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LETTER TO THE EDITOR

A multimodal imaging features of the brain in adult-onset neuronal intranuclear inclusion disease

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Dear Editor,

Neuronal intranuclear inclusion disease (NIID) is a rare neurodegenerative disorder, with highly variable clinical manifestations such as cerebellar ataxia, neuropathy, and cognitive dysfunction [1], which was characterized pathologically by eosinophilic hyaline intranuclear inclusions in the central and autonomic neurons [2]. However, skin biopsy reveals intranuclear inclusions in somatic cells had been discovered in recent years [3]. Additionally, high signal intensity in the corticomedullary junction on diffusion-weighted imaging (DWI) had been found in NIID patients with leukoencephalopathy diagnosed by a skin biopsy [1]. However, the metabolic alterations of the brain in NIID patients have never been reported. We herein report the case of an adult-onset NIID patient with cognitive dysfunction along with multimodal imaging features of the brain, including MRIs findings and the metabolic alterations of the brain.

A 67-year-old woman was referred to our hospital with dementia and gait disturbance. She had a 4-year history of dizziness and gradually developed forgetfulness. Two years later, her movement slowed down accompanied with anesthesia. Ten months before admission, gait disturbance occurred. She had a past medical history of hypertension, with no family history of dementia. Neurological examination revealed dementia, Mini-Mental State Examination (MMSE) with a score of 9/30, and Montreal Cognitive Assessment (MoCA) with a score of 6/30, which were much worse than 2 years ago (MMSE 20/30, MoCA 18/30, data from the previous hospital). Additionally, neurological examination showed diminished reflexes in the four limbs, bradykinesia, gait disturbance, and impairment of postural reflexes, but the muscle testing was normal. She showed relatively slowed sensory nerve conductive velocities (NCVs) in the median nerves and ulnar nerves, so as the motor NCVs. The results of NCVs indicated that she had neuropathy. Laboratory tests showed normal including vitamin B12, thiamine, and thyroid hormone. According to the cerebrospinal fluid examination, we found the cell counts, levels of protein, and glucose were normal. Magnetic resonance imaging (MRI) demonstrated cerebral white matter hyperintensity on fluid-attenuated inversion recovery (FLAIR) images, white matter tracts lesions on diffusion tensor imaging (DTI), and hyperintensity of the corticomedullary junction on DWI (Fig.1). A review of her MRI/CT in the past 4 years showed the white matter lesions gradually worsened (Fig.1). Brain magnetic resonance spectroscopy (MRS) revealed a decreased ratio of N-acetylaspartate/creatine (NAA/Cr). Positron emission tomography/computed tomography with 18F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) showed glucose hypometabolism in bilateral cerebral hemisphere, especially the frontoparietal cortex. A skin biopsy of the left leg showed ubiquitin-positive intranuclear inclusions in the fibroblasts, adipocytes, and sweat gland cells (Fig. 2). These findings confirmed that the patient had NIID.

NIID is a rare neurodegenerative disorder, until 2000s, only 30 cases were reported; thus, it had been a pathologic entity diagnosed by autopsy histological examination. However, skin biopsy was useful for antemortem diagnosis of NIID, discovered in recent years, based on nuclear inclusions in sweat gland cells, fibroblasts, and adipocytes in cutaneous

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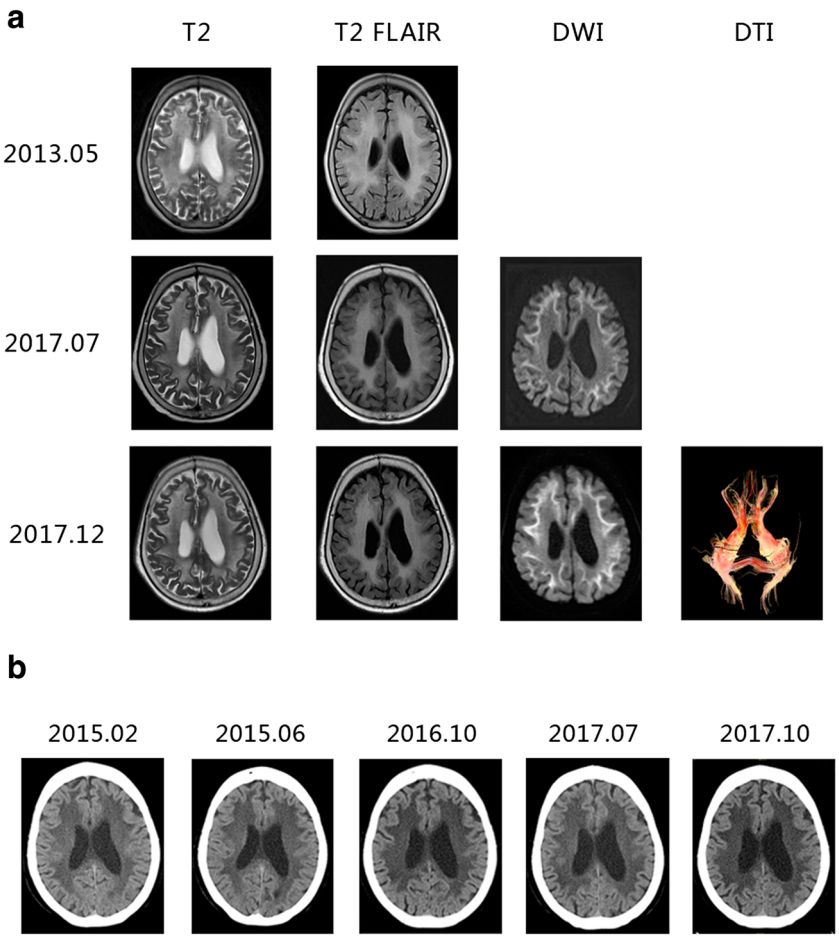

Fig. 1 Brain MRI (**a**) and CT (**b**) showed leucoencephalopathy and cerebral atrophy. High signal intensity in the corticomedullary junction were observed on DWI, and white matter tracts lesions on DTI

tissue [1, 2]. As a result, the number of case reports about NIID is increasing. While there are many reports on the neurologic symptoms of NIID, descriptions about metabolic alterations of the brain in NIID patients are hardly recognized in previous reports.

We reported a patient presenting with dementia, dizziness, gait disturbance, and hyporeflexia. Neuropsychological testing showed memory loss, cognitive dysfunction, especially in language, and executive functions. Her total scores in MMSE deteriorated from 20 to 9 and MoCA deteriorated from 18 to 6

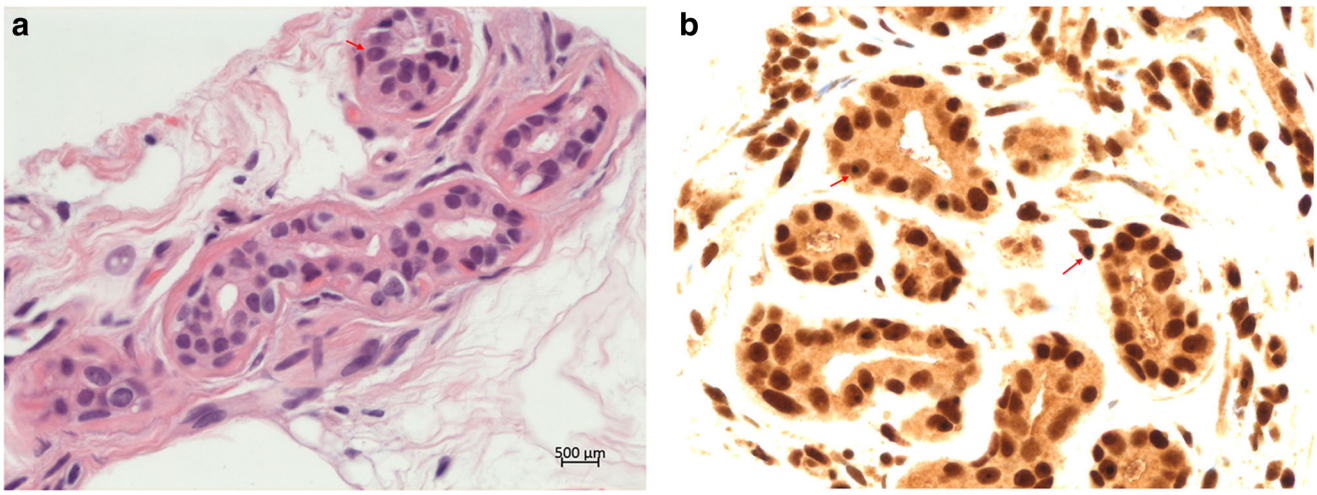

Fig. 2 Intranuclear structures in skin biopsies from a NIID patient. In NIID, eosinophilic nuclear inclusions (NIs) were observed in sweat gland cells (**a**), and other cell lines (Data not shown). The NIs were immunopositive to ubiquitin (**b**)

across 2 years. And the cognitive impairment progressed along with abnormal intensity lesions in DWIs and leukoencephalopathy in FLAIR. Subsequently, we diagnosed our patient as having NIID by a skin biopsy combined with these MRI findings.

In addition, we found a reduced ratio of NAA/Cr and glucose hypometabolism in bilateral cerebral hemisphere according to MRS and PET/CT. MRS is specific and capable of detecting subtle metabolic alterations in the human brain [4], including N-acetylaspartate (NAA), creatine (Cr), choline-containing metabolites (Cho), myoinositol, glycine, glucose, glutamine/glutamate, lipids, alanine, acetate, lactate, and taurine [4]. NAA levels are correlated to the regeneration of neurons. It mainly exists in neurons and is synthesized by chondriosome from acetyl-coenzyme A and aspartate. The reductions of NAA reflect impaired neuronal functioning rather than a reduced number of neurons per se [5]. Therefore, a reduced concentration of NAA may reflect both a decrease in neuronal density as well as impaired function. In our patient, cognitive dysfunction was the most prominent symptom, and we found that the ratio of NAA/Cr was lower compared to normal individuals [6]. The decline of NAA level in NIID patient may be associated with cognitive dysfunction. Because of the limitation of the case study, it is necessary to investigate the expression of NAA in more NIID patients, which may be a predictive factor for disease progression.

Apart from MRS, it is now well established that ^{18}F-FDG PET imaging is a highly useful imaging modality for the diagnosis of neurodegenerative disorders. ^{18}F-FDG is a radiolabeled glucose analogue, and provides tissue metabolism information by entering the glucose metabolic pathway. Thus, measuring its uptake in brain tissue by PET is a good approach for reflecting downstream neuronal injury, providing evidence about cognitive impairment [7, 8]. In our patient, we found the glucose hypometabolism in bilateral cerebral hemisphere, and the range of hypometabolism is wider than leukoencephalopathy in MRI. As far as we know, this is the first article reporting the brain metabolism pattern in NIID. For some reason, we lacked data about arterial spin labeling (ASL). However, in neurodegenerative disorders, perfusion on ASL are synchronized with glucose metabolism on ^{18}F-FDG PET/CT generally. It is necessary to accumulate more cases with detailed pathological examinations and imaging examination.

In conclusion, our case indicates that adult-onset NIID patients may show a cognitive dysfunction, and the presence of a high signal intensity in the corticomedullary junction on DWI with leukoencephalopathy is a characteristic change of MRI of NIID patients. Besides, the ratio of NAA/Cr and glucose hypometabolism in bilateral cerebral hemisphere declined according to MRS and PET/CT, which may relate to cognitive impairment. However, a greater accumulation of cases is required to elucidate the pathogenesis of the disease.

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Authors' contribution Yajing Liu and Jiancong Lu equally contributed to the paper. Yukai Wang and Yan Shao equally contributed to the paper.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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