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【 CASE REPORT 】

Possible Combined Central and Peripheral Demyelination Presenting as Optic Neuritis, Cervical Myelitis, and Demyelinating Polyneuropathy with Marked Nerve Hypertrophy

Yasutaka Tajima, Mariko Matsumura, Hiroaki Yaguchi and Yasunori Mito

Abstract:
A 27-year-old woman with optic neuritis and cervical myelitis developed hypertrophic demyelinating polyneuropathy. It was hypothesized that the diagnosis was combined central and peripheral demyelination. A hypertrophic nerve was observed subcutaneously, and magnetic resonance imaging demonstrated marked hypertrophy of the nerve roots. The patient was negative for anti-aquaporin 4 antibodies. Her anti-neurofascin 155 antibody levels was slightly elevated, but it was not definitely positive. Pulsed steroid therapy and the administration of immunoglobulin ameliorated her symptoms. Molecules in both the peripheral and central nervous systems might be target antigens, but further investigations will be needed to clarify the precise pathogenic mechanisms.

Key words: combined central and peripheral demyelination, multiple sclerosis, chronic inflammatory demyelinating polyneuropathy, neurofascin

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Introduction

There have been some cases of multiple sclerosis (MS) with peripheral neuropathy or chronic inflammatory demyelinating polyneuropathy (CIDP) with demyelinating plaques in the brain that are similar to those of MS (1). It has been hypothesized that these conditions represent a new disease entity called combined central and peripheral demyelination (CCPD) (2-5). With regard to the pathogenesis, various autoimmune mechanisms involving the common targeted neural antigens residing in both the peripheral and central nervous systems have been considered (6). Among these, the specific antibody for neurofascin (NF), which is located on the Ranvier node or the paranodal areas, has recently gained attention (4-9). In addition, hypertrophic changes of the involved nerves have often been seen in CIDP (10-13). We herein present a case of concurrent optic neuritis, cervical myelitis and demyelinating polyneuropathy with marked homogenous nerve hypertrophy with the appearance of clusters of grapes. Based on this case, we discuss some of the factors associated with the immunological disturbances observed in this complicated syndrome.

Case Report

A 27-year-old woman presented with the gradual worsening of tingling sensations on all four extremities and weakness of both legs. At 12 years of age, she had optic neuritis, which recovered after corticosteroid treatment. At 23 years of age, she developed difficulty in ambulation. T2-weighted magnetic resonance imaging (MRI) revealed a high-intensity signal in the cervical cord; this lesion was partially enhanced on gadolinium-diethylenetriaminepentaacetate (DTPA) T1-weighted MRI (Fig. 1). No hypertrophic changes were observed in the nerve roots. Cranial MRI did not demonstrate any signal abnormalities; nerve conduction studies did not indicate peripheral nervous system involvement, and her family history was unremarkable. The patient was diagnosed with MS, and corticosteroid treatment was

Department of Neurology, Brain Science Center, Sapporo City General Hospital, Japan
Received for publication January 19, 2016; Accepted for publication November 20, 2016
Correspondence to Dr. Yasutaka Tajima, yasutaka.tajima@doc.city.sapporo.jp

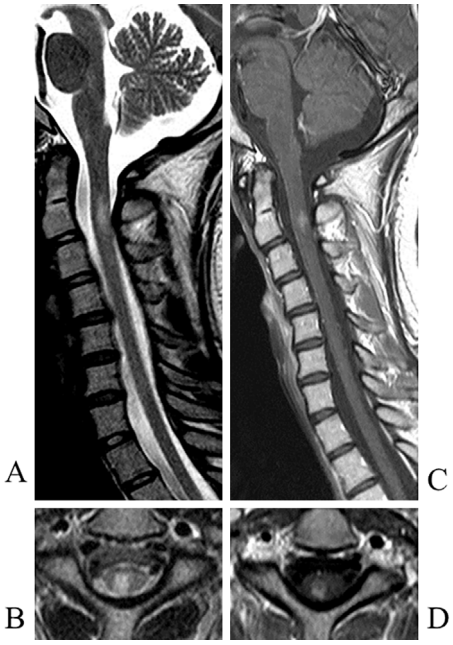

Figure 1. **T2-weighted MRI showed a high-intensity signal in the cervical cord (A: sagittal view, B: axial view), which was partially enhanced on gadolinium-DTPA T1-weighted MRI (C: sagittal view, D: axial view). The patient was 23 years of age.**

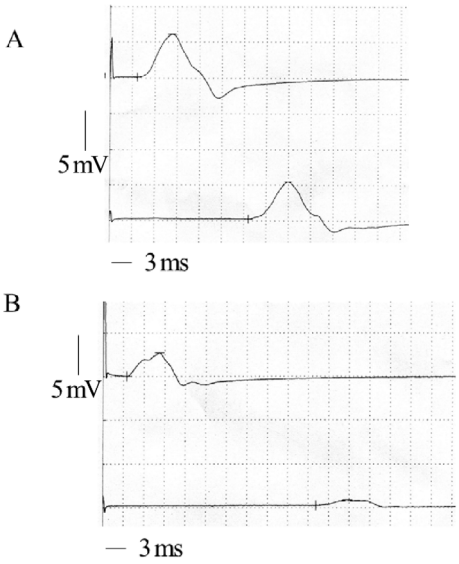

Figure 3. **Nerve conduction studies showed a marked delay (A: right median nerve, conduction velocity [CV] 14.7 m/s, B: left ulnar nerve, CV 10.5 m/s), and prominent temporal dispersion.**

administered again, after which she fully recovered. We did not measure the patient's anti-aquaporin-4 antibody level. Although we proposed additional interferon therapy to inhibit the recurrence of MS, she refused the therapy. She was followed on a regular basis after her recovery but received no disease modifying therapies.

At the time of examinations, her blood pressure was 110/70 mmHg and her body temperature was 36.1℃. A neurological examination revealed muscle weakness and atrophy on all four extremities, with depressed deep tendon reflexes, glove-and-stocking-type sensory loss, and bilateral foot drop. Pes cavus and hammertoes, which would suggest inherited polyneuropathy, were not observed. There was no apparent clinical evidence of cranial nerves or cerebellar involvement. An enlarged subcutaneous nerve was observed on the right side of the neck (Fig. 2). Ultrasound investigations confirmed this finding.

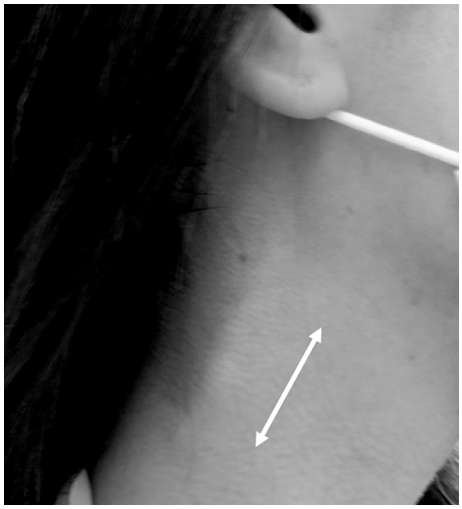

Figure 2. **A hypertrophic nerve in the subcutaneous area of the patient's right neck was observed. The patient was 27 years of age.**

The results of hematology, serum biochemistry, and a urinalysis revealed no abnormalities. Serum monoclonal gammopathy and Bence-Jones protein were not detected in the urine. There was no evidence of abnormal glucose tolerance or infectious disease, including hepatitis C, hepatitis B, or acquired immunodeficiency syndrome. The vitamin levels were within the normal limits, and tests for collagen vascular diseases were negative. The patient was negative for anti-GM1, anti-GQ1b, and anti-aquaporin 4 antibodies.

An electrophysiological examination showed a marked delay in the patient's motor nerve conduction velocities and decreased nerve action potentials. The distal latencies were not prolonged, and temporal dispersion was very prominent (Fig. 3A: right median nerve, 3B: left ulnar nerve). The frequency of F wave appearance was significantly decreased. The sensory action potentials could not be elicited. A cerebrospinal fluid (CSF) examination revealed a protein concentration of 39 mg/dL and a cell count of 1/mm^3. No oligoclonal bands were detected. The patient's myelin basic protein level was not elevated. MRI showed hypertrophy of the cervical nerves (Fig. 4), lumbar roots, and cauda equina (Fig. 5). The hypertrophic nerves showed homogenous swelling and the lumbar roots exhibited the appearance of grape-like clusters. Repeated cranial and spinal MRI did not demonstrate any signal alterations in the central nervous systems. An analysis of the PMP-22 gene showed a normal pattern; the patient refused to undergo a further genetic analy-

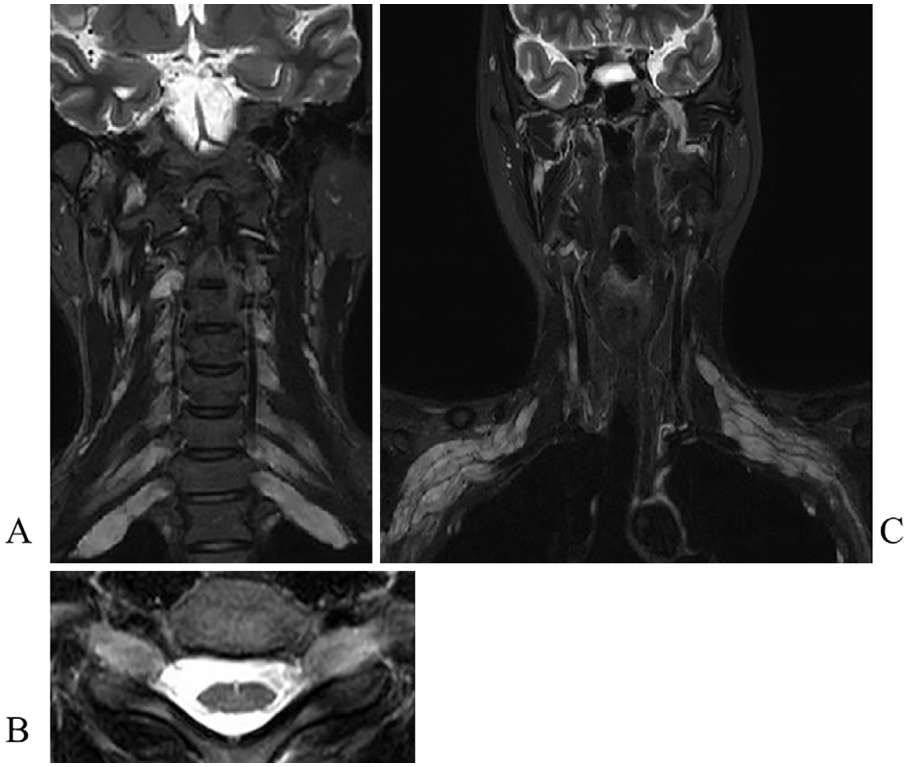

Figure 4. **T2-weighted cervical MRI demonstrates homogenous swelling and strong signals in the nerve roots (A, B: coronal view, C: axial view). The patient was 27 years of age.**

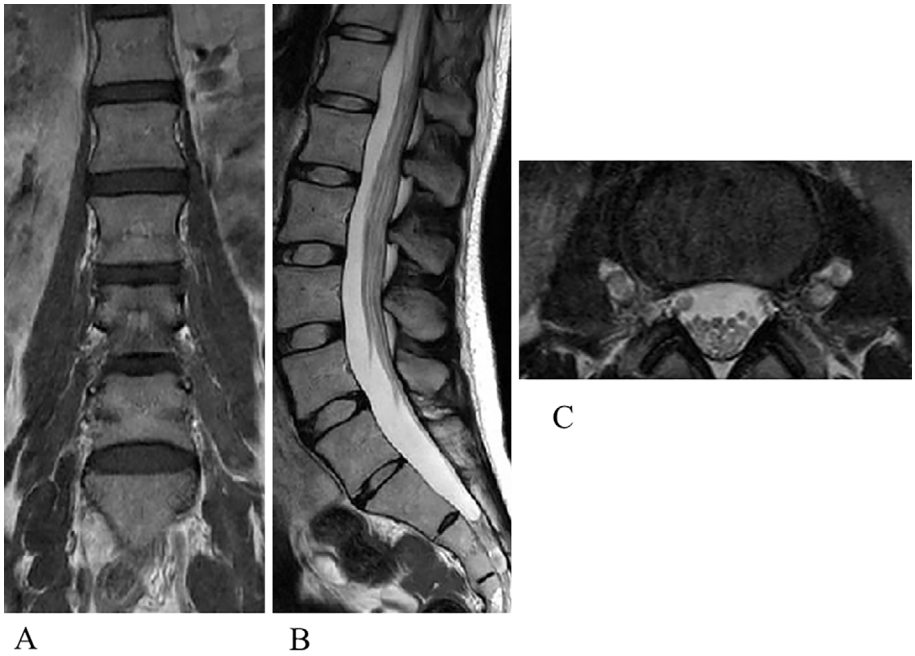

Figure 5. **T1-weighted MRI showed marked homogenous swelling of the lumbar roots (A: coronal view). T2-weighted MRI showed hypertrophy of the cauda equina (B: sagittal view) and hypertrophic nerves outside the canal that appeared as grape-like clusters (C: axial view). The patient was 27 years of age.**

sis. However, her parents agreed to undergo nerve conduction studies, and their results did not indicate any evidence of peripheral neuropathy.

The patient was treated with pulsed steroid therapy and additional administration of intravenous immunoglobulin (IVIg) therapy. Her muscle strength improved. Although she was able to resume ambulation, her subcutaneous nerve hypertrophy persisted. She was subsequently discharged. On outpatient follow-up, her neurological condition seemed to be stable. Later, cooperative investigations with Dr. Ogata of

Kyushu University revealed that her anti NF155 antibody titer was slightly elevated; however, it was not definitely positive (the mean fluorescence intensity ratio : the current case, 5.26; healthy control, 1.51; SD: 0.2)

Discussion

In the present case, the patient initially developed corticosteroid-responsive optic neuritis and cervical myelitis. Her cranial MRI did not reveal any signal alterations, but the observation of short intraspinal cord lesions on cervical MRI and the serum negativity for anti-aquaporin 4 antibody and CSF oligoclonal bands made the differential diagnosis between neuro-myelitis optica (NMO) spectrum disorder and MS difficult; nevertheless, some immunological disturbances were suspected to have been generated in her central nervous systems. At that time, electrophysiological investigations did not reveal any evidence of peripheral nervous system involvement.

Four years after presenting with cervical myelitis, she developed peripheral neuropathy with marked nerve hypertrophy. The results of nerve conduction studies demonstrated mostly demyelination processes and proximal nerve involvement. Nerve hypertrophy, which has been reported in 11-54% of CIDP patients, may further worsen with a longer disease duration (11, 12). Repeated demyelination and remyelination may induce Schwann cell proliferation, resulting in nerve hypertrophy. A few cases of nerve hypertrophy causing spinal cord compression and myelopathy have been reported (13). The pathological examination of those cases showed onion-bulb formations on the nerves. In the current case, the lumbar roots characteristically exhibited the appearance of grape-like clusters, which has rarely been reported.

Although the PMP-22 gene analysis showed a normal pattern and nerve conduction studies of the patient's parents did not any show evidences of peripheral neuropathy, we cannot completely exclude the possibility that she suffered from hereditary peripheral neuropathy, such as a *de-novo* mutation. However, the treatment effects of pulsed steroid therapy and IVIg therapy, which ameliorated her symptoms, are suggestive of immunomediated peripheral neuropathy. In addition, Ormerod et al. reported that some CIDP patients presented MS-like intracranial lesions on MRI, and that most of the intracranial lesions had high periventricular signal intesities (14). Conversely, in our case, the patients did not show any intracranial lesions, even on repeated MRI. Thus, it is possible that unknown immunological dissimilarities exist among CIDP, CIDP accompanied by MS-like intracranial lesions, and the present case.

The autoantibodies in CIDP have been a topic of research for several years (2, 4, 7). Recently, some groups have identified specific antibodies, such as contaction-1, NF155, NF 186, gliomedin, and neuroglial cell adhesion molecule-related cell adhesion molecule (NrCAM), which were presumed to target molecules on the node of Ranvier or the paranodal areas (4, 7, 15). Mutual action between the axons and myelin are important for stable neuronal transmission, and it is suspected that the nodal or paranodal areas were more immunologically fragile. Anti-contactin 1 antibody belongs to the IgG4 subclass; patients with this antibody often exhibit sensory ataxia and preferential responses to corticosteroids, but not IVIg treatment (15).

NF has a neuronal isoform (NF186), and a glial isoform (NF155). NF186 molecules reside at the node of Ranvier and bind to gliomedin in the peripheral nervous system; this complex is crucial for sodium channel clustering. NF155 molecules are expressed at the pararnodal areas and form complexes with contactin and contactin associated protein (Caspr); this complex works to maintain proper formation of the paranodal junction (7, 16). Human autoantibodies to NF were first detected in MS and anti-NF monoclonal antibody-mediated axonal injuries in experimental models of autoimmune encephalomyelitis (17). Another report described anti-gliomedin and anti-NF antibodies in experimental models of allergic neuritis (14, 18). These antibodies inhibited the clustering of voltage-dependent sodium channels to induce the demyelination of the paranode (7).

Anti-NF155 antibody-positivity has been reported in 18% of CIDP cases. Patients with this antibody often show similar clinical characteristics, such as a young age at onset, the distal acquired demyelinating symmetric type of CIDP, prominent nerve hypertrophy, high levels of proteins in the CSF, and the prolonged delay of distal latencies (15). It is likely that the destruction of paranodal structures by this anti-NF155 antibody exerts relatively uniform pathological alterations and a similar clinical presentation. Previous reports have identified that the anti-NF155 antibody could inhibit myelination by blocking the formation of the Caspr/contactin/NF155 complex, which was the core structure at the paranodal loops of cellular adhesion between axon and glial cells (7). This disruption of the paranodal junctions could result in the severe reduction of the conduction velocity, even in the absence of obvious demyelination.

It was hypothesized that anti-NF186 antibodies interfere with nerve conduction in the presence of complements; another hypothesis is that the binding of the antibody to the NF186 molecule itself could hinder the binding of NF186 to the extracellular ligands. The functional role of NF186 molecules is to stabilize the voltage-dependent sodium channels in the node by combining with several extracellular matrixes. As described previously, these matrixes comprise the NrCAM or gliomedin in the peripheral nervous system and the Brevican, Versican V2, and Bral 1 molecules in the central nervous systems (16, 17, 19). Thus, the pathogenic mechanisms of NF186 that damage the peripheral and central nervous systems might be more varied and complicated.

According to Dr. Ogata's investigation, our patient's anti-NF155 antibody titer was inconclusive. There is a possibility that molecules other than NF155 are more closely associated with the precise pathogenesis of combined central and peripheral demyelination, but this hypothesis needs to be con-

firmed by further cumulative studies. Moreover, the complicated pathogenic mechanisms underlying the development of CCDP and CIDP remain to be elucidated.

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

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