Neuronal Intranuclear Inclusion Disease in Patients with Adult-onset Nonvascular Leukoencephalopathy

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Aim

The present study aims to explore the prevalence, clinical presentations, and brain MRI features of neuronal intranuclear inclusion disease (NIID) presenting with adult-onset nonvascular leukoencephalopathy , and examine the diagnostic accuracy of the imaging biomarkers.

Material and Method

1. 32 of 161 unrelated patients with genetically undiagnosed nonvascular leukoencephalopathy were diagnosed with NIID after analyzed the *NOTCH2NLC* GGC repeat expansions utilizing fragment analysis, repeat-primed PCR, southern blot analysis, and/or nanopore sequencing with Cas9-related enrichment.
2. Two additional affected family members of one patient were included. Skin biopsy were performed in five patients, revealing typical features of NIID. All the medical records and neuroimages were reviewed, and the images of NIID were compared with the rest of the patients.

Results

1. Among the 34 NIID patients (9 men, 25 women), the median age at onset was 61 years (range, 41-78 years), and the onset manifestations were cognitive decline (44.1%; 15/34), acute encephalitis-like episodes (32.4%; 11/34), limb weakness (11.8%, 4/34), and parkinsonism (11.8%; 4/34).
2. The two most common overall symptoms were cognitive decline (64.7%) and acute encephalitis-like episodes (55.9%). Either bladder dysfunction or visual disturbance developed in two-thirds of the patients.
3. To differentiate between NIID and other undetermined leukoencephalopathies, corticomedullary junction (CMJ) lesion on diffusion weighted imaging (DWI) was the best imaging diagnostic indicator (sensitivity 88.2%, specificity 98.4%), followed by white matter hyperintense lesions (WMH) either in paravermis or middle cerebellar peduncles (MCP) (sensitivity 76.5%, specificity 85.3%).
4. 10 patients received MRI within 5 days of the onset of acute encephalitis-like episodes. Five demonstrated cortical DWI hyperintensity, while two showed edematous change in the brain parenchyma.

Conclusions

1. In our cohort, NIID explained 19.9% (32/161) of adult-onset genetically undiagnosed nonvascular leukoencephalopathies.
2. CMJ hyperintensities on DWI, WMH in paravermis or MCP on FLAIR, bladder dysfunction, and visual disturbance are important clues in diagnosing NIID.

Abbreviations:
CMJ: corticomedullary junction; DWI: Diffusion weighted imaging; FLAIR: fluid attenuated inversion recovery images; MCP: middle cerebellar peduncles; WMH: white matter hyperintense lesions.

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Table 1. Demographic and Clinical Features

Variables	N (%) or Median (range)
NOTCH2NLC GGC repeat size	
normal allele	16 (4 - 56)
expanded allele	115.5 (73 - 323)
First manifestation, onset age (y)	
Cognitive decline	15 (44.1%), 61 (54 - 72)
Acute encephalitis-like episodes	11 (32.4%), 64 (53 - 78)
Weakness with/without sensory deficit	4 (11.8%), 44 (41 - 78)
Parkinsonism	4 (11.8%), 57 (41 - 64)
Overall manifestations	
Cognitive decline	22 (64.7%)
Dementia with MMSE scores < 24	13 (38.2%)
Acute encephalitis-like episodes	19 (55.9%)
Tremor, bradykinesia, or rigidity	17 (50.0%)
Gait disturbance	16 (47.1%)
Bladder dysfunction	14 (41.2%)
Visual disturbance	14 (41.2%)
Muscle weakness/wasting at distal limbs	12 (35.3%)
Psychiatric problems	9 (26.5%)
Epilepsy	9 (26.5%)
Sensory deficit at distal limbs	6 (17.6%)
Orthostatic hypotension	3 (8.8%)

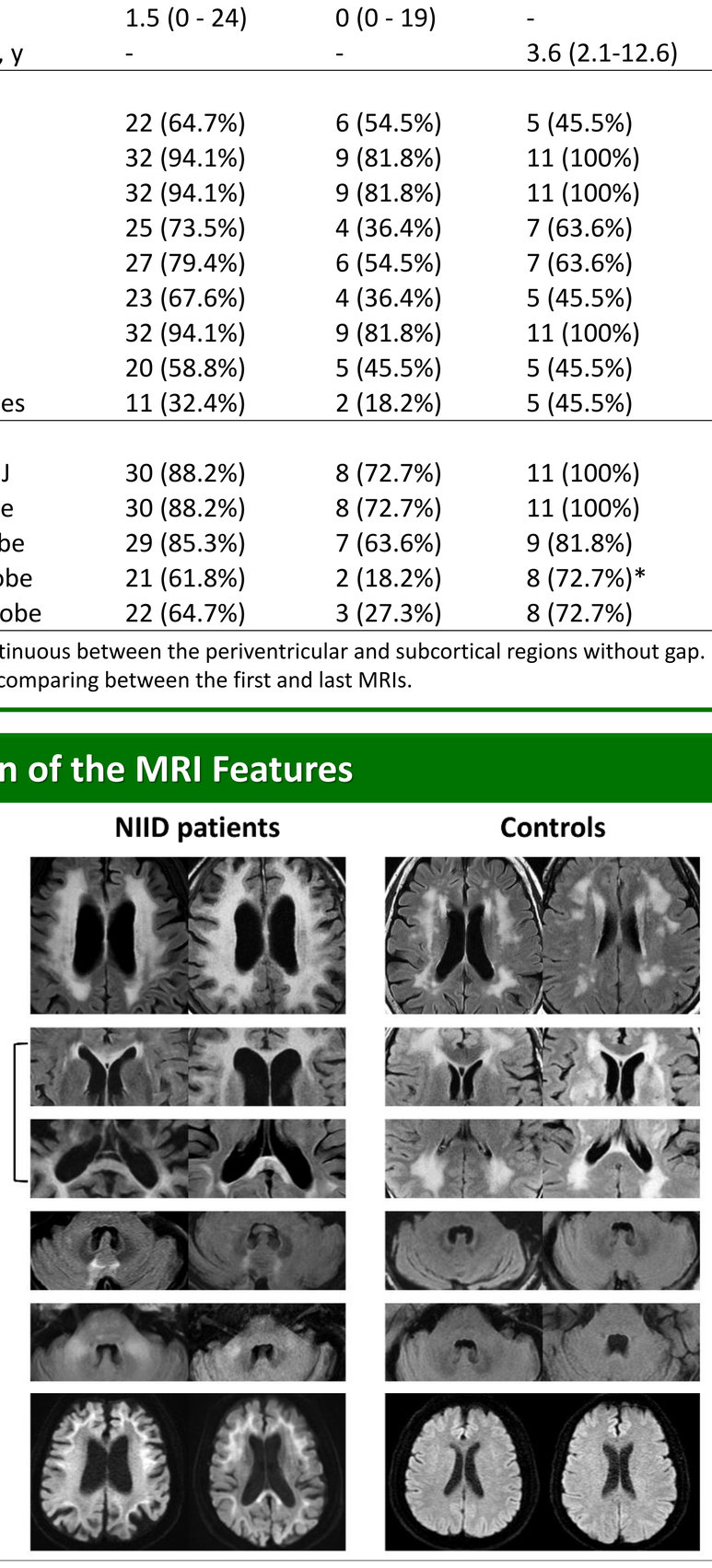
MMSE: mini-mental state examination; y: years.

Table 2. MRI Features of NIID patients

N (%) or Median (range)	All patients (N = 34)	Serial MRI Follow-ups (N = 11)	
		First MRI	Last MRI
Age at MRI, y	64 (52 - 78)	61 (52 - 72)	66 (59 - 83)
Disease duration, y	1.5 (0 - 24)	0 (0 - 19)	-
Interval between two MRIs, y	-	-	3.6 (2.1-12.6)
FLAIR			
Symmetric WMH	22 (64.7%)	6 (54.5%)	5 (45.5%)
Frontal region	32 (94.1%)	9 (81.8%)	11 (100%)
Parietal region	32 (94.1%)	9 (81.8%)	11 (100%)
Occipital region	25 (73.5%)	4 (36.4%)	7 (63.6%)
Temporal region	27 (79.4%)	6 (54.5%)	7 (63.6%)
No WMH gap [a]	23 (67.6%)	4 (36.4%)	5 (45.5%)
Corpus callosum	32 (94.1%)	9 (81.8%)	11 (100%)
Paravermis	20 (58.8%)	5 (45.5%)	5 (45.5%)
Middle cerebellar peduncles	11 (32.4%)	2 (18.2%)	5 (45.5%)
DWI			
Hyperintensities along CMJ	30 (88.2%)	8 (72.7%)	11 (100%)
CMJ lesions in frontal lobe	30 (88.2%)	8 (72.7%)	11 (100%)
CMJ lesions in parietal lobe	29 (85.3%)	7 (63.6%)	9 (81.8%)
CMJ lesions in occipital lobe	21 (61.8%)	2 (18.2%)	8 (72.7%)*
CMJ lesions in temporal lobe	22 (64.7%)	3 (27.3%)	8 (72.7%)

[a] No WMH gap: WMH were continuous between the periventricular and subcortical regions without gap.
* $p < 0.05$ at Fisher's exact test comparing between the first and last MRIs.

Figure 1. Comparison of the MRI Features



All are FLAIR images except the last row.