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Brief Report

An interesting case of combined central and peripheral demyelination with antibodies against paranodal protein neurofascin 186

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Abstract

We report the diagnostic process of a rare patient with a combined central and peripheral demyelinating disease with antibodies against paranodal protein neurofascin 186 (anti–NF186)—the patient presented with weakness in both lower limbs. The clinical process and evidence are similar to subacute combined degeneration. However, thoracic spinal MRI shows T1 equal signal, and T2 high signal lesions in thoracic vertebrae 5-7 mainly involve white matter. The Aquaporin 4 antibody of the central nervous system indicates the disease is of an optic neuromyelitis pedigree. The antibodies against paranodal protein neurofascin 186 indicate demyelinating peripheral nerve pathogenesis. The final diagnosis was a combined central and peripheral demyelinating disease based on the results of various examinations. The patient's condition improved after methylprednisolone therapy and intravenous immunoglobulin.

Keywords: Subacute combined degeneration of spinal cord; neuromyelitis optic spectrum disease; combined central and peripheral demyelination.

Introduction

Combined central and peripheral demyelination (CCPD) is a rare entity in which central and peripheral nervous system demyelination coexist. It also is an entity with heterogeneous immune pathogenesis and clinical characteristics, overlapping between multiple sclerosis (MS) and chronic inflammatory demyelinating polyneuropathy (CIDP) [1-2]. CCPD with NF - 155 has been reported in the past, but CCPD with NF - 186 is rare. Herein, we present a patient with CCPD with antibodies against paranodal protein neurofascin 186 (anti–NF186). In the last years, a set of autoantibodies against proteins located at the node of Ranvier has been identified in patients with chronic inflammatory demyelinating polyneuropathy (CIDP). These antibodies target neurofascin, contactin1, or contactin-associated protein 1, and we propose to name CIDP patients with these antibodies collectively as seropositive. They have unique clinical characteristics that differ from seronegative CIDP [3].

When inflammatory demyelinating disorders affect the central nervous, it may be multiple sclerosis (MS). When inflammatory demyelinating disorders affect the peripheral nervous system, it can be called chronic inflammatory demyelinating polyneuropathy (CIDP). Both central and peripheral demyelination phenomena were firstly reported in 2 cases of MS and polyneuritis in 1979 by Forrester and Lascelles [4]. In 1987 a series of 6 cases were reported, firstly proposing the name of CCPD [5]. Since then, some case reports have been reported about CCPD but using different diagnostic names such as MS with peripheral neuropathy, CIDP with central demyelination or Guillain-Barre syndrome (GBS) and acquired central nervous system (CNS) demyelinating, etc.[6-9].

Under CCPD, demyelinating changes occur simultaneously or successively in the peripheral nervous system and the central nervous system, which is rare in the clinic. CCPD is a pedigree disease and cannot be considered a simple combination of MS and CIDP [10-15]. At present, there is no unified diagnostic standard for CCPD.

The criteria of CCPD are determined as follows, referring to a nationwide survey of CCPD in Japan [16]: (1) peripheral nervous system (PNS) involvement criteria: (a) Supportive symptoms: lower paralysis, glove and stocking sensory disturbance, muscle atrophy, hyporeflexia (>1month). (b) Necessary: NCS indicated immediate, prolonged distal latency, decreased motor conduction velocity (MCV)/sensory

conduction velocity (SCV), decreased or absent compound muscle action potential (CMAP)/sensory nerve action potential (SNAP), F-Waves/H-reflex abnormalities; CSF albumi-nocytologic dissociation; (2) central nervous system (CNS) involvement criteria: (a) Supportive symptoms: upper paralysis, sphincter disturbance, sensory level, hyperreflexia, pathological sign, decreased vision, epilepsy, mental disturbance, and unconsciousness.(b) Necessary: T2 high-signal intensity lesions in the brain, optic nerves or spinal cord on MRI, or abnormalities on visual-evoked potentials (VEPs); (3) exclusion criteria: secondary demyelinating diseases or changes, such as infectious diseases (e.g., human T-lymphocyte trophic virus type 1-associated myelopathy, syphilis, neuroborreliosis, HIV infection or progressive multifocal leukoencephalopathy), pre-existing inflammatory diseases (e.g., sarcoidosis, Behçet's disease, Sjögren's syndrome, vasculitis or other collagen diseases), mitochondrial disease, metabolic/toxic diseases(e.g., Vitamin deficiency, amyloidosis, chronic alcoholism, diabetes mellitus or subacute myelo-optic neuropathy due to clioquinol in-toxication, cervical spondylotic myelopathy, syringomyelia, spinocerebellar degeneration, multiple myeloma, other tumors, inherited diseases (e.g., leucodystrophies), cerebrovascular disease and non-specific lesions on T2-weighted MRI (e.g., leucoaraiosis).

A positive antibody of Neurofascin also accompanies CCPD. Neurofascin (NF) is a cell surface protein involved in forming nerve bundles, which plays an important role in the formation and stability of Ranvier’s nodes. NF can interfere with the conduction of nerve impulses and may be involved in the pathophysiological process of demyelinating diseases such as MS, CIDP and CCPD [17-19].

Seropositive CIDP patients have a specific clinical phenotype distinct from seronegative CIDP: They typically respond poorly to corticosteroids or IVIg but may benefit from plasmapheresis and rituximab (RTX). This case of CCPD (with antibodies against paranodal protein neurofascin 186) responded well to corticosteroids and intravenous immunoglobulin (IVIg).

2. Case report

A 57-years-old female patient presented with progressive symmetrical distal lower limb weakness for 7 months on April 6, 2020. Neurological examination showed the proximal muscle strength of both lower limbs was 1/5 on MRC grading with wasting and areflexia, while the distal muscle strength was 2/5 on MRC grading with wasting and areflexia. The sensation of pain, temperature and acupuncture was decreased below the bilateral anterior superior iliac spine, and the vibration sensation was decreased below the bilateral anterior superior iliac spine. Otherwise, biceps brachii, triceps brachii and knee-tendon reflexes were hyporeflexic (1+) bilaterally. Babinski's sign was negative bilaterally.

Laboratory results: blood cell analysis showed that white blood cells were 3.48 $X10^9$ / L, red blood cells were 3.64 x 10^{12} / L, hemoglobin was 110 g / L, and hematocrit was 33.8%; no obvious abnormality was found in other biochemical examination. C-reactive protein 37.98 mg / L; Procalcitonin 1.058 ng/ml; Rheumatic immune series examination showed that ESR was 53 mm / at the end of the first hour, antinuclear antibody spectrum: UL snRNP ribonucleoprotein was weakly positive (±), SSA / ro52kd was weakly positive (±), and antinuclear antibody was 64.97 U / ml. Vasculitis autoantibodies ANCA, IgM, IgG, IgA, and complement c3c4 were in the normal range. Serum vitamin B12 (he was treated outside the hospital) was in the normal range, and the anti- gastric parietal cell antibody was 1:320 (+).

Electromyography of both lower limbs: (1) The amplitude of the common peroneal nerve decreased with prolonged latency; the sensory nerve conduction velocity of the right sural nerve and right superficial peroneal nerve was not measured; the latency of the F wave of the right tibial nerve was prolonged. (2) The Somatosensory evoked potential of both lower limbs showed that the primary response P40 of the bilateral cortex was delayed, and the conduction of the bilateral proprioceptive pathway was slowed. These results suggested multiple peripheral sensory and motor nerve damage of both lower limbs.

Thoracic spinal MRI (see **Fig. 1**) showed T1 equal signal and T2 high signal lesions, which can be seen in thoracic vertebrae 5-7, mainly involving white matter.

Cerebrospinal fluid investigation showed colorless and transparent liquid with the leukocytes 11× 10^6 / L, sugar 3.35 mmol / L, protein 0.8600 g / L, chloride 122.00 mmol / L. The demyelinating autoantibody of the central nervous system (**Fig. 2 and Fig. 3**) showed that the antibody concentration of AQP4 (Aquaporin 4) IgG, whether in serum or cerebrospinal fluid, was

higher (1:1000 + + +, CBA method), and the oligoclonal band, paraneoplastic associated antibody spectrum, ganglioside antibody spectrum was normal.

The patient has not had an injury to the optic nerve. There has been no obvious swelling or other changes in the optic nerve MRI, and there has been no obvious abnormality in visual evoked potential.

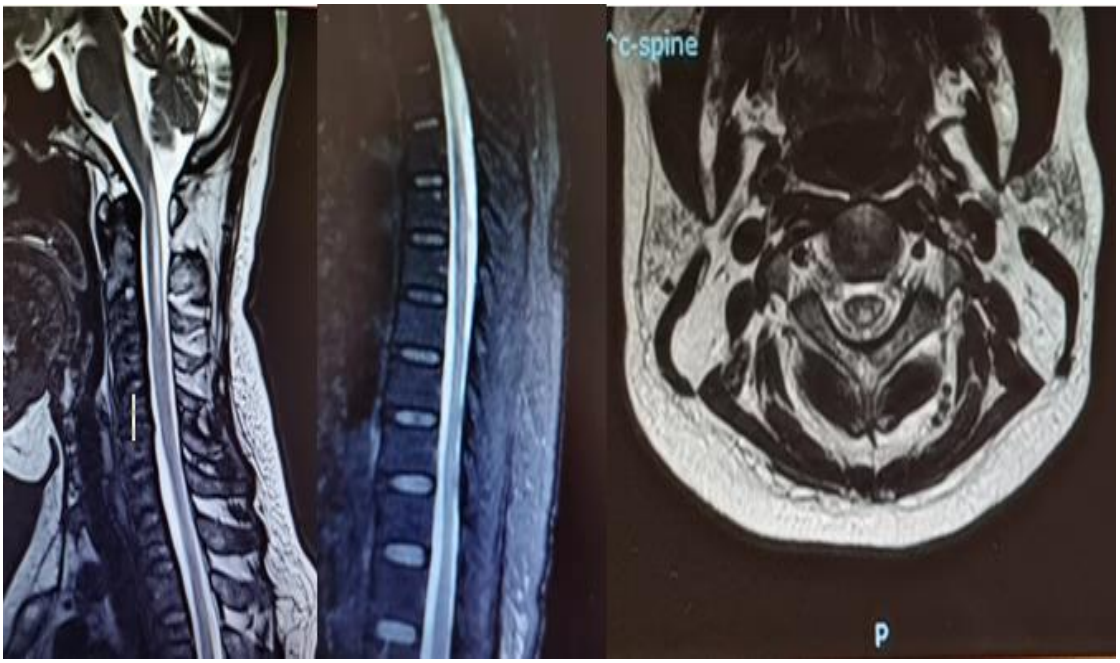

Figure 1: *A cervical MRI B: thoracic MRI C: high signal lesions on the T2 image can be seen in the cross-section of cervical MRI, close to the posterior cord of the spinal cord.*

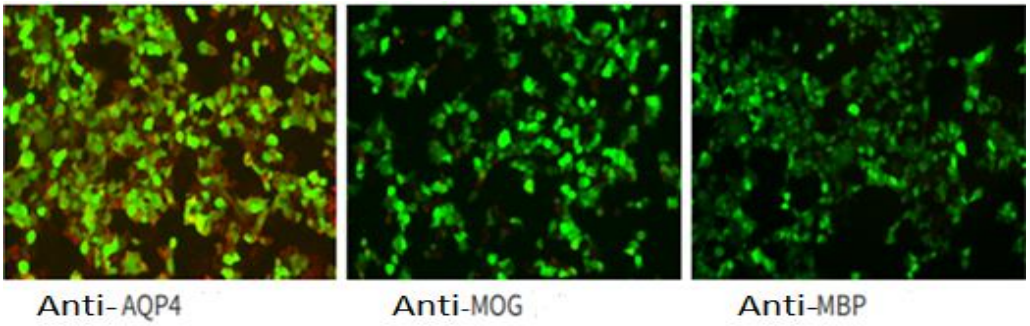

Figure 2: *The results of serum demyelinating autoantibody of the central nervous system. By CBA method, AQP4 antibody IgG is positive (1:1000 + + +). MOG (myelin oligodendrocyte glycoprotein) antibody IgG was negative, and MBP (myelin basic protein) antibody IgG was negative.*

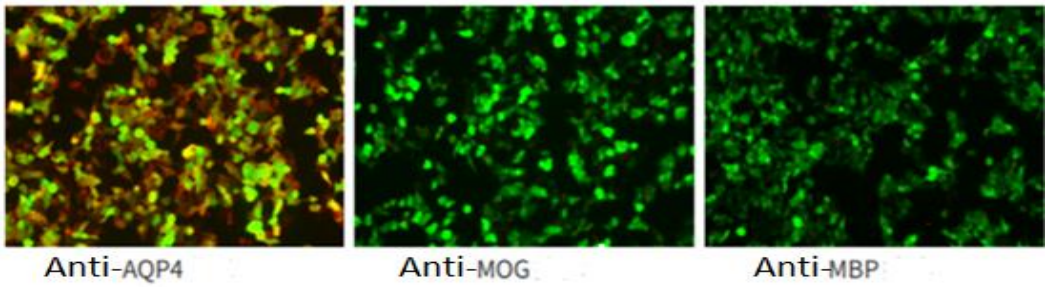

Figure 3: *The results of demyelinating autoantibodies in cerebrospinal fluid and central nervous system. By CBA method, AQP4 antibody IgG was positive (1:1000 + + +). MOG (myelin oligodendrocyte glycoprotein) antibody IgG was negative, and MBP (myelin basic protein) antibody IgG was negative.*

The patient's Electromyography of both lower limbs showed multiple peripheral nerve injuries (sensory and motor nerves are involved). Serum neurofascin 186(NF186) antibody IgG at 1:32 (+) (**Fig. 4**) suggests the Nodes of Ranvier and its adjacent area were damaged.

Based on thoracic spinal MRI results, higher concentration antibody AQP4 (serum and cerebrospinal fluid) and increased concentration of IgG against neurofascin 186, CCPD were concluded.

Then the patient was given hormone shock therapy on May 15, 2021: methylprednisolone 1000mg (3 days) - 500mg (3 days) - 250mg (3 days) - 120mg (3 days). After a gradual reduction, oral prednisone acetate 60mg (once a day, 1 week) - prednisone 55mg (once a day, 1 week) were given until prednisone was reduced to 20mg. On May 15, 2021, Intravenous immunoglobulin (0.4g/kg for 5 consecutive days) was administered. On May 18, 2021, mycophenolate mofetil 0.25g/day was given. Routine blood tests, liver and kidney function, the absolute value of B cells and serum IgG level were checked intermittently. The dosage was gradually increased to the current maintenance dose of 0.75g/day. At the same time, Proton pump inhibitor, calcium supplement and potassium supplement were given to resist the side effects of methylprednisolone. The patient also received anticoagulation to prevent lower extremity deep venous thrombosis, and B vitamins were given to repair the myelin sheath. The patient was involved with exercise rehabilitation. After six months of treatment, the proximal muscle strength of both lower limbs was 3/5 on MRC grading, still with wasting and areflexia. The distal muscle strength was 4/5 on MRC grading with wasting and areflexia. Further follow-up is continued.

3. Discussion

The patient was admitted with weakness in both lower limbs and had suffered from "anemia" in the past. The blood cell analysis showed that the hemoglobin was low, the patient's anti gastric parietal cell antibody was 1:320 (+), and the somatosensory evoked potential examination showed bilateral proprioceptive conduction slowed down. It is easy to diagnose subacute combined spinal cord degeneration. However, subacute combined degeneration cannot explain the antibodies in peripheral and central nerves.

The central nervous system demyelinating antibody AQP4 IgG suggests this condition is an optic neuromyelitis pedigree disease. However, the peripheral nerve antibody (nodes of Ranvier and its adjacent area antibody) shows that the NF186 (neurofascin 186) is also higher. It is rare in the clinic that the two antibodies (central nerve demyelinating antibody and peripheral nerve demyelinating antibody) are positive at the same time. NF186 antibody is less common than the NF155 antibody in the clinic. NF155 antibody higher is characterized by less tremor, more common sensory ataxia, and some patients will have gamma globulin resistance. The two antibodies (AQP4 and NF186) appear simultaneously, almost unreported. Combined central and peripheral demyelination (CCPD) was officially named in 1999, i.e., demyelinating changes occurred simultaneously

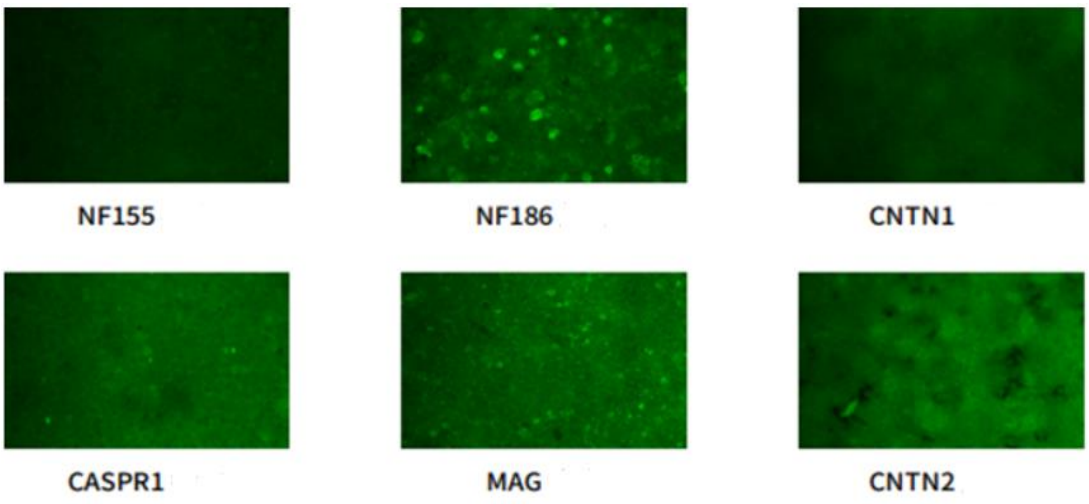

Figure 4: *The CBA method is the antibody spectrum test results of 6 items of CIDP (Ranvier's node / paranodal disease). NF186 (neurofascin 186) antibody IgG: positive (1:32 +), NF155 (neurofascin 155) antibody IgG: negative, CNTN1 (contactin-1) antibody IgG: negative, CASPR1 (contactin- associated protein 1) antibody IgG: negative, MAG (Myelin associated glycoprotein) antibody IgM: negative, CNTN2 (contactin-2) antibody IgG: negative.*

or successively in the peripheral nervous system and the central nervous system, which is rare in the clinic.

Antibodies against neurofascin 155 were subsequently detected among a subset of patients with CIDP and MS and, therefore, also found among patients with CCPD. Still, the clinical distinction between CCPD with and without these antibodies remains unclear [20-21]. Antibodies against neurofascin 186 were less reported among patients with CCPD.

Seropositive CIDP patients have a specific clinical phenotype distinct from seronegative CIDP. They typically respond poorly to corticosteroids or IVIg but may benefit from plasmapheresis and rituximab (RTX). This case of CCPD responded well to corticosteroids and IVIg.

Neuromyelitis optical spectrum disorders (NMOSD) is a serious disabling autoimmune inflammatory demyelinating disease of the central nervous system. The immune tolerance to the AQP4 antibody is considered to be the etiology of the disease. When the blood-brain barrier is injured, the concentration of AQP4 antibody is higher, and it will combine with AQP4 antigen (on the foot process of astrocytes), which will lead to the down-regulation of AQP4 expression. The activation of the complement system and the infiltration of granulocytes will eventually lead to the demyelination of nerve cells and the decline in nerve function, resulting in the corresponding clinical symptoms.

NF proteins include: NF140, NF155, NF166, NF180 and NF186. In the central and peripheral nervous system, two subtypes of glial NF155 and axon NF186 are mainly expressed. On the axon of mature neurons, NF186 maintains the stability of neuronal structure through the interaction with cytoskeletal component ankyrin G; In the peripheral nervous system, NF186 interacts with glial proteins in the substrate and Schwann cell microvilli. The main function of NF186 is to form a node complex as a molecular barrier to limit the diffusion and migration of proteins and molecules in the nodal region to the other node region. This promotes the composition of the myelinated axon domain and the jumping conduction of signals along axons. The patient's anti NF186 antibody was higher, which could explain the mechanism of peripheral nerve injury shown by electromyography.

Demyelination of the peripheral nervous system and the central nervous system occurs simultaneously or successively, is a pedigree disease and cannot be considered a simple combination of MS and CIDP [20-21]. At present, there is no unified diagnostic standard for CCPD. The diagnosis of CCPD should admit the following conditions: (1) there are manifestations of central nerve damage such as intracranial, spinal cord or optic nerve MRI T2 high signal or abnormal visual evoked potential; (2) At least two nerves of the median nerve, ulnar nerve or tibial nerve had evidence of demyelination of peripheral nervous systems, such as nerve conduction delay, conduction block and abnormal F-wave; (3) Except direct infection [syphilis, human immunodeficiency virus (HIV), human T cell virus infection, etc.), systemic immune diseases (sarcoidosis, Behcet's disease, Sjogren's syndrome, vasculitis, connective tissue disease, etc.), mitochondrial diseases, metabolic disorders and poisoning (vitamin deficiency, subacute spinal neuropathy, chronic alcoholism, amyloidosis, diabetes, etc.), cervical spondylotic myelopathy, spinal cord degeneration, cerebrovascular diseases, tumor and genetic diseases.

Conflict of Interest

The authors declare no conflict of interest.

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