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CASE REPORT

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A case of neuronal intranuclear inclusion disease (NIID) presenting with hydrocephalus-like clinical features: case report

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Abstract

Background Neuronal intranuclear inclusion disease (NIID) is a rare neurodegenerative disorder characterized by the presence of inclusions within the nuclei of various cell types. The clinical manifestations of patients with NIID are diverse. Here, we present the case of a patient with NIID whose clinical presentation and magnetic resonance features closely resembled those of hydrocephalus.

Case presentation The patient was 71-year-old woman with no significant family history. Seven years previously, she began to experience tremors in both hands, which occurred at rest and while holding objects; this was accompanied by urinary incontinence. Four years previously, she developed weakness in both lower limbs, an unstable gait, and dizziness. Over the past year, she noticed stiffening at the root of her tongue, cognitive decline, and slower reaction times compared to her previous state. Upon admission, cranial magnetic resonance imaging (MRI) revealed hydrocephalus-like changes. A cerebrospinal fluid drainage test returned negative results. The patient presented with tremors and urinary incontinence. Physical examination indicated pupillary constriction, and electromyography suggested peripheral neuropathy. Genetic testing revealed 91 GGC repeats in the *NOTCH2NLC* gene, indicating abnormal expansion. The final diagnosis was NIID. We provided symptomatic treatment for the tremor and cognitive impairment, but there was no significant improvement in the clinical symptoms.

Conclusions Our case suggests that when a patient presents with clinical symptoms and MRI findings resembling hydrocephalus, the possibility of NIID should be considered, especially in the presence of tremors and autonomic symptoms.

Keywords Neuronal intranuclear inclusion disease, Hydrocephalus-like MRI imaging, *NOTCH2NLC* gene, Case report

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Background

NIID is a rare neurodegenerative disorder characterized by the presence of inclusions within the nuclei of various cell types. The clinical manifestations of NIID are complex and diverse, potentially involving symptoms related to the cortex, pyramidal tract, extrapyramidal system, cerebellum, peripheral nerves, and autonomic nerves. This condition is linked to a GGC repeat expansion mutation (exceeding 60 repeats) in the 5′-UTR region of the *NOTCH2NLC* gene [1].

In 1968, Lindenberg et al. reported the case of a 28-year-old patient with a neurodegenerative disease exhibiting intranuclear inclusions in nerve and visceral cells [2]. In 1980, Sung et al. documented these clinical and pathological changes in another patient and formally named this disease as NIID [3]. In 2019, multiple research teams identified a GGC repeat expansion mutation in the 5′-untranslated region of the *NOTCH2NLC* gene as the primary genetic cause of NIID in affected patients [4–6]. With the widespread application of *NOTCH2NLC* gene screening, researchers have found that the number of GGC repeats closely correlates with the age of onset and clinical symptoms. Notably, there is a negative correlation between the repeat expansion number and the age of onset, although the number of repeats is not directly related to disease severity [7].The clinical phenotype of NIID is varied. In this article, we present a case of an NIID patient whose clinical symptoms and MRI findings hydrocephalus-like, a feature seldom reported in previous literature.

Case presentation

A 71-year-old woman diagnosed with neuronal intranuclear inclusion disease (NIID) presented to our hospital for consultation. The patient reported that seven years previously, she began experiencing tremors in both hands, occurring at rest or when holding objects, particularly during emotional excitement. There was no slowness in upper limb movements; dressing and buttoning were generally normal. However, the patient experienced difficulty during urination, with a residual urine volume of 400 to 800 ml, and was diagnosed with a 'neurogenic bladder' at a local hospital. Four years previously, the patient developed weakness in both lower limbs, dizziness, an unsteady gait, and dizziness upon turning, without nausea, vomiting, or a reduced sense of smell. The medical history included hypertension for ten years, diabetes for four years, with well-controlled blood sugar, and surgery for lung cancer five years previously. The family history was unremarkable.

During neurological examination at admission, the patient's blood pressure was 154/128 mmHg in the supine position and 145/84 mmHg in the standing position after three minutes, with a heart rate of 96 and 104 beats per minute, respectively. The patient was conscious and alert, and responded to questions appropriately. Facial expressions were normal. Bilateral pupils were equal in size (1.0 mm). Eye movements were smooth, with horizontal nystagmus observed when looking to the right. Bilateral forehead wrinkles and nasolabial folds were symmetrical. The eyelids closed firmly. The uvula was positioned in the center, and both sides of the soft palate rose in a powerful manner. The gag reflex was present and the tongue extended at the midline. Limb muscle strength was graded 5/5, and muscle tone was normal. The patient exhibits bradykinesia in bilateral upper limb finger movements, fist clenching, and alternating movements. There is slowness in raising the legs and tapping the toes in the lower limbs. The patient requires two attempts to stand from a seated position and demonstrates a slow gait without freezing. While standing, the patient has a forward-leaning posture and needs to take 3 to 5 steps backward to regain balance when the examiner pulls their shoulders. Spontaneous movements are reduced, and both upper limbs show postural and action tremors with variable amplitude. Deep tendon reflexes were diminished and bilateral pathological signs were absent. There were no abnormalities in terms of deep or superficial sensation. The bilateral finger-to-nose test was stable. The bilateral heel-to-shin test was stable and accurate. We were not able to perform the tandem gait test. The Romberg test was negative. The unified Parkinson's disease rating scale (UPDRS) III score was 42, the Mini-Mental State Examination (MMSE) score was 19, and the Montreal Cognitive Assessment (MOCA) score was 12. During hospitalization, a range of auxiliary tests were performed, including complete blood count, homocysteine, ceruloplasmin, comprehensive biochemical panel, folic acid, vitamin B12, immune panel (five indices), rheumatoid panel (three indices), D-dimer, coagulation panel (four indices), tumor markers, and erythrocyte sedimentation rate. All of the results were within the normal range. Electromyography revealed peripheral nerve damage in all four limbs and that the sensory nerve stimulus response (SSR) was abnormal in both lower limbs. Tremor analysis indicated no fixed frequency in the tremors occurring in both upper limbs. MRI scanning at Xuanwu Hospital, revealed multiple infarct foci and ischemic lesions in the brain, hydrocephalus-like, changes in the white matter, and bilateral hippocampal atrophy. Evan's index was > 3.0, with a positive Disproportionately Enlarged Subarachnoid Space Hydrocephalus (DESH) sign (Fig. 1). No restricted diffusion signals are observed on diffusion-weighted imaging (DWI) (Fig. 2). A drainage test was performed to consider normal pressure hydrocephalus. The cerebrospinal fluid pressure was measured at 170 mmHg. Eight hours post-drainage, there was over a 10% improvement in both walking time and steps over

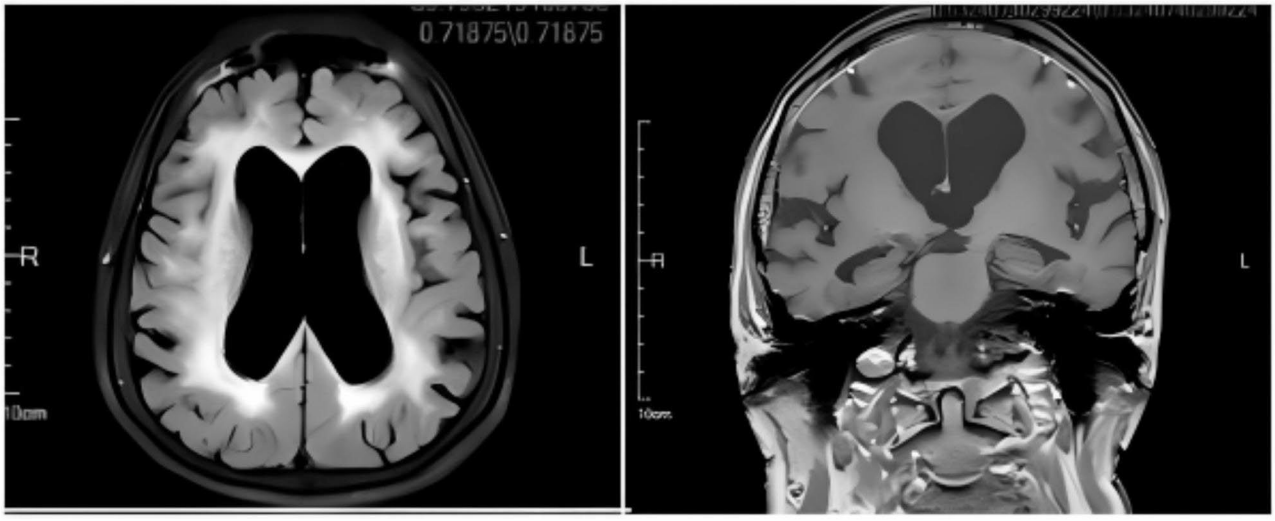

Fig. 1 The ventricular system is enlarged, with widening of some sulci and fissures. There is high signal intensity on T2WI/FLAIR imaging in the periventricular white matter of both sides, and enlargement of the temporal horns and choroidal fissures of both lateral ventricles. This suggests the presence of DESH (disproportionate enlargement of the subarachnoid space in hydrocephalus

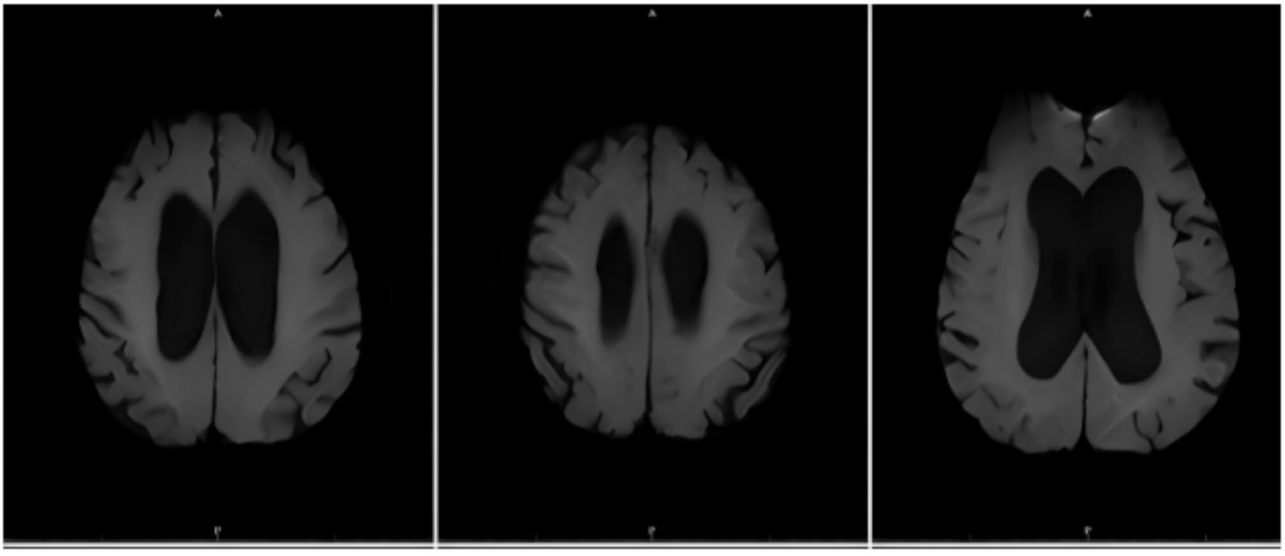

Fig. 2 No restricted diffusion signals are observed on diffusion-weighted imaging (DWI)

a distance of 10 m, and a 10% improvement in the number of steps for a 5 m return. However, after 24 h, symptom improvement remained < 10%. The drainage test was negative. Although the negative drainage test did not rule out idiopathic normal pressure hydrocephalus (iNPH), the patient exhibited significant tremors in both hands, bilateral miosis, peripheral nerve involvement, and extensive white matter lesions in both cerebral hemispheres, all of which are inconsistent with the symptoms typically associated with normal pressure hydrocephalus. These findings suggested the presence of other underlying conditions. Further investigations, including blood tests, electromyography, and MRI, revealed peripheral nerve damage, abnormalities in the lower limbs, brain lesions, brain atrophy, and an abnormality in the *NOTCH2NLC* gene (Fig. 3). The final diagnosis was NIID. We provided symptomatic treatment for the tremor and cognitive impairment, but there was no significant improvement in the clinical symptoms.

Discussion

In the present study, we report a case of sporadic adult-onset NIID with primary clinical manifestations of gait disturbance and cognitive decline, resembling normal pressure hydrocephalus. Coincidentally, MRI findings also showed similarities to normal pressure

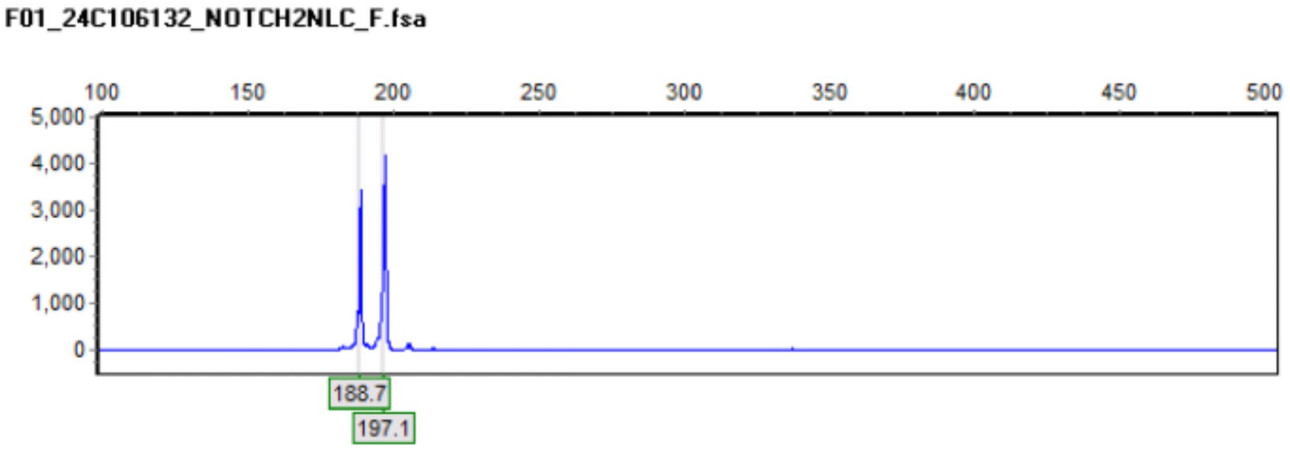

Fig. 3 The repeat number of the NOTCH2NLC gene (GGC) in the tested individual is approximately 7 and 91, showing abnormal amplification, which supports the diagnosis of neuronal intranuclear inclusion body disease in the patient

hydrocephalus. However, due to the presence of tremors and autonomic nervous symptoms, genetic testing was conducted, confirming the diagnosis of NIID.

The etiology and pathogenesis of NIID remains unclear. Both NIID and nuclear inclusions in polyglutamine diseases are ubiquitinated and feature proteins associated with the ubiquitin/proteasome system, which is the primary pathway for intracellular protein degradation [8]. Research indicates that the formation of nuclear inclusions in NIID may follow a similar pathophysiological mechanism as polyglutamine diseases. These neurodegenerative disorders are triggered by specific gene amplifications of trinucleotide repeat sequences that encode polyglutamine [2]. In polyglutamine diseases, abnormally expanded polyglutamine-related proteins may aggregate in the nucleus, thus forming nuclear inclusions. Similarly, in NIID, the aggregation of abnormal proteins or dysfunction in the nuclear protein degradation system might contribute to disease progression [9].

The main clinical feature of NIID is cognitive impairment; this is one of the earliest (23.1%) and most common (49.4%) symptoms of NIID, with episodic amnesia presenting as the most prevalent form [7]. In a clinical analysis of 54 NIID patients, Sone et al. found that dementia was the most prominent initial symptom in sporadic adult-onset NIID and familial NIID patients over 40 years-of-age [10]. Patients with adult-onset NIID may initially exhibit white matter damage, followed by hippocampal and neocortical atrophy, leading to executive dysfunction, memory impairment, and progressive cognitive decline [10, 18]. Some patients, that had previously been diagnosed with Alzheimer's disease (AD), were subsequently found to carry a GGC repeat expansion in the *NOTCH2NLC* gene [5], thus suggesting that NIID should be considered in the differential diagnosis of AD. In our case, although the patient exhibited cognitive impairment, cranial MRI indicated hydrocephalus-like changes, with cognitive impairment manifesting later in the disease course and without progressive exacerbation. Approximately 50.2% of all patients with NIID exhibit various motor dysfunction symptoms, commonly including tremors, Parkinsonism and ataxia [7]. Parkinsonism is considered as another prevalent and characteristic feature in NIID patients. Cases of familial PD, or patients with idiopathic tremor, should be evaluated for potential NIID or *NOTCH2NLC* gene-related conditions [11]. In our case, the patient exhibited tremors early in the disease course, and tremor analysis indicated inconsistency with PD. Most patients do not exhibit obvious clinical symptoms or signs, although neuroelectrophysiological examinations can facilitate clinical diagnosis [7]. Recent studies have shown that many diseases, involving limb weakness, such as amyotrophic lateral sclerosis (ALS) and oculopharyngeal distal myopathy, are associated with NIID or GGC repeat expansion disorders related to the *NOTCH2NLC* gene [12–15]. Various ophthalmological manifestations of NIID have been documented, including abnormal pupillary function, miosis, oculogyric crisis, reduced eye movement, nystagmus, blepharospasm, ptosis, and loss of pigment in the retinal pigment epithelium [12, 16]. In our patient, urinary retention was noted in the early stages, and physical examination revealed miosis, indicating autonomic dysfunction [5]. Another common feature of NIID is paroxysmal symptoms; approximately 32.8% of NIID patients experience paroxysmal symptoms in the early stages of the disease [17]. Furthermore, 66.8% of NIID patients exhibit at least one paroxysmal symptom, such as encephalitis-like episodes, stroke-like episodes, seizures, or chronic headaches [18]. Various types of seizures have also been reported in NIID patients [19]. In our case, the patient did not exhibit any paroxysmal symptoms during the course of the disease. Sone et al. categorized patients based on their initial symptoms into a "dementia-dominant group"and a "limb

weakness group" [9]. In the dementia-dominant group, most patients exhibited cognitive decline and miosis. Approximately half of all patients experience cerebellar ataxia and bladder dysfunction. Less frequent clinical signs include tremors, rigidity, and abnormal behavior. Cognitive impairment did not manifest early in the disease course for our patient. However, cerebellar ataxia and bladder dysfunction appeared relatively early, along with cognitive issues, but without significant limb weakness. Therefore, we still classified this patient within this category.

Adult-onset NIID is a rare neurodegenerative disorder characterized by distinctive MRI features. In 2014, Sone et al. reported high-intensity signals at the corticomedullary junction on DWI [20]. This appearance, referred to as the 'ribbon sign' or 'diaper sign' [10, 21], is highly characteristic of NIID. Typical imaging features include bilateral curvilinear high-intensity DWI signals at the subcortical white matter-corticomedullary junction, initially affecting the frontal lobes and gradually extending posteriorly to the parietal and occipital lobes as the disease progresses. These changes advance over time but generally do not extend into the deep white matter. However, this distinctive DWI pattern is observed in only 37% of NIID patients [22]. A minority of NIID patients may show mild leukoaraiosis, progressive leukoencephalopathy, or brain atrophy, with recent reports documenting various atypical MRI features. One report documented a patient with sporadic adult-onset NIID who did not exhibit any high-intensity signals on DWI or T2-weighted imaging (T2WI) [21]. In contrast to other studies, one research group identified DWI abnormalities in the basal ganglia, particularly around the peri-globus pallidus and the thalamus [23]. A case of a 76-year-old female NIID patient with a 19-year history of urinary incontinence and a 5-year history of cognitive impairment and gait instability has been reported; her MRI indicated signs of hydrocephalus without extensive white matter lesions [23]. Here, we propose a mechanism by which NIID may lead to hydrocephalus. We hypothesize that in NIID patients, eosinophilic inclusions form within neurons and glial cells, thus impairing glial cell function. This dysfunction may cause cerebral small vessel disease, reducing arterial inflow and venous outflow. In addition, neuroglial cell dysfunction can compromise the tight junctions of endothelial cells in the blood-brain barrier, diminishing barrier function, altering signal transduction pathways in the neurovascular unit, and promoting the production of inflammatory cytokines. This process triggers chronic inflammation in neuroglial cells, dysregulation of cerebral blood flow, and fluctuations in interstitial fluid and ventricular pressure with blood pressure, potentially leading to ventricular enlargement [24, 25]. In our case, the patient showed gait disturbances, and a cranial MRI revealed hydrocephalus along with extensive deep white matter lesions, which is a relatively rare presentation. If a MRI-cerebrospinal fluid flow study could have been incorporated, it might have provided a better explanation for this phenomenon. However, due to technical feasibility issues, we were unable to perform this diagnostic procedure. We hope that future studies will integrate this approach to offer a more comprehensive perspective on similar cases and contribute to a deeper understanding of the mechanisms underlying hydrocephalus-like imaging changes caused by NIID.

Conclusions

In this report, we present a case of an elderly patient with NIID, who initially displayed symptoms of urinary incontinence, gait disturbances, and cranial MRI findings that were hydrocephalus-like. Accompanying signs, such as tremor and miosis, led to comprehensive genetic testing, which confirmed the diagnosis of NIID. The clinical presentation of NIID is highly variable and heterogeneous, encompassing a wide range of differential diagnoses. When patients exhibit hydrocephalus-like features and white matter lesions, it is crucial to consider the possibility of NIID by evaluating the distribution of white matter involvement, clinical symptoms, and family history, with genetic testing as necessary.

Abbreviations

NIID	Neuronal intranuclear inclusion disease
MRI	Magnetic resonance imaging
UPDRS	Unified Parkinson's disease rating scale
MMSE	Mini-Mental State Examination
MOCA	Montreal Cognitive Assessment
SSR	Sensory nerve stimulus response
DESH	Disproportionately Enlarged Subarachnoid Space Hydrocephalus
AD	Alzheimer's disease
PD	Parkinson's disease
ALS	Amyotrophic lateral sclerosis
DWI	Diffusion-weighted imaging
T2WI	T2-weighted imaging
iNPH	idiopathic normal pressure hydrocephalus

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Author contributions

Critical revision of the manuscript and supervision of the project were performed by YW. Clinical data were acquired by YL, WP and YS. The manuscript was drafted by YW, SZ and JL, and revised by YL and YP. The author(s) read and approved the final manuscript.

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Data availability

All data related to this case report are documented within this manuscript.

Declarations

Ethics approval and consent to participate

Informed consent was obtained from the patient to publish her case, and approval for this study was provided by the Research Ethics Committee of The Second Hospital of Liaocheng.

Consent for publication

Written informed consent for publication of this Case Report was obtained from the patient.

Competing interests

The authors declare no competing interests.

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