JCN Open Access LETTER TO THE EDITOR

pISSN 1738-6586 / eISSN 2005-5013 / J Clin Neurol 2024;20(2):220-222 / https://doi.org/10.3988/jcn.2023.0336

Mitochondrial-Membrane-Protein-Associated Neurodegeneration in Longitudinal Magnetic Resonance Imaging Over 11 Years of Follow-Up

Jiyun Lee[a,b]
Jin Ju Kim[c,d]
Chul Hyoung Lyoo[b,e]
Yun Joong Kim[a,b]

[a]Department of Neurology, Yongin Severance Hospital, Yonsei University Health System, Yongin, Korea
[b]Department of Neurology, Yonsei University College of Medicine, Seoul, Korea
[c]Department of Laboratory Medicine, Yongin Severance Hospital, Yonsei University Health System, Yongin, Korea
[d]Department of Laboratory Medicine, Yonsei University College of Medicine, Seoul, Korea
[e]Department of Neurology, Gangnam Severance Hospital, Yonsei University Health System, Seoul, Korea

Received August 30, 2023
Revised October 28, 2023
Accepted November 11, 2023

Correspondence
Yun Joong Kim, MD, PhD
Department of Neurology, Yongin Severance Hospital, Yonsei University Health System, 363 Dongbaekjukjeon-daero, Giheung-gu, Yongin 16995, Korea
Tel +82-31-5189-8140
Fax +82-31-5189-8565
E-mail yunjkim@yuhs.ac

Dear Editor,

Neurodegeneration with brain iron accumulation (NBIA) is characterized by abnormal iron accumulation in the basal ganglia, especially the globus pallidus (GP) and substantia nigra (SN), which is easily to detect using brain magnetic resonance imaging (MRI).[1] Mitochondrial-membrane-protein-associated neurodegeneration (MPAN, MIM #614298) caused by mutations in *C19orf12* is a subtype of NBIA. MPAN is characterized by dystonia, behavioral disturbances, and cognitive impairment with a variable prognosis. Neuropsychiatric problems such as emotional lability, depression, compulsions, and impulsivity are also common early during the disease progression.[2] Here we report on the first Korean patient with MPAN carrying compound heterozygous mutations in *C19orf12* with longitudinal MRI performed over 11 years.

A 23-year-old female who was admitted for pulmonary thromboembolism associated with oral contraceptive use was consulted for generalized dystonia over an 11-year period. She was born at full term via a normal spontaneous vaginal delivery without perinatal injury and had no family history of any movement disorders. Her developmental milestones were not delayed before she was diagnosed as having attention deficit hyperactivity disorder at the age of 8 years. This progressed to gait disturbance with postural instability and mild cognitive decline at 9 years of age, optic nerve atrophy at 11 years, generalized dystonia and progressive cognitive decline at 12 years, ataxic gait and spasticity at 14 years, not being able to stand up or walk by herself and becoming wheelchair-bound at 16 years, mild dysphagia resulting in occasional aspiration and dysarthria at 17 years, and memory impairment and compulsive behavior at 18 years. She also had emotional incontinence with a silly smile. A neurological examination revealed severe dysarthria, generalized dystonia, oromandibular dystonia, and severe spasticity. Her Mini-Mental State Examination score was 9, and she could speak only a few short phrases intermittently. Comprehensive neuropsychological tests at the age of 23 years revealed damage in all cognitive domains.

Whole-exome sequencing conducted at the age of 23 years revealed a novel mutation in *C19orf12* (NM_001031726.3), c.386dupA (p.Gln130AlafsTer22), which was compound heterozygous with the known mutation c.199dupG (p.Ala67fs*16).[3] Analysis of her parents revealed that the c.386dupA and c.199dupG mutations were on the maternal and paternal alleles, respectively (Supplementary Fig. 1 in the online-only Data Supplement). According to the American College of Medical Genetics and Genomics (ACMG) guideline, the novel mutation was classified as pathogenic (PVS1, PM2, PM3, and PP4).[4]

Follow-up brain MRI at the age of 23 years revealed that iron accumulation was confined to the GP and SN, sparing the dentate nucleus, and that the degree of iron accumulation had not changed markedly. However, mild and diffuse cerebral atrophy and cerebellar atrophy

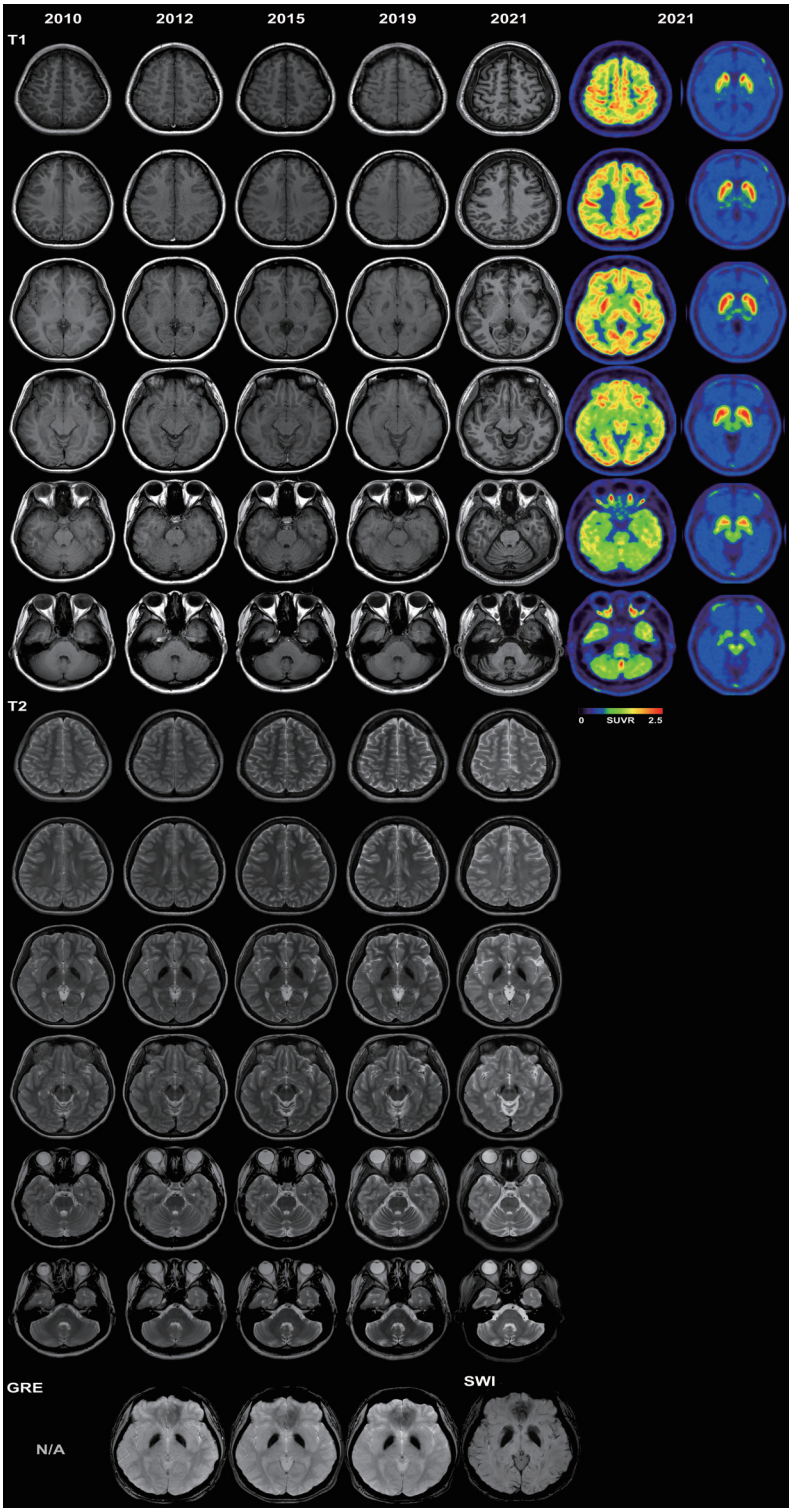

Fig. 1. MRI findings of a patient with mitochondrial-membrane-protein-associated neurodegeneration (MPAN) over a 11-year follow-up. Bilateral hypointensities in the globus pallidus and substantia nigra in axial T2-weighted brain MRI were obvious since the age of 13 years in 2010. Follow-up brain MRI at the age of 23 years showed that iron accumulation had not changed markedly. However, cerebellar atrophy had progressed during the preceding 3 years. FDG PET showed substantial decreases in FDG uptake in the bilateral cerebellar hemispheres, nucleus accumbens, and caudate nucleus, and slight uptake decreases in bilateral frontal and parietal lobes. ^{18}F-FP-CIT PET showed that dopamine transporter binding was preserved bilaterally in the posterior putamen. FDG, ^{18}F-fluorodeoxyglucose; ^{18}F-FP-CIT, (3-[^{18}F]fluoropropyl)-2β-carbon ethoxy-3β-(4-iodophenyl) nortropane; GRE, gradient echo; MRI, magnetic resonance imaging; N/A, not available; PET, positronemission tomography; SUVR, standardized uptake value ratio; SWI, susceptibility-weighted images.

had progressed during the preceding 3 years (Fig. 1). ^{18}F-fluorodeoxyglucose (FDG) positron-emission tomography (PET) showed substantial decreases in FDG uptake in the bilateral cerebellar hemispheres, nucleus accumbens, and caudate nucleus, and slight uptake decreases in bilateral frontal and parietal lobes. ^{18}F-FP-CIT [(3-[^{18}F] fluoropropyl)-2β-carbon ethoxy-3β-(4-iodophenyl) nortropane] PET showed that dopamine transporter binding was preserved bilaterally in the posterior putamen (Fig. 1).

Her dystonia improved notably but only temporarily after introducing anticholinergics, which were discontinued due to deterioration of her cognition. The cholinomimetic rivastigmine improved her cognition for only a few weeks. Side effects such as acneiform eruption and dermatitis resulted in rivastigmine being discontinued.

Most MPAN cases have been reported in Caucasian and Middle Eastern patients, with only rare reports in East Asian patients.[5,6] The present case shows major phenotypes of MPAN[2] that evolved from gait disturbance to optic atrophy, generalized dystonia, spasticity, and ataxia. Despite progressive motor dysfunction and cognitive decline, there were no gross changes in the abnormal longitudinal MRI findings over a 11-year follow-up except for mild atrophy of cerebellum and cerebral hemisphere. Disease progression in MPAN is known to be slow, with the exception of a few adult onset cases with rapid progression leading to death.[7-9] Dystonia is the most common extrapyramidal sign in MPAN, followed by parkinsonism. A comprehensive review of phenotypes in 141 reported cases revealed that only 7% of MPAN patients showed cerebellar atrophy and that 3% of patients showed ataxia (Supplementary Material and Supplementary Fig. 2 in the online-only Data Supplement). Widespread alpha-synuclein-positive Lewy body pathologies have been found in the brain of MPAN patients, but neuronal loss in the SN is variably reported.[2,7] Presynaptic dopamine transporter imaging in our case showed that the putamen was spared.

This is the first reported genetic analysis of MPAN patients in Korea. Although no prior cases have been documented, this report emphasizes the importance of considering MPAN identification and *C19orf12* genetic testing in Korean NBIA patients.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2023.0336.

Ethics Statement

This study study was approved by Yonsei University College of Medicine, Yongin Severance Hospital, Institutional Review Board (approval number: 9-2023-0070).

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

ORCID iDs

Jiyun Lee https://orcid.org/0009-0006-4469-5205
Jin Ju Kim https://orcid.org/0000-0001-9166-1848
Chul Hyoung Lyoo https://orcid.org/0000-0003-2231-672X
Yun Joong Kim https://orcid.org/0000-0002-2956-1552

Author Contributions

Conceptualization: Chul Hyoung Lyoo, Yun Joong Kim. Data curation: Jiyun Lee. Formal analysis: Jin Ju Kim, Chul Hyoung Lyoo. Investigation: Jiyun Lee, Chul Hyoung Lyoo. Methodology: Yun Joong Kim. Resources: Chul Hyoung Lyoo. Supervision: Yun Joong Kim. Visualization: Jiyun Lee, Chul Hyoung Lyoo. Writing—original draft: Jiyun Lee. Writing—review & editing: Jiyun Lee, Jin Ju Kim, Yun Joong Kim.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Funding Statement

This research was supported by a grant of the Korea Health Technology R&D Project through the Korean Healthy Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: RS-2023-00265377).

REFERENCES

1. Hogarth P. Neurodegeneration with brain iron accumulation: diagnosis and management. *J Mov Disord* 2015;8:1-13.
2. Hogarth P, Gregory A, Kruer MC, Sanford L, Wagoner W, Natowicz MR, et al. New NBIA subtype: genetic, clinical, pathologic, and radiographic features of MPAN. *Neurology* 2013;80:268-275.
3. Deschauer M, Gaul C, Behrmann C, Prokisch H, Zierz S, Haack TB. C19orf12 mutations in neurodegeneration with brain iron accumulation mimicking juvenile amyotrophic lateral sclerosis. *J Neurol* 2012;259:2434-2439.
4. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015;17:405-424.
5. Chen S, Lai X, Fu J, Yang J, Zhao B, Shang H, et al. A novel C19ORF12 mutation in two MPAN sisters treated with deferiprone. *BMC Neurol* 2023;23:134.
6. Yang Y, Zhang S, Yang W, Wei T, Hao W, Cheng T, et al. Case report: identification of a de novo C19orf12 variant in a patient with mitochondrial membrane protein-associated neurodegeneration. *Front Genet* 2022;13:852374.
7. Hartig MB, Iuso A, Haack T, Kmiec T, Jurkiewicz E, Heim K, et al. Absence of an orphan mitochondrial protein, C19orf12, causes a distinct clinical subtype of neurodegeneration with brain iron accumulation. *Am J Hum Genet* 2011;89:543-550.
8. Dogu O, Krebs CE, Kaleagasi H, Demirtas Z, Oksuz N, Walker RH, et al. Rapid disease progression in adult-onset mitochondrial membrane protein-associated neurodegeneration. *Clin Genet* 2013;84:350-355.
9. Olgiati S, Doğu O, Tufekcioglu Z, Diler Y, Saka E, Gultekin M, et al. The p.Thr11Met mutation in C19orf12 is frequent among adult Turkish patients with MPAN. *Parkinsonism Relat Disord* 2017;39:64-70.