Clinical Features and Classification of Neuronal Intranuclear Inclusion Disease

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Abstract

Background and Objectives
Neuronal intranuclear inclusion body disease (NIID) is a neurodegenerative disease with highly heterogeneous clinical manifestations. The present study aimed to characterize clinical features and propose a classification system based on a large cohort of NIID in China.

Methods
The Chinese NIID registry was launched from 2017, and participants’ demographics and clinical features were recorded. Brain MRI, skin pathologies, and the number of GGC repeat expansions in the 5’ untranslated region of the NOTCH2NL gene were evaluated in all patients.

Results
In total, 223 patients (64.6% female) were recruited; the mean (SD) onset age was 56.7 (10.3) years. The most common manifestations were cognitive impairment (78.5%) and autonomic dysfunction (70.9%), followed by episodic symptoms (51.1%), movement disorders (50.7%), and muscle weakness (25.6%). Imaging markers included hyperintensity signals along the corticomedullary junction on diffusion-weighted imaging (96.6%), white matter lesions (98.1%), paravermis (55.0%), and focal cortical lesions (10.1%). The median size of the expanded GGC repeats in these patients was 115 (range, 70–525), with 2 patients carrying >300 GGC repeats. A larger number of GGC repeats was associated with younger age at onset ($r = -0.329$, $p < 0.0001$). According to the proposed clinical classification based on the most prominent manifestations, the patients were designated into 5 distinct types: cognitive impairment-dominant type (34.1%, n = 76), episodic neurogenic event-dominant type (32.3%, n = 72), movement disorder-dominant type (17.5%, n = 39), autonomic dysfunction-dominant type (8.5%, n = 19), and neuromuscular disease-dominant type (7.6%, n = 17). Notably, 32.3% of the episodic neurogenic event-dominant type of NIID has characteristic focal cortical lesions on brain MRI presenting localized cortical edema or atrophy. The mean onset age of the neuromuscular disease-dominant type was 47.2 (17.6) years, younger than the other types ($p < 0.001$). There was no significant difference in the sizes of GGC repeats among the patients in the 5 types ($p = 0.547$, Kruskal-Wallis test).

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Neuronal intranuclear inclusion disease (NIID) is a progressive neurodegenerative disease characterized by pathologic eosinophilic hyaline intranuclear inclusions in the central and peripheral nervous systems and multiple visceral organs.\(^1\) Since the application of skin biopsy for diagnosis and the identification of GGC repeat expansion in the 5’-untranslated region (5’-UTR) of the NOTCH2NLC gene as the causative variation,\(^4\) an increasing number of NIID cases have been reported.\(^5\) As the number of cases has grown, the scope of clinical manifestations has expanded to encompass cognitive impairment, parkinsonism, tremor, autonomic dysfunction, peripheral neuropathy, myopathy, encephalitic episodes, epileptic seizure, stroke-like episodes, disturbances of consciousness, cerebellar ataxia, headache, and vision loss.\(^6\) Moreover, MRI signs including hyperintensity in the corticomedullary junction on diffusion-weighted imaging (DWI), focal cortical edema/enhancement, and white matter lesions involving the paravermis, middle cerebellar peduncle, and corpus callosum have been reported to be characteristic imaging for NIID.\(^7\) However, these clinical characteristics were mostly described in case reports or case series, and overall knowledge of the clinical features of NIID is still limited.

GGC repeat expansion in NOTCH2NLC has been identified in a variety of neurologic diseases, including Alzheimer disease,\(^8\) Parkinson disease (PD),\(^9\) frontotemporal dementia,\(^10\) amyotrophic lateral sclerosis,\(^11\) essential tremor (ET),\(^12\) multiple system atrophy (MSA),\(^13\) leukoencephalopathy,\(^14\) oculopharyngodistal myopathy (OPDM),\(^15\) Charcot-Marie-Tooth disease.\(^16\) These findings indicate that the clinical manifestations of NIID are highly heterogeneous, and the diagnosis of NIID is challenging. Previously, studies have classified NIID into “dementia-dominant type,” “muscle weakness-dominant type,” with/without “parkinsonism-dominant type.”\(^17\) Apparently, the existing clinical classifications are not inclusive enough for all the predominant manifestations of the disease. Here, we conducted a cross-sectional observational study of 223 patients with NIID from multiple centers; we summarize the clinical, imaging, and genetic features of these patients and propose an informative classification of NIID.

**Glossary**

5’-UTR = 5’-untranslated region; DWI = diffusion-weighted imaging; ET = essential tremor; H&E = hematoxylin and eosin; IQR = interquartile range; MELAS = mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; MSA = multiple system atrophy; NIID = neuronal intranuclear inclusion disease; OPDM = oculopharyngodistal myopathy; PD = Parkinson disease.

**Discussion**

This observational study of NIID establishes an overall picture of the disease regarding clinical, imaging, and genetic characteristics. The proposed clinical classification of NIID based on the most prominent manifestation divides patients into 5 types.

**Methods**

**Study Design and Participants**

The China NIID Collaboration Alliance was launched in October 2017, and patients suspected to have NIID were recruited from across the country. Patients were examined by at least 2 experienced neurologists and included in the study only if they met the following inclusion criteria: (1) clinically presenting with neurologic symptoms in accordance with NIID, including cognitive impairment, parkinsonism, tremor, autonomic dysfunction, peripheral neuropathy, myopathy, epileptic seizures, stroke-like episodes, disturbances of consciousness, headache, and encephalitic episodes; (2) pathology of skin biopsy showed eosinophilic hyaline intranuclear inclusions on hematoxylin and eosin (H&E) staining in adipocytes, fibroblasts, sweat gland cells, or other cells, which were anti–p62 positive on immunohistochemical staining and were composed of filamentous material with no limiting membrane as determined using electron microscopy; (3) the number of GGC repeats in the 5’-UTR of the NOTCH2NLC gene was larger than 60\(^9\)\(^1\); and (4) results of a series of laboratory tests ruled out metabolic, toxic, inflammatory, and other diseases that may have accounted for the patient’s symptoms. For familial NIID, only the proband was included in the final analysis.

**Clinical Assessment**

Full records of the patient’s clinical data, including sex, age at onset, disease duration, clinical symptoms, time of appearance of specific symptoms, family history, physical examination, and ancillary test results, were collected using standardized case report forms. Neurologic examinations were performed repetitively by neurologists. Cranial nerves, muscle strength, muscle tension, coordination movement, sensory impairment, tendon reflexes, and autonomic function were assessed. The Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) were used to evaluate cognitive and executive functions. EMG features were analyzed in the 37 consecutive patients enrolled at Beijing Tiantan Hospital, motor and sensory nerve conduction studies, F-wave, and needle EMG were conducted based on standard methods.
protocols, and all results were assessed against the reference values established in our laboratory.28

Neuroimaging
All participants underwent routine brain MRI examination with a 3.0 Tesla (T) or 1.5 T MR scanner, and the images were separately assessed by at least 2 neuroimaging specialists who were blind to clinical information. White matter lesions were graded according to their scope on T2W1: grade 0 was defined as no T2 hyperintensities; grade 1 as punctate or patchy T2 hyperintensities; grade 2 as moderate changes with confluent symmetric periventricular hyperintensities; and grade 3 as severe changes with confluent periventricular hyperintensities extending to the gray/white matter border. Brain atrophy was graded based on visual evaluation of the width of cortical sulci and the size of the ventricles: grade 0 was defined as no atrophy; grade 1 as slight widening of the subarachnoid space; grade 2 as marked widening of the subarachnoid space and mild widening of the ventricles; and grade 3 as marked atrophy with a pronounced widening of subarachnoid space and ventricles29 (as shown in eFigure 1, links.lww.com/NXG/A581).

Skin Biopsy, Muscle Biopsy, and Histology
Skin biopsies were performed on all patients; 16 consecutive patients from 1 center underwent muscle biopsies from the biceps brachii following routine histologic staining. Immunohistochemical staining was performed using anti-p62 (56416, Abcam) and anti-ubiquitin (33893, Abcam) antibodies. The density of intranuclear inclusions in 148 skin biopsies was determined by counting the mean number of p62 immunoreactive inclusion bodies in 5 visual fields per sample at ×20 magnification.

Genetic Analysis
Blood samples were processed to extract genomic DNA following a standard phenol-chloroform method. We performed a repeat-primed PCR protocol to test repeat expansions in the 5’UTR of NOTCH2NLC as reported in the literature.30 A saw-tooth tail pattern in the electropherogram was considered to indicate a repeat expansion. Fluorescence amplicon-length PCR was used to detect the length of GGC repeat expansions. Electrophoresis was performed on a 3500xL Genetic Analyzer (Thermo Fisher Scientific). The data were analyzed using GeneMapper software (Thermo Fisher Scientific). The length of the highest signal peak of the expanded allele was used to calculate the repeat number.31 Long-read whole-genome sequencing was performed using a PromethION sequencer on 2 individuals who had a saw-tooth tail repeat-primed PCR, but no peak was seen on amplicon-length PCR. Library preparation was performed using ligation sequencing 1D kits (SQK-LSK109, Oxford Nanopore Technologies, UK) according to the manufacturer’s protocol. About 800 ng DNA libraries were constructed and sequenced on the PromethION platform (Oxford Nanopore Technologies, UK).

Statistical Analyses
Imaging, genetic, and pathologic analysts were all blinded to the patient’s clinical information. Statistical analyses were performed using SPSS version 25.0 (SPSS Inc.). Age at onset, cognitive scores, and the number of GGC repeats were presented as the mean ± SD. Disease duration and the number of GGC repeats in subgroups were presented as the median (interquartile range [IQR]). One-way analysis of variance and the Kruskal-Wallis test were used to compare multiple groups. The relationship between MMSE/MoCA score and disease duration was tested using multiple linear regression. The correlation between the number of GGC repeats and age at onset was assessed using Pearson correlation analysis. p Values ≤ 0.05 (2 tailed) were considered statistically significant.

Data Availability
Deidentified participant data that are not published within this article will be made available to qualified investigators on request.

Results
In total, 223 consecutive patients with suspected NIID were recruited from 104 clinical centers across various geographic regions of mainland China between October 2017 and July 2022.

Clinical Manifestations
The participant demographics and clinical features are summarized in Table 1. The male-to-female ratio was 1:1.82. The mean (SD) age at onset was 56.7 (10.3) years, and the median (IQR) disease duration was 4.0 (2.0–9.0) years, ranging from 1 to 44 years. The most common initial symptom of NIID was cognitive impairment (24.7%), followed by autonomic dysfunction (16.1%), tremor (13.9%), encephalitic episodes (9.0%), headache (6.7%), disturbances of consciousness (6.3%), dizziness (6.3%), and other less common initial symptoms; the appearance time points of various symptoms are presented in Figure 1A.

Among all patients, 78.5% developed cognitive impairment before consultation and exhibited progressive deterioration in memory and orientation. 55.3% of the patients fulfilled the diagnostic criteria of dementia using the cutoff value of the MMSE score of 24. The MMSE and MoCA scores were negatively correlated with the disease duration after adjusting for the age at onset (multiple linear regression: \( \beta_1 = -0.243, p_1 = 0.01 \) for MMSE, \( n = 164; \beta_2 = -0.322, p_2 = 0.001 \) for MoCA, \( n = 150 \)). Autonomic dysfunction (70.9%) was the second most common symptom in patients with NIID.
Table 1 Clinical Features of Patients With NIID and in Different Types

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Cognitive impairment-dominant type</th>
<th>Episodic neurogenic event-dominant type</th>
<th>Movement disorder-dominant type</th>
<th>Autonomic dysfunction-dominant type</th>
<th>Neuromuscular disease-dominant type</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>223</td>
<td>76 (34.1%)</td>
<td>72 (32.3%)</td>
<td>39 (17.5%)</td>
<td>19 (8.5%)</td>
<td>17 (7.6%)</td>
</tr>
<tr>
<td>Age at onset, mean ± SD (range)</td>
<td>56.7 ± 10.3 (10–75)</td>
<td>59.6 ± 7.4 (39–75)</td>
<td>56.6 ± 10.5 (18–75)</td>
<td>55.7 ± 8.5 (26–67)</td>
<td>55.8 ± 8.3 (40–71)</td>
<td>48.4 ± 18.6 (10–67)</td>
</tr>
<tr>
<td>Disease duration, median (IQR)</td>
<td>4.0 (2.0–9.0)</td>
<td>3.0 (2.0–5.0)</td>
<td>4.5 (1.1–9.0)</td>
<td>5.0 (4.0–11.0)</td>
<td>4.0 (2.0–13.0)</td>
<td>5.0 (2.5–8.0)</td>
</tr>
<tr>
<td>Clinical manifestations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cognitive impairment</td>
<td>175/223 (78.5%)</td>
<td>76/76</td>
<td>49/72</td>
<td>29/39</td>
<td>7/19</td>
<td>14/17</td>
</tr>
<tr>
<td>Autonomic dysfunction</td>
<td>158/223 (70.9%)</td>
<td>55/76</td>
<td>45/72</td>
<td>29/39</td>
<td>19/19</td>
<td>10/17</td>
</tr>
<tr>
<td>Rectal and bladder dysfunction</td>
<td>124/223 (55.6%)</td>
<td>43/76</td>
<td>34/72</td>
<td>25/39</td>
<td>13/19</td>
<td>9/17</td>
</tr>
<tr>
<td>Vomiting</td>
<td>72/223 (32.3%)</td>
<td>25/76</td>
<td>28/72</td>
<td>5/39</td>
<td>10/19</td>
<td>4/17</td>
</tr>
<tr>
<td>Miosis</td>
<td>67/223 (30.0%)</td>
<td>21/76</td>
<td>19/72</td>
<td>17/39</td>
<td>4/19</td>
<td>6/17</td>
</tr>
<tr>
<td>Syncope/OH</td>
<td>58/223 (26.0%)</td>
<td>20/76</td>
<td>12/72</td>
<td>12/39</td>
<td>10/19</td>
<td>4/17</td>
</tr>
<tr>
<td>Movement disorders</td>
<td>113/223 (50.7%)</td>
<td>36/76</td>
<td>26/72</td>
<td>39/39</td>
<td>5/19</td>
<td>7/17</td>
</tr>
<tr>
<td>Tremor</td>
<td>82/223 (36.8%)</td>
<td>23/76</td>
<td>18/72</td>
<td>33/39</td>
<td>4/19</td>
<td>4/17</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>55/223 (24.7%)</td>
<td>19/76</td>
<td>11/72</td>
<td>17/39</td>
<td>2/19</td>
<td>6/17</td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>7/223 (3.1%)</td>
<td>1/76</td>
<td>3/72</td>
<td>3/39</td>
<td>0/19</td>
<td>0/17</td>
</tr>
<tr>
<td>Behavior and psychiatric symptoms</td>
<td>70/223 (31.4%)</td>
<td>27/76</td>
<td>25/72</td>
<td>11/39</td>
<td>3/19</td>
<td>4/17</td>
</tr>
<tr>
<td>Muscle weakness*</td>
<td>57/223 (25.6%)</td>
<td>19/76</td>
<td>13/72</td>
<td>6/39</td>
<td>2/19</td>
<td>17/17</td>
</tr>
<tr>
<td>Sensory disturbance*</td>
<td>24/223 (10.8%)</td>
<td>7/76</td>
<td>5/72</td>
<td>5/39</td>
<td>1/19</td>
<td>6/17</td>
</tr>
<tr>
<td>Disturbance of consciousness</td>
<td>12/76</td>
<td>32/72</td>
<td>1/39</td>
<td>2/19</td>
<td>3/17</td>
<td></td>
</tr>
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</table>

Continued
Table 1 Clinical Features of Patients With NIID and in Different Types (continued)

<table>
<thead>
<tr>
<th>Feature</th>
<th>Total</th>
<th>Cognitive impairment-dominant type</th>
<th>Episodic neurogenic event-dominant type</th>
<th>Movement disorder-dominant type</th>
<th>Autonomic dysfunction-dominant type</th>
<th>Neuromuscular disease-dominant type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke-like episode</td>
<td>50/223 (22.4%)</td>
<td>8/76</td>
<td>20/72</td>
<td>6/39</td>
<td>1/19</td>
<td>2/17</td>
</tr>
<tr>
<td>Encephalitic episode</td>
<td>32/223 (14.3%)</td>
<td>3/76</td>
<td>26/72</td>
<td>0/39</td>
<td>0/19</td>
<td>3/17</td>
</tr>
<tr>
<td>Epileptic seizure</td>
<td>19/223 (8.5%)</td>
<td>2/76</td>
<td>13/72</td>
<td>1/39</td>
<td>0/19</td>
<td>3/17</td>
</tr>
<tr>
<td>Headache</td>
<td>55/223 (24.7%)</td>
<td>16/76</td>
<td>29/72</td>
<td>7/39</td>
<td>1/19</td>
<td>2/17</td>
</tr>
<tr>
<td>Dizziness</td>
<td>54/223 (24.2%)</td>
<td>28/76</td>
<td>13/72</td>
<td>10/39</td>
<td>2/19</td>
<td>1/17</td>
</tr>
<tr>
<td>Ataxia</td>
<td>38/223 (17.0%)</td>
<td>16/76</td>
<td>11/72</td>
<td>4/39</td>
<td>2/19</td>
<td>5/17</td>
</tr>
<tr>
<td>Vision loss</td>
<td>32/223 (14.3%)</td>
<td>5/76</td>
<td>13/72</td>
<td>9/39</td>
<td>2/19</td>
<td>3/17</td>
</tr>
<tr>
<td>Cognitive function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE, mean ± SD (n)</td>
<td>21.32 ± 6.54</td>
<td>20.54 ± 5.91 (n = 57)</td>
<td>18.87 ± 7.32 (n = 47)</td>
<td>24.19 ± 5.83 (n = 32)</td>
<td>24.81 ± 4.07 (n = 16)</td>
<td>22.25 ± 6.46 (n = 12)</td>
</tr>
<tr>
<td>MoCA, mean ± SD (n)</td>
<td>16.85 ± 6.82</td>
<td>15.57 ± 6.23 (n = 56)</td>
<td>14.66 ± 7.13 (n = 38)</td>
<td>19.03 ± 6.12 (n = 31)</td>
<td>21.50 ± 5.98 (n = 14)</td>
<td>18.82 ± 7.57 (n = 11)</td>
</tr>
</tbody>
</table>

Abbreviations: MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; NIID = neuronal intranuclear inclusion disease; OH = orthostatic hypotension.

* Muscle weakness and sensory disturbance caused by peripheral neuropathy and/or myopathy.
Among all patients, more than half (55.6%) presented with rectal and bladder dysfunction, followed by gastrointestinal dysfunction manifesting as recurrent nausea and vomiting (32.3%), miosis (30.0%), and orthostatic hypotension/syncope (26.0%).

Episodic neurogenic events occurred in 51.1% of the patients, including disturbances of consciousness, encephalitic episodes, stroke-like episodes, epileptic seizure, and episodic headaches. 28.7% of the patients presented episodic symptoms as the initial manifestation of the disease. Recurrent disturbances of consciousness were observed in 22.4% of patients. The duration of these disturbances varied from several hours to days and occasionally resolved spontaneously. Stroke-like episodes occurred in 16.6% of patients, presenting as acute neurologic deficits (e.g., hemiplegia, aphasia, and dysphagia) in the absence of infarction lesions indicative of vascular distribution or vascular stenosis on imaging. 14.3% of patients with NIID had encephalitic episodes, presenting as any combination of fever (29/32), unconsciousness (18/32), mental and behavioral abnormality (14/32), headache (13/32), and generalized convulsions (5/32). Cognitive decline in patients with episodic symptoms was more severe compared with patients without episodic symptoms (MMSE: 19.94 ± 6.85 vs 22.60 ± 5.97, p = 0.009; MoCA: 15.73 ± 6.60 vs 17.83 ± 6.91, p = 0.06).

Tremor occurred in 36.8% (82/223) of the patients, including 63.4% (52/82) with ET and 36.6% (30/82) with parkinsonism tremor. Behavior and psychiatric symptoms were observed in 31.4% (70/223) of the patients, manifesting as irritability, cryptic speech, hallucinations, and disinhibition. Muscle weakness caused by peripheral neuropathy or myopathy occurred in 25.6% (57/223) of the patients, most of whom (43/57) presented with mild weakness and could walk independently. Other common clinical manifestations included parkinsonism (24.7%), cerebellar ataxia (17.0%), vision loss (14.3%), and somatosensory disturbances (10.8%).

EMG was analyzed in 37 patients from 1 center. Fifteen of them had muscle weakness and/or sensory disturbance associated with peripheral neuropathy. Under needle EMG
examination, 94.6% (35/37) of the patients had peripheral nerve damage; 22 patients had demyelinating sensorimotor polyneuropathy, whereas the other 12 cases had both demyelination and axonal neuropathy. Muscle biopsies were taken for 16 patients (Figure 2, E–H), of which 3 patients had muscle weakness involving both proximal and distal limbs and 2 patients complained of fatigue. All patients (16/16) showed p62-positive intranuclear inclusion...
bodies in muscle cells. Fifteen of the patients (15/16) showed fiber size variation with small round and/or angular atrophic fibers, and 1 of them had additional angular fiber clustering and fiber grouping. Twelve of the patients (12/16) had scattered rimmed vacuoles on H&E and modified Gomori trichrome staining. Fiber-type disproportion was very common, with type I fiber dominant in 10 and type II fiber dominant in 5. Among the 16 patients, only 1 patient had a slight increase in the serum creatine kinase level, and none of them showed myogenic change in needle EMG. The clinical features of these patients were shown in eTable 1, links.lww.com/NXG/A581.

Neuroradiologic Findings
Imaging data were available for 209 patients. Two patients had completely normal brain MRI. High-intensity signal along the corticomедullary junction on DWI was seen in 96.6% (202/209) of patients, which was more frequently observed in the frontal-parietal lobes (100%) than the temporo-occipital lobes (68.8%). Most of the patients (98.1%, 205/209) had white matter lesions, including 34 patients in grade 1, 72 patients in grade 2, and 99 patients in grade 3, which typically manifest as T2WI hyperintensity involving bilateral paraventricular and subcortical areas with blurred edges. Brain atrophy was seen in 98.6% (206/209) patients, including 24 patients, 104 patients, and 78 patients in grade 1 to grade 3, respectively. Both the grades of white matter lesions and brain atrophy were correlated with the MMSE and MoCA score cognitive function (all p < 0.05, analysis of variance, eTable 2, links.lww.com/NXG/A581). T2/FLAIR hyperintensities in other locations were found in the corpus callosum (83.7%), paravermis (55.0%), brainstem transverse fibers (42.1%), bilateral thalamic lamellae (30.6%), and bilateral middle cerebellar peduncles (24.4%) (Figure 2, I–P).

Focal cortical lesions showing T2WI/FLAIR hyperintensity in localized cortical regions were found in 21 patients (10.1%) (Figure 2, Q–T), and all of them had episodic symptoms, including encephalitic-like episodes, disturbance of consciousness, stroke-like episodes, and recurrent headache (eTable 3, links.lww.com/NXG/A581). Brain MRIs were obtained with a median interval of 13 days (range, 1–130 days) from the last episodic symptom onset. Fifteen of 21 patients (71.4%) showed focal cortical edema in the regions of hyperintensity on T2WI/Flair, and 13 patients showed restricted diffusion on DWI. Cortical enhancement on T1WI was found in 4 of the 7 patients (57.1%) who underwent gadolinium-enhanced MRI. The other 6 patients (6/21) showed prominent localized cortical atrophy. The cortical lesions were preferentially distributed in the temporal-parietal

Figure 3 Association Between the Number of GGC Repeats in the 5′-Untranslated Regions of the NOTCH2NLC Gene and Clinical Features of NIID

(A) A larger number of GGC repeats in patients with NIID was associated with younger age at onset (Pearson correlation analysis, r = −0.329, p < 0.0001, 2 outliers of GGC repeats were truncated). (B) A larger number of GGC repeats was associated with higher density of intranuclear inclusions in skin biopsy (Pearson correlation analysis, r = 0.207, p = 0.012, n = 148). (C) The median (quartiles) number of GGC repeats in patients with different types of NIID. NIID = neuronal intranuclear inclusion disease.
Table 2 Protocol for the Clinical Classification of NIID Based on Prominent Manifestations

I. Cognitive impairment-dominant type
   - mainly manifested as gradual and progressive decline in memory and/or other cognitive function reported by patient or informant over more than 2 mo and objective evidence of impairment in 1 or more cognitive domains, including memory, executive function, attention, language, and visuospatial function, etc.

II. Movement disorder-dominant type, take any of the following as the main manifestation:
   1. Isolated tremor, postural, resting, or both
   2. Parkinsonism manifested as bradykinesia plus at least 1 of items b–d
      a. Bradykinesia (slowness of voluntary movement with a progressive reduction in speed and amplitude during repetitive actions)
      b. Rigidity
      c. Postural instability (not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction)
      d. Tremor (postural, resting, or both)
   3. Other forms of hyperkinesia, characterized by involuntary muscle movements and reduced muscle tone, such as athetosis, chorea, tics, hemiballismus, and dystonia.

III. Episodic neurogenic event-dominant type, manifested as item (1) or item (2)
   1. Isolated tremor, postural, resting, or both
   2. Parkinsonism manifested as bradykinesia plus at least 1 of items b–d
      a. Bradykinesia (slowness of voluntary movement with a progressive reduction in speed and amplitude during repetitive actions)
      b. Rigidity
      c. Postural instability (not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction)
      d. Tremor (postural, resting, or both)

IV. Autonomic dysfunction-dominant type
   - Present autonomic dysfunction as the sole or predominant manifestation of NIID, including
     a. Rectal and bladder dysfunction: urinary incontinence or incomplete bladder emptying (accompanied by erectile dysfunction in men), difficulty defecation/constipation, or both
     b. Orthostatic hypotension (by 20 mm Hg systolic or 10 mm Hg diastolic) or syncope
     c. Miosis
     d. Gastrointestinal dysfunction: gastroparesis, indigestion, abdominal distension, abdominal pain, nausea, and vomiting
     e. Thermoregulatory dysfunction: hyperhidrosis.

V. Neuromuscular disease-dominant type
   - Present peripheral neuropathy (a) and/or myopathy (b) as the predominant or sole manifestation of NIID, leading to muscle weakness (muscle strength is usually less than or equal to grade 4/5), with or without sensory disturbance.
     a. Peripheral neuropathy: muscle weakness in the distal limbs, sensory disturbance in line with peripheral nerve distribution, decreased or absent tendon reflexes, with or without high arches, and hammertoes; the nerve conduction study suggests demyelination and axonal sensorimotor polyneuropathy, with neurogenic change on EMG.
     b. Myopathy: muscle weakness involving proximal and distal limbs; EMG suggests a myogenic change or normal; muscle pathology shows small round atrophic fibers, rimmed vacuoles, and/or fiber-type disproportion.

Abbreviation: NIID = neuronal intranuclear inclusion disease.

(20/21) and occipital (17/21) lobes relative to the frontal lobe (8/21).

GGC Repeat Expansions in the NOTCH2NLC Gene

In the present study, the number of GGC repeats in the 5’-UTR of the NOTCH2NLC gene in patients with NIID ranged from 70 to 525, and 99.1% (221/223) of the patients had fewer than 200. Notably, there were 2 cases with many repeats, including one with recurrent syncope and excessive sweating carrying 363 repeats and the other with peripheral neuropathy and mild cognitive impairment carrying 525 repeats. A larger number of GGC repeats was associated with younger age at onset (Pearson correlation analysis, $r = −0.329, p < 0.0001$, n = 223) and higher density of intranuclear inclusions in skin biopsy (Pearson correlation analysis, $r = 0.207, p = 0.012$, n = 148) (Figure 3, A–B), but not with the MMSE or MoCA scores (multiple linear regression, adjusting for age at onset, disease duration, and education level, MMSE: $p = 0.311$, MoCA: $p = 0.332$).

Clinical Classifications

After evaluation of clinical symptoms and physical examination, patients with NIID were divided into 5 types based on their most prominent manifestations: (1) cognitive impairment-dominant type (n = 76), (2) episodic neurogenic event-dominant type (n = 72), (3) movement disorder-dominant type (n = 39), (4) autonomic dysfunction-dominant type (n = 19), and (5) neuromuscular disease-dominant type (n = 17) (Table 1). A protocol for clinical classification of NIID was proposed, as shown in Table 2.1,2,32-33

Cognitive impairment-dominant type: accounted for 34.1% (76/223) of the patients, characterized by a progressive decline in cognitive function in 1 or more domains, and the course of disease ranged from 2 months to 30 years (median course 3 [2–5] years). More than half of the patients (45/76) presented cognitive impairment as the initial symptom of NIID, and the most common complaint was memory decline. The average MMSE and MoCA scores...
were 20.54 ± 5.91 points (n = 57) and 15.57 ± 6.23 points (n = 56), respectively. The MMSE and MoCA scores were negatively correlated with the disease duration, after adjusting for the age at onset and education (multiple linear regression: \( \beta_1 = -0.276, p_1 = 0.065 \) for MMSE; \( \beta_2 = -0.365, p_2 = 0.019 \) for MoCA).

Episodic neurogenic event-dominant type: accounted for 32.3% (72/223) of the patients. Among them, 19 patients had episodic neurologic symptoms as the only clinical manifestation of NIID. The total number of recurrent attacks in patients with this type was greater than or equal to 3, and the frequency of attacks was greater than 1 time/yr. The forms and distribution of episodic symptoms are shown in Figure 1B, with episodic unconsciousness as the most prevalent (32/72), followed by episodic headache (29/72), encephalitic episodes (26/72), stroke-like attack (20/72), and epileptic seizure (13/72). 68.1% (49/72) of the patients in this type had concomitant cognitive impairment.

Movement disorder-dominant type: accounted for 17.5% (39/223) of the patients, characterized by different forms of movement disorder: in addition to 16 patients who presented with parkinsonism, there were 20 patients presented with ET, and the other 3 patients manifested chorea, athetosis, or dystonia.

Autonomic dysfunction-dominant type: accounted for 8.5% (19/223) of the patients. The clinical manifestations of the 19 patients are shown in eTable 4, links.lww.com/NXG/A581, and the median disease duration was 4.0 (IQR 2.0–13.0) years. They all started with various forms of autonomic symptoms and mainly present with rectal and bladder dysfunction (13/19), orthostatic hypotension/syncope (10/19), vomiting and indigestion (10/19), miosis (6/19), excessive sweating (4/19), erectile dysfunction (4/6 men), and palpitation (2/19). Among them, 12 patients had autonomic dysfunction as the only clinical manifestation of NIID, with a course of disease longer than 4–14 years in 5 cases.

Neuromuscular disease-dominant type: accounted for 7.6% (17/223) of the patients, and the clinical features of the 17 patients are shown in eTable 5, links.lww.com/NXG/A581. The mean onset age was 48.4 (18.6) years, younger than the other types (\( p < 0.001 \)). All patients were characterized by muscle weakness, affecting both distal and proximal limbs in 15, and the remaining 2 patients had only proximal or distal weakness. Sensory disturbance in distal limbs was present in 6 patients. Neuropathologic studies suggested demyelinating and axonal polyneuropathy.

**Comparison of Imaging and Genetic Features Among Different Clinical Types**

Comparing the imaging features of the 5 clinical types, 32.3% (21/65) of patients with episodic neurogenic event-dominant NIID showed focal cortical edema and enhancement or marked focal cortical atrophy. The mean grades of white matter lesions (1.75 ± 1.07) and brain atrophy (1.75 ± 1.12) in patients with neuromuscular disease-dominant NIID were much lower than the other 4 types (\( p = 0.045, p = 0.038 \), respectively, analysis of variance). There was no significant difference among the types for the involvement of the paravermis, middle cerebellar peduncle, brain stem, or corpus callosum (all \( p > 0.05, \chi^2 \) test, eTable 6, links.lww.com/NXG/A581).

There was no significant difference in the number of GGC repeats among the patients of the 5 types (\( p = 0.547, \chi^2 \) test), with a median of 113 (101–126) in cognitive impairment-dominant type, 114 (99–134) in the episodic neurogenic events-dominant type, 120 (105–133) in the movement disorder-dominant type, 113 (101–125) in the autonomic dysfunction-dominant type, and 120 (99–152) in the neuromuscular disease-dominant type (Figure 3C).

**Discussion**

Clinical manifestations of NIID are highly variable, and previous studies have divided NIID into “dementia-dominant,” “muscle weakness-dominant,” with/without “parkinsonism-dominant” NIID.\(^1,4\) Based on the observation of 223 patients with NIID, we provide an overall picture of NIID with respect to clinical, imaging, and genetic features. Then, according to the most prominent manifestations of these patients, we proposed a clinical classification including 5 NIID types: cognitive impairment-dominant type, episodic neurogenic event-dominant type, movement disorder-dominant type, neuromuscular disease-dominant type, and autonomic dysfunction-dominant type. Our study made expansion on the classification to describe the clinical features more accurately.

Cognitive impairment-dominant NIID is the most common type of NIID. In 2 previous studies, there were about 40% (8/19 and 16/40, respectively) of patients presented dementia as the main manifestation and were classified into dementia-dominant NIID.\(^1,4\) The proportion in the cohort examined in the present study was 34.1% (76/223). Despite that cognitive decline is the main symptom and patients will progress into dementia at a later stage, nearly 40% of patients do not reach the diagnostic criteria of dementia at the time of diagnosis; hence, we prefer to term this as cognitive impairment-dominant NIID.

The second most common type is episodic neurogenic event-dominant NIID, which accounts for one-third of patients. Previous studies have reported a series of patients with NIID characterized by various forms of episodic symptoms, including stroke-like episodes, encephalitic episodes, disturbance of consciousness, epileptic seizure, and recurrent headache.\(^10,11,16,36−39\) The incidence of episodic symptoms in patients with NIID can be as high as 50%. In addition, we found one-third of the patients who presented recurrent episodic symptoms had characteristic imaging features, that was focal cortical edema and restricted diffusion preferentially
in the temporal-parietal and occipital lobes, much different from other patients with NIID. These findings demonstrate that patients with prominent episodic neurogenic events were a distinctive type, which accounts for a large proportion of NIID.

PD is a common neurodegenerative disease characterized by bradykinesia, rest tremor, rigidity, and gait disturbance. Several studies have reported patients with NIID with parkinsonism as the primary manifestation, and it has been considered to constitute a separate type of NIID. In a familial parkinsonism cohort, 3/205 (1.5%) of parkinsonism-affected families were identified harboring the expanded GGC repeats in NOTCH2NLC. ET, characterized by postural tremor, is also associated with NIID, especially at the early stage, as previous studies have found that expansion in NOTCH2NLC accounts for 0.9%–5.6% in patients with ET. In our cohort, we found 16 (7.2%) patients with parkinsonism and 20 (9.0%) patients with ET as the most prominent manifestation. Particularly, there are 3 patients with hyperkinesia, and similar NIID cases with oromandibular and leg dystonia have been reported. These different forms of movement disorder may have a similar mechanical and/or structural basis and constitute the movement disorder-dominant NIID.

Recently, patients with NIID with early onset of bladder dysfunction and some requiring permanent cystostomy had been described. Some patients present with pan-autonomic dysfunction for many years without cognitive or motor deficits. In our study, there are 19 (8.5%) patients presenting prominent autonomic symptoms, with a median disease duration of 4.0 years, and one-fourth of these patients did not develop additional symptoms after 4–14 years of disease progression. Therefore, a type of autonomic dysfunction-dominant NIID is needed to describe this circumstance. One study has reported GGC expansion in NOTCH2NLC identified in 5 patients with MSA, all of whom initially presented with severe urinary dysfunction (4 with urinary retention and 1 with urinary incontinence); these patients also have prominent autonomic dysfunction.

An important clinical type proposed in previous studies is muscle weakness-dominant NIID. We know that muscle weakness can be caused by both CNS lesions and neuromuscular disease. This study clearly indicates that some NIID patients present muscle weakness due to prominent peripheral neuromuscular damage, and we classify them as “neuromuscular disease dominant type”. Recently, a series of studies have successively identified GGC expansions in NOTCH2NLC in patients with Charcot-Marie-Tooth (5.5%) and OPDM (3.3%–16.7%). Concurrent peripheral motor neuropathy and vacular myopathy in patients with NIID have also been reported. These findings suggest that peripheral neuropathy and myopathy are a noteworthy type of NIID, and they could be easily misdiagnosed in the early stage of the disease. In our cohort, 7.6% of the patients presented peripheral neuropathy and/or myopathy as predominant presentations. Compared with the 4 types mentioned above, patients in this type tend to have a younger age at onset and milder neuroimaging changes. In addition, the incidence of peripheral neuropathy and muscle damage may be underestimated in NIID: we found that up to 90% of patients with NIID without symptoms of peripheral neuropathy and myopathy had abnormal EMG results or muscle biopsies, as these damages are mild or subclinical.

In agreement with previous studies, high-intensity signals in the corticomedullary junction on DWI and white matter lesions (paravermis, MCPs, and corpus callosum) are characteristic imaging features of NIID. In the present study, the corticomedullary junction lesions are absent in 3.4% of patients with NIID, lower than Taiwanese (11.8%) and Japanese cohorts (18.2%). NIID is one of the important causes for patients with adult leukoencephalopathies. It explains 10% of adult patients with genetic leukoencephalopathy and exceeds cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy as the most frequent cause. In the group of patients with adult-onset nonvascular leukoencephalopathy, the proportion of NIID is as more as nearly 20%.

It has been shown that patients with NIID could develop focal cortical edema with restricted diffusion and gadolinium enhancement during encephalitis-like episodes. Our study points out that focal cortical lesions are not only seen in patients with encephalitis-like episodes but also in patients with other forms of episodic symptoms including stroke-like attacks, episodic headache, and episodic unconsciousness. The incidence of focal cortical lesions in patients with episodic neurogenic event-dominant NIID can be as high as 32.3% and is never seen in patients with other types. Therefore, focal cortical lesions can be used as a specific imaging marker for episodic neurogenic event-dominant NIID. Because these MRI features and clinical manifestations of patients with NIID during episodic events are very similar to mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) in acute attacks (headache, seizure, stroke-like episodes, altered mental status, and consciousness change), as well as the dynamic changes of focal cortical perfusion during and after the attack, there may be some common pathophysiologic mechanisms between MELAS and NIID-related episodic events, such as energy crisis or transient hypoperfusion.

Consistent with previous studies, we found that the number of GGC repeats in the 5′-UTR of the NOTCH2NLC gene in most NIID cases was between 60 and 200, and there was no significant difference between clinical types in the size of repeat expansions. Few studies have reported patients with extremely large GGC repeats (>300): 1 patient presenting with cognitive impairment, encephalitic episode, and muscle weakness carried a repeat number of 376, and 1 patient with OPDM carrying 2 long GGC expansions of 217 and 674, and the other patient with predominant muscle weakness carrying a repeat number of 517. In the present study, we identified 2 patients carrying >300 GGC repeats (363 in 1 patient with autonomic dysfunction-dominant
NIID and 525 in 1 patient with neuromuscular disease-dominant NIID). It can be established that patients carrying extremely large GGC repeats tend to present with the neuromuscular disease- and autonomic dysfunction-dominant NIID, as reported in the previous literature and our study.4,25

This observational study gives comprehensive clinical, imaging, and genetic features of NIID. The prominent presentation of patients with NIID is designated to 5 types; accordingly, we propose a protocol for clinical classification of NIID. In this study, all patients were diagnosed with a combination of clinical, pathologic, and genetic evidence, and only the probands were included, which avoided the influence of kinship on the distribution of clinical types. While complete pedigree-based studies including clinical and imaging evaluation and long-term follow-up of both symptomatic members and asymptomatic NOTCH2NLC variation carriers are needed in the future to further explore the phenotype-genotype correlation.

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**References**


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