Journal of the Neurological Sciences 466 (2024) 123259

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Clinical short communication

Characteristics and outcome of chronic inflammatory demyelinating polyradiculoneuropathy patients according to their diagnostic certainty based on the 2021 EAN/PNS criteria

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ARTICLE INFO

Keywords:
CIDP
Outcome
Diagnostic certainty
EAN/PNS

ABSTRACT

Introduction: To describe the clinical characteristics and long term outcome of CIDP patients according to 2021 EAN/PNS diagnostic certainty categories.

Methods: We reviewed clinical data, response to treatment, cerebrospinal fluid examination, and nerve conduction studies parameters of 39 adult "CIDP" and 24 "possible CIDP" patients. Data were collected at diagnosis and after one (T1), two (T2), three (T3) and five years (T5).

Results: At diagnosis, "possible CIDP" patients' phenotypes were more atypical (especially focal/multifocal, $p < .01$) and "CIDP" patients had a higher NIS and INCAT scores ($p = .08$ and 0.08). Compared to baseline: median NIS score decreased in "CIDP" and was stable in "possible CIDP" patients at T1 ($p < .05$), T2 ($p < .05$) and T3 ($p < .01$); median MRC score slightly increased in "CIDP" and was stable in "possible CIDP" patients at T2 ($p < .05$); and INCAT disability scale slightly decreased in "CIDP" and was stable in "possible CIDP" patients at T3 ($p < .05$). The proportion of moderate to severely disabled (mRS > 2) patients in "possible CIDP" group was higher than in "CIDP" group (not significant). "CIDP" patients had a better objective response to immunotherapy (59 % responders) than "possible CIDP" patients (29 % responders, $p < .05$), especially among typical CIDP patients (86 % of responders in "CIDP" versus 33 % of responders in "possible CIDP" patients, $p < .05$).

Conclusion: "CIDP" patients had a more severe neuropathy, estimated with the NIS and INCAT scores, and "possible CIDP" patients had a more atypical phenotype at baseline. Our data suggest that long-term patient outcome and response to immunotherapy is better in "CIDP" than "possible CIDP".

1. Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an immune-mediated neuropathy with heterogeneous presentation and clinical course [1]. Diagnosis relies on satisfying key clinical characteristics and demonstration of demyelinating features on nerve conduction studies (NCS), and can be supported by additional criteria, such as cerebrospinal fluid (CSF) high protein levels, suggestive abnormalities on nerve imaging and objective response to immunotherapy, with several sets of criteria developed in the recent years [2,3]. Currently, diagnosis relies on the fulfillment of the latest European Academy of Neurology/Peripheral Nerve Society (EAN/PNS) criteria, revised in 2021 [4], in which, based on the strength of the electrodiagnostic evidence for demyelination, two levels of diagnostic certainty are defined: "CIDP" and "possible CIDP".

Most patients respond to immunotherapy and have a favorable outcome. Indeed, a recent meta-analysis demonstrated that good outcome without disability as well as remission was obtained in almost half of CIDP patients [5]. However, significant number of patients are treatment-dependent in the long term [6–8] and, in a recent study, 24 % of CIDP patients had a poor outcome with a severe handicap, defined as a Rankin score > 2, after a 2 year-follow-up [8]. This discrepancy in treatment response and prognosis might be related to the heterogeneity of clinical, electrophysiological and immunological features of the disease. For example, patients with multifocal CIDP have been shown to have a poorer response to immunotherapy and a more severe long-term disability [9,10]. Those differences could be attributable to different underlying disease pathomechanisms. Prognosis also depends on

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https://doi.org/10.1016/j.jns.2024.123259
Received 23 July 2024; Received in revised form 12 September 2024; Accepted 24 September 2024
Available online 25 September 2024

electrophysiological characteristics: the presence of demyelinating features on nerve conduction studies (NCS) has been associated with higher treatment response in CIDP patients [11,12]. On the other hand, features of axonal dysfunction such as compound muscle action potential (CMAP) amplitude reduction was seen in non-responders and correlated with long-term disability [13,14].

There are no data in the literature concerning the characteristics and evolution of CIDP patients according to the two levels of diagnostic certainty defined with the 2021 EAN/PNS criteria. The aims of this study were to 1) describe the clinical characteristics and 2) look for prognosis difference, in patients with "CIDP" compared to "possible CIDP", in the monocentric cohort of a Swiss reference center for rare neuromuscular disorders.

2. Material and methods

2.1. Study population

In this retrospective observational monocentric study, we selected patients from our inflammatory neuropathy registry, which includes all patients ≥16 years with an inflammatory neuropathy followed in our reference center since 2008. We selected patients who fulfilled the following inclusion criteria: age > 18yo, fulfillment of the clinical and NCS EAN/PNS 2021 criteria for "CIDP" or "possible CIDP", including CIDP variants and at least one year of follow-up. We excluded patients with nodal/paranodal region antibodies (auto-immune nodopathy) and patients with anti-MAG neuropathy. Nodal/paranodal region antibodies were tested in only a minority of patients. Patients with severe comorbidities having an impact on clinical outcome were also excluded from the study. Patients with long-lasting poorly controlled diabetes which could explain the electrophysiological abnormalities were also excluded. All patients were treatment naïve at the first evaluation.

Typical CIDP was defined, according to EAN/PNS 2021 criteria, as a progressive or relapsing symmetric, proximal and distal muscle weakness of upper and lower limbs, with sensory involvement of at least two limbs, developing over at least 8 weeks, with absent or reduced tendon reflexes in all limbs [4]. Other phenotypes were considered as CIDP variants (distal, multifocal, focal, motor or sensory).

2.2. Clinical variables

We analyzed clinical and biological data that were prospectively collected in the registry: demographics, clinical history, physical examination, laboratory test results. Diagnostic delay was defined as the time from symptom onset to diagnosis. Impairment was assessed with the neuropathy impairment score (NIS) and the Medical Research Council (MRC) sum score [15,16]. Disability was assessed with the Inflammatory Neuropathy Cause and Treatment (INCAT) disability scale [17] and the modified Rankin Scale (mRS) [18]; patients with a mRS > 2 were defined as having a moderate to severe handicap. Objective response to immunomodulatory treatment (IVIg, corticosteroids, plasma exchange) was defined, according to EAN/PNS 2021 criteria, as an improvement on at least one disability scale and one impairment scale [4]. We defined an objective response to treatment as an improvement on one impairment scale (a decrease of ≥10 points of the NIS or an increase of ≥2 points of the MRC sum score) and one disability scale (a decrease of ≥1 point of the INCAT disability scale or ≥ 1 of the mRS).

CSF analysis were performed routinely in the majority of the patients. Albumino-cytologic dissociation was defined as an elevation of CSF protein >500 mg/l in patients younger than 50 years and > 600 mg/l in patients older than 50 years, with normal CSF leucocyte count [19,20].

2.3. NCS variables

All NCS were performed with the same device (Nicolet Viking EDX, Natus Medical GmbH) using the standard techniques of percutaneous supramaximal stimulation and surface electrode in standardized conditions at a skin temperature of at least 33 °C at the palm and 30 °C at the external malleolus. Age- and height-adjusted NCS reference values were used, according to the standards of our laboratory. Median, ulnar, fibular, tibial and sural NCS were performed, and data from the right side of the body were analyzed. Motor NCS data included CMAP negative peak amplitude (measured from baseline to peak), distal motor latency, distal CMAP negative peak duration, nerve conduction velocity (NCV), presence of a conduction block or temporal dispersion and minimal F-wave latency. For distal motor latency calculation, standardized distances between distal stimulation and recording sites were used. Because of their impersistance, F-wave of the fibular nerves were not considered. Motor NCV was assessed in the wrist to elbow segments for the median and ulnar nerve, ankle to fibular head for the fibular nerve and ankle to popliteal fossa for the tibial nerve. Sensory nerve conduction was measured orthodromically for the median and ulnar nerve and antidromically for the sural nerve. Sensory NCS included sensory nerve action potential (SNAP) amplitude (measured from negative to positive peak) and NCV.

2.4. Timepoint assessments

We collected the clinical variables from the patient's first assessment in our clinic, at time of diagnosis (T0) and after one year of follow-up (T1). For some patients, clinical variables were also collected after two (T2), three (T3) and five years (T5) of follow-up. Initial clinical and NCS data were used to classify the CIDP diagnostic certainty as "CIDP" or "possible CIDP" according to 2021 EAN/PNS criteria. Supportive criteria (such as response to immunotherapy) were not considered to classify the CIDP diagnostic certainty.

2.5. Treatment

For most patients, there was not a standardized IVIg or corticosteroid treatment protocol. For IVIg, patients who were recently diagnosed were generally treated according to the ICE trial protocol, i.e. an initial course of 2 g/kg, followed by maintenance courses of 1 g/kg every 3 weeks [21]. For corticosteroids, patients were usually treated with oral 1 mg/kg/d prednisone, for a variable duration. Treatment efficacy was usually evaluated 2–4 weeks after the first three courses of IVIg.

2.6. Ethics

Our registry follows our institutional regulations for clinical and research databases and was approved by the regional ethics committee (CER-VD AO_2023–00021). This study was approved by the regional ethics committee (CER-VD 2023–00435). All patients signed a consent for data reuse.

2.7. Statistical analysis

For descriptive statistics, mean, standard deviation (SD), median and interquartile range (IQR) were used. For univariate comparisons of independent data, we used the Mann-Whitney *U* test for continuous variables and the Fisher's exact test for categorical and binary variables. Multivariable linear regression analysis was used to explore disease severity according to diagnostic certainty and other variables. In all cases, statistical significance was set at $p < .05$. GraphPad Prism version 9.3.1 was used to generate the graphics. Calculations were performed using IBM SPSS for Windows, version 28.0.1.1 (IBM Corp., Armonk, N. Y., USA).

3. Results

3.1. Patients baseline characteristics

From the 86 patients included in our registry, 63 fulfilled the inclusion criteria, including 15 females (24 %). Three patients were excluded because of a modification in their diagnosis during follow-up (one patient was further diagnosed with AL amyloidosis, one with pan-neurofascin nodopathy and the last one with chronic ataxic neuropathy with ophtalmoplegia, IgM paraprotin, cold agglutinis and disialosyl antibodies). Characteristics of included patients are summarized in Table 1.

Among the 6 patients with a monoclonal gammopathy, 3 were IgM kappa, 2 IgG kappa and 1 IgG lambda. Two monoclonal gammopathies were MGUS and 4 were associated with a lymphoproliferative disease (2 chronic lymphocytic leukemia, 1 lymphoma and 1 Waldenström disease). 7 patients had type 2 diabetes, with mean HbA1c at the time of the diagnosis of 6.9 % (SD 1.2). There were 10 patients with a history of cancer (2 chronic lymphocytic leukemia, 1 lymphoma, 1 Waldenström disease, 1 prostate cancer, 1 colorectal cancer, 2 hepatic cancer, 1 spinocellular carcinoma and 1 testicular seminoma). 6 patients had an associated auto-immune disease (2 Hashimoto thyroiditis, 1 Sjögren syndrome, 1 vitiligo, 1 axial spondylarthritis and 1 interstitial lung disease).

3.2. Baseline characteristics according to the diagnostic certainty

According to EAN/PNS 2021 criteria, 39 patients had an initial diagnostic certainty of "CIDP" and 24 of "possible CIDP". Among the 31 patients with a typical CIDP phenotype, 22 had an initial diagnostic certainty of "CIDP" and 9 of "possible CIDP". Demographics, clinical and paraclinical characteristics of CIDP patients, stratified according to the diagnostic certainty, are summarized in Table 2 for all CIDP patients and Table 3 for typical CIDP patients.

Among the whole cohort, there were more focal/multifocal CIDP phenotypes in the "possible CIDP" group ($p < .01$), and overall, more CIDP variants, although not statistically significant ($p = .20$). Diagnostic delay was slightly longer in "possible CIDP" patients although not significant (p = .20). Regarding clinical characteristics, the NIS, INCAT disability scale and mRS scores were slightly higher and MRC sum score slightly lower in "CIDP" patients, although not significant ($p = .08$, 0.08, 0.24 and 0.10 respectively). Associated monoclonal gammopathies were only found in the "CIDP" group ($p = .07$). Other variables did not differ significantly.

Among typical CIDP patients ($n = 31$), there was no significant difference according to diagnostic certainty. "CIDP" patients had also a slightly higher NIS and a lower MRC sum scores ($p = .19$ and 0.07 respectively), and higher CSF protein concentration ($p = .13$) compared to the "possible CIDP", although not significant.

Table 1
Baseline characteristics of all CIDP patients.

	CIDP patients ($n = 63$)
Epidemiological data	
Age at onset in years	53.1 (±14.5)
Female sex, n (%)	15 (24)
Diagnostic delay in years	3.1 (±5.8)
Typical CIDP, n (%)	31 (49)
CIDP variants, n (%)	32 (51)
	13 (41)
• Sensory/sensory-predominant CIDP*	6 (19)
• Motor/motor predominant CIDP*	10 (31)
• Focal/multifocal CIDP*	3 (9)
• Distal CIDP*	
Comorbidities, n (%)	
	7 (11)
• Diabetes	10 (16)
• Cancer	6 (10)
• Auto-immune disease	
Clinical scores	
NIS	34.9 (±24.7)
MRC sum score	56.1 (±5.2)
INCAT disability scale	2.8 (± 1.8)
mRS	2.3 (±0.8)
Cerebrospinal fluid ($n = 59$)	
Proteins in mg/l	888 (±545)
Leucocytes/mm^3	0.8 (±1.6)
Albumino-cytologic dissociation, n (%)	40 (68)
Laboratory values	
Monoclonal gammopathy, n (%)	6 (10)

Continuous variables are presented as mean (±SD). * percentage of CIDP variants.
CIDP = chronic inflammatory demyelinating polyradiculoneuropathy, MRC = modified research council, mRS = modified rankin scale, NIS = neuropathy impairment score.

Table 2
Baseline characteristics of all CIDP patients according to the diagnostic certainty.

	CIDP ($n = 39$)	Possible CIDP ($n = 24$)	*p*-value
Epidemiological data			
Age at onset in years	53.0 (46.0, 67.0)	51.0 (43.0, 56.8)	0.15
Female sex, n (%)	10 (26)	5 (21)	0.77
Diagnostic delay in years	1.0 (0.4, 3.2)	2.3 (0.7, 4.4)	0.20
Typical CIDP, n (%)	22 (56)	9 (38)	0.20
CIDP variants, n (%)	17 (42)	16 (62)	
	9 (53)	4 (25)	0.75
• Sensory/sensory-predominant CIDP*	5 (29)	1 (6)	0.39
• Motor/motor predominant CIDP*	2 (12)	8 (50)	**<0.01**
• Focal/multifocal CIDP*	1 (6)	2 (13)	0.55
• Distal CIDP*			
Comorbidities, n (%)			
	5 (13)	2 (8)	0.70
• Diabetes	6 (15)	4 (17)	1.0
• Cancer	2 (5)	4 (17)	0.19
• Other auto-immune disease			
Clinical scores			
NIS	36.0 (18.0, 52.0)	23.5 (10.0, 44.0)	0.08
MRC sum score	58.0 (52,0, 60.0)	60.0 (54.5, 60.0)	0.24
INCAT disability scale	3.0 (2, 4)	2.0 (1,3)	0.08
mRS	2 (2, 3)	2 (2, 2.8)	0.10
Cerebrospinal fluid ($n = 37$) (n = 24)			
Proteins in mg/l	765 (526, 1317)	668 (456, 875)	0.15
Leucocytes/mm^3	0 (0,1)	0 (0,2)	0.27
Albumino-cytologic dissociation, n (%)	26 (70)	14 (58)	0.57
Laboratory values			
Monoclonal gammopathy, n (%)	6 (15)	0 (0)	0.07

Continuous variables are presented as median (IQR) given the limited number of patients in each group. Mann-Whitney U test was used for continuous variables and Fisher's exact test for categorical or binary variables. * percentage of CIDP variants.
CIDP = chronic inflammatory demyelinating polyradiculoneuropathy, MRC = modified research council, mRS = modified rankin scale, NIS = neuropathy impairment score.

Table 3
Baseline characteristics of typical CIDP patients according to the diagnostic certainty.

	CIDP (n = 22)	Possible CIDP (n = 9)	p-value
Epidemiological data			
Age at onset in years	51.0 (42.8, 63.3)	54.0 (42.5, 60.5)	0.98
Female sex, n (%)	6 (26)	5 (50)	0.42
Diagnostic delay in years	0.6 (0.2, 2.5)	1.4 (0.1, 5.2)	0.88
Comorbidities, n (%)			
	2 (9)	1 (10)	1.0
• Diabetes	2 (9)	2 (20)	0.56
• Cancer	1 (4)	2 (20)	0.20
• Other auto-immune disease			
Clinical scores			
NIS	39.0 (26.8, 69.3)	28.0 (11.5, 51.3)	0.19
MRC sum score	56.0 (48.0, 60.0)	60.0 (55.0, 60.0)	0.07
INCAT disability scale	3.0 (2, 5)	2.0 (1.5, 5)	0.36
mRS	3.0 (2, 3)	2.0 (2, 3)	0.59
Cerebrospinal fluid (n = 21) (n = 9)			
Proteins in mg/l	1194 (549, 1478)	651 (438, 918)	0.13
Leucocytes/mm^3	0 (0, 1)	1.0 (0, 2)	0.28
Albumino-cytologic dissociation, n (%)	15 (71)	7 (77)	1.0
Laboratory values			
Monoclonal gammopathy, n (%)	2 (9)	0 (0)	1.0

Continuous variables are presented as median (IQR) given the limited number of patients in each group. Mann-Whitney U test was used for continuous variables and Fisher's exact test for categorical or binary variables. * percentage of CIDP variants.
CIDP = chronic inflammatory demyelinating polyradiculoneuropathy, MRC = modified research council, mRS = modified rankin scale, NIS = neuropathy impairment score.

3.3. Evolution of patients according to diagnostic certainty (Fig. 1)

All patients were followed at T1, 55 (87 %) at T2, 50 (79 %) at T3 and 44 (70 %) at T5. Due to the low number of NCS performed during follow-ups, with a low number of motor and sensory nerves explored, we did not consider NCS data for analysis during follow-ups. In 6/32 patients with a CIDP variant phenotype, diagnosis was changed to typical CIDP during follow-up (3 sensory-predominant, 2 motor-predominant and 1 distal CIDP). On the opposite, none of the typical CIDP phenotype were reclassified. Eight out of 24 patients (4 typical CIDP and 4 CIDP variants) who were initially classified as « possible CIDP », were reclassified as "CIDP" according to follow-up NCS.

The change from baseline in the NIS score was significantly lower in "CIDP" than in "possible CIDP" patients at T1 ($p < .05$), T2 ($p < .05$) and T3 ($p < .01$) (Fig. 1A). The change from baseline in the MRC score was significantly higher in "CIDP" than "possible CIDP" patients at T2 ($p < .05$) (Fig. 1B). The change from baseline in the INCAT disability scale was significantly lower in "CIDP" than "possible CIDP" patients at T2 ($p < .05$), T3 ($p < .01$) and T5 ($p < .05$) (Fig. 1C). The proportion of moderate to severely disabled patients (defined as a mRS >2) was higher in "possible CIDP" than "CIDP" group during follow-ups, although not statistically significant (Fig. 1D).

A multiple linear regression was performed to identify the strongest associations to NIS and INCAT disability scores at T5 (**eTable1, appendix**). The diagnostic certainty of "CIDP" (compared to "possible CIDP") was not a strong predictor of NIS score and INCAT disability scale at T5 in this model ($\beta = -0.163$, $p = .32$ and $\beta = -0.128$, $p = .42$ respectively).

3.4. Evolution of typical CIDP patients according to diagnostic certainty (Fig. 2)

Among the 31 typical CIDP patients, all had a follow-up at T1, 26 (84 %) at T2, 24 (77 %) at T3 and 20 (65 %) at T5.

The change from baseline in the NIS score was significantly lower in "CIDP" than in "possible CIDP" patients at T1 ($p < .05$), T2 ($p < .05$) and T3 ($p < .01$) (Fig. 2A). The change from baseline in the MRC score was significantly higher in "CIDP" than "possible CIDP" patients at T2 ($p < .05$) (Fig. 2B). The change from baseline in the INCAT disability scale was significantly lower in "CIDP" than "possible CIDP" patients at T3 ($p < .05$) (Fig. 2C). The proportion of moderate to severely disabled patients (defined as a mRS >2) was higher in "possible CIDP" than "CIDP" group during follow-ups, although not statistically significant (Fig. 2D).

A multiple linear regression was performed to identify the variables with the strongest association to the NIS and INCAT disability scale at T5 (**eTable2, appendix**). The diagnostic certainty of "CIDP" (compared to "possible CIDP") was not a strong predictor of NIS score and INCAT disability scale at T5 in this model ($\beta = -0.234$, $p = .40$ and $\beta = -0.086$, $p = .72$ respectively).

3.5. Response to immunotherapy

Among patients with at least 1 year of follow-up (63 patients), 97 % received IVIg (mean duration 20.5 months), 33 % corticosteroids (mean duration 12.3 months), 6 % plasma exchanges (mean exchanges 7) and 41 % another immunosuppressive drug (13 rituximab, 10 ciclosporin, 7 azathioprine, 2 cyclophosphamide, 1 mycophenolate mofetil and 1 secukinumab). All patients received at least one line of immunotherapy.

Just under half of the patients (30/63, 48 %) were objective responders to first line immunotherapy. Patients with a diagnostic certainty of "CIDP" had better objective response to immunotherapy (23/39 responders, 59 %) than "possible CIDP" group (7/24 responders, 29 %, $p = .04$). Among typical CIDP patients, 71 % (22/31) of patients were objective responders to first line immunotherapy. Among them, patients with a diagnostic certainty of "CIDP" had a significantly better objective response to immunotherapy (19/22 responders, 86 %) than "possible CIDP" group (3/9 responders, 33 %, $p = .007$). Among CIDP variant patients, only 25 % (8/32) of patients were objective responders to first line immunotherapy (0/13 responders if sensory-predominant CIDP, 3/6 responders if motor-predominant CIDP, 3/10 responders if focal/multifocal CIDP and 2/3 responders if distal CIDP). Among them, there was no significant difference in treatment response according to diagnostic certainty, with 4/17 (53 %) responders in the "CIDP" group and 4/11 (36 %) responders in the "possible CIDP" group ($p = 1.0$).

4. Discussion

In our cohort, epidemiological characteristics were slightly different in CIDP patients according to diagnostic certainty. "Possible CIDP" patients had more atypical phenotype (CIDP variants, especially focal/multifocal CIDP) and tended to have a longer diagnostic delay. The more atypical clinical presentation of CIDP variants could partly explain the longer diagnostic delay, as already reported in the literature [22].

"CIDP" patients in our study had a more severe neuropathy at baseline, estimated with the NIS, MRC sum score and INCAT disability scale, compared to "possible CIDP" patients, but surprisingly this was not correlated with a worst outcome at follow-up. Medium to long term follow-up showed a better prognosis in "CIDP" patients when looking at both deficit (NIS and MRC sum scores) and function (mRS and INCAT disability scale). This more favorable outcome was also associated with a better response to immunotherapy in "CIDP" patients (59 % of responders) than in "possible CIDP" patients (29 % of responders, $p = .04$). As a result, the proportion of moderate to severely disabled patients

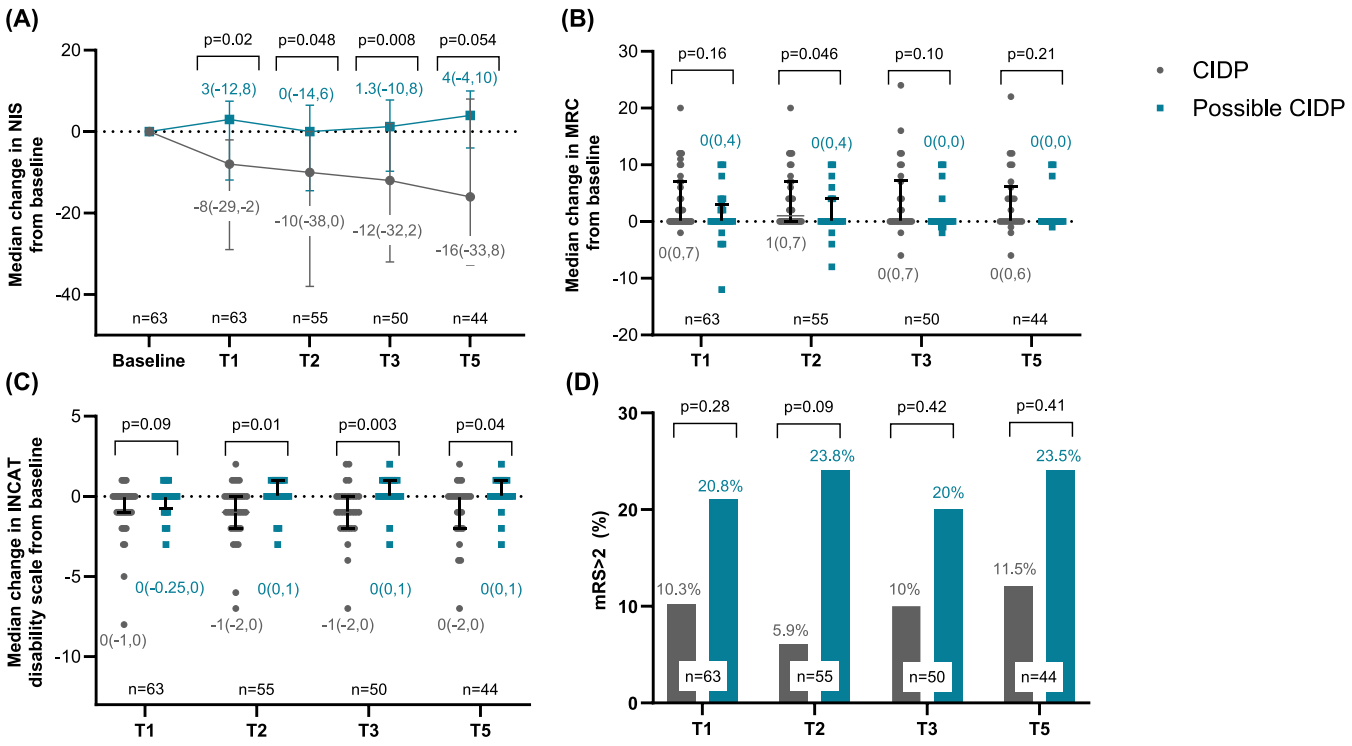

Fig. 1. Evolution of clinical scores of all patients according to their diagnostic certainty. Median (IQR) change of NIS (**A**), MRC sum score (**B**) and INCAT disability scale (**C**) from baseline during follow-ups. Proportion of patients with a moderate to severe handicap (mRS >2) during follow-ups (**D**).

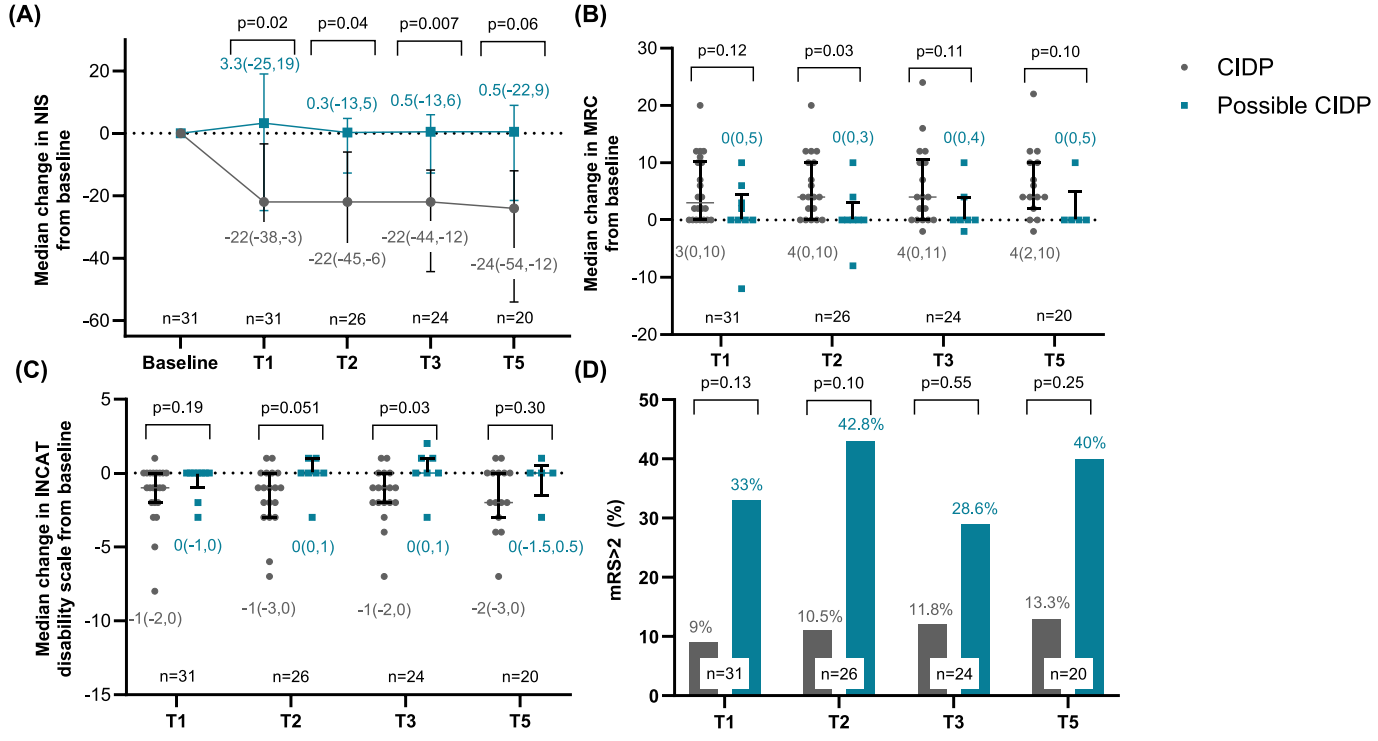

Fig. 2. Evolution of clinical scores of typical patients according to their diagnostic certainty. Median (IQR) change of NIS (**A**), MRC sum score (**B**) and INCAT disability scale (**C**) from baseline during follow-ups. Proportion of patients with a moderate to severe handicap (mRS >2) during follow-ups (**D**).

(mRS >2) at long-term follow-up tended to be higher in the "possible CIDP" group (23.5 %) compared to the "CIDP" group (11.5 %), although not significant (p = .41). This better response to treatment is a new, interesting finding. In a previous study, the fulfillment of the INCAT electrophysiological criteria did not predict a higher rate of response to immunotherapy [23]. Discrepancy among these previous data and our

results might be explained by a better performance of the updated diagnostic criteria, a different definition of treatment response and a different follow-up duration, which was longer in our study. As patients with "possible CIDP" were more represented by CIDP variants, it may explain a poorer response to immunotherapy and a worse prognosis. Indeed, it is already known that CIDP variants, particularly multifocal CIDP and distal CIDP, have worse response to immunotherapy and may have a worse prognosis [9,10]. In our cohort, response to immunotherapy among CIDP variants is indeed poor (25 % of responders), with no significant difference according to diagnostic certainty. Moreover, the scores we used to capture the severity and functional impact of the neuropathy probably underestimate the deficit in patients with variants, for example the NIS score in sensory-predominant CIDP. However, this better prognosis and response to immunotherapy is also evident in the more homogeneous subpopulation of typical CIDP patients, suggesting that the diagnostic certainty itself does have an impact on patient prognosis and response to therapy. Among typical CIDP patients, deficit and functional scores are better in "CIDP" patients and response to immunotherapy also (86 % and 33 % of responders in "CIDP" and "possible CIDP" patients respectively, $p = .007$). The proportion of moderate to severely disabled typical CIDP patients at medium-term follow-up tend also to be higher in the "possible CIDP" group (40 %) compared to the "CIDP" group (13.3 %, $p = .25$). Patients with possible CIDP seem to remain stable in terms of deficit and disability during follow-up, including in the typical CIDP subgroup, probably partly due to a poorer response to immunotherapy.

The better outcome in CIDP patients fulfilling EAN/PNS 2021 diagnostic criteria may be explained by several factors, including a shorter delay from disease onset to diagnosis, thus allowing earlier treatment introduction. Disease duration before diagnosis and treatment introduction has already been shown to have a strong influence on treatment efficacy, disability, and impairment in CIDP patients [24–26]. One of the potential reasons why patients fail to fulfill the electrophysiological criteria for CIDP is the presence of a significant and early axonal loss at the time of the diagnosis, masking signs of demyelination. This axonal loss, which could be secondary to demyelination or a primary manifestation of the disease due to a nodal or paranodal involvement, is a well-known negative prognostic factor in patients with CIDP, predictive of long-term disability [13,14,27,28]. "Possible CIDP" patients may have an earlier and/or more important axonal loss, accounting for a poorer response to immunotherapy and a worse prognosis. In the present study, we did not evaluate electrophysiological marker of axonal loss, which need further evaluation especially in the "possible CIDP" category. Finally, one factor that may contribute to the poor response to immunotherapy in CIDP patients not fulfilling diagnostic criteria is misdiagnosis. It is well known that misdiagnosis is not uncommon in CIDP patients, especially in variant phenotypes or when NCS criteria are not completely fulfilled [29]. In our cohort, when diagnosis was unclear, especially when EAN/PNS 2021 were not fulfilled, additional exams were usually performed, such as lumbar puncture (almost in every patient), plexus MRI, nerve biopsies or genetic testing, to rule-out alternative diagnosis.

Our results should be interpreted in the light of some limitations. The sample size was relatively small and clinical and electrophysiological data were heterogenous, especially in earlier cases, when a standardized CIDP protocol was not yet available in our unit. Due to a lack of standardized treatment protocol in earlier cases, there was also a high heterogeneity in treatment modalities and interval, making it difficult to assess and compare treatment response. Despite the retrospective nature of the analysis, data were entered prospectively in the registry, which adds a longitudinal value to follow-up data. Because of missing data on R-ODS, INCAT and ONLS scales in our registry, mRS and INCAT disability scale were calculated retrospectively. As a consequence, those scores may have been subject to imprecision. Regarding the mRS, this score is not frequently used in neuropathies, and its pertinence in outcome determination in CIDP patients' needs to be clarified. Nevertheless, a recently published meta-analysis did use the mRS score, to estimate loss of ambulation, as their main outcome measure in typical CIDP patients [5]. The use of NIS and MRC score to assess response to treatment might have led to an underestimation of treatment response in some patients (it is usually easier to improve on a functional score rather than on a deficit one), especially in CIDP variants.

5. Conclusion

Altogether, our data displays a clinical distinction between patients fulfilling "CIDP" versus "possible CIDP" diagnostic criteria at the time of the diagnosis, with a more typical phenotype and a more severe neuropathy in "CIDP" patients. Moreover, with a follow-up up to 5 years after diagnosis, our results suggest a correlation between a more clinically severe, neurophysiologically demyelinating, "CIDP" profile and better prognosis and response to immunotherapy. The presence of a more severe axonal loss in "possible CIDP" patients, probably a longer delay in diagnosis and treatment initiation, and a higher possibility of misdiagnosis, are the three main hypotheses explaining this worse outcome.

Our results show that fulfillment of the EAN/PNS 2021 criteria for CIDP may provide an additional prognostic value and should be widely implemented in clinical practice. "Possible CIDP" patients should be offered additional investigations to exclude a misdiagnosis and allow the rapid introduction of the appropriate therapy. Further studies are needed to confirm those results, especially combined with a detailed electrophysiological analysis of markers of axonal loss (EMG, MUNIX etc.) [30].

Table A1
Multiple linear regression analysis to predict the NIS and INCAT disability scale at T5 in all CIDP patients.

	NIS at T5			INCAT disability scale at T5		
	B (SE)	β	p-value	B (SE)	β	p-value
Age at onset (in years)	0.212 (0.182)	0.207	0.25	0.014 (0.015)	0.166	0.35
Diagnostic delay (in years)	0.416 (0.326)	0.209	0.21	0.052 (0.026)	0.322	0.053
CIDP phenotype (typical vs variant)	−8.496 (4.814)	−0.318	0.09	−0.545 (0.384)	−0.251	0.17
Diagnostic certainty (CIDP vs possible CIDP)	−4.432 (4.375)	−0.163	0.32	−0.283 (0.349)	−0.128	0.42
NIS score at T0	0.064 (0.174)	0.119	0.72	−0.003 (0.014)	−0.075	0.82
MRC score at T0	−0.219 (0.658)	−0.092	0.74	−0.079 (0.053)	−0.407	0.14
mRS scale at T0	−0.415 (4.371)	−0.023	0.93	0.017 (0.011)	0.048	0.96
INCAT disability scale at T0	3.066 (1.573)	0.401	0.06	0.171 (0.126)	0.275	0.18

B = regression coefficient, SE = standard error, β = standardized regression coefficient, CIDP = chronic inflammatory demyelinating polyradiculoneuropathy, NIS = neuropathy impairment score, mRS = modified Rankin scale.

Table A2
Multiple linear regression analysis to predict the NIS and INCAT disability scale at T5 in typical CIDP patients.

	NIS at T5			INCAT disability scale at T5		
	B (SE)	β	p-value	B (SE)	β	p-value
Age at onset (in years)	−0.031 (0.296)	−0.032	0.92	0.009 (0.021)	0.118	0.68
Diagnostic delay (in years)	0.318 (0.447)	0.199	0.49	0.057 (0.032)	0.448	0.10
Diagnostic certainty (CIDP vs possible CIDP)	−7.948 (9.005)	−0.234	0.40	−0.235 (0.644)	−0.086	0.72
NIS score at T0	−0.074 (0.257)	−0.133	0.78	−0.001 (0.018)	−0.031	0.94
MRC score at T0	−0.838 (1.019)	−0.379	0.43	−0.123 (0.073)	−0.69	0.12
mRS scale at T0	3.035 (2.284)	0.435	0.21	0.166 (0.163)	0.297	0.33
INCAT disability scale at T0	−1.027 (8.919)	−0.047	0.91	−0.703 (0.637)	−0.399	0.29

B = regression coefficient, SE = standard error, β = standardized regression coefficient, CIDP = chronic inflammatory demyelinating polyradiculoneuropathy, NIS = neuropathy impairment score, mRS = modified Rankin scale.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethics approval

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. Our registry follows our institutional regulations for clinical and research databases. This study was approved by the regional ethics committee (CER-VD 2023–00435).

Consent to participate

All patients approved and signed our institutional general consent to research.

Consent for publication

Not applicable.

Code availability

Not applicable.

CRediT authorship contribution statement

Valentin Loser: Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Alex Vicino:** Writing – review & editing. **Katia Staedler:** Writing – review & editing. **Thierry Kuntzer:** Writing – review & editing. **Marie Théaudin:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization.

Declaration of competing interest

None of the authors has any conflict of interest to disclose.

Data availability

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

References

[1] S. Puttini, P.A. Panaite, N. Mermod, et al., Gene expression changes in chronic inflammatory demyelinating polyneuropathy skin biopsies, J. Neuroimmunol. 270 (1–2) (2014) 61–66.
[2] M.B. Bromberg, Review of the evolution of electrodiagnostic criteria for chronic inflammatory demyelinating polyradiculoneuropathy, Muscle Nerve 43 (6) (2011) 780–794.
[3] P.E. Doneddu, A. De Lorenzo, F. Manganelli, et al., Comparison of the diagnostic accuracy of the 2021 EAN/PNS and 2010 EFNS/PNS diagnostic criteria for chronic inflammatory demyelinating polyradiculoneuropathy, J. Neurol. Neurosurg. Psychiatry 93 (12) (2022) 1239–1246.
[4] P.Y.K. Van den Bergh, P.A. van Doorn, R.D.M. Hadden, et al., European academy of neurology/peripheral nerve society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force-second revision, J. Peripher. Nerv. Syst. 26 (3) (2021) 242–268.
[5] A. Al-Zuhairy, J Jakobsen, Outcome in chronic inflammatory demyelinating polyneuropathy: A systematic review and meta-analysis, Muscle Nerve 68 (4) (2023) 388–396.
[6] I.S.J. Merkies, I.N. van Schaik, J.M. Léger, et al., Efficacy and safety of IVIG in CIDP: combined data of the PRIMA and PATH studies, J. Peripher. Nerv. Syst. 24 (1) (2019) 48–55.
[7] M. Kapoor, L. Compton, A. Rossor, et al., An approach to assessing immunoglobulin dependence in chronic inflammatory demyelinating inflammatory polyneuropathy, J. Peripher. Nerv. Syst. 26 (4) (2021) 461–468.
[8] K. Viala, T. Maisonobe, T. Stojkovic, et al., A current view of the diagnosis, clinical variants, response to treatment and prognosis of chronic inflammatory demyelinating polyradiculoneuropathy, J. Peripher. Nerv. Syst. 15 (1) (2010) 50–56.
[9] G. Fargeot, T. Maisonobe, D. Psimaras, et al., Comparison of Lewis–Sumner syndrome with chronic inflammatory demyelinating polyradiculoneuropathy patients in a tertiary care centre, Eur. J. Neurol. 27 (2020) 522–528.
[10] P.E. Doneddu, D. Cocito, F. Manganelli, et al., Atypical CIDP: diagnostic criteria, progression and treatment response. Data from the Italian CIDP database, J. Neurol. Neurosurg. Psychiatry 90 (2019) 125–132.
[11] A. Abraham, M. Alabdali, M. Qrimli, et al., Treatment responsiveness in CIDP patients with diabetes is associated with higher degrees of demyelination, PLoS One 10 (2015) e0139674.
[12] M. Iijima, M. Yamamoto, M. Hirayama, et al., Clinical and electrophysiologic correlates of IVIg responsiveness in CIDP, Neurology 64 (2005) 1471–1475.
[13] V. Bril, M. Banach, M.C. Dalakas, et al., Electrophysiologic correlations with clinical outcomes in CIDP, Muscle Nerve 42 (2010) 492–497.
[14] T. Grüter, J. Motte, Y. Bulut, et al., Axonal damage determines clinical disability in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP): a prospective cohort study of different CIDP subtypes and disease stages, Eur. J. Neurol. 29 (2) (2022) 583–592.
[15] V. Bril, NIS-LL: the primary measurement scale for clinical trial endpoints in diabetic peripheral neuropathy, Eur. Neurol. 41 (Suppl1) (1999) 8–13.
[16] R.P. Kleyweg, F.G. van der Meché, P.I. Schmitz, Interobserver agreement in the assessment of muscle strength and functional abilities in Guillain-Barré syndrome, Muscle Nerve 14 (11) (1991) 1103–1109.
[17] I.S. Merkies, P.I. Schmitz, F.G. van der Meche, J.P. Samijn, P.A. van Doorn, et al., Clinimetric evaluation of a new overall disability scale in immune mediated polyneuropathies, J. Neurol. Neurosurg. Psychiatry 72 (2002) 596–601.
[18] J.C. van Swieten, P.J. Koudstaal, M.C. Visser, et al., Interobserver agreement for the assessment of handicap in stroke patients, Stroke 604–607 (1988).
[19] A. Breiner, P.R. Bourque, J.A. Allen, Updated cerebrospinal fluid total protein reference values improve chronic inflammatory demyelinating polyneuropathy diagnosis, Muscle Nerve 60 (2) (2019) 180–183. Aug.
[20] A. Breiner, D. Moher, J. Brooks, W. Cheng, H. Hegen, F. Deisenhammer, 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. 266 (3) (2019) 616–624.
[21] R.A. Hughes, Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy: the ICE trial, Expert. Rev. Neurother. 9 (6) (2009) 789–795.
[22] Y.C. Chan, D.C. Allen, D. Fialho, et al., Predicting response to treatment in chronic inflammatory demyelinating polyradiculoneuropathy, J. Neurol. Neurosurg. Psychiatry 77 (1) (2006) 114–116.
[23] P.A. Panaite, S. Renaud, R. Kraftsik, et al., Impairment and disability in 20 CIDP patients according to disease activity status, J. Peripher. Nerv. Syst. 18 (3) (2013) 241–246.

[24] A. Al-Zuhairy, S.H. Sindrup, H. Andersen, et al., A population-based study of long-term outcome in treated chronic inflammatory demyelinating polyneuropathy, Muscle Nerve 61 (3) (2020) 316–324.
[25] M. Rabin, G. Mutlu, T. Stojkovic, et al., Chronic inflammatory demyelinating polyradiculoneuropathy: search for factors associated with treatment dependence or successful withdrawal, J. Neurol. Neurosurg. Psychiatry 85 (8) (2014) 9016–9906.
[26] B. Tackenberg, J.D. Lunemann, A. Steinbrecher, et al., Classifications and treatment responses in chronic immune-mediated demyelinating polyneuropathy, Neurology 68 (19) (2007) 1622–1629.
[27] A. Al-Zuhairy, J. Jakobsen, C. Krarup, Early axonal loss predicts long term disability in chronic inflammatory demyelinating polyneuropathy, Clin. Neurophysiol. 132 (2021) 1000–1007.
[28] A. Al-Zuhairy, J. Jakobsen, M. Moldovan, C. Krarup, Axonal loss at time of diagnosis as biomarker for long-term disability in chronic inflammatory demyelinating polyneuropathy, Muscle Nerve 66 (6) (2022) 715–722.
[29] M.C. Broers, C. Bunschoten, J. Drenthen, et al., Misdiagnosis and diagnostic pitfalls of chronic inflammatory demyelinating polyradiculoneuropathy, Eur. J. Neurol. 28 (6) (2021) 2065–2073.
[30] S. Paramanathan, H. Tankisi, H. Andersen, et al., Axonal loss in patients with inflammatory demyelinating polyneuropathy as determined by motor unit number estimation and MUNIX, Clin. Neurophysiol. 127 (1) (2016) 898–904.