

The clinical features of combined central and peripheral demyelination and antibodies against the node of Ranvier

Xiaodan Hou, Yan Liang, Pan Cui and Junwei Hao

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Abstract

Background: Combined central and peripheral demyelination (CCPD) is a disease of inflammatory demyelination that affects central and peripheral nerves simultaneously or temporally separated.

Objectives: This study evaluated the clinical characteristics and the existence of antinodal/paranodal antibodies in patients with CCPD.

Methods: We reviewed the clinical manifestations, laboratory tests, electrophysiological examinations, neuroimaging findings, treatment, and prognosis of 31 patients with CCPD. Using a live cell-based assay, we tested antinodal/paranodal antibodies.

Results: The most common symptoms were motor weakness (83.3%), hyporeflexia (63.3%), and sphincter disturbance (58.1%). In total, 16.6% of patients had impaired vision symptoms, whereas 33.3% of patients had abnormal visual-evoked potentials (VEPs). A total of 21.1% (4/19) of patients were positive for anti-AQP4 (aquaporin 4) antibodies, 20.0% (2/10) of patients were positive for anti-NF155 (neurofascin-155) antibodies, and 10.0% (1/10) of patients were positive for anti-MAG (myelin-associated glycoprotein) antibodies. The effective rates of intravenous corticosteroids, intravenous immunoglobulins, and rituximab were 72.2%, 37.5%, and 100%, respectively. At the illness peak, 75% of patients with CCPD had an mRS (modified Rankin Scale) score of 4 or greater. In remission, 37.5% had an mRS score of 4 or greater.

Conclusion: The clinical manifestations of patients with CCPD are highly heterogeneous. We recommend testing antinodal/paranodal antibodies for patients with CCPD.

Correspondence to:

Junwei Hao
Department of Neurology,
Xuanwu Hospital, Capital
Medical University,
Changchun Avenue 45,
Xicheng District, Beijing
100032, China.
haojunwei@vip.163.com

Junwei Hao
Yan Liang
Pan Cui
Department of Neurology,
Xuanwu Hospital, Capital
Medical University, Beijing,
China

Xiaodan Hou
Department of Neurology,
Xuanwu Hospital,
Capital Medical University,
Beijing, China
Department of Neurology,
Tianjin Neurological
Institute, Tianjin Medical
University General Hospital,
Tianjin, China

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Introduction

Inflammatory demyelinating diseases are generally classified into two categories: those that affect only the central nervous system (CNS), such as multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMOSDs), and those that affect only the peripheral nervous system (PNS), such as chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and Guillain-Barré syndrome. However, there is a demyelinating condition involving both the CNS and the PNS simultaneously or temporally separated, namely, combined central and peripheral demyelination (CCPD).¹ This entity is relatively infrequent and often presents a diagnostic challenge to clinical neurologists.

To date, a few case reports¹⁻³ and retrospective cohort studies⁴⁻⁶ reporting clinical characteristics in patients with CCPD have been published. The frequency of preceding infections, the mode of onset, the clinical course, the presence of antibodies, the treatment response, and outcomes differ among patients with CCPD in these studies.

Antibodies to neurofascin-155 (NF155) have been identified in variable proportions of patients with CCPD. It has previously been observed that anti-NF155 antibodies were positive in 71.4%³ and 45.5%⁵ of patients with CCPD, respectively. However, another study⁷ suggested that patients with CCPD do not have anti-NF155 antibodies.

The conclusions on the clinical characteristics of CCPD are not completely consistent. Research on different races and regions should be performed to determine the characteristics of CCPD. In addition, research on anti-NF155 antibodies has only been performed in small cohort studies of patients with CCPD. More data need to be obtained to understand the prevalence of anti-NF155 antibodies in patients with CCPD. Moreover, the prevalence of autoantibodies against proteins localized to the node of Ranvier, such as anti-NF186 antibodies and anti-MAG (myelin-associated glycoprotein) antibodies, in patients with CCPD remains largely unknown. We aimed to assess the clinical characteristics and evaluate the existence of anti-nodal/paranodal antibodies in patients with CCPD.

Methods

Participants and research design

This study was an observational study performed at Xuanwu Hospital Capital Medical University in China. Our definition of CCPD was based on the following criteria, according to a national survey conducted in Japan:⁵

1. Criteria for CNS lesions: Brain or spinal cord T2 high-signal-intensity lesions on magnetic resonance images (MRIs) or abnormalities in visual-evoked potentials (VEPs).
2. Criteria for PNS lesions: Conduction block, conduction delay, F-wave, and H reflex abnormalities or temporal dispersion, an implication of demyelinating neuropathy with regard to nerve conduction studies (NCSs). Herein, it was compulsory for at least two nerves among the median, ulnar, tibial, and peroneal nerves to have abnormal findings indicating demyelination.
3. Exclusion criteria: Secondary demyelination diseases, including metabolic or toxic diseases, such as vitamin B12 deficiency, diabetes mellitus, chronic alcoholism, or amyloidosis; infectious diseases, for example, syphilis infection, HIV infection, Lyme neuroborreliosis, or progressive multifocal leukoencephalopathy; pre-existing inflammatory diseases, such as Sjögren's syndrome, Behçet's disease, vasculitis, sarcoidosis, or other collagen diseases; multiple myeloma or other tumors; cervical spondylotic myelopathy; syringomyelia; cerebrovascular disease; mitochondrial disease; spinocerebellar degeneration and inherited diseases, such as leukodystrophies; and nonspecific lesions on T2-weighted MRI, for example, leukoaraiosis.

This research included patients with CCPD who visited our hospital between 1 January 2010 and 30 June 2020, and met the diagnostic criteria listed above. This study enrolled 91 patients. After excluding 60 patients (26 with diabetes mellitus, 10 with infectious diseases, 3 with Hashimoto's thyroiditis, 1 with collagen diseases, 1 with metabolic disease, 13 with tumors, 4 with trauma, and 2 with the spinal vascular disease), 31 participants were finally diagnosed with CCPD (Figure 1).

The current study was approved by the Ethics Committee of Xuanwu Hospital, Capital Medical University, Beijing, China. All patients provided written informed consent.

Data collection

We used clinical information from medical records. Data such as onset age, sex, history of preceding infection, onset mode, clinical course, clinical symptoms and signs, Kurtzke Expanded Disability Status Scale (EDSS) score at admission, laboratory findings such as records of antibodies testing if available, spinal cord and brain magnetic resonance imaging (MRI) findings, VEPs, and NCS findings were collected. We also followed up with the patients and recorded the medication status and prognosis. This study defined the onset mode as acute (reaching disease peak within 1 week), subacute (reaching disease peak between 1 week and 1 month), or chronic (reaching disease peak after 1 month). We divided the clinical course into four categories: monophasic, which is characterized by a single demyelination incident that was not accompanied by subsequent events; relapse-remitting, which is accompanied by a recurrence of previously experienced symptoms or a clinical relapse of novel symptoms more than 3 months after the preliminary episode; chronic progressive, which is characterized by the occurrence of gradual symptom deterioration (typically months to years); and rapid progressive, which is characterized by the occurrence of rapid symptom deterioration (typically days to weeks). Patients with CNS damage as the primary symptom were classified as having p-CNS involvement, and patients with PNS damage as the primary symptom were classified as having p-PNS involvement.

Assays for the detection of serum antibodies

In this study, antigen-specific live cell-based assays were performed on patient sera for the following antigens as previously described:^{8,9} aquaporin 4 (AQP4), myelin oligodendrocyte glycoprotein (MOG), neurofascin 155 (NF155), NF186, contactin 1

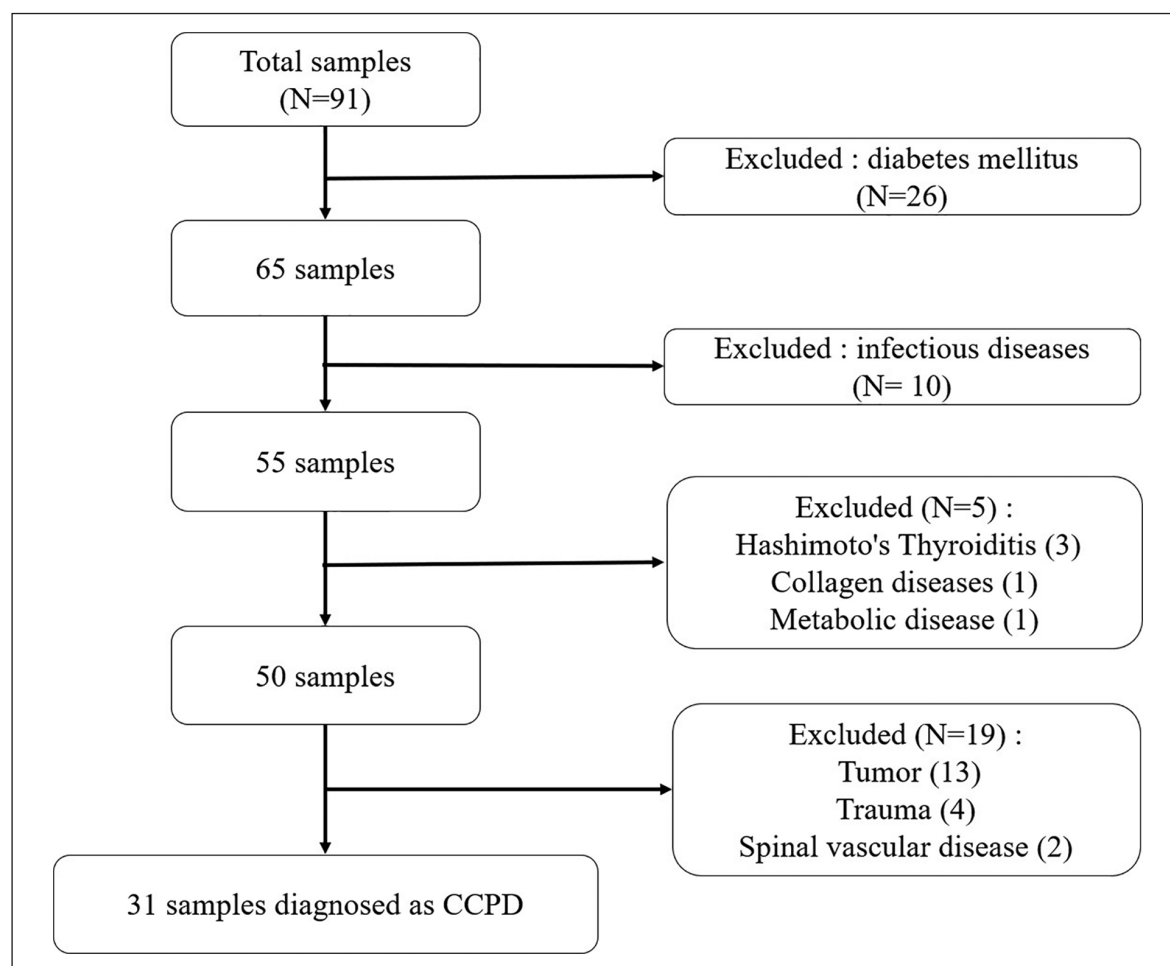


Figure 1. The flowchart of population selection.

In total, 91 patients were recruited from Xuanwu Hospital, Capital Medical University. After excluding 26 patients with diabetes mellitus, 10 patients with infectious diseases, 3 patients with Hashimoto's thyroiditis, 1 patient with collagen diseases, 1 patient with metabolic disease, 13 patients with a tumor, 4 patients with trauma, 2 patients with spinal vascular disease among them, 31 participants were diagnosed with CCPD finally.

(CNTN1), CNTN2, contactin-associated protein-like 1 (CASPR1), CASPR2, MAG, and neuronal cell adhesion molecule (NrCAM).

Statistical analysis

The data were analyzed using descriptive statistics. Continuous variables are presented as means, and categorical variables are presented as counts and percentages. SPSS software (IBM Corp., Armonk, NY, USA) was used to conduct all analyses.

Results

Demographic characteristics

The demographic characteristics of patients with CCPD are highlighted in Table 1. The ratio of males to

females was 1:1.2 (14/17). The average onset age was 38.9 ± 14.3 years, and the average age at examination was 41.6 ± 14.4 years. The disease duration was 39.6 ± 89.4 months. The onset mode was acute in 64.5%, subacute in 6.5%, and chronic in 29.0% of patients. Regarding the clinical course, 3 (10.7%) were monophasic, 9 (32.1%) were relapsing-remitting, 11 (39.3%) were chronic progressive, and 5 (17.9%) were rapid progressive. Primary symptoms related to CNS involvement were reported in 11 patients (35.5%), those related to PNS involvement were observed in 8 patients (25.8%), and those related to both CNS and PNS lesions were observed in 12 patients (38.7%). Ten (33.3%) patients had antecedent infections.

Neurological symptoms and signs

Throughout the disease course, the most common symptom was motor weakness (83.3%), the second

Table 1. Demographic and clinical features of patients with CCPD.

Basic demographics	
Sex ratio (male/female)	1:1.2 (14/17)
Age at onset (years, mean \pm SD)	38.9 \pm 14.3
Age at admission (years, mean \pm SD)	41.6 \pm 14.4
Disease duration (months, mean \pm SD)	39.6 \pm 89.4
n/N (%)	
Mode of onset	
Acute	20/31 (64.5)
Subacute	2/31 (6.5)
Chronic	9/31 (29.0)
Clinical course	
Monophasic	3/28 (10.7)
Relapse-remitting	9/28 (32.1)
Chronic progressive	11/28 (39.3)
Rapid progressive	5/28 (17.9)
Primary symptoms	
p-CNS involvement	11/31 (35.5)
p-PNS involvement	8/31 (25.8)
Both	12/31 (38.7)
Previous infection	10/30 (33.3)
Symptoms and signs during the entire course	
Seizure	2/31 (6.5)
Mental disturbance	3/31 (9.7)
Headache	3/30 (10.0)
Visual disturbance	5/30 (16.6)
Unilateral	1/30 (3.3)
Bilateral	4/30 (13.3)
Diplopia	2/30 (6.7)
Cranial nerve involvement (other than the optic nerves)	9/30 (30.0)
Motor weakness	25/30 (83.3)
Monoplegia	3/30 (10.0)
Hemiplegia	0/30
Weakness of upper limb	3/30 (10.0)
Weakness of lower limb	13/30 (43.3)
Weakness of 4 extremities	6/30 (20.0)
Muscle atrophy	7/31 (22.6)
Respiratory disturbance	5/31 (16.1)
Gait disturbance	4/30 (13.3)
Ataxia	3/30 (10.0)
Sensory disturbance	17/30 (56.7)
Half-body involvement	1/30 (3.3)
Sensory level	8/30 (26.7)
Glove and stocking type	8/30 (26.7)
Banded feeling	4/30 (13.3)
Deep tendon reflexes	
Hyporeflexia	19/30 (63.3)
Normal	3/30 (10.0)
Hyperreflexia	4/30 (13.3)
Both hyporeflexia and hyperreflexia	4/30 (13.3)

(Continued)

Table 1. (Continued)

	<i>n/N (%)</i>
Pathological reflexes	13/30 (43.3)
Sphincter disturbance	18/31 (58.1)
EDSS	
<3	3/31 (9.7)
3–6	6/31 (19.4)
≥6	22/31 (71.0)
All-cause death	3/31 (9.7)

SD: standard deviation; CCPD: combined central and peripheral demyelination; CNS: central nervous system; PNS: peripheral nervous system; EDSS: Expanded Disability Status Scale; *n*, number of involved cases; *N*: number of cases collated.

was hyporeflexia of deep tendon reflexes (63.3%), and the third was sphincter disturbance (58.1%). These symptoms were followed by sensory disturbance (56.7%), pathological reflexes (43.3%), cranial nerve involvement (30.0%), and muscle atrophy (22.6%). Visual disturbance was present in 16.6% of patients, and respiratory disturbance was observed in 16.1%. Gait disturbance was observed in 13.3% of patients. A banded sensation disturbance was reported by 13.3% of patients. Ataxia was present in 10.0% of patients. The proportions of patients with hyporeflexia and hyperreflexia were 63.3% and 13.3%, respectively, and four patients had both hyporeflexia and hyperreflexia. Seizure, mental disturbance, headache, and diplopia were only occasionally observed. A total of 71.0% of patients had an EDSS score greater than 6 at admission, and the all-cause mortality rate was 9.7% (Table 1).

Findings of blood and cerebrospinal fluid laboratory examinations

Common autoantibodies were detected in a small number of patients. Anti-AQP4 antibodies were found in 4/19 (21.1%) patients, anti-NF155 antibodies were found in 2/10 (20.0%) patients, and anti-MAG antibodies were found in 1/10 (10.0%) patients (Figure 2). None of the patients were positive for MOG, NF186, CNTN1, CNTN2, CASPR1, CASPR2, or NrCAM. Cerebrospinal fluid (CSF) protein levels were elevated in 60.0% of patients. Twelve patients (41.4%) showed increased cell counts. In addition, the CSF oligoclonal bands (OCB) positivity rate was 36.0%, and 60.0% of the patients had an elevated intrathecal IgG synthesis rate (Table 2 and supplementary material).

Neuroimaging and VEP findings

Table 3 shows the brain and spinal cord neuroimaging and VEP findings in patients with CCPD. Brain lesions were found in 47.8% (11/23) of patients.

Gadolinium (Gd)-enhanced lesions were observed in only 6.7% of patients with brain lesions. Spinal cord lesions were found in 89.7% (26/29) of patients, and the lesions in 38.1% (8/21) of patients were Gd-enhanced. Spinal longitudinally extensive transverse myelitis lesions that span more than three vertebral segments were found in 69.2% (18/26) of patients. VEPs were abnormal in 33.3% (5/15) of patients, and sensory-evoked potentials (SEPs) were abnormal in 62.5% (10/16) of patients.

NCS findings

The most common results of motor NCS were decreased or absent compound muscle action potential, prolonged H reflex latency, and prolonged F-wave latency, which were found in 75.0%, 69.6%, and 67.9% of patients with CCPD, respectively (Table 4). Decreased sensory nerve conduction velocity and absent or decreased sensory nerve action potential were present in 50% of patients, and prolonged distal latency was found in 46.4% of patients with sensory NCS.

Treatment response of patients with CCPD

Among patients with CCPD, 18 patients received intravenous corticosteroids with an effective rate of 72.2% (13/18). In addition, 8 patients received intravenous immunoglobulins, with an effective rate of 37.5% (3/8). One patient received rituximab and reported it to be effective. By contrast, plasmapheresis was performed in only one patient and was reported to be ineffective. Moreover, two patients who received interferon- β (IFN- β) also reported ineffectiveness (Table 5).

Prognosis of patients with CCPD

Among patients with CCPD, 75% (12/16) had severe disabilities with an mRS (modified Rankin Scale) score of 4 or greater at the illness peak. In remission, 37.5% (6/16) of patients with CCPD still had severe

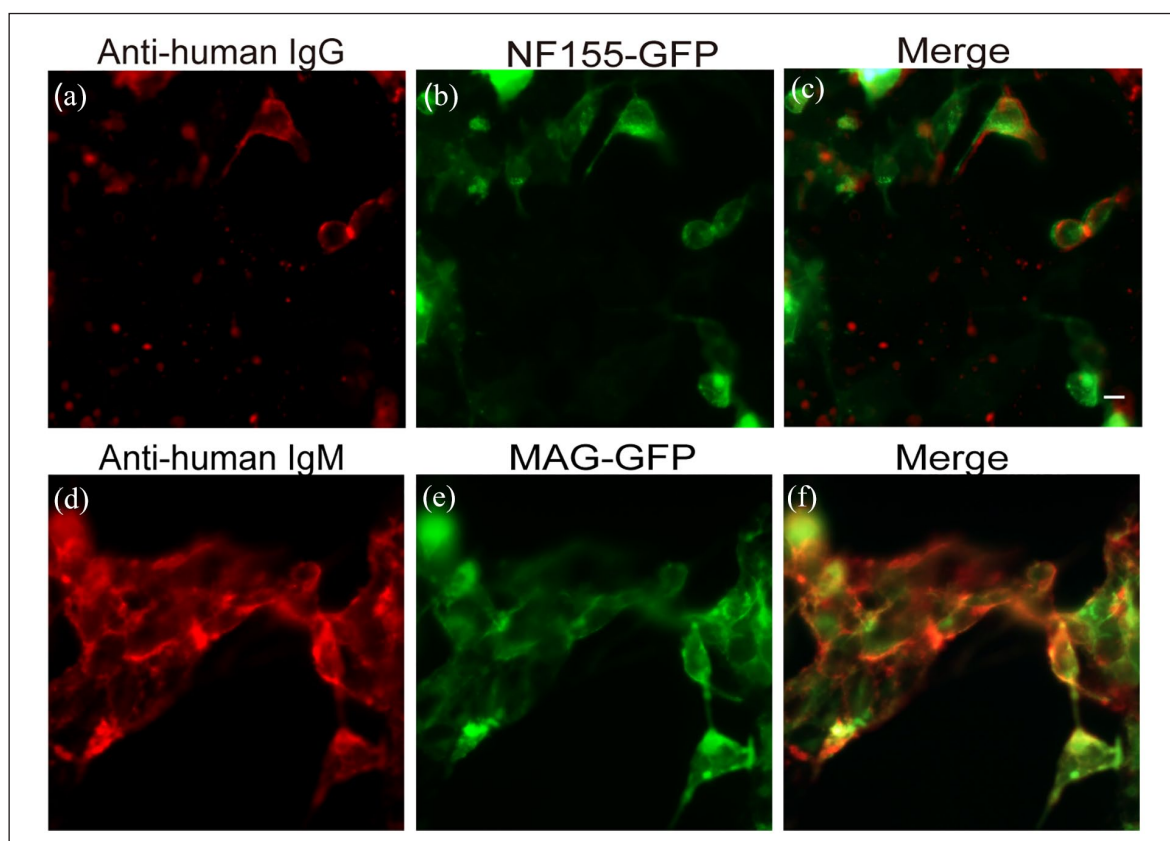


Figure 2. Detection of anti-NF155 and anti-MAG antibodies in patients with CCPD. Cell-based assay for anti-NF155 and anti-MAG antibodies in patients' serum with CCPD. Serum reacted well to HEK293 cells expressing human NF155 protein and human MAG protein with a GFP tag on the cell surface. (a-c) Serum from patients seropositive for anti-NF155 antibodies (red) bound specifically to HEK293 cells transfected with human NF155 plasmids (green). (d-f) Serum from patients seropositive for anti-MAG antibodies (red) bound specifically to HEK293 cells transfected with human MAG plasmids (green). Bar: 10 μ m.

disabilities with an mRS score of 4 or greater (Figure 3). In the remission period, 62.5% (10/16) of patients with CCPD had a lower mRS score than that at the illness peak (mRS score reduced by 4 points in 1 patient, mRS score reduced by 2 points in 3 patients, and mRS score reduced by 1 point in 6 patients). The mRS score did not change in 6 patients.

Discussion

CCPD is an uncommon and heterogeneous disorder. The study showed that the chronic progressive course was most common in this cohort, exceeding the relapsing-remitting or monophasic course. A majority of patients with CCPD eventually develop chronic disease, with either a relapsing-remitting or a chronic progressive disease course.⁴ Indeed, to date, most of the patients with CCPD have relapsing-remitting or chronic progressive disease course.^{1,2,10–12} Nevertheless, a study⁶ showed that a monophasic course is more frequent than a relapsing-remitting or a chronic progressive course.

One-third of patients in this study had an infection that preceded CCPD onset. Although this value is greater than that noted in a Japanese CCPD cohort (10%),⁵ this fraction is lower than that reported in an Italian cohort⁴ (65%) and in another observational study showed that CCPD in a substantial majority (85%) of pediatric patients followed an infection.¹³ The high infection rate before the onset of CCPD indicates that the infectious agent might be the trigger for the subsequent self-sustaining autoimmune process. According to the findings of this study, CCPD predominantly occurred in young adults and females. However, the onset age range was between 18 and 66 years, suggesting a wide age range of patients with CCPD. This finding is comparable with that of a previous study,⁵ demonstrating that CCPD exhibits sex and age preferences such that it mainly affects females and young people.

The most common symptom of patients with CCPD was motor weakness (83.3%). Consistent with the present results, previous studies⁵ have demonstrated that CCPD has very high motor weakness frequencies. In

Table 2. Laboratory findings of blood and CSF.

	<i>n/N (%)</i>
Blood	
Rheumatoid factor	0/29 (0.0)
ANA \geq 1:160	2/26 (7.7)
Anti-SSA Ab	2/25 (8.0)
Anti-SSB Ab	0/25 (0.0)
Anticardiolipin Ab	0/23 (0.0)
PR3-ANCA	0/23 (0.0)
MPO-ANCA	0/23 (0.0)
Anti-AQP4 Ab	4/19 (21.1)
Anti-MOG Ab	0/10 (0.0)
Anti-NF155 Ab	2/10 (20.0)
Anti-NF186 Ab	0/10 (0.0)
Anti-CNTN1 Ab	0/10 (0.0)
Anti-CNTN2 Ab	0/10 (0.0)
Anti-CASPR1 Ab	0/10 (0.0)
Anti-CASPR2 Ab	0/10 (0.0)
Anti-MAG Ab	1/10 (10.0)
Anti-NrCAM Ab	0/10 (0.0)
CSF	
Amounts of protein > 45 mg/dL	18/30 (60.0)
Cell counts > 5/mL	12/29 (41.4)
Albuminocytological dissociation	7/29 (24.1)
IgG level > 5.86 g/L	16/28 (57.1)
IgM level > 0.2 g/L	12/28 (42.9)
OCB	9/25 (36.0)
24 hours intrathecal IgG synthesis rate > 9 mg/24 hours	15/25 (60.0)

CSF: cerebrospinal fluid; CCPD: combined central and peripheral demyelination; ANA: antinuclear antibody; PR3-ANCA: proteinase-3-antineutrophil cytoplasmic antibody; MPO-ANCA: myeloperoxidase-antineutrophil cytoplasmic antibody; Ab: antibodies; AQP4: aquaporin 4; MOG: myelin oligodendrocyte glycoprotein; NF: neurofascin; CNTN: contactin; CASPR: contactin-associated protein; MAG: myelin-associated glycoprotein; NrCAM: neural glial-related cell adhesion molecule; OCB: oligoclonal IgG bands; *n*: number of involved cases; *N*: number of cases collated.

addition, it is worth noting that 16.6% of patients had impaired vision symptoms; however, 33.3% of patients had abnormal VEP findings, indicating that a considerable number of patients had subclinical optic nerve damage. Consistent with the present findings, a previous study demonstrated that decreased vision occurred in only four patients, yet optic nerve demyelination, as revealed by VEPs, occurred in 50% of their patients.⁶ Therefore, we recommend that patients with CCPD should undergo VEP examinations if possible.

A feature different from MS was observed in this study; specifically, the positive rate of the CSF OCB

Table 3. MRI and VEP findings in 31 patients with CCPD.

	<i>n/N (%)</i>
Brain MRI	
T2 lesions	11/23 (47.8)
Topography	
Cortical or juxtacortical lesions	4/23 (17.4)
Periventricular lesions	5/23 (21.7)
Infratentorial lesions	7/23 (30.4)
Deep gray matter lesions	2/23 (8.7)
T1 lesions with Gd enhancement	1/15 (6.7)
Spine MRI	
T2 lesions	26/29 (89.7)
Distribution	
Cervical	15/24 (62.5)
Thoracic	19/25 (76.0)
Lumbosacral	6/9 (66.7)
Type of lesion	
Focal	19/26 (73.1)
Multifocal	7/26 (26.9)
LETM	18/26 (69.2)
T1 lesions with Gd enhancement	8/21 (38.1)
VEPs	
Abnormal findings	5/15 (33.3)
SEPs	
Abnormal findings	10/16 (62.5)

MRI: magnetic resonance images; CCPD: combined central and peripheral demyelination; Gd: gadolinium; LETM: longitudinally extensive transverse myelitis; VEPs: visual-evoked potentials; SEPs: somatosensory-evoked potentials; *n*: number of involved cases; *N*: number of cases collated.

was low. In our study, the positive rate of CSF OCB was 36%. However, the positive rate of OCB in MS can reach more than 87%.¹⁴ Ogata *et al.*⁵ reported that the positive rate of OCB in CCPD was only 7.4%. Zéphir *et al.*² also reported that CSF OCB existed in less than 30% of patients with CCPD. Collectively, these studies show that CCPD is different from MS in several aspects.

In this study, intravenous corticosteroids, intravenous immunoglobulins, and rituximab were effective in patients with CCPD. In contrast, plasmapheresis and interferon- β were ineffective in this cohort. Most patients with CCPD are effective with intravenous corticosteroids.^{3,5,6} For patients with CCPD who do not respond to steroid therapy, intravenous immunoglobulin,^{3,5} plasma exchange therapy,^{3,5} rituximab,⁴ natalizumab,⁴ fingolimod¹⁵ could be administered. However, interferon- β may exacerbate the disease.⁵ Identification of the most effective drug for patients

Table 4. Abnormal findings of NCS in patients with CCPD.

	Total	Median	Ulnar	Tibial	Peroneal
Motor nerve, <i>n/N</i> (%)					
Decreased MCV	15/28 (53.6)	8/41 (19.5)	6/41 (14.6)	15/51 (29.4)	17/51 (33.3)
Prolonged distal latency	14/28 (50.0)	5/41 (12.2)	3/42 (7.1)	15/51 (29.4)	17/51 (33.3)
Decreased or absent CMAP	21/28 (75.0)	17/41 (41.5)	9/42 (21.4)	14/51 (27.5)	19/51 (37.3)
Prolonged F-wave latency	19/27 (67.9)	4/12 (33.3)	0/1	15/23 (65.2)	
Decreased F-wave occurrence	13/27 (48.0)	8/12 (66.7)	1/1 (100)	8/23 (34.8)	
Prolonged H reflex latency	15/22 (68.2)			16/23 (69.6)	
Decreased H reflex amplitude	12/22 (54.5)			13/23 (56.5)	
Sensory nerve, <i>n/N</i> (%)					
Decreased SCV	14/28 (50.0)	23/79 (29.1)	10/40 (25.0)	20/48 (41.7)	12/49 (24.5)
Prolonged distal latency	13/28 (46.4)	11/79 (13.9)	6/40 (15.0)	16/48 (33.3)	12/49 (24.5)
Decreased or absent SNAP	14/28 (50.0)	31/79 (39.2)	13/40 (32.5)	16/48 (33.3)	12/49 (24.5)

NCS: nerve conduction studies; CCPD: combined central and peripheral demyelination; MCV: motor nerve conduction velocity; CMAP: compound muscle action potential; SCV: sensory nerve conduction velocity; SNAP: sensory nerve action potential.

Table 5. Treatment of patients with CCPD.

Treatment	Efficacy, <i>n/N</i> (%)
Corticosteroid pulse therapy	13/18 (72.2)
IVIg	3/8 (37.5)
Plasmapheresis	0/1
IFN- β	0/2
Rituximab	1/1 (100)

CCPD: combined central and peripheral demyelination; IFN- β : interferon- β ; IVIg: intravenous immunoglobulin; *N*: number of cases collated; *n*: number of efficacious cases.

with CCPD and assessment of whether new immune-modifying drugs, such as sinimod, can be used require further research.

The condition of patients with CCPD was severe. At admission to the hospital, more than two-thirds of patients had an EDSS score greater than 6. At the illness peak, three-fourths of patients with CCPD had an mRS score of 4 or greater, and in remission, there were still more than one-third of patients who had an mRS score of 4 or greater. Moreover, the all-cause mortality rate was approximately 10%. One patient died of multiple organ failure. The specific causes of death of the other two patients remain unclear. It is inferred that one patient died of pulmonary embolism due to swelling of the lower limbs and possibly venous thrombosis. The other patient died of pneumonia, which may be related to the long-term bed rest caused by CCPD. A previous study showed that in the acute stage of the disease, 64% of patients with CCPD had an mRS score ≥ 4 , and in the follow-up period (average follow-up time of 84 months), 71%

of patients with CCPD had an mRS score ≥ 4 , which means these patients were unable to walk independently and needed to rely on others in their daily lives.⁴ A study in children with CCPD also showed that children with CCPD had a poor prognosis. A total of 61.6% of patients had an EDSS score greater than 5 at discharge, and 54% of patients had an EDSS score greater than 5 during the follow-up period (average follow-up time of 9 months).¹³

In our study, patients with CCPD were positive for anti-AQP4 antibodies, anti-NF155 antibodies, and anti-MAG antibodies. However, we did not find anti-MOG, NF186, CNTN1, CNTN2, CASPR1, CASPR2, or NrCAM antibodies in any patient.

Some attempts have been made to reveal serological markers and antigen targets in CCPD syndrome in recent years. The incidence of autoantibodies against the node of Ranvier among patients worldwide shows considerable heterogeneity among countries.

In this study, 20.0% (2/10) of patients were anti-NF155 antibody positive. Studies have identified that anti-NF155 antibodies are positive in 45.5% (5/11) of patients and 71.4% (5/7) of patients with CCPD.^{3,5} On the contrary, some research^{7,16} indicated that no anti-NF155 antibodies were present in patients with central plus peripheral nerve demyelination. Although the structures of NF186 and NF155 are very similar, few studies have reported anti-NF186 antibody positivity in patients with CCPD.^{3,17}

In our study, one patient (1/10, 10.0%) with CCPD had anti-MAG antibodies. In accordance with this

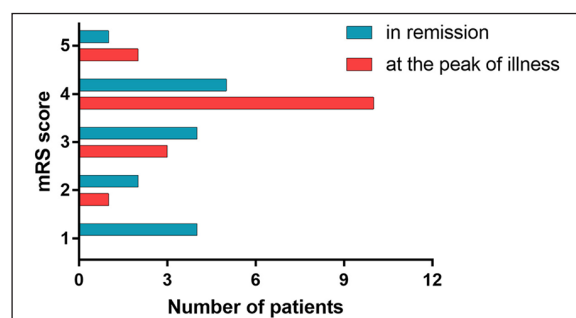


Figure 3. Prognosis in patients with CCPD. Number of patients with CCPD with each mRS score at the peak of illness and in remission.

result, a case study¹⁸ reported a patient who was positive for anti-MAG antibodies and had damage to the dorsal column, as shown in an SEPs study, followed by peripheral neuropathy. In addition, Zis et al.¹⁹ identified four patients with cerebellar dysfunction and neuropathy in the context of positive anti-MAG antibodies. Furthermore, Sotgiu et al.²⁰ also reported a patient who was positive for anti-MAG IgM antibodies and showed MS-like lesions on MR images and demyelinating sensory polyneuropathy in an electrophysiological study.

In this study, we did not find anti-CASPR2 antibodies in the serum of patients with CCPD. In a previous study, 19 patients with CNS and PNS involvement were screened from 271 MOGAD (myelin oligodendrocyte glycoprotein antibody-associated disorders) patients, including 3 patients who demonstrated swollen and enhancing nerve roots. Among these 19 patients, one patient with CNS involvement first and bilateral distal upper and lower limb pain and paresthesia was positive for anti-CASPR2 antibodies.²¹

In this study, we did not find anti-CNTN1 antibodies in the serum of patients with CCPD. In the past, some CCPD patients were tested for anti-CNTN1 antibodies, and no anti-CNTN1 antibodies were observed.^{22–24}

In this study, 21.0% (4/19) of patients were anti-AQP4 antibody positive. A recent study⁶ indicated that the positive rate of AQP4 antibodies in patients with CCPD was 37.5%. Aquaporin 4, which is present in the transition zone of the roots between peripheral nerves and central nerves, might be a potential target of radiculitis in CCPD.²⁵ However, another cohort study⁵ reported no AQP4 antibodies among the patients enrolled in their study. In this study, we did not find MOG antibodies, whereas a cohort study²¹ and two case studies^{24,26} reported MOG antibodies in patients with CCPD.

This variability in the antibody-positive rate is potentially attributable to differences in ethnicity (Caucasian vs East Asians). The various methods adopted for antibody detection, including ELISA (enzyme-linked immunosorbent assay), cell-based assays, and immunohistochemistry, may be the partial reason for the discrepancies. In addition, the sample size is comparatively small. Extensive studies are warranted to confirm these findings of antibodies in patients with CCPD.

This study also has several limitations. First, only a small proportion of patients had preserved serum samples that were ready for examination. To confirm the related antibodies in CCPD, we still need further large-scale studies. Moreover, we recruited only patients hospitalized in our hospital, which may lead to some research biases.

Conclusion

The clinical manifestations of patients with CCPD are highly heterogeneous. CCPD has features that vary from classic demyelinating diseases, and its prognosis is poor. Patients suspected of having CCPD are recommended for anti-AQP4, MOG, and nodal/paranodal antibody tests.

Declaration of Conflicting Interests

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Supplemental material

Supplemental material for this article is available online.

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