ORIGINAL ARTICLE

Chronic inflammatory demyelinating polyradiculoneuropathy: can a diagnosis be made in patients not fulfilling electrodiagnostic criteria?

G. Liberatore[a], F. Manganelli[b], P. E. Doneddu[a], D. Cocito[c], R. Fazio[d], C. Briani[e], M. Filosto[f], L. Benedetti[g,h], A. Mazzeo[i], G. Antonini[j], G. Cosentino[k,l,m], S. Jann[n], A. Cortese[l,m,o], G. A. Marfia[p], A. M. Clerici[q], G. Siciliano[r], M. Carpo[s], M. Luigetti[t], G. Lauria[u,v], T. Rosso[w], G. Cavaletti[x], L. Santoro[b], E. Peci[c], S. Tronci[d], M. Ruiz[e], S. Cotti Piccinelli[f], A. Schenone[g], L. Leonardi[j], A. Toscano[i], G. Mataluni[p], E. Spina[b], L. Gentile[i], E. Nobile-Orazio[a,y] on behalf of the Italian CIDP Database Study Group*

[a]*Neuromuscular and Neuroimmunology Service, IRCCS Humanitas Clinical and Research Institute, Milan;* [b]*Department of Neuroscience, Reproductive Sciences and Odontostomatology, University of Naples 'Federico II', Naples;* [c]*Presidio Sanitario Major, Istituti Clinici Scientifici Maugeri, Turin;* [d]*Department of Neurology, Division of Neuroscience, Institute of Experimental Neurology (INSPE), San Raffaele Scientific Institute, Milan;* [e]*Neurology Unit, Department of Neuroscience, University of Padova, Padova;* [f]*Center for Neuromuscular Diseases and Neuropathies, Unit of Neurology, ASST 'Spedali Civili', University of Brescia, Brescia;* [g]*Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa and IRCCS AOU San Martino-IST, Genoa;* [h]*Neurology Unit, Sant'Andrea Hospital, La Spezia;* [i]*Department of Clinical and Experimental Medicine, Unit of Neurology, University of Messina, Messina;* [j]*Unit of Neuromuscular Diseases, Department of Neurology Mental Health and Sensory Organs (NESMOS), Faculty of Medicine and Psychology, Sant'Andrea Hospital, 'Sapienza' University of Rome, Rome;* [k]*Department of Experimental BioMedicine and Clinical Neurosciences (BioNeC), University of Palermo, Palermo;* [l]*IRCCS Foundation C. Mondino National Neurological Institute, Pavia;* [m]*Department of Brain and Behavioral Sciences, University of Pavia, Pavia;* [n]*Department of Neuroscience, Niguarda Ca' Granda Hospital, Milan, Italy;* [o]*Molecular Neurosciences, University College London, London, UK;* [p]*Dysimmune Neuropathies Unit, Department of Systems Medicine, Tor Vergata University of Rome, Rome;* [q]*Neurology Unit, Circolo and Macchi Foundation Hospital, Insubria University, DBSV, Varese;* [r]*Neurology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa;* [s]*Neurology Unit, ASST Bergamo Ovest-Ospedale Treviglio, Treviglio;* [t]*Fondazione Policlinico Universitario A. Gemelli IRCCS, UOC Neurologia, Università Cattolica del Sacro Cuore, Rome;* [u]*Unit of Neuroalgology, IRCCS Foundation 'Carlo Besta' Neurological Institute, Milan;* [v]*Department of Biomedical and Clinical Sciences 'Luigi Sacco', University of Milan, Milan;* [w]*ULSS2 Marca Trevigiana, UOC Neurologia-Castelfranco Veneto, Treviso;* [x]*School of Medicine and Surgery and Experimental Neurology Unit, University of Milano-Bicocca, Monza; and* [y]*Department of Medical Biotechnology and Translational Medicine, Milan University, Milan, Italy*

Keywords:
chronic inflammatory demyelinating polyradiculoneuropathy, diagnostic criteria, electrophysiology

Received 10 June 2020
revision requested 10 September 2020
Accepted 11 September 2020

European Journal of Neurology 2021, **28:** 620–629

doi:10.1111/ene.14545

Abstract

Background and purpose: The aim was to identify the clinical and diagnostic investigations that may help to support a diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) in patients not fulfilling the European Federation of Neurological Societies and Peripheral Nerve Society (EFNS/PNS) electrodiagnostic criteria.

Methods: The data from patients with a clinical diagnosis of CIDP included in a national database were retrospectively reviewed.

Results: In all, 535 patients with a diagnosis of CIDP were included. This diagnosis fulfilled the EFNS/PNS criteria in 468 patients (87.2%) (definite in 430, probable in 33, possible in three, while two had chronic immune sensory polyradiculopathy). Sixty-seven patients had a medical history and clinical signs compatible with CIDP but electrodiagnostic studies did not fulfill the EFNS/PNS criteria for CIDP. These patients had similar clinical features and frequency of abnormal supportive criteria for the diagnosis of CIDP compared to patients fulfilling EFNS/PNS criteria. Two or more abnormal supportive criteria were present in 40 (61.2%) patients rising to 54 (80.6%) if a history of a relapsing course as a possible supportive criterion was also included.

Correspondence: E. Nobile-Orazio, Neuromuscular and Neuroimmunology Service, IRCCS Humanitas Research Hospital, Via Manzoni 56, Rozzano, Milan 20089, Italy (tel.: +390282242209; fax: +390282242298; e-mail: eduardo.nobile@unimi.it).
*See Appendix.

[Correction added on 24 Dec 2020, after first online publication: Affiliation 'm' has been added for G. Cosentino and the subsequent affiliations in the list have been re-ordered accordingly.]

Increased cerebrospinal fluid proteins and response to immune therapy most frequently helped in supporting the diagnosis of CIDP. Response to therapy was similarly frequent in patients fulfilling or not EFNS/PNS criteria (87.3% vs. 85.9%).

Conclusions: Patients with a clinical diagnosis of CIDP had similar clinical findings, frequency of abnormal supportive criteria and response to therapy compared to patients fulfilling EFNS/PNS criteria. The presence of abnormal supportive criteria may help in supporting the diagnosis of CIDP in patients with a medical history and clinical signs compatible with this diagnosis but non-diagnostic nerve conduction studies.

Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a chronic and often disabling neuropathy with a prevalence ranging from 1 to 9 cases per 100 000 [1,2]. The cause of CIDP is still unclear even if several data point to an immune-mediated pathogenesis, as also indicated by the frequent improvement of patients after immune therapies [3–6]. The majority of patients with CIDP have a mostly symmetric proximal and distal motor and sensory impairment with decreased or absent deep tendon reflexes and a progressive or relapsing course [3–6]. Several variants have been described, however, based on the distribution of symptoms and signs, broadening the spectrum of this disorder [3–7].

The diagnosis of CIDP can be challenging and, in recent years, several different sets of diagnostic criteria have been proposed with variable combinations of electrophysiological and clinical features [8–11]. Currently, the most widely accepted criteria are those recommended by the European Federation of Neurological Societies and Peripheral Nerve Society (EFNS/PNS) [11] that were shown to provide the best combination of sensitivity and specificity (about 75% and 90%, respectively) for the diagnosis of CIDP compared with other criteria [12–14]. These criteria allow this diagnosis only in the presence of demyelinating features in at least one motor nerve. In most reported series, there is indeed a consistent proportion of patients who have the clinical features compatible with a diagnosis of CIDP but who do not fulfill the EFNS/PNS electrodiagnostic criteria [14] and therefore might be denied access to effective therapy. In these patients, a clinical diagnosis of CIDP is often supported by the presence of abnormal ancillary investigations. It is not clear, however, which and how many supportive criteria may help in the diagnosis of these patients, and whether their clinical features and response to therapy are similar to those of the patients who fulfill the EFNS/PNS criteria.

The data included in the Italian CIDP database from patients with a medical history and clinical signs compatible with CIDP and electrodiagnostic criteria not fulfilling the EFNS/PNS electrodiagnostic criteria were reviewed to clarify whether the clinical features, disease course and treatment response was similar to patients fulfilling EFNS/PNS criteria and to identify the relevance of ancillary tests in supporting the diagnosis of CIDP.

Patients and methods

Database and study population

From January 2015 to June 2019, 582 patients with a clinical diagnosis of CIDP in our web-based database (CINECA, Bologna, Italy) were enrolled. 24 patients were excluded for the presence of a different diagnosis and 23 patients for unavailable neurophysiological data. A total of 535 patients were included in the study. At the time of enrollment, 468 (87.5%) patients fulfilled the EFNS/PNS clinical and electrodiagnostic criteria for CIDP including 430 (92%) patients with a definite, 33 (7%) with a probable and three (1%) with a possible diagnosis of CIDP. Also included among them were two patients (0.4%) with a typical chronic immune sensory polyradiculopathy [15] and normal motor conduction studies. The other 67 (12.5%) patients had a medical history and clinical signs compatible with the diagnosis of CIDP or one of its variants but did not fulfill the EFNS/PNS electrodiagnostic criteria. The data from these patients were reviewed and compared to those of patients fulfilling these criteria [16]. The Ethics Committee of each participating center approved the study. All the patients gave written informed consent.

Clinical assessment and ancillary tests

All patients were subjected to detailed clinical history including time of onset, distribution and progression of symptoms including weakness, sensory symptoms,

ataxia, pain, cranial nerve impairment, autonomic dysfunction and the presence of concomitant diseases. Muscle strength was assessed with the Medical Research Council scale [17], range 1–60. Neurological disability was evaluated with the Inflammatory Neuropathy Cause and Treatment (INCAT) scale [18], range 0–10.

The treating neurologist defined the course of the disease as progressive or relapsing. A relapsing course was defined as a clinical worsening after an initial improvement that was not related to a suspension or reduction of the dose of therapy. However, some patients with a delayed worsening (>3 months) after treatment suspension or reduction might have also been included in this group. An acute onset of CIDP was also reported and defined as a neuropathy that was initially diagnosed as Guillain–Barré syndrome but that continued to progress or relapse after more than 2 months from disease onset. The diagnosis of a typical or atypical CIDP phenotype was reviewed in all the patients by the coordinating center at the time of inclusion in the study according to our criteria [7]. Response to previously performed therapy was defined as a subjective amelioration confirmed by the treating neurologist as an improvement of at least 2 points on the Medical Research Council sum score or 1 point on the INCAT score [19].

The results of cerebrospinal fluid (CSF) examination performed during the course of the disease were reported including total protein level and cell count. As to protein counts, upper reference limits of 50 mg/dl for patients aged ≤50 years and 60 mg/dl for those aged >50 years were adopted [20]. The results of brachial/lumbosacral plexus and root magnetic resonance imaging (MRI) examination were reported and defined by the local examiner of possible supportive value for the diagnosis of CIDP if they showed an enlargement or T2-hyperintense signal and/or gadolinium enhancement [11]. The results of nerve ultrasound (US) were considered of possible supportive value for the diagnosis of CIDP if the local examiner reported an enlargement of the examined nerves beyond their normal values [21]. The results of nerve biopsy, mostly of the sural nerve, were considered relevant for the diagnosis if the examiner reported signs of demyelination or remyelination by teased fiber analysis or electron microscopy or inflammatory cell infiltrates on paraffin sections.

The results of diagnostic nerve conduction studies performed during the course of the disease were included. Motor nerve conduction studies were planned to be performed bilaterally in the median, ulnar, common peroneal and tibial nerves and included distal and proximal (up to the elbow in most patients) compound muscle action potential (CMAP) amplitude (onset to peak) and duration, motor conduction velocities, distal and proximal motor latencies and in most patients F-wave latency. Sensory conduction studies were planned to be performed bilaterally in the median, ulnar and sural nerves and included sensory action potential amplitude, distal latency and conduction velocity. There was no definite time point for the examination since each center was asked to include the most complete and diagnostic examination. Some patients also underwent somatosensory evoked potentials that were considered of diagnostic value if they reflected abnormal conduction velocity in proximal sensory fibers in the absence of signs of central nervous system disease. The reason for suspecting the diagnosis of CIDP beyond the results of nerve conduction studies was also reported in the database by each center including the abnormality of any supportive criteria and the history of a relapsing course.

All the patients had been extensively investigated in each center for the presence of a possible alternative cause of the neuropathy by clinical and laboratory investigations in accordance with the EFNS/PNS guidelines [11]. Patients with serum immunoglobulin M monoclonal gammopathy were excluded if they had increased titers of anti-myelin-associated glycoprotein (MAG) immunoglobulin M antibodies (over 7000 U by the Buhlman method in our laboratory) [22]. Patients with a concomitant disease including diabetes and monoclonal gammopathy without anti-MAG antibodies were included in the study, as their presence does not exclude the diagnosis of CIDP according to EFNS/PNS criteria. In all the patients, the clinical features and the results of ancillary tests were centrally reviewed and the results of motor and sensory nerve conduction studies were classified according to the EFNS/PNS criteria, to determine the diagnosis of definite, probable or possible CIDP [11].

Statistical analysis

Descriptive statistics were reported for the sample of patients with CIDP overall and separately for the two subgroups of patients fulfilling or not the EFNS/PNS diagnostic criteria. Categorical variables were described using frequencies and percentages, with continuous variables using mean, median and range. Demographic and clinical features were compared, including response to therapy, between different subgroups of patients with the chi-squared or the Fisher's exact test for categorical variables and the *t* test or the Wilcoxon–Mann–Whitney test for continuous variables. The analyses were performed with IBM SPSS Statistics for Windows, Version 19.0 (IBM Corp., Armonk, NY, USA).

Results

Clinical findings and disease course

The 67 included patients were 45 men (67.2%) and 22 women (32.8%) (ratio 2.0:1), aged 32–87 years (mean 60.5; median 62) with a mean age at onset of 52.2 years (median 55; range 15–77 years), a mean disease duration of 8.0 years (median 6; range 0.2–37 years) and a mean INCAT score of 2.4 (median 2; range 0–8). In 49 (73.1%) patients, the clinical phenotype was of typical CIDP and in 18 (26.9%) of atypical CIDP (Table 1). The progression of the disease was relapsing in 33 patients (50%) and progressive in 33 (50%), while in one the data were missing. Two (3.3%) patients had an acute onset evolving in both cases into a relapsing course. None of the examined demographic and clinical parameters significantly differed from patients with the EFNS/PNS criteria with the only exception of dysphagia or dysphonia that was more frequent in EFNS/PNS patients (Table 1).

Role of supportive criteria

A similar proportion of patients fulfilling or not the EFNS/PNS electrodiagnostic criteria had increased

Table 1 Comparison of demographic and clinical findings in patients with CIDP fulfilling or not EFNS/PNS criteria

	EFNS/PNS CIDP (N = 468)	Not EFNS/PNS CIDP (N = 67)	P value
Gender (F/M, ratio)	166/302 (1:1.8)	23/44 (1:2.0)	>0.1
Age at onset (years, mean ± SD)	49.7 ± 16.91	52.2 ± 16.05	>0.1
Age at enrollment (years, mean ± SD)	57.7 ± 15.29	60.5.±14.82	>0.1
Disease duration (years, mean ± SD)	7.9 ± 8.33	8.1 ± 7.76	>0.1
INCAT at enrollment (±SD)	2.6 ± 2.01	2.4 ± 1.66	>0.1
Symptoms at onset			
Motor	71 (15.2%)	9 (13.4%)	>0.1
Sensory	144 (30.7%)	26 (38.8%)	>0.1
Sensory and cranial nerves	7 (1.5%)	1 (1.5%)	>0.1
Sensorimotor	242 (51.9%)	31 (46.3%)	>0.1
Pain	1 (0.2%)	0	NA
Diplopia	3 (0.6%)	0	NA
Symptoms at enrollment			
Motor	423 (90.4%)	58 (86.7%)	>0.1
Sensory	449 (95.9%)	63 (94.0%)	>0.1
Fatigue	250 (53.4%)	31 (42.3%)	>0.1
Pain	149 (31.8%)	26 (37.7%)	>0.1
Cramps	64 (13.7%)	14 (20.9%)	>0.1
Ataxia	140 (29.9%)	22 (32.8%)	>0.1
Tremor	53 (11.3%)	6 (9.0%)	>0.1
Total cranial nerves	92 (19.7%)	8 (11.9%)	>0.1
Diplopia	34 (7.3%)	3 (4.5%)	>0.1
Facial palsy	29 (6.2%)	1 (1.5%)	>0.1
Dysphagia/dysphonia	*39 (8.3%)*	*1 (1.5%)*	*0.046*
Facial hypoesthesia	12 (2.6%)	3 (4.5%)	>0.1
Dysautonomia	35 (7.5%)	4 (6.0%)	>0.1
Clinical phenotype			
Typical/atypical (% atypical)	377/91 (19.4%)	49/18 (26.9%)	>0.1
DADS	34 (7.3%)	10 (14.9%)	0.052
Sensory	17 (3.6%)	3 (4.5%)	>0.1
Motor	18 (3.8%)	4 (6.0%)	>0.1
Lewis–Sumner	18 (3.8%)	0	>0.1
Focal	4 (0.9%)	1 (1.5%)	>0.1
Disease course			
Progressive/relapsing (% relapsing)	212/252 (54.3%)	33/33 (50.0%)	>0.1
Acute onset	43 (9.2%)	2 (3.0%)	>0.1
Concomitant diseases			
Diabetes	59 (12.6%)	3 (4.5%)	0.064
Monoclonal gammopathy (not anti-MAG)	21 (5.7%)	4 (6.0%)	>0.1

CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; DADS, Distal Acquired Demyelinating Symmetric neuropathy; EFNS/PNS, European Federation of Neurological Societies and Peripheral Nerve Society; INCAT, Inflammatory Neuropathy Cause and Treatment; MAG, myelin-associated glycoprotein. P-value <0.05 are indicated in italic

CSF proteins and comparable levels of the proteins were found in the two groups (Table 2). Sensory nerve conduction abnormalities consistent with demyelination according to the EFNS/PNS criteria were more frequently found in patients with EFNS/PNS CIDP. Only one patient without EFNS/PNS criteria had delayed somatosensory evoked potentials in the lower limbs. This patient also had reduced sensory conduction velocity in the ulnar nerve. Even if they were rarely analyzed in both groups, nerve biopsy findings consistent with demyelination or with inflammatory infiltrates and nerve or root enlargement or enhancement by MRI or US were similarly frequent in patients fulfilling or not EFNS/PNS criteria. A similarly frequent overall response to therapy was also observed between patients fulfilling (85.9%) or not (87.3%) the EFNS/PNS criteria with a similarly frequent response to intravenous immunoglobulin, corticosteroids, plasma exchange or other immune therapies (Table 2).

The presence of abnormal supportive criteria for the diagnosis of CIDP was examined in all patients not fulfilling electrodiagnostic criteria (mean number of supportive criteria examined 2.9, range 1–4) with a mean number of abnormal tests of 1.8 (range 1–4). Two or more supportive criteria were found in 41 patients (61.2%) while 12 (17.9%) patients had three or more supportive criteria for the diagnosis of CIDP (Fig. 1a). When the presence of a relapsing course was added to the supportive criteria, 54 (80.6%) patients had at least two supportive criteria (Fig. 1b) including 26 (38.8%) with three or more criteria. Similar figures applied to the 18 patients with an atypical phenotype with eight patients (55.5%) having at least two supportive criteria (13 including a relapsing course; 72.2%) and two (11.1%) with three criteria (seven including relapse; 38.9%). Since the diagnosis of CIDP should be considered before starting therapy, when response to therapy from the supportive criteria was excluded, two or more supportive criteria were found in 12 (17.9%) rising to 32 (47.8%) if the presence of a relapsing course was added.

Electrodiagnostic studies

The number of examined motor nerves was lower in patients not fulfilling the EFNS/PNS electrodiagnostic criteria (mean 4.8, median 5, range 2–8) than in EFNS/PNS patients (mean 5.6, median 6, range 2–8; $P < 0.0015$). However, at least four motor nerves were examined in 50 non- EFNS/PNS patients (74.6%) and six or more nerves in 26 (38.8%) patients. There was no difference between patients with less than four motor nerves examined and those with four or more nerves examined as to the frequency of each abnormal supportive criterion, the proportion of patients with two or more abnormal supportive criteria and the response to therapy. There was no statistically significant difference in the time of executing electrodiagnostics in relation to the onset of symptoms between patients fulfilling or not electrodiagnostic criteria (5.1 vs. 3.9 years, respectively; $P > 0.05$).

Some minor, non-diagnostic signs of demyelination were also found in 39 (73.1%) non-EFNS/PNS patients (14 cases in upper limb nerves, 23 in lower limb nerves and two in both). These abnormalities

Table 2 Comparison of diagnostic and therapeutic findings in patients with CIDP fulfilling or not EFNS/PNS criteria

	EFNS/PNS CIDP (n = 468)	Not EFNS/PNS CIDP (n = 67)	P value
Supportive criteria			
Increased CSF proteins/tested	280/358 (78.2%)	41/50 (82.0%)	>0.1
Mean (mg/dl)	103.3	97.2	>0.1
Median (mg/dl)	77	75	>0.1
Sensory nerve demyelination/tested	148/423 (35.0%)	13/61 (23.2%)	0.041
Sensory CV/abnormal median nerve-normal sural nerve	120/18	12/1	>0.1
Delayed SEP (+ other sensory impairment)	10 (+4)	0 (+1)	>0.1
Demyelination, inflammation at nerve biopsy/tested	20/35 (57.1%)	7/11 (63.6%)	>0.1
US, MRI abnormalities/tested	51/64 (79.7%)	7/9 (77.8%)	>0.1
Response to overall therapies/treated	366/426 (85.9%)	53/63 (84.1%)	>0.1
Response to IVIg/treated	265/360 (73.6%)	38/52 (73.1%)	>0.1
Response to steroids/treated	134/249 (53.8%)	21/42 (50.0%)	>0.1
Response to plasma exchange/treated	25/43 (58.1%)	2/6 (33.3%)	>0.1
Response to immunosuppressants/treated	29/77 (37.7%)	3/10 (30.0%)	>0.1

CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CSF, cerebrospinal fluid; CV, conduction velocity; EFNS/PNS, European Federation of Neurological Societies and Peripheral Nerve Society; IVIg, intravenous immunoglobulin; MRI, magnetic resonance imaging; SEP, somatosensory evoked potential; US, ultrasound.

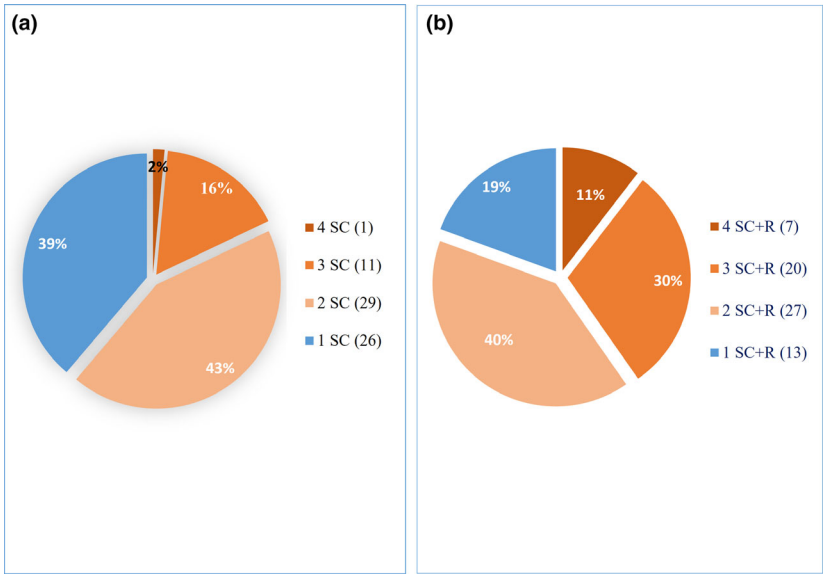

Figure 1 Number of supportive criteria (SC), including (a) or not including (b) a relapsing course (R), in 67 patients with clinical CIDP not fulfilling EFNS/PNS electrodiagnostic criteria (numbers in parentheses refer to number of patients).

included 30%–49% reduction of proximal-to-distal CMAP amplitude reduction in one nerve excluding the tibial nerve (five patients); 20%–29% reduction of proximal-to-distal CMAP amplitude in one (five patients) or more nerves (one patient) excluding the tibial nerve and the site of nerve compression; 40%–49% proximal-to-distal CMAP amplitude in one tibial nerve (three patients); 20%–29% reduction of motor conduction velocity in one (11 patients) or two nerves (five patients) including 10 with normal or less than 20% distal CMAP amplitude reduction (five in upper and five in lower limb nerves) and six with a more pronounced reduction of CMAP amplitude (all in lower limb nerves); F-waves absent in two or more nerves (five patients) in the absence of other demyelinating features; and 40%–49% increased distal latency in one nerve (two patients). In all required cases [10], the distal CMAP amplitude of the negative peak was higher than 20% of the lower normal limit. The other 28 patients either had minimal sign of possible demyelination (10%–20% reduction of motor conduction velocity or 20%–30% reduction of proximal-to-distal CMAP amplitude or 30%–39% in the tibial nerve, 17 patients) or absence or reduced amplitude distal CMAP (11 patients) in the upper (three patients) or lower (22 patients) limbs or both (three patients). Significant differences between patients with or without these signs were not found beside a higher number of males and higher frequency of abnormal sensory conduction studies in patients having these signs (Table S1).

Discussion

Since the first formal definition of CIDP by Dyck *et al.* in 1975 [23], at least 15 diagnostic criteria have been proposed with different combinations of clinical, electrophysiological, laboratory and biopsy features. Different comparison studies confirm that the best combination in terms of sensitivity/specificity [12–14] is offered by the EFNS/PNS criteria [11], which are currently used in most clinical trials in CIDP. A number of supportive investigations were included in these criteria to improve the diagnostic certainty in patients not fulfilling the electrodiagnostic criteria. These investigations, however, support the diagnosis in patients already fulfilling a possible or probable diagnosis of CIDP but do not allow this diagnosis in patients not having demyelinating features in at least one motor nerve.

In our series of 535 patients with a diagnosis of CIDP or one of its variants, 468 (87.5%) patients fulfilled the diagnostic criteria of the EFNS/PNS, while 67 (12.5%) had a medical history and clinical signs compatible with CIDP with electrodiagnostic studies not fulfilling the EFNS/PNS criteria. None of these patients had clinical or laboratory signs of other possible causes for their neuropathy. These data are in line with the reported sensitivity of these criteria [12–14]. Rajabally and colleagues [14], for instance, reported that 81.3% of the patients with CIDP fulfilled the EFNS/PNS criteria for definite or probable CIDP. This percentage is similar to the proportion of our patients with definite or probable CIDP (86.5%).

Our patients not fulfilling the EFNS/PNS criteria had a similar gender distribution, age at onset,

symptoms at onset and during the course of the disease, typical or atypical presentation, disease duration and INCAT score at enrollment in comparison to EFNS/PNS patients. The progression of the disease was relapsing in about half of the patients in both groups. This figure is higher than in some series [23,24] but similar to others [25,26] possibly reflecting a difference in the definition of relapse [4]. It is also possible that some of our patients with a delayed worsening after treatment suspension or reduction were deemed to have a relapsing form but this applied for both groups of patients. The only difference between the two groups was a slightly lower frequency of dysphagia or dysphonia in EFNS/PNS patients and a higher frequency of sensory conduction studies consistent with demyelination in this group that is probably consistent with the difference observed in motor nerve conduction studies. There was also no significant difference in the proportion of each abnormal supportive criterion between the two groups. Most importantly, non-EFNS/PNS patients had a similarly frequent overall response to therapy and to each individual therapy compared to EFNS/PNS patients. Even if these data should be considered with caution in a retrospective study, in all our patients the treating neurologist confirmed the subjective amelioration using clinically relevant measures [19].

When the factors that might have contributed to the diagnosis of CIDP were analyzed beside the medical history and clinical presentation, it was found that 41 (61.2%) patients had at least two supportive criteria for this diagnosis. This figure rose to 54 (80.6%) if a relapsing course was also considered as a possible supportive criterion for the diagnosis. Even if a relapsing course is part of the clinical definition of CIDP its consideration as a possible supportive criterion is justified by its occurrence in only few other neuropathies including vasculitis, acute porphyria and episodes of exposure to toxic agents. The distinction with hereditary neuropathy with liability to pressure palsy may be more difficult given the similar presence of signs of demyelination and conduction block. However, the combination of clinical history, presence of other supportive abnormalities, response to therapy and absence of familial history might help in the distinction from these neuropathies. A better definition of relapse in CIDP might also be necessary to uniform the data from different series. The number of supportive criteria in our patients might have been even higher if it is considered that nerve US or MRI and nerve biopsy were only performed in a minority of patients to improve the diagnostic definition. This could explain why an invasive test like nerve biopsy was performed in a higher proportion of patients not fulfilling (16.4%) than fulfilling (7.5%, $P = 0.0321$) EFNS/PNS criteria while non-invasive tests like nerve US or MRI were performed in a similar proportion of patients (12.9% and 13.8%).

One limit of this study is the lower number of examined motor nerves in patients not fulfilling than in those fulfilling the EFNS/PNS electrodiagnostic criteria. Most of non-EFNS/PNS patients (73%), however, had four or more motor nerves examined and 38.8% at least six nerves. Even if there was no difference between patients who had four of more nerves examined or fewer, it is possible that some patients might have fulfilled the EFNS/PNS electrodiagnostic criteria with a more extensive and complete electrophysiological examination inclusive of a more proximal nerve stimulation in the upper limbs. There was also no difference between patients with or without minor non-diagnostic signs of demyelination indicating that the use of less restrictive electrodiagnostic criteria did not permit the sensitivity of the diagnosis for CIDP to be implemented.

Even if it is difficult to propose new diagnostic criteria in the absence of a control population, our data suggest that in patients with a medical history and clinical signs compatible with CIDP and no other sign of a possible alternative diagnosis and non-diagnostic nerve conduction studies, a diagnosis of possible clinical CIDP might be supported by the presence of two supportive criteria (43.3% in our series, 40.3% adding a relapsing course to the criteria), of probable CIDP by three criteria (16.4%, 29.9% adding relapse) and of definite clinical CIDP by four criteria (1.5%, 10.4% adding relapse). It is also thought that the presence of at least two supportive criteria may also justify the initiation of treatment in these patients. This would have allowed initiation of therapy in almost 50% of our patients if a history of a relapsing course is also considered.

Even if these criteria may favor access to diagnosis and therapy for patients not fulfilling the EFNS/PNS electrodiagnostic criteria, they may also increase the risk of over-diagnosis of CIDP, especially in patients with an atypical presentation or with only axonal changes on nerve conduction studies [27,28]. It is thought, however, that an objective assessment of the medical history and clinical presentation of the patients, the exclusion of other possible causes for the neuropathy and an accurate search for possible supportive criteria for the diagnosis of CIDP might limit this risk and favor the access to treatment of patients who would otherwise be denied a possibly effective therapy.

The limitations of this study include its retrospective nature and the lack of a control population of

patients not affected by CIDP. Moreover, US/MRI and nerve biopsy were not routinely performed, and so the percentages of clinical CIDP patients with at least two supportive criteria could be even higher than in our analysis. Data on response to therapy should also be considered with caution considering the retrospective nature of this study. This response was similar, however, to what is reported in the literature [29–34], probably reflecting the fact that the study was performed in centers with expertise in immune-mediated neuropathies. Despite these limitations, this study provides the opportunity to verify the usefulness and the critical issues related to the use of current diagnostic criteria for CIDP and supports the opportunity of the revision of these criteria.

Acknowledgements

This study was supported by a grant from Regione Lombardia, Italy, for patients from this region and by a grant of the Italian Ministry of Health 'Ricerca Finalizzata 2016' (grant code: RF-2016-02361887) to Humanitas Clinical and Research Center, IRCCS. The study was also supported by unrestricted grants from Kedrion Biopharma (Italy), CSL Behring (Italy), Humanitas Clinical and Research Institute (Milan, Italy) and GBS-CIDP Foundation International (USA). The funding organizations had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; decision to submit the manuscript for publication.

Disclosure of conflicts of interest

E.N.O. reported personal fees for advisory or scientific boards from Kedrion, Italy, Baxter, Italy, Novartis, Switzerland, CSL Behring, Italy, LFB, France, Astellas, the Netherlands, outside the submitted work and travel grants to attend scientific meetings from Baxter, Grifols, Kedrion and Novartis, Italy. P.E.D. reported travel grants to attend scientific meetings from CSL Behring and Kedrion. G.L. reported travel grants to attend scientific meetings from CSL Behring and Kedrion. D.C. reported honoraria for lecturing from Shire, CSL Behring and Kedrion and travel grants to attend scientific meetings from Shire, Kedrion and CSL Behring. E.P. reported travel grants to attend scientific meetings from CSL Behring. R.F. has served on scientific advisory boards for CSL Behring and has received travel grants from Kedrion and CSL Behring to attend scientific meetings. M.C. reported travel grants to attend scientific meetings from Kedrion. A.M. reported travel grants from Kedrion and CSL Behring to attend scientific meetings. C.B. has served on scientific advisory boards for Pfizer and has received travel grants from Kedrion and CSL Behring to attend scientific meetings. G.C. reported travel grants to attend scientific meetings from CSL Behring and Kedrion. B.F. reported travel grants to attend scientific meetings from CSL Behring and a liberal contribution from CSL Behring for the neuromuscular diseases center, outside the submitted work. A.C. reported travel grants to attend scientific meetings from Kedrion. M.L. reported honoraria for a scientific board from Pfeizer and Alnylam and travel grants from Pfeizer, Grifols and Kedrion to attend scientific meetings. L.S. reported personal fees for scientific events from CSL Behring and has received travel grants to attend scientific meetings from CSL Behring and Kedrion. F.M. reported personal fees for scientific events from CSL Behring and has received travel grants to attend scientific meetings from CSL Behring and Kedrion. G.C. reported honoraria for lecturing and travel grants to attend scientific meetings from Kedrion. M.F. has served on scientific advisory boards for CSL Behring and Sarepta Therapeutics and has received travel grants from Sanofi Genzyme, Kedrion, Baxter and CSL Behring to attend scientific meetings. S.J. reported research grants from Grifols, outside this work, and travel grants from Grifols and Kedrion. G.A.M. reported consultancy fees and travel funding from CSL Behring, Kedrion, Shire and Grifols. G.A. reported honoraria for lecturing from Kedrion and Sanofi Genzyme, travel grants from Kedrion, Sanofi Genzyme and LJ Pharma. G.M. reported consultancy fees and travel funding from CSL Behring, Kedrion, Shire and Grifols. The other authors declare no conflict of interest.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Comparison of demographic, clinical, diagnostic and therapeutic findings in patients with CIDP not fulfilling EFNS/PNS criteria in relation to the presence of minor signs of demyelination.

References

1. Lunn MP, Manji H, Choudhary PP, Hughes RA, Thomas PK. Chronic inflammatory demyelinating polyradiculoneuropathy: a prevalence study in south east England. *J Neurol Neurosurg Psychiatry* 1999; **66:** 677–680.
2. Laughlin RS, Dyck PJ, Melton LJ III, Leibson C, Ransom J, Dyck PJ. Incidence and prevalence of CIDP and the associations with diabetes mellitus. *Neurology* 2009; **73:** 39–45.
3. Koller H, Kieseier BC, Jander S, Hartung HP. Chronic inflammatory demyelinating polyneuropathy. *N Engl J Med* 2005; **352:** 1343–1356.
4. Vallat JM, Sommer C, Magy L. Chronic inflammatory demyelinating polyradiculoneuropathy: diagnostic and therapeutic challenges for a treatable condition. *Lancet Neurol* 2010; **9:** 402–412.
5. Nobile-Orazio E. Chronic inflammatory demyelinating polyradiculoneuropathy and variants: where we are and where we should go. *J Peripher Nerv Syst* 2014; **19:** 2–13.
6. Lehmann HC, Broke N, Kuwabara S. Chronic inflammatory demyelinating polyneuropathy: update on diagnosis, immunopathogenesis and treatment. *J Neurol Neurosurg Psychiatry* 2019; **90:** 981–987.
7. Doneddu PE, Cocito D, Manganelli F, *et al*. Atypical CIDP: diagnostic criteria, progression, and treatment response. Data from the Italian CIDP Database. *J Neurol Neurosurg Psychiatry* 2019; **90:** 125–132.
8. Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force. Criteria for diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP). *Neurology* 1991; **41:** 617–618.
9. Koski CL, Baumgarten M, Magder LS, *et al*. Derivation and validation of diagnostic criteria for chronic inflammatory demyelinating polyneuropathy. *J Neurol Sci* 2009; **277:** 1–8.
10. Hughes RA, Bouche P, Cornblath DR, *et al*. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. *Eur J Neurol* 2006; **13:** 326–332.
11. Van den Bergh PY, Hadden RD, Bouche P, *et al*. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society – First Revision. *Eur J Neurol* 2010; **17:** 356–363. Corrigendum. In: *Eur J Neurol* 2011; 18: 276.
12. Bromberg MB. Review of the evolution of electrodiagnostic criteria for chronic inflammatory demyelinating polyradiculoneuropathy. *Muscle Nerve* 2011; **43:** 780–794.
13. Breiner A, Brannagan TH III. Comparison of sensitivity and specificity among 15 criteria for chronic inflammatory demyelinating polyneuropathy. *Muscle Nerve* 2014; **50:** 40–46.
14. Rajabally YA, Nicolas G, Piéret F, Bouche P, Van den Bergh PY. Validity of diagnostic criteria for chronic inflammatory demyelinating polyneuropathy: a multicentre European study. *J Neurol Neurosurg Psychiatry* 2009; **80:** 1364–1368.
15. Sinnreich M, Klein CJ, Daube JR, *et al*. Chronic immune sensory polyradiculopathy. A possibly treatable sensory ataxia. *Neurology* 2004; **63:** 1662–1669.
16. Liberatore G, Manganelli F, Cocito D, *et al*. Relevance of diagnostic investigations in chronic inflammatory demyelinating polyradiculoneuropathy: data from the Italian CIDP Database. *J Peripher Nerv Syst* 2020; **25:** 152–161.https://doi.org/10.1111/jns.12378
17. Kleyweg RP, van der Meché FG, Schmitz PI. Interobserver agreement in the assessment of muscle strength and functional abilities in Guillain–Barré syndrome. *Muscle Nerve* 1991; **14:** 1103–1109.
18. Hughes RAC, Bensa S, Willison HJ, *et al*. Randomized controlled trial of intravenous immunoglobulin versus oral prednisolone in chronic inflammatory demyelinating polyradiculoneuropathy. *Ann Neurol* 2001; **50:** 195–201.
19. Merkies ISJ, van Nes I, Hanna K, Hughes RAC, Deng C. Confirming the efficacy of intravenous immunoglobulin in CIDP through minimum clinically important differences: shifting from statistical significance to clinical relevance. *J Neurol Neurosurg Psychiatry* 2010; **81:** 1194–1199.
20. Breiner A, Moher D, Brooks J, *et al*. Adult CSF total protein upper reference limits should be age partitioned and significantly higher than 0.45 g/L: a systematic review. *J Neurol* 2019; **266:** 616–624.
21. Goedee HS, Jongbloed BA, van Asseldonk J-TH, *et al*. A comparative study of brachial plexus sonography and magnetic resonance imaging in chronic inflammatory demyelinating neuropathy and multifocal motor neuropathy. *Eur J Neurol* 2017; **24:** 1307–1313.
22. Liberatore G, Giannotta C, Sajeev BP, *et al*. Sensitivity and specificity of a commercial ELISA test for anti-MAG antibodies in patients with neuropathy. *J Neuroimmunol* 2020; **345:** 577288.
23. Dyck PJ, Lais AC, Ohta M, Bastron JA, Okazaki H, Groover RV. Chronic inflammatory polyradiculoneuropathy. *Mayo Clin Proc* 1975; **50:** 621–637.
24. Hattori N, Misu K, Koike H, Nagamatsu M, Hirayama M, Sobue G. Age of onset influences clinical features of chronic inflammatory demyelinating polyneuropathy. *J Neurol Sci* 2001; **184:** 57–63.
25. McCombe PA, Pollard JD, McLeod JG. Chronic inflammatory demyelinating polyradiculoneuropathy: a clinical and electrophysiological study on 92 cases. *Brain* 1987; **110:** 1617–1630.
26. Barohn RJ, Kissel JT, Warmolts JR, Mendell JR. Chronic inflammatory demyelinating polyradiculoneuropathy: clinical characteristics, course and recommendations for diagnostic criteria. *Arch Neurol* 1989; **46:** 878–884.
27. Allen JA, Lewis RA. CIDP diagnostic pitfalls and perception of treatment benefit. *Neurology* 2015; **85:** 498–504.
28. Allen J, Ney J, Lewis RA. Electrodiagnostic errors contribute to chronic inflammatory demyelinating polyneuropathy misdiagnosis. *Muscle Nerve* 2018; **57:** 542–549.
29. Cocito D, Paolasso I, Antonini G, *et al*. A nationwide retrospective analysis on the effect of immune therapies in patients with chronic inflammatory demyelinating polyradiculoneuropathy. *Eur J Neurol* 2010; **17:** 289–294.

30. Eftimov F, Winer JB, Vermeulen M, de Haan R, van Schaik IN. Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy. *Cochrane Database Syst Rev* 2013; **12:** CD001797.
31. Mehndiratta MM, Hughes RA. Corticosteroids for chronic inflammatory demyelinating polyradiculoneuropathy. *Cochrane Database Syst Rev* 2012; **8:** CD002062.
32. Mehndiratta MM, Hughes RA, Agarwal P. Plasma exchange for chronic inflammatory demyelinating polyradiculoneuropathy. *Cochrane Database Syst Rev* 2012; **9:** CD003906.
33. Cocito D, Grimaldi S, Paolasso I, *et al*. Immunosuppressive treatment in refractory chronic inflammatory demyelinating polyradiculoneuropathy. A nationwide retrospective analysis. *Eur J Neurol* 2011; **18:** 1417–1421.
34. Nobile-Orazio E, Cocito D, Jann S, *et al*. Intravenous immunoglobulin versus intravenous methylprednisolone for chronic inflammatory demyelinating polyradiculoneuropathy: a randomised controlled trial. *Lancet Neurol* 2012; **11:** 493–502.

Appendix

Italian CIDP Database study group

Pietro Emiliano Doneddu, Giuseppe Liberatore, Francesca Gallia and Eduardo Nobile-Orazio from the Department of Medical Biotechnology and Translational Medicine, Neuromuscular and Neuroimmunology Service, Humanitas Clinical and Research Institute, Milan University, Rozzano, Milan, Italy; Erdita Peci and Dario Cocito from the Department of Neuroscience, University of Turin, Turin, Italy; Stefano Tronci and Raffaella Fazio from the Division of Neuroscience, Department of Neurology, Institute of Experimental Neurology (INSPE), San Raffaele Scientific Institute, Milan, Italy; Fiore Manganelli, Lucio Santoro and Emanuele Spina from the Department of Neuroscience, Reproductive Sciences and Odontostomatology, University of Naples 'Federico II', Naples, Italy; Marta Ruiz and Chiara Briani from the Neurology Unit, Department of Neuroscience, University of Padua, Padua, Italy; Stefano Cotti Piccinelli and Massimiliano Filosto from the Center for Neuromuscular Diseases and Neuropathies, Unit of Neurology ASST 'Spedali Civili', University of Brescia, Brescia, Italy; Alessandro Beronio and Luana Benedetti from the Neurology Unit, Sant'Andrea Hospital, La Spezia, Italy; Antonio Toscano, Luca Gentile and Anna Mazzeo from the Department of Clinical and Experimental Medicine, Unit of Neurology, University of Messina, Messina, Italy; Giorgia Mataluni and Girolama Alessandra Marfia from the Dysimmune Neuropathies Unit, Department of Systems Medicine, Tor Vergata University of Rome, Rome, Italy; Laura Piccolo and Andrea Cortese from the IRCCS Foundation C. Mondino National Neurological Institute, Pavia, Italy; Giuseppe Cosentino and Brigida Fierro from the Department of Experimental BioMedicine and Clinical Neurosciences (BioNeC), University of Palermo, Palermo, Italy; Verrengia Elena Pinuccia and Stefano Jann from the Department of Neuroscience, Niguarda Ca' Granda Hospital, Milan, Italy; Elisa Bianchi and Ettore Beghi from the Laboratorio di Malattie Neurologiche, IRCCS-Istituto Mario Negri, Milan, Italy; Angelo Maurizio Clerici from the Neurology Unit, Circolo and Macchi Foundation Hospital, Insubria University, DBSV, Varese, Italy; Federica Scrascia and Marinella Carpo from the ASST Bergamo Ovest-Ospedale Treviglio, Treviglio, Italy; Martina Garnero and Angelo Schenone from the Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa and IRCCS AOU San Martino-IST, Genoa, Italy; Marco Luigetti and Mario Sabatelli from the Department of Neurology, Catholic University of Sacred Heart, Rome, Italy; Patrizia Dacci and Giuseppe Lauria from the Unit of Neuroalgology, IRCCS Foundation 'Carlo Besta' Neurological Institute, Milan, Italy; Luca Leonardi and Giovanni Antonini from the Unit of Neuromuscular Diseases, Department of Neurology Mental Health and Sensory Organs (NESMOS), Faculty of Medicine and Psychology, 'Sapienza' University of Rome, Sant'Andrea Hospital, Rome, Italy; Tiziana Rosso from the Azienda UL.SS. 8 Asolo, Castelfranco Veneto, Italy; Erika Schirinzi and Gabriele Siciliano from the Neurology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; Claudia Balducci and Guido Cavaletti from the School of Medicine and Surgery and Experimental Neurology Unit, University of Milano-Bicocca, Monza, Italy.