JCN Open Access LETTER TO THE EDITOR
pISSN 1738-6586 / eISSN 2005-5013 / J Clin Neurol 2020;16(3):494-496 / https://doi.org/10.3988/jcn.2020.16.3.494

Encephalitic Episodes Followed by Leukoencephalopathy: A Novel Indication for Neuronal Intranuclear Inclusion-Body Disease

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Received February 18, 2020
Revised February 25, 2020
Accepted February 27, 2020

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Dear Editor,

Neuronal intranuclear inclusion-body disease (NIID) is a rare progressive neurodegenerative disease characterized by eosinophilic hyaline intranuclear inclusions in neuronal and visceral-organ cells.[1] The clinical manifestations of NIID are highly variable, including movement disorders, dementia, neuropathy, and autonomic dysfunction,[2-4] which makes its early diagnosis difficult. Detecting intranuclear inclusions (both morphologically and immunohistochemically) in skin or central nervous system tissues is valuable for diagnosing both familial and sporadic NIID cases.[5,6] In addition, a characteristic high-intensity signal in the corticomedullary junction in brain MRI diffusion-weighted imaging (DWI) has become another clue for a NIID diagnosis.[6] We investigated a patient who suffered from multiple encephalitic episodes and had been misdiagnosed several times as viral encephalitis. She was finally diagnosed as NIID based on the skin pathology despite not having the typical sign of high-intensity DWI signal along the corticomedullary junction. We followed up this patient for 3 years while observing the MRI changes in NIID.

A 62-year-old female presented with acute-onset fever, headache, and altered mental status. She had experienced three similar episodes during the previous 3 years. Each episode lasted for a few days, and resolved spontaneously without treatment. A neurological examination performed after admission showed impaired short-term memory. Blood-test findings were all within the normal ranges. The cerebrospinal fluid showed normal white blood cell count, glucose level, and protein levels. The result of an autoimmune encephalitis antibody test was negative. Cranial MRI after the first admission revealed cortical swelling that was mainly confined to the left temporal and occipital lobes (Fig. 1A).

The findings in this patient resolved 5 days later without applying any specific treatments. However, 3 months after this attack, repeated MRI showed focal leukoencephalopathy in the left temporal and occipital lobes without cortical swelling (Fig. 1B). Susceptibility-weighted imaging did not reveal any microbleeding. This focal leukoencephalopathy reversed 2.5 years later. Cerebral atrophy was observed after attack, more significantly in the left lobe (Fig. 1C). In March 2019 we performed a skin biopsy, which showed round p62-positive intranuclear inclusions in fibroblast cells and vascular endothelium cells (Fig. 1D and E). Electron microscopy revealed dense filament material without membrane in fibroblasts (Fig. 1F and G). Genetic testing for *FMR1* CGG repeat expansion produced negative findings. NIID antemortem was finally diagnosed based on the clinical symptoms and pathology.[1]

All previously reported sporadic NIID cases were characterized by high-intensity DWI signals along the corticomedullary junction, which is considered an imaging feature. However, our patient did not show this feature, and she had been misdiagnosed several times as viral encephalitis due to experiencing several encephalitic episodes with unknown etiology. Based

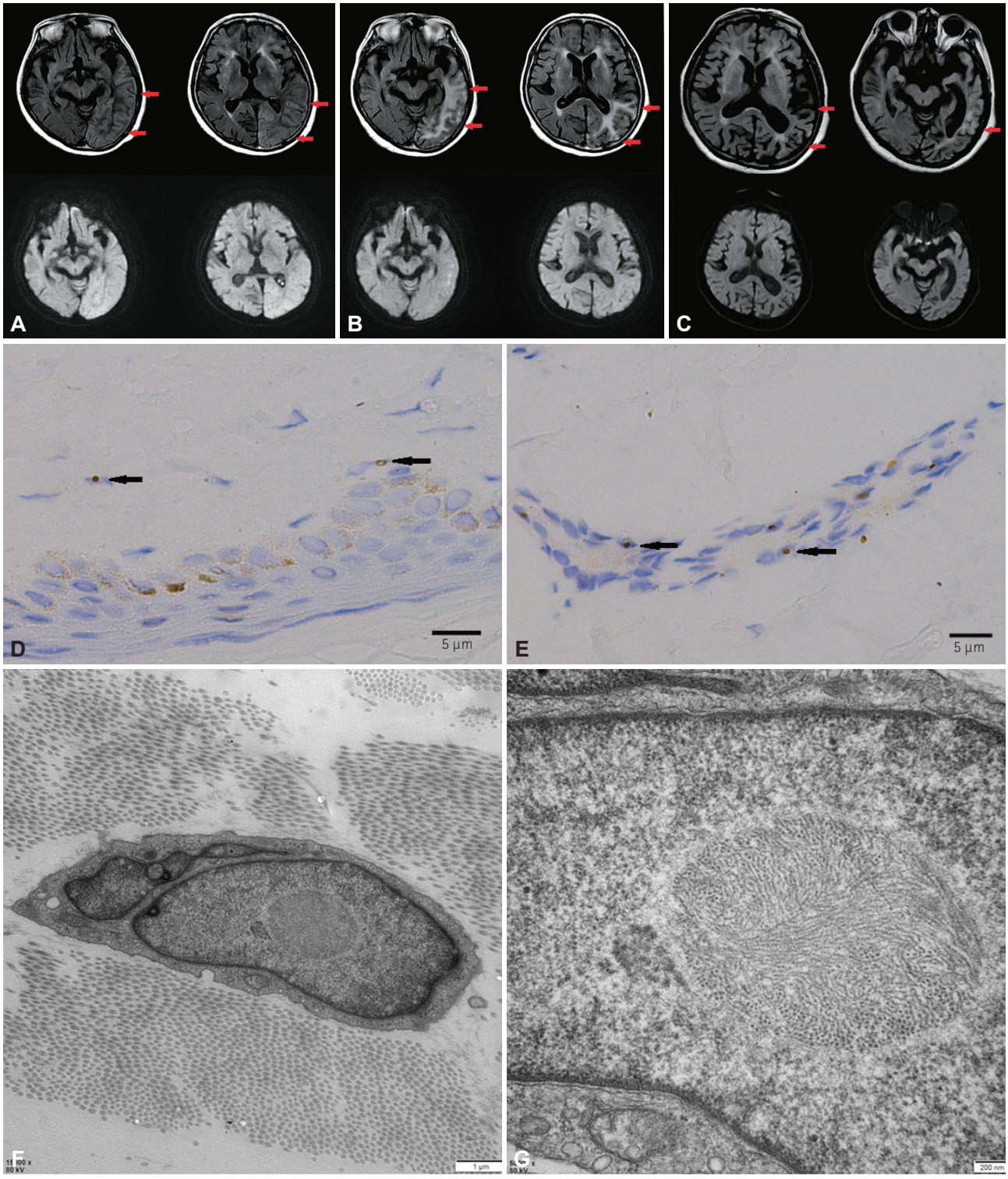

Fig. 1. The cranial MRI findings and skin biopsy results of the patient. Hyperintensities and atrophy (marked by red arrows) in the left temporal and occipital cortical/subcortical regions on T2-weighted fluid-attenuated inversion recovery images in May 2016 (A), September 2016 (B), and March 2019 (C). No typical sign of high-intensity signals along the corticomedullary junction was seen in diffusion-weighted imaging. Light microscopy revealed p62-positive intranuclear inclusions (black arrows) in fibroblast cells (D) and vascular endothelium cells (E). Electron microscopy revealed inclusion bodies within fibroblasts (F and G).

on long-term follow-up, encephalitic episodes followed by reversible asymmetric leukoencephalopathy—as seen in our patient—may represent a new indication for this disease. Although the present patient already had brain atrophy before this attack, the cerebral atrophy obviously deteriorated thereafter. We speculate that each attack can aggravate cerebral atrophy, and so describe this as a "ghost attack."

In summary, we consider that any patients who experience encephalitic episodes followed by leukoencephalopathy should be suspected as NIID, even in the absence of the typical sign of high-intensity DWI signals along the corticomedullary junction.

Author Contributions

Conceptualization: Sheng Chen, Jun Liu. Data curation: Sheng Chen. Formal analysis: Liche Zhou, Xinghua Luan. Investigation: Sheng Chen, Jun Liu. Methodology: Xinghua Luan, Sheng Chen. Project administration: Sheng Chen, Jun Liu. Resources: Xinghua Luan, Sheng Chen. Software: Liche Zhou, Xinghua Luan. Supervision: Sheng Chen, Jun Liu. Validation: Jun Liu. Visualization: Liche Zhou, Xinghua Luan. Writing—original drift: Liche Zhou, Xinghua Luan. Writing—review & editing: Sheng Chen, Jun Liu.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Acknowledgements

None.

REFERENCES

1. Sone J, Mori K, Inagaki T, Katsumata R, Takagi S, Yokoi S, et al. Clinicopathological features of adult-onset neuronal intranuclear inclusion disease. *Brain* 2016;139:3170-3186.
2. Sone J, Hishikawa N, Koike H, Hattori N, Hirayama M, Nagamatsu M, et al. Neuronal intranuclear hyaline inclusion disease showing motor-sensory and autonomic neuropathy. *Neurology* 2005;65:1538-1543.
3. Woulfe JM. Abnormalities of the nucleus and nuclear inclusions in neurodegenerative disease: a work in progress. *Neuropathol Appl Neurobiol* 2007;33:2-42.
4. Takahashi-Fujigasaki J, Nakano Y, Uchino A, Murayama S. Adult-onset neuronal intranuclear hyaline inclusion disease is not rare in older adults. *Geriatr Gerontol Int* 2016;16 Suppl 1:51-56.
5. Sone J, Tanaka F, Koike H, Inukai A, Katsuno M, Yoshida M, et al. Skin biopsy is useful for the antemortem diagnosis of neuronal intranuclear inclusion disease. *Neurology* 2011;76:1372-1376.
6. Sone J, Kitagawa N, Sugawara E, Iguchi M, Nakamura R, Koike H, et al. Neuronal intranuclear inclusion disease cases with leukoencephalopathy diagnosed via skin biopsy. *J Neurol Neurosurg Psychiatry* 2014;85:354-356.