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A Novel *GFAP* Mutation in Late-Onset Alexander Disease Showing Diffusion Restriction

Tai-Seung Nam[a]
Jeeyoung Oh[b]
Michael Levy[c]
Kyung-Wook Kang[a]
Seok-Yong Choi[d]
Myeong-Kyu Kim[a]

[a]Departments of Neurology and [d]Biomedical Sciences, Chonnam National University Medical School, Gwangju, Korea
[b]Department of Neurology, Konkuk University School of Medicine, Seoul, Korea
[c]Department of Neurology, Johns Hopkins University, Baltimore, MD, USA

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Correspondence
Myeong-Kyu Kim, MD, PhD
Department of Neurology, Chonnam National University Medical School, 160 Baekseo-ro, Dong-gu, Gwangju 61469, Korea
Tel +82-62-220-6161
Fax +82-62-236-0839
E-mail mkkim@jnu.ac.kr

Jeeyoung Oh, MD, PhD
Department of Neurology, Konkuk University School of Medicine, 120-1 Neungdong-ro, Gwangjin-gu, Seoul 05030, Korea
Tel +82-2-2030-7564
Fax +82-2-2030-5169
E-mail serein1002@naver.com

Dear Editor,

A 16-year-old woman who had a history of febrile seizure at the age of 3 years presented with unsteady gait and urinary difficulties with a 5-year history, and with progressive learning difficulty over the previous year. A neurological examination revealed gaze-evoked nystagmus, cerebellar ataxia, and pyramidal signs, but no bulbar signs were present. The Wechsler Adult Intelligence Scale was used to evaluate her intelligence quotient (IQ): her full-scale IQ was 54 (verbal IQ of 53 and performance IQ of 67), indicating mental retardation. She was diagnosed with spastic bladder based on a uroflowmetry study showing severe dysfunction during the filling and storage phases.

Magnetic resonance imaging (MRI) of the brain revealed extensive cerebral white matter (WM) hyperintensities in the bilateral periventricular regions with frontal predominance (Fig. 1A). Atrophy was observed in the brainstem and cerebellum, and thinning of the corpus callosum was noted (Fig. 1B). Pial signal changes on fluid-attenuated inversion recovery (FLAIR) images were prominent along the brainstem (Fig. 1C, D, and E) and around the fourth ventricle. Additionally, multifocal lesions with a diffusion restriction pattern (DRP) were observed in cortical regions as well as the periventricular area (Fig. 1F and G), which remained prominent or increased in the follow-up MRI performed 1 year later (Fig. 1H and I).

Glial fibrillary acidic protein gene (*GFAP*) sequencing analysis revealed a novel heterozygous missense mutation (c.1087A>G) that caused the highly conserved amino acid isoleucine-to-valine transition (p.Ile363Val) (Fig. 1J), which was not found in 200 normal controls nor in her asymptomatic parents (Fig. 1K). PolyPhen-2 analysis predicts that this mutation would probably be damaging (Fig. 1L). Among leukodystrophies, metachromatic leukodystrophy, Krabbe's disease, and adrenoleukodystrophy were also excluded through serological and genetic testing.

The patient was diagnosed with Alexander disease (AxD) based on the following findings: 1) clinical features of gait disturbance with spasticity/hyperreflexia, autonomic dysfunction, nystagmus, and neurocognitive deficits, 2) radiological features of pial FLAIR signal changes and atrophy in the brainstem and cerebellum as well as bilateral cerebral WM hyperintensities, and 3) *GFAP* sequencing analysis.

AxD is a progressive neurological disorder that primarily affects the cerebral WM and which is caused by dominant mutations in *GFAP*.[1] AxD has been traditionally divided into three forms depending on the age of the patient at the onset of symptoms: infantile-onset AxD (birth to 2 years), juvenile-onset AxD (2–14 years), and adult-onset AxD (>14 years).[1] AxD is also classified into two types based on both the age at onset and the degree of cortical involvement:[1] type I usually presents before an age of 4 years with cortical dominant features including seizures and macrocephaly, while type II usually presents in the second decade of life or later with brainstem and cerebellar dominant signs.[1] Clinically, the present

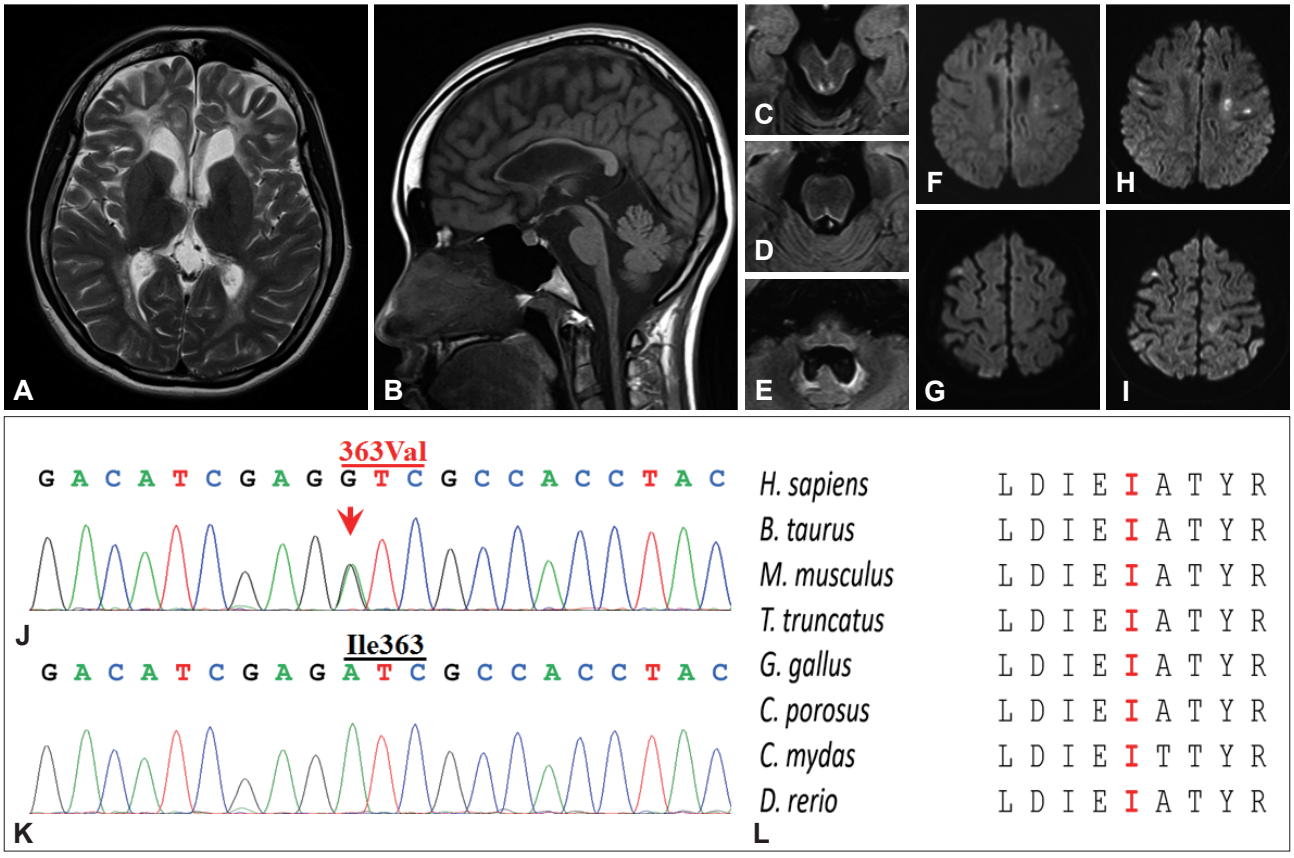

Fig. 1. MRI findings and mutational analysis of the patient. A: T2-weighted axial MRI image showing high-signal-intensity lesions in the bilateral periventricular WM with frontal predominance. B: T1-weighted sagittal MRI image showing atrophy in the brainstem, cerebellum, and upper cervical cord as well as thinning of the corpus callosum. C, D, and E: Axial fluid-attenuated inversion recovery MRI images showing abnormal hyperintensities along the pia in the midbrain (C), pons (D), medulla oblongata, and around the fourth ventricle (E). F and G: Axial DWI images showing multifocal hyperintensities within the periventricular WM and cerebral cortex. H and I: DWI images obtained 1 year later showing newly developed multifocal small hyperintensities in the right cortical region as well as the previously existing lesions. J: Electropherogram of the patient reveals a nonsynonymous heterozygous A-to-G missense mutation (c.1087A>G, p.Ile363Val, red arrow) in exon 6 of the *GFAP*. K: Representative electropherogram of *GFAP* from a normal control. L: The p.Ile363 residue is highly conserved, and found in evolutionary distant orthologs down to zebra fish. The sequences were derived from GenBank with the following accession numbers of the orthologs: *Homo sapiens* (NM_002055.4), *Bos taurus* (cattle; NM_174065.2), *Mus musculus* (house mouse; NM_010277.3), *Tursiops truncatus* (dolphin; XM_019939330.1), *Gallus gallus* (chicken; XM_418091.5), *Crocodylus porosus* (Australian saltwater crocodile; XM_019554575.1), *Chelonia mydas* (green sea turtle; XM_007053824.1), and *Danio rerio* (zebra fish; NM_131373.2). DWI: diffusion-weighted MRI, *GFAP*: glial fibrillary acidic protein gene, MRI: magnetic resonance imaging, WM: white matter.

case is typical of the type II form with a later age at onset, gait disturbance, ocular movement abnormalities, autonomic dysfunction, and the predominance of posterior fossa WM abnormalities.[1,2] However, her neurocognitive deficits, history of febrile seizure, and radiologically extensive cerebral WM abnormalities with frontal predominance as well as the absence of bulbar signs is more typical of type I.[1,2]

A particularly interesting finding in this case was of multifocal cerebral lesions with a DRP. Such a pattern within the periventricular rim has been described previously in two patients with juvenile-onset AxD, but no images were provided.[3] A DRP can be caused by cytotoxic edema, intramyelinic edema, hypercellularity, hyperviscosity, vacuolization, or the compartmentalization of water.[4] A DRP in leukodystrophies may be explained by cytotoxic intramyelinic edema related to active demyelination.[4] However, the complicated mechanism of demyelination in AxD involves an astrogliopathy rather than a pure leukodystrophy.[1] Therefore, the DRP in the present case may have been caused by a decrease in extracellular fluids or an increase in intracellular water due to the hypercellularity of astrocytes in the affected area.[3,4] Multifocal cerebral lesions with the DRP in this case were found or increased on the serial MRI scans performed while the patient complained of progressive learning difficulty or cognitive decline, which suggests that a DRP is related to clinical disease progression. However, further studies are needed to determine the relationship between the radiological features of AxD and disease progression.

Conflicts of Interest

The authors have no financial conflicts of interest.

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