Neuronal intranuclear inclusion disease characterized by multiple stroke-like episodes and visual hallucinations: a case report and literature review

Fan Zhou  
Jingzhou Central Hospital, Yangtze University

Yong Fang  
Jingzhou Central Hospital, Yangtze University

Shengjun Xie  
Jingzhou Central Hospital, Yangtze University

Daokai Gong (✉️ 29783133@qq.com)  
Jingzhou Central Hospital, Yangtze University

Case Report

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Abstract

Neuronal intranuclear inclusion disease (NIID) is a rare progressive neurodegenerative disease featured by eosinophilic intranuclear inclusions in the central nervous system and multiple systems of the body. For the reasons stated above, the clinical manifestation of NIID has high heterogeneity, such as dementia, parkinsonism, and psychiatric. Thus, in this report we describe a rare case of NIID characterized by multiple stroke episodes in China. A 79-year-old female was admitted to our hospital with multiple stroke-like episodes for seven years and visual hallucinations for a week. Magnetic resonance imaging (MRI) of the brain suggested chronic infarction in the right occipital lobe, multiple ischemic infarction lesions of bilateral half oval centers and radial crowns. However, the patient did not have risk factors for cerebrovascular disease, such as diabetes mellitus, hyperlipidemia, hypertension, and coronary heart disease. The stroke-like episodes of patient gradually improved after improving the circulations, providing the nerves nutrition and giving treatments aiming to patients’ current symptoms. Considering patient’s restorable stroke-like symptoms episode repeatedly without other neuro injured symptoms and diffusion weighted images (DWI) did not show new infarctions all the time, we observed her oromandibular dystonia and head tremor phenomenon additionally, as well as her reduced pupils (~ 1.5mm). We suggest the patient do a genetic testing for CGG repeat expansion of NOTCH2NLC showing a positive result. This case report highlights that the necessity of genetic testing in atypical NIID patients. Additionally, we reviewed previously reported cases of NIID, which will facilitate more accurate clinical diagnosis in the future and help us better understand the diagnostic flow of adult-onset NIID.

Introduction

Caused by an expansion of GGC repeats in the 5′-untranslated region of NOTCH2NLC, neuronal intranuclear inclusion disease (NIID) is a slowly progressing neurodegenerative disease (1, 2). Due to NIID could involve multiple systems, its clinical manifestations are various involving dementia, limb weakness, parkinsonism (for example, autonomic dysfunction, ataxia), psychiatric, seizures, sensory disturbance, and related ocular symptoms (for example, contracted pupil, night blindness, photophobia) (2, 3). In the neuroimaging findings, compared with underdiagnosed leukoencephalopathies individuals, the diffusion weighted images (DWI) features of NIID patients showed the striking similarities-corticomedullary junction curvilinear lesions, which presences in 88.2% of the NIID patients (4). However, the definitive diagnosis depends on the result of skin biopsy exhibiting extensive intranuclear eosinophilic inclusions or the identified evidences of GGC repeat expansions in the NOTCH2NLC gene (5). Here, we describe a 79-year-old woman who was diagnosed with NIID identified by genetic test, presented with multiple stroke-like episodes and visual hallucinations, and without corticomedullary DWI hyperintensity. Based on these clinicopathological features, we proposed a diagnosis flow of NIID.

Case report

A 79-year-old female with multiple stroke-like episodes within seven years, complained of visual hallucinations for one week. The main manifestations of stroke-like episodes in patients were transient
blurred consciousness and (or) unclear speech. The symptom of visual hallucinations appeared seven
days before admission and did not have obvious fluctuations. The patient had no past medical history or
drug history. In 2015 and 2018, this patient was admitted to hospital both for cerebral infarctions
performing blurred consciousness and unclear speech. In January 2021, during neurological physical
examination of the patient, the patient was conscious and able to answer basic questions. frequently.
Extraocular movements were normal. The optical examination showed that pupil diameter was normal
(\sim 3.0 \text{ mm}), pupils are sensitive to light reflection and the eyes’ vision both were good. In June 2021, the
patient was unclear speech and decreased vision, and the pupil diameter was also normal. Until
December 2021, she appeared visual hallucinations and her pupil diameter was reduced (\sim 1.5 \text{ mm},
Fig. 1). The laboratory test results revealed normal: blood glucose, complete blood cell count, C-reactive
protein, blood lipids, homocysteine, liver and renal function tests. Hepatitis B virus, human
immunodeficiency virus (HIV), syphilis antibodies, and rapid plasma reaction blood draw tests were
negative. After admission of the patient, we observed that the patient had oromandibular dystonia and
head tremor phenomenon. One day after admission, the patient had thyroid function tests that were
normal ranges.

Furthermore, magnetic resonance imaging (MRI) of the brain was performed and the results showed
chronic infarction in the right occipital lobe, multiple ischemic infarction lesions of bilateral half oval
centers and radial crowns (Fig. 2). This patient had no history of diabetes mellitus, hyperlipidemia,
hypertension, coronary heart disease, or neurological genetic disorders. She had no inherited family
history. Magnetic resonance angiography (MRA) of head and neck were also performed and the results
both were normal. Moreover, using the fluorescent probe polymerase chain reaction (PCR), tri-prime-PCR
(TP-PCR) and capillary electrophoresis technique, repeated expansion of GGC in the 5’ region of
NOTCH2NLC gene was revealed (\sim 81 \text{ bp}, the repeat number of normal people is generally less than 60
bp) (Fig. 3, Fig. 4).

Therefore, the patient was diagnosed with NIID according to positive genetic testing result. For stroke-like
episodes of patient, she was given treatments including improve the circulations, provide the nerves
nutrition and give treatments aiming to patients’ current symptoms. Her symptoms gradually improved
and finally restored completely.

**Discussion**

NIID, a multisystem neurodegenerative disease, is characterized by the pathology of eosinophilic
intranuclear inclusions not only in the central, peripheral, and autonomic nervous systems, also in the
multiple visceral organs (3, 6). In 1968, first case of NIID was reported by Lindenberg et al (1) and NIID
was named in 1980 by Sung who reported a female patient with 21 years old (7). Besides, Sung
speculated that etiology of NIID may related to genetic susceptibility (7). At present, more than 150 NIID-
affected case subjects had been described worldwide (8–12). The diagnosis of adult-onset NIID is
challenging because its manifestations are highly heterogeneous. The patients were diagnosed mostly by
post-mortem brain biopsy before 2011, but now the skin biopsy and genetic testing both are the most
mainstream diagnostic methods (6, 13). In addition, automatic nerves dysfunction (such as arrhythmia, bladder dysfunction, postural hypotension, visual disturbance), corticomedullary junction hyperintense lesions in DWI, episodic encephalopathy (such as awareness indifference, consciousness disorder, delirium, psychiatric symptoms), white matter hyperintensities in the paravermis or middle cerebellar peduncles, are considered useful in the diagnosis of NIID (3, 4).

It also has been confirmed that NIID is associated with GGC repeat expansion in the 5' region of the NOTCH2NLC gene, which consistent with the suppose of Sung (7). And it has been identified that noncoding CGG trinucleotide repeat expansions in the 5' UTR region of the FMR 1 gene on the X chromosome as the causative mutations for fragile X-related tremor/ataxia syndrome (FXTAS) (14). There have been reported that FXTAS has striking overlapping clinical symptoms, radiological and histopathological features with NIID (15, 16). Therefore, genetic tests for both NOTCH2NLC and FMR1 genes should be taken into account for differential diagnosis of NIID and FXTAS. Ocular symptoms may be the earlier performance of NIID, however, they are usually misdiagnosed as single opthalmic diseases (17). In other words, NIID is not rare and our understanding of NIID is limited. But hardly cases reported visual hallucination and pupil diameter reduction in patients with NIID actually.

This report presented a multiple stroke-like episodes case for many years and visual hallucinations for a week with reduced pupil diameter suggesting that ophthalmological examination is an essential role for the early diagnosis of NIID-related retinopathy. Moreover, after improving the circulations, nutriting the nerves and giving treatments aiming to patient’s current symptoms, the stroke-like episodes of patient gradually improved and finally restored. Combing patient's restorable stroke-like symptoms episode repeatedly without other novel neuro injured symptoms (such as hemiplegic paralysis, aphasia) and DWI did not show new infarctions all the time, we observed her oromandibular dystonia and head tremor phenomenon additionally, as well as her reduced pupils in the last hospitalized time. Her DWI images did not show “silk ribbon sign” (high-signal intensity changes in the corticomedullary junction), while NIID was the first diagnosis to be considered for clinician. In this way, a variety of treatments, for example dangerous thrombolytic therapy, unnecessary antiplatelet aggregation and plaque stabilization therapies, can be avoid for patients with multiple stroke-like episodes to a large degree.

**Conclusion**

Here, we report an adult-onset NIID case with multiple stroke-like episodes for seven years and visual hallucinations for seven days. Since a number of cases were diagnosed single disease and thus did not undergo further genetic tests, the actual morbidity rate of adult-onset NIID may be larger than previously thought. NIID needs to be considered when a patient has visual hallucinations or some insidious symptoms of NIID combining with some atypical imaging features, and excluding FXTAS using genetic testing. We must use the NIID diagnostic flow to diagnose adult-onset NIID cases clearly. In the future, our finding will assist clinicians to identify more accurate clinical diagnosis and promote researchers to determine causative genes. Except for typical radiological change strongly suggesting NIID, Skin biopsies or genetic testing should be carried out early in patients with highly suspected NIID.
Abbreviations

NIID, neuronal intranuclear inclusion disease; DWI, diffusion weighted images; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; MRA, magnetic resonance angiography; PCR, polymerase chain reaction; TP, tri-prime; FXTAS, fragile X-related tremor/ataxia syndrome.

Declarations

Data Availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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Author information

Authors and Affiliations

Department of Neurology, Jingzhou Central Hospital, Yangtze University, Renming Road No. 1, Jingzhou 434020, China

Fan Zhou, Yong Fang, Shengjun Xie, Daokai Gong

Contributions

FZ and YF wrote the main manuscript text and SX prepared figures 1-4. All authors reviewed the manuscript.

Corresponding author

Correspondence to Daokai Gong.

Ethics declarations

Not applicable.

Consent for publication

The authors have obtained written informed consent from the patient for the publication of this paper.
Competing interests

The authors declare no competing interests.

Availability of data and materials

Not applicable.

References


Figures

Figure 1

The contracted pupil diameter (~ 1.5 mm) of patient (December 2021).
Figure 2

Brain MRI images. January 2021 (A)(B), and June 2021 (C) (D) suggested chronic infarction in the right occipital lobe, multiple ischemic infarction lesions of bilateral half oval centers and radial crowns. T2 (A) and T2 (D) both did not show definite restricted diffusion in the involved regions. Also noted were normal MRA results of head and neck.
Figure 3

The PCR and the fragment analysis both showed GGC repeated expansions in the NOTCH2 NLC gene.

Figure 4

The TP-PCR and the fragment analysis both showed GGC repeated expansions in the NOTCH2 NLC gene.