GA, and Walker RH, et al. PLA2G6-associated dystonia–parkinsonism: Case report and literature review. Tremor Other Hyperkinet Mov 2015; 5.
13. Rohani M, Shahidi G, Vali F, Lang AE, Slow E, Gahl WA, et al. Oculogyric crises in PLA2G6 associated neurodegeneration. Parkinsonism Relat Disord. 2018 Jul; 52:111-112.
14.Paisán-Ruiz C, Li A, Schneider SA, Holton JL, Johnson R, Kidd D, Chataway J, Bhatia KP, Lees AJ, Hardy J, Revesz T. Widespread Lewy body and tau accumulation in childhood and adult onset dystonia-parkinsonism cases with PLA2G6 mutations. Neurobiology of aging. 2012 Apr 1;33(4):814-23.
15. Aicardi J and Castelein P: Infantile neuroaxonal dystrophy. Brain 102: 727-748, 1979.
16. Brief report: systematic review of Rett syndrome in males. Reichow B, George-Puskar A, Lutz T, Smith IC, Volkmar FR. J Autism Dev Disord. 2015; 45:3377–3383.
17. Kulkarni SD, Meenal G, Rafat S and Patil VA: Two unusual cases of PLA2G6-associated neurodegeneration from India. Ann Indian Acad Neurol 19: 115-118, 2016.
18. BAOTIAN WANG, DE WU and JIULAI TANG. Infantile neuroaxonal dystrophy caused by PLA2G6 gene mutation in a Chinese patient: A case report. EXPERIMENTAL AND THERAPEUTIC MEDICINE 16: 1290-1294, 20181290.
19. Farina L, Nardocci N, Bruzzone MG, D'Incerti L, Zorzi G, Verga L, et al. Infantile neuroaxonal dystrophy: neuroradiological studies in 11 patients. Neuroradiology 1999; 41:376-80.
20. Solomons J, Ridgway O, Hardy C, Kurian MA, Kurian M, Jayawant S, et al. Infantile neuroaxonal dystrophy caused by uniparental disomy. Dev Med Child Neurol 2014; 56:386-9.
21. Mascalchi M, Mari F, Berti B, Bartolini E, Lenge M, Bianchi A, et al. Fast Progression of Cerebellar Atrophy in PLA2G6-Associated Infantile Neuronal Axonal Dystrophy. Cerebellum (London, England). 2017;16(3):742-5.