Original research

# Unclassified clinical presentations of chronic inflammatory demyelinating polyradiculoneuropathy

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## ABSTRACT

**Background** To assess the ability of the 2021 European Academy of Neurology/Peripheral Nerve Society (EAN/PNS) clinical criteria for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) to include within their classification the whole spectrum of clinical heterogeneity of the disease and to define the clinical characteristics of the unclassifiable clinical forms.

**Methods** The 2021 EAN/PNS clinical criteria for CIDP were applied to 329 patients fulfilling the electrodiagnostic (and in some cases also the supportive) criteria for the diagnosis of CIDP. Clinical characteristics were reviewed for each patient not strictly fulfilling the clinical criteria ('unclassifiable').

**Results** At study inclusion, 124 (37.5%) patients had an unclassifiable clinical presentation, including 110 (89%) with a typical CIDP-like clinical phenotype in whom some segments of the four limbs were unaffected by weakness ('incomplete typical CIDP'), 10 (8%) with a mild distal, symmetric, sensory or sensorimotor polyneuropathy confined to the lower limbs with cranial nerve involvement ('cranial nerve predominant CIDP') and 4 (1%) with a symmetric sensorimotor polyneuropathy limited to the proximal and distal areas of the lower limbs ('paraparetic CIDP'). Eighty-one (65%) patients maintained an unclassifiable presentation during the entire disease follow-up while 13 patients progressed to typical CIDP. Patients with the unclassifiable clinical forms compared with patients with typical CIDP had a milder form of CIDP, while there was no difference in the distribution patterns of demyelination.

**Conclusions** A proportion of patients with CIDP do not strictly fulfil the 2021 EAN/PNS clinical criteria for diagnosis. These unclassifiable clinical phenotypes may pose diagnostic challenges and thus deserve more attention in clinical practice and research.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The 2021 European Academy of Neurology/Peripheral Nerve Society (EAN/PNS) guidelines have refined the diagnostic criteria for typical chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and its variants, posing more stringent clinical definition. The efficiency of these criteria to successfully classify each patient into a specific category remains, however, unclear.

### WHAT THIS STUDY ADDS

⇒ Almost 40% of the patients fulfilling the 2021 EAN/PNS electrodiagnostic criteria (and for possible CIDP also the supportive criteria) for a diagnosis of CIDP did not strictly fulfil the clinical criteria for either typical CIDP or its variants. In patients with unclassifiable clinical presentation, three distinct clinical phenotypes may be recognised, namely incomplete typical CIDP, cranial nerve predominant CIDP and paraparetic CIDP.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study draws attention to the presence of clinical phenotypes that do not strictly fall within the 2021 EAN/PNS clinical diagnostic criteria for CIDP. The scarce awareness of these clinical phenotypes might be responsible for diagnostic and treatment delay.

## INTRODUCTION

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an immune-mediated neuropathy characterised by progressive, stepwise or recurrent symmetric proximal and distal weakness,



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sensory dysfunction and absent or reduced tendon reflexes at four limbs, developing over a period of at least 2 months. Besides the typical form, some clinical variants have been reported, including multifocal CIDP, focal CIDP, distal CIDP, sensory or sensory-predominant CIDP, and motor or motor-predominant CIDP, widening the spectrum of this neuropathy.[1 2] Whether the pathogenic mechanism underlying these clinical phenotypes is different or not is not clear, but they all share the common features of demyelination and response to immune therapy.[1] There is also evidence that CIDP variants may evolve over time to typical CIDP.[2] The 2010 European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) criteria had not precisely defined the diagnostic criteria of the individual variants of CIDP,[3] and this may explain their reported variable frequency (from 1% to 49%) and response to treatment.[2 4] The 2021 European Academy of Neurology/Peripheral Nerve Society (EAN/PNS) task force have refined the diagnostic criteria for typical CIDP and its variants, posing more stringent clinical definition also for typical CIDP, which requires symmetric proximal and distal muscle weakness of upper and lower limbs and sensory involvement of at least two limbs.[1] The efficiency of these criteria to successfully classify each patient into a specific category remains, however, unclear. Clinical experience suggests that a proportion of patients with CIDP does not fit into the clinical criteria for either typical CIDP or its variants. Recognition of the clinical phenotype of the variants is crucial since the diagnostic workflow and the differential diagnosis may differ compared with typical CIDP.[1] In patients with CIDP variants the diagnosis can be difficult and delayed, as highlighted by recent studies,[5–8] and this may result in accumulation of residual neurological deficit and disability.[8]

In this study, we strictly applied the 2021 EAN/PNS clinical criteria for typical CIDP and its variants to a large cohort of patients with CIDP included in the Italian CIDP database to assess their ability to include within their classification the whole spectrum of clinical heterogeneity of the disease. We also aimed to define the clinical presentation and course of the patients not fulfilling these clinical criteria.

## METHODS

### Database and study population

Patients with a clinical diagnosis of CIDP were included by treating neurologists in the Italian CIDP database, a web-based electronic registry expressly prepared by CINECA, Bologna, Italy. The diagnosis of CIDP was reviewed by the coordinating Centre (PED and ENO) in accordance with the treating neurologist and classified according to the 2010 EFNS/PNS diagnostic criteria and subsequently reviewed according to the 2021 EAN/PNS criteria. Patients with a medical history and clinical signs compatible with the diagnosis of CIDP or one of its variants not fulfilling the EFNS/PNS electrodiagnostic criteria were also included in the database.[9] All the patients had been extensively investigated in each centre for the presence of a possible alternative cause of the neuropathy by clinical and laboratory investigations in accordance with the EFNS/PNS guidelines.[3] Data monitoring included diagnosis revision, suspect of double entries, missing data and plausibility checks.

At the time of enrolment, all eligible patients underwent a detailed clinical history including time of onset, distribution and progression of signs and symptoms including weakness, sensory symptoms, ataxia, pain, cramps, tremor, fatigue, cranial nerve impairment, dysphagia and autonomic dysfunction. This information was integrated with the data reported in the medical records. The treating neurologist defined the course of the disease as monophasic, 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.[9] However, some patients with a delayed worsening (>3 months) after treatment suspension or reduction might have been also included in this group.[9] An acute onset of CIDP was also reported and defined as a neuropathy that was initially diagnosed as Guillain-Barré syndrome (GBS) but that continued to progress or relapse after more than 2 months from disease onset. A complete neurological assessment was performed at the time of enrolment including measurement of muscle strength using the Medical Research Council (MRC) sumscore on 12 muscles (range 0–60), neurological disability using the Inflammatory-Rasch Overall Built Disability Scale (range 1–48) and the Inflammatory Neuropathy Cause and Treatment (INCAT) Scale (range 0–10). Quality of life (QoL) was assessed with the EuroQol-5D-3L scale (five items, each with a score from 1-best to 3-worst). Response to treatment was defined as a subjective improvement that had been confirmed by an increase of at least 2 points in the MRC sum score (range 0–60) or at least 1 point reduction in the INCAT disability score (range 0–10).[1 3] Results of previously performed examinations including cerebrospinal fluid (CSF) analysis, nerve ultrasound or brachial/lumbosacral plexus MR examination, somatosensory evoked potentials and sural nerve biopsy, were reported when available. As to CSF protein counts, we considered as upper reference limit 50 mg/dL for patients aged ≤50 years and 60 mg/dL for those aged >50 years.[10] The results of 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 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. All nerve conductions were performed at a temperature of at least 33°C at the palm and 30°C at the external malleolus. Results were analysed according to each laboratory's range of normal values, and presence of demyelinating range values determined for each relevant parameter. To evaluate temporal dispersion, nerve conduction studies waveforms of the CIDP patients were reviewed and measurements were redone following the indications of the 2021 EAN/PNS criteria.[1] Patients for whom nerve conduction study waveforms were not available for revision were excluded from the analysis of temporal dispersion.

### Patients' inclusion

In this study, only patients fulfilling the 2021 EAN/PNS electrodiagnostic (and in some patients also the supportive) criteria for a diagnosis of CIDP were included. Of the initial 666 patients, 133 were excluded for incomplete clinical or electrophysiological data, 28 patients for having an alternative diagnosis for the neuropathy including high titers of anti-MAG (myelin-associated glycoprotein) antibodies (over 7000 Bühlmann titre units by Bühlmann method), and 14 patients for having a diagnosis of chronic immune sensory polyradiculopathy or autoimmune nodopathy, currently excluded from CIDP.[1] Fifty-two patients with a diagnosis of possible CIDP and 95 not fulfilling the 2021 EAN/PNS criteria for CIDP or possible CIDP were excluded



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from the analysis. We decided that a minimum of 1-year duration of symptoms and signs specific to each CIDP form was necessary to establish a diagnosis of typical CIDP or its variants.[2] This decision was made because even typical CIDP may initially present with purely sensory or motor symptoms evolving over a few months to a typical sensorimotor form. After excluding patients with a disease duration of less than 1 year (n=15), 329 patients were included in the final analysis.

Two recent studies showed that the 2021 EAN/PNS electrophysiological and supportive criteria for a diagnosis of CIDP have very good diagnostic accuracy.[11 12] In this study, the 2021 EAN/PNS clinical criteria for typical CIDP and its variants were applied both at symptoms onset and at study inclusion to explore the clinical categorisation of the 2021 EAN/PNS guidelines for CIDP. Patients fulfilling the 2021 EAN/PNS electrophysiological (and in some cases also the supportive) criteria for a diagnosis of CIDP, but not the clinical criteria for typical CIDP or its variants, were compared with patients with typical CIDP regarding clinical features, results of additional investigations, disease severity and response to treatment.

### Statistical analysis

Descriptive statistics were reported for the entire sample of patients with CIDP, and for each clinical subgroup separately. Categorical variables were described using frequencies and percentages, while continuous variables using mean, median and ranges. Demographic, clinical and electrophysiological features, treatment response, strength deficit, disability level and QoL were compared between the different subgroups of patients with the Fisher's exact test for categorical variables and with the t-test for continuous variables. All tests were two tailed, and the significance level was set to 0.05. Analyses were performed with SAS V.9.4 (SAS Institute).

## RESULTS

Overall 329 patients consisted of 204 men and 125 women, aged 12–92 years (mean 57; median 58) with a mean disease duration at study inclusion of 8 years (range 1–52; median 6). At study inclusion, 91 (27.5%) patients satisfied the 2021 EAN/PNS clinical criteria for typical CIDP with symmetric, proximal and distal muscle weakness at upper and lower limbs, and sensory involvement of at least two limbs. Forty-eight patients (14.5%) fulfilled the 2021 EAN/PNS clinical criteria for distal CIDP, 26 (8%) for sensory CIDP, 22 (7%) for multifocal CIDP, 1 (0.5%) for focal and 17 (5%) for motor CIDP. One hundred and 24 (37.5%) patients did not completely fulfil the clinical criteria for either typical CIDP or its variants. These patients were defined as 'unclassified'. When we retrospectively reviewed the symptoms and signs at disease onset of all patients, we found that 60 (18%) patients fulfilled the 2021 EAN/PNS clinical criteria for typical CIDP, 62 (19%) for distal CIDP, 53 (16%) for sensory CIDP, 31 (9.5%) for motor CIDP, 26 (8%) for multifocal CIDP and 3 (1%) patients for focal CIDP, while 94 (28.5%) patients were unclassified. Figure 1 shows the frequency of the CIDP clinical forms at symptoms onset (figure 1A) and study entry (figure 1B). Eighteen (16%) patients with one of the CIDP variants at onset progressed to typical CIDP after mean disease duration of 7 years (range 1–17, median 6), including 7 with sensory CIDP, 4 with distal CIDP, 3 with motor CIDP, 3 with multifocal CIDP and 1 with focal CIDP.

Of the 124 unclassified patients at study inclusion, 43 (35%) had progressed to an unclassified form from one of the CIDP variants after a mean of 6 years (range 1–29, median 5) of disease duration. These included 20 (16%) patients with sensory CIDP, 11 (9%) with motor CIDP, 10 (8%) with distal CIDP, 1 (1%) with multifocal CIDP and 1 (1%) with focal CIDP. The change in clinical presentation of the latter group of patients cannot be attributed to the effect of therapy as in all the patients there was a greater spread of the peripheral neuropathy towards a typical CIDP-like phenotype in which some segments of the four limbs were spared ('incomplete typical CIDP'). The remaining 81 (65%) patients maintained an unclassifiable presentation during the entire disease duration (mean 6 years; range 1–36, median 5). On the other hand, 13 patients who had an unclassifiable

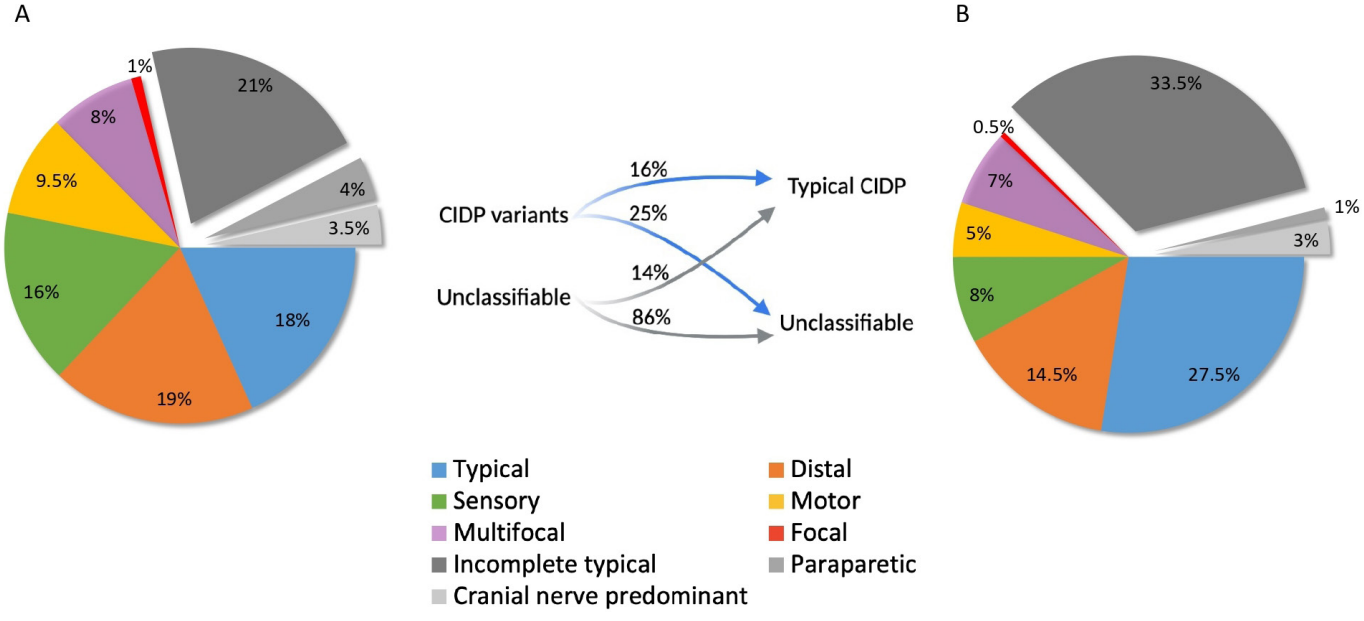


**Figure 1** CIDP clinical form according to the 2021 EAN/PNS clinical criteria for CIDP, at onset of symptoms (A) and at study entry (B) (mean 8 years after onset) in 329 patients with CIDP fulfilling the 2021 EAN/PNS electrodiagnostic (and in a proportion of patients also the supportive) criteria for CIDP. CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; EAN/PNS, European Academy of Neurology/Peripheral Nerve Society.



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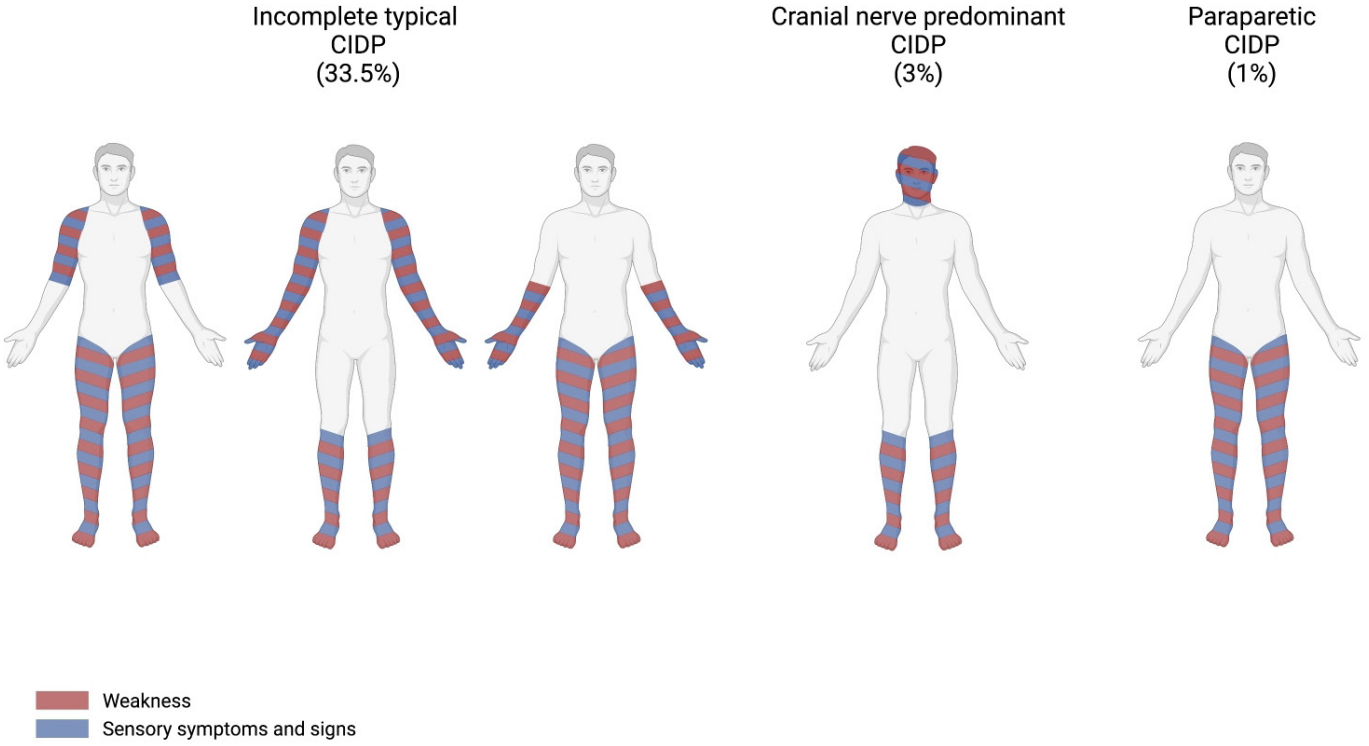


**Figure 2** Type of symptoms and their distribution in incomplete typical CIDP, cranial nerve predominant CIDP and paraparetic CIDP. Percentage of the whole CIDP population at the time of study inclusion. CIDP, chronic inflammatory demyelinating polyradiculoneuropathy.

presentation at onset progressed to typical CIDP after mean disease duration of 7 years (range 1–20, median 6).

## Clinical characteristics of the 'unclassifiable' patients

A detailed investigation of the clinical presentations of the 124 patients with an 'unclassifiable' phenotype permitted to identify three main subgroups with distinct clinical characteristics. The most frequent form, that we named 'incomplete typical CIDP', was observed at inclusion in 110 (89%) patients and consisted of a clinical presentation resembling typical CIDP but in which some segments of the four limbs (eg, proximal areas of the upper limbs in 47 patients, distal areas of the upper limbs in 30 patients, proximal areas of the lower limbs in 22 patients) were unaffected by weakness (figure 2). All patients had a symmetrical distribution of sensory symptoms and signs and weakness. Fifty-nine (54%) patients maintained this clinical form during their entire disease history (mean 7 years; range 1–35), while 51 (46%) had a different clinical presentation at onset (43 patients a CIDP variant and 8 another unclassified form). Ten patients with an incomplete typical CIDP at onset progressed to typical CIDP after a mean of 7 years (range 1–20).

The second most frequent clinical presentation, that we named 'cranial nerve predominant CIDP', was found in 10 (8%) patients at inclusion and presented as a mild distal, symmetric, sensory or sensorimotor polyneuropathy confined to the lower limbs with cranial nerve involvement (figure 2). The most common cranial symptomatology seen in these patients was oculomotor palsy (III bilaterally in four patients, III and VI in three patients, IV bilaterally in one patient), followed by dysphagia (left IX in two patients), oculomotor and facial palsy (III and VII in two patients). Ten (100%) patients maintained this clinical presentation during their entire disease history (mean 8 years; range 1–18), while one patient with cranial predominant CIDP at onset progressed to incomplete typical CIDP and one to typical CIDP after a mean of 2 years (range 1–3). In 6 (60%) patients, cranial nerve involvement preceded the onset of limb symptoms by a mean of 3 years (range 2–5).

The least frequent clinical form, that we named 'paraparetic CIDP', was observed in 4 (3%) patients at inclusion and was characterised by symmetric sensory and motor symptoms limited to the proximal and distal areas of the lower limbs (figure 2). Four (100%) patients maintained this clinical picture during the entire disease course (mean 6 years; range 1–16) while 7 patients with this clinical presentation at onset progressed to incomplete typical CIDP and 2 to typical CIDP after a mean of 9 years (range 1–25).

Table 1 shows comparison of the clinical characteristics and treatment response at the time of study inclusion of incomplete typical CIDP, cranial nerve predominant CIDP and paraparetic CIDP with typical CIDP. Since some patients with incomplete typical CIDP and with cranial nerve predominant CIDP had purely distal weakness and sensory symptoms in some limbs, these two clinical forms were also compared with distal CIDP.

Compared with typical CIDP, patients with incomplete typical CIDP had a higher MRC sum score (mean 55 vs 51; p=0.0027), lower disability levels at INCAT (mean 2.5 vs 3.5; p=0.0012) and more frequent response to intravenous immunoglobulin (IVIg) (81% vs 65%; p=0.0201), while those with cranial nerve predominant CIDP had less frequent pain (0% vs 35%; p=0.02083), higher MRC sum score (mean 57 vs 51; p=0.0295) and lower disability levels at INCAT (mean 1.5 vs 3.5; p=0.0067). No statistically significant difference between paraparetic CIDP and typical CIDP was found. Compared with distal CIDP, patients with incomplete typical CIDP had lower MRC sum score (mean 55 vs 58; p=0.0012), and higher disability levels at INCAT (mean 2.5 vs 2.3; p=0.0031), while those with cranial nerve predominant CIDP had less frequent pain (0% vs 42%; p=0.0109).



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**Table 1** Comparison of clinical features and treatment response of incomplete typical CIDP, paraparetic CIDP and cranial nerve predominant CIDP, with typical CIDP and distal CIDP at the time of study inclusion.

| Clinical features | Incomplete typical CIDP (n=110) | Cranial nerve predominant CIDP (n=10) | Paraparetic CIDP (n=4) | Typical CIDP (n=91) | Distal CIDP (n=48) | P value |
|---|---|---|---|---|---|---|
| Gender (M:F) | 58:52 | 7:3 | 2:2 | 57:34 | 30:18 | NS |
| Age at onset, years; mean (range) | 48 (12–80) | 50 (19–71) | 53 (22–66) | 47 (9–86) | 53 (20–84) | NS |
| Disease duration, years; mean (range) | 9 (1–52) | 8.5 (1–18) | 6 (1–16) | 10 (1–42) | 8 (1–34) | NS |
| Increased CSF proteins; positive/tested (%) | 65/78 (83%) | 7/9 (78%) | 1/2 (50%) | 62/74 (84%) | 31/37 (84%) | NS |
| Mean CSF proteins, mg/dL (range) | 124 (50–595) | 90 (51–152) | 126 | 134 (45–1000) | 117 (50–379) | NS |
| Nerve imaging; positive/tested | 12/18 (67%) | 2/3 (67%) | 1/2 (50%) | 9/15 (60%) | 6/10 (60%) | NS |
| Nerve biopsy; positive/tested | 7/11 (64%) | 0 | 1/1 (100%) | 7/13 (54%) | 2/3 (67%) | NS |
| Pain | 41 (37%) | 0 | 1 (25%) | 32 (35%) | 20 (42%) | 0.0283†<br>0.0109§ |
| Fatigue | 70 (64%) | 5 (50%) | 2 (50%) | 56 (62%) | 27 (56%) | NS |
| Ataxia | 33 (30%) | 4 (40%) | 1 (25%) | 35 (38%) | 13 (27%) | NS |
| Disease course; relapsing/progressive | 56/50 | 5/4 | 1/3 | 45/43 | 26/22 | NS |
| Acute onset | 7 (6%) | 3 (30%) | 0 | 10 (11%) | 3 (6%) | NS |
| MRC sum score; mean (range) | 55 (38–60) | 57 (56–60) | 58 (54–60) | 51 (0–60) | 58 (54–60) | 0.0027*<br>0.0295†<br>0.0012‡ |
| INCAT disability score; mean (range) | 2.5 (0–8) | 1.5 (0–3) | 2 (1-4) | 3.5 (0–10) | 2.3 (0–6) | 0.0012*<br>0.0067†<br>0.0031‡ |
| I-RODS score; mean (range) | 32 (2–48) | 37 (22–48) | 40 (34–47) | 32 (6–48) | 30 (4–44) | NS |
| Quality of life score; mean (range) | 8 (5–13) | 8 (5–11) | 7 (6–9) | 8 (3–11) | 8 (5–12) | NS |
| Overall treatment response (%) | 95/102 (93%) | 9/10 (90%) | 3/3 (100%) | 74/88 (85%) | 39/45 (87%) | NS |
| Response to corticosteroids (%) | 31/55 (56%) | 3/5 (60%) | 1/1 (100%) | 37/65 (57%) | 14/26 (54%) | NS |
| Response to intravenous immunoglobulin (%) | 70/86 (81%) | 6/8 (75%) | 2/2 (100%) | 48/74 (65%) | 27/37 (73%) | 0.0201* |

*incomplete typical CIDP versus typical CIDP.
†cranial nerve predominant CIDP versus typical CIDP.
‡incomplete typical CIDP versus distal CIDP.
§cranial nerve predominant CIDP versus distal CIDP.
CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CSF, cerebrospinal fluid; F, female; INCAT, Inflammatory Neuropathy Cause and Treatment Disability Scale; I-RODS, Inflammatory Rasch Overall Disability Scale; M, male; MRC, Medical Research Council; NS, not significant.

There was no difference between the three unclassified forms and typical CIDP in terms of distribution of demyelinating electrophysiological abnormalities along the nerves (table 2).

## DISCUSSION

In this study, 38% of the patients with CIDP did not strictly fulfil the clinical criteria for either typical CIDP or its variants. These patients, however, fulfilled the 2021 EAN/PNS electrodiagnostic (and in some cases also the supportive) criteria for CIDP, which have a specificity of 94%–98%.[11 12] The diagnosis of CIDP in these patients was further supported by the similar age at symptoms onset and similar proportion of patients with increased CSF protein levels and response to therapy compared with typical CIDP. Diagnostic workup in these patients revealed no other cause of peripheral neuropathy, even after a follow-up of 6–9 years. The findings in these patients, therefore, suggest that these phenotypes may be a first clinical presentation or persistent form in a proportion of patients with CIDP.

To our knowledge, only a few studies reported patients with these clinical presentations. Gorson *et al* found that 4% of 67 patients with CIDP had a paraparetic pattern with severe leg weakness and sensory loss with little or no upper limbs involvement.[13] Busby and Donaghy found that 5% of 102 patients with CIDP had a symmetrical sensory deficit with prominent sensory ataxia, mild or absent of weakness and ophthalmoparesis.[14] Viala *et al* found that 2% of 146 patients with CIDP had isolated cranial nerve involvement.[15] Shibuya *et al* reported nine patients with distal acquired demyelinating symmetric polyneuropathy (DADS) having bulbar palsy (IX and X).[16] In our opinion, our patients with cranial predominant CIDP cannot fall within the 2021 EAN/PNS clinical criteria for distal CIDP, in which sensory and motor disturbances are confined to the distal segments of the upper and lower limbs.[1] Moreover, in most of our patients with cranial nerve predominant CIDP, cranial nerve palsy preceded by several years the onset of limb symptoms.

Compared with typical CIDP, patients with incomplete typical CIDP, cranial nerve predominant CIDP and paraparetic CIDP were relatively mildly affected, although their perception of QoL was similar to that of the patients with typical CIDP. Patients with incomplete typical CIDP versus typical CIDP had more frequent response to IVIg, while those with cranial nerve predominant CIDP had less frequent pain. A small proportion (14%) of patients with an unclassified clinical presentation at onset progressed to typical CIDP during the disease course, while incomplete typical CIDP was the clinical phenotype towards which patients with one of the CIDP variants at onset most frequently progressed. Still, 25% of our patients maintained an unclassified clinical presentation throughout the entire duration of the disease follow-up (6–8 years). Together, these findings indicate that incomplete typical CIDP, paraparetic CIDP and cranial nerve predominant CIDP are mild or regional forms of CIDP that may evolve over time to typical CIDP. Recent electrophysiological and sural nerve biopsy studies suggest that the distribution of lesions in the peripheral nervous system is



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**Table 2** Comparison of electrophysiological features in patients with incomplete typical CIDP, paraparetic CIDP, cranial nerve predominant CIDP and typical CIDP

| Electrophysiological features* | Incomplete typical form (n=110) | Cranial nerve predominant form (n=10) | Paraparetic form (n=4) | Typical CIDP (n=91) | P value |
|---|---|---|---|---|---|
| No of motor nerves examined; mean, (range) | 6 (2–8) | 7 (3–8) | 6 (4–7) | 6 (2–8) | NS |
| Increased DML in: | | | | | |
| ≥1 nerve, n., (%) | 47 (44%) | 4 (40%) | 0 | 43 (47%) | NS |
| ≥2 nerves, n., (%) | 38 (35%) | 2 (20%) | | 36 (40%) | NS |
| ≥50% tested nerves, n., (%) | 25 (23%) | 0 | | 25 (27%) | NS |
| Reduced CMAP amplitude in: | | | | | |
| ≥1 nerve, n., (%) | 83 (77%) | 8 (80%) | 1 (33%) | 69 (76%) | NS |
| ≥2 nerves, n., (%) | 58 (53%) | 4 (40%) | 1 (33%) | 47 (52%) | NS |
| ≥50% tested nerves, n., (%) | 0 | 0 | 1 (33%) | 0 | NS |
| Motor CB in: | | | | | |
| ≥1 nerve, n., (%) | 66 (61%) | 7 (70%) | 1 (33%) | 62 (68%) | NS |
| ≥2 nerves, n., (%) | 46 (42%) | 4 (40%) | 1 (33%) | 41 (45%) | NS |
| ≥50% tested nerves, n., (%) | 22 (20%) | 2 (20%) | 0 | 27 (30%) | NS |
| Reduced MCV in: | | | | | |
| ≥1 nerve, n., (%) | 73 (68%) | 7 (70%) | 1 (33%) | 60 (66%) | NS |
| ≥2 nerves, n., (%) | 60 (55%) | 6 (60%) | 1 (33%) | 52 (57%) | NS |
| ≥50% of tested nerves, n., (%) | 42 (38%) | 4 (40%) | 1 (33%) | 40 (44%) | NS |
| Temporal dispersion † in: | | | | | |
| ≥1 nerve, n., (%) | 41/53 (77%) | 1/4 (25%) | 2/3 (67%) | 38/55 (69%) | NS |
| ≥2 nerves, n., (%) | 36/53 (68%) | 1/4 (25%) | 1/3 (33%) | 29/55 (53%) | NS |
| ≥50% of tested nerves, n., (%) | 18/53 (16%) | 0 | 0 | 12/55 (13%) | NS |
| Increased F wave latency: | | | | | |
| ≥1 nerve; positive/tested, n., (%) | 10/53 (19%) | 2/4 (50%) | 1/3 (33%) | 20/55 (36%) | NS |
| ≥2 nerves; positive/tested, n., (%) | 10/53 (19%) | 2/4 (50%) | 1/3 (33%) | 18/55 (33%) | NS |
| ≥50% of tested nerves, n., (%) | 5/53 (9%) | 2/4 (50%) | 0 | 10/55 (18%) | NS |
| Absent F wave: | | | | | |
| ≥1 nerve; positive/tested, n., (%) | 9/53 (17%) | 1/4 (25%) | 1/3 (33%) | 16/55 (29%) | NS |
| ≥2 nerves; positive/tested, n., (%) | 9/53 (17%) | 1/4 (25%) | 1/3 (33%) | 12/55 (22%) | NS |
| ≥50% of tested nerves, n., (%) | 8 (15%) | 1/4 (25%) | 0 | 10 (18%) | NS |

*as per EAN/PNS criteria.[1]
† Analysis of temporal dispersion was performed only in patients for whom nerve conduction study waveforms were available for revision.
CB, conduction block; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CMAP, compound motor action potential; DML, distal motor latency; MCV, motor nerve conduction velocity; n, number; NS, not significant.

different between typical CIDP and its variants.[17 18] Our results, showing similar electrophysiological features among the three subforms and typical CIDP, possibly suggest that the underlying pathological mechanisms of the four clinical groups are similar. On the other hand, the more frequent response to IVIg in incomplete typical CIDP compared with typical CIDP seems to suggest the opposite, although this finding must be confirmed by other studies. It is also possible that the greater response to IVIg in this group is related to a selection bias, that is the inclusion of treatment responsive patients given the equivocal clinical diagnosis. Compared with distal CIDP, patients with incomplete typical CIDP were more severely affected, as expected from a more extensive neuropathy, while those with cranial nerve predominant CIDP differed not only in the involvement of cranial nerves but also in a less frequent presence of pain.

Early recognition of CIDP is crucial for accurate monitoring and treatment in the initial phase of disease.[5–8] Previous studies indicate that the diagnosis may be delayed in atypical clinical presentations,[5–8] and that this may lead to greater disability and more frequent fatigue and treatment dependency.[8] The clinical relevance of this study is to draw attention to the presence of clinical phenotypes that do not strictly fall within the 2021 EAN/PNS clinical diagnostic criteria for CIDP and, therefore, could be underdiagnosed, particularly by physicians and neurologists who do not routinely deal with peripheral neuropathies. In addition, these patients may not be eligible for IVIg therapy in some countries.[1 19] Although most of these patients had a clinical presentation quite similar to typical CIDP (incomplete typical CIDP, 33%), there was a not negligible number who had a clinical presentation very different from the clinical forms recognised by the 2021 EAN/PNS criteria (cranial nerve predominant and paraparetic CIDP, 4%). The current study shows that CIDP should be included among the differential diagnoses of patients with symmetrical paraparesis with sensory disturbances confined to the lower limbs and of patients with a mild distal sensorimotor polyneuropathy associated with cranial nerve palsy. Of note, 3/10 (30%) patients with cranial nerve predominant CIDP had an acute onset that could be easily misdiagnosed with GBS.

Limitations of our study include its retrospective nature and the inclusion of CIDP patients recruited from tertiary referral centres with the risk of selection bias of more severe cases. The investigated patient cohort may be biased towards cases of CIDP that fulfil the clinical criteria for typical CIDP or its variants to certify diagnosis of CIDP and inclusion in the database, resulting in an underestimation of the actual frequency of unclassified CIDP phenotypes. With the lack of diagnostic biomarker, it



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cannot be excluded that some patients in our cohort were misdiagnosed with CIDP. It is, however, unlikely that all the patients with an unclassified form in our cohort have another disease given their long follow-up, the fulfilment of electrophysiological criteria for CIDP and, in a proportion of patients, also the presence of supportive criteria including response to therapy, and the fact that such clinical phenotypes had already been described in the literature. In addition, none of the patients with an unclassified form received another diagnosis during the follow-up. Finally, most of the patients included in the database were enrolled before the publication of the 2021 EAN/PNS criteria, therefore, response to treatment was measured using only an impairment or a disability measure.

In summary, a proportion of patients with CIDP, who fulfill the 2021 EAN/PNS electrophysiological and supportive criteria for the diagnosis of CIDP, do not strictly meet the clinical 2021 EAN/PNS criteria for either typical CIDP or its variants. The scarce awareness of these clinical phenotypes might result in a delay in the diagnosis and treatment of these patients.

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**Contributors** PED contributed to the conception of the research project, performed the statistical analysis, wrote the first draft of the report, reviewed the report and accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. HA, FM, CB, DC, LB, AM, RF, MF, GC, VDS, GA, GAM, MI, GS, AMC, MC, AS, ML, GL, SM, TR, GMM, ML, GC, GL, ES, MC, EP, FG, LG, CS, SCP, EV, LL, GM, MC, ES and MR contributed to the conception, organisation and execution of the research project, reviewed and commented on the statistical analysis and the report. EN-O conceived, organised and designed the study, reviewed and commented on the statistical analysis, reviewed the report.

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**Competing interests** PED has received travel grants to attend scientific meetings from CSL Behring and Kedrion. Fiore Manganelli reports personal fees for scientific events from CSL Behring and has received travel grants to attend scientific meetings from CSL Behring and Kedrion. Dario Cocito has received honoraria for lecturing from Shire, CSL Behring, and Kedrion and travel grants to attend scientific meeting from Shire, Kedrion and CSL Behring. RF has served on scientific advisory boards for CSL Behring and has received travel grants from Kedrion and CSL Behring to attend scientific meeting. CB has served on scientific advisory boards for Pfizer, Alnylam, and Akcea, and has received travel grants from Kedrion and CSL Behring to attend scientific meeting. AM has received travel grants from Kedrion and CSL Behring to attend scientific meeting. MF has served on scientific advisory boards for CSL Behring, Sanofi and Amicus and has received travel grants from Sanofi, Biogen, Kedrion and CSL Behring to attend scientific meeting. GC has received travel grants to attend scientific meetings from CSL Behring and Kedrion. ML has received travel grants to attend scientific meetings from Kedrion. GAM has received travel grants to attend scientific meetings from CSL Behring and Kedrion. GL has received travel grants to attend scientific



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meetings from CSL Behring and Kedrion. EP has received travel grants to attend scientific meetings from CSL Behring. TR has received travel grants to attend scientific meetings from CSL Behring. EN-O reports personal fees for Advisory or Scientific Board from ArgenX—Belgium, Takeda—Italy and USA, CSL-Behring—Italy and USA, Janssen—USA, Kedrion—Italy, LFB—France, Roche—Switzerland, Sanofi—USA. The other authors declare no conflict of interest.

**Patient consent for publication** Not applicable.

**Ethics approval** The study was approved by the Ethical Committee of IRCCS Humanitas Clinical and Research Center (ID: DM 8/2/13-20/15) and of each participating Center. Participants gave informed consent to participate in the study before taking part.

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**Data availability statement** Anonymised data used for this study are available on reasonable request from the corresponding author.

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