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Adult-Onset Neuronal Intranuclear Inclusion Disease: First Korean Case Confirmed by Skin Biopsy

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Dear Editor,

Neuronal intranuclear inclusion disease (NIID) is a progressive neurodegenerative disease with various clinical features, including dementia, peripheral neuropathy, autonomic dysfunctions, ataxia, and seizure.[1] NIID should be diagnosed based on histopathological findings of intranuclear inclusions that are immunopositive for ubiquitin, SUMO1, and p62 in a skin biopsy.[1,2] High signals in corticomedullary junctions in diffusion-weighted imaging (DWI) is a pathognomonic finding of NIID that may aid its diagnosis.[3] We report the first case of NIID with progressive cognitive impairment, peripheral neuropathy, and autonomic dysfunction in South Korea.

A 65-year-old female was admitted to the Department of Neurology due to rapidly progressive cognitive dysfunction over the previous 5 months. She had a history of seropositive rheumatic arthritis with secondary amyloid A (AA) amyloidosis, chronic kidney disease (CKD), and neurogenic bladder. She had no family history of neurological diseases, but two sisters had CKD with hemodialysis. At the age of 62 years she was forced to stop driving after several car collisions. One year later she experienced loss of spontaneity, topographic disorientation, and delusion. A neurological examination showed mild dysarthria, phonemic paraphasia, agraphesthesia, impairment in sequential motor tasks, and decreased tendon reflexes. Five months earlier her Korean Mini Mental State Examination (K-MMSE) score was 24 and her Clinical Dementia Rating (CDR) score was 1. At the present admission her follow-up K-MMSE and CDR scores were 15 and 2, respectively. Formal neuropsychological test results revealed global cognitive impairment.

Brain magnetic resonance imaging (MRI) showed high-signal lesions along the corticomedullary junctions in DWI (Fig. 1A) that had progressed significantly 17 days later (Fig. 1B). Fluid-attenuated inversion recovery images demonstrated extensive white-matter hyperintensities. Generalized sensorimotor polyneuropathies and cardiovagal autonomic nervous system dysfunction were found. A skin biopsy revealed intranuclear inclusions in immunohistochemical staining of ubiquitin and SUMO1 (Fig. 1C and D). Electron microscopy revealed intranuclear aggregation with a filamentous structure (Fig. 1E).

To the best of our knowledge, this is the first Korean case of adult-onset NIID confirmed by a skin biopsy and concurrent pathognomonic MRI features. Given that many cases of NIID have been reported in Japan and China, the present report of a Korean case may provide an additional clue to the racial tendencies in NIID.[4]

An increasing number of reports on NIID suggest that this disease is not rare, but that its exact diagnosis is difficult due to the varying clinical features.[1] DWI should be performed in patients presenting with progressive cognitive impairment and peripheral or autonomic neuropathy in order to exclude NIID. The characteristic high signals in the corticomedullary junction in DWI may indicate spongiotic changes related to the eosinophilic hyaline inclusions in astrocytes.[3] A skin biopsy along with antibodies for ubiquitin such as SUMO1 or p62

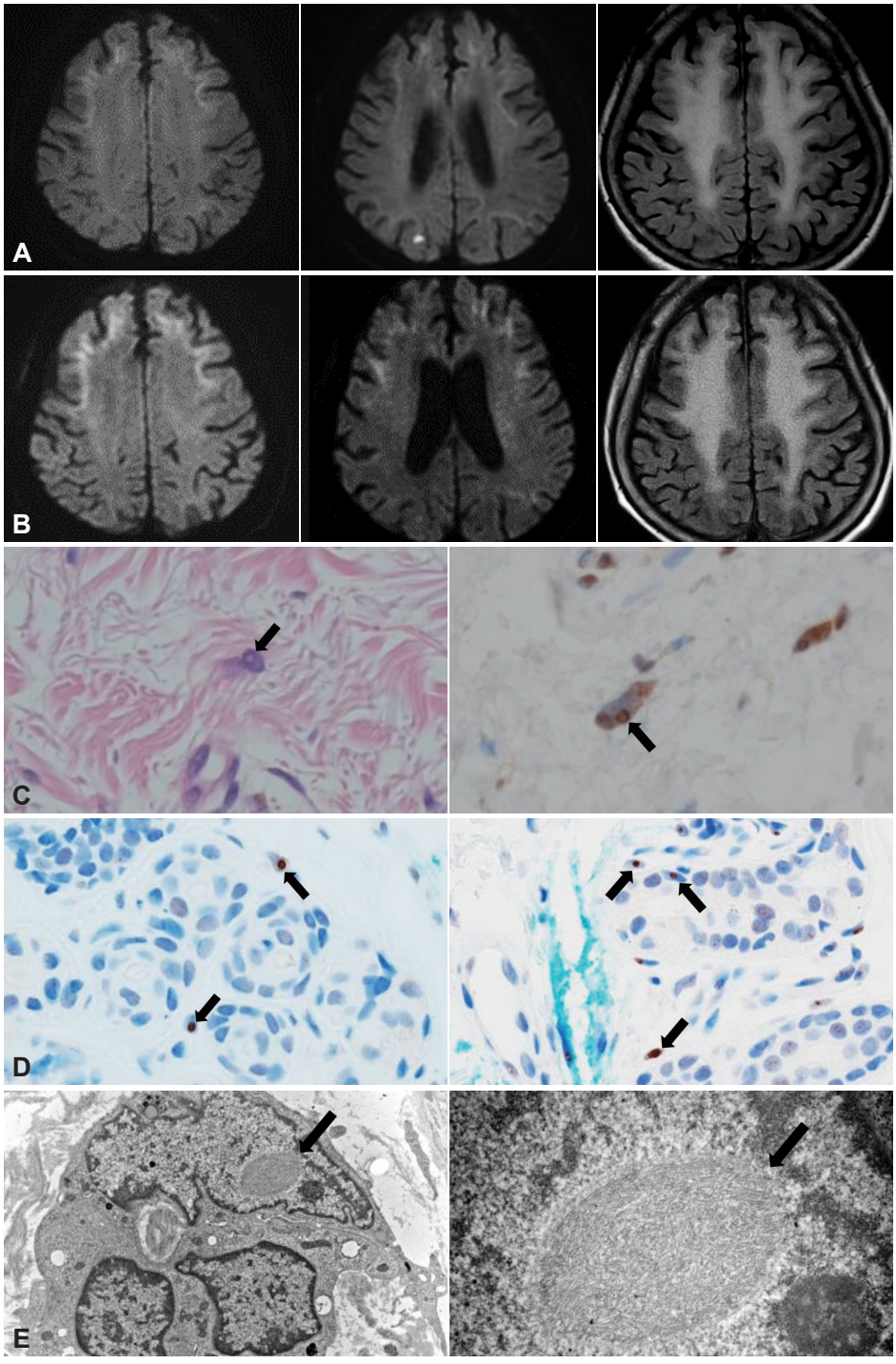

Fig. 1. Findings in brain MRI and skin biopsy of this patient with neuronal intranuclear inclusion disease. A: Initial MRI on admission. B: Follow-up MRI performed 17 days later. A symmetric high signal intensity along the corticomedullary junctions predominantly in the frontal region in DWI progressed over 17 days. The initial assessment revealed a focal DWI high-signal lesion at the right parietal lobe suggesting subacute stage infarction, but it had disappeared in the follow-up images obtained 17 days later. The fluid-attenuated inversion recovery image showed leukoencephalopathy with diffuse symmetric hyperintensities in the bilateral supratentorial and infratentorial regions with diffuse brain atrophy. C: A skin biopsy sample shows an intranuclear eosinophilic inclusion in fibroblasts of the dermis (arrows). Immunohistochemistry of ubiquitin shows positive staining in an intranuclear inclusion of a dermal fibroblast (Z0458, DAKO; ×400). D: Immunohistochemical staining of SUMO1 (D-11) (Santa Cruz, ×200 dilution) shows positive intranuclear inclusions not only in dermal fibroblasts (left, arrows) but also in sweat glands (right, arrows) (×400). E: Electron microscopy of the biopsied skin shows intranuclear aggregation with a filamentous structure without membrane bounding (×10,000; uranium acetate and lead citrate) (left, arrow), also under higher magnification (×40,000; uranium acetate and lead citrate) (right, arrow). DWI: diffusion-weighted imaging, MRI: magnetic resonance imaging.

should be performed to confirm NIID.[1,2]

The pathomechanism of NIID remains uncertain, but the abnormal accumulation of intranuclear proteins or dysfunction of the ubiquitin-mediated protein degradation system could be related to the pathogenesis of intranuclear neuronal inclusions found in multiple organs. NIID is a heterogeneous disorder that affects not only the nervous system but also the respiratory, gastrointestinal, endocrine, urinary, locomotor, and miscellaneous other systems.[1] Rheumatic arthritis with secondary AA amyloidosis, CKD, and neurogenic bladder can be presumed to be associated with NIID. There is a very recent report of the GGC repeat expansion in the *NOTCH2NLC* gene possibly being related to NIID.[5] However, genetic testing could unfortunately not be performed in the present case since it is not available in Korea.

Author Contributions

Conceptualization: Min Young Chun. Data curation: Sun Hee Sung, Yae Won Park. Investigation: Soo-Hyun Kim. Supervision: Jee Hyang Jeong. Validation: Seung-Ah Lee. Writing—original draft: Min Young Chun. Writing—review & editing: Hee Kyung Park, Geon Ha Kim, Jee Hyang Jeong.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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