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【 CASE REPORT 】

Temporal Changes in Brain Magnetic Resonance Imaging Findings over 16 Years in a Patient with Neuronal Intranuclear Inclusion Disease

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Abstract:
Leukoencephalopathy with high-intensity signals in the corticomedullary junction on diffusion-weighted imaging (DWI) is a diagnostic hallmark for neuronal intranuclear inclusion disease (NIID). We herein report a 65-year-old man who developed dementia and was diagnosed with NIID 2 years later. Of note, he had coincidentally undergone brain magnetic resonance imaging 14 and 10 years before the onset of dementia. No abnormalities were discerned on DWI on either of these occasions, but high-intensity signals in the corticomedullary junction on DWI were revealed two years before the clinical onset. The early recognition of this pathognomonic white matter change may facilitate the presymptomatic diagnosis of NIID.

Key words: longitudinal, neuronal inclusion intranuclear disease, magnetic resonance imaging, leukoencephalopathy, dementia

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Introduction

Neuronal intranuclear inclusion disease (NIID) is a progressive neurodegenerative disease characterized by eosinophilic hyaline intranuclear inclusions in the central and peripheral nervous systems and in certain visceral organs. Patients with sporadic NIID usually develop dementia, leukoencephalopathy on brain magnetic resonance imaging (MRI) and a high signal intensity in the corticomedullary junction on diffusion-weighted imaging (DWI) (1, 2).

A high-intensity signal in the subcortical U-fiber on DWI is a radiologic hallmark of NIID that often prompts physicians to perform a skin biopsy for an antemortem diagnosis (3, 4). However, how such radiological features develop over the clinical course and whether the DWI features precede or follow the clinical manifestation of NIID remain unclear.

Abe et al. reported the prion-like progression of high-intensity subcortical U-fibers on DWI over 7 years in a 62-year-old woman with NIID (5). At her first presentation at 52 years old, she had exhibited a normal cognitive function; however, unfortunately, DWI was not performed at that initial visit.

We herein report a sporadic case of NIID with radiological follow-up, including presymptomatic DWI, over 16 years. The MRI series of this patient included DWI 14 years before the onset of dementia, and we demonstrate the chronological development of white matter pathology, including the preclinical stage of dementia.

Case Report

A 65-year-old man visited our institution because of an episode of temporary amnesia lasting for several hours. Two weeks prior to the index visit, he suddenly became confused because he was unable to understand where he was and became unaware of where he ought to go. The amnesic period lasted for several hours, resolving completely by the evening.

The findings of a neurological examination, his including cognitive and memory functions, were normal on the day of

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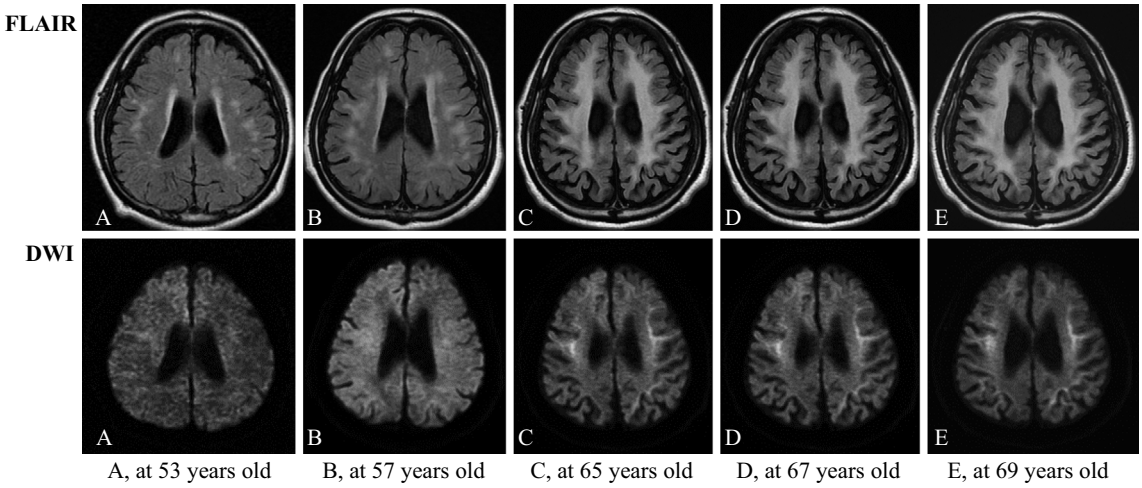

Figure 1. Chronological series of FLAIR images and DWI scans of the patient's brain. (A) Fourteen years before the symptom onset (53 years old). FLAIR images showed sporadic high-intensity lesions in the subcortical white matter, while DWI showed no specific abnormalities. (B) Ten years before the symptom onset (57 years old). FLAIR images showed confluent subcortical high-intensity lesions in the subcortical area, whereas the DWI findings never changed. (C) At the first visit and 2 years before the symptom onset (65 years old). The hyperintense lesions had transformed to leukoencephalopathy on FLAIR, and curvilinear high intensity in the cortimomedullary junction on DWI appeared. (D) At the symptom onset (67 years old). Leukoencephalopathy on FLAIR and a high-intensity signal in the corticomedullary junction on DWI had expanded from the first visit. (E) Two years after the symptom onset (69 years old). Leukoencephalopathy on FLAIR and the high-intensity signal in the corticomedullary junction on DWI had slightly expanded after the symptom onset. DWI: diffusion-weighted imaging, FLAIR: fluid attenuation inversion recovery, MRI: magnetic resonance imaging

the index visit. His medical history included hypertension and bipolar disorder. None of his family members had suffered either early- or late-onset dementia. A neurological examination was unremarkable, and the Mini-Mental State Examination (MMSE) was 30/30 at the first visit. MRI showed no high-intensity signal in the hippocampus, which is the diagnostic hallmark of transient global amnesia (TGA); however, the high-intensity area along the subcortical white matter was discerned on both fluid-attenuated inversion recovery (FLAIR) and DWI (Fig. 1C). At this point, a diagnosis of possible TGA was made, and no further investigations were performed.

At 67 years old, 2 years after the index visit, his wife noticed a gradual decline in his cognition and brought him to our hospital for a further evaluation. A neurological examination was again unremarkable except for the deterioration of the MMSE to 26/30. MRI revealed a high-intensity signal along the subcortical white matter on DWI and FLAIR (Fig. 1D), without any apparent interval change from the previous images. At 69 years old, his cognitive function had further deteriorated with frequent delirium. The MMSE score at this visit had decreased to 23, and his frontal assessment battery score was 14 out of 18 points. Aside from this cognitive impairment, his neurological examination findings were unremarkable, including tendon reflexes, gait and autonomic symptoms, such as anisocoria and urinary symptoms.

The complete blood count and biochemical examination findings, including lactic acid and pyruvic acid, were normal. The cerebrospinal fluid examination showed an elevated protein level of 112 mg/dL with a normal glucose level (67 mg/dL) and normal cell count (0/μL). A nerve conduction study revealed slightly delayed distal motor latency in the left and right median nerves, although the motor conduction velocities were within the normal range. Brain MRI showed extensive high intensities in the cerebral white matter on FLAIR imaging and curvilinear high intensities along the corticomedullary junction on DWI (Fig. 1E), showing a slight deterioration from the previous two evaluations (Fig. 1C, D). Single photon-emission computed tomography (SPECT) with [^{123}I] iodoamphetamine implied a decreased regional cerebral blood flow (rCBF) in the bilateral frontal, left parietal, left precuneous, and bilateral posterior cingulate cortices (Fig. 2). The pathognomic high intensities in the corticomedullary junction on DWI (Fig. 1C, D, E) prompted us to perform a skin biopsy, which revealed numerous p62-positive intranuclear inclusions in the sweat glands, adipocytes and fibroblasts (Fig. 3), confirming the antemortem diagnosis of NIID. Genetic testing for NOTCH2NLC was not performed because he was referred to a local physician due to a decline in his activity of daily living (ADL), in response to his family's request.

When searching the imaging record of this patient, we found that he had serendipitously undergone MRI on 2 different occasions: at 53 and 57 years old as brain checkups at our institution. Those scans corresponded to 14 and 10

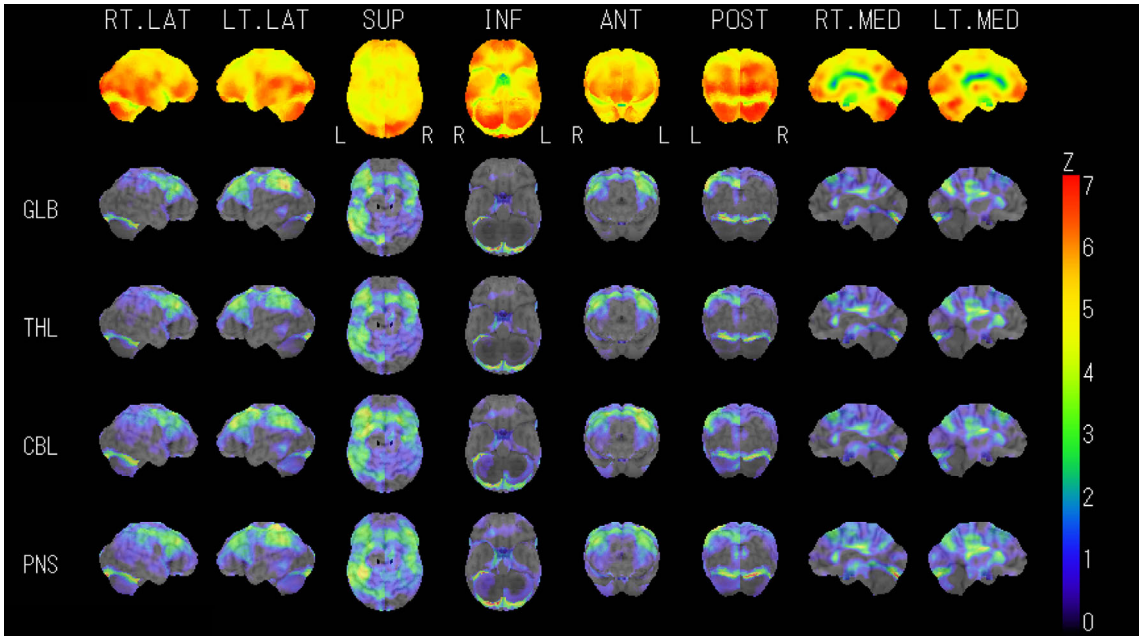

Figure 2. **A three-dimensional stereotactic surface projection (3D-SSP) of single photon-emission computed tomography with N-isopropyl-4-[^{123}I]-iodoamphetamine (IMP) showed hypoperfusion in the front-parietal regions.**

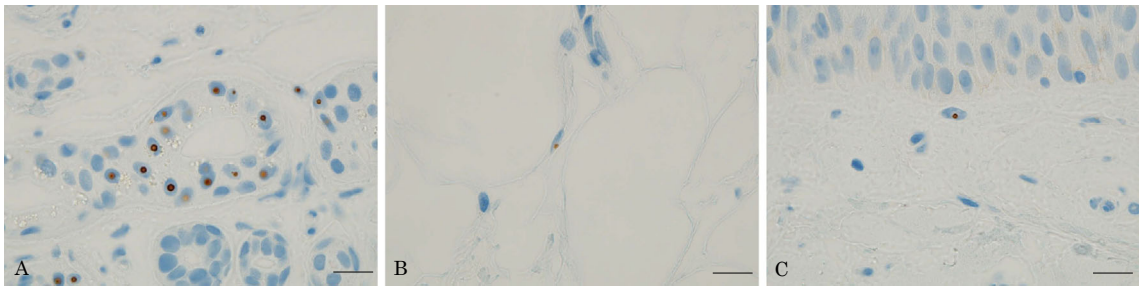

Figure 3. **Skin biopsy findings for immunohistochemistry for p62. Intranuclear inclusions were identified in sweat gland cells (A), adipose cells (B) and fibroblasts (C). Scale bar is 10 μm.**

years before the decline in his MMSE score at 67 years old (Fig. 1A, B; respectively).

FLAIR imaging had revealed numerous punctate high intensities in the white cerebral matter 14 years before the onset of dementia (Fig. 1A), which gradually became confluent 4 years later (Fig. 1B). Two years before the onset of dementia at 65 years old, high intensities on FLAIR had already grown extensive over the white matter (Fig. 1C). By the onset of cognitive decline at 67 and 69 years old, those FLAIR high intensities had dispersed into the white matter (Fig. 1D, E; respectively).

On DWI, however, presymptomatic scanning revealed negligible changes in the white matter at 14 and 10 years before the symptom onset (Fig. 1A, B), and the curvilinear high intensities at corticomedullary junction appeared 2 years before the onset of clinical symptoms. These changes remained almost the same or were only slightly deteriorated after the onset of cognitive decline (Fig. 1D, E; respectively).

Discussion

Diffuse high intensity in the cerebral white matter on FLAIR and high intensity in the corticomedullary junction on DWI are known to be characteristic radiological features of NIID (1, 2). Since the introduction of a skin biopsy as a method for the antemortem diagnosis of NIID (3, 4), patients with NIID with such radiological features have increased in number. However, how radiological changes develop over time and whether they precede or follow the onset of dementia in NIID remain unclear.

Abe et al. reported an NIID patient who had undergone MRI for the first time three years prior to the presentation of dementia (5). They reported that a diffuse high intensity had already been observed in the corpus callosum on FLAIR before the onset of dementia. Unfortunately, since DWI had not been carried out in the patient, whether or not corticomedullary high intensities on DWI, a pathognomic feature of NIID, preceded the clinical onset of dementia was

unclear.

The present patient had serendipitously undergone brain MRI twice at our institution 14 and 10 years prior to the onset. The punctate high-intensity areas on FLAIR images had already been present 14 years before the clinical onset, whereas DWI findings seemed normal (Fig. 1A). Four years later, the high intensity on FLAIR images started to become confluent, while DWI findings still seemed normal (Fig. 1B). Eight years later, at his first presentation to our institution, curvilinear high intensity in the cortimomedullary junction on DWI appeared (Fig. 1C) despite a normal MMSE score. Two years later, when his wife noticed his forgetfulness, the high intensity on DWI became evident, and high intensity on FLAIR spread over the white matter (Fig. 1D). Both high intensities on FLAIR and those on DWI gradually enlarged over time in parallel with the deterioration of his MMSE score in this case (Fig. 1E).

Takeshita et al. reported a patient who had developed two episodes of TGA before the clinical presentation of NIID (6). They argued that the recurrent TGA episodes in their patient might be a clinical presentation of NIID due to the temporary impairment of the limbic system. Whether or not TGA is a harbinger of NIID should be explored in further research in a large case series; however, the similar pattern of the co-occurrence of TGA episode and NIID in our patient is intriguing.

The correlation between the radiological features and the pathological findings in NIID has been discussed in some autopsy-proven cases. Yokoi et al. revealed that multiple focal spongiosis in the subcortical white matter proximal to the U-fibers corresponded to areas of hyperintensity on FLAIR and DWI (7). In their reports, numerous intranuclear inclusions were widespread in the cerebral white matter and cortices, but fewer inclusions were observed in spongiotic lesions. In addition, they found that the myelin pallor areas without spongiosis in pathology corresponded to areas of hyperintensity on FLAIR and normal intensity on DWI (7). Yamaguchi et al. also revealed that the distribution of spongiosis corresponded to high-intensity lesions on DWI in another patient (8).

The MR series in this patient illustrated the temporal profile of the radiological features of NIID over 16 years, including at the presymptomatic stage. First, punctate high intensities on cerebral white matter appeared 14 years before the symptom onset, followed by the confluent fusion of high intensities 4 years later. Of note, the typical curvilinear high intensity on DWI already appeared two years prior to his cognitive decline. In addition, the temporal sequence of high intensities on FLAIR to those on DWI may imply that the initial pathological changes, such as myelin pallor or the presence of intranuclear inclusions, precede the evolution of spongiotic changes, a proposed pathologic substrate of DWI high intensity in NIID.

To our knowledge, this is the first case of NIID with presymptomatic DWI scans. We showed in the present patient that white matter high intensities on FLAIR images proceeded those of DWI and that pathognomic DWI features seem to emerge before the clinical onset of NIID.

The authors state that they have no Conflict of Interest (COI).

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