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Combined central and peripheral demyelination: Clinical features, diagnostic findings, and treatment

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ABSTRACT

Combined central and peripheral demyelination (CCPD) is rare, and current knowledge is based on case reports and small case series. The aim of our study was to describe the clinical features, diagnostic results, treatment and outcomes in a large cohort of patients with CCPD. Thirty-one patients entered this retrospective, observational, two-center study. In 20 patients (65%) CCPD presented, after an infection, as myeloradiculoneuropathy, encephalopathy, cranial neuropathy, length-dependent peripheral neuropathy, or pseudo-Guillain-Barré syndrome. Demyelinating features of peripheral nerve damage fulfilling European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) electrodiagnostic criteria for CIDP were found in 23 patients (74%), and spatial dissemination of demyelinating lesions on brain MRI fulfilling the 2010 McDonald criteria for multiple sclerosis (MS) in 11 (46%). Two thirds of the patients had a relapsing or progressive disease course, usually related to the appearance of new spinal cord lesions or worsening of the peripheral neuropathy, and showed unsatisfactory responses to high-dose corticosteroids and intravenous immunoglobulins. The clinical presentation of CCPD was severe in 22 patients (71%), who were left significantly disabled. Our data suggest that CCPD has heterogeneous features and shows frequent post-infectious onset, primary peripheral nervous system or central nervous system involvement, a monophasic or chronic disease course, inadequate response to treatments, and a generally poor outcome. We therefore conclude that the current diagnostic criteria for MS and CIDP may not fully encompass the spectrum of possible manifestations of CCPD, whose pathogenesis remains largely unknown.

1. Introduction

Inflammatory demyelinating diseases are a broad group of disorders characterised by immune-mediated myelin damage, leading to conduction abnormalities, and often accompanied by axonal loss. The demyelinating lesions are usually limited either to the central nervous system (CNS) or to the peripheral nervous system (PNS). The simultaneous occurrence of combined central and peripheral demyelination (CCPD) is rare and data are limited to case reports and small case series [1, 11, 13].

We previously found that 36% of a selected cohort of patients with post-infectious inflammatory demyelinating disorders of the CNS showed either clinical or electroneurographic evidence of PNS involvement. Notably, these patients with CCPD showed a worse prognosis and a higher relapse rate compared to those with CNS-restricted variants [8].

The aim of this study was to examine the clinical and paraclinical features of a large cohort of patients with CCPD in order to gain information about clinical presentation, disease course, response to treatments and outcome.

2. Patients and methods

This is a retrospective, observational, two-centre study. The inclusion criteria for CCPD patient selection were: A) acute (within the previous month), subacute (1–2 months previously) or chronic (over 2 months previously) onset of symptoms of CNS and/or PNS impairment; B) presence of CNS lesions suggestive of demyelination shown by brain and/or spine MRI; C) presence of peripheral neuropathy shown by nerve conduction studies (NCS); and D) exclusion of other causes of combined CNS and PNS involvement, as detailed below.

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Of 276 cases with idiopathic inflammatory diseases of the CNS or PNS who were identified from clinical databases and followed up at the C. Mondino and C. Besta Neurological Institutes, 31 patients fulfilled all the inclusion criteria and entered the study (Supplementary Fig. 1). The study was approved by the C·Mondino Institutional Review Board and written informed consent was obtained from all the subjects.

Clinical data were collected from inpatient and outpatient hospital charts. For descriptive purposes, disease course was classified into three categories: 1) monophasic, if characterised by a single episode of acute demyelination, not followed by any further events; 2) relapsing, if the first event was followed, at least 3 months after the initial episode, by a clinical relapse defined by acute/subacute onset of new symptoms, or recurrence of previously experienced symptoms; and 3) chronic progressive, defined by the presence of a steady or stepwise worsening of the symptoms. Original MRI scans (1.5 T), cerebrospinal fluid (CSF) examination, including agarose isoelectric focusing for oligoclonal IgG band (OCB) determination, and NCSs were reviewed for technical and interpretation accuracy. In the NCS analyses we did not include: a) nerve roots and peripheral nerves stemming from metameres affected by inflammatory lesions, as detected by spine MRI; b) nerves showing alterations at entrapment points, possibly related to prolonged immobility.

The following investigations were performed in all the patients in order to exclude other causes of combined CNS and PNS involvement, as well as distinct causes of neuropathy: fasting blood glucose, Hb1Ac, vitamin B12, folates, homocysteine, serum immunofixation, serology for HIV, HCV, Lyme disease, syphilis, ANA, ENA, ANCA, anti-cerebellum, anti AQP-4 antibodies (cell-based assay), anti-gangliosides, including anti GQ1b, and anti-sulfatide antibodies, serum ACE. In patients with a chronic progressive disease course, metabolic testing for phytanic acid, galactocerebrosidase, arylsulfatase, very long chain fatty acids, and genetic testing for mutations in *PMP22* (CMT1A) and *GJB1* (CMTX1) were also performed.

The clinical charts were reviewed and the following information was recorded for all the patients: demographics, general medical history, risk factors for neuropathy, symptoms at presentation, previous infections and vaccinations, outcome and response to treatment. The modified Rankin scale (mRS) was used to measure disability level and outcome. Responders were defined as patients recording an increase of at least one point on the mRS after treatment. The first available neurological examination from disease onset was recorded. Muscle weakness was graded as mild (from 5- to 4 of Medical Research Council (MRC) scale), moderate (from 4- to 3 of MRC scale) and severe/paralysis (<3).

Original NCSs were evaluated for fulfilment of European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) electrodiagnostic criteria for chronic inflammatory demyelination polyradiculoneuropathy (CIDP) [4]. Original brain MRI scans were reviewed for fulfilment of the 2010 McDonald criteria for multiple sclerosis (MS) [10].

Data were analysed using descriptive statistics methods. Continuous data were shown as means or medians (standard deviation, min-max).

3. Results

3.1. Clinical presentation

Table 1 shows the demographic and clinical features at disease onset and at follow-up of 31 patients with CCPD. Each patient's disease history is summarised in Supplementary Table 1. The majority of the patients were male with a mean age at onset of 57 years (range, 14–82). A previous infection or vaccination was reported in 20 subjects (65%), mostly infections of the upper respiratory tract, although a specific trigger was identified in only four cases (1 flu vaccine, 1 *Streptococcus pneumoniae* vaccine, 1 *Campylobacter jejuni* gastroenteritis and 1 *Streptococcus pyogenes* pharyngitis). The majority of the patients presented with lower limb sensory-motor impairment and sphincter dysfunction, suggesting the presence of spinal cord lesions. However other symptoms, such as altered mental status and cranial nerve involvement, could also characterise the onset of the disease. Primary PNS damage was present in 11 patients who presented with distal paraesthesia, and in four subjects with pseudo-Guillain-Barré syndrome, i.e. with ascending sensory-motor impairment and abolished osteotendinous reflexes.

Table 1
Clinical features of CCPD patients at disease onset and in the chronic phase of the disease.

Demographics	
Age at onset in years (standard deviation, range)	57 (17, 14–82)
Males	23 (74%)
Disease course	
Monophasic	10 (32%)
Relapsing	13 (42%)
Chronic progressive	8 (26%)[b]

	Disease onset	Follow-up[a]
Previous infection	20 (65%)	1 (5%)
Clinical features		
Lower limb sensory-motor impairment	29 (94%)	19 (90%)
Urinary incontinence/retention	26 (84%)	2 (9%)
Distal paresthesia	11 (35%)	4 (19%)
Altered mental status	5 (16%)	–
Upper limb sensory-motor impairment	8 (26%)	7 (33%)
Headache	2 (6%)	–
Ascending four limb sensory-motor impairment	4 (13%)	–
Other	7 (23%)	4 (19%)
Response to treatments		
Steroids	17/23 (74%)	4/16 (25%)
IVIg	4/8 (50%)	4/11 (36%)
Other	1/1 (100%)	1/4 (25%)
Overall response	19 (73%)	6 (19%)
Disability (mRS)	N = 25[c]	N = 31
0	1 (4%)	2 (7%)
1	1 (4%)	2 (7%)
2	1 (4%)	1 (3%)
3	6 (24%)	4 (13%)
4	12 (48%)	4 (13%)
5	4 (16%)	18 (58%)

All data are reported as number of cases (%) or mean (standard deviation, min-max). CCPD: combined central and peripheral demyelination; IVIg: intravenous immunoglobulins; mRS: modified Rankin Scale.

[a] Follow-up data for previous infection and clinical features refer only to cases with a relapsing or chronic progressive disease course (N = 21).

[b] Including 6 cases with a primary progressive disease course.

[c] Primary progressive CCPD cases are excluded.

3.2. Neurological examination

In 27 patients (87%), neurological examination at disease peak showed lower limb weakness which was severe in 67% of them, with distal predominance in five. Upper limb weakness was found in 12 patients (39%). Tone was increased at the four limbs in 11 patients, decreased at the four limbs in six, and mixed (increased at the upper limbs and decreased at the lower limbs) in two. Osteotendinous reflexes were more often increased at the upper limbs (48% of the cases) and reduced or abolished at the lower limbs (52%). Babinski sign was present in 58% of the cases. Dystonia was observed in one case (Supplementary Table 2).

3.3. Disease course

The patients were followed up for a mean of 84.3 months (range, 43.3–134). One third of the patients showed a monophasic disease course. Overall, in 21 cases (68%) we observed a progression of the disease: either a relapse, with subacute onset of new symptoms (13 cases, 42%), or a steady chronic progression (8 cases, 26%). Notably, six patients who presented with distal paraesthesia showed a progressive disease course from onset. In the relapsing subgroup, the mean delay between inflammatory events was 12 months (50.3–126). In five