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LETTER TO THE EDITOR

A case of recurrent vomiting: extending the spectrum of neuronal intranuclear inclusion disease

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Introduction

Neuronal intranuclear inclusion disease (NIID) is a rare progressive neurodegenerative disorder characterized by eosinophilic hyaline intranuclear inclusions presented in the central and peripheral nervous systems and in the visceral organs [1]. Recently, it has been found that skin biopsy is an effective and less invasive ante-mortem diagnostic tool for NIID and shows similar pathological changes to post-mortem dissection [2]. The clinical manifestations differ among patients and can be classified into three categories according to the age of onset: infantile, juvenile, and adult forms [1]. Here we report a sporadic adult-onset NIID case mainly manifested as recurrent vomiting, hypertension and decreased level of consciousness.

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Case presentation

A 60-year-old Chinese woman, who used to be a farmer, was admitted to our medical center due to recurrent vomiting and decreased level of consciousness for the past 3 years, and the symptoms recurred during the recent 12 days. Three years ago, the patient developed nausea and vomiting coupled with elevated blood pressure, urinary incontinence, somnolence, and mutism. During the episode of symptoms, blood pressure elevated to 150~170/80~100 mmHg from baseline of 125/75 mmHg. There were not any prodromal symptoms of fever, dizziness, or headache before disease episode. Symptoms appeared periodically for every half a month or 2 months and lasted for about 7~10 days and could be relieved after conventional supportive treatment. Her reaction had been slowing down for 2 years. Twelve days before administration, the patient had similar symptoms with longer time. She had a past medical history of diabetes mellitus, cataract, and family history of fundus macular hole.

The patient had a poor health condition with a body weight index of 17.6 kg/m^2. Physical examination revealed blood pressure of 130/84 mmHg and body temperature of 36.1 °C. The neurological examination revealed that she was dysphoric and did not respond to external stimulation. Her right pupil was irregular after cataract surgery and left pupil was normal. Fine nystagmus was noticed in her right eye. Deep reflexes, including biceps reflex, triceps reflex, patellar reflex, and Achilles reflex disappeared. Active movement of limbs were visible and muscular tone was decreased. Both Babinski sign and Chaddock sign were positive bilaterally.

Cranial computed tomography (CT) scan (Fig. 1) performed 3 years ago immediately after her first clinical episode showed diffuse low density in the bilateral paraventricular white matter. Further examinations were proposed to clarify the diagnosis after her administration. Laboratory examinations revealed elevated blood glucose of 7.17 mmol/L, decreased albumin of 35.8 g/L, and a HbA1c concentration of 7.3%. Lumbar puncture was performed and the opening

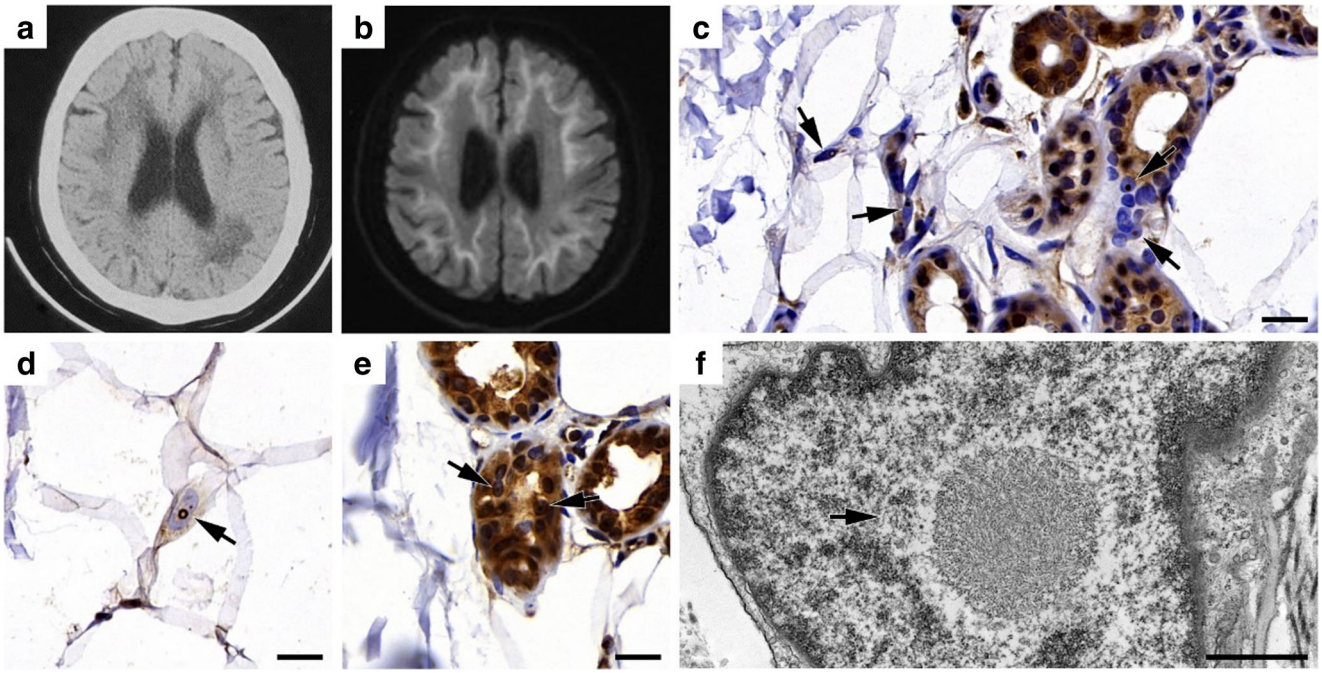

Fig. 1 **a** Cranial CT at disease onset showing diffuse low density in the bilateral paraventricular white matter. **b** DWI imaging 3 years after disease onset showing a linear high-intensity signals alone the corticomedullary junction. **c** Immunohistochemical staining of P62, the left two arrows indicate intranuclear inclusions in fibroblasts, the right two arrows indicate intranuclear inclusions in sweat gland cells; bar = 20 um. **d** Immunohistochemical staining of P62. The arrow indicates intranuclear inclusion in adipocyte; bar = 20 um. **e** Immunohistochemical staining ubiquitin. The arrows indicate intranuclear inclusions in sweat gland cells; bar = 20 um. **f** Electron microscopic image of fibroblast showing intranuclear inclusions; bar = 1 um

pressure was 140 cmH_2O. Cerebrospinal fluid examination revealed no pleocytosis or elevated protein level and normal glucose level. Complete blood count, liver and renal functions, antinuclear antibody spectrum, and ANCA series were normal. Viral markers, syphilis test, catecholamines, and hematuria organic acid were negative. Enhanced adrenal CT scan did not find hyperplasia or adenoma. Brain magnetic resonance imaging (MRI) (Fig. 1) revealed mild cerebral atrophy and moderate cerebellar atrophy. T2-weighted imaging (T2WI) and fluid-attenuated inversion recovery imaging (FLAIR) showed symmetrical high intensity signals in the cerebral white matter. The diffusion-weighted imaging (DWI) showed typical linear high intensity signals in the corticomedullary junction. The video electroencephalogram (EEG) showed asymmetrical posterior rhythm with lower amplitude on the left side. Nerve conduction studies showed a multiple and symmetrical reduction in both motor and sensory nerve conduction velocity. Screening of thoracic CT scan and abdominal and gynecological ultrasound did not find sign of tumor. Skin biopsy (Fig. 1) performed in left leg showed chronic inflammatory cells infiltration in hematoxylin and eosin staining and intranuclear inclusions in adipocytes, sweat gland cells, and fibroblasts in immunohistochemical staining and under electron microscope.

Three days after nutrition support therapy, the patient regained consciousness and was able to communicate in language, while the memory and understanding was impaired. Her mini mental state examination (MMSE) score and frontal assessment battery (FAB) score were 12/30 (illiterate) and 4 (14.5/18), respectively. Mild weakness was present in both upper and lower limbs. Algesthesia, pallesthesia, and topognosis were abated in the right side. Coordinate movements were steady and accurate. Orthostatic hypotension was observed in Schellong test, with a decrement of systolic blood pressure by 22 mmH_2O. The fragile X mental retardation1 (FMR1) permutation repeats of CGG were in normal range. With all the data from clinical examination listed above, we diagnosed her with adult-onset neuronal intranuclear inclusion disease (NIID).

Discussion

Autonomic symptoms are the initial and main clinical characters of this patient, including paroxysmal nausea, vomiting, hypertension following recurrent decreased consciousness, and orthostatic hypotension; other symptoms such as cognitive impairment, peripheral neuropathy, mild muscle weakness, and sensory disturbance are also presented. The typical linear high intensity signals in the corticomedullary junction on DWI images trigger the skin biopsy, which reveals ubiquitin and P62 positive intranuclear inclusions. We diagnosed

this patient as a sporadic adult-onset NIID by the combination of clinical symptoms, characteristic DWI signals, intranuclear inclusions, and the negative of FMRI gene premutation.

NIID is a rare neurodegenerative disease with highly variable clinical manifestations. Adult-onset NIID includes sporadic and familial NIID, and recently, the clinicopathological features were described. The sporadic cases mostly present with dementia in the beginning, while the familial cases can also present with limb weakness initially [3].

Previously, the highly variable clinical manifestations of NIID render the ante-mortem diagnosis to be difficult, and medical professionals relay on the typical corticomedullary high intensity on DWI image as a strong indicator of the ante-mortem diagnosis of NIID [3, 4]. Recently, it has been found that skin biopsy is an effective and less invasive ante-mortem diagnostic tool for NIID and shows similar pathological changes to post-mortem dissection [2]. The onset age of sporadic cases is between 51 and 76 years old, and the disease duration ranges from 1 to 19 years. Most sporadic NIID cases (94.7%) presented dementia as the initial and main clinical manifestation and were recognized as dementia dominant group. Miosis and bladder dysfunction manifesting as urinary incontinence were the most common autonomic impairments. Vomiting was also presented in some (15.8%) of these patients, but rarely considered as the initial and main symptom. There were also case reports of sporadic and familial adult-onset NIID patients presenting bladder dysfunction, fecal incontinence, or orthostatic hypotension as the initial symptoms [5, 6]. With that, we propose there is another subtype of autonomic dominant group in addition to the dementia dominant group in those sporadic adult-onset NIID patients.

Despite the diagnosis efforts, the pathogenesis of NIID remains unclear. Intranuclear inclusions are not restricted to the central nervous system, but also distributed in peripheral nerves systems and visceral organs [7, 8]. Intranuclear inclusions in the skin biopsy specimens show similar immunopositivity for ubiquitin and p62 to the central nervous system [4, 9]. Intranuclear inclusions are formed when there is excessive accumulation of proteins in the nucleus, and the abnormal alteration of nuclear bodies might be related to the pathogenesis of NIID [10, 11]. Excessive protein accumulation in intranuclear inclusions might impair the ubiquitin-dependent degradation process and consequently result in dysfunction of neurons or somatic cells. We suppose that the asymmetrical distribution of intranuclear inclusions leads to different clinical phenotypes. However, further pathological and molecular research is needed to fully understand the pathogenesis.

The prevalence rate of adult-onset NIID may be higher than previously thought [3]. We present a sporadic adult-onset NIID case with autonomic symptom as initial and main clinical characters and propose that there may be another subtype of autonomic dominant group in addition to the dementia dominant group in those sporadic adult-onset NIID patients. DWI images and skin biopsy are critical in the correct diagnosis of NIID and should be considered as an essential step during diagnosis.

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Availability of data and materials All data and materials are available.

Authors' contributions XYL and LL participated the design of this case report. XYL, XHL, YFD, CCL, CXL, and LL collected and analyzed the raw clinical data. XYL wrote the manuscript. All authors have read and approved the final manuscript.

Compliance with ethical standards

Competing interests The authors declare that they have no conflicts of interest.

Ethics approval and consent to participate This study was approved by the Institutional Review Board of Shandong Provincial Hospital Affiliated to Shandong University. Informed consent was obtained from the patient.

Consent to publish Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the editor of this journal.

Abbreviations *NIID,* neuronal intranuclear inclusion disease; *MRI,* magnetic resonance imaging; *CT,* computed tomography; *FLAIR,* fluid-attenuated inversion recovery; *DWI,* diffusion-weighted imaging; *ANCA,* anti-neutrophil cytoplasmic antibodies; *EEG,* electroencephalogram; *MMSE,* mini mental state examination; *FAB,* frontal assessment battery; *FMR1,* fragile X mental retardation 1

References

1. Takahashi-Fujigasaki J (2003) Neuronal intranuclear hyaline inclusion disease. Neuropathology 23(4):351–359
2. Sone J, Tanaka F, Koike H, Inukai A, Katsuno M, Yoshida M, Watanabe H, Sobue G (2011) Skin biopsy is useful for the antemortem diagnosis of neuronal intranuclear inclusion disease. Neurology 76(16):1372–1376
3. Sone J, Mori K, Inagaki T, Katsumata R, Takagi S, Yokoi S, Araki K, Kato T, Nakamura T, Koike H, Takashima H, Hashiguchi A, Kohno Y, Kurashige T, Kuriyama M, Takiyama Y, Tsuchiya M, Kitagawa N, Kawamoto M, Yoshimura H, Suto Y, Nakayasu H, Uehara N, Sugiyama H, Takahashi M, Kokubun N, Konno T, Katsuno M, Tanaka F, Iwasaki Y, Yoshida M, Sobue G (2016) Clinicopathological features of adult-onset neuronal intranuclear inclusion disease. Brain 139(Pt 12):3170–3186
4. Sone J, Kitagawa N, Sugawara E, Iguchi M, Nakamura R, Koike H, Iwasaki Y, Yoshida M, Takahashi T, Chiba S, Katsuno M, Tanaka F, Sobue G (2014) Neuronal intranuclear inclusion disease cases with leukoencephalopathy diagnosed via skin biopsy. J Neurol Neurosurg Psychiatry 85(3):354–356
5. Zannolli R, Gilman S, Rossi S, Volpi N, Bernini A, Galluzzi P, Galimberti D, Pucci L, D'Ambrosio A, Morgese G, Giannini F

(2002) Hereditary neuronal intranuclear inclusion disease with autonomic failure and cerebellar degeneration. Arch Neurol 59(8): 1319–1326
6. Nakamura M, Ueki S, Kubo M, Yagi H, Sasaki R, Okada Y, Akiguchi I, Kusaka H, Kondo T (2018) Two cases of sporadic adult-onset neuronal intranuclear inclusion disease preceded by urinary disturbance for many years. J Neurol Sci 392:89–93
7. Lindenberg R, Rubinstein LJ, Herman MM, Haydon GB (1968) A light and electron microscopy study of an unusual widespread nuclear inclusion body disease. Acta Neuropathol 10(1):54–73
8. Tateishi J, Nagara H, Ohta M, Matsumoto T, Fukunaga H, Shida K (1984) Intranuclear inclusions in muscle, nervous tissue, and adrenal gland. Acta Neuropathol 63(1):24–32
9. Mori F, Miki Y, Tanji K, Ogura E, Yagihashi N, Jensen PH, Wakabayashi K (2011) Incipient intranuclear inclusion body disease in a 78-year-old woman. Neuropathology 31(2):188–193
10. Takahashi-Fujigasaki J et al (2010) SUMOylation substrates in neuronal intranuclear inclusion disease. Neuropathol Appl Neurobiol 32(1):92–100
11. Nakano Y, Takahashi-Fujigasaki J, Sengoku R, Kanemaru K, Arai T, Kanda T, Murayama S (2017) PML nuclear bodies are altered in adult-onset neuronal Intranuclear hyaline inclusion disease. J Neuropathol Exp Neurol 76(7):585–594