Abstract:
We herein report a woman with chronic inflammatory demyelinating polyneuropathy (CIDP) in whom positivity for anti-neurofascin 155 antibodies was revealed 23 years after the onset of neuropathy. The patient initially reported numbness in the face at 50 years of age and subsequently manifested features compatible to typical CIDP. Steroid administration initiated at 54 years of age ameliorated her neuropathic symptoms. Although the nerve conduction indices at 59 years of age deteriorated, those at 68, 72, and 73 years of age showed a gradual recovery. The deterioration and subsequent restoration of compound muscle action potential amplitudes was the most dramatic, suggesting that a conduction block can be reversed earlier than other electrophysiological indices.

Key words: chronic inflammatory demyelinating polyneuropathy, conduction block, neurofascin, paranode, prognosis, treatment

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Introduction
Chronic inflammatory demyelinating polyneuropathy (CIDP) is an immune-mediated neuropathy characterized by electrophysiological features suggestive of demyelination. Phagocytosis of myelin by macrophages that have infiltrated the endoneurial space has been thought to be the cause of demyelination, resulting in nerve conduction abnormalities in CIDP (1-5). However, recent studies have suggested the association of autoantibodies directed against paranodal junctional molecules in a subpopulation of patients (6-13). Among these autoantibodies, anti-neurofascin 155 antibodies induce the dissection of paranodes that results in nerve conduction abnormalities (14). This mechanism-inducing conduction abnormality is completely different from the classical macrophage-mediated mechanism of demyelination (14). Patients with anti-neurofascin 155 antibodies receive much attention from physicians because they tend to manifest unique clinical features. For example, patients with anti-neurofascin 155 antibodies tend to show distal limb involvement, sensory ataxia, tremor, and a poor response to an intravenous immunoglobulin treatment (8, 11-14). As these antibodies have only recently been recognized in CIDP patients, the long-term sequelae associated with this type of CIDP have not been clarified.

We herein report a patient with CIDP who was revealed to be positive for anti-neurofascin 155 antibodies 23 years after the onset of neuropathy. This case has not been included in other studies of anti-neurofascin 155 antibodies.
she was alert and well-oriented. Mild paresthesia in the <V>remarkable personal or family history.</V>
hospital and was hospitalized at 54 years of age. She had no
three years later. As they gradually worsened, she visited our
side of her face at 50 years of age. Although the numbness
spread to cover the whole face, it gradually subsided there-
atolescence. Light touch and pain sensations were moderately impaired, and the vi-
was preserved (26,479 fibers/mm²). Marked endoneurial edema with a substantial in-
epidural inflammatory cellular infiltration was not observed. Teased-
fiber preparations showed little axonal degeneration (2.1%;
control value, 1.8%±1.6%), with fibers showing slight wid-
crease in the subperineurial space was observed. Epineurial
in the brain or spinal cord. Thickening of the cauda equina was not evident.

A neurologic examination on admission revealed that
she was alert and well-oriented. Mild paresthesia in the V2
and 4,789 fibers/mm²). An assessment of longitudinal sections
were flexor on both sides. A cerebrospinal fluid examination
revealed an increased protein level and normal cell count
(176 mg/dL; normal, 15-45 mg/dL). The findings of nerve
conduction studies (NCSs), which were performed as de-
scribed previously (15, 16), indicated demyelinating neuro-
pathy (Table). The amplitudes of compound muscle action
potentials (CMAPs) in the tibial nerve and sensory nerve ac-
ion potentials in the median, ulnar, and sural nerves were
potentials (CMAPs) in the tibial nerve and sensory nerve ac-
action potentials in the median, ulnar, and sural nerves were
markedly decreased or not elicited. Magnetic resonance im-
aging revealed no significant abnormalities in the brain or
spinal cord. Thickening of the cauda equina was not evident.

Under light microscopy, a sural nerve biopsy revealed
preserved large and small myelinated fiber densities (2,786
and 4,789 fibers/mm²). Marked endoneurial edema with a substantial in-
crease in the subperineurial space was observed. Epineurial
inflammatory cellular infiltration was not observed. Teased-
fiber preparations showed little axonal degeneration (2.1%;
control value, 1.8%±1.6%), with fibers showing slight wid-
ening of the node of Ranvier (i.e. segmental demyelination,
5.2%). Electron microscopy showed that unmyelinated fibers
were preserved (26,479 fibers/mm²; control value, 30,655±
2,731 fibers/mm²). An assessment of longitudinal sections
revealed the detachment of the myelin terminal loops from

Case Report

A 73-year-old woman first noted numbness on the left side of her face at 50 years of age. Although the numbness
spread to cover the whole face, it gradually subsided thereafter. Numbness and weakness in the lower limbs appeared
three years later. As they gradually worsened, she visited our hospital and was hospitalized at 54 years of age. She had no
remarkable personal or family history.

A neurologic examination on admission revealed that
she was alert and well-oriented. Mild paresthesia in the V2 and V3 branches of the left trigeminal nerve and moderate
weakness of the bilateral sternocleidomastoides and trape-
zius muscles were noted, while the other cranial nerves were intact. Moderate weakness was diffusely present bilaterally
in both the upper and lower extremities. Muscle atrophy was not evident on inspection. Her grasp powers were 16/18 kg
(right/left, respectively). A sensory deficit was noted in a distally accentuated globe-and-stocking pattern. Light touch
and pain sensations were moderately impaired, and the vibra-
tion sensation was reduced severely in the distal portions of the lower limbs. No hand tremors were noted. The deep
tendon reflexes were reduced in the upper extremities and absent entirely in the lower limbs. The plantar responses
were flexor on both sides. A cerebrospinal fluid examination
revealed an increased protein level and normal cell count
(176 mg/dL; normal, 15-45 mg/dL). The findings of nerve
conduction studies (NCSs), which were performed as de-
scribed previously (15, 16), indicated demyelinating neuro-
pathy (Table). The amplitudes of compound muscle action
potentials (CMAPs) in the tibial nerve and sensory nerve ac-

Table. Serial Nerve Conduction Studies.

<table>
<thead>
<tr>
<th>Nerve conduction</th>
<th>The first examination</th>
<th>After 2 years</th>
<th>After 5 years</th>
<th>After 14 years</th>
<th>After 18 years</th>
<th>After 19 years</th>
<th>Controls*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Right)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>mean (SD)</td>
</tr>
<tr>
<td>Median nerve</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCV (m/s)</td>
<td>25.0</td>
<td>36.0</td>
<td>23.0</td>
<td>27.0</td>
<td>31.0</td>
<td>32.0</td>
<td>57.6 (3.8)</td>
</tr>
<tr>
<td>DL (ms)</td>
<td>9.1</td>
<td>9.8</td>
<td>7.4</td>
<td>8.6</td>
<td>6.9</td>
<td>7.1</td>
<td>3.4 (0.4)</td>
</tr>
<tr>
<td>Distal CMAP duration (ms)**</td>
<td>6.7</td>
<td>5.6</td>
<td>5.1</td>
<td>5.5</td>
<td>5.7</td>
<td>6.3</td>
<td>4.7 (0.9)</td>
</tr>
<tr>
<td>CMAP (mV)</td>
<td>12.8</td>
<td>5.7</td>
<td>0.9</td>
<td>4.3</td>
<td>6.3</td>
<td>8.3</td>
<td>8.2 (2.9)</td>
</tr>
<tr>
<td>FO (%)</td>
<td>38.0</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>43.8</td>
<td>43.8</td>
<td>67.6 (20.3)</td>
</tr>
<tr>
<td>F latency</td>
<td>45.7</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>50.0</td>
<td>43.6</td>
<td>22.3 (1.9)</td>
</tr>
<tr>
<td>SCV (m/s)</td>
<td>16.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>56.3 (5.3)</td>
</tr>
<tr>
<td>SNAP (μV)</td>
<td>1.8</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>1.5</td>
<td>28.0 (11.5)</td>
</tr>
<tr>
<td>Ulnar nerve</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCV (m/s)</td>
<td>26.0</td>
<td>30.0</td>
<td>29.0</td>
<td>32.0</td>
<td>35.0</td>
<td>35.0</td>
<td>58.0 (4.6)</td>
</tr>
<tr>
<td>DL (ms)</td>
<td>7.6</td>
<td>6.6</td>
<td>6.4</td>
<td>6.1</td>
<td>5.6</td>
<td>5.3</td>
<td>2.6 (0.3)</td>
</tr>
<tr>
<td>Distal CMAP duration (ms)**</td>
<td>7.0</td>
<td>5.9</td>
<td>5.2</td>
<td>5.7</td>
<td>6.1</td>
<td>6.7</td>
<td>5.1 (0.7)</td>
</tr>
<tr>
<td>CMAP (mV)</td>
<td>7.5</td>
<td>4.1</td>
<td>2.4</td>
<td>3.6</td>
<td>4.8</td>
<td>4.0</td>
<td>7.4 (1.8)</td>
</tr>
<tr>
<td>SCV (m/s)</td>
<td></td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>21.0</td>
<td>22.8</td>
</tr>
<tr>
<td>SNAP (μV)</td>
<td></td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>1.0</td>
<td>2.0</td>
<td>23.8 (10.3)</td>
</tr>
<tr>
<td>Tibial nerve</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCV (m/s)</td>
<td>20.0</td>
<td>29.0</td>
<td>13.0</td>
<td>26.0</td>
<td>26.0</td>
<td>26.0</td>
<td>46.0 (3.8)</td>
</tr>
<tr>
<td>DL (ms)</td>
<td>17.2</td>
<td>13.8</td>
<td>7.6</td>
<td>15.3</td>
<td>11.5</td>
<td>7.8</td>
<td>4.0 (0.6)</td>
</tr>
<tr>
<td>CMAP (mV)</td>
<td>1.0</td>
<td>0.6</td>
<td>1.1</td>
<td>1.7</td>
<td>1.1</td>
<td>1.0</td>
<td>11.8 (3.5)</td>
</tr>
<tr>
<td>Sural nerve</td>
<td></td>
<td></td>
<td>19</td>
<td></td>
<td></td>
<td>49.2 (4.8)</td>
<td></td>
</tr>
<tr>
<td>SCV (m/s)</td>
<td></td>
<td>NE</td>
<td>NE</td>
<td>0.8</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>SNAP (μV)</td>
<td></td>
<td>NE</td>
<td>NE</td>
<td>0.8</td>
<td>NE</td>
<td>NE</td>
<td>16.8 (7.8)</td>
</tr>
</tbody>
</table>

*Control values were based on previously published reports (15, 16).

**Duration from onset to the first crossing of the baseline in CMAP was measured (15).
the axolemma at the paranode, a finding consistent with a previous report on neurofascin 155 antibody-positive CIDP cases (Fig. 1) (14, 18, 19).

Based on the diagnosis of CIDP, steroid pulse treatment was administered intravenously (1,000 mg daily dose of methylprednisolone for 3 days); subsequently, 50 mg of prednisolone was administered orally for 1 month. The weakness and numbness gradually improved; therefore, the dosage of prednisolone was tapered by 5 mg every 2 weeks. She was discharged at 4 months after the initiation of treatment, at which time her grasp powers were 26/26 kg, and the cerebrospinal fluid protein level was 157 mg/dL. However, numbness in the face and limbs remained.

Five months after the discharge, the dosage of prednisolone was reduced to 15 mg/daily. Her grasp powers had increased to 30/34 kg, and she was able to run. Although she began to complain of mild hand tremors, the tapering of the prednisolone dosage continued because the numbness and weakness were not exacerbated. At 56 years of age, when she was taking a 5-mg daily dose of prednisolone, she complained of worsening of her sensory symptoms and difficulty walking. The prednisolone dose was increased to 10 mg daily. An NCS performed at that time revealed improvement in the motor conduction velocities despite a reduction in the CMAP amplitudes in the median and ulnar nerves. Muscle computed tomography (CT) performed at 57 years of age, as described previously (16), revealed no muscle atrophy of the arms, legs, or trunk.

An NCS performed at 59 years of age revealed a further reduction in the CMAP amplitudes in the median and ulnar nerves, particularly in the former (Fig. 2A). The reduction in the CMAP amplitudes in these nerves was not accompanied by a prolonged duration or polyphasia (i.e. temporal dispersion). At 60 years of age, she again complained of a worsening of numbness and gait disturbance; therefore, the dosage of prednisolone was increased to 20 mg daily and then tapered to 5 mg daily by 61 years of age. Although the patient complained of an unsteady gait, numbness in the lower limbs, and tremor in the upper limbs, her neuropathic symptoms have remained largely stable since then. Now, at 73

Figure 1. Electron microscopic findings of longitudinal sections of a sural nerve biopsy specimen. A clear space was frequently observed between the myelin terminal loops and the axolemma (arrows). A high-powered view of the region in the box in (A) is shown in (B). Uranyl acetate and lead citrate staining. Scale bars=0.5 μm (A) and 0.1 μm (B).
was mildly positive. Hands and moderately reduced in the feet. Romberg’s sign was 22/23 kg. Mild impairment of the light touch and pain distribution compatible with a distal acquired demyelinating syndrome may have occurred in our patient (25). Passive transfer of antibodies against paranodal junctional protein induced the conduction block (26). However, this model did not show a slowing of the nerve conduction indices, which is ubiquitously observed in patients with antibodies to paranodes at these sites. Marked abnormalities in the distal and F-wave latencies in our patient may support such a mechanism.

Some anti-neurofascin 155 antibody-positive CIDP patients are refractory to immunotherapies (24). In our patient, the nerve conduction indices improved after long-term steroid treatment, although neuropathic symptoms remained. The sequential changes in the CMAP amplitudes in the median nerve (Fig. 2B). A serum examination using a cell-based assay (11) at 73 years of age revealed positivity for anti-neurofascin 155 antibodies (delta mean fluorescence intensity, 422.8). Muscle CT performed at that time revealed no muscle atrophy, which was similar to the results from 16 years earlier. A neurological examination at that time revealed mild weakness in the distal portions of the extremities. By contrast, her muscle strength was preserved in the proximal portions of the limbs, indicating a distribution compatible with a distal acquired demyelinating symmetric (DADS) form of CIDP (20). Her grasp power was 22/23 kg. Mild impairment of the light touch and pain sensations was noted in the distal portions of the lower limbs. The vibration sensation was mildly reduced in the hands and moderately reduced in the feet. Romberg’s sign was mildly positive.

Discussion

The initial symptom of CIDP in this patient seems to have been numbness in the face that appeared at 50 years of age. Although a transient improvement in that symptom was observed, exacerbation was noted as neuropathy in the extremities developed over the following three years. Facial sensory disturbance has been reported in some patients with anti-neurofascin 155 antibodies (11). A recent report demonstrated thickening of the cranial nerves in a patient manifesting facial sensory symptoms (21). In the present case, positivity for anti-neurofascin 155 antibodies was detected at 23 years after the onset of facial symptoms and 19 years after the initiation of steroid treatment. An antibody examination was not performed in the initial phase of neuropathy, but a sural nerve biopsy specimen obtained before the initiation of treatment showed a typical axo-glial detachment at the paranode, which has also been previously reported in anti-neurofascin 155 antibody-positive CIDP cases (14, 18, 19).

Previous studies of neurofascin 155 and contactin 1-deficient mice revealed the loss of transverse bands at the paranodal axo-glial junctions and slowing of the nerve conduction velocities (22, 23). These studies suggest that abnormalities of paranodal axo-glial junctional proteins may affect the tight connection between the myelin terminal loops and axolemma, inducing nerve conduction abnormalities. Therefore, the participation of anti-neurofascin 155 antibodies is strongly suggested in the pathogenesis of neuropathy, even in its early phase, in our patient. The lack of the blood-nerve barrier at the distal nerve terminals and nerve roots might enable anti-neurofascin 155 antibodies to access the paranodes at these sites. Marked abnormalities in the distal and F-wave latencies in our patient may support such a mechanism.

Some anti-neurofascin 155 antibody-positive CIDP patients are refractory to immunotherapies (24). In our patient, the nerve conduction indices improved after long-term steroid treatment, although neuropathic symptoms remained. The sequential changes in the CMAP amplitudes in the median and ulnar nerves, particularly in the former, were dramatic compared to the changes in the motor conduction velocities and distal latencies. Because the reduction in the CMAP amplitudes did not accompany a temporal dispersion in these nerves, a reversible conduction block similar to that in the acute motor axonal neuropathy form of Guillain-Barré syndrome may have occurred in our patient (25). Passive transfer of antibodies against paranodal junctional protein induced the conduction block (26). However, this model did not show a slowing of the nerve conduction indices, which is ubiquitously observed in patients with antibodies to paranodal junctional proteins, including anti-neurofascin 155 antibodies (11, 13, 14). Given the shorter duration of exposure to antibodies in animal models than in patients, this conduction block may represent a reversible functional deficit. As the duration of exposure to antibodies become longer, morphological abnormalities refractory to immunotherapies, such as paranodal dissection, as reported in patients with these antibodies (14), may occur at the paranode. This may result in additional abnormalities of conduction indices, such
as slowing of nerve conduction velocities and distal latencies.

According to previous studies, the key clinical features suggesting that a patient with CIDP has anti-neurofascin 155 antibodies before the initiation of treatment are the features of DADS, sensory ataxia, and hand tremors (8, 11-14). On admission to our hospital at 54 years of age, our patient manifested symmetric, diffuse weakness in the upper and lower limbs, which is compatible with the definition of typical CIDP and not DADS (20). As hand tremors were not conspicuous in the initial phase of neuropathy, it was unlikely that the patient had anti-neurofascin 155 antibodies. However, as the weakness in the proximal portions of the upper limbs finally recovered, the patient exhibited features compatible with DADS. The tremors also became gradually evident with the increasing duration of neuropathy.

A previous study of 38 patients with CIDP found that approximately two-thirds of the patients did not require immunotherapies 5 years after the initiation of treatment (27). The present case suggests that the pathological condition caused by anti-neurofascin 155 antibodies persists for a long time and that long-term treatment in patients with these antibodies is required. However, the conduction block may be reversible to some extent. Further studies are needed to clarify the long-term outcomes of CIDP with anti-neurofascin 155 antibodies.

The authors state that they have no Conflict of Interest (COI).

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References

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