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A Case of Neuronal Intranuclear Inclusion Disease with Isolated Bladder Dysfunction

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Abstract: Neuronal intranuclear inclusion disease (NIID) is a progressive neurodegenerative disease caused by GGC repeat expansion in the NOTCH2NLC gene. The clinical manifestations are highly heterogeneous, ranging from chronic symptoms such as cognitive impairment and autonomic dysfunction to acute symptoms like encephalitis-like episodes or seizures. This report describes a case of adult-onset NIID with a disease course of 10 years, presenting solely with urinary retention and bladder dysfunction. The patient's head MRI demonstrated characteristic subcortical "band-like" high signals on DWI, and genetic testing confirmed the diagnosis. This case highlights the need for clinicians to consider the possibility of NIID when encountering unexplained urinary symptoms and to use imaging and genetic testing for definitive diagnosis.

Keywords: Neuronal Intranuclear Inclusion Disease; Micturition Disorder; Bladder Dysfunction; Neurogenic Bladder.

1. Introduction

The patient, female, 60 years old, presented to our hospital with "dysuria for 10 years" on December 05, 2023. The patient began to have dysuria without obvious cause 10 years ago, and the symptoms gradually worsened, followed by urinary retention. Color Doppler ultrasound examination of the urinary system ruled out the possibility of mechanical obstruction, and the patient was diagnosed with neurogenic bladder dysfunction caused by dynamic obstruction, but the specific cause was unknown, and he had long relied on intermittent catheterization. The head CT in the other hospital showed that "the white matter density of the bilateral brain was generally reduced, which was considered to be ischemic lesions; Accompanied by brain atrophy. For further diagnosis and treatment, the patient came to the outpatient department of Neurology, the First Affiliated Hospital of Jinan University, and was admitted to the hospital with the diagnosis of "leukoencephalopathy". The general condition of the patient had been good since the onset of the disease, but he had poor sleep, poor appetite, and low spirits in the past 3 days, and there was no significant change in weight.

Past history: He had chronic bronchitis with emphysema for 10 years. He will undergo "bilateral cataract surgery" in 2022. He denied a history of hypertension, coronary heart disease, diabetes and other diseases, and had no history of infectious diseases. He denied any other history of surgery, trauma, blood transfusion, drug or food allergy. His vaccination history was unknown. He had no history of smoking or alcohol consumption. She was postmenopausal at the age of 50 and had no abnormal vaginal bleeding or bleeding after menopause.

Family history: The father, siblings, spouse and children were all healthy, and there was no obvious infectious disease or genetic history in the family.

On admission, the patient's temperature was 36.2℃, pulse 68 beats/min, respiration 18 breaths/min, and blood pressure 126/68 mmHg. His height was 148 cm and weight 49 kg. The patient had normal development, short stature, and moderate nutrition. Physical examination of the heart, lungs, and abdomen showed no abnormalities. Physical examination of the nervous system showed that the patient was right-handed, with clear consciousness, clear language, pertinent answers, normal memory, calculation and orientation. Cranial nerve examination showed no abnormalities. The muscle strength and tone of the extremities were normal. Finger-nose test, heel-knee-tibia test, and difficult standing sign with eyes closed were negative. Bilateral sensory symmetry and bilateral tendon reflexes were present. Babinski's sign was negative bilaterally. The neck was soft, and Kirschner's sign and Buchner's sign were negative bilaterally. The Mini-mental state examination score was 27.

Laboratory tests: routine blood test, routine stool test, liver and kidney function test, blood glucose, blood lipid, homocysteine, troponin, glycosylated hemoglobin, procalcitonin, cerebrospinal fluid routine test, cerebrospinal fluid biochemistry, cerebrospinal fluid IgG test, and three major stains of cerebrospinal fluid (mycobacteria acid-fast stain, bacterial Gram stain, Cryptococcus ink stain) were normal. Urinalysis and urine sediment quantification: 88.00/uL for bacteria (normal range: 0-5 /uL), 25 ERY/uL for occult blood (or) red blood cells (normal range: 0-10 ERY/uL), 500LEU/L for leukocyte esterase (normal range: 0-10 ERY/ ul) 0-24 LEU/uL), white blood cell 107.00/ uL (normal range: 0-20 /uL).

Imaging inspection

Routine electrocardiogram showed sinus bradycardia with ST-segment changes. Brain MRI+DWI+MRA showed that there were diffuse and symmetrical distributed patches of long T1 and long T2 signal lesions in the white matter around the bilateral ventricles and the bilateral dentate nucleus, and the T2 FLAIR sequence showed high signal changes. On DWI, some lesions at the cortico-medullary junction showed mild diffusion restriction, which was consistent with the typical imaging findings of NIID (Figure 1).

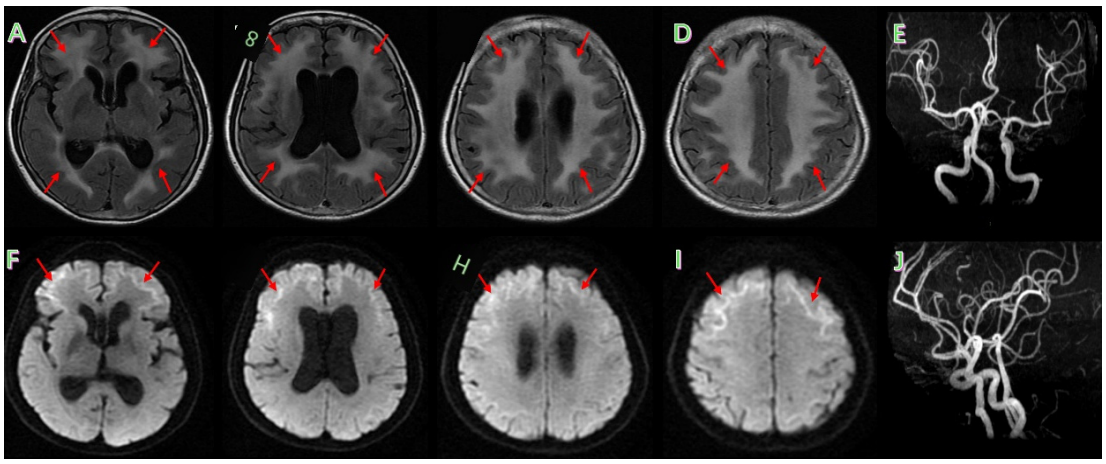


Figure 1. Results of brain MRI +DWI+ MRA (2023-12-07)

Note: A-D - brain T2 FLAIR showed multiple abnormal high signal demyelinating lesions in the white matter of bilateral periventricular, centrum semiovale and corona radiatum (red arrow). F-i brain DWI showed the bilateral cerebral cortico-medullary junction with limited diffusion hyperintense focus-subcortical ribbon sign [9] (red arrow). E and J MRA showed no abnormality.

Treatment and outcome: combined with imaging, the possibility of NIID was considered, but the possibility of demyelinating disease of the central nervous system could not be ruled out. Then blood samples were collected for NIID-related NOTCH2NLC gene detection and central nervous system demyelinating disease-related antibodies detection. At the same time, lumbar puncture was performed to obtain cerebrospinal fluid and demyelinating disease-related antibodies were detected. Genetic testing results (provided by Guangzhou Ouimengwei Medical Laboratory Laboratory) suggested that the NOTCH2NLC gene GGC repeat sequence >100 (see Figure 2), while the central nervous system demyelinating disease-related antibody test was negative, and a clear diagnosis of NIID was made with only isolated bladder dysfunction. The patient was treated with intravenous injection of betahistine hydrochloride 30 mg once a day to improve circulation, and symptomatic treatments such as potassium supplementation and intermittent catheterization were given. At the time of discharge, the patient still could not urinate independently, and intermittent catheterization was needed, but there were no discomfort symptoms such as fever, dizziness, and fatigue.

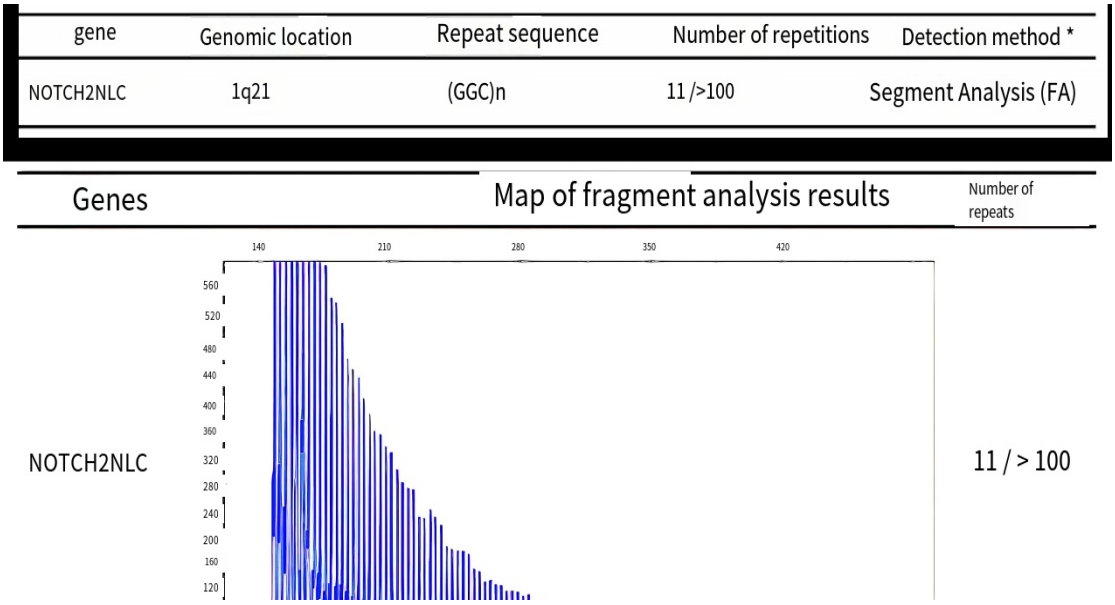


Figure 2. Results of NOTCH2NLC gene test for NIID (2023-12-08)

Note: The GGC repeat amplification of the 5' untranslated region (5'UTR) of the NOTCH2NLC gene by repeated primer PCR showed a decreased zigzag extension, which was initially estimated to be more than 100 times. Note: The reference value of normal GGC repeat amplification was ≤38, and the reference value of abnormal GGC repeat amplification was ≥60.

Final diagnosis:

Neuronal intranuclear inclusion disease

Neurogenic bladder dysfunction

Urinary tract infections

Hypokalemia

Bilateral cataract surgery

Chronic bronchitis

Prognosis and follow-up: Half a year after discharge, the patient was still unable to urinate independently, without other new symptoms, and the general condition was acceptable.

2. Discourse

Lindenberg et al. first reported a 28-year-old male patient in 1970 who presented with mental retardation, progressive paralysis, and ataxia. Autopsy pathology revealed the presence of eosinophilic inclusions in neurons, which led to the designation of NIID [10]. NIID is a hereditary neurodegenerative disease. Studies have found that GGC repeat expansion in the NOTCH2NLC gene is the main genetic marker of NIID. NIID related to NOTCH2NLC GGC gene fits an autosomal dominant pattern of inheritance. GGC repeat expansion of the gene induces the formation of polyglycine protein, which in turn participates in the formation of eosinophilic inclusions in neuronal nuclei. Its pathological features are the presence of eosinophilic inclusions in the nuclei of various tissue cells in the central and peripheral nervous system and internal organs, accompanied by regional neuronal loss[3,11]. In recent years, with the wide application[7] of skin biopsy technology, the characteristic high signal[3,7] at the cortico-medullary junction on DWI, and the discovery [1,2]of NOTCH2NLC GGC repeat amplification pathogenic genes, the diagnosis of NIID has become more rapid and accurate, which has significantly increased the number of NIID patients. Studies have shown that the head MRI of adult NIID patients usually shows T2WI hyperintensity in the white matter, and the "roost-like" or "ribbon" high signal at the corticomedul-medullary junction can be seen on DWI. This kind of high signal lesions selectively involving arcuate fibers on DWI is a characteristic change [9,12] of NIID. A review of the imaging and genetic testing results of this case revealed the typical imaging features of NIID: extensive white matter hyperintensity and band-like hyperintensity at the epithelial-medulla junction on DWI, and the NOTCH2NLC gene GGC repeat amplification for more than 100 times. Although the patient refused skin biopsy and pathological evidence could not be obtained, the literature reported that there was a high degree of consistency [12] between skin biopsy pathology and GGC pathogenic amplification of NOTCH2NLC gene, so the diagnosis of NIID was confirmed.

With the progress of diagnostic technology, the high clinical heterogeneity of NIID has been gradually revealed. The symptoms of NIID can present as either chronic manifestations, such as cognitive impairment, parkinsonism, tremor, cerebellar ataxia, autonomic dysfunction, peripheral neuropathy and myopathy, or episodic symptoms, such as encephalitis, stroke-like episodes, disturbance of consciousness, episodic headache and seizures[3-5, 6–8]. Autonomic Dysfunction (AutD) is particularly common in adult-onset NIID patients, which is characterized by urinary incontinence, miosis, vomiting, gastrointestinal dysfunction, orthostatic hypotension, arrhythmia, and sexual dysfunction[1,3,4, 11,13]. A large cohort study in China showed that 64.0% (158/247) of NIID patients had AutD, and bladder dysfunction, miosis, vomiting and orthostatic hypotension were the most common manifestations [14]. Another large cohort study in China also found that 14.75% (18/122) of NIID patients had AutD as the initial symptom, which was called AutD NIID episode. All patients with AutD as the first symptom had onset of unexplained urinary tract symptoms, and the related symptomatic treatment was ineffective. The median course of disease was [15]4 years. Therefore, AutD can be used as a potential biomar[16]ker for the identification of NIID.

However, NIID cases with isolated bladder dysfunction as the main clinical manifestation are still rare. This case reports a patient with NIID whose course of disease lasted for 10 years and whose only symptom was bladder dysfunction without other autonomic dysfunction or systemic involvement. The patient did not present the typical clinical manifestations of NIID, such as limb weakness, cognitive impairment, and paroxysmal symptoms, and only presented with bladder dysfunction during the course of the disease. Only when the characteristic subcortical "ribbon sign" of NIID was found on DWI, the possibility of NIID was considered. The diagnosis was further confirmed by NOTCH2NLC GGC gene detection, which revealed the underlying cause of bladder dysfunction in the patient. Unfortunately, there is no effective treatment for NIID at present, and most patients usually die more than 10 years after the onset. The only symptom of this patient was bladder dysfunction, and she had relied on intermittent catheterization for a long time. Intermittent catheterization, as the gold standard therapy [17] for neurogenic bladder dysfunction, was still the main symptomatic treatment during this hospitalization, and no specific treatment was implemented. Due to the limited case reports and the lack of large-scale clinical trials, there is no effective treatment for NIID at present. Therefore, clinicians should be highly alert to patients with unexplained urinary symptoms and consider the possibility of NIID. For such patients, head DWI examination, genetic testing and skin biopsy are recommended to confirm the diagnosis and rule out NIID.

Restriction:

Some objective tests for autonomic dysfunction, such as quantitative sudomotor axon reflex testing or active head-up tilt test, could not be completed because of the patient's strong request for early discharge and the short length of hospital stay. Moreover, due to the patient's long-term indwelling catheter, it was difficult to perform urodynamic evaluation and bladder residual urine volume examination. Also, a skin biopsy could not be performed. In addition, although the NOTCH2NLC *GGC* gene-related NIID was consistent with an autosomal dominant inheritance pattern, the patient's family refused genetic testing, which failed to be further verified by the family.

3. Conclusion

In conclusion, this article reports a rare case of adult-onset NIID with isolated bladder dysfunction as the main clinical manifestation. The patient had a 10-year course of NIID with the sole manifestation of bladder dysfunction and no typical neurological symptoms such as cognitive impairment or motor abnormalities. The diagnosis of NIID was confirmed by cranial imaging and NOTCH2NLC GGC gene detection. This case suggests that clinicians should consider the possibility of NIID when facing unexplained urinary symptoms, especially when the symptoms persist for a long time and conventional treatment is ineffective.

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