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CASE REPORT

Adult-onset neuronal nuclear inclusion disease presenting with mental and behavioral disorders: A case report and literature review

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1 | INTRODUCTION

Neuronal nuclear inclusion disease (NIID) is a rare neurological degenerative disease,[1] and it typically presents with chronic or subacute onset. The clinical manifestations of NIID are highly heterogeneous and include disturbance of consciousness, seizures, motor and sensory abnormalities, dementia, ataxia, peripheral neuropathy, and autonomic dysfunction. These symptoms are often misdiagnosed as other nervous system diseases. At present, the etiology and pathogenesis of NIID are not clear. Immunohistochemical studies showed that eosinophilic inclusion bodies were positive for ubiquitin and ubiquitin-related proteins, including P62, SUMO1, FUS, MYO6, and OPTN-C, suggesting that the ubiquitin–proteasome pathway may play a role in the pathogenesis of NIID.[2–5] In recent years, studies in NIID families have found that GGC sequence in the 5′ region of the human-specific NOTCH2NLC gene, which is the pathogenic gene of adult-onset NIID, is abnormally repeated, so the NOTCH2NLC gene is associated with the pathogenesis of familial NIID.[6–9]

In the past, the diagnosis of NIID required an autopsy. Together with Japanese scholars, Sone[10] reported that the disease can be diagnosed by skin biopsy, and the number of reports of the disease has increased in recent years. Furthermore, the magnetic resonance imaging (MRI) technique of diffusion weighted imaging (DWI) showed line-like signals of high intensity along the corticomedullary junction, which is also of great value for diagnosis.

We report adult-onset NIID in a patient whose first symptoms manifested as mental and behavioral disorders. This case report describes a rare clinical manifestation of adult-onset NIID, and furthering our understanding of NIID clinical characteristics may be helpful for clinicians.

2 | CASE PRESENTATION

A 68-year-old man was referred to our department due to a paroxysmal orientation disorder 1 year prior, and mental and behavioral disorders occurring for 2 days. The patient lost his way while walking in his own community 1 year prior. He could not find his way home and walked to the neighboring community. After being found by his family, he said that he did not know where he was. After the symptoms lasted for 1 day, he recovered and could complete his daily routine. However, he could not recall what happened on the day that he got lost. Two days ago, the patient did not know his family members, spoke in gibberish, answered irrelevant questions, and presented with abnormal behaviors, such as urinating in the room, splashing water in the room, and attacking family members. He went to a

nearby hospital and underwent a brain computed tomography scan (CT), which showed no abnormalities. The patient had no history of hypertension, diabetes, cerebrovascular disease, or cardiovascular disease. There was no family history of cerebrovascular disease, cardiovascular disease, dementia, or mental disorders in the family.

The patient's physical examination showed a temperature of 37.8°C, the level of consciousness was normal, the content of consciousness was decreased, his comprehension was impaired, his orientation of time, place, and character was impaired, he was unable to calculate, the content of speech expression was confused, the bilateral pupils were small, with a diameter of 2 mm, and the bilateral direct and indirect responses to light existed. His bilateral upper and lower limb muscle strength was 4.0/5.0. The tendon reflex of his extremities was (+), the bilateral Babinski and Chaddock signs were (−), and meningeal irritation was negative. The patient was unable to cooperate during the sensory system and ataxia examinations.

Laboratory investigation revealed hemoglobin was 144 g/L, the white blood cell count (WBC) was 9.6×10^9/L (N 72.7, L20.2, M6.3%), the platelet count was 245×10^9/L, sodium was 134.60 mmol/L, potassium was 3.73 mmol/L, chloride was 98.8 mmol/L, glucose was 5.62 mmol/L, TSH was 3.745 μU/ml, FT4 was 1.20 ng/dl, FT3 was 2.77 pg/ml, anti-thyroglobulin was 29.00 U/ml, anti-thyroid peroxidase was 41.20 U/ml, and the level of the tumor markers were all normal. Next, we performed a lumbar puncture on this patient. Cerebrospinal fluid (CSF) analysis revealed colorless fluid with a CSF pressure of 90 mmH_2O, WBC 0 cells/mm^3, protein 0.44 g/L and glucose 4.0 mmol/L. Serum and CSF analysis of paratumor antibodies and autoimmune encephalitis antibodies were all negative through the immunospot assay.

The patient underwent a brain MRI examination that showed high signals of diffusion restriction on DWI along the bilateral corticomedullary junction and corpus callosum and a slightly low signal on the apparent diffusion coefficient (ADC) (Figure 1). One month and two months later, brain MRI still showed high signals on DWI along the bilateral corticomedullary junction and corpus callosum, and the high signals on DWI in the anterior horn of the left paraventricular ventricle and corpus callosum were enlarged. EEG examination showed that low-amplitude α waves were scattered in the

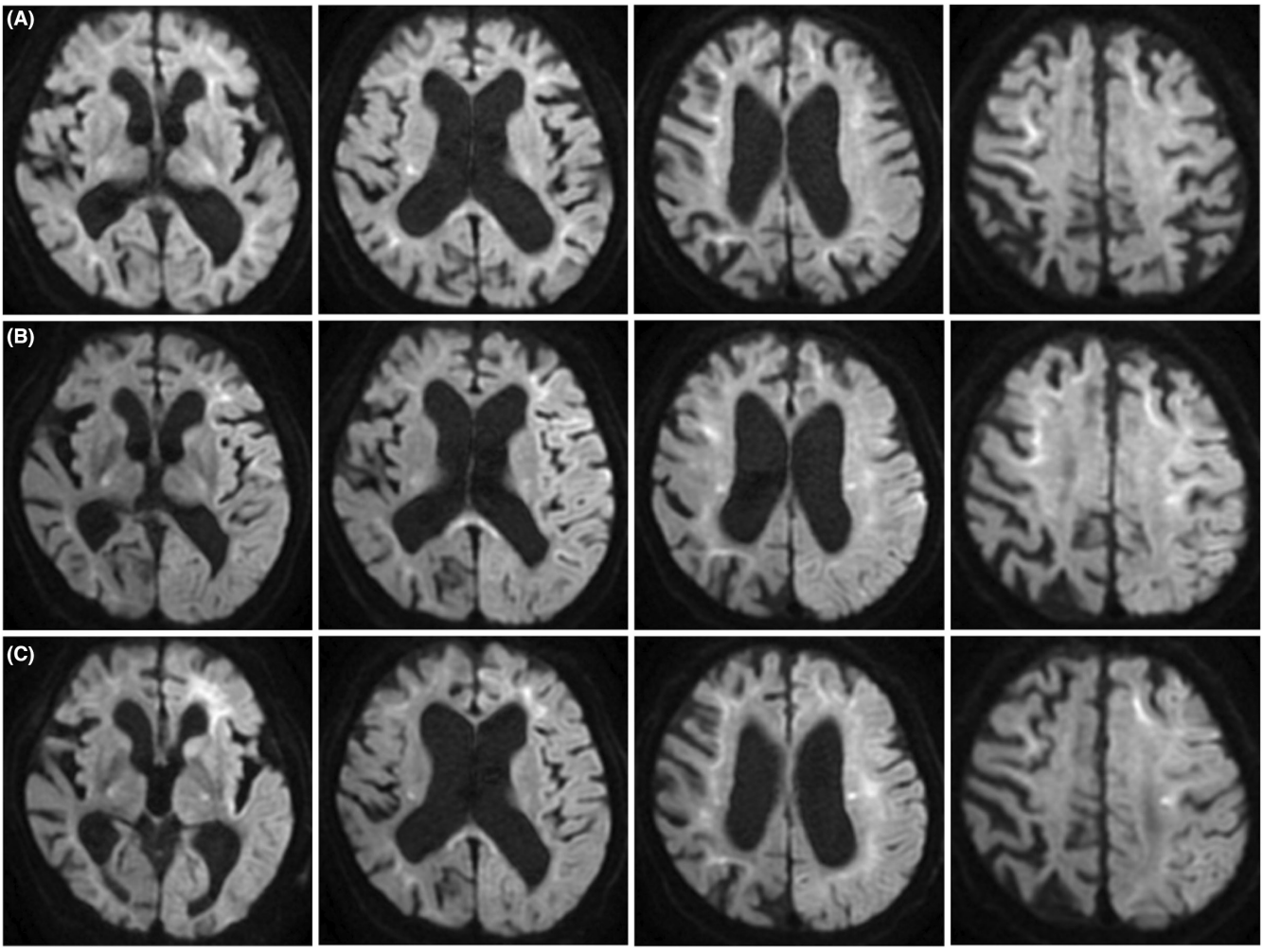

FIGURE 1 Brain MRI findings on diffusion-weighted images (DWIs). High signals were observed along the bilateral corticomedullary junction and corpus callosum (A); 1 month (B) and 2 months (C) later, high signals on DWI in the anterior horn of the left paraventricular ventricle and corpus callosum were enlarged.

occipital region, a large number of low to high amplitude 4–7 Hz θ waves were scattered, and a small number of low to medium amplitude 2–3 Hz δ waves were scattered. Nerve conduction velocity examination showed that the sensory nerve conduction velocity of the bilateral superficial branch of the median nerve and ulnar nerve slowed down, and the motor conduction velocity of the bilateral median nerve, ulnar nerve, tibial nerve, and common peroneal nerve slowed down.

Then a skin biopsy was performed 10 cm above the right lateral malleolus. Hematoxylin–eosin (HE) staining showed pink eosinophilic inclusion bodies in the nuclei of eccrine gland cells and adipocytes. Immunohistochemical staining and immunofluorescence showed anti-p62 positivity in the nuclei of eccrine gland cells and adipocytes (Figure 2). Then, through capillary electrophoresis (CE), GeneScan and triprimer polymerase chain reaction (TP-PCR), we revealed that the number of physiological repeats of GGC in the 5′ region of the NOTCH2NLC gene was 106. Normally, the number of repeats is less than 40, and it is considered pathogenic when the number of repeats is more than 60 (Figure 3).

The patient had paroxysmal encephalopathy symptoms 1 year prior, and currently, this patient presented with sudden mental and behavioral abnormalities and a low-grade fever. Cerebrospinal fluid and serological tests ruled out intracranial infection, autoimmune encephalitis, and paraneoplastic syndrome. The brain MRI of the patient showed high signals on DWI along the bilateral corticomedullary junction and corpus callosum, and the high signals on DWI did not disappear by the 1 month and 2 month follow-ups. Subsequently, the HE staining of the skin pathology of the patient showed eosinophilic inclusion bodies in the nucleus of eccrine gland cells and adipocytes, and immunohistochemistry and immunofluorescence showed p62 antibody positivity. The number of GGC repeat sequences in the NOTCH2NLC gene was greater than 40 in this patient, so the diagnosis of neuronal intranuclear inclusion disease was confirmed.

Because there is no effective treatment for NIID, we administered nutritional support and anti-infection treatment. During hospitalization, the patient experienced paroxysmal disturbance of consciousness and could not wake up during the attack. The level of consciousness returned to normal after 1–2 days. Fifteen days after onset, the patient had recurrent seizures, each attack lasted 1–3 minutes, and there were 1–2 seizures every day. The seizures were stopped by intravenous injection of diazepam 5 mg, followed by nasal administration of 0.5 g sodium valproate once a day, which was increased to 0.5 g twice a day; the attack of seizures was reduced

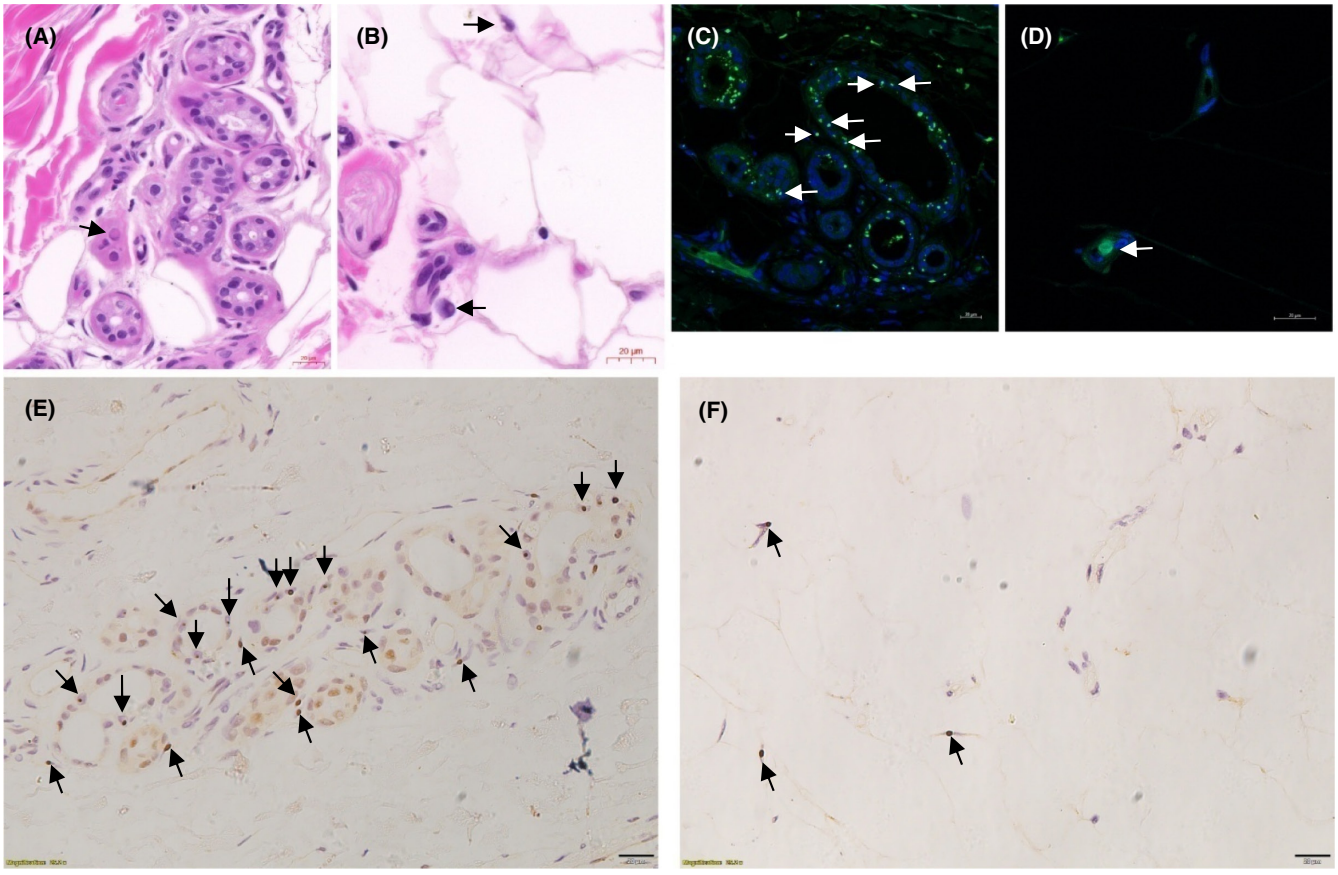

FIGURE 2 Skin biopsy samples underwent immunohistochemical staining: hematoxylin–eosin staining (×400 magnification), the arrows refer to eosinophilic spherical inclusion bodies in the nuclei of eccrine gland cells (A) and adipocyte (B); immunofluorescence (arrows, green fluorescence) were anti-p62 positive in the nuclei of eccrine gland cells (C, ×200 magnification) and adipocyte (D, ×400 magnification); immunohistochemical staining (arrows, ×400 magnification) were anti-p62 positive in the nuclei of eccrine gland cells (E) and adipocyte (F).

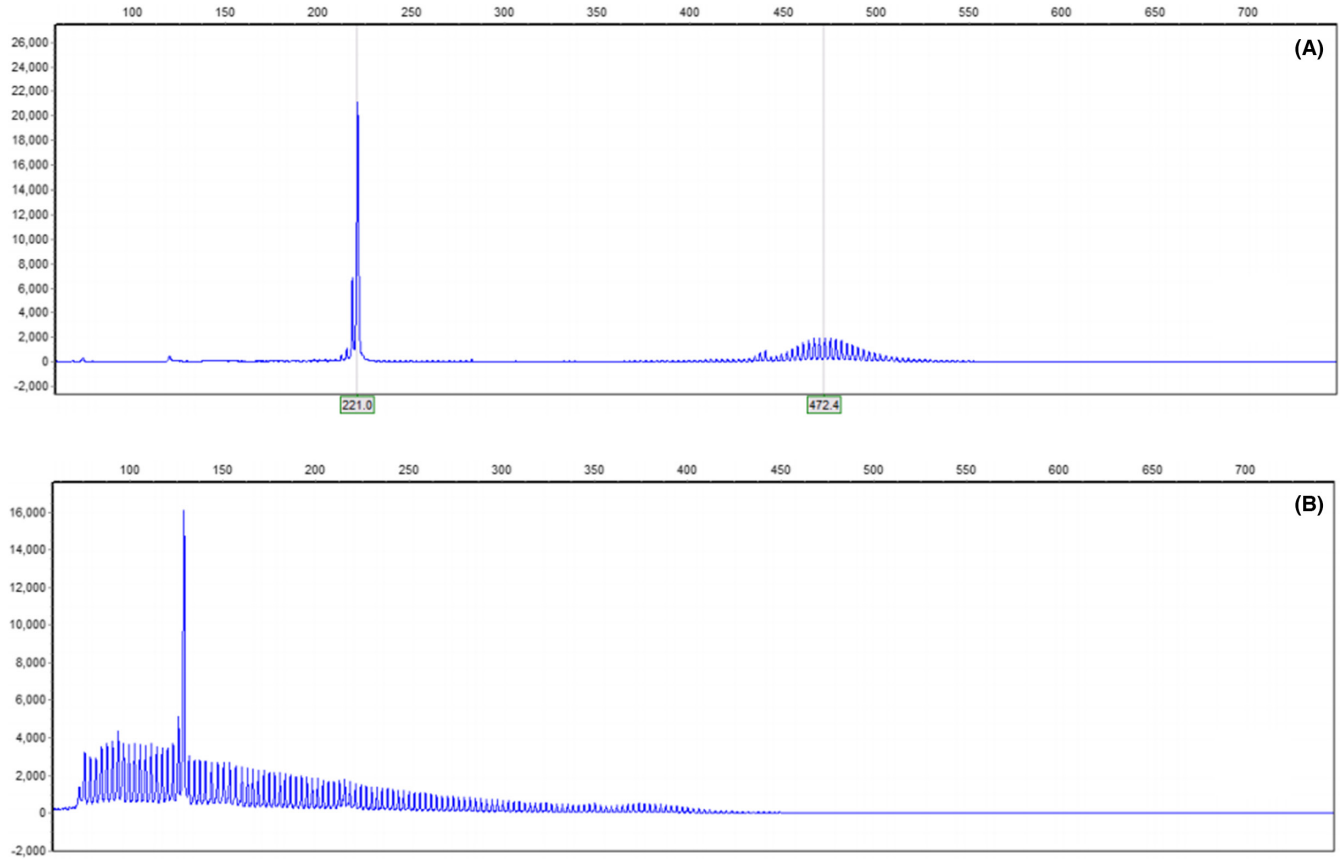

FIGURE 3 Genetic analyses of the patient. (A) Capillary electrophoresis (CE) –genescan showing GC-rich regions using PCR. (B) Tri-primer polymerase chain reaction (TP –PCR) indicated the patient had 102 GGC repeats in the 5′ UTR of NOTCH2NLC.

to once every 3–4 days. Then, the patient was given a nasal administration of perampanel 2 mg once a day, and the seizures stopped.

The patient still experienced paroxysmal disturbance of consciousness, urinary retention, recurrent pneumonia, poor expectoration ability due to cough, and aggravation of pneumonia after 2 months. His blood oxygen saturation decreased to less than 80%, so endotracheal intubation was given to assist breathing. At present, 1 year after hospitalization, the patient is still alive, but in the intensive care unit. Assisted ventilation is needed to maintain life.

3 | DISCUSSION AND CONCLUSION

Neuronal intranuclear inclusion disease, also known as intranuclear eosinophilic inclusion disease, is a rare neurodegenerative disease with slow progression.[1,5] The onset of NIID is usually subacute or chronic, with a course ranging from 1 to 44 years. Patients have been reported from ages 2 to 78 years old, with a male-to-female ratio of approximately 1:2. According to the age of onset, NIID can be divided into infant-onset, adolescent-onset, and adult-onset NIID, and adult-onset NIID is the main type in China and East Asia.[1,11] The clinical manifestations of NIID are highly heterogeneous. The clinical symptoms of adult-onset NIID mainly involve three major systems: (1) the central nervous system: dementia, ataxia, paroxysmal disturbance of consciousness, behavioral abnormalities, subacute encephalitis-like manifestations, ankylosis, tremors, seizures, and stroke-like attack; (2) the peripheral nervous system: paresthesia and decreased distal muscle strength; (3) the autonomic nervous system: miosis, urinary incontinence, vomiting, and syncope. Some studies have found that the abnormal repetitive amplification of GGC in the 5′ region of the NOTCH2NLC gene can also indicate essential tremors,[12] Alzheimer's disease,[13] Parkinson's disease,[14] multiple system atrophy,[15] and motor neuron disease.[14] In addition, NIID may also have nonneurological manifestations, such as pseudointestinal obstruction, proteinuria, and lupus nephritis. The patient showed mental and behavioral disorders of acute onset. After obtaining the medical history, it was found that there was a paroxysmal orientation disorder in the past, which was not the common initial symptom of adult-onset NIID. Thus, the diagnosis was rather perplexing. In addition, the patient developed unexplained difficulty in urination a few days later and eventually developed indwelling catheterization. Clinically, the possibility of NIID should be considered for prominent dysuria.[1,16] In addition, although the patient had no complaints of decreased muscle strength and sensory disturbance, our nerve conduction velocity examination showed that there was a decrease in the conduction velocity of the sensorimotor peripheral nerve in both the upper and lower extremities. Therefore, the patient had damage to the central nervous system, autonomic nerves, and peripheral nerves simultaneously.

The characteristic brain MRI changes of adult-onset NIID patients include five aspects. (1)With the development of the disease, the DWI

line-like high signals in the fronto-parietal–temporal corticomedullary junction gradually extend from the anterior to the posterior of the brain, forming a subcortical "cockscomb pattern" or "ribbon sign" of the high intensity DWI high signals.[11] This selective arcuate fasciculus is involved and the high intensity DWI signals, which were not easy to dissipate, have certain characteristics. However, the above DWI changes are only found in 37.5% of the pedigree patients with NIID,[14] and the abnormal change did not occur in a small proportion of sporadic patients.[17] (2) High signals of DWI along the corpus callosum. Some patients only showed high signals of DWI along corpus the callosum in the early stage of the disease, suggesting that the corpus callosum communicating fibers and subcortical arcuate fasciculus have similar susceptibility.[1] (3) Symmetrical white matter lesions, especially the white matter lesions that significantly involve the corona and the centrum ovale.[6,18] (4) Extensive brain atrophy and cerebellar white matter lesions are distributed axisymmetrically along the cerebellum.[19] (5) Cortical swelling and enhancement. Some patients showed high DWI and FLAIR signals along the cortex at certain stages of the disease course, often accompanied by linear enhancement along the cortical surface, which were usually distributed in the posterior cortex.[17] The patient showed high signals on DWI along the corticomedullary junction and corpus callosum and extensive brain atrophy. With the development of the disease, the DWI high signals did not disappear, and the DWI high signals in the frontal lobe corticomedullary junction and the corpus callosum enlarged with the progression of the disease. It has been previously reported that the high signals of DWI in NIID can spread along the corticomedullary junction,[20] but the specific reason is unknown. This patient is consistent with the imaging findings of adult-onset NIID, which provides very important evidence for our diagnosis.

Neuronal nuclear inclusion disease can only be diagnosed if intranuclear inclusions are found pathologically. In 1984, an autopsy of a pair of identical twins by Haltia[21] showed that a pathological feature was massive loss of neurons, and eosinophilic nuclear inclusion bodies were observed in the nuclei of most nerve cell types of the central and peripheral nervous systems and retina. Immunohistochemistry showed that the inclusion body was ubiquitin positive, and ultrastructurally, the inclusions appeared as masses of filaments without a limiting membrane. Eosinophilic inclusions with halos in the nucleus appear not only in neurons but also in glial cells, colonic ganglion cells, cardiomyocytes, skeletal muscle cells, renal tubular epithelial cells, peripheral nerve Schwann cells, and other tissues and cells of the entire body.[5] There were multiple proteins expressed in these inclusions, and they were positive for ubiquitin and p62 proteins. Under the electron microscope, these inclusions appear as a bunch of winding filament structures with a diameter of 8 ~ 12 nm. The inclusions did not have a membrane structure, and there was often a halo around them. Wang's study shows that as long as there are typical clinical manifestations, eosinophilic inclusions found in skin biopsies under light microscopy, and p62 protein positivity, NIID can be diagnosed without the support of further electron microscopic examination.[1] In this case, several eosinophilic inclusion bodies were found in the nuclei of eccrine ductal epithelial cells and adipocytes, and positivity for the p62 antibody was found by immunohistochemistry and immunofluorescence. Thus, the diagnosis of NIID was reliable.

Adult-onset NIID can be divided into sporadic type and familial type[22] ; at present, many families of NIID have been found. By gene sequencing, it was found that the abnormal repetitive amplification of GGC in the 5′ region of the human-specific NOTCH2NLC gene is the pathogenic gene of adult-onset NIID.[6–9] The GGC physiological repetition number of the 5′ region of the NOTCH2NLC gene in normal adults does not exceed 40, and the number of repetitions exceeding 60 is pathogenic.[12] The patient was confirmed to have 106 GGC repeats by genetic analysis. Therefore, the patient we reported has a rare clinical phenotype, typical imaging findings, clear pathological changes, and a pathological genetic variation.

Currently, there is no effective specific treatment for NIID, and the patient generally receives symptomatic treatment. The use of hormone therapy is controversial; some studies have suggested that short-term high-dose hormone shock can relieve the symptoms of dementia,[23] while some studies suggest that patients with and without hormone therapy can recover to varying degrees within days or weeks, the use of hormone therapy in patients with paroxysmal encephalopathy has no definite effect, and only symptomatic support is needed.[1,5] The patient was not on hormone therapy, only received supportive treatment such as anti-epilepsy, anti-infection, and nutritional support therapy and vitamin B and C supplementation. The seizures of the patient were controlled, and the pneumonia was relieved. However, the patient's state of consciousness did not improve. In fact, the mental disorder worsened progressively and never recovered to the preillness level.

In summary, we present a rare case of adult-onset NIID with mental and behavioral disorders. Unlike previously reported paroxysmal encephalopathy symptoms that improved within days to weeks, the patient's mental and behavioral abnormalities still progressively worsened after symptomatic treatment. The patient was diagnosed based on characteristic DWI signals, intranuclear inclusions, and increased GGC repeats in NOTCH2NLC. Therefore, for patients with atypical clinical symptoms that show a characteristic high intensity signal in the dermatomedullary junction on DWI, NIID should be considered, and further skin biopsy and gene analysis are required to confirm the diagnosis.

AUTHOR CONTRIBUTIONS

YL contributed to manuscript writing and interpretation of the data. JYY and ZFS contributed to HE staining and immunohistochemical staining. TZ collected and analyzed patient information. YWW examined the NOTCH2NLC gene. XLL contributed to the critical revision of the manuscript for intellectual content. All authors have read and approved the final manuscript.

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no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

All data generated during this study are available from the corresponding author upon reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study has passed the ethical review of Zhejiang Hospital and was approved.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the patient's daughter for the publication of this case report and accompanying images.

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