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Original research

Clinical features of *NOTCH2NLC*-related neuronal intranuclear inclusion disease

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ABSTRACT

Background Abnormal expanded GGC repeats within the *NOTCH2NLC* gene has been confirmed as the genetic mechanism for most Asian patients with neuronal intranuclear inclusion disease (NIID). This cross-sectional observational study aimed to characterise the clinical features of *NOTCH2NLC*-related NIID in China.

Methods Patients with *NOTCH2NLC*-related NIID underwent an evaluation of clinical symptoms, a neuropsychological assessment, electrophysiological examination, MRI and skin biopsy.

Results In the 247 patients with *NOTCH2NLC*-related NIID, 149 cases were sporadic, while 98 had a positive family history. The most common manifestations were paroxysmal symptoms (66.8%), autonomic dysfunction (64.0%), movement disorders (50.2%), cognitive impairment (49.4%) and muscle weakness (30.8%). Based on the initial presentation and main symptomatology, NIID was divided into four subgroups: dementia dominant (n=94), movement disorder dominant (n=63), paroxysmal symptom dominant (n=61) and muscle weakness dominant (n=29). Clinical (42.7%) and subclinical (49.1%) peripheral neuropathies were common in all types. Typical diffusion-weighted imaging subcortical lace signs were more frequent in patients with dementia (93.9%) and paroxysmal symptoms types (94.9%) than in those with muscle weakness (50.0%) and movement disorders types (86.4%). GGC repeat sizes were negatively correlated with age of onset ($r=-0.196$, $p<0.05$), and in the muscle weakness-dominant type (median 155.00), the number of repeats was much higher than in the other three groups ($p<0.05$). In NIID pedigrees, significant genetic anticipation was observed ($p<0.05$) without repeat instability ($p=0.454$) during transmission.

Conclusions NIID is not rare; however, it is usually misdiagnosed as other diseases. Our results help to extend the known clinical spectrum of *NOTCH2NLC*-related NIID.

INTRODUCTION

Neuronal intranuclear inclusion disease (NIID) is a rare neurodegenerative disease characterised by

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Neuronal intranuclear inclusion disease (NIID) is a heterogeneous disease entity with variable clinical manifestations; however, there is little evidence available from large-sample studies, and the genotype-phenotype correlation remains unknown.

WHAT THIS STUDY ADDS

⇒ According to the initial and main symptomatology, we suggested dividing NIID into four subgroups: muscle weakness-dominant, dementia-dominant, movement disorder-dominant and paroxysmal symptom-dominant type.
⇒ The typical diffusion-weighted imaging subcortical lace sign was less common in muscle weakness and movement disorder types, making diagnosis difficult.
⇒ GGC repeat sizes were correlated with clinical phenotype and age at onset. Genetic anticipation without repeat instability was also observed in NIID pedigrees.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study systematically evaluated the clinical features of NIID with *NOTCH2NLC* GGC repeat expansions and extended the known clinical spectrum of NIID.

highly variable clinical manifestations and multiple systematic involvements.^{1,2} Clinical manifestations vary and include cognitive dysfunction,³ peripheral neuropathy,^{4,5} dyskinesia,^{6–8} paroxysmal symptoms^{9,10} and autonomic dysfunction.⁴ Widespread distribution of eosinophilic intranuclear inclusions has been observed in the central and peripheral nervous systems, and visceral organs.² Classical brain MRI revealed extensive leukoencephalopathy,

with a symmetrical diffusion-weighted imaging (DWI) high signal in the corticomedullary junction, as an NIID indicator.^{11 12}

NIID is sporadic or inherited in an autosomal dominant manner. In 2019, an abnormal repeat expansion of GGC (>65 repeats) within the 5' UTR of the *NOTCH2NLC* gene was identified by our group and two Japanese groups as the major genetic cause of NIID.^{6 13 14} Subsequently, *NOTCH2NLC* GGC repeat expansions have also been identified in patients with essential tremor (ET),^{7 15–17} Alzheimer's disease (AD),^{6 18} frontotemporal dementia,¹⁸ Parkinson's disease (PD),^{6 8} multiple system atrophy,¹⁹ amyotrophic lateral sclerosis,²⁰ Charcot-Marie-Tooth,⁵ leukoencephalopathy¹¹ and oculopharyngodistal myopathy,^{21 22} with typical pathological findings of eosinophilic intranuclear inclusions. More than 400 cases of NIID have been reported worldwide, most of which were in East Asia.^{23–25} Little evidence is available from large-sample studies. We investigated clinical features of 247 NIID-affected Han Chinese patients with *NOTCH2NLC* GGC repeat expansions in multiple centres within China.

MATERIALS AND METHODS

Study participants

A total of 247 patients with NIID, including 98 patients from 53 pedigrees and 149 sporadically affected individuals, were enrolled from January 2018 to December 2021. All individuals were evaluated by ≥ 2 neurologists. NIID was diagnosed based on clinical features and abnormal GGC repeats (>65) within *NOTCH2NLC*, with or without skin biopsy. Some familial NIID cases, unable to undergo genetic testing, were defined when at least one family member was genetically diagnosed, and the additional family member had high intensity in the corticomedullary junction on DWI and similar clinical phenotype, consistent with the genetically diagnosed NIID family member.

Clinical assessment

Clinical manifestation data were collected during clinical examination interviews. The Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA) and Frontal Assessment Battery (FAB) were used to screen for cognitive impairments. The Neuropsychiatric Inventory (NPI) was used to assess mental problems. Patients were recommended to undergo head MRI scan, electroencephalogram and electromyography (EMG).

Genetic testing

Repeat-primed PCR (RP-PCR) and GC-rich PCR (GC-PCR) assays were performed to confirm GGC expanded repeats within *NOTCH2NLC*.⁶

Skin biopsy and immunohistochemistry

Skin biopsy specimens were obtained 10 cm above the lateral malleolus. Immunohistochemical samples were fixed in 10% formalin, embedded in paraffin and sectioned at 6 mm thickness; this was followed by staining with H&E, anti-ubiquitin (3936; Cell Signaling) and anti-p62 (610833; BD Biosciences) antibodies.

Statistical analyses

Descriptive summaries are reported as medians (IQR) for continuous variables and percentages for categorical variables. For normally distributed data, statistics used t-tests or one-way analyses of variance. For non-normally distributed data, Mann-Whitney U or Kruskal-Wallis tests were performed. For

categorical variables, we used χ^2 test or Fisher's exact. Spearman's rank was used for correlation analysis. Differences with $p < 0.05$ were considered statistically significant. Statistical analyses were performed using SPSS V.22.0.

RESULTS

Genetic tests with/without biopsy

A total of 247 patients with NIID, including 98 from 53 affected families and 149 sporadically affected, were recruited. There were 115 male patients and 132 female patients, with a median onset age of 59 (IQR 50.00–63.00) years (range 17–78 years). Disease duration ranged from 0 to 49 years (median (IQR), 5 (2.00–10.00 years)) (table 1).

Patients were diagnosed with NIID by confirmation of abnormal GGC repeat expansion numbers of >65, as previously described (online supplemental figure S1A, B).⁶ Among them, 122 genetically diagnosed patients with NIID underwent skin biopsy, revealing p62 and ubiquitin-positive intranuclear inclusions (online supplemental figures S1C, E). However, four did not present with typical eosinophilic intranuclear inclusions in their dermal cells. This could be due to the lesion site misidentification, or the patient was early on in the disease, without pathological changes.

Clinical manifestation

Highly variable clinical manifestations are summarised in table 1.

Cognitive impairment

Cognitive dysfunction was usually the initial (23.1%) and most common (49.4%) symptom in patients with NIID (online supplemental table S1). Episodic memory loss was most common, while some patients struggled with personality changes or abnormal mental behaviour, which gradually progressed, resulting in a decline in their performance of daily activities.

Peripheral neuropathy and myopathy

Incidence rates of limb weakness and sensory disturbances were 22.0% and 14.8%, respectively (table 1). Most patients did not have obvious clinical symptoms and signs, but clinical (42.7%) and subclinical (49.1%) peripheral neuropathy was observed in 91.8% of NIID cases, evaluated by neurophysiological examination (table 2). A few patients had ptosis and bulbar paralysis with elevated creatine kinase, indicating muscle involvement.

Movement disorders

Movement disorders (50.2%) manifest in many ways, such as tremors, parkinsonism, ataxia and others. Notably, some patients only experienced tremors in the first decades, with an incidence rate of 18.6%. Parkinsonism (21.1%), manifesting as bradykinesia with either muscle rigidity or resting tremor, is frequently observed. Ataxia was observed in 15.4% of our patients with NIID (table 1).

Paroxysmal symptoms

Surprisingly, 32.8% of patients with NIID developed paroxysmal symptoms during initial stages of the disease (online supplemental table S1). At most, 66.8% of NIID-affected cases presented with at least one paroxysmal symptom, such as disturbance of consciousness (35.6%), encephalitic episodes (23.5%), stroke-like episodes (35.6%), generalised convulsions (5.7%) or chronic headache (10.9%) (table 1). Among them, disturbance of consciousness, encephalitic episodes and stroke-like episodes were highly suggestive of NIID.

Table 1 Clinical manifestation of patients with NIID

	Total (n=247)	Clinical phenotype			
		Dementia-dominant type (n=94)	Movement disorder-dominant type (n=63)	Muscle weakness-dominant type (n=29)	Paroxysmal symptom-dominant type (n=61)
Sex ratio (male/female)	115/132	38/56	27/36	23/6	27/34
Family history	98/247 (39.7%)	37/94 (39.4%)	27/63 (42.9%)	25/29 (86.2%)	9/61 (14.8%)
Age at onset, years, median (IQR)	59 (50.00–63.00)	60 (54.50–63.00)	59 (54.00–63.00)	35 (30.00–48.50)	60 (52.50–66.00)
Age at diagnosis, years, median (IQR)	65 (59.00–69.00)	65 (62.00–70.00)	65 (59.00–70.00)	51 (42.50–62.50)	64 (59.50–68.00)
Disease duration, years, median (IQR)	5 (2.00–10.00)	7 (3.00–10.25)	5 (3.00–10.00)	9 (3.00–18.00)	3 (0.00–6.50)
Cognitive impairment	122/247 (49.4%)	93/94 (98.9%)	27/63 (42.9%)	2/29 (6.9%)	0/61 (0.0%)
Abnormal behaviour	39/247 (15.8%)	31/94 (33.0%)	4/63 (6.3%)	4/29 (13.8%)	0/61 (0.0%)
Muscle weakness	76/247 (30.8%)	19/94 (20.2%)	25/63 (39.7%)	28/29 (96.6%)	4/61 (6.6%)
Bulbar paralysis	51/235 (21.7%)	11/86 (12.8%)	20/61 (32.8%)	16/29 (55.2%)	5/59 (8.8%)
Limb weakness	54/246 (22.0%)	12/93 (12.9%)	13/63 (20.6%)	28/29 (96.6%)	1/61 (1.6%)
Sensory disturbance	36/244 (14.8%)	9/93 (9.7%)	13/63 (20.6%)	7/27 (25.9%)	7/61 (11.5%)
Movement disorder	124/247 (50.2%)	41/94 (43.6%)	63/63 (100.0%)	20/29 (69.0%)	0/61 (0.0%)
Tremor	87/247 (35.2%)	19/94 (20.2%)	51/63 (81.0%)	17/29 (58.6%)	0/61 (0.0%)
Rigidity	38/247 (15.4%)	11/94 (11.7%)	26/63 (41.3%)	1/29 (3.4%)	0/61 (0.0%)
Bradykinesia	62/247 (25.1%)	22/94 (23.4%)	37/63 (58.7%)	3/29 (10.3%)	0/61 (0.0%)
Ataxia	38/247 (15.4%)	19/94 (20.2%)	15/63 (23.8%)	4/29 (13.9%)	0/61 (0.0%)
Paroxysmal symptom	165/247 (66.8%)	69/94 (73.4%)	28/63 (44.4%)	7/29 (24.1%)	61/61 (100.0%)
Disturbance of consciousness	88/247 (35.6%)	45/94 (47.9%)	14/63 (22.2%)	6/29 (20.7%)	23/61 (37.7%)
Encephalitic episodes	58/247 (23.5%)	29/94 (30.9%)	7/63 (11.1%)	2/29 (6.9%)	20/61 (32.8%)
Stroke-like episodes	88/247 (35.6%)	34/94 (36.2%)	16/63 (25.4%)	3/29 (10.3%)	35/61 (57.4%)
Generalised convulsions	14/247 (5.7%)	7/94 (7.4%)	1/63 (1.6%)	0/29 (0.0%)	6/61 (9.8%)
Chronic headache	27/247 (10.9%)	12/94 (12.8%)	4/63 (6.3%)	0/29 (0.0%)	11/61 (18.0%)
Autonomic dysfunction	158/247 (64.0%)	66/94 (70.2%)	38/63 (60.3%)	12/29 (41.4%)	42/61 (68.9%)
Bladder dysfunction	119/246 (48.4%)	54/93 (58.1%)	31/63 (49.2%)	9/29 (31.0%)	25/61 (41.0%)
Miosis	49/236 (20.8%)	23/88 (26.1%)	4/62 (6.5%)	3/25 (12.0%)	19/61 (31.1%)
Orthostatic hypotension	33/244 (13.5%)	14/91 (15.4%)	9/63 (14.3%)	1/29 (3.4%)	9/61 (14.8%)
Emesis	36/247 (14.6%)	10/94 (10.6%)	10/63 (15.9%)	2/29 (6.9%)	14/61 (23.0%)
Visual loss	50/247 (20.2%)	23/94 (24.5%)	19/63 (30.2%)	0/29 (0.0%)	8/61 (13.1%)

NIID, neuronal intranuclear inclusion disease.

Autonomic dysfunction

Sixty-four per cent of patients with NIID suffered autonomic dysfunction, including bladder dysfunction (48.4%), miosis (20.8%), orthostatic hypotension (13.5%) and emesis (14.6%) (table 1). Unexplained bladder dysfunction, including increased urinary frequency, urgency, incontinence and retention, were the most common symptoms. Miosis, with an incidence rate of 20.8% (table 1), should be considered in NIID diagnosis. Notably, 11.7% of NIID-affected individuals initially presented with autonomic dysfunction (online supplemental table S1).

Other symptoms

Visual loss occurred in 20.2% of patients (table 1).

Clinical phenotype

Initial symptoms of NIID vary and include paroxysmal symptoms (32.8%), cognitive impairment (23.1%), movement disorders (22.3%), autonomic dysfunction (11.7%) and muscle weakness (10.1%) (online supplemental table S1). Evolution of main symptoms of NIID were shown in figure 1. The frequency of autonomic dysfunction, paroxysmal symptoms and cognitive impairment progressed rapidly within the first 10 years after disease onset, while the frequency of movement disorders remained stable after the third year of disease (figure 1). The majority of affected individuals presented with no more than three of the above symptoms, indicating high

clinical heterogeneity. Patients with paroxysmal symptoms or autonomic dysfunction initially, usually develop the other three symptoms later in their disease progression. Since a few individuals presented with pure paroxysmal symptoms, we suggested dividing NIID into four subgroups according to the patients' initial and main clinical manifestations: dementia-dominant, movement disorder-dominant, muscle weakness-dominant and paroxysmal symptom-dominant types.

Dementia-dominant type

The dementia-dominant type was the most common (94/247), and the majority of cases were sporadic (60.6%). Main clinical manifestations are cognitive impairment or abnormal behaviour. Age of onset was between 17 and 74 years, with a median age of 60 (IQR 54.50–63.00); disease duration varied from 0 to 44 years (median (IQR), 7 (3.00–10.25)) (table 1). As cognitive decline progresses, autonomic impairments and paroxysmal symptoms are frequently observed. Notably, a few affected individuals started with autonomic or paroxysmal symptomatology initially, and their clinical symptoms remained stable for several years before cognitive decline appeared. More than 90% of affected individuals showed symmetrical, high DWI signals in the corticomedullary junction and severe white matter hyperintensities. Peripheral neuropathy was found in 86.8% of patients (table 2).

Table 2 Clinical examination of patients with NIID

	Total	Clinical phenotype			
		Dementia-dominant type	Movement disorder-dominant type	Muscle weakness-dominant type	Paroxysmal symptom-dominant type
Brain MRI					
DWI U-fibre high signal	190/212 (89.6%)	77/82 (93.9%)	51/59 (86.4%)	6/12 (50.0%)	56/59 (94.9%)
Severe leukoencephalopathy	177/213 (83.1%)	75/82 (91.5%)	46/57 (80.7%)	6/15 (40.0%)	50/59 (84.7%)
Peripheral neurophysiological study	101/110 (91.8%)	33/38 (86.8%)	25/28 (89.3%)	18/18 (100.0%)	25/26 (96.2%)
Sensorimotor neuropathy	84/110 (76.4%)	31/38 (81.6%)	21/28 (75.0%)	15/18 (83.3%)	17/26 (65.4%)
Pure motor neuropathy	16/110 (14.5%)	2/38 (5.3%)	4/28 (14.3%)	3/18 (16.7%)	7/26 (26.9%)
Pure sensory neuropathy	1/110 (0.9%)	0/38 (0.0%)	0/28 (0.0%)	0/18 (0.0%)	1/26 (3.8%)
Normal	9/110 (8.2%)	5/38 (13.2%)	3/28 (10.7%)	0/18 (0.0%)	1/26 (3.8%)
Nerve conduction study	100/110 (90.9%)	33/38 (86.8%)	25/28 (89.3%)	17/18 (94.4%)	25/26 (96.2%)
Motor					
MCV slowing	98/110 (89.1%)	33/38 (86.8%)	24/28 (85.7%)	17/18 (94.4%)	24/26 (92.3%)
CMAP reduction	56/110 (50.9%)	21/38 (55.3%)	11/28 (39.3%)	14/18 (77.8%)	10/26 (38.5%)
Sensory					
SCV slowing	83/110 (75.5%)	31/38 (81.6%)	20/28 (71.4%)	14/18 (77.8%)	18/26 (69.2%)
SNAP reduction	51/110 (45.9%)	16/38 (42.1%)	12/28 (42.9%)	15/18 (83.3%)	8/26 (30.8%)
Needle EMG study					
Neurogenic damage	48/69 (69.6%)	12/20 (60.0%)	13/19 (68.4%)	17/17 (100.0%)	6/13 (46.2%)
Myogenic damage	1/69 (1.4%)	0/20 (0.0%)	1/19 (5.3%)	0/17 (0.0%)	0/13 (0.0%)
Normal	20/69 (29.0%)	8/20 (40.0%)	5/19 (26.3%)	0/17 (0.0%)	7/13 (53.8%)
Positive skin biopsy	118/122 (96.7%)	42/44 (95.5%)	35/36 (97.2%)	10/10 (100%)	31/32 (96.7%)
GGC repeat sizes, median (IQR)	120 (103.00–143.00)	118.5 (103.00–135.00)	120.5 (99.50–142.50)	155 (108.00–253.00)	123 (105.75–141.00)

CMAP, compound muscle action potential; DWI, diffusion-weighted imaging; EMG, electromyography; MCV, motor nerve conduction velocity; NIID, neuronal intranuclear inclusion disease; SCV, sensory nerve conduction velocity; SNAP, sensory nerve action potential.

Movement disorder-dominant type

Patients with movement disorder type presented with parkinsonism (58.7%), isolated tremor (33.3%) and ataxia (23.8%) as initial and main clinical manifestations. However, a minority of patients presented with autonomic dysfunction (4.8%) or paroxysmal symptoms (7.9%), followed by movement disorders. Median age of onset was 59 (IQR 54.00–63.00) years, with a median disease duration of 5 (IQR 3.00–10.00) years. Cognitive impairment developed with disease progression in 42.9% of these patients (table 1). The frequency of classical DWI linear

high signals was approximately 86%, lower than the dementia type. Peripheral neuropathy was observed in 89.3% of patients (table 2).

Muscle weakness-dominant type

Muscle weakness-dominant type is characterised when muscle weakness is the main and initial clinical manifestation, with minimal cognitive deterioration over many years. Most patients had family history of muscle weakness (25/29, 86.2%). Median onset age (35

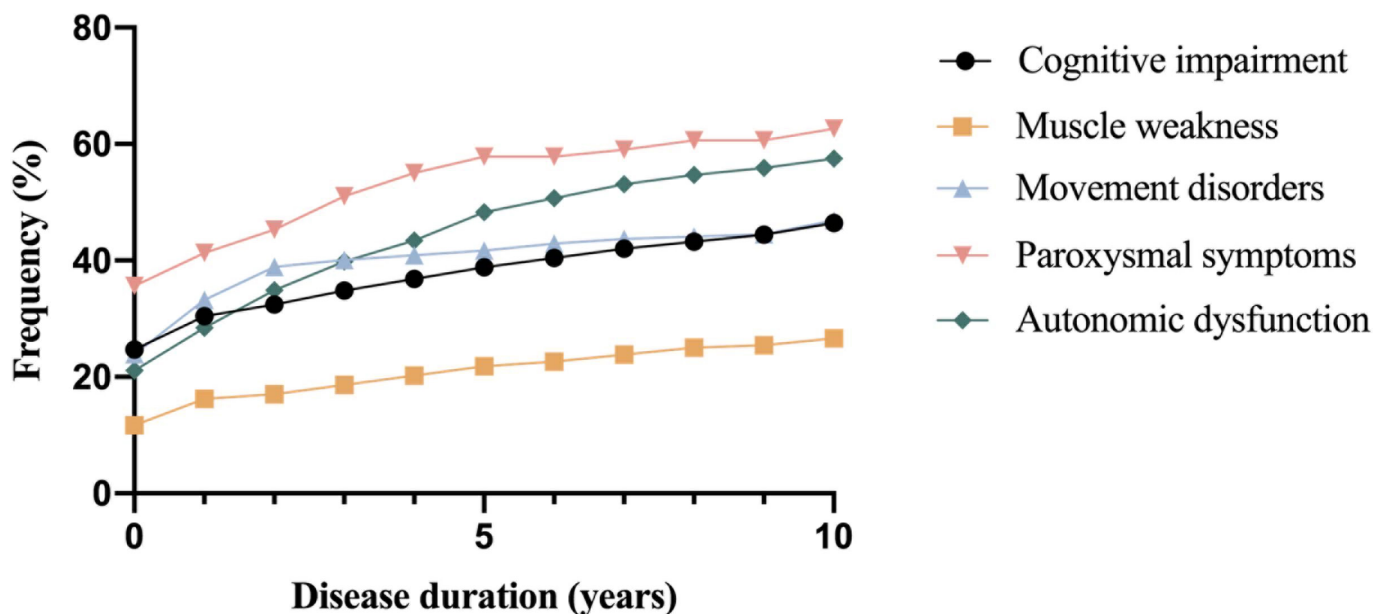


Figure 1 Frequency of main clinical symptoms during disease progression.

(IQR 30.00–48.50) years) was the earliest among the four phenotypes, and the disease duration (median (IQR), 9 (3.00–18.00) years) was relatively longer due to slower progression (table 1). Muscle weakness usually starts with the distal lower limbs and moves up to the throat and facial muscles. The severity and areas of the muscle weakness varied greatly among individuals. Most patients displayed more distal than proximal muscle weakness, whereas a few experienced muscle weakness predominantly in proximal limbs or in a diffuse pattern. Symptoms of the lower limbs were usually more severe than those of the upper limbs. Twenty-three out of 29 (79.3%) patients had difficulty walking, 10 out of 29 (34.5%) required walking assistance and 6 out of 29 (20.7%) were wheelchair-dependent. Reduced tendon reflexes (92.6%) and muscle atrophy (69.0%) were also frequently observed. Bulbar paralysis (55.2%) usually occurs in late stages. Additionally, only a small number of patients had ptosis or ophthalmoplegia. Sensory symptoms were milder than motor symptoms. Only 25.9% of muscle weakness type patients complained of mild sensory disturbances. For pathological involvements, peripheral neuropathy, with and without muscle involvement, contributes to muscle weakness. Tremor (58.6%), autonomic dysfunction (41.4%) and paroxysmal symptoms (24.1%) were frequently observed in affected members, whereas cognitive impairment (6.9%) was rare (table 1). Only 50.0% of this subgroup showed the typical NIID neurological findings of symmetrical DWI high-intensity signals at the cortico-medullary junction. Peripheral neuropathy was confirmed in every patient that presented with the muscle weakness-dominant type, who underwent EMG (table 2). Generally, both motor and sensory nerves were involved in the muscle weakness type. Most patients (83.3%) displayed moderate-to-severe mixed sensorimotor neuropathy, while 16.7% were reported to have pure motor nerve involvement (table 2).

Paroxysmal symptom-dominant type

In the paroxysmal symptom type, patients presented with disturbance of consciousness, stroke-like episodes, encephalitic

episodes, generalised convulsions or chronic headaches, and usually experienced autonomic dysfunction. The majority of cases were sporadic (52/61, 85.2%). Median onset age was 60 (IQR 52.50–66.00) years, and disease duration (median (IQR), 3 (0.00–6.50) years) was the shortest among all types. No dementia or movement disorder was observed; patients with paroxysmal symptoms displayed a much milder phenotype compared with other groups (table 1). However, disease duration of the paroxysmal symptom type was so short that the possibility of developing other severe syndromes in the future could not be ruled out. Up to 94.9% showed classical DWI linear high signals, and 84.7% had severe white matter hyperintensity. Almost 96.2% of patients had peripheral neuropathy, but only 10% complained of muscle weakness or sensory disturbances (table 2).

Neuropsychological assessment

Patients with NIID usually present with cognitive impairments; thus, more than 100 patients with NIID received comprehensive cognitive function evaluations at a single centre (table 3). General cognitive impairment was observed in 42.9% and 85.8% of patients with NIID using the MMSE and MoCA tests, respectively. Episodic memory was seriously impaired in all subgroups, followed by visuospatial/executive function, language and abstraction, according to the MoCA. Naming and orientation were better preserved in comparison. The muscle weakness type presented with milder cognitive impairments, and language domain as well as episodic memory, remained nearly normal. Median FAB score declined in patients with NIID (12.25 (IQR 9.00–15.00)) and was significantly reduced in patients with dementia (9.00 (IQR 7.00–12.00), $p < 0.05$), indicating impaired attentional/executive cognitive domains. Although no patients in the paroxysmal symptom group had a lower MMSE score, as many as 83.3% of them showed reduced scores on the MoCA assessment, suggesting possible conversion to the dementia-dominant type in future. Overall, more patients had lower scores

Table 3 Cognitive evaluation of patients with NIID

	Total	Clinical phenotype			
		Dementia-dominant type	Movement disorder-dominant type	Muscle weakness-dominant type	Paroxysmal symptom-dominant type
General cognition					
MMSE score, median (IQR)	24.00 (18.00–27.00)	16.50 (13.75–22.00)	25.00 (20.00–27.00)	28.00 (26.00–29.00)	27.00 (25.00–28.00)
MMSE (<education-matched average)	62/159 (42.9%)	46/58 (79.3%)	14/45 (31.1%)	2/19 (10.5%)	0/37 (0.0%)
MoCA score, median (IQR)	17.00 (12.00–22.00)	11.00 (8.75–17.00)	17.00 (12.75–20.00)	24.00 (21.00–26.00)	20.00 (15.50–24.50)
MoCA (<education-matched average)	91/106 (85.8%)	35/37 (94.6%)	29/32 (90.6%)	7/13 (53.8%)	20/24 (83.3%)
Detailed MoCA item/scores					
Visuospatial/ executive/5, median (IQR)	2.00 (1.00–3.00)	1.00 (0.00–2.00)	2.00 (1.00–3.00)	3.00 (3.00–3.50)	2.50 (1.00–3.00)
Naming/3, median (IQR)	3.00 (2.00–3.00)	2.00 (0.25–3.00)	3.00 (2.00–3.00)	3.00 (2.00–3.00)	2.00 (2.00–3.00)
Attention/6, median (IQR)	4.00 (3.00–6.00)	3.00 (2.00–4.00)	4.00 (2.00–6.00)	6.00 (4.50–6.00)	5.00 (3.75–5.25)
Language/3, median (IQR)	1.00 (1.00–2.00)	1.00 (0.00–2.00)	2.00 (1.00–2.00)	3.00 (2.00–3.00)	1.00 (0.00–2.00)
Abstraction/2, median (IQR)	1.00 (0.00–2.00)	0.00 (0.00–1.75)	1.00 (1.00–2.00)	1.00 (1.00–2.00)	1.00 (0.00–2.00)
Memory/5, median (IQR)	0.00 (0.00–2.00)	0.00 (0.00–1.00)	1.00 (0.00–2.00)	3.00 (1.50–4.00)	0.50 (0.00–2.25)
Orientation/6, median (IQR)	5.00 (4.00–6.00)	4.00 (2.00–5.00)	5.00 (4.00–6.00)	6.00 (6.00–6.00)	6.00 (4.75–6.00)
Frontal lobe function					
FAB score, median (IQR)	12.25 (9.00–15.00)	9.00 (7.00–12.00)	12.00 (10.00–15.00)	15.00 (12.25–16.00)	12.50 (10.00–15.00)
FAB (<age and education-matched average)	45/101 (44.6%)	23/35 (65.7%)	11/32 (34.4%)	3/12 (25.0%)	8/22 (36.4%)

MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NIID, neuronal intranuclear inclusion disease.

Table 4 Prevalence of neuropsychiatric symptoms in patients with NIID

NPI symptoms	Total	Clinical phenotype			
		Dementia-dominant type	Movement disorder-dominant type	Muscle weakness-dominant type	Paroxysmal symptom-dominant type
NPI score, median (IQR)	3.00 (0.00–11.00)	4.00 (1.00–20.00)	5.00 (1.00–13.00)	0.00 (0.00–2.00)	4.00 (0.00–7.00)
NPI (>=1)	86/121 (71.1%)	34/45 (75.6%)	29/37 (78.4%)	5/13 (38.5%)	18/26 (69.2%)
Delusion	19/121 (15.7%)	9/45 (20.0%)	4/37 (10.8%)	1/13 (7.7%)	5/26 (19.2%)
Hallucinations	20/121 (16.5%)	11/45 (24.4%)	3/37 (8.1%)	1/13 (7.7%)	5/26 (19.2%)
Agitation/aggression	21/121 (17.4%)	10/45 (22.2%)	6/37 (16.2%)	1/13 (7.7%)	4/26 (15.4%)
Depression/dysphoria	36/121 (29.8%)	18/45 (40.0%)	12/37 (32.4%)	0/13 (0.0%)	6/26 (23.1%)
Anxiety	45/121 (37.2%)	15/45 (33.3%)	18/37 (48.6%)	2/13 (15.4%)	10/26 (38.5%)
Euphoria	16/121 (13.2%)	7/45 (15.6%)	5/37 (13.5%)	0/13 (0.0%)	4/26 (15.4%)
Apathy	33/121 (27.3%)	18/45 (40.0%)	10/37 (27.0%)	1/13 (7.7%)	4/26 (15.4%)
Disinhibition	22/121 (18.2%)	11/45 (24.4%)	5/37 (13.5%)	0/13 (0.0%)	6/26 (23.1%)
Irritability/liability	47/121 (38.8%)	18/45 (40.0%)	15/37 (40.5%)	3/13 (23.1%)	11/26 (42.3%)
Aberrant motor behaviour	18/121 (14.9%)	10/45 (22.2%)	7/37 (18.9%)	0/13 (0.0%)	1/26 (3.8%)
Nighttime disturbance	24/121 (19.8%)	12/45 (26.7%)	10/37 (27.0%)	0/13 (0.0%)	2/26 (7.7%)
Eating disturbance	24/121 (19.8%)	11/45 (24.4%)	7/37 (18.9%)	3/13 (23.1%)	3/26 (11.5%)

NIID, neuronal intranuclear inclusion disease; NPI, Neuropsychiatric Inventory.

on the FAB and MoCA than on the MMSE, indicating the FAB and MoCA were more sensitive for patients with NIID.

NPI assessment revealed that 86 out of 121 patients (71.1%) experienced neuropsychological symptoms, with a median score of 3.00 (IQR 0.00–11.00). Behaviour in NIID varied widely; irritability (38.8%), anxiety (37.2%), depression (29.8%) and apathy (27.3%) (table 4) were present. The muscle weakness-dominant subgroup had fewer and milder psychiatric symptoms, while patients with the dementia-dominant type showed more statistically severe psychiatric symptoms ($p < 0.05$).

MRI images

In DWI, a symmetrical high signal in the corticomedullary junction is called the subcortical lace sign (figure 2A–B). In this study, 190 out of 212 patients (89.6%) presented with the classical subcortical lace sign (table 2). High intensity was also observed in the corpus callosum (46.7%) (figure 2A). One patient with NIID showed diffuse DWI high signal in the white matter of subcortical region (figure 2C).

Severe leukoencephalopathy (Fazekas score=3) from the subcortical to the periventricular region was seen on T2 and FLAIR imaging in 177 out of 213 patients with NIID (83.1%) (figure 2D–E). Some patients displayed specific high signals in the paravermal area (88.7%), corpus callosum (61.0%) and in the middle cerebellar peduncle (35.2%) (MCP) on FLAIR images (figure 2E,F). A few patients revealed focal cortical lesions on T2 and FLAIR images, with obvious linear enhancement during encephalitic episodes. This occurred even before the DWI subcortical lace sign, and leukoencephalopathy emerged (figure 2H–J). Cerebral atrophy and lateral ventricle enlargement were also commonly observed in late stages (figure 2K–M).

Electrophysiological study

Abnormal findings of motor or sensory nerve conduction were found in 90.9% cases (100/110) (table 2). Motor and sensory nerve conduction velocity significantly decreased, and relatively mild compound muscle action potential (CMAP) and sensory nerve action potential (SNAP) reductions were observed in the four extremities of patients with NIID. EMG showed a prolonged duration and increased amplitude of muscle motor unit potential in the upper and lower limbs, suggesting

neurogenic damage. In the muscle weakness-dominant type, patients showed more frequent CMAP and SNAP reductions than in other subtypes ($p < 0.05$) (table 2), and all of them presented with neurogenic damage on needle EMG examination (table 2 and online supplemental table S2). Reductions in both amplitude and velocity of nerve conduction were severe (online supplemental table S2). Generally, the majority of the muscle weakness-dominant subtype displayed moderate-to-severe mixed demyelinating and axonal sensorimotor neuropathy, while other types usually showed demyelinating sensorimotor neuropathy with or without mild axonal damage (table 2 and online supplemental table S2).

A significantly prolonged latency of P100 by visual evoked potential (VEP) was surprisingly observed in six out of seven patients, regardless of whether they complained of abnormal vision. Therefore, the visual pathway may also be impaired during the early stages of NIID.

Genotype-phenotype correlation

The number of GGC repeats ranged from 66 to 517 (median (IQR), 120 (103.00–143.00) repeats). The GGC repeat sizes were significantly higher in the muscle weakness type (median (IQR), 155 (108.00–253.00) repeats) than in the other three subgroups (figure 3A) ($p < 0.05$). Moreover, correlation analysis validated that GGC repeat sizes were positively correlated with muscle weakness ($r = 0.142$, $p < 0.05$) and negatively correlated with paroxysmal symptoms ($r = -0.160$, $p < 0.05$) (online supplemental table S3). A comparison of GGC repeat sizes between patients with different initial symptoms was performed, but there were no statistically significant differences ($p = 0.226$) (online supplemental table S4). GGC repeat number was negatively correlated with age at disease onset ($r = -0.196$, $p < 0.05$) (figure 3B, online supplemental table S5). The larger the repeat size, the younger the onset age. The MMSE, MoCA, FAB and NPI scales were used to assess neuropsychological symptoms, and there was no correlation between repeat size and any scale (online supplemental table S5). Number of GGC repeats was related to age at disease onset and clinical phenotypes but was not associated with disease severity or initial symptomatology.

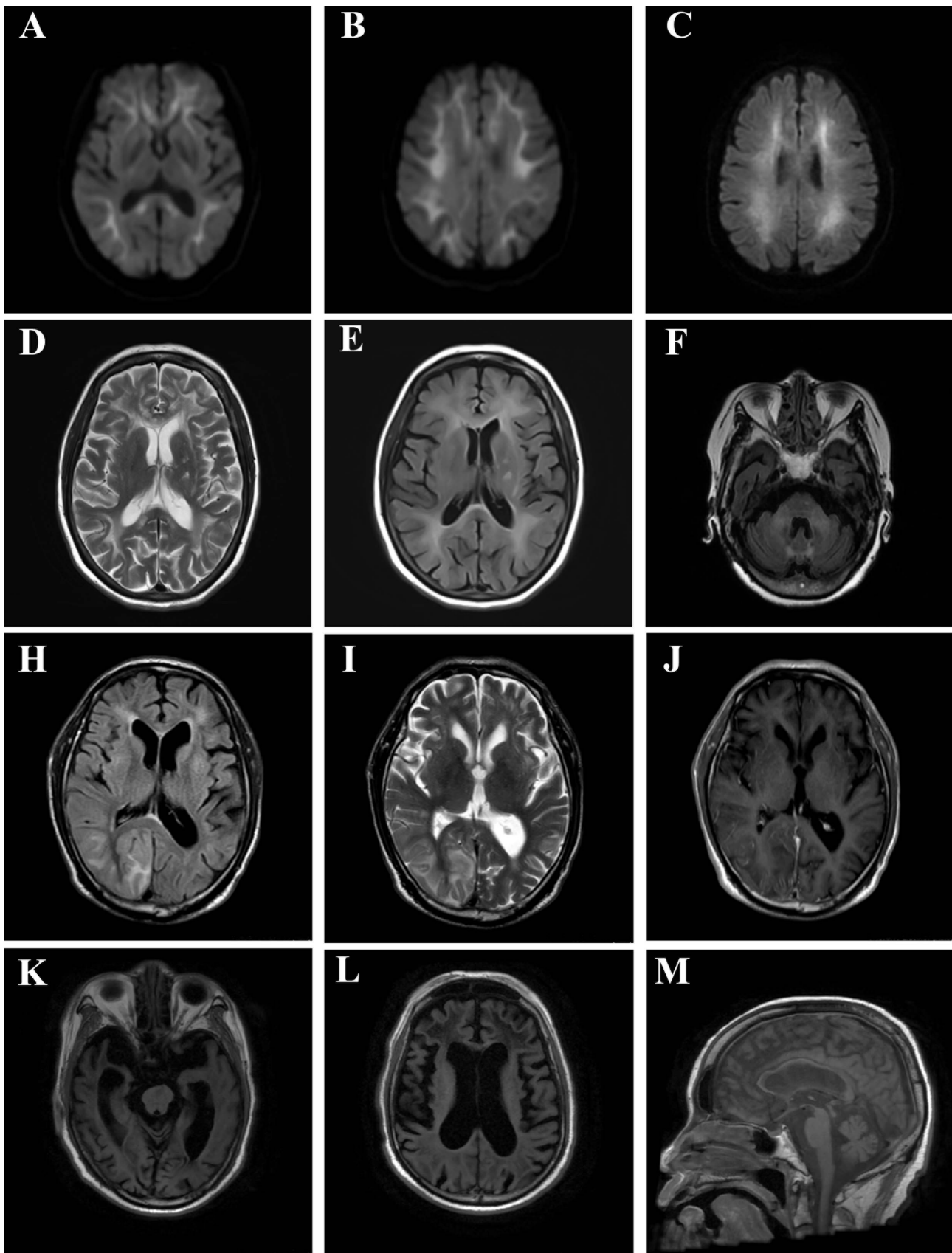


Figure 2 Head MRI finding of neuronal intranuclear inclusion disease (NIID). (A, B) Diffusion-weighted imaging (DWI) images revealed subcortical lacune sign in the corticomedullary junction (A, B) and high intensity in the corpus callosum (A). (C) Diffuse DWI high signal in white matter was observed in one NIID case. (D, E) Severe leukoencephalopathy using T2 (D) and FLAIR (E) imaging. (F) High signal in the middle cerebellar peduncle (MCP sign) and in the paravermal area on FLAIR images. (H–J) Focal cortical lesions on FLAIR (H) and T2 (I) images with obvious linear enhancement (J). (K–M) Presentative T1 images presented with cerebral atrophy and lateral ventricle enlargement.

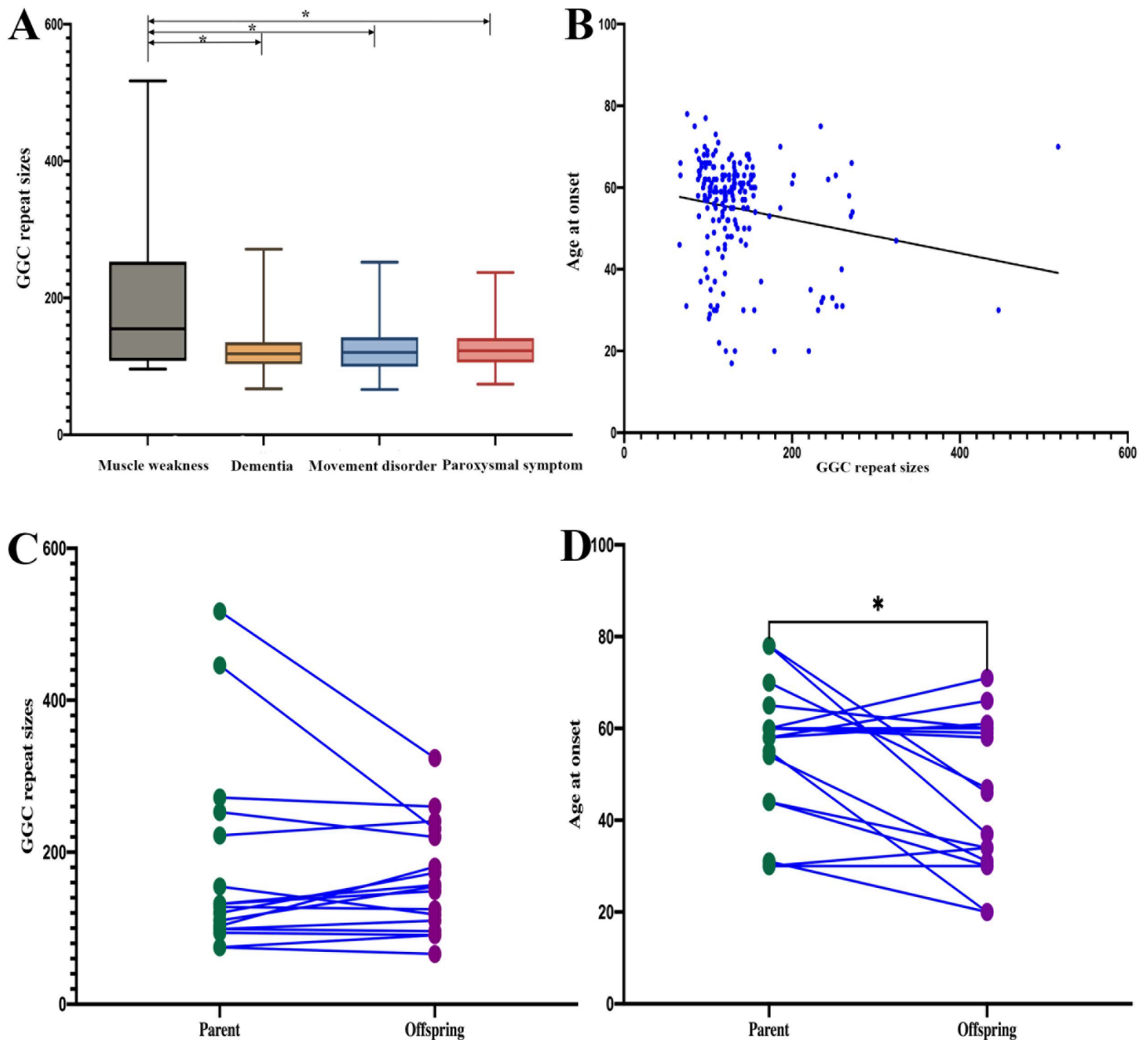


Figure 3 Genotype-phenotype correlation. (A) Difference in GGC repeat sizes in different neuronal intranuclear inclusion disease (NIID) subgroups. (B) Scatter plot and linear regression representation of the relationships between GGC repeat sizes and age at onset in patients with NIID. GGC repeat sizes showed a significantly negative relationship with onset age ($r = -0.196, p < 0.05$). (C) Paired comparison of GGC repeat sizes between parents and offspring showed GGC repeat stability. Lines between spots represent corresponding parent-offspring pairs. (D) Paired comparison of onset ages between parents and offspring revealed genetic anticipation. Lines between spots represent corresponding parent-offspring pairs. $p < 0.05$ were considered statistically significant.

Repeat stability/genetic anticipation

We compared GGC repeat sizes between parents and offspring using a paired sample *t*-test. No significant differences in GGC repeat sizes were observed between the parent and offspring groups ($p = 0.454$), indicating repeat numbers were stable in NIID (figure 3C). There were 20 affected parent-offspring pairs whose onset ages were known. Median age at onset in the affected offspring group was 52.5 (IQR 31.75–60.00) years, significantly lower than the parents (median (IQR), 60 (46.50–65.00) years) ($p < 0.05$) (figure 3D). Median anticipation was 5 (IQR 0.00–20.75) years (–11 to 41 years), suggesting that genetic anticipation exists in these pedigrees.

DISCUSSION

NIID-related disorders (NIIDRD) are a group of neurodegenerative diseases, caused by abnormal GGC repeat expansions. Clinical manifestations are highly variable.² Paroxysmal symptoms, autonomic dysfunction, movement disorders and cognitive impairment were observed in almost half of patients. Stroke-like and encephalitic episodes, disturbances of consciousness, tremor, bradykinesia, limb weakness, bulbar paralysis and miosis were also frequently observed in more than one-fifth of patients with NIID. Additionally, we documented visual loss and chronic headache, rarely mentioned in previous NIID studies.^{26–28}

Based on the initial and main manifestations, we divided NIID into three subgroups: muscle weakness-dominant,

dementia-dominant and parkinsonism-dominant subtypes.⁶ Subsequently, we found essential tremor with GGC repeat expansions in the *NOTCH2NLC* gene may be a subphenotype of NIID, due to eosinophilic intranuclear inclusion pathology.⁷ Therefore, we described the movement disorder-dominant type for patients presenting with parkinsonism, tremor or ataxia initially. We previously identified a new phenotype with only paroxysmal symptoms in sporadic NIID.⁶ Taken together, we suggest dividing NIID into four subtypes: dementia-dominant, movement disorder-dominant, muscle weakness-dominant and paroxysmal symptom-dominant. The clinical manifestations of each subgroup overlap. Some patients with the paroxysmal symptom-dominant type could later convert to other subgroups with development of new symptoms.

Cognitive impairment is common in NIID²⁹; however, few studies have focused on characteristic features of cognitive and/or behavioural changes in NIID. In this study, variable domains including episodic memory, visuospatial/executive function, abstraction and language were impaired, while naming and orientation were relatively preserved. Episodic memory loss is the initial complaint for most NIID patients with cognitive impairments, making it difficult to differentiate from AD. Visuospatial/executive function, abstraction and language impairment can help distinguish NIID from AD. MoCA and FAB assessments showed good sensitivity for patients with NIID, especially for those with muscle weakness and paroxysmal symptoms, who scarcely presented with cognitive impairment. We believe that both white matter and cortical damage contribute to dementia in patients with NIID. Additionally, behavioural assessments demonstrated widespread changes, with more irritability, anxiety, depression and apathy.

The identical DWI subcortical high intensity was thought to be a specific sign for NIID^{30 31}; however, it was less common in the muscle weakness and movement disorder types, making it difficult to be associated with NIID. Furthermore, it was also reported in other CGG repeat expansion diseases, including fragile X-associated tremor/ataxia syndrome (FXTAS) and oculopharyngeal myopathy with leukoencephalopathy.^{14 32 33} In addition, we reported diffuse DWI high signal in the white matter of patients with NIID.³⁴ High DWI signals in the corpus callosum, severe leukoencephalopathy involving the corpus callosum, middle cerebellar peduncle, paravermal area, cortical oedema with gadolinium enhancement, brain atrophy and lateral ventricle enlargement were also observed in patients with NIID, as previously reported.^{12 35} Among them, high intensity in the paravermal area has rarely been reported in other patients with leukoencephalopathies, indicating it could also be a useful indicator for NIID.

Peripheral nerve involvement is common.² They usually showed demyelinating sensorimotor neuropathy with or without mild axonal damage. Subclinical peripheral neuropathy was observed in half of our patients with NIID. Recently, ocular involvement, including retinal dystrophy, rod-cone dysfunction and corneal nerve changes, has been reported in NIID.^{36 37} We further reported that VEP examination revealed a significantly prolonged latency of P100 in many patients who never complained of abnormal vision, implicating development of visual pathway impairments in early stages, similar to subclinical peripheral neuropathy.

Several diseases also carry abnormal repeat expansions of GGC/CGG, including fragile X syndrome and FXTAS.³⁸ When the number of CGG repeats is >200, the *FMR1* gene is highly methylated; silencing the expression of *FMR1* mRNA leads to fragile X syndrome. When the number of CGG repeats is

between 50 and 200, excessive mRNA is produced, resulting in RNA toxicity in FXTAS. Therefore, different CGG repeat sizes can lead to different clinical phenotypes.³⁹ Interestingly, we found that the number of GGC repeat expansions in the muscle weakness group was significantly higher than the other groups, suggesting the number of GGC repeats may be an important mechanism for clinical phenotypes. GGC repeat sizes were also related to onset age, rather than disease severity or initial symptomatology. In repeat expansion diseases, genetic anticipation is common due to unstable nucleotides (microsatellites).⁴⁰ Genetic anticipation was observed in NIID pedigrees, but GGC expanded repeats were stable over generations, suggesting other mechanisms account for anticipation.

Limitations

This study has limitations in its cross-sectional design. The number of GGC repeats may be correlated with the clinical phenotype; however, it is not the only factor contributing to variety in NIID presentation. It is important to further explore the mechanism of genotype-phenotype correlations in future.

CONCLUSION

In summary, we reported a study of 247 patients with NIID with *NOTCH2NLC* GGC repeat expansions from multiple centres in China. We systematically characterised the clinical symptoms, phenotypes, MRI features, electrophysiological study findings, histopathological features and genotype-phenotype correlations of adult-onset NIID.

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