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Genetic and Imaging Characteristics of a Family With Neuronal Intranuclear Inclusion Disease

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Dear Editor,

Neuronal intranuclear inclusion disease (NIID) is a rare slowly progressive neurodegenerative disease characterized by intranuclear inclusions in the central, peripheral, and autonomic nervous systems and visceral organ cells.[1] The various reported clinical manifestations of NIID include pyramidal and extrapyramidal symptoms, dementia, neuropathy, and autonomic dysfunction.[1] We present the first case of genetically confirmed familial NIID in Korea, including MRI findings from its early stages.

A 56-year-old female (Patient 1) experienced recurrent vomiting and dizziness approximately once yearly, recovering spontaneously within a couple of days. At 61 years of age she lost consciousness every few months, recovering without complications within 24 hours. At 62 years of age she was referred to our neurology department due to a stuporous mental state lasting 9 days. Her mental state and cognition improved slowly. She could say her name at 26 days after the onset (Mini-Mental State Examination [MMSE] score=4) and showed significant improvement 3 months later (MMSE score=16). Loss of consciousness with confusion recurred twice at 62 and 67 years of age (MMSE score=2 at the attack when 67 years of age). During nonrecurrence periods between 62 and 67 years of age, she could do housework, including cooking, and perform the activities of daily living. After the last attack at 67 years of age, she showed obvious cognitive impairment and needed help from other people, but remained living in her own home with an alert mental state while consuming normal meals and walking independently (MMSE score=10, Clinical Dementia Rating=1).

A younger brother of Patient 1 (Patient 2) began experiencing an episodic visual field defect at 54 years of age. At 56 years of age he began experiencing periodic nausea and vomiting lasting for several days. At 57 years of age he experienced the subacute onset of left homonymous hemianopsia, for which he visited our neurology department. His left hemianopsia disappeared after 5 months. Detailed neuropsychological tests showed global cognitive impairment (MMSE score=25). He subsequently frequently experienced nausea, vomiting, and loss of consciousness. At 58 years of age he exhibited confusion and neuropsychiatric symptoms, including occasional visual hallucinations and aggression (MMSE score=22), and repeated episodic visual field defect that alternated between the right and left sides. His ophthalmology assessment results were normal. At 61 years of age he presented with daily vigorous vomiting and loss of consciousness (MMSE=27). He died of malnutrition and sepsis at 62 years of age despite receiving supportive care.

Laboratory test results revealed sensorimotor and autonomic neuropathy and neurogenic bladder in both patients. Their mother exhibited dementia symptoms at 69 years of age and their father had a stroke (Supplementary Fig. 1 in the online-only Data Supplement). We found subcortical white-matter hyperintensities (WMH) in fluid-attenuated inversion recovery (FLAIR) imaging and high-intensity signals at the corticomedullary junction in diffusion-weighted imaging (DWI) (Fig. 1A and B). A skin biopsy revealed ubiquitin-positive intranu-

clear inclusions in the sweat-gland cells of both patients. Electron microscopy revealed intranuclear inclusions with fine filaments in sweat-gland cells (Fig. 1C). Genetic testing performed using the method described in the Supplementary Material (in the online-only Data Supplement) revealed 149 and 107 GGC-repeat expansions in *NOTCH2NLC* in Patient 1 and Patient 2, respectively (disease-causing range, 41 to 300 repeats)[2] (Fig. 1D). The wide variation in repeat length in

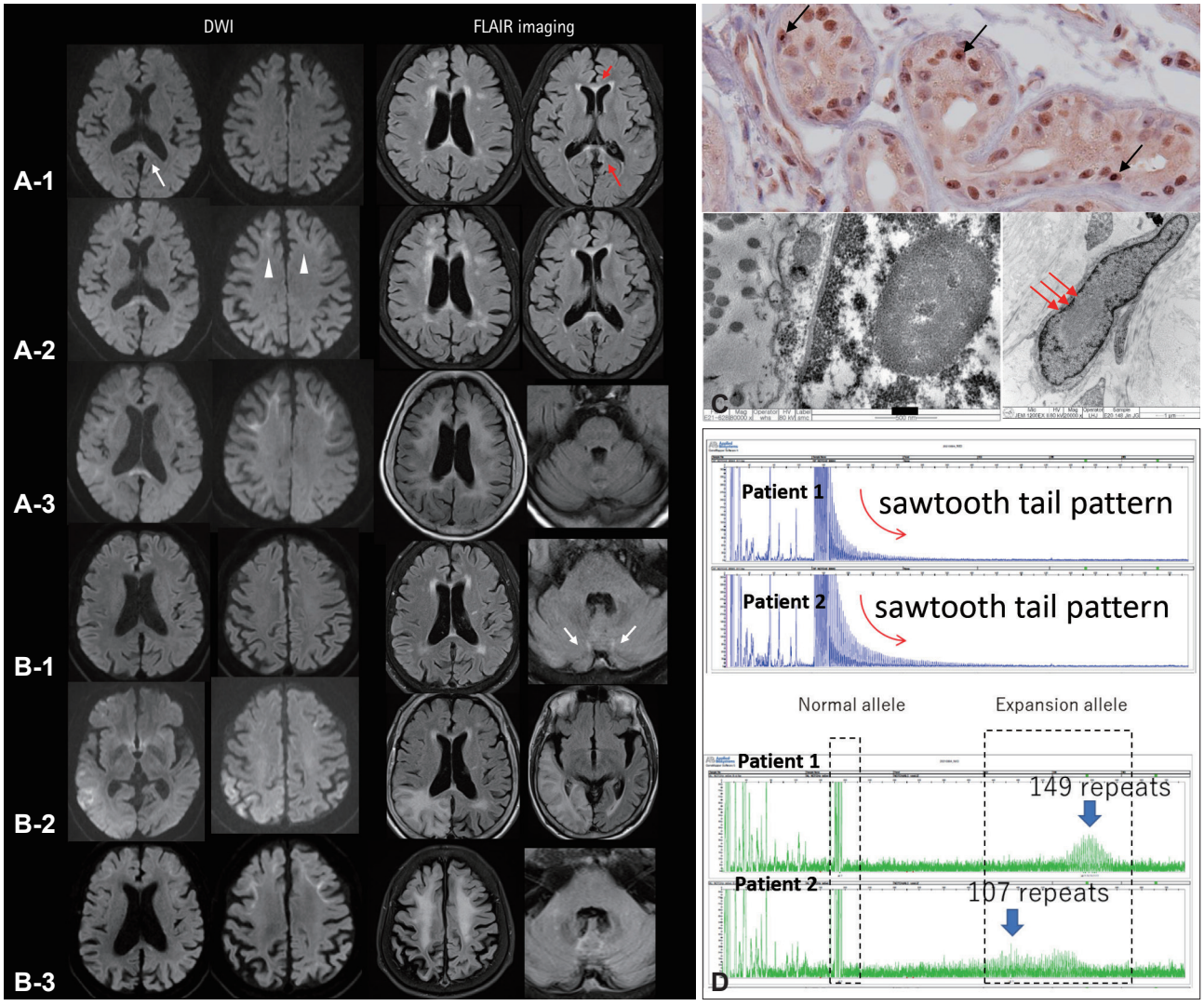

Fig. 1. Findings of brain MRI, skin biopsy, and genetic analysis of the patients with neuronal intranuclear inclusion disease. A-1: Patient 1 at 56 years of age, with symptoms of dizziness and vomiting. MRI shows high-intensity signals in the splenium (white arrow) in DWI, and high-intensity signals in the splenium and genu (red arrows) along with mild WMH in FLAIR images. A-2: Patient 1 at 59 years of age, with symptoms of dizziness and vomiting. MRI shows high-intensity signals in the corticomedullary junction in DWI (arrowheads) and aggravated WMH. A-3: Patient 1 at 62 years of age, with a decreased mental state. MRI shows high-intensity signals in the frontal and parietal corticomedullary junction, and severe WMH. B-1: Patient 2 at 54 years of age, with a visual field defect. There are no abnormalities in DWI. FLAIR images reveal high-intensity signals in the splenium, genu, and cerebellar hemisphere adjacent to the vermis (arrows), and mild WMH. B-2: Patient 2 at 57 years of age, with left hemianopsia. DWI shows multifocal diffusion-restricted foci along the sulci of the right parietal, occipital, temporal, and both frontal lobes. FLAIR images show high-intensity signals in the subcortical white matter of the right parietal, occipital, and temporal lobes. B-3: Patient 2 at 61 years of age, with vomiting and loss of consciousness. MRI shows high-intensity signals in the frontal and parietal corticomedullary junction in DWI and severe WMH, along with diffuse cerebral atrophy. C: Immunohistochemical staining of skin samples showing ubiquitin-positive intranuclear inclusions in sweat-gland cells in Patient 2 (arrows in upper panel; Z0458, Dako, Carpinteria, CA, USA; ×400). Electron microscopy demonstrates that the intranuclear inclusions comprised a haphazard meshwork of fine, straight filaments with no limiting membranes in fibroblasts (Patient 1, left lower panel; ×80,000) or sweat-gland cells (Patient 2, arrows in right lower panel; ×20,000). D: Repeat-primed PCR demonstrates a sawtooth tail pattern, suggesting GGC-repeat expansion in both patients (upper panel). AL-PCR detected AL-PCR amplicon signals in both patients, which are 149 and 107 GGC-repeats expansions for Patient 1 and Patient 2, respectively, in the 50-untranslated region of *NOTCH2NLC* (lower panel). The number of repeats was calculated using the highest peak in the AL-PCR signal. AL-PCR, amplicon-length PCR; DWI, diffusion-weighted imaging; WMH, white-matter hyperintensities; FLAIR, fluid-attenuated inversion recovery.

Patient 2 suggests repeat instability and/or somatic mosaicism. We found that the fragile X mental retardation 1 (*FMR1*) permutation CGG repeats were within the normal range in Patient 2. The *FMR1* gene was not analyzed for Patient 1.

These two patients were diagnosed with familial adult-onset NIID based on clinical symptoms, characteristic MRI findings, intranuclear inclusions on skin biopsy, and *NOTCH2NLC* GGC-repeat expansions. Patient 1 experienced relatively long episodes of unconsciousness and cognitive impairment (lasting several weeks), and eventually developed dementia, whereas Patient 2 presented with stroke-like encephalopathy and recurrent short episodes of unconsciousness (lasting about 20 minutes) and vigorous vomiting. Variations in repeat length may have been responsible for the phenotypic variations. However, the length of the GGC repeats was not correlated with clinical symptoms in a previous study.[3]

Abnormal DWI findings in the corticomedullary junction are strongly related to NIID, appearing in 100% of sporadic cases and 81% of familial cases.[1] However, in our patients, typical DWI findings appeared 2−3 years after the first symptom and presented as larger areas of high-intensity signals when WMH became extensive. We found high-intensity signals in the splenium and genu, with mild WMH in FLAIR images during the early stages. Other early findings included high-intensity signals in the splenium in DWI (Fig. 1A-1) and the cerebellar hemisphere adjacent to the vermis in FLAIR images (Fig. 1B-1). High-intensity signals in the cerebellar hemisphere adjacent to the vermis were observed previously in FLAIR images, even in the absence of DWI abnormalities.[4,5]

Two sporadic cases confirmed by skin biopsy were reported in Korea, with clinical manifestations including rapidly progressive dementia,[6] repeated confusion, and slowly progressive cognitive impairment.[7] Our patients exhibited clinical manifestations and/or abnormal findings for the central, autonomic, and peripheral nerve systems. In particular, periodic vomiting, which is considered an autonomic symptom,[8,9] was one of the main symptoms in our patients. Approximately 15% of sporadic cases and 31% of familial cases present with vomiting.[1] Clinicians must consider NIID in the differential diagnosis of repeated unconsciousness and vomiting even before obvious cognitive impairment or DWI abnormalities are detected.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2022.18.3.358.

Ethics Statement

This case was approved by the Institutional Review Board of the Pusan National University Yangsan Hospital (IRB No. 05-2021-239) and exempted from informed consent.

Availability of Data and Material

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

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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