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案例报告：一位步态不稳的男性¹神经元核内包涵体病的典型影像学表现

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Abstract

BACKGROUND

Neuronal intranuclear inclusion disease (NIID) is a rare neurological degenerative disorder with diverse manifestations and inadequate awareness. Only a few cases of NIID have been reported, and typical imaging findings can provide certain clues for the diagnosis of the disease. Furthermore, skin biopsy and genetic testing are important to confirm the diagnosis.

CASE SUMMARY

An 84-year-old man presented to the Neurology Department of our hospital complaining of a progressive course of cognitive impairment and unsteady gait for 2 years. The symptoms gradually progressed and affected his daily life. The patient was initially diagnosed with Parkinson's disease and vascular dementia. The patient did not respond to conventional treatment, such as dopasehydrazine. Therefore, magnetic resonance imaging (MRI) was performed. Based on the imaging findings, we suspected an NIID diagnosis. During the 3-year follow-up in our hospital, his clinical symptoms gradually progressed, and imaging findings became more significant. A high signal intensity along the corticomedullary junction persisted on MRI. Gene testing and skin biopsy were recommended in our hospital; however, the patient refused these procedures. NIID was also considered when he went to a superior hospital in

Shanghai. The patient eventually agreed to undergo gene testing. This revealed abnormal GGC repeat expansions in the *NOTCH2NLC* gene.

CONCLUSION

The clinical manifestations of NIID are diverse. Patients with clinical manifestations similar to Parkinson's disease and dementia may have NIID.

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INTRODUCTION

Neuronal intranuclear inclusion disease (NIID) is characterised by the formation of eosinophilic hyaline intranuclear inclusions in the nervous system; however, these inclusion bodies widely exist in other cells and systems, such as in adipocytes, renal tubules, and dermal cells. As a rare progressive neurodegenerative disease, the clinical manifestations vary. NIID may be familial or sporadic, juvenile-onset (even infantile-onset), or adult-onset. NIID mostly has a chronic course, but acute attacks of headaches^[1], epilepsy^[2], and stroke-like^[3] onset have also been reported. Sone *et al.*^[4] divided adult-onset NIID into two groups. In the dementia-dominant group, dementia was the most prominent initial symptom followed by miosis, ataxia, and unconsciousness. In the limb weakness group, muscle weakness was the most common symptom, followed by sensory disturbances, miosis, bladder dysfunction, and dementia. However, these two groups are not separate entities. The variety of symptoms and age of onset make NIID difficult to diagnose. Here, we report a case of NIID.

CASE PRESENTATION

Chief complaints

An 84-year-old man was admitted to our hospital in March, 2018 because of slow reactions and gait instability for 2 years.

History of present illness

The patient gradually developed unsteady walking and lags in response since 2016. He was found wearing clothes inside out or backwards. He felt that his limbs were inflexible and his movement were obviously slow, especially in the right limb.

History of past illness

He had a history of type II diabetes mellitus with good glycaemic control.

Personal and family history

He denied having any familially-inherited disease.

Physical examination

Physical examination revealed normal cranial nerve evaluation and grade V limb muscle strength; involuntary movements and ataxia were not detected.

Laboratory examinations

Lumbar puncture examination revealed white blood cells $< 1 \times 10^6/L$, red blood cells $1 \times 10^6/L$, glucose 5.2 mmol/L, protein 1,123 mg/L, and chloride 121 mmol/L in the cerebrospinal fluid (CSF). The results of CSF ink staining, smear and fungus testing, and tumour cell screening were all negative. CSF pressure was normal. There was no improvement in gait and cognitive assessment after releasing 30 mL of CSF.

Skin biopsy and genetic testing were suggested to confirm the diagnosis; however, at first, the patient refused to undergo these procedures.

Imaging examinations

Brain magnetic resonance imaging (MRI) (Figures 1–3) revealed high signal intensity along the corticomedullary junction on diffusion-weighted imaging (DWI). During the 2-year follow-up, the patient showed progressive deterioration in motor retardation and cognitive impairment. In 2021, superior hospital cranial MRI showed multiple patchy

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foci of abnormal signal intensity in the white matter of the bilateral frontal and parietal lobes and periventricular area, high signal intensity on fluid-attenuated inversion recovery (FLAIR), high serrated marginal signal on DWI, and an enlarged ventricular system.

LABORATORY EXAMINATIONS

Lumbar puncture examination revealed white blood cells $< 1 \times 10^6/L$, red blood cells $1 \times 10^6/L$, glucose 5.2 mmol/L, protein 1,123 mg/L, and chloride 121 mmol/L in the cerebrospinal fluid (CSF). The results of CSF ink staining, smear and fungus testing, and tumour cell screening were all negative. CSF pressure was normal. There was no improvement in gait and cognitive assessment after releasing 30 mL of CSF.

Skin biopsy and genetic testing were suggested to confirm the diagnosis; however, at first, the patient refused to undergo these procedures.

FINAL DIAGNOSIS

With these findings, we considered the diagnosis of NIID.

TREATMENT

The patient was administered aspirin, drugs for prevention of cerebrovascular disease and dopasehydrazine, and other anti-Parkinson's disease drugs. However, the therapeutic effect was poor.

OUTCOME AND FOLLOW-UP

Currently, the patient is being followed-up regularly in our outpatient clinic.

DISCUSSION

NIID is a heterogeneous disease. Auxiliary examination is useful for NIID diagnosis. Brain MRI plays an important role in the diagnosis of NIID, and some studies have suggested that MRI can be a prerequisite for skin biopsy and provide new diagnostic

clues for NIID^[5]. DWI findings of high signal intensity along the corticomedullary junction have been generally accepted as MRI features of NIID. High signal intensities in the paravermal area (the medial part of the cerebellar hemisphere right beside the vermis) and middle cerebellar peduncle, diffuse high signal intensities of the cerebral white matter on FLAIR images, and atrophy of the cerebellum have also been observed in patients with NIID. In addition, abnormal FLAIR signals of the cerebellum have been considered as characteristic MRI features of NIID^[6]. It has been reported that high DWI signal intensities disappear during long-term radiological follow-up of patients with NIID^[7]. Therefore, typical imaging findings and pathological features may be absent in some cases of NIID.

A study conducted in Japan identified a GGC repeat expansion in the 5'-UTR region of the *NOTCH2NLC* gene using long-read sequencing, elucidating the genetic cause of familial and sporadic NIID^[8,9]. Boivin *et al.*^[10] found that GGC repeats are embedded in a small upstream open reading frame and are translated into a polyglycine protein, which forms intranuclear inclusions, and is toxic in cell and animal models. Similar clinical, histopathological, and genetic features were found in fragile X-associated tremor/ataxia syndrome (FXTAS) and NIID^[10]. Because FXTAS resembles NIID, *FMR1* gene mutation analysis should also be performed^[7]. GGC repeat length is correlated with the clinical manifestations of NIID. Carriers of intermediate size (40–80) GGC repeats are susceptible to parkinsonism-dominant NIID^[11], and cases with longer GGC repeats have a higher risk of dementia- and limb weakness-dominant NIID^[8]. In a case study, intranuclear inclusions were prominently distributed in hippocampal neurones, indicating that NIID may be a complex pathological entity^[12].

The clinical manifestations of NIID are highly heterogeneous and are easily misdiagnosed in clinical practice. For this patient, the following diseases needed to be considered and differentiated. First, the patient's main clinical manifestations were gait instability and cognitive impairment; therefore, normal pressure hydrocephalus should be considered. However, Evans' index was less than 0.3 and no disproportionately enlarged subarachnoid space hydrocephalus was found in this patient's brain

MRI. Further, we performed a fluid discharge test, but no improvement was seen in the patient's clinical symptoms. Second, it has been found that the GGC repeat expansion in the 5' untranslated region of the *NOTCH2NLC* gene is associated with many neurodegenerative diseases, such as NIID, Alzheimer's disease, frontotemporal dementia, Parkinson's disease, adult leucoencephalopathy, essential tremor, and multiple system atrophy^[13]. Therefore, the concept of NIID-related disorders has been proposed, which includes NIID and other diseases caused by the GGC repeat expansion of *NOTCH2NLC*^[14]. These neurodegenerative diseases overlap, making diagnosis difficult, and further research on *NOTCH2NLC* is required to reveal the pathological mechanisms of these diseases.

The patient's characteristic imaging findings and genetic analysis facilitated the consideration of a NIID diagnosis; however, previous reports have indicated that GGC repeat expansion can also be observed in Alzheimer's disease^[14], Parkinson's disease^[14], adult leucoencephalopathy^[15], essential tremor^[16], and multiple system atrophy^[17]. Skin biopsy is an important diagnostic clue that greatly increases the rate of antemortem diagnosis. Sone *et al.* suggested that a favourable skin biopsy region is 10 cm above the lateral malleolus^[4]. Intranuclear inclusions have been observed in neurons, fat cells, sweat duct epithelial cells, and other cell types. Nerve conduction studies of motor and/or sensory nerve damage and autonomic neuropathy are also indicative of NIID^[4]. Unfortunately, the patient still refused skin biopsy despite our recommendation. Nevertheless, skin biopsy alone is not sufficient to distinguish NIID from other diseases, such as FXTAS^[18].

NOTCH2NLC GGC repeat expansions were also found in some patients with sporadic Parkinson's disease, in whom typical imaging and clinical features of NIID were not detected^[19]

CONCLUSION

This study provides a further understanding of NIID through the follow-up of an elderly man with an unsteady gait. In conclusion, the diagnosis of NIID requires a

comprehensive judgement of clinical manifestations, imaging findings, biopsy and genetic analysis. Although the patient refused to undergo skin biopsy to confirm the diagnosis, this case may further our understanding of NIID.

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