A Case report of Recurrent Vomiting: Extending the Spectrum of Neuronal Intranuclear Inclusion Disease

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Case report

Keywords: Neuronal intranuclear inclusion disease; recurrent vomiting; skin biopsy; electron microscope; diffusion-weighted imaging

Posted Date: April 4th, 2019

DOI: <https://doi.org/10.21203/rs.2.1814/v1>

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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 mainly manifested as recurrent vomiting, hypertension and decreased level of consciousness.

Case Presentation

A 60-year-old Chinese woman, who was used to be a farmer, was admitted to our medical center due to recurrent vomiting and decreased level of consciousness for the past three years and the symptoms recurred during the recent 12 days. 3 years before administration, the patient developed nausea and vomiting coupled with decreased level of consciousness, 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 usual supportive treatment. She became slow in response speed from 2 years ago. 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/m². 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 cmH₂O. 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, and showed high intensity in the cerebral white matter on T2-weighted imaging, fluid-attenuated inversion recovery (FLAIR) and in corticomedullary junction on diffusion-weighted imaging. 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. Algesia, paresthesia, 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 22mmH₂O. 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 initial and main clinical characters of this patient, including paroxysmal nausea, vomiting and hypertension following recurrent brief loss of 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 sporadic and familial NIID, and recently the clinicopathological features were described[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 and bladder dysfunction manifesting as urinary incontinence were the most common autonomic impairments. Vomiting was also present in some (15.8%) of these patients, but rarely considered as the initial and presenting 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. Nuclear inclusions (NIs) are not restricted to the central nervous system, but are also distributed in peripheral nerves systems and visceral organs[7, 8]. NIs in the skin biopsy specimens show similar immunopositivity for ubiquitin and p62 to the central nervous system [4, 9]. NIs 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 NIs might impair the ubiquitin-dependent degradation process and consequently result in dysfunction of neurons or somatic cells, 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, and that NIID may be underdiagnosed[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.

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.

Funding

No funding support.

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.

Acknowledgements

The authors are grateful to the patient for her participation in our study. This case report was completed by the efforts of all authors.

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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 microscopical image of fibroblast showing intranuclear inclusions; bar=1um.

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