Acute Combined Central and Peripheral Demyelination Showing Anti-Aquaporin 4 Antibody Positivity

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Abstract

Neuromyelitis optica spectrum disorder (NMOSD) is characterized by optic neuritis or transverse myelitis with anti-aquaporin 4 (AQP4) antibodies (1). We herein present the case of a patient with NMOSD who also was affected with peripheral neuropathy. A 58-year-old woman developed gait disturbance and sensory impairment in the lower limbs. She exhibited longitudinally extensive transverse myelitis with anti-AQP4 antibodies. Nerve conduction studies showed demyelinating changes. Laboratory findings showed hepatitis-C virus (HCV) infection. Her peripheral neuropathy improved after immunotherapy. There have been no previous reports of NMO or NMOSD associated with neuropathy. The HCV infection or undetermined humoral factors other than the anti-AQP4 antibodies may have caused her peripheral neuropathy.

Key words: neuromyelitis optica, neuropathy, anti-aquaporin 4 antibody

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Introduction

Neuromyelitis optica (NMO) is thought to be an autoimmune channelopathy associated with the development of antibodies against aquaporin 4 (AQP4) (1, 2). Anti-AQP4 antibodies are also detected in the serum of patients with limited forms of NMO, including myelitis associated with longitudinally extensive spinal cord lesions or isolated optic neuritis. In such cases, as long as they present with anti-AQP4 antibodies, they are generally regarded to have a NMO spectrum disorder (SD), even if they do not fulfill the criteria for NMO (1). NMO also is included in the classification of NMOSD. Multiple sclerosis (MS) is an autoimmune disease characterized by chronic inflammation, demyelination and gliosis affecting the central nervous system (CNS), but subclinical peripheral nervous system (PNS) involvement has occasionally been described (3). In contrast, there have so far been no previous reports of PNS involvement in NMO or NMOSD. We herein present a patient with NMOSD who was also affected with peripheral neuropathy.

Case Report

A 58-year-old woman exhibited a fever. Five days later, she experienced gait disturbance and numbness in her lower extremities. Furthermore, two days later, urinary retention and disturbance of consciousness appeared. A physical examination showed erythema and edema in the distal part of both arms and dry eyes. She also had a disturbance of consciousness (Glasgow Come Scale; E4, V4, M6). Her cranial nerves were not involved. Muscle strength testing revealed a value of 1/5 (Medical Research Council grade) in the left side lower extremity and 3/5 in the right side lower extremity. There was an impairment of all modalities of sensations in the lower extremities, with distal and left side dominancy. Areflexia of the lower extremities and positive Babinski signs were observed. As noted above, urinary retention was also observed.

Brain magnetic resonance imaging (MRI) showed mildly abnormal lesions of the white matter around the posterior horns of the lateral ventricle without hypothalamus lesions on T2-weighted images (Fig. 1). Spinal MRI showed long

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Figure 1. Brain MRI showed mildly abnormal lesions of the white matter around the posterior horns of the lateral ventricle, without hypothalamus lesions on T2-weighted images (arrows).

Figure 2. Spinal MRI on admission showed LCL with cord swelling from the cervical to 10th thoracic level on sagittal T2-weighted images (A). Axial T2-weighted images showed lesions around the central canal of the spinal cord (1, 2).

cord lesions (LCL) from the cervical to the 10th thoracic level with partial gadolinium enhancement (Fig. 2). There was no cauda equina lesion noted after gadolinium enhancement. In addition, optic neuritis was not seen. Nerve conduction studies (NCS) revealed prolonged terminal latencies and F wave latencies, reduced compound muscle action potentials (CMAP), sensory nerve action potentials (SNAP), and conduction velocities in almost all nerves studied. There were no conduction blocks or temporal dispersion. For each nerve, the electrophysiological data are considered to be normal if they are within 2.0 standard deviations (SD) from the means for healthy age-matched controls in our hospital

(Table). In the present patient, the tibial somatosensory evoked potential (SEP) could not be evoked, while the median SEP was normal.

A cerebrospinal fluid (CSF) examination showed pleocytosis (422/ μ L; 91% lymphocytes), an elevated IL-6 level (35.4 pg/mL) and a total protein concentration of 115 mg/dL. There were not oligoclonal IgG bands. The laboratory findings showed hyponatremia (111 mEq/L), transfusion hepatitis-C virus (HCV) and euthyroidism, with slightly elevated anti-TPO Ab (0.5 U/mL) and anti-Tg Ab (0.4 U/mL) levels. The patient's plasma osmolality was 245 Osm/kg, whereas her urinary osmolality was elevated to 304 Osm/kg. The level of antidiuretic hormone was 1.26 pg/mL. Her adrenal and renal functions were normal. These findings indicated that she had the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

The following findings were either within the normal limits or were negative; liver enzyme levels, including GOT (26 U/L), GPT (28 U/L) and γ -GT (16 U/L), cryoglobulins, anti-nuclear antibodies, anti ds-DNA, SS-A, and SS-B antibodies, cytoplasmic antineutrophil cytoplasmic antibodies (C-ANCA), and perinuclear antineutrophil cytoplasmic antibodies (P-ANCA). Blood examinations for HIV, lyme disease, syphilis, and hepatitis B were negative, but she tested positive for HCV antibodies (the HCV RNA level in the blood was 2,000 copies/mL). Antiglycolipid antibodies (GM1, GM2, GM3, GD1a, GD1b, GD3, GT1b, GQ1b, Gal-C) were negative. There were no elevated levels of tumor markers or antineuronal antibodies, such as anti-Hu, CV2, Ma2, Ma1, Yo, Ri, or amphiphysin. The serum sample obtained on admission was positive for anti-AQP4 antibodies (1:1,024), as revealed by a sensitive detection method (4). Although Schirmer's test showed low tear production (1 mm in 5 minutes, in both eyes), there was normal salivary flow in the gum test. A minor salivary gland biopsy showed no fibrosis and an inflammatory infiltrate. The diagnostic criteria for Sjögren's syndrome (SS) were not fulfilled (5).

Table. Nerve Conduction Studies

	Normal value	Pre treatment		Post treatment	
		L	R	L	R
Motor nerve conduction					
DL(ms)					
Median	<4.0	4.6	4.9	4.2	4.0
Ulnar	<3.1	3.9	3.8	2.7	2.8
Tibial posterior	<5.7	5.9	6.0	6.3	5.6
CMAP(mV)					
Median	>3.95	5.12	3.39	7.15	5.25
Ulnar	>4.22	7.44	9.05	8.88	7.54
Tibial posterior	>7.28	12.79	13.18	7.85	9.77
MCV(m/s)					
Median	>54.3	41.1	42.7	55.4	68.9
Ulnar	>55.5	60.2	47.6	63.3	64.0
Tibial posterior	>43.9	46.2	44.9	43.5	46.4
F waves(median)	>58.4	51.2	47.4	71.9	57.2
F waves(tibial)	>49.2	41.6	39.3	50.6	49.7
F wave frequency(%)					
Median		62.5	81.3	93.8	100
Tibial posterior		100	100	93.8	100
Sensory nerve conduction					
DL(ms)					
Median	<2.9	4.2	3.2	2.8	2.9
Ulnar	<2.4	2.9	2.6	2.4	2.3
Sural	<3.6	2.8	3.9	3.3	2.8
SNAP(μV)					
Median	>13.86	4.49	2.24	25.8	11.57
Ulnar	>10.77	26.20	16.62	34.5	26.04
Sural	>7.71	3.84	5.26	10.91	29.44
SCV(m/s)					
Median	>58.3	40.4	43.7	57.1	55.3
Ulnar	>58.9	37.9	40.3	50.4	63.1
Sural	>44.5	50.0	35.5	42.4	56.4

DL:distal latency, CMAP:compound muscle action potential, MCV:motor conduction velocity, SNAP:sensory nerve action potential, SCV:sensory conduction velocity

The neurophysiological results showed prolonged terminal latencies and F wave latencies, reduced compound muscle action potentials (CMAP), sensory nerve action potentials (SNAP), and conduction velocities in almost all nerves studied at admission. After the immunomodulatory therapies, the NCS abnormalities were almost normalized. For each nerve, the electrophysiological data were considered to be normal if they were within 2.0 standard deviations (SD) from the means for healthy age-matched controls in our hospital.

The patient was therefore diagnosed with a NMO spectrum disorder as well as with neuropathy and SIADH. Two courses of high-dose intravenous methylprednisolone (one course of 1,000 mg/day for three days) led to complete recovery from the erythema and edema in the distal part of both arms, hyponatremia, disturbance of consciousness, and weakness and sensory impairment in the lower extremities. However, the numbness in the lower extremities and urinary retention continued, and spasticity in the lower extremities was exhibited. Plasma exchange, followed by the oral administration of prednisolone (20 mg/day) led to a gradual recovery from the urinary retention and spasticity in the lower extremities. Although the NCS abnormalities were almost normalized (Table), the spinal MRI signal changes without gadolinium enhancement partially remained. The numbness in the lower extremities diminished after the use of carbamazepine. A follow-up serum examination on the 48 th hospital day showed a decrease in anti-AQP4 antibody (1:16). She has not had any additional relapses for 7 months

after disease onset, and has been taking 15 mg of prednisolone daily without elevated liver enzyme levels or any increase in the HCV-RNA level.

Discussion

There are many papers reporting combined central and peripheral demyelination. MS is an autoimmune disease characterized by chronic inflammation, demyelination and gliosis affecting the CNS, but usually not the PNS. Subclinical PNS involvement has occasionally been described (3). It has been discussed that they could be caused by autoimmune reactivity against myelin antigens common to both the CNS and PNS (e.g., MBP, P1). However, the clinical, CSF and MRI features in patients with both the CNS and PNS involvement were atypical for MS, including bilateral optic neuropathy, the absence of oligoclonal bands in CSF and grey matter involvement, and pseudotumoral lesions on brain MRI (3, 6). Whether the same molecules in both the

PNS and CNS are the antigenic targets in such cases remains to be determined. In the present case, the central and peripheral nervous tissues were involved simultaneously. In 1991, Aimoto et al. (7) reported that demyelination of bilateral optic nerves, the spinal cord, and peripheral nerves occurred at the same time in Devic disease. However, an examination of anti-AQP4 antibodies was not performed in these patients. The present case is, to our knowledge, the first report of the occurrence of NMOSD with peripheral neuropathy. NMOSD is now thought to be an auto-immune channelopathy associated with antibodies to AQP4 (1, 2). AQP4 is a cell membrane water channel that is expressed at the astrocyte foot processes of the blood-brain barrier (BBB) (8, 9). When the BBB becomes leaky due to inflammatory processes, such as infection, anti-AQP4 antibodies infiltrate into the CNS and cause damage via complement pathways (10). In the present case, a similar mechanism may have occurred at the blood-nerve barrier (BNB), but there are no astrocytes in the PNS, supporting that anti-AQP4 antibodies cannot cause peripheral neuropathy.

It has been described that NMOSD frequently coexists with autoimmune disorders, such as SS, systemic lupus erythematosus (SLE) and thyroid disease. These autoimmune disorders can be associated with peripheral neuropathy, as well as CNS disorders. However, the present case was not diagnosed with any of these autoimmune disorders, because the diagnostic criteria were not fulfilled. The etiology of the erythema and edema in the distal part of both arms is unknown, but may have been associated with the autoimmune involvement in the present case.

Recent studies have shown that HCV infection is often associated with the appearance of autoimmune diseases, including SLE, SS, and thyroid disease, and can cause peripheral neuropathy even in the absence of cryoglobulinemia (11, 12). Most peripheral neuropathy in patients with HCV infection is the axonal type of symmetrical sensorimotor neuropathy or multifocal mononeuropathy. Peripheral demyelinating neuropathy has also been rarely described, most often in cryoglobulin negative patients (13, 14). The link between HCV and demyelinating neuropathies could be related to a virus-triggered immune-mediated process (15). In addition, HCV infection can cause myelitis (16, 17). Aktipi et al. reported seven cases of recurrent myelitis with HCV infection. However, NMO-IgG (anti-AQP4) antibodies were evaluated in six of the seven patients, and all were negative. It was considered that the myelitis in those cases was caused by an immune-mediated mechanism related to HCV infection. Interestingly, peripheral nerve involvement was detected in six of the seven patients.

Electrophysiological studies showed prominent proximal and motor damage such as delayed/unexcitable F wave responses, together with motor nerve conduction velocity slowing or decreased CMAP, but the SNAP and conduction velocities were spared, suggesting poly-radiculoneuritis (17). In our present case, the electrophysiological studies showed prolonged terminal latencies and reduced

SNAP, in addition to proximal and motor damage, thus suggesting that the demyelination was widespread in the peripheral nerves, involving both distal and intermediate areas, as well as the proximal roots. HCV infection may therefore be related to the pathogenesis of myelitis, as well as the peripheral neuropathy, in the present case. Otherwise, the possibility exists that some undetermined humoral factor other than anti-AQP4 antibodies might have been present in the serum, which caused widespread demyelination in the peripheral nerves. Future investigations of the pathogenesis of peripheral neuropathy associated with NMOSD are necessary.

Several studies have reported cases of MS and NMO with SIADH (18-24). In the majority of these reported cases, demyelinating lesions in the hypothalamus have been detected on brain MRI. It is considered that damage of the hypothalamus causes SIADH, even if hypothalamic lesions are not detected (24). SIADH has also been documented in patients with peripheral neuropathies such as Guillain-Barré syndrome (25-27), acute autonomic and sensory neuropathy (28), and paraneoplastic autonomic and sensorimotor neuropathy (29). In previous reports of neuropathies with SIADH, most patients had severe autonomic dysfunction (28, 29). Although several hypotheses have been proposed to explain these findings, including downward osmotic resetting and enhanced renal tubular sensitivity to ADH (27), the pathogenesis of SIADH in peripheral neuropathy is still not fully understood.

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

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