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Severe and refractory autonomic failure in diffusion-weighted imaging-negative neuronal intranuclear inclusion disease: A case with progressive leukoencephalopathy

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Abstract

Neuronal intranuclear inclusion disease (NIID) is a heterogeneous neurodegenerative disorder most commonly associated with GGC repeat expansions in the NOTCH2NLC gene. Although curvilinear hyperintensity along the corticomedullary junction on diffusion-weighted imaging (DWI) is considered a hallmark diagnostic feature, a proportion of patients present without this characteristic finding. The clinical course and disease activity of DWI-negative NIID remain poorly defined. We describe a 55-year-old man with genetically and pathologically confirmed NIID who exhibited a markedly aggressive autonomic phenotype. After a six-year history of nonspecific dizziness, he developed acute, severe, and refractory autonomic failure, characterized by catheter-dependent urinary retention, pharmacoresistant constipation, and generalized hyperhidrosis. Despite the persistent absence of typical DWI abnormalities, serial brain MRI over a 12-month period demonstrated progressive confluent white matter hyperintensities accompanied by worsening cerebral atrophy. In conclusion, this case highlights that DWI-negative NIID can present with severe, rapidly progressive autonomic dysfunction alongside active structural neurodegeneration. Clinicians should maintain a high suspicion for NIID in patients with atypical leukoencephalopathy and prominent autonomic failure, even in the absence of characteristic DWI findings, to facilitate prompt genetic diagnosis.

Keywords: Neuronal intranuclear inclusion disease, DWI-negative, autonomic dysfunction, leukoencephalopathy, NOTCH2NLC

INTRODUCTION

Neuronal intranuclear inclusion disease (NIID) is a heterogeneous neurodegenerative disorder pathologically characterized by the widespread accumulation of eosinophilic, p62-positive intranuclear inclusions.[1] The identification of GGC repeat expansions in the NOTCH2NLC gene has established a definitive genetic basis for the disease, enabling broader recognition.[2] Classically, high-intensity signals along the corticomedullary junction on diffusion-weighted imaging (DWI) are considered a hallmark diagnostic biomarker, facilitating rapid identification in typical cases.[3] However, the diagnostic utility of this imaging sign is limited in atypical presentations. Emerging evidence indicates that a proportion of patients lack these characteristic DWI abnormalities, particularly during the early stages of disease.[3,4]

Recent longitudinal studies suggest that radiological conversion to typical DWI signals may occur substantially later than symptom onset.[5] Consequently, recognizing NIID during this "DWI-negative" window remains a major clinical challenge, necessitating a greater reliance on extra-neurological clues. Among these clues, autonomic involvement is a core component of the NIID clinical spectrum.[6,7] Patients frequently present with diverse visceral symptoms, including urinary retention, gastrointestinal dysmotility,

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and orthostatic intolerance.[6] Despite its importance, severe autonomic failure occurring in isolation or preceding radiological changes is often underappreciated, leading to potential misdiagnosis and confusion with other autonomic neuropathies or neurodegenerative disorders.

In this report, we present a patient with genetically confirmed NIID who developed acute, severe, and refractory autonomic dysfunction. Despite persistent DWI negativity over a 12-month follow-up, serial MRI demonstrated progressive leukoencephalopathy and marked cerebral atrophy. This case underscores the potential for aggressive disease progression in the absence of restricted diffusion and highlights the critical value of screening for NOTCH2NLC expansions in patients with unexplained autonomic failure accompanied by atypical white matter changes.

CASE REPORT

A 55-year-old man from Shangrao, China, with no family history of similar disorders, was admitted to the neurology department in May 2023 for recurrent dizziness that had persisted for the previous six years and had markedly worsened over the preceding four months. Initially, episodes lasted minutes to hours and resolved spontaneously.

Beginning in February 2023, the patient experienced approximately eleven consecutive weeks of sustained sleep deprivation, defined as sleeping fewer than four hours per night on most nights. He attributed this to pronounced anxiety related to his long-standing dizziness as well as ongoing emotional stress stemming from his adult son's recent unemployment and prolonged stay at home.

Following this period of disturbed sleep, his condition deteriorated abruptly, with the onset of catheter-dependent urinary retention, persistent constipation, and generalized hyperhidrosis. He also reported occasional lightheadedness upon standing. Bedside orthostatic vital sign measurements demonstrated a systolic blood pressure drop of approximately 20–25 mmHg and a diastolic drop of 10–15 mmHg within three minutes of standing. In the months preceding hospitalization, he had noticed some changes in sexual function, though he was uncertain about their onset or significance and did not consider them a major complaint.

He had no history of smoking, alcohol use, or vascular risk factors, including hypertension, diabetes, or hyperlipidemia. Neurological examination revealed stable supine vital signs, symmetrically brisk tendon reflexes, a positive Romberg sign, and mild bilateral limb weakness (Medical Research Council scale strength 4+/5). Sensation to pain and light touch was intact bilaterally, and no pathological reflexes were elicited. Cognitive screening demonstrated normal scores on both the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). The Hamilton Anxiety Rating Scale (HAMA) score was 23, indicating clinically significant anxiety.

Further evaluation included urodynamic studies (June 2023), which revealed markedly reduced detrusor contractility and impaired bladder sensation. Bladder filling was tolerated to volumes exceeding 600 mL without an urge to void, and the post-void residual volume was consistently large (>400 mL). Constipation was assessed according to the Rome IV criteria and remained refractory to combined osmotic and stimulant laxatives. Abdominal radiography showed marked fecal loading in the ascending and transverse colon without evidence of obstructive lesions. Brain MRI (2023) demonstrated bilateral periventricular white matter hyperintensities (Figures 2A and 3A), widened cerebral sulci (Figure 1A), and no abnormal signal on diffusion-weighted imaging (DWI) sequences (Figure 4A). Thoracoabdominal CT revealed no evidence of malignancy. Cerebrospinal fluid (CSF) analysis showed negative oligoclonal bands, and paraneoplastic antibody testing (anti-Hu, anti-Yo, anti-Ri) was also negative. Laboratory investigations demonstrated normal results for complete blood count, liver and kidney function, lipid profile, coagulation studies, thyroid function, folate, vitamin B12, and serum homocysteine levels.

Diagnosis was confirmed through multimodal testing. Skin biopsy revealed p62-positive eosinophilic intranuclear inclusions within eccrine sweat gland epithelial cells (Figures 5A–B), and genetic analysis identified a pathogenic NOTCH2NLC GGC repeat expansion (>41 repeats). The patient was treated with anxiolytics and supportive measures, including chronic catheterization.

At the 12-month follow-up (May 2024), autonomic symptoms persisted — urinary retention requiring long-term catheterization, refractory constipation, occasional orthostatic dizziness, and perceived changes in sexual function — despite restoration of regular sleep and adequate anxiety control. Repeat brain

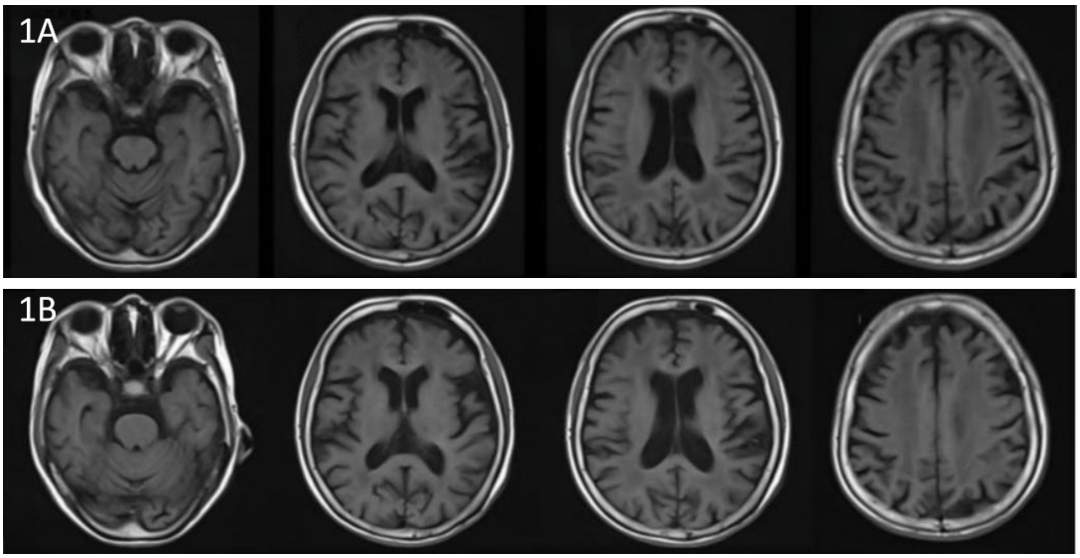

Figure 1. T1 FLAIR images demonstrating progressive cerebral atrophy. **(A)** Baseline image (2023) showing widened cerebral sulci and periventricular white matter hypointensities. **(B)** Follow-up image (2024) revealing further sulcal widening and ventricular enlargement, consistent with advancing cerebral atrophy.

MRI (2024) demonstrated progression of white matter lesions (Figures 2B and 3B), further sulcal widening indicating advancing cortical atrophy (Figure 1B), and continued absence of DWI abnormalities (Figure 4B).

Written informed consent was obtained from the patient for publication of the clinical details, neuroimaging data, and histopathological findings. Specific consent for public sharing of raw genetic sequencing data was not obtained.

DISCUSSION

This case represents a distinct clinical phenotype of NIID—an acute, severe autonomic crisis occurring in the setting of persistent DWI negativity. While recent studies have broadened understanding of the heterogeneity of NIID, our case adds to the literature by documenting the rapid trajectory of autonomic failure and confirming that structural neurodegeneration can progress actively even in the absence of

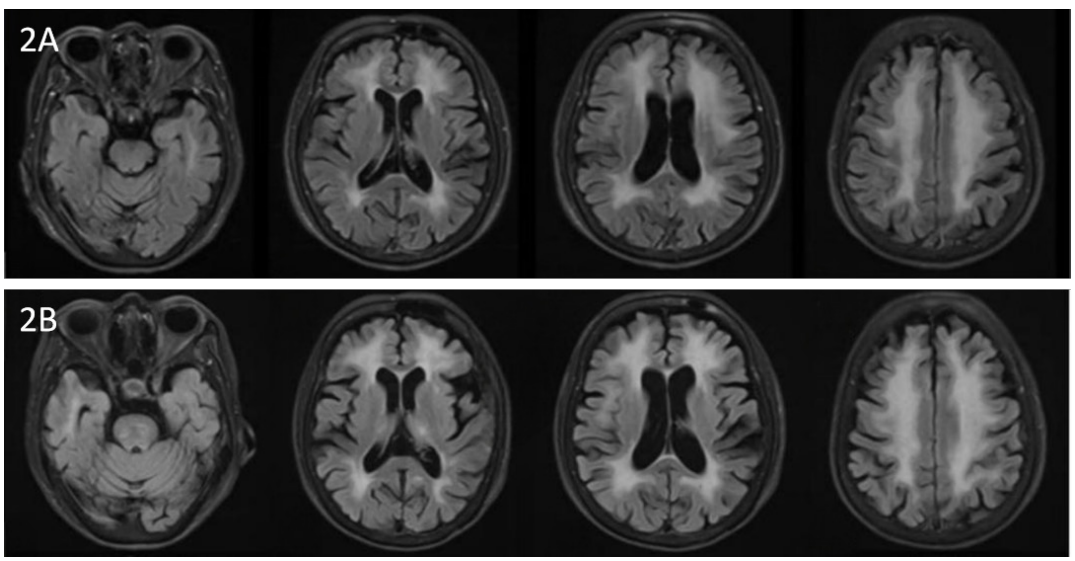

Figure 2. Progressive white matter lesions on T2-FLAIR sequences. **(A)** Baseline scan (2023) demonstrating confluent periventricular hyperintensities. **(B)** Follow-up scan (2024) revealing mildly increased extent and confluence of patchy periventricular hyperintensity, consistent with disease progression.

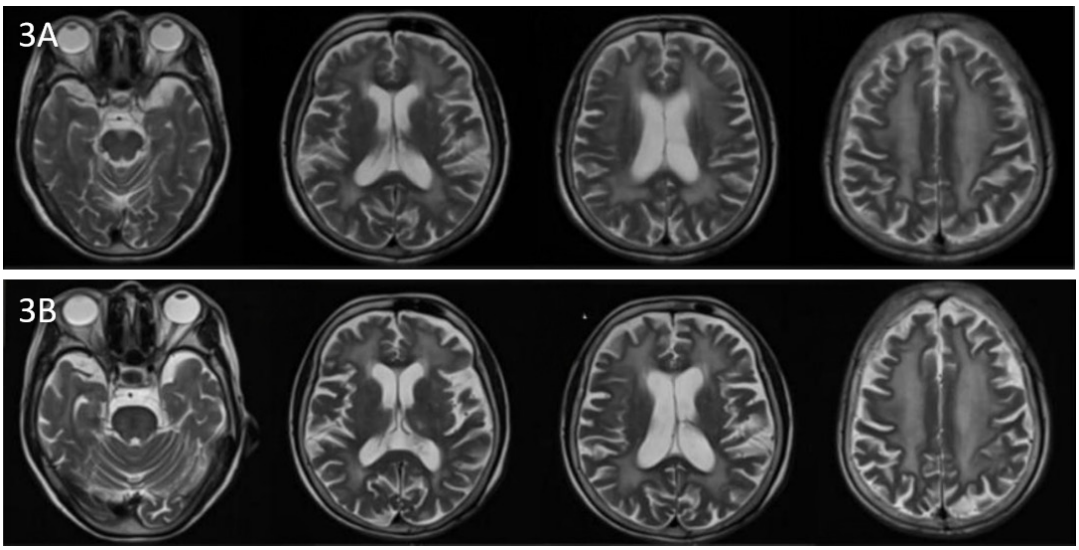

Figure 3. Progressive confluent white matter hyperintensities on T2-weighted imaging (T2WI). **(A)** Baseline scan (2023) demonstrating extensive symmetric periventricular hyperintensities (Fazekas grade 3). **(B)** Follow-up scan (2024) revealing increased confluence and patchiness of periventricular hyperintensity.

characteristic DWI biomarkers.

To contextualize our findings, we reviewed prior reports on autonomic involvement in NIID. Autonomic dysfunction is a hallmark feature, with a prevalence of approximately 64-70% in large cohorts.[8,9] The typical autonomic phenotype described in the literature is chronic, insidious, and sometimes overshadowed or preceding other deficits.[3,10] Common manifestations include neurogenic bladder, constipation, and orthostatic hypotension, which usually progress slowly over years.[7,9,11] This presentation aligns with the multisystem, progressive nature of NIID. In sharp contrast to this classical pattern, our patient developed an abrupt "acute autonomic exacerbation" over a period of

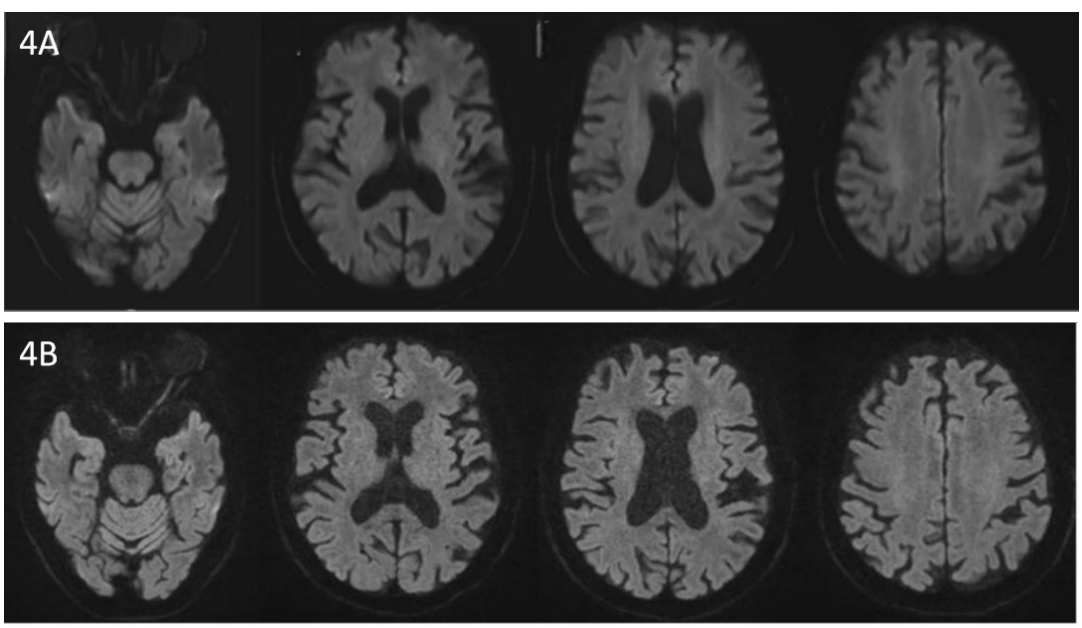

Figure 4. Persistent diffusion-weighted imaging (DWI) negativity despite progressive cerebral atrophy. **(A)** Baseline DWI (2023) showing no restricted diffusion or abnormal hyperintensity. **(B)** Follow-up DWI (2024) confirming continued absence of pathological signals, while concomitant structural sequences reveal advancing sulcal widening.

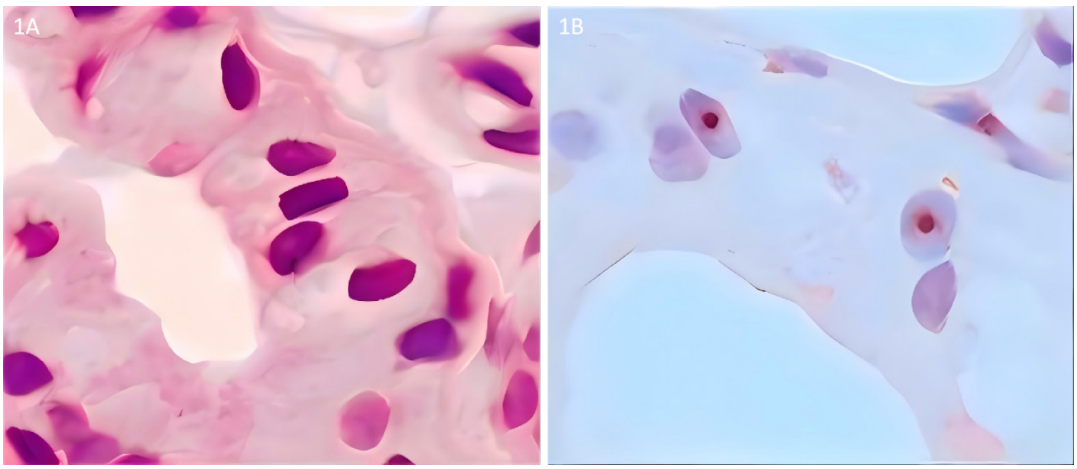

Figure 5. Pathological confirmation of neuronal intranuclear inclusion disease (NIID) via skin biopsy. **(A)** Hematoxylin and eosin (H&E) staining of eccrine sweat gland epithelium demonstrating eosinophilic hyaline intranuclear inclusions. **(B)** P62 immunohistochemistry confirming ubiquitinated protein aggregates within nuclei, exhibiting characteristic perinuclear halos.

weeks, characterized by catheter-dependent urinary retention, intractable constipation, and generalized hyperhidrosis. This presentation was pharmacoresistant and became the primary source of disability, outweighing other neurological deficits. Although severe autonomic failure is recognized in NIID, its manifestation as a rapid, monophasic crisis leading to catheter dependence is uncommon and may represent a particularly aggressive disease variant. The neuropathological basis for such symptoms is well supported by prior post-mortem studies, which have demonstrated widespread accumulation of p62-positive intranuclear inclusions within the sympathetic ganglia, dorsal root ganglia, and the myenteric plexus of the gastrointestinal tract.[11,12] The severity of autonomic failure in our patient suggests that, in some individuals, the pathological burden in the peripheral autonomic nervous system may disproportionately exceed that in the central nervous system.

It is notable that the acute exacerbation in this case was temporally associated with a prolonged period of severe sleep deprivation. Although a causal relationship cannot be established and may not be distinguishable from the natural disease course, this observation raises the possibility that environmental stressors could influence symptom fluctuations in genetically predisposed individuals—a hypothesis warranting further investigation.

The absence of curvilinear hyperintensity along the corticomedullary junction on DWI—traditionally considered the radiological hallmark of NIID—posed a diagnostic challenge. Cohort studies indicate that 11.8–20% of genetically confirmed NIID patients are DWI-negative at initial presentation.[3,13,14] Longitudinal data from Liu et al. suggest that typical DWI signals may emerge 4–5 years after symptom onset.[15] Our case supports this finding by illustrating active disease progression during the DWI-negative window: although follow-up DWI remained negative, structural MRI revealed progressive confluent white matter hyperintensities and cerebral atrophy. These findings confirm that the absence of restricted diffusion does not imply a static or benign disease state. Clinicians should recognize that aggressive leukoencephalopathy may precede DWI conversion and should consider genetic testing for NOTCH2NLC expansions in cases of unexplained autonomic failure with atypical white matter changes, irrespective of DWI findings.

The primary limitations of our report include its single-case nature and relatively short follow-up period, which precluded assessment of potential future DWI conversion. Additionally, although pathological confirmation was achieved via skin biopsy, autonomic ganglia biopsy was not performed, preventing direct correlation of clinical severity with pathological burden.

In summary, this case exemplifies an autonomic-dominant phenotype of NIID characterized by acute, refractory visceral dysfunction. It reinforces that DWI-negative NIID can represent a progressive neurodegenerative condition. Awareness of this presentation

is crucial for avoiding diagnostic delays in patients with atypical leukoencephalopathy and unexplained autonomic failure.

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