

**eFigure 1** White matter lesions in patients of NIID were rated in four grades according to their scope on T2WI: grade 0 was defined as no T2 hyperintensities (A); grade 1 as punctate or patchy T2 hyperintensities (B); grade 2 as moderate changes with confluent symmetric periventricular hyperintensities (C); grade 3 as severe changes with confluent periventricular hyperintensities extending to the grey/white matter border (D).

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 (E); grade 1 as slight widening of the subarachnoid space (F); grade 2 as marked widening of the subarachnoid space and mild widening of the ventricles (G); grade 3 as marked atrophy with a pronounced widening of subarachnoid space and ventricles (H).

**eTable 1 The clinical features of the 16 NIID patients who had undergone muscle biopsy.**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| No.  | Sex/age | Disease duration (years) | Clinical manifestations | Serum CK (U/L, normal range 0-194) | EMG pattern | Rimmed vacuoles | Fiber-type disproportion | GGC repeats |
| P139 | F/64 | 10 | Recurrent episodic symptoms, cognitive impairment, rectal and bladder dysfunction | 46.6 | Normal | - | Type I dominant | 89 |
| P140 | M/66 | 5 | Parkinsonism, mild cognitive impairment, muscle weakness | 79.8 | Neurogenic change | + | Normal | 153 |
| P141 | M/63 | 3 | Tremor, mild cognitive impairment, bladder dysfunction, fatigue | 158.7 | Normal | + | Type I dominant | 111 |
| P143 | F/63 | 1 | Cognitive impairment, headache, urinary incontinence, syncope | 27.6 | Normal | - | Type I dominant | 101 |
| P150 | M/60 | 9 | Cognitive impairment, tremor, urinary incontinence | 31.4 | NA | + | Type I dominant | 93 |
| P151 | M/68 | 20 | Parkinsonism, cognitive impairment, syncope, constipation | 159.5 | Normal | - | Type II dominant | 128 |
| P152 | F/65 | 10 | Recurrent episodic symptoms, dizziness, cognitive impairment, tremor, urinary incontinence | 29.7 | Normal | - | Type I dominant | 134 |
| P153 | F/15 | 5 | Muscle weakness, headache, gastrointestinal dysfunction, cognitive impairment | 122.8 | Neurogenic change | + | Type II dominant | 95 |
| P203 | F/47 | 2 | Cognitive impairment, headache, ataxia | 66.8 | Normal | + | Type I dominant | 124 |
| P207 | M/61 | 14 | Autonomic dysfunction, cognitive impairment, stroke-like episode, muscle weakness | 82.7 | NA | + | Type I dominant | 129 |
| P208 | M/59 | 5 | Tremor, cognitive impairment, orthostatic hypotension | 125.2 | Normal | + | Type II dominant | 113 |
| P209 | F/58 | 12 | Headache, tremor | 69.6 | NA | + | Type II dominant | 108 |
| P211 | M/65 | 5 | Autonomic dysfunction, disturbances of consciousness, cognitive impairment | 58.6 | Normal | + | Type I dominant | 113 |
| P212 | M/61 | 3 | Autonomic dysfunction, cognitive impairment | 37.4 | Normal | + | Type I dominant | 99 |
| P215 | M/63 | 2 | Muscle weakness, tremor, ataxia | 151.4 | Normal | + | Type II dominant | 150 |
| P223 | M/58 | 3 | Parkinsonism, cognitive impairment, bladder dysfunction, ataxia | 214.2 | Normal | + | Type I dominant | 110 |

M: male; F: female; CK: creatine kinase; EMG: electromyography; NA: not available.

**eTable 2 The grades of white matter lesions and brain atrophy and their correlation with cognitive function.**

|  |  |  |
| --- | --- | --- |
|  | White matter lesions | Generalized brain atrophy |
|  | Grade 0 | Grade 1 | Grade 2 | Grade 3 | *p* value | Grade 0 | Grade 1 | Grade 2 | Grade 3 | *p* value |
| N (%) | 4 (1.9%) | 34 (16.3%) | 72 (34.4%) | 99 (47.4%) | - | 3 (1.4%) | 24(11.5%) | 104 (49.8%) | 78 (37.3%) | - |
| Cognitive impairment | 0/4 | 23/34 | 54/72 | 88/99 | *p*<0.001 (Fisher) | 0/3 | 14/24 | 80/104 | 71/78 | *p*<0.001(Fisher) |
| MMSE | 29.0$\pm 1.0$ | 23.8$\pm 4.9$ | 22.5$\pm 5.8$ | 18.6$\pm 6.8$ | *p*<0.001 | 29.0$\pm 1.4$ | 24.7$\pm 4.2$ | 22.2$\pm 6.5$ | 18.7$\pm 6.6$ | *p*<0.001 |
| MOCA | 27.0$\pm 1.0$ | 19.0$\pm 5.7$ | 18.3$\pm 6.2$ | 14.1$\pm 7.1$ | *p*<0.001 | 27.5$\pm 0.7$ | 19.2$\pm 6.2$ | 17.3$\pm 6.7$ | 14.9$\pm 6.9$ | *p*=0.01 |

**eTable 3 Clinical and imaging features of NIID patients having focal cortical lesions on brain MRI.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Patient | Sex, age | Episodic events | Interval\*\* | Focal cortical lesions |
| T2WI/Flair | DWI restricted diffusion | T1WI+C cortical enhancement |
| Cortical hyperintense distribution | Cortical edema/atrophy |
| P19 | F, 58y | Disturbance of consciousness\*; headache | 5 days | R- temporal, parietal, occipital | Atrophy  | (-) | Not done |
| P23 | M, 62y | Encephalitis-like episode | 13 days | R- frontal, temporal, parietal, occipital | Edema  | Restricted | Not done |
| P32 | F, 52y | Encephalitis-like episode | 34 days | L- frontal, temporal, parietal, occipital | Edema  | (-) | Not done |
| P41 | F, 68y | Disturbance of consciousness | 1 day | L- frontal, temporal, parietal, occipital | Edema  | Restricted | Enhancement |
| P44 | M, 58y | Encephalitis-like episode\*; Disturbance of consciousness | 22 days | R- temporal, parietal | Atrophy  | (-) | Not done |
| P45 | F, 64y | Encephalitis-like episode\*; Disturbance of consciousness | 20 days | R- temporal, parietal, occipital | Atrophy | (-) | Not done |
| P69 | F, 70y | Stroke-like episode | 1 day | L- temporal, parietal, occipital | Atrophy | (-) | Not done |
| P71 | F, 54y | Encephalitis-like episode\*; stroke-like episode | 8 days | R- temporal, parietal, occipital | Edema | Restricted | Enhancement |
| P86 | M, 29y | Disturbance of consciousness | 6 days | L- frontal；R- frontal, temporal, parietal, occipital | Bi- edema | Bi-restricted | (-) |
| P93 | M, 69y | Stroke-like episode | 30 days | L- temporal, parietal, occipitalR- frontal, temporal, parietal, occipital | L- atrophyR- edema | L- (-)R- restricted | Not done |
| P119 | M, 67y | Disturbance of consciousness\*; stroke-like episode | 12 days | L- temporal, parietal, occipital | Edema | (-) | (-) |
| P125 | F, 59y | Disturbance of consciousness | 6 days | R- temporal, parietal, occipital | Atrophy  | (-) | Not done |
| P134 | F, 61y | Encephalitis-like episode | 7 days | R- frontal, temporal, parietal, occipital | Edema  | Restricted | Not done |
| P146 | M, 63y | Disturbance of consciousness | 130 days | L- temporal, parietal, occipital | Edema  | Restricted | Not done |
| P167 | M, 59y | Encephalitis-like episode | 20 days | L- frontal, temporal, parietal, occipital | Edema  | Restricted | Enhancement |
| P176 | F, 70y | Stroke-like episode | 22 days | L- temporal, parietal | Edema | Restricted | Not done |
| P191 | M, 45y | Stroke-like episode | 13 days | L- frontal, parietal | Edema  | Restricted | Not done |
| P202 | F, 53y | Headache  | 46 days | R- temporal, parietal | Atrophy  | (-) | Not done |
| P214 | M, 67y | Encephalitis-like episode | 12 days | L- temporal, parietal, occipital | Edema | Restricted | Enhancement |
| P217 | F, 71y | Disturbance of consciousness | 7 days | R- temporal, occipital | Edema | Restricted | Not done |
| P222 | M, 47y | Encephalitis-like episode\* | 20 days | L- temporal;R- temporal, parietal | Bi- edema | Bi- restricted | (-) |

\*: the form of the last episodic event; \*\*: time interval between the last episodic event and brain MRI; M: male; F: female; L: left; R: right; Bi: bilateral; T2WI: T2 weighted images; Flair: fluid attenuated inversion recovery images; DWI: diffusion weighted imaging; T1WI +C: T1 weighted images with gadolinium contrast; (-): not found.

**eTable 4 The clinical features of patients with autonomic dysfunction- dominant NIID.**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Patient  | Sex  | Age of onset | Disease duration (years) | Initial symptom | Rectal and bladder dysfunction | Syncope/ orthostatic hypotension | Vomiting | Miosis | Palpitation or BP fluctuation | Excessive sweating | Erectile dysfunction | Other symptoms | GGC repeats |
| P1 | M | 40y | 14 | Nausea and vomiting | Urinary retention | (-) | (+) | (-) | (-) | (-) | (-) | Tremor | 82 |
| P2 | F | 50y | 13 | Nausea and vomiting | Constipate | (-) | (+) | (-) | (-) | (-) | / | Tremor, depression | 113 |
| P70 | F | 63y | 2 | Syncope  | Urinary incontinence | (+) | (-) | (-) | (-) | (-) | / | None | 101 |
| P77 | F | 59y | 0.5 | Nausea and vomiting | (-) | (-) | (+) | (-) | (-) | (-) | / | None | 131 |
| P85 | M | 58y | 0.5 | Bladder dysfunction | Dysuria and constipate | (-) | (-) | (-) | (-) | (+) | (+) | None | 120 |
| P98 | F | 55y | 10 | Bladder dysfunction | Neurogenic bladder, indwelling urinary catheter | (-) | (+) | (+) | (+) | (-) | / | None | 121 |
| P100 | F | 52y | 5 | Orthostatic hypotension | Constipate | (+) | (+) | (-) | (-) | (-) | / | None | 108 |
| P111 | F | 60y | 4 | Bladder dysfunction | Dysuria, constipate | (-) | (+) | (-) | (-) | (-) | / | None | 88 |
| P113 | F | 57y | 2 | Bladder dysfunction | Dysuria, constipate | (-) | (-) | (-) | (-) | (-) | / | None | 140 |
| P154 | M | 71y | 0.1 | Blood pressure fluctuation | (-) | (+) | (-) | (-) | (+) | (-) | (-) | None | 105 |
| P155 | F | 62y | 4 | Bladder dysfunction | Urinary incontinence | (+) | (+) | (-) | (-) | (-) | / | Tremor, depression | 125 |
| P159 | F | 62y | 0.003 | Abdominal pain and vomiting | (-) | (+) | (+) | (-) | (-) | (-) | / | None | 79 |
| P175 | F | 61y | 3 | Syncope  | (-) | (+) | (-) | (+) | (-) | (+) | / | None | 363 |
| P190 | F | 61y | 2.3 | Syncope  | (-) | (+) | (-) | (-) | (-) | (-) | / | Cognitive impairment | 118 |
| P206 | F | 40y | 14 | Syncope | (-) | (+) | (+) | (-) | (-) | (+) | / | None | 122 |
| P207 | M | 47y | 14 | Erectile dysfunction | Urinary retention, constipate | (+) | (-) | (+) | (-) | (+) | (+) | Mild cognitive impairment, stroke-like episode for one time, fatigue | 129 |
| P211 | M | 60y | 5 | Erectile dysfunction | Urinary incontinence | (-) | (-) | (+) | (-) | (-) | (+) | Disturbance of consciousness for one time | 113 |
| P212 | M | 58y | 3 | Erectile dysfunction | Cystostomy, fecal incontinence | (-) | (-) | (+) | (-) | (-) | (+) | None | 99 |
| P218 | F | 44y | 14 | Nausea and vomiting | Urinary incontinence, dysuria, constipate | (+) | (+) | (+) | (-) | (-) | / | Vision loss, depression | 107 |

M: male; F: female; BP: blood pressure.

**eTable 5 The clinical features of patients with neuromuscular disease- dominant NIID.**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Patient | Sex | Age of onset | Disease duration(years) | Muscle weakness | Muscle strength (MRC) | Tendon reflexes | Sensory disturbance | NCS | EMG | Leukodystrophy on Brain MRI | Other symptoms | GGC repeats |
| upper | lower |
| P11 | M | 36y | 30 | Lower limbs | 4/5 | 4/5 | (+) | None | MCV↓SCV↓CMAP↓ | Chronic neurogenic damage | Leukodystrophy | Mild cognitive impairment, epileptic seizure | 107 |
| P38 | F | 61y | 2 | Four limbs | 4/5 | 4/5 | (+) | None | NA | NA | Leukodystrophy | Mild cognitive impairment, parkinsonism | 90 |
| P54 | F | 44y | 11 | Four limbs | 4/5 | 5/5 | (++) | None | NA | NA | Leukodystrophy | Disturbance of consciousness, headache | 146 |
| P56 | M | 61y | 4 | Lower limbs | 5/5 | 4/5 | (+) | Numbness in bilateral lower limbs | MCV↓SCV↓ | Normal  | Leukodystrophy | Mild cognitive impairment, autonomic dysfunction | 96 |
| P126 | F | 59y | 10 | Four limbs | pro. 4/5dis. 5/5 | pro. 4/5dis. 5/5 | (++) | None | NA | NA | Leukodystrophy | Mild cognitive impairment, tremor, autonomic dysfunction | 107 |
| P136 | F | 58y | 6 | Lower limbs | 5/5 | pro. 4/5dis. 5/5 | (++) | Numbness in bilateral feet | NA | NA | Leukodystrophy | Ataxia, blurred vision | 102 |
| P153 | F | 10y | 5 | Four limbs | 4/5 | 4/5 | (-) | None | MCV↓SCV↓CMAP↓SNAP↓ | SP + chronic neurogenic damage | Leukodystrophy | Autonomic dysfunction, headache | 95 |
| P165 | F | 58y | 5 | Four limbs | 4/5 | 4/5 | (+) | None | MCV↓SCV↓ | Chronic neurogenic damage | Leukodystrophy | Mild cognitive impairment, encephalitic episode, autonomic dysfunction, | 120 |
| P168 | F | 34y | 19 | Four limbs | pro. 5/5dis. 3/5 | pro. 4/5dis. 0/5 | (-) | Hypoesthesia in bilateral distal lower limbs | MCV↓SCV↓CMAP↓SNAP↓ | SP + chronic neurogenic damage | None | none | 154 |
| P169 | M | 24y | 3 | Four limbs | 4/5 | 4/5 | (+) | None | MCV↓CMAP↓ | SP + chronic neurogenic damage | None | none | 180 |
| P170 | F | 64y | 6 | Lower limbs | 5/5 | 3/5 | (+) | Hypoesthesia in bilateral lower limbs | MCV↓CMAP↓ | Chronic neurogenic damage | Leukodystrophy | Mild cognitive impairment | 125 |
| P186 | M | 62y | 2 | Lower limbs | 5/5 | 4/5 | (+) | Hypoesthesia in bilateral lower limbs | MCV↓SCV↓CMAP↓SNAP↓ | Normal | Leukodystrophy | Mild cognitive impairment, ataxia | 138 |
| P189 | F | 67y | 2 | Lower limbs | 5/5 | 4/5 | (++) | None | MCV↓CMAP↓ | Chronic neurogenic damage | Leukodystrophy | Epileptic seizure | 94 |
| P195 | M | 11y | 5 | Four limbs | L: 5/5R: 4/5 | L: 3/5R: 3/5 | (+) | Hypoesthesia in distal upper and lower limbs | MCV↓SCV↓CMAP↓SNAP↓ | SP + chronic neurogenic damage | Leukodystrophy | Mild cognitive impairment | 525 |
| P213 | M | 60y | 5 | Four limbs | L: pro. 3/5, dis. 1/5R: 4/5 | L: pro. 3/5, dis. 1/5R: 4/5 | (-) | Hypoesthesia in distal upper and lower limbs | MCV↓SCV↓SNAP↓ | Normal | Leukodystrophy | Mild cognitive impairment, parkinsonism, autonomic dysfunction | 174 |
| P215 | M | 61y | 2 | Four limbs | pro. 4/5;dis. 3/5 | pro. 4/5;dis. 4/5 | (+) | None | MCV↓SCV↓CMAP↓SNAP↓ | Normal | Leukodystrophy | Tremor, ataxia | 150 |
| P221 | F | 53y | 5 | Four limbs | pro. 4/5;dis. 3/5 | pro. L:4/5, R:2/5;dis. 3/5 | Upper: (+)Lower: (-) | None | MCV↓SCV↓ | Chronic neurogenic damage | None | Tremor, parkinsonism, mild cognitive impairment | 107 |

M: male; F: female; MRC: Medical Research Council; L: left; R: right; NCS: nerve conduction study; EMG: electromyography; NA: not available; MCV: motor conduction velocity; SCV: sensory conduction velocity; CMAP: compound motor action potential; SNAP: sensory nerve action potential; SP: spontaneous potential; NC: neurogenic change.

**eTable 6 The imaging features of brain MRI among the five clinical subtypes.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Cognitive impairment-dominant type | Episodic neurogenic event-dominant type | Movement disorder-dominant type | Autonomic dysfunction-dominant type | Neuromuscular disease-dominant type |  |
| DWI hyperintensity | 71/72 (98.6%) | 63/65 (96.9%) | 37/38 (97.3%) | 18/18 (100%) | 13/16 (81.3%) | *p*=0.047\* |
| Paravermis hyperintensity | 46/72 (63.9%) | 35/65 (53.8%) | 17/38 (44.7%) | 11/18 (61.1%) | 6/16 (37.5%) | *p*=0.185 |
| MCP hyperintensity | 17/72 (23.6%) | 15/65 (23.1%) | 12/38 (31.6%) | 3/18 (16.7%) | 4/16 (25.0%) | *p*=0.784 |
| Brain stem hyperintensity | 37/72 (51.4%) | 24/65 (36.9%) | 13/38 (34.2%) | 8/18 (44.4%) | 6/16 (37.5%) | *p*=0.353 |
| Corpus callosum hyperintensity | 65/72 (90.3%) | 52/65 (80.0%) | 32/38 (84.2%) | 16/18 (88.9%) | 10/16 (62.5%) | *p*=0.072 |
| Focal cortical lesions | 0/72(0.0%) | 21/65 (32.3%) | 0/38(0.0%) | 0/16(0.0%) | 0/11(0.0%) | *p*<0.001 |
| Mean white matter lesion grades | 2.38±0.80 | 2.32±0.60 | 2.32±0.70 | 2.06±0.73 | 1.75±1.07 | *p*=0.045 |
| Mean brain atrophy grades | 2.35±0.65 | 2.23±0.66 | 2.26±0.64 | 2.11±0.58 | 1.75±1.12 | *p*=0.038 |

DWI: diffusion weighted imaging; MCP: middle cerebellar peduncle; \*: Fisher exact test.