Neuronal intranuclear inclusion disease: a case report and literature review

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Case Report

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Abstract

Neuronal intranuclear inclusion disease (NIID) is a slowly progressive neurodegenerative disorder characterized by the presence of eosinophilic intranuclear inclusions in the nervous system and multiple visceral organs. Clinical manifestations of NIIDs vary widely, with familial and sporadic cases reported. The clinical manifestations of NIIDs are highly heterogeneous, complex and diverse, and may present with damage to the corticosphere, pyramidal bundles, extrapyramidal lineages, cerebellum, peripheral nerves, and autonomic nerves. At present, there are no cases in China where skin biopsy and genetic testing have been confirmed at the same time. We reported a case of NIID patient with dementia and behavioral abnormalities as the main clinical features, reviewed the relevant literature, analyzed its clinical characteristics, imaging changes, skin biopsy pathological changes, genetic test results, and reviewed the relevant literature, aiming to help clinicians improve their understanding of NIID.

Introduction

Neuronal intranuclear inclusion disease (NIID) is a rare multisystem neurodegenerative disease characterized by pathological features of eosinophilic intranuclear inclusion bodies in the central, peripheral and autonomic nervous systems and visceral organs[1,2]. The first case affected by NIID was reported in 1968[3]. However, until 2011, only about 40 NIID-affected subjects were described worldwide, and these cases were diagnosed by post-mortem brain biopsy[4–13]. Since eosinophilic intranuclear inclusion bodies are also present in the dermal cells of NIID-affected individuals[14,15], skin biopsy has become a useful tool to confirm the diagnosis of NIID[2], and the number of reported cases has increased to more than 100.

Case Presentation

Clinical data: Clinical data Patient woman, 63 years old, housewife, admitted to the hospital because of "progressive memory loss for more than 2 years and bradykinesia for 1 year". The patient began to have memory decline more than 2 years ago, mainly near memory decline, which was progressively aggravated. The initial manifestations were easy to forget what she had just done and difficulty in remembering what she had been familiar with. She now gradually could not remember the previously familiar person or name. She began to have bradykinesia and clumsiness 1 year ago, and recently began to walk and fall easily. Most of her daily life required her husband's care, without mental and behavioral abnormalities, limb twitching, limb weakness, or limb tremor. Past medical history: The patient had a history of diabetes for more than 1 month, and now orally took Metformin Tablets 0.25g bid for hypoglycemic therapy, with good blood glucose control. He denied any history of hypertension, psychosis, cerebrovascular disease, or coronary heart disease. She denied any family history of similar diseases or genetic diseases.

Physical examination: BP: 120/75 mmHg, no obvious abnormality were seen in the heart, lung and abdomen. The consciousness was clear, the time, place, character and orientation were fair, the near

memory was significantly decreased, the long-term memory was fair, the calculation was 100-7 = ?, the comprehension ability was poor, there was no obvious dysphonia or aphasia, and Patients cannot dress or undress. Bilateral pupils are equal and are round, there is a light reflex, bilateral frontal striations and nasolabial folds are symmetrical, the tongue was extended in the middle, and the gag reflex existed; the muscle strength of the extremities was grade 5, the muscle tension of the extremities was moderate, and the Babinski's sign was negative. Auxiliary examination: In November 2019, head MRI + DWI showed multiple white matter hyperintensities in brainstem, cerebellum and paraventricular area (Fazekas grade 3).

Discussion

The pathogenesis of NIID remains unknown. Immunohistochemistry showed that intranuclear inclusions were positive for ubiquitin and ubiquitin-related proteins, including p62, SUMO1, FUS, MYO6 and OPTN-C protein[5,12,13,16,17], suggesting that the ubiquitin-proteasome system in the nucleus may play a role in NIID. In addition, some intranuclear inclusion bodies were found to stain positive for anti-polyglutamine antibodies and anti-ataxin3 antibodies[4,13]. However, this may be the result of cross-reactivity. No CAG repeat amplification was observed in NIID[18].

NIID is a rare chronic progressive neurodegenerative disease with variable clinical features, mainly manifesting as cognitive impairment, limb weakness, sensory abnormalities, autonomic dysfunction, ataxia, Parkinson's symptoms, epilepsy, seizure disorder, stroke-like seizures, and encephalitis-like seizures, etc. It is often considered a heterogeneous disease, and in the past, autopsy was required to confirm the diagnosis of the disease, so that patients were more difficult to diagnose during their lifetime. In the past, autopsy was required to confirm the diagnosis of the disease, so the patients were more difficult to diagnose during their lifetime. Currently, the diagnosis can be confirmed by typical imaging changes, skin pathology biopsy and genetic testing.

The pathophysiological mechanisms of NIID are unclear. In patients with NIID, intranuclear inclusion bodies are frequently present in morphologically essentially normal neurons, and their pathological significance is unknown. Even when extensive intranuclear inclusion bodies are present on pathological examination, they are not necessarily accompanied by neuronal degeneration and loss. Intranuclear inclusion bodies are not necessarily cytotoxic. Intranuclear inclusion bodies in NIID contain some proteins of the ubiquitin-proteasome protein degradation system, such as ubiquitin and p62, whose formation is associated with dysfunction of the ubiquitin-proteasome protein degradation system. It has been suggested that intranuclear inclusion body formation in NIID may have a similar pathophysiological pathway to polyglutamine disease, and is a neurodegenerative disease caused by amplification of genes specific for trinucleotide repeats (cytosine-adenine-guanine, encoding glutamine)[11,18].

In 2003, Takahashi-Fujigasaki classified NIID into infantile, adolescent, and adult forms according to the age of onset and into epidemic and familial forms according to the mode of inheritance[1]. In this case, there is no history of similar disease in the family, so we consider disseminated adult neuronal

intranuclear inclusion disease. Disseminated NIID most often starts at the age of 51–76 years, and the duration of the disease varies from 1 to 19 years. The symptoms are diverse and can be divided into three groups of symptoms: central nervous system, peripheral nerve, and autonomic nerve involvement[2]. The symptoms of CNS involvement include: dementia (94.7%), which is the first and core symptom; ataxia (52.8%); episodic disorders of consciousness (39.5%), which vary in severity and last from a few hours to several days; behavioral abnormalities (26.3%), which manifest as irritability, slurred speech, disuse disorder, and addiction to gambling; and subacute encephalitis-like manifestations (21%), which manifest as fever, headache, vomiting, etc. manifested as fever, headache, vomiting, impaired consciousness, and inactive mutism signs in late stages; others such as tonicity (23.7%), tremor (18.4%), and generalized tonic seizures (13.2%). Peripheral nerve involvement manifested: sensory impairment (28.6%), mild hypoesthesia, terminal limb numbness; decreased muscle strength (27%), mild decrease in muscle strength of distal extremities. Autonomic nerve involvement manifested: pupillary constriction (94.4%), bladder dysfunction (urinary incontinence; 33.8%), vomiting (15.8%), and syncope (8.1%). The clinical presentation of familial NIID is similar to that of the disseminated type, but the proportion of symptoms occurring is slightly different and can be divided into 2 subgroups according to their symptoms: the dementia group and the limb weakness group. The age of onset of dementia is over 40 years old, with dementia as the first and core symptom, which may be accompanied by mild autonomic dysfunction and subclinical peripheral neuropathy; the limb weakness group: The age of onset is 16–39 years old, with lower limb weakness as the first symptom, and sensory impairment and autonomic dysfunction gradually appear. Dementia with white matter lesions may appear in the course of the disease up to about 20 years[19].

Imaging studies have their characteristic features: (1) White matter abnormal signals. Diffuse symmetrical and patchy hyperintense lesions are common in the subcortical white matter area beside the lateral ventricles (mainly in the frontoparietal lobe) on T2WI and T2-FlairWI, and may also be present in areas such as the brainstem, cerebellum, and corpus callosum; (2) cerebellar atrophy or demyelinating changes in the cerebellar white matter area; and (3) DWI characteristic features: curvilinear hyperintensity along the corticomedullary junction, which we call silk or diaper distribution.

In 2011, Japanese scholar Sone et al found that acidophilic and transparent inclusions were also observed in the nuclei of sweat gland cells, adipocytes, and fibroblasts in skin biopsy specimens from NIID patients. The composition and structural features of these bodies are consistent with those of intranuclear inclusion bodies of neurons, thus confirming that skin biopsy can be effective in the diagnosis of NIID[14]. Sone et al. recommended that the best area for skin biopsy is 10 cm above the outer ankle. This area is considered to have a moderate density of fat and sweat gland cells in the skin. In this patient, the skin pathology was taken in accordance with the optimal area for skin biopsy recommended by Sone et al.

Prof. Shen Lu and Prof. Tang Beisha's team identified the causative gene on chromosome 1p13.3-q23.1 by chain analysis of a five-generation family with myasthenia gravis phenotype NIID, and after whole-exome sequencing (WES) did not find the suspected causative mutation, long read long sequencing

(LRS) identified the human-specific NOTCH2NLC gene within the interval with abnormal GGC repeat amplification associated with this family. sequencing (LRS) identified an aberrant repeat amplification of GGC within the human-specific NOTCH2NLC gene in the interval associated with this family. Further abnormal GGC repeats (≥ 66) at the 5' end of the NOTCH2NLC gene were identified by RP-PCR and GC-PCR in other NIID families (40 patients) and in patients with disseminated NIID[3]. This study revealed for the first time internationally that the pathogenesis of neuronal intranuclear inclusion body disease is associated with abnormal GGC repeat amplification in the NOTCH2NLC gene, thus identifying the NOTCH2NLC gene as the causative gene of NIID for the first time in the world.

For adult NIID, the following disorders need to be distinguished primarily: (1) Fragile X-associated tremor/ataxia syndrome (FXTAS), a rare genetic neurodegenerative disorder manifesting mainly as cerebellar ataxia. typical MRI features of FXTAS are FLAIR, T2WI symmetrical high signal foci in the cerebellar midfoot and total cerebellar atrophy, deep peri-lateral ventricular brain White matter lesions, which may appear as high signal foci in the corpus callosum compression. FMR1 gene testing and skin biopsy may be useful for differentiation. (2) Binswanger's disease, a cerebral small vessel disease with chronic progressive dementia as the main manifestation, is characterized by varying degrees of brain atrophy and ventricular enlargement, with symmetrical distribution of crescentic long T1 and long T2 signals in the deep cerebral white matter around the lateral ventricles, and common infarcts in the basal ganglia, thalamus and brainstem. In contrast, patients with NIID had almost no foci of lacunar cerebral infarction in the basal ganglia, thalamus, and central hemi-oval region.

There is no specific treatment for NIID, and no method has been found for the disappearance of intranuclear inclusion bodies or neurological recovery. Symptomatic management may delay the development of some symptoms (e.g., seizures, dementia, Parkinson's syndrome)[20], but none of them can stop the course of the disease. NIID, due to its multiple heterogeneities, produces a large number of associated complications, which can manifest in completely different ways. Therefore, we propose to define a term NIID-related diseases (NIIDRD), which includes NIID and other related neurodegenerative diseases caused by human-specific GGC repeat sequence expansions *NOTCH2NLC.*

Declarations

Consent for publication: All subjects participating in the image acquisition signed the consent form. I agree to allow the researcher(s) to take photographs of me and grant permission for these to be used by the researcher(s) and their project partners in publications, press articles and websites, exclusively for non profit-making purposes.

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Zhou revised the manuscript and wrote cover letter.

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Figures

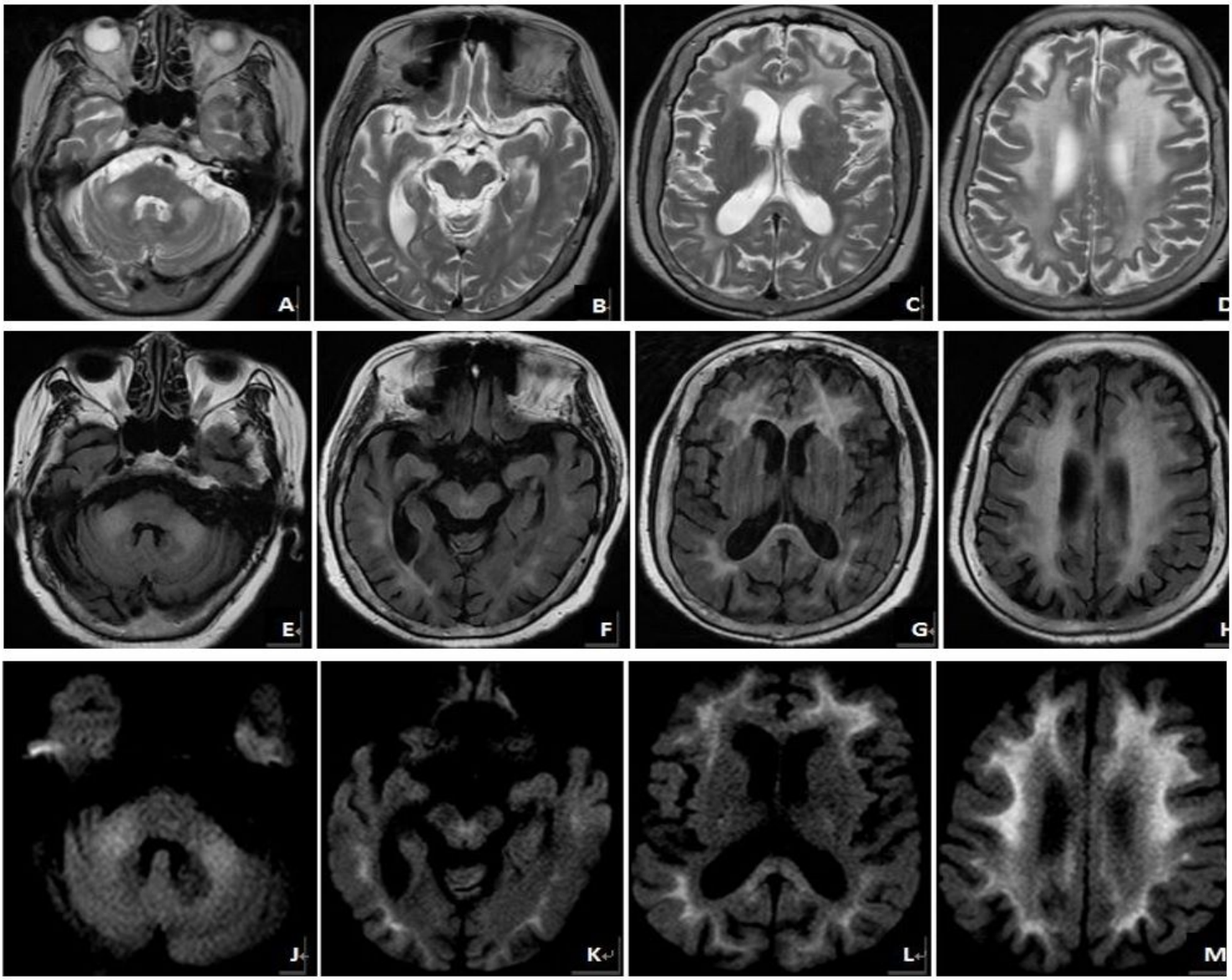

Figure 1

T2-weighed imaging(A-D), T2-Flair weighed imaging E-H shows symmetric high signal in the pontine arm, brainstem, bilateral paraventricular, corpus callosum and subcortical white matter with bilateral lateral ventricular enlargement and cerebellar atrophy; Diffusion-weighted imaging (J-M) shows symmetrical or asymmetrical high signal in the subcortical gray-white matter junction area in a ribbon-like or diaper-like distribution. Dermatopathological biopsy (10 cm of skin above the outer ankle was taken).

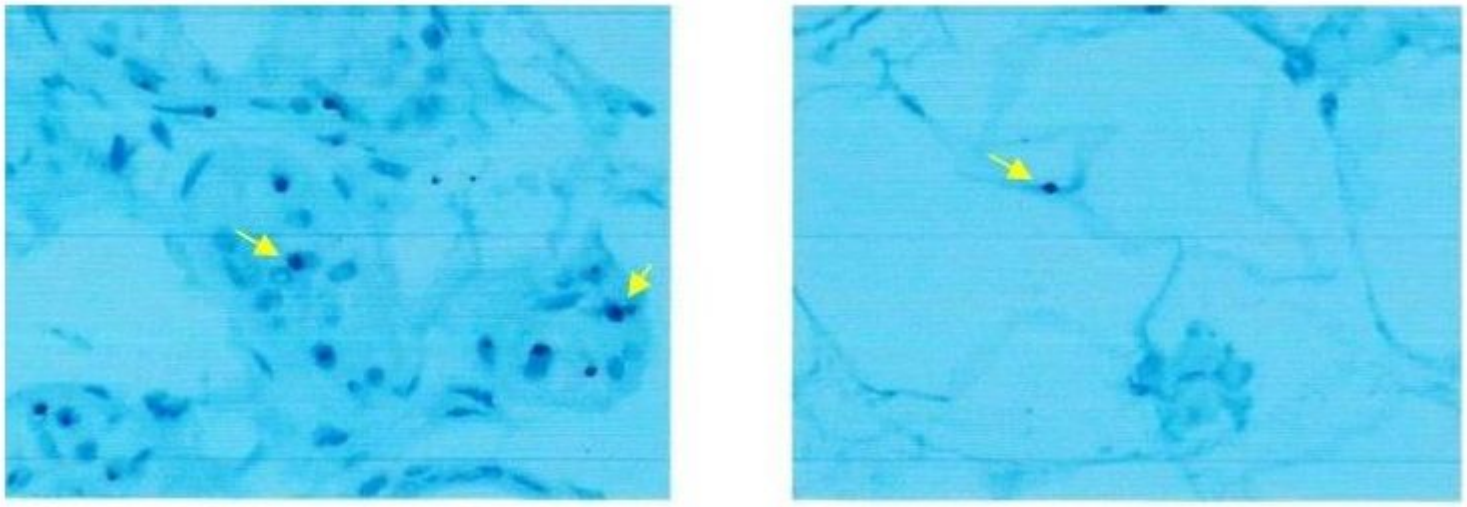

Figure 2

Pathological pictures showed eosinophilic inclusions in the nuclei of some eccrine cells and fibroblasts. Immunohistochemical results: P62 (intranuclear +), ubiquitin (intranuclear +).

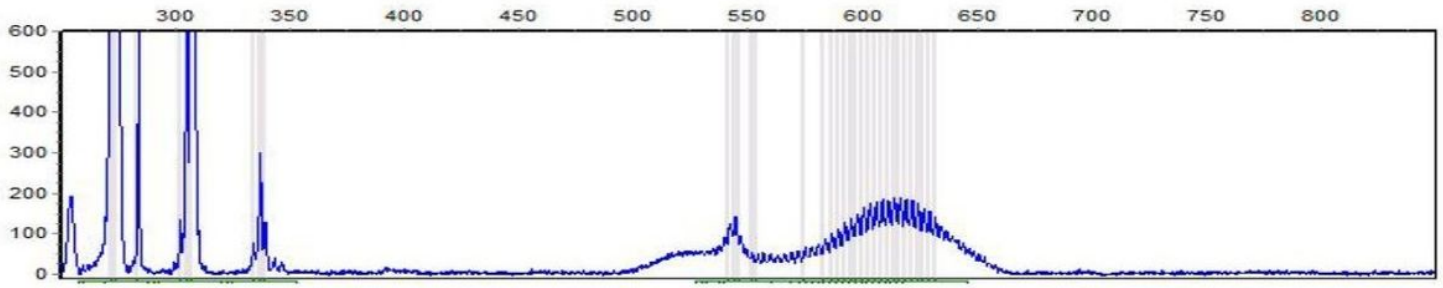

Figure 3

Abnormal repeat amplification of GGC at the 5' end of NOTCH2NLC gene, which has a normal range of <43 GGC repeats and may lead to neuronal intranuclear inclusion body disease when the number of GGC repeats is >66.