

# An unusual Neuronal Intranuclear Inclusion Disease with Chief Complaint of Autonomic Dysfunction

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## Case report

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# Abstract

Background Neuronal intranuclear inclusion disease (NIID) is a recently defined disease entity of progressive neurodegenerative disease with characterizations of eosinophilic hyaline intranuclear inclusions in neuronal and somatic cells. The sporadic adult-onset NIID cases were previously described as 'dementia dominant group'. Here we present a NIID case manifested prominently with recurrent vomiting. Case presentation A 60-year-old woman presented with paroxysmal vomiting, hypertension and decreased level of consciousness for 3 years. She was diagnosed with NIID based on history, clinical features, brain magnetic resonance imaging (MRI), skin biopsy. Conclusion Autonomic symptoms may manifest as the initial and predominant presentation of NIID. This case presentation may extend the spectrum of NIID and may give new insights in exploring the pathogenic mechanisms of NIID.

## 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 3 categories according to the age of onset: infantile, juvenile, and adult forms [1]. Here we report a sporadic adult-onset NIID case with the chief complaint of recurrent vomiting, hypertension and decreased level of consciousness.

## Case Presentation

A 60-year-old Chinese woman, who was a housewife, 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. 3 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 but could manage the daily housework and go shopping. 12 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 has a poor health condition with a body weight index of 17.6 kg/m<sup>2</sup>. 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 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 pressure was 140 cmH<sub>2</sub>O. Cerebrospinal fluid examination revealed no pleocytosis or elevated protein level and normal glucose level. Complete blood count, liver and renal functions, antinuclear antibody spectrum, ANCA series were normal. Viral markers, syphilis test, catecholamines, hematuria organic acid were negative. Enhanced adrenal CT scan did not find hyperplasia or adenoma. Brain magnetic resonance imaging (MRI) 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, abdominal and gynecological ultrasound did not find sign of tumor. Skin biopsy 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, 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 22mmH<sub>2</sub>O. The fragile X mental retardation1 (FMR1) permutation repeats of CGG was 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 chief complaint of this patient, including paroxysmal nausea, vomiting, urinary incontinence and hypertention following recurrent decreased consciousness, and orthostatic hypotension, other symptoms such as cognitive impairment, peripheral neuropathy, mild muscle weakness, sensory disturbance are also presented. The typical linear high intensity signals in the corticomedullary junction on DWI images triggers the skin biopsy, which reveals ubiquitin and P62 positive intranuclear inclusions also visible under an electron microscope. 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 the sporadic or familial dementia-dominant, familial limb weakness dominant and familial phenotypes with both dementia and limb weakness subdivided mainly according to family history, initial major symptom and presence of neuropathy. Both the microscopic features of intranuclear inclusions and frequency distribution of intranuclear inclusion of neurons and astrocytes was similar among sporadic and familial NIID cases[ 3]. . Previously, the highly variable clinical manifestations of NIID renders the ante-mortem diagnosis to be difficult, and medical professionals rely 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(94.4%), bladder dysfunction(33.3%) manifesting as urinary incontinence and vomiting(15.8%) were the most common autonomic impairments. Vomiting was the chief complaint and clue for diagnosis of NIID in this case. There were also case reports of sporadic and familial adult-onset NIID patients presenting vomiting, bladder dysfunction, fecal incontinence or orthostatic hypotension as the main or partial symptoms[ 5-8]. Repeated episode of vomiting may suggest underlying myenteric neuronal damage and provide a clue of the diagnosis of NIID[ 8]. So we suppose that the autonomic dysfunction may serve as the clue for the diagnosis of NIID, especially accompanied by the high intensity signals in the corticomedullary junction on DWI imaging.

Despite the diagnosis efforts, the pathogenesis of NIID remains unclear. Intranuclear inclusions are not restricted to the central nervous system, but are also distributed in peripheral nerves systems and visceral organs[ 9, 10]. Intranuclear inclusions in the skin biopsy specimens show similar immunopositivity for ubiquitin and p62 to the central nervous system [ 4, 11]. 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 [ 12, 13]. 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 studies will be necessary to fully understand the pathogenesis of NIID.

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 the chief complaint and playing as an important clue for diagnosis. DWI images and skin biopsy are critical in the correct diagnosis of NIID and should be considered as an essential step during diagnosis.

## 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 retardation1; NIs: Nuclear inclusions.

## Declarations

# 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.

## Availability of data and materials

All data and material supporting our findings are contained within the manuscript and additional supporting files.

## Competing interests

The authors declare no conflicts of interest with respect to the research, authorship, and/or publication of this article.

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## 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.

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## Figures

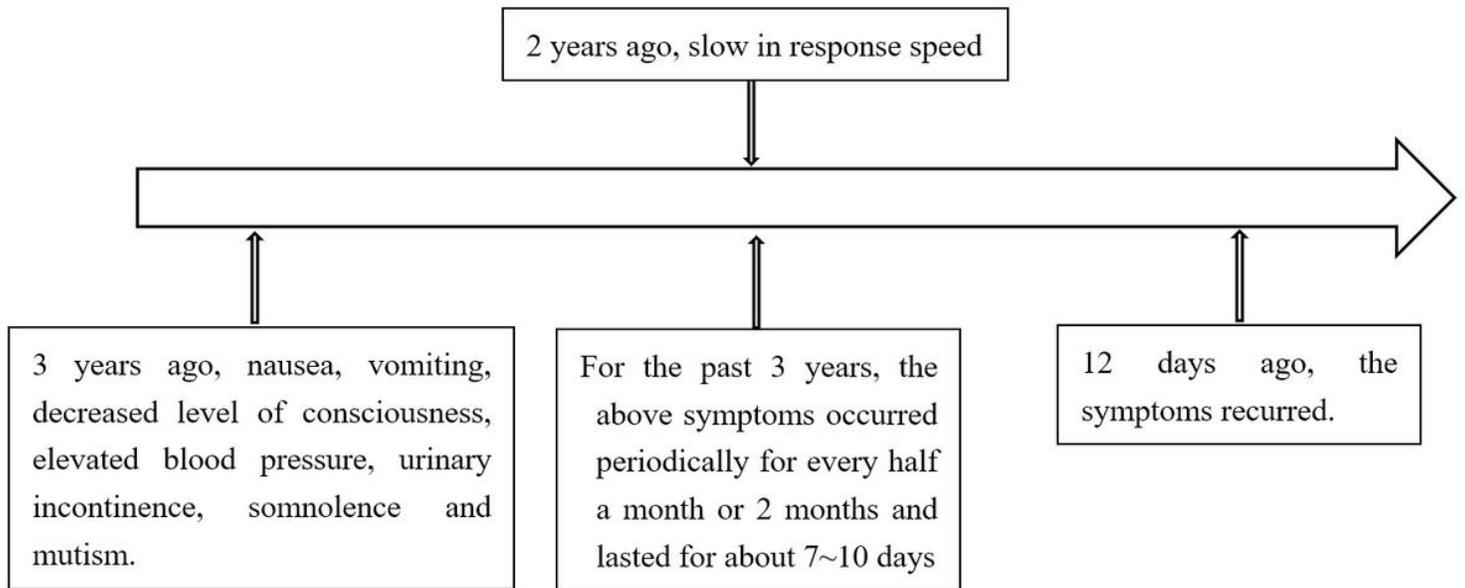


Figure 1

Timeline of the patient.

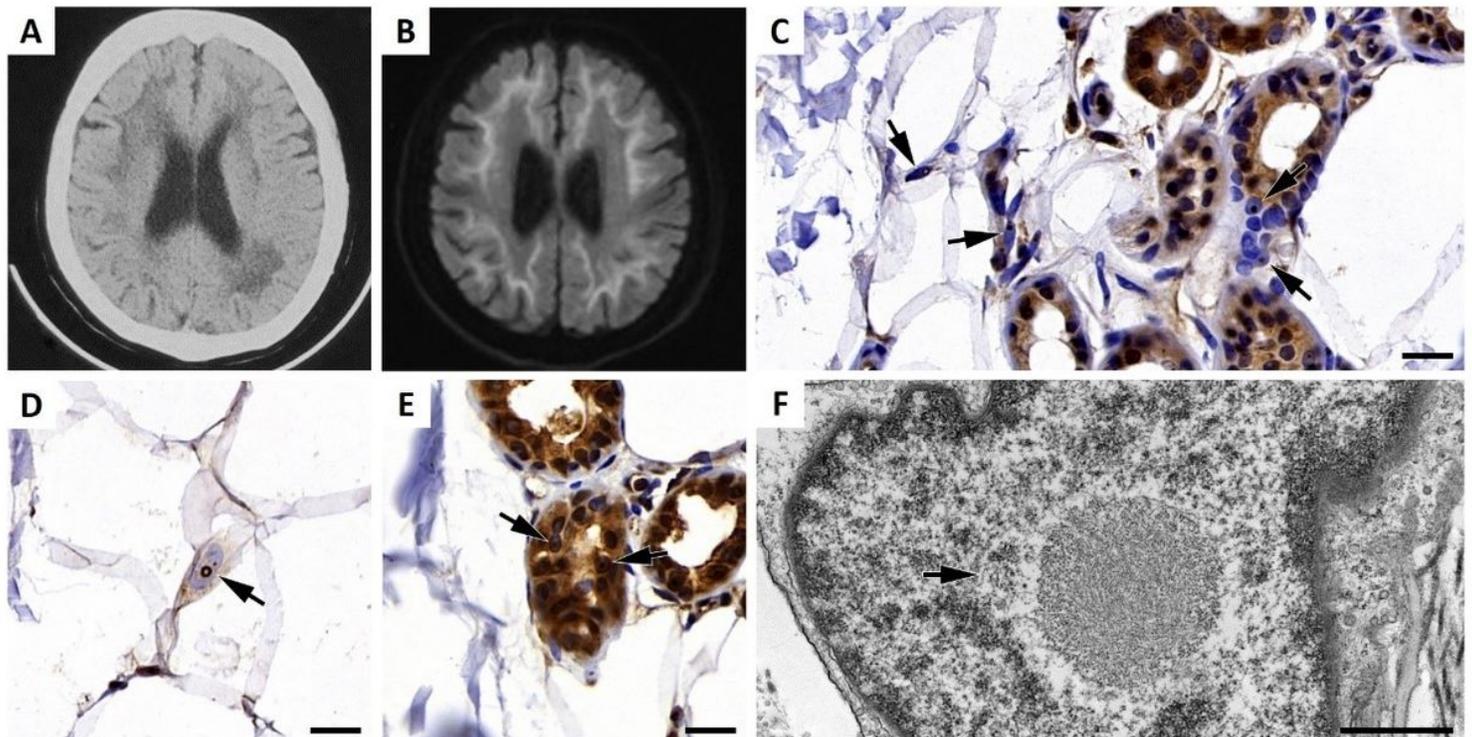


Figure 2

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 along the corticomedullary junction; C Immunohistochemical staining of P62, the left 2 arrows indicate intranuclear inclusions in fibroblasts, the right 2 arrows indicate intranuclear inclusions in sweat gland cells; bar=20um; D Immunohistochemical staining of P62, the arrow indicates intranuclear inclusion in adipocyte; bar=20um; E Immunohistochemical staining of ubiquitin, the arrows indicate intranuclear inclusions in sweat gland cells; bar=20um; F Electron microscopic image of fibroblast showing intranuclear inclusions; bar=1um.

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