Neuroendocrinology Letters Volume 41 No. 4 2020
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

CASE REPORT

Adult-onset neuronal intranuclear inclusion disease mimicking Parkinson's disease in a Chinese patient: a case report and literature reviews

Zi-Yi Wang[1*], Jiao-Jiao Guo[1*], Meng Wang[1], Zhao-Xia Wang[2], Dao-Jun Hong[2], Xue-Fan Yu[1]

1 Department of Neurology and Neuroscience, The First Hospital of Jilin University, Changchun 130021, China
2 Department of Neurology, Peking University First Hospital, Beijing 100000, China

*These authors contributed equally to this work.

Correspondence to: Xue-Fan Yu, PhD
Department of Neurology and Neuroscience, The First Hospital of Jilin University
71 Xinmin St, Changchun 30021, China
TEL.: +86 17681020128; FAX: 0086-431-88782378; E-MAIL: xuefan@jlu.edu.cn

Submitted: 2020-06-16 Accepted: 2020-09-06 Published online: 2020-09-08

Key words: **Neuronal intranuclear inclusion disease; Parkinson's disease; Skin biopsy; Genetic testing; Case report**

Neuroendocrinol Lett 2020; **41**(4):155–161 **PMID:** 33307649 NEL410420C01

Abstract

Neuronal intranuclear inclusion disease is a rare hereditary neurodegenerative disease characterized by localized eosinophilic intracytoplasmic inclusion bodies in cells of the nervous system and internal organs. This disorder is frequently missed or misdiagnosed, as there is significant heterogeneity of its clinical presentation. Recently, genetic sequencing has revealed complex links between neuronal intranuclear inclusion disease and other neurodegenerative diseases, potentially explaining the diversity of clinical manifestations. Herein, we describe the case of a 68-year-old male Chinese patient who was initially diagnosed with Parkinson's disease based on classic symptomatology and ^{123}I-metaiodobenzylguanidine scintigraphy results and was subsequently treated with oral methyldopa for 3 years. He developed a paroxysmal tic before he presented to our hospital for treatment after a convulsive seizure. Brain magnetic resonance imaging identified signal hyperintensity at the corticomedullary junction on diffusion-weighted imaging. Skin biopsy results and genetic testing confirmed a revised diagnosis of neuronal intranuclear inclusion disease. This report highlights that patients clinically diagnosed with Parkinson's disease may actually be in the early stages of neuronal intranuclear inclusion disease, suggesting that patients with suspected Parkinson's disease should also be screened for this disease.

Abbreviations:

CSF	- cerebrospinal fluid	MRI	- magnetic resonance imaging
DWI	- diffusion-weighted imaging	NIID	- neuronal intranuclear inclusion disease
FXTAS	- fragile X-associated tremor-ataxia syndrome	PD	- Parkinson's disease
HE	- hematoxylin eosin	TCD	- transcranial doppler
MIBG	- ^{123}I-metaiodobenzylguanidine		

INTRODUCTION

Neuronal intranuclear inclusion disease (NIID) is a rare inherited neurodegenerative disorder with onset in all age groups and significant variability in clinical symptoms. The characteristic pathological feature of NIID is the appearance of localized eosinophilic hyaluronic nuclear inclusions in central and peripheral nervous system and visceral organ cells (Sone *et al.* 2016).

The clinical manifestations of NIID vary greatly with dementia, convulsions, dysuria, and constipation reported in patients. In the early stages of NIID, the observed symptoms may partially overlap with those of Parkinson's disease (PD), including tremors, autonomic nerve damage, and other physical examination findings. Recently, amplified GGC nucleotide repeats have been identified in the human-specific NOTCH2NLC gene in patients with NIID and in some families with PD, indicating that NIID may be related to this neurodegenerative disease and others (Tian *et al.* 2019).

We report a case of a male patient who was misdiagnosed with PD three years prior to presentation at our hospital. He was eventually diagnosed with NIID based on imaging, biopsies, and genetic testing. In addition, we have provided a literature review of recent findings related to genes that are associated with NIID to demonstrate that extended repeating mutations of the same base sequences in noncoding regions may lead to similar clinical manifestations or overlapping disease processes. We present the following case in accordance with the CARE reporting checklist.

CASE PRESENTATION

A 68-year-old Chinese man presented to our hospital after a convulsive seizure that left him unconscious. According to the patient's wife, his seizure was characterized by flexion of both upper limbs, straightening of both lower limbs, tongue biting, and uroclepsia that lasted 3 minutes. At presentation, the patient was treated with diazepam. He remained unconscious for approximately 20 minutes, after which his level of consciousness improved, though he still exhibited lethargy.

The patient noted development of bilateral symmetrical quiescent hand tremors, myotonia, dysuria, and constipation three years prior to presentation. A previous ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy demonstrated a reduction of ^{123}I-MIBG accumulation in his heart; therefore, he was diagnosed with PD and had been receiving oral methyldopa therapy. The patient's wife stated that his symptoms had improved significantly after taking the medication, though he still occasionally experienced involuntary tremors. In addition, he had experienced a single episode of loss of consciousness and another episode of persistent hiccups, both of which were relieved without medications. During the year prior to presentation, he often could not remember where he was and occasionally did not recognize the people around him. The patient had no personal history of hypertension, diabetes, or family members with similar symptomatology.

The patient's vital signs were stable at initial presentation. On neurological examination, he was found to be unconscious and unable to respond to external conversation or requests. His pupils were equally elliptical, reactive to light, and accommodated sensitively; however, they were abnormally sized with diameters of 1.0 mm. Though he could not cooperate with a muscle strength examination of the limbs, his muscle tension was increased, and his tendon reflexes were normal. His Babinski and Chaddock signs were bilaterally positive. After he regained consciousness, we examined his memory, computation, and orientation in detail and found no abnormalities. Other neurological examinations were unremarkable.

A lumbar puncture demonstrated a normal intracranial pressure of 160 mm H20, and his cerebrospinal fluid (CSF) showed a high protein level of 0.63 g/L (normal 0.15–0.45 g/L), high immunoglobulin G level of 45.2 mg/L (normal 0–34 mg/L), and normal levels of glucose, ions, and cell numbers. Routine blood tests revealed that the patient's leukocyte count was high at 13.59×10^9/L (normal $4–9 \times 10^9$/L) with a neutrophilic percentage of 80.30%. His liver and renal functions, electrolytes, trace elements, folic acid, blood corticotrophin levels, thyroid function, tumor markers, hepatitis B test, and HIV test were normal. Antibody tests for autoimmune and paraneoplastic disorders were also negative in his serum and CSF.

The patient's brain magnetic resonance imaging (MRI) revealed an abnormal high-intensity signal at the corticomedullary junction and marked leukoencephalopathy surrounding the lateral ventricles (Figure 1). A slightly hyperintense signal was evident in the periventricular white matter on the T2-weighted (Figure 1A) and fluid attenuation inversion recovery (Figure 1B) sequences. On diffusion-weighted imaging (DWI) (Figure 1C), we observed a line-like hyperintense signal fusion at the corticomedullary junction, especially in the frontal lobe and a portion of the parietal lobe. On the apparent diffusion coefficient sequence (Figure 1D), the line-like high-intensity signal that was observed on DWI was only slightly hyperintense, and the changes in the periventricular white matter showed a high signal intensity.

Electrophysiological testing of the patient showed that the peripheral nerves of his upper and lower extremities were slightly damaged, with motor conduction velocities of 42.4 m/s for the right median nerve, 39.8 m/s for the left ulnar nerve, 34.5 m/s for the right common peroneal nerve, and 38 m/s for the right superficial peroneal nerve. The patient's somatosensory evoked potentials were normal. His 24-hour electroencephalogram showed an increase in nonspecific slow brainwave activity and no typical epileptic

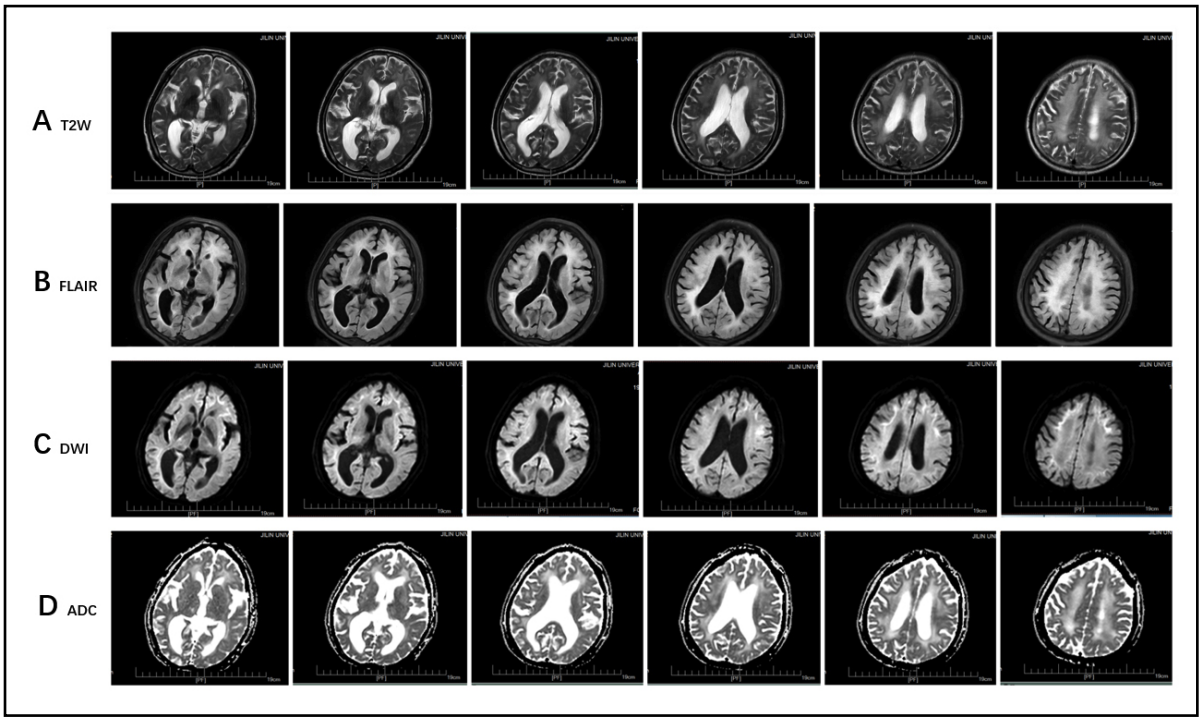

Fig. 1. Magnetic resonance imaging showed significant leukoencephalopathy around bilateral lateral ventricles. (A) On T2-weighted (T2W) and (B) fluid attenuation inversion recovery (FLAIR) sequences, the lesion presented with a slightly hyperintense signal in the periventricular region. (C) On diffusion-weighted imaging (DWI), a hyperintense signal lesion was noted in the frontal lobe and a part of the parietal lobe, with a line-like hyperintense signal lesion at the junction of the cortex and medulla that fused together like garland. (D) On apparent diffusion coefficient (ADC) sequence, the hyperintense signal noted on DWI had an isointense signal.

discharges. Electrocardiogram and echocardiography showed no abnormalities. Transcranial Doppler (TCD) revealed that the substantia nigra echo was significantly enhanced to a Grade III, indicating excessive iron deposition (Figure 2).

The patient's written consent was obtained, and a subsequent skin biopsy was performed 10 cm above the lateral malleolus. Under light microscopy, hematoxylin and eosin (HE) staining showed eosinophils in the nuclei of some sweat duct epithelial cells. Anti-p62 immunocytochemistry showed positive staining for inclusion bodies (Figure 3). Electron microscopy showed an inclusion body without a membrane in the nucleus of a sweat duct epithelial cell (Figure 4).

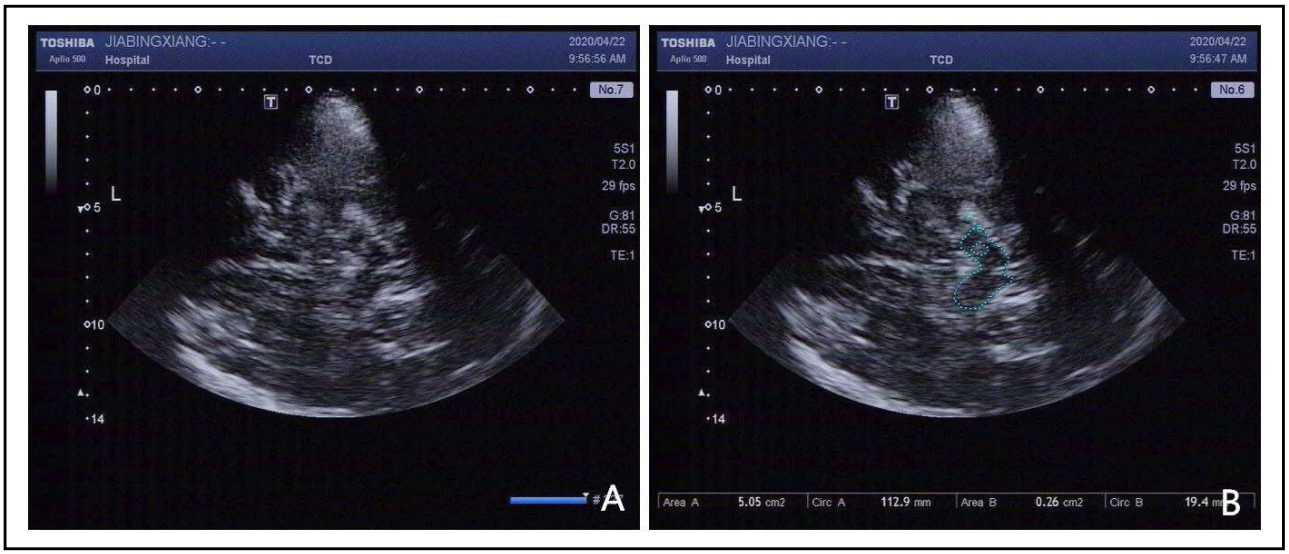

Fig. 2. Transcranial Doppler evaluation. (A, B) Transcranial Doppler showed that the echo of the substantia nigra was enhanced to Grade III. The hyperechoic area of the substantia nigra was 0.38 cm2 (green border).

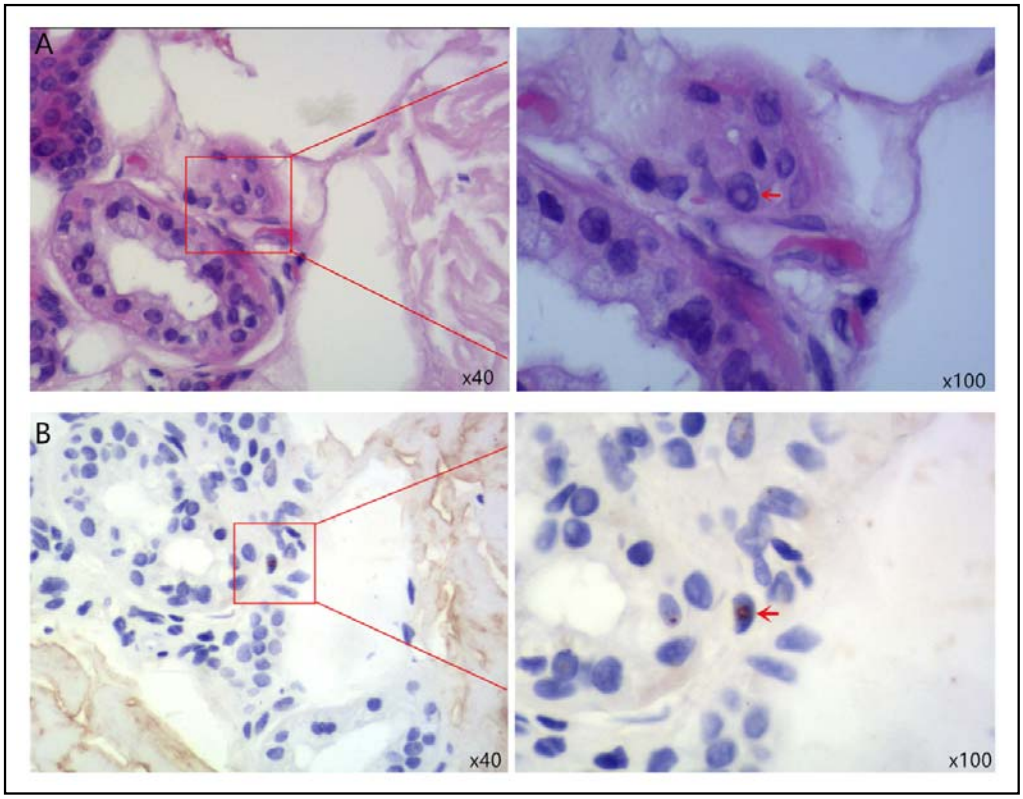

Fig. 3. Light microscopy of the skin biopsy. (A) Eosinophilic inclusion bodies (red arrow) in the epithelial cells of sweat glands revealed by hematoxylin and eosin staining. (B) Inclusion bodies (red arrow) were positive for anti-P62 staining.

Furthermore, repeat-primed PCR of the skin biopsy showed 105 repeats of a GGC amplification in the 5′UTR of the *NOTCH2NLC* gene, which was significantly more than in the normal control group (Figure 5). Additionally, we excluded the possibility of Fragile X-associated tremor-ataxia syndrome (FXTAS) using the FMR1 premutation test. Based on the results of all these tests, we diagnosed the patient with NIID.

The patient received only symptomatic treatment after admission. After 3 days, he was able to communicate normally and could perform activities of daily living. We recommended that the patient stop taking oral methyldopa due to its side effects. At the patient's follow-up 3 months after discharge, he reported occasionally experiencing transient and slight hand tremors but no constipation or dysuria. The patient took no medications during this follow-up period.

DISCUSSION

We have presented the case of a male patient who showed typical symptoms of PD for some time, and both MIBG scintigraphy and TCD supported this diagnosis. Although his wife stated that oral methyldopa, which is a standard treatment for PD, was effective at improving his symptoms, the symptoms of NIID are typically intermittent. Therefore, the improvement in his symptoms may not have been a response to the drug.

Convulsive seizures, peripheral nerve damage, narrowed pupils, and worsened dementia were the primary indicators of NIID in this patient; furthermore, imaging, pathology, and genetic tests helped us confirm this diagnosis. A previous case report described a patient with juvenile Parkinsonism who was diagnosed with NIID after a skin biopsy (O'Sullivan *et al.* 2019). However, to our knowledge, we are the first to describe a patient misdiagnosed with PD who was eventually diagnosed with adult-onset NIID using genetic testing. We believe that both genetic testing and brain MRI should be performed on patients with PD to exclude early NIID.

Cranial MRI is of significant importance in the diagnosis of NIID. One typical MRI manifestation of NIID is a continuous subcortical linear hypersignal (Han *et al.* 2019) or a so-called 'line-like' sign on DWI, which rarely extends to the deep white matter. This abnormally high signal, which appeared in the frontal and parietal lobes of our patient, is likely related to multiple focal spongiotic changes in the white matter at the proximal ends of U fibers. This signal was previously thought to be permanent once observed; however, researchers have recently identified a case in which this signal eventually disappeared, likely due to absorption of edema (Kawarabayashi *et al.* 2018). This line-like sign has also been shown to occur in patients with oculopharyngeal myopathy with leukoencephalopathy

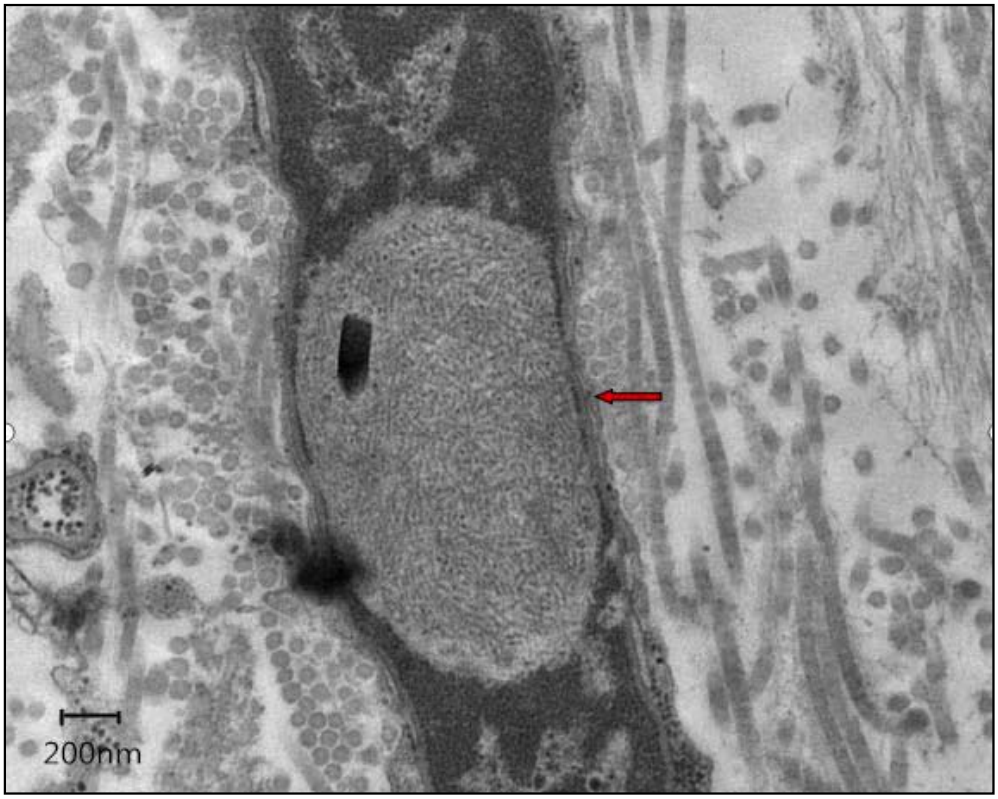

Fig. 4. Using electron microscopy, an oblong inclusion body without a membrane was observed in the nucleus of a sweat gland epithelial cell (red arrow).

and FXTAS (Ishiura *et al.* 2019). In addition, the vast majority of patients with NIID have some degree of brain atrophy and diffuse leukoencephalopathy on MRI, though these findings are not specific. Finally, some patients with NIID can have high signal intensity around the cerebellum on DWI (Sugiyama *et al.* 2017), necessitating the differentiation of NIID from cerebellar encephalitis and demyelinating diseases. While the literature suggests that only 37.5% (Tian *et al.* 2019) of patients with NIID have the aforementioned characteristic findings on brain MRI, similar findings can appear in patients with other diseases, including FXTAS and Creutzfeldt-Jakob disease.

A skin biopsy, which was once considered the gold-standard approach to diagnosing NIID, is safer, easier, and less stressful to patients than rectal or sural nerve biopsies (Sone *et al.* 2011). The main cellular mechanisms underlying NIID include an abnormal accumulation of protein in the nuclei and dysfunction of the protein degradation system, which lead to the characteristic inclusion bodies identified on biopsies. Similar nuclear inclusion bodies can be found in other neurodegenerative diseases, including FXTAS (Gelpi *et al.* 2017); polyglutamine diseases (Takahashi *et al.* 2000), such as Huntington's disease; and spinocerebellar ataxias. The skin biopsy of our patient revealed inclusion bodies in the nuclei of sweat gland epithelial cells, but no nuclear inclusion bodies were found in fat cells or fibroblasts, possibly indicating a shorter disease duration in this patient. Although these inclusion bodies are known to be immunopositive, the diagnostic sensitivity of skin biopsies for NIID needs to be verified with further large-scale studies.

The *NOTCH2NLC* gene is highly expressed in a variety of radial glial cell populations, including astrocytes and microglia, and thought to be closely related to the evolutionary development of the human cerebral cortex (Fiddes *et al.* 2018). By sequencing the genomes of patients with familial and sporadic NIID, Sone *et al.* (2019) demonstrated that amplification of a GGC trinucleotide repeat in the 5' region of the human-specific *NOTCH2NLC* gene can occur in patients with NIID and can be used to distinguish this disorder from certain types of dementia. Subsequently, amplification of the *NOTCH2NLC* gene was demonstrated to be associated with some types of neurodegenerative dementias and leukoencephalopathy (Okubo *et al.* 2019; Jiao *et al.* 2020). Researchers also found GGC amplifications in the *NOTCH2NLC* gene of some patients with multisystem atrophy (Fang *et al.* 2020), PD, Alzheimer's disease, and peripheral neuropathy (Tian *et al.* 2019); consequently, these diseases were grouped together as so-called 'NIID-related' disorders, which include NIID and other neurodegenerative diseases caused by an amplified GGC repeat sequence in the human-specific *NOTCH2NLC* gene (Tian *et al.* 2019). Interestingly,

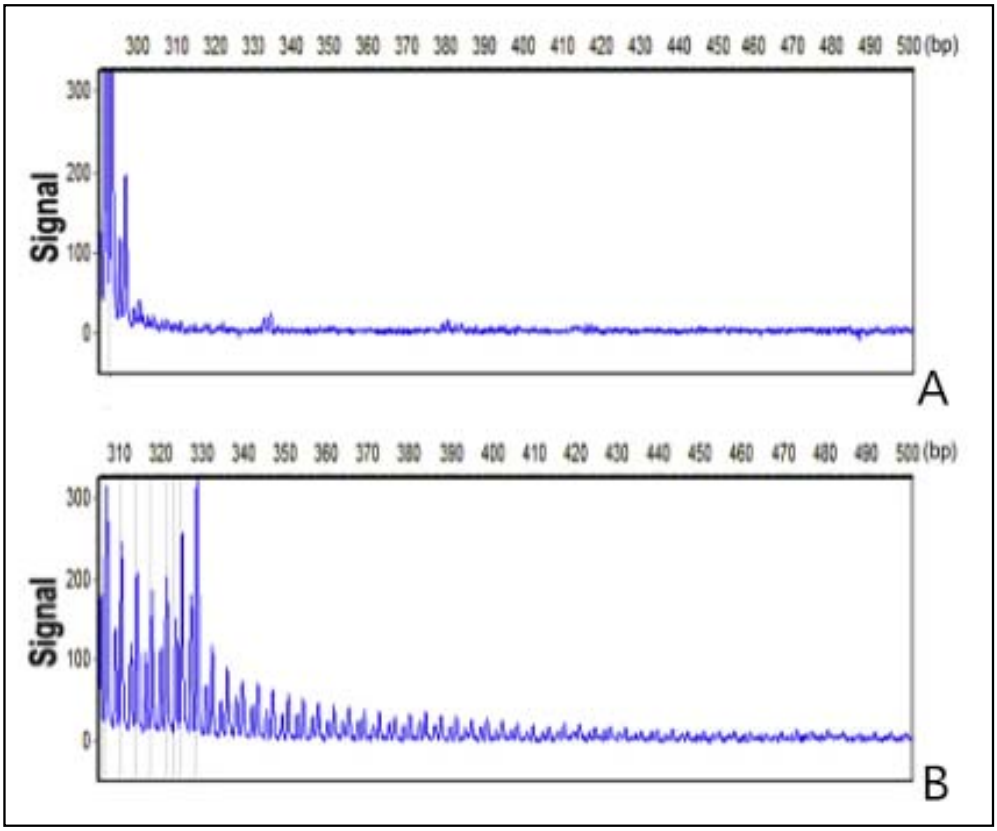

Fig. 5. Electropherogram of the RP-PCR. (A). The control group showed no repeat amplification in normal patient. (B) The panel of the patient revealed the jagged pattern of repeat amplification.

researchers have detected intranuclear inclusion bodies in the skin biopsies of patients with essential tremor, although these patients had no clinical manifestations of NIID over the preceding ten years except for a tremor (Sun *et al.* 2020).

No postmortem pathological information has been confirmed for patients with NIID thus far; however, genetic studies have helped us to understand the relationship between NIID-related disorders and NIID. Among healthy subjects, the number of GGC repeats in the *NOTCH2NLC* gene has been shown to be less than 40 (Tian *et al.* 2019). However, the clinical manifestations of patients may differ based on the varying levels of GGC amplification, which is certainly a future research direction. A previous study reported that some patients with NIID in Japan did not have the GGC repeat amplification mutation in the *NOTCH2NLC* gene, indicating genetic heterogeneity in NIID (Sone *et al.* 2019). Further identification of GGC repeat amplifications in other gene sets or repeat amplifications containing similar sequences are another future research direction. Accordingly, these persistent gaps in knowledge indicate that a single type of test cannot definitively diagnose NIID; instead, a combination of evaluations of symptoms, imaging, biopsy, and genes should be employed.

NIID can affect multiple organs, which often leads to multiple sets of symptoms. As the pathogenesis of NIID is not entirely clear at present, research on the treatment of this disease is lacking. Hormone therapy has been shown to have some short-term efficacy for patients with NIID and subacute episodic encephalitis, with improvement believed to result from hormonally induced relief of local brain edema. Other studies have identified patients with NIID who were treated with levodopa for their quiescent tremor (Espay *et al.* 2010) and who, as in our case, did not experience a definitive therapeutic effect from the medication.

In conclusion, patients with NIID exhibit significant clinical heterogeneity in their symptomatology, often leading to delays in diagnosis and misdiagnoses with other neurodegenerative diseases, such as PD. Moreover, as our case demonstrates, MIBG scintigraphy and TCD are limited in their ability to distinguish between PD and NIID. Therefore, screening for extended GGC repeats in the *NOTCH2NLC* gene is highly recommended in order to distinguish between PD and NIID. Additionally, when patients with suspected PD develop seizures or a transient loss of consciousness, NIID should be included in the differential diagnosis.

DECLARATIONS

Reporting Checklist:

The authors have completed the CARE reporting checklist.

Conflict of interest:

All authors have completed the ICMJE uniform disclosure form. The authors have no conflicts of interest to declare.

Ethics Statement:

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

ACKNOWLEDGMENTS

Not applicable.

REFERENCES

1 Espay AJ, Paviour DC, O'Sullivan JD, et al (2010). Juvenile levodopa-responsive Parkinsonism with early orobuccolingual dyskinesias and cognitive impairment. Mov. Disord. **25:** 1860–7.
2 Fang P, Yu Y, Yao S, et al (2020). Repeat expansion scanning of the NOTCH2NLC gene in patients with multiple system atrophy. Ann Clin Transl Neurol. **7:** 517–26.
3 Fiddes IT, Lodewijk GA, Mooring M, et al (2018). Human-Specific NOTCH2NL Genes Affect Notch Signaling and Cortical Neurogenesis. Cell. **173:** 1356–69. e22.
4 Gelpi E, Botta-Orfila T, Bodi L, et al (2019). Neuronal intranuclear (hyaline) inclusion disease and fragile X-associated tremor/ataxia syndrome: a morphological and molecular dilemma. Brain. **140:** e51.
5 Han X, Han M, Liu N, et al (2019). Adult-onset neuronal intranuclear inclusion disease presenting with typical MRI changes. Brain Behav. **9:** e01477.
6 Ishiura H, Shibata S, Yoshimura J, et al (2019). Noncoding CGG repeat expansions in neuronal intranuclear inclusion disease, oculopharyngodistal myopathy and an overlapping disease. Nat Genet. **51:** 1222–32.
7 Jiao B, Zhou L, Zhou Y, et al (2020). Identification of expanded repeats in NOTCH2NLC in neurodegenerative dementias. Neurobiol. Aging. **89:** 142. e1–e7.
8 Kawarabayashi T, Nakamura T, Seino Y, et al (2018). Disappearance of MRI imaging signals in a patient with neuronal intranuclear inclusion disease. J Neurol Sci. **388:** 1–3.
9 O'Sullivan JD, Hanagasi HA, Daniel SE, et al (2019). Neuronal intranuclear inclusion disease and juvenile parkinsonism. Mov. Disord. **105:** 166–76.
10 Okubo M, Doi H, Fukai R, et al (2019). GGC Repeat Expansion of NOTCH2NLC in Adult Patients with Leukoencephalopathy. Ann. Neurol. **86:** 962–8.
11 Sone J, Mitsuhashi S, Fujita A, et al (2019). Long-read sequencing identifies GGC repeat expansions in NOTCH2NLC associated with neuronal intranuclear inclusion disease. Nat. Genet. **51:** 1215–21.
12 Sone J, Mori K, Inagaki T, et al (2016). Clinicopathological features of adult-onset neuronal intranuclear inclusion disease. Brain. **139:** 3170–86.
13 Sone J, Tanaka F, Koike H, et al (2011). Skin biopsy is useful for the antemortem diagnosis of neuronal intranuclear inclusion disease. Neurology. **76:** 1372–6.
14 Sugiyama A, Sato N, Kimura Y, et al (2017). MR Imaging Features of the Cerebellum in Adult-Onset Neuronal Intranuclear Inclusion Disease: 8 Cases. AJNR Am J Neuroradiol. **38:** 2100–4.
15 Sun QY, Xu Q, Tian Y, et al (2020). Expansion of GGC repeat in the human-specific NOTCH2NLC gene is associated with essential tremor. Brain. **143:** 222–33.
16 Takahashi J, Fukuda T, Tanaka J, et al (2000). Neuronal intranuclear hyaline inclusion disease with polyglutamine-immunoreactive inclusions. Acta Neuropathol. **99:** 589–94.
17 Tian Y, Wang JL, Huang W, et al (2019). Expansion of Human-Specific GGC Repeat in Neuronal Intranuclear Inclusion Disease-Related Disorders. Am J Hum Genet. **105:** 166–76.