Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.5536-20
Intern Med 60: 305-308, 2021
http://internmed.jp

【 CASE REPORT 】

The Oldest Japanese Case of Combined Central and Peripheral Demyelination, which Developed Nine Years After the First Instance of Optic Neuritis

Emi Nomura[1], Yuko Kawahara[1], Yoshio Omote[1], Koh Tadokoro[1], Mami Takemoto[1], Nozomi Hishikawa[1], Toru Yamashita[1], Hidenori Ogata[2] and Koji Abe[1]

Abstract:
Combined central and peripheral demyelination (CCPD) causes demyelination in both the central and peripheral nervous systems. Anti-neurofascin 155 antibody plays an important pathogenic role in CCPD, but evidence concerning an association between this antibody and CCPD remains inconclusive. Although there have been no reports of precedent optic neuritis developing into CCPD, we herein report a Japanese man in whom optic neuritis recurred four times over nine years and who developed CCPD without positive anti-neurofascin 155 antibody. This case suggests the possibility of developing CCPD after optic nerve neuritis and the existence of an unknown antibody that induces CCPD.

Key words: Combined central and peripheral demyelination (CCPD), recurrent optic neuritis

(Intern Med 60: 305-308, 2021)
(DOI: 10.2169/internalmedicine.5536-20)

Introduction

Combined central and peripheral demyelination (CCPD) causes demyelination in both the central and peripheral nervous systems. Anti-neurofascin 155 antibody plays an important pathogenic role in patients with CCPD (1, 2), but evidence concerning an association between this antibody and CCPD remains inconclusive.

Optic neuritis may occur in the course of multiple sclerosis (MS) or neuromyelitis optica (NMO) (3). The rate of progression optic neuritis to MS or NMO is generally low, and there have been no reports of precedent optic neuritis developing into CCPD (4).

We herein report a Japanese man who was suspected of having a demyelinating disease as the oldest case of CCPD without antibody, about nine years after the first instance of optic neuritis.

Case Report

From 62 years old, a man developed recurrent optic neuritis four times and noticed muscle weakness and numbness in the left lower limb at 71 years old. He then became aware of muscle weakness in the left hand and numbness in right hand and bilateral lower limbs at 72 years old. The muscle weakness in his legs worsened, and he became unable to walk without support at 73 years old.

When he was admitted to our hospital, he presented with left hemiparesis and left limping gait with support. He noticed numbness in the right hand and bilateral lower limbs and hyporeflexia in the bilateral lower limbs without a pathological reflex. Serum anti-aquaporin 4 (AQP4), anti-glycolipid, anti-myelin oligodendrocyte glycoprotein (MOG), anti-myelin associated glycoprotein, and anti-neurofascin 155 antibodies were all negative. Cerebrospinal fluid (CSF) protein was high (206 mg/dL) with a normal IgG index (0.66). Myelin basic protein (MBP) was high (136 pg/mL), but oligoclonal band (OCB) was negative. A

[1]Department of Neurology, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Japan and [2]Department of Neurology, Neurological Institute, Graduate School of Medical Sciences, Kyushu University, Japan
Received: June 5, 2020; Accepted: July 21, 2020; Advance Publication by J-STAGE: September 12, 2020
Correspondence to Dr. Emi Nomura, pvq50q2x@okayama-u.ac.jp

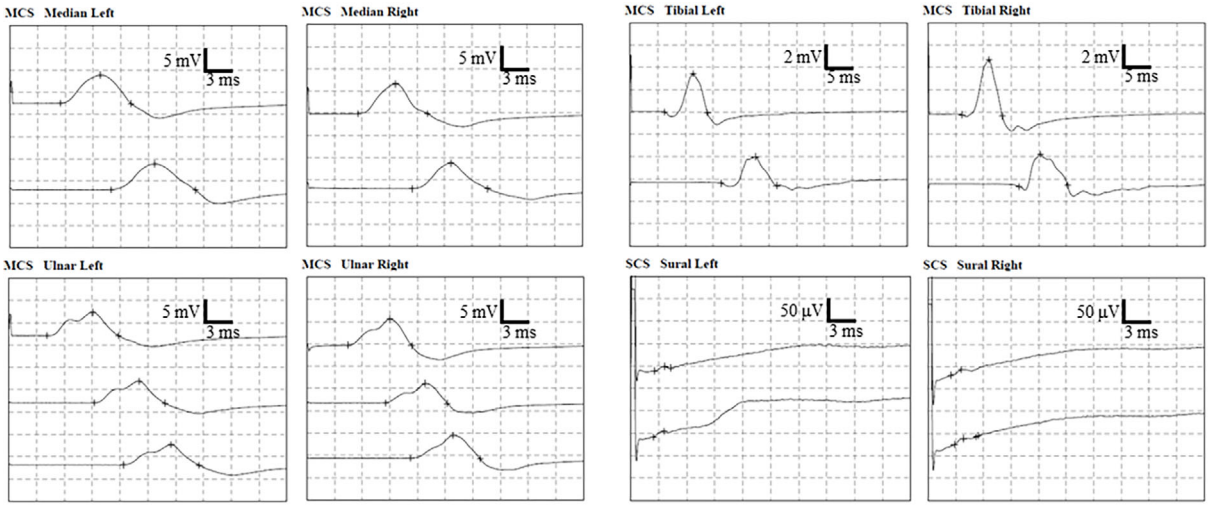

Figure 1. **Nerve conduction studies on admission, showing prolonged terminal latencies and reduced conduction velocities in the bilateral median, ulnar, tibial, and sural nerves. A reduced compound muscle action potential was observed in the bilateral tibial nerves. MCS: motor nerve conduction study, SCS: sensory nerve conduction study**

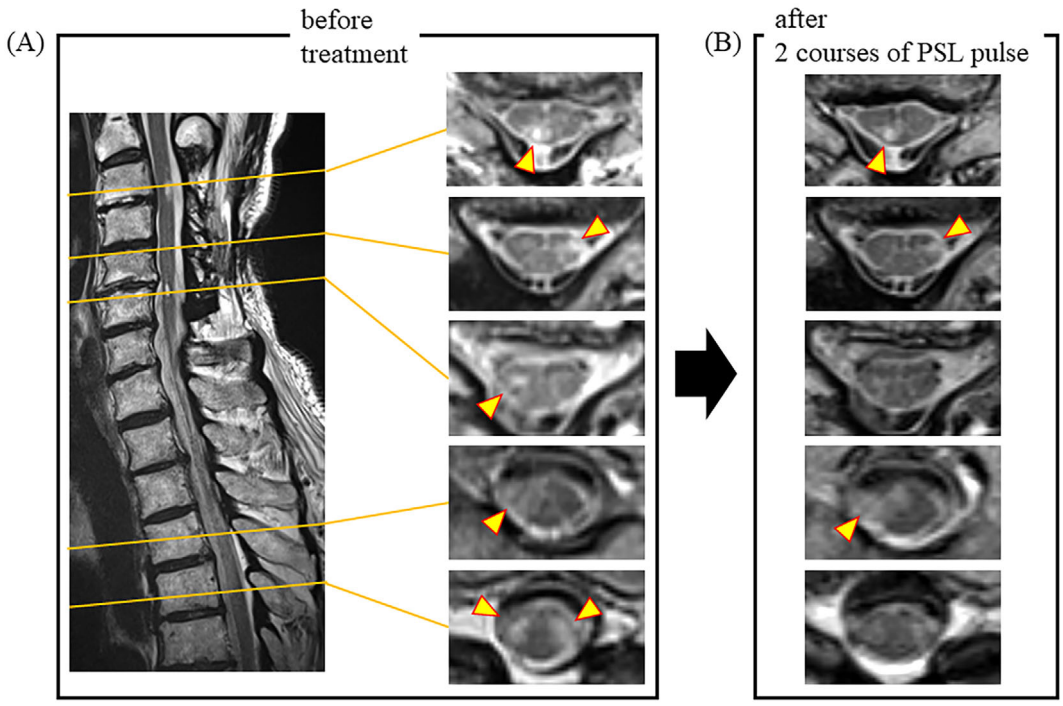

Figure 2. **Spinal magnetic resonance imaging findings. (A) Spinal MRI of pretreatment shows abnormal lesions in both the cervical (C3-6) and thoracic (Th4-5) spinal cords (arrowheads). (B) Spinal MRI at posttreatment shows improved abnormal lesions.**

nerve conduction study (NCS) showed prolonged terminal latencies (mean; motor nerves: upper limbs 4.9 msec, lower limbs 6.2 msec, sensory nerves: upper limbs 4.3 msec, lower limbs 2.5 msec) and reduced conduction velocity (mean; motor nerves: upper limbs 33.1 m/s, lower limbs 32.9 m/s, sensory nerves: upper limbs 31.9 m/s, lower limbs 44.0 m/s) in the bilateral median, ulnar, tibial, and sural nerves (Fig. 1). Reduced compound muscle action potential was observed in the bilateral tibial nerves (mean; 2.6 mV) (Fig. 1). Short latency somatosensory evoked potential (SSEP) and visual evoked potentials (VEP) showed prolonged latencies. Brain magnetic resonance imaging (MRI) showed no evident abnormal lesions. Spinal MRI showed cervical and thoracic cord lesions without gadolinium enhancement (Fig. 2A). A nerve biopsy of the sural nerve showed not only findings of demyelination but also axonal degeneration (Fig. 3A, B).

We suspected the existence of inflammation in both cen-

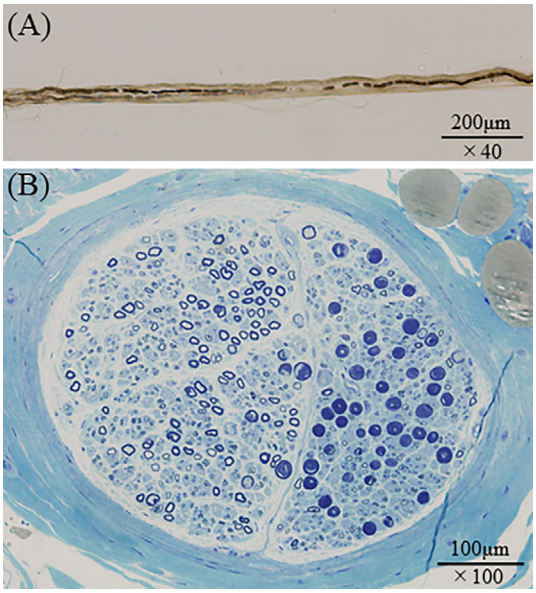

Figure 3. A sural nerve biopsy, showing (A) segmental demyelination in the teased nerve fiber and (B) a reduced myelinated fiber density, decreased incidence of large- and small-diameter fibers, myelin ovoids suggesting increased axonal degeneration, and perineurial edema in the epoxy-embedded section. The nerve showed findings of both demyelination and axonal degeneration.

tral and peripheral nerves and his symptoms to indicate a demyelinating disease, such as CCPD. Two courses of steroid pulse therapy (1,000 mg/day) improved the muscle weakness in the left hand and left lower limb and the numbness in the right hand and bilateral lower limbs. He became able to walk without support after two courses of steroid pulse therapy. CSF protein improved from 206 to 174 mg/dL. Spinal MRI showed reduced abnormal lesions (Fig. 2B).

Discussion

CCPD causes demyelination in both the central and peripheral nervous systems and is very rare in Japan, with an average onset age of 31.7±14.1 (range: 8-59) years old (2, 5). To our knowledge, this case was the oldest onset (71 years old) of both spinal and peripheral demyelination as CCPD in Japan. In addition, optic neuritis had recurred 4 times from 62 years old, against which steroid therapy was very effective. MRI showed abnormal lesions on the optic nerves in the acute phase of each instance of recurrent optic neuritis, with no new or old brain and spinal lesions.

Optic neuritis is a demyelinating disease of the central nervous system and may occur in the course of MS or NMO (3). The development rate of optic neuritis to MS or NMO is generally low (14.4% and 12.5% at 5 years, and 29.8% and 12.5% at 10 years) (4), and there have been no reports of optic neuritis developing into central or peripheral demyelination, such as CCPD. This is thus the first case report of CCPD developing after recurrent optic neuritis.

Anti-neurofascin 155 antibody positivity is more common in patients with CCPD (45.5-86.0%) than in those with other demyelinating diseases, such as MS, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and Guillain-Barré syndrome (GBS), playing an important pathogenic role (1, 2). However, some CCPD cases have shown positivity for anti-AQP4 and anti-MOG antibodies (6, 7). The evidence concerning an association between these antibodies and CCPD thus remains inconclusive. Despite the fact that no positivity for such antibodies was observed, the symptoms observed in the present case, including CSF protein, physiological tests, spinal MRI lesions, and the effect of immunosuppressive therapy indicated a diagnosis of CCPD with a still unknown antibody (8).

Previous CCPD case reports have shown demyelination in the findings of nerve biopsies (7, 9). However, the nerve biopsy in the present case showed findings of both demyelination and axonal degeneration. Given the nerve biopsy results and other clinical examination findings, we considered the pathology of this case to be demyelination-predominant. There have been few reports describing the nerve biopsy findings of CCPD, so why axonal degeneration occurs in CCPD remains unclear. More histological studies will be needed to confirm the pathology of CCPD.

We herein report a Japanese man who was suspected of having a demyelinating disease as the oldest cases of CCPD, occurring about nine years after the first instance of optic neuritis. This suggests the possibility of developing a demyelinating disease such as CCPD after optic nerve neuritis. It is important to carefully follow cases of recurrent optic neuritis. This case also suggested that cases of late-onset CCPD after recurrent optic neuritis may have unknown antibodies that induce demyelination in both the central and peripheral nervous systems.

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

Financial Support

This work was partly supported by Grant-in-Aid for Scientific Research (B) 17H0419611, (C) 15K0931607, 17H0975609 and 17K1082709, and by Grants-in-Aid from the Research Committees (Kaji R, Toba K, and Tsuji S) of the Japan Agency for Medical Research and Development (AMED).

Acknowledgement

We appreciate the cooperation of the patients. We also thank Dr. Hidenori Ogata (Kyusyu University), and Dr. Susumu Kusunoki (Kindai University) for their assistance in measuring the anti-neurofascin 155 and anti-glycolipid antibodies.

References

1. Kawamura N, Yamasaki R, Yonekawa T, et al. Anti-neurofascin antibody in patients with combined central and peripheral demyelination. Neurology **81**: 714-722, 2013.
2. Ogata H, Matsuse D, Yamasaki R, et al. A nationwide survey of combined central and peripheral demyelination in Japan. J Nerurol Neurosurg Psychiatry **87**: 29-36, 2016.

3. Benoilid A, Tilikete C, Collongues N, et al. Relapsing optic neuritis: a multicentre study of 62 patients. Mult Scler **20**: 848-853, 2014.
4. Pirko I, Blauwet LA, Lesnick TG, Weinshenker BG. The natural history of recurrent optic neuritis. Arch Neurol **61**: 1401-1405, 2004.
5. Kira J, Yamasaki R, Ogata H. Anti-neurofascin autoantibody and demyelination. Neurochem Int **130**: 104360, 2019.
6. Kitada M, Suzuki H, Ichihashi J, et al. Acute combined central and peripheral demyelination showing anti-aquaporin 4 antibody positivity. Intern Med **51**: 2443-2447, 2012.
7. Vazquez Do Campo R, Stephens A, Marin Callazo IV, Rubin DI. MOG antibodies in combined central and peripheral demyelination syndromes. Neurol Neuroimmunol Neuroinflamm **5**: e503, 2018.
8. Kawamura N. Neurofascin: a novel target for combined central and peripheral demyelination. Clin Neurol **54**: 978-980, 2014.
9. Nonaka T, Fujimoto T, Eguchi K, et al. A case of combined central and peripheral demyelination. Clin Neurol **55**: 389-394, 2015.