

Frequency of diabetes and other comorbidities in Chronic Inflammatory Demyelinating Polyradiculoneuropathy and their impact on clinical presentation and response to therapy

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ABSTRACT

Objectives to determine the prevalence of different comorbidities in Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP), and their impact on outcome, treatment choice and response.

Methods using a structured questionnaire we collected information on comorbidities from 393 CIDP patients fulfilling the EFNS/PNS criteria included in the Italian CIDP database.

Results one or more co-morbidities were reported by 294 patients (75%) and potentially influenced treatment choice in 192 (49%) leading to a less frequent use of corticosteroids. Response to treatment did not differ however from that in patients without comorbidities. Diabetes (14%), MGUS (12%) and other immune disorders (16%) were significantly more frequent in CIDP patients than expected in the general European population. Patients with diabetes had higher disability scores, worse quality of life (QoL), and a less frequent treatment response compared to patients without diabetes. Patients with IgG-IgA or IgM MGUS had an older age at CIDP onset while patients with other immune disorders had a younger age at onset and were more frequently females. IgM MGUS was more frequent in patients with motor CIDP than in patients with typical CIDP.

Conclusions comorbidities are frequent in patients with CIDP and in almost 50% of them have an impact on treatment choice. Diabetes, MGUS and other immune diseases are more frequent in patients with CIDP than in the general population. Only diabetes seems however to have an impact on disease severity and treatment response possibly reflecting in some patients a co-existing diabetic neuropathy.

Keywords: Chronic inflammatory demyelinating polyneuropathy; Diabetes mellitus; monoclonal gammopathy of undetermined significance; comorbidities; lymphoma

INTRODUCTION

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a chronic disabling neuropathy, postulated to have an immune-mediated basis.[1] A number of concomitant disorders have been reported to occur in patients with CIDP[1] including diabetes mellitus (DM),[2-6] lymphoma,[7-9] solid cancer,[9] monoclonal gammopathy of undetermined significance (MGUS),[10-13] plasma cell dyscrasias,[9,14] and other disorders.[15-18] Most of these associations have been reported in isolated cases or small series of patients so that their frequency in CIDP and possible clinical and pathogenic relevance, impact on disability, quality of life (QoL), and response to treatment remains unclear. There are also conflicting data on the association and clinical impact of DM in CIDP. The frequency of DM has been reported to be increased in some series of CIDP patients[2,5] but not in others[3,4] with a variable effect on the response to treatment, leading to the exclusion of these patients from some clinical trials on CIDP. Some of these comorbidities may also theoretically interfere with the pathogenesis, clinical presentation, accumulation of disability, and treatment response of CIDP by causing additional axonal damage or a perturbation of the immune homeostasis. We collected data on comorbidities from a large cohort of patients with CIDP to determine (1) the prevalence of comorbidities in CIDP, (2) their impact on treatment choice (3) outcome and response to treatment, and (4) association with a specific clinical phenotype of CIDP.

PATIENTS AND METHODS

Study design

We implemented a web-based database on Italian CIDP patients where data from 435 patients with CIDP diagnosed according to the European Federation of Neurological Societies and Peripheral Nerve Society (EFNS/PNS) criteria were included.[1] At enrolment, all eligible patients underwent a detailed clinical history including timing and distribution of neurological signs, a number of

disability scales, and a neurophysiological study. We used the same methodology as the one employed in a previous study.[19] We also collected information on the presence and duration of concurrent medical illnesses.[20] These were classified as: bone marrow transplantation, DM, HIV infection, chronic active hepatitis, IgG or IgA MGUS, IgM MGUS including those with low titers of anti-MAG (myelin-associated glycoprotein) antibodies (defined in laboratory as less than 7000 [BTU] Bühlmann Titer Unit), other hematological diseases, systemic lupus erythematosus or other connective tissue diseases, lymphoma, sarcoidosis, vasculitis, other immune mediated diseases, thyroid diseases, solid neoplasms, glomerulonephritis, nephropathy, thrombosis, cardiovascular diseases, arterial hypertension, gastrointestinal diseases, others conditions. Duration of each comorbidity was considered from the time when the patients first developed symptoms or, in case of paucisymptomatic diseases such as arterial hypertension, from the time they were diagnosed as having that specific comorbidity by their physician. Information on comorbidities was retrieved by demographic and clinical data from medical charts and by a detailed clinical history with the individual patient using a structured questionnaire.

All the data were included by the treating neurologist in a web-based electronic database expressly prepared by CINECA, Bologna, Italy. The diagnosis of CIDP was made by the treating neurologist and reviewed by the coordinating Centre (P.E.D. and E.N.O.) and classified according to the EFNS/PNS diagnostic criteria.[1] Informed consent was obtained from all participants at enrollment, and the Ethical Committee of each participating Center approved the study.

Prevalence of different comorbidities in CIDP and their impact on treatment choice

The prevalence (as percentage of the total) of each individual comorbidity and of combined comorbidity groups (e.g. cardiovascular diseases including chronic heart failure, coronary heart disease, valvular heart disease, etc) was calculated. The prevalence of comorbidities potentially affecting treatment choice was also assessed. These comorbidities were defined as those known to be associated with an increased risk of side effects after steroids, intravenous immunoglobulin (IVIg), or plasma exchange (PEX) therapy, including arterial hypertension, DM, gastrointestinal diseases, cardiovascular diseases, thrombosis, nephropathy, glomerulonephritis, and chronic active

hepatitis. Given the small number of patients treated with immune suppressants in our database, the analysis did not include these therapies.

Given the observed elevated frequency of DM and MGUS in our CIDP patients, we compared the data with the estimated age- and gender-specific prevalence rates of DM and of MGUS in Italy.[21,22] The expected number of patients with MGUS was also determined using the general population of a community in Minnesota as reference.[23] We excluded patients younger than 50 years from the comparison with the study by Kyle *et al* and younger than 51 years from that by Vernocchi *et al* since these patients were not included in these studies.[22,23] We also evaluated fulfillment of the recently proposed diagnostic criteria of CIDP in patients with DM.[24]

Role of comorbidities in the clinical presentation, disability and treatment response of CIDP

We evaluated the impact of comorbidities on the clinical presentation, outcome, and treatment response of CIDP by comparing patients with and without these comorbidities. The comparison was performed only for comorbidities with a number of patients sufficient for statistical analysis. We also looked for differences in the frequency of comorbidities between patients with typical and atypical CIDP and evaluated their association with progression from atypical to typical CIDP. Atypical CIDP was defined as pure motor or sensory CIDP, distal acquired demyelinating symmetric polyneuropathy (DADS), and Lewis-Sumner syndrome (LSS).[19] Response to treatment was defined as a subjective improvement that was objectively confirmed by an increase of at least 2 points in the MRC sum score (range 0-60)[25,26] or at least 1 point in the INCAT score (range 0-10).

Statistical analysis

Descriptive statistics were reported as frequencies and percentages for categorical variables, or as means, medians and ranges for continuous variables. To determine if the prevalence of DM and MGUS in CIDP patients differs from the prevalence in the general population, the observed prevalence was compared to the expected prevalence calculating age- and gender-standardized prevalence ratios (SPR), with 95% confidence intervals. Age and gender-specific prevalence from

the reference population was used to estimate the number of expected cases of DM and MGUS in each age and sex category. SPR were then calculated as the ratio between the observed and expected number of cases. Demographic and clinical features, treatment response, impairment, disability level and quality of life were compared between different subgroups of patients with the chi-square or the Fisher's exact test for categorical variables, and with the t-test for continuous variables. The effect of each comorbidity on disability and quality of life was assessed using linear regression models, adjusting for disease duration. The effect of each comorbidity on treatment response was evaluated using logistic regression models, adjusting for disease duration. All tests were two-tailed and the significance level was set to 0.05.

RESULTS

By October 2019, 435 patients with CIDP fulfilling the EFNS/PNS criteria were enrolled in our database including 428 with definite or probable CIDP. Twenty-four patients were excluded from the analysis for the presence of an alternative diagnosis (19 patients with anti-MAG titers over 7000 BTU, one with Charcot-Marie Tooth 1A, three with amyloidosis, and one with only cranial nerve palsy) and 21 patients for unavailable neurophysiological data. A total 393 patients (252 men and 141 women, aged 11-92 years [mean 58; median 60 years], mean disease duration of 8.2 years [range 0.5-52 years, median 5 years]), had complete data on comorbidities and were included in the analysis.

Frequency of comorbidities in CIDP and their impact on treatment choice

Table 1 shows the frequency and percentage of different comorbidities in our cohort of patients with CIDP. These are also grouped as comorbidity combinations in figure 1. Seventy-five per cent (n. 294) of patients reported at least one comorbidity, and 54% (214 patients) two or more comorbidities. Diabetes (14%), MGUS (12%) and other immune disorders (16%) were significantly more frequent in CIDP patients than expected in the general European population (see below). Arterial hypertension (35%), cardiovascular diseases (11%), thyroid diseases (11%) and solid neoplasms (9%) were also frequent in our population but their prevalence did not significantly differ from what reported in the Italian population.[27,28]

Table 1. Frequency distribution of comorbidities in 393 patients with CIDP

Comorbidities	Number of patients; Frequency (%)
Arterial hypertension	138 (35%)
Other immune diseases	61 (15%)
a) Autoimmune thyroiditis; b) Rheumatic immune diseases; c) Gastrointestinal immune diseases;	a) 22 (5%); b) 13 (3.5%); c) 9 (2%);
d) Dermatologic immune diseases e) Neurological immune diseases f) Miscellany	d) 6 (1.5%); e) 5 (1.5%); f) 6 (1.5%)
Diabetes mellitus	56 (14%)
Cardiovascular diseases	45 (11%)
a) Coronary disease; b) Arrhythmia; c) Stroke; d) Valvular heart disease	a) 31 (8%); b) 9 (2%); c) 3 (1%); d) 2 (0.5%)
Thyroid diseases	42 (11%)
a) Hypothyroidism; b) Thyroid nodules; c) Goiter; d) Hyperthyroidism; e) NS	a) 13 (3%); b) 8 (2%); c) 4 (1%); d) 2; e) 7 (2%)
Solid neoplasm	35 (9%)
a) Urological cancer; b) Gastrointestinal cancer; c) Head and Neck cancer; d) Breast cancer; e) Others	a) 11 (3%); b) 5 (1.5%); c) 4 (1%); d) 4 (1%); e) 11 (3%)
IgG-IgA MGUS	25 (6%)
IgM MGUS	24 (6%)
Other hematological disorders	21 (5%)
a) Polycythemia vera; b) Thalassemia minor; c) Anemia; d) Thrombocytopenia; e) Others	a) 4 (1%); b) 2; c) 2; d) 2; e) 11 (2.5%)
Gastrointestinal diseases	21 (5%)
a) GERD and gastritis; b) Hepatic and pancreatic disorders; c) Peptic ulcer disease; d) Others	a) 9 (2%); b) 3 (1%); c) 3 (1%); d) 5 (1.5%)
Thrombosis	11 (3%)
Nephropathy	8 (2%)
a) Renal insufficiency; b) Others	a) 6 (2%); b) 2
Chronic active hepatitis	7 (2%)

a) HBV infection; b) NS	a) 6 (1.5%); b) 1
Lymphoma	7 (2%)
Bone marrow transplantation	5 (1.5%)
Glomerulonephritis	3 (1%)
Others	66 (17%)
a) Miscellany; b) Other Neurologic/Psychiatric disorders; c) Metabolic disorders;	a) 16 (4%); b) 13 (3%); c) 13 (3%);
d) Urologic disorders; e) Respiratory disorders; f) Skeletal disorders	d) 10 (2.5%); e) 7 (2%); f) 7 (2%)
HIV infection	0

GERD= gastroesophageal reflux disease; MGUS= monoclonal gammopathy of undetermined significance; NS= not specified;

One or more comorbidities potentially influencing the choice of treatment were present in 192 (49%) patients (figure 2), and two or more comorbidities in 77 (19.5%) patients. Corticosteroids were used less frequently in these patients compared to those without these comorbidities (49% vs 61%; $p= 0.0199$). There was no difference between the two groups in terms of use of IVIg (74% vs 79%; $p= 0.3407$) and PEx (11% vs 9%; $p= 0.6001$), number of not treated patients (7% vs 8%; $p= 0.7044$), number of treatments performed (mean 1.9 vs 1.9; $p= 0.5139$), and response to treatment (85% vs 87%; $p= 0.6445$).

CIDP and Diabetes

Fifty-six out of our 393 (14%) patients with CIDP had DM. This percentage is higher than expected in the general Italian population (8.6%). Information about type of DM (1 or 2) was not however systematically collected in our database. The corresponding SPR was 1.66 (95% CI, 1.31–2.07), indicating that the frequency of DM was significantly higher than expected in the general population (supplementary table 1). An increased risk of DM was found in both sexes and younger patients (< 55 years) showed the greatest risk increase. Mean score of the recently proposed diagnostic criteria for CIDP in DM[24] among our patients was 12 (median 12; mode 12; range 1-

18; SD \pm 3.6; reported reference score: \geq 11 points = definite, 5-10 points = probable, 2-4 points = possible, $<$ 2 points = unlikely), with only one patient with a score below 2 points, 11 patients with a score of 5-10 points, and 44 patients with a score of at least 11 points. The patient with a score of 1 point had a sensorimotor DADS with reduced motor conduction velocity in three nerves improved after IVIg therapy.

CIDP and MGUS

Forty-nine (12%) CIDP patients had MGUS, including 25 (6%) with IgG or IgA MGUS and 24 (6%) with IgM MGUS. These figures were significantly higher compared to the American sample, in all age decade with the exception of patients above 80 years (supplementary table 2). An increased risk of MGUS was also found in comparison with the Italian sample (supplementary table 3) apart from the age ranges 51-60 and 81-90, even if in the former decade the frequency was double than in the Italian general population.

CIDP and other immune diseases

Sixty-one (15%) of our CIDP patients had another immune disorders (excluding DM). This figure was more than three times higher compared to the estimated prevalence of immune diseases in the general population in Europe[29] and is similar to what observed in other immune diseases where an increased risk of other immune diseases was also reported.

Role of comorbidities on the clinical presentation, disability and treatment response

Compared to CIDP patients without DM, patients with CIDP and DM had an older age at symptoms onset, more frequent signs of autonomic impairment, increased CSF proteins levels, higher disability by RODS and INCAT, and a worse QoL (table 2). They also had a less frequent response to treatment compared to patients without DM. There was not, however, a significant difference in the response to IVIg or steroids. Patients with CIDP and IgG-IgA MGUS had an older age at symptoms onset and a more frequent cranial nerve involvement compared to those without IgG-IgA MGUS. An older age at CIDP symptoms onset was also found in patients with IgM MGUS and in

patients with a medical history of solid neoplasm. Patients with CIDP and other immune disorders had a younger age at symptoms onset, more frequently were females, had a longer disease duration, and a more frequent cranial nerve involvement compared to those without other immune disorders. No other differences were found among groups.

Table 2. Role of comorbidities in the clinical presentation, disability and treatment response of CIDP

	Diabetes (n. 56)	Without Diabetes (n. 337)	IgG-IgA MGUS (n. 25)	Without IgG-IgA MGUS (n. 368)	IgM MGUS (n. 24)	Without IgM MGUS (n. 369)	Lymphoma (n. 7)	Without lymphoma (n. 386)	Solid neoplasm (n. 35)	Without solid neoplasm (n. 358)	Other immune diseases (n. 61)	Without other immune diseases (n. 332)
Time (years) from CIDP to index comorbidity; mean (range)	8 (1-29)		6.5 (1-44)		4 (1-16)		18 (8-39)		8.5 (1-21)		16 (1-34)	
Time (years) from index comorbidity to CIDP; mean (range)	10 (1-29)		8 (1-17)		5 (1-10)		8 (7-10)		10 (1-25)		11 (1-37)	
Gender (M:F)	42:14	210:127	17:8	235:133	13:11	239:130	3:4	249:137	23:12	229:129	28:33*	224:108
Age at onset; years; mean (range)	54 (14-85)*	49 (6-86)	59.5 (24-86)**	49 (6-85)	56.5 (24-75)*	49 (6-86)	50 (15-67)	50 (6-86)	57 (10-82)**	49 (6-86)	43 (9-80)**	51 (6-86)
Disease duration; years; mean (range)	8.5 (0.5-31)	8 (0.5-52)	7 (0.5-45)	8 (0.5-52)	9 (0.5-33)	8 (0.5-52)	14 (2-46)	8 (0.5-52)	6.5 (0.5-32)	8 (0.5-52)	11 (0.5-52)*	8 (0.5-46)
Fatigue	31 (55%)	182 (54%)	11 (44%)	202 (55%)	13 (54%)	200 (54%)	2 (28.5%)	211 (55%)	18 (51%)	195 (54%)	33 (54%)	180 (54%)
Pain	21 (37.5%)	102 (30%)	7 (28%)	116 (31.5%)	8 (33%)	115 (31%)	3 (43%)	120 (31%)	6 (17%)	117 (33%)	24 (39%)	99 (30%)
Cranial nerve involvement	9 (16%)	74 (22%)	11 (44%)*	72 (19.5%)	2 (8%)	81 (22%)	0	83 (21.5%)	7 (20%)	76 (21%)	20 (33%)*	63 (19%)
Ataxia	22 (39%)	96 (28%)	10 (40%)	108 (29%)	7 (29%)	111 (30%)	4 (57%)	114 (29.5%)	10 (28.5%)	108 (30%)	19 (31%)	99 (30%)
Tremor	10 (18%)	37 (11%)	3 (12%)	44 (12%)	5 (21%)	42 (11%)	2 (28.5%)	45 (12%)	6 (17%)	41 (11%)	10 (16%)	37 (11%)
Dysautonomia	8 (14%)*	19 (5%)	3 (12%)	24 (6%)	2 (8%)	25 (7%)	1 (14%)	26 (7%)	4 (11%)	23 (6%)	7 (11%)	20 (6%)
Increased CSF proteins; positive/tested	39/41 (95%)*	206/256 (80%)	18/20 (90%)	225/277 (81%)	15/21 (71%)	229/276 (83%)	6/6 (100%)	238/291 (82%)	24/27 (89%)	220/269 (82%)	37/44 (84%)	207/252 (82%)
Mean CSF proteins; mg/dL (range)	127 (45-540)	121 (45-1000)	120 (45-540)	122 (45-1000)	135 (45-540)	120 (45-1000)	141 (59-240)	121 (45-1000)	139 (45-1000)	118 (45-679)	152 (45-1000)	116 (45-679)
Nerve imaging; positive/tested	4/6 (67%)	37/45 (82%)	3/3 (100%)	38/48 (79%)	2/3 (67%)	39/48 (81%)	0	41/51 (80%)	4/6 (67%)	37/45 (82%)	6/6 (100%)	35/45 (78%)

Nerve biopsy; positive/tested	4/6 (67%)	16/28 (57%)	0/0	19/33 (57.5%)	1/1 (100%)	19/32 (59%)	0	20/33 (61%)	1/3 (33%)	19/30 (63%)	5/6 (83%)	15/27 (55%)
MRC sum score; least squares mean (std. err.) ¹	52.7 (0.9)	54.6 (0.4)	55.7 (1.4)	54.2 (0.4)	53.5 (1.4)	54.4 (0.4)	54.7 (2.6)	54.3 (0.3)	54.0 (1.1)	54.3 (0.4)	54.6 (0.9)	54.3 (0.4)
I-RODS score; least squares mean (std. err.) ¹	28.1 (1.6)**	33.4 (0.6)	32.6 (2.5)	32.7 (0.6)	28.5 (2.5)	33.0 (0.6)	25.6 (5.4)	32.8 (0.6)	36.2 (2.1)	32.4 (0.6)	32.5 (1.5)	32.8 (0.6)
INCAT disability score; least squares mean (std. err.) ¹	3.3 (0.3)**	2.5 (0.1)	2.3 (0.4)	2.7 (0.1)	3.4 (0.4)	2.6 (0.1)	3.0 (0.8)	2.6 (0.1)	2.7 (0.3)	2.6 (0.1)	2.7 (0.3)	2.6 (0.1)
Quality of life score; least squares mean (std. err.) ¹	8.9 (0.3)**	7.9 (0.1)	8 (0.5)	8 (0.1)	8.2 (0.5)	8.0 (0.1)	9.4 (1.0)	8.0 (0.1)	7.6 (0.4)	8.0 (0.1)	8 (5-12)	8 (1-14)
Treatment response	36/51 (71%)**	266/304 (88%)	17/21 (81%)	285/334 (85%)	18/23 (78%)	284/332 (86%)	4/5 (80%)	298/350 (85%)	27/31 (87%)	275/324 (85%)	51/57 (89%)	251/298 (84%)
Corticosteroids	11/20 (55%)	101/200 (51%)	9/15 (60%)	103/205 (50%)	7/17 (41%)	105/203 (52%)	1/3 (33%)	111/217 (51%)	13/23 (57%)	99/197 (50%)	23/39 (59%)	89/181 (59%)
Intravenous immunoglobulin	29/44 (66%)	190/258 (74%)	13/17 (76%)	206/285 (72%)	12/19 (63%)	207/283 (73%)	3/5 (60%)	216/297 (73%)	19/27 (70%)	200/275 (73%)	33/48 (69%)	186/254 (73%)

CSF= cerebrospinal fluid; F= females; M= males; MGUS= monoclonal gammopathy of undetermined significance; MRC= Medical Research Council

*p<0.05; **p<0.01; least square means obtained from a linear model adjusted for disease duration;

¹ std. err.=standard error.

There was no significant difference in the distribution of comorbidities among the different CIDP phenotypes with the only exception of a more frequent IgM MGUS in patients with pure motor CIDP compared to patients with typical CIDP (23% vs 5.5%, $p= 0.0393$). There was no significant difference in the prevalence of comorbidities between patients with atypical CIDP progressed or not to typical CIDP.

DISCUSSION

In this study, 75% of the patients with CIDP had at least one comorbidity and about half of them at least two comorbidities. These figures are higher than those reported by other studies, where the observed frequency of comorbidities ranged from 25% to 43%,^[13,30,31] possibly reflecting the larger number of patients in our cohort, differences in age distribution, or in the methods of ascertainment. Most importantly, about half of the patients had one or more comorbidities that potentially influenced the choice of treatment. Although in these patients steroid therapy was less frequently used to avoid the increased risk of side effects,^[6] the overall response to treatment was similar to that of patients without these comorbidities. Our data indicate that the recommendation of the EFNS/PNS on basing the choice of therapy on the presence of relative contraindications to individual therapy ^[1], probably applies to a much larger population of CIDP patients than currently presumed.

DM was significantly more frequent in our patients with CIDP compared to what expected from a representative sample of the Italian population.^[21] The increased risk of DM was present in both sexes, and mostly involved younger age groups even if the mean age of patients with DM was older than that of patients without. Conflicting data emerge from previous studies on the association of CIDP with DM.^[2-6] It might be difficult in some patients to establish whether a neuropathy with some electrodiagnostic features consistent with demyelination is caused by DM itself or by CIDP.^[5,6,32] It is well known that a certain degree of motor conduction slowing may be seen in diabetic neuropathy.^[6] Compared to previous studies, most of which are population-based and possibly used less stringent inclusion and exclusion criteria, in all our patients the diagnosis of

CIDP was made by neurologists expert in peripheral neuropathies and all the patients with DM fulfilled the EFNS/PNS diagnostic criteria for probable or definite CIDP.[1] In addition, the increased prevalence of DM in CIDP in our population was confirmed using the recently proposed diagnostic criteria for CIDP in DM.[24] Although these criteria have not yet been validated, the parameters taken into consideration were reported to allow a distinction between CIDP and diabetic polyneuropathy.[5,6] Apart from two patients with LSS and one patient with DADS, all our patients with DM had a non-length dependent sensory-motor neuropathy that was clinically distinguishable from diabetic neuropathy. The more frequent occurrence of dysautonomia in patients with DM may however reflect that in some patients DM might have influenced the neuropathy as possibly confirmed by the higher levels of disability and worse QoL in DM than non-DM patients, suggesting a possible coexistence of diabetic neuropathy and CIDP in some patients. Similar conclusion may also derive from the less frequent response to therapy in these patients compared to those without DM, even if this was not associated with a different response to IVIg or steroids. This discrepancy may explain the previously reported conflicting results on the response to therapy in CIDP patients with DM in small series of patient, even if most of them reported a similar response in patients with DM.[5,6,32-35] The reasons for the possible association of CIDP with DM remains however unclear. Putative pathogenic mechanisms underlying the link between CIDP and DM may include an increased activation of proinflammatory cytokines and matrix metalloproteinase-9 in the peripheral nerves,[33] or exposure to the immune system of nerve antigen released by diabetes induce nerve damage, as possibly indicated by the reported presence of low levels of antibodies against phospholipid, gangliosides and sulfatide in diabetic neuropathy.[34]

We confirmed the high prevalence of MGUS (IgG, IgA or IgM MGUS) (12%) in our cohort of CIDP patients. This figure is four-fold higher than that found in an American sample,[23] and almost twice that found in an Italian sample[22] where the more sensitive capillary electrophoresis was used. Our results are in line with a previous population study in Olmsted county, reporting an increased risk of CIDP in persons with MGUS (relative risk: 5.9; 95% CI 1.2–28.4),[36] and with studies on small groups of patients reporting an increased frequency (range 17-36%) of MGUS in

patients with CIDP.[10-13,30,37] We also confirmed the increased prevalence of IgM than IgG MGUS in our CIDP patients (1:1)[10-13,37] compared to what observed in the general population (about 1:4).[23] IgM MGUS is known to be more frequently associated with peripheral neuropathy compared to IgG or IgA MGUS but so far only anti-MAG antibody specificity has shown a clear relationship with a specific clinical phenotype.[38] All our patients with IgM MGUS did not have however anti-MAG antibodies. Only three of the 24 patients with IgM MGUS had the DADS phenotype currently associated with anti-MAG antibodies, while most of them had the typical CIDP phenotype. IgM MGUS was more frequent in patients with pure motor CIDP compared to patients with typical CIDP. Two of the three patients with pure motor CIDP and IgM MGUS had high anti-GM1 antibodies (1:2400 and 1:80.000). Both patients had symmetric weakness at the four limbs and one also reduced sensory nerve conduction velocities making it unlikely a misdiagnosis with multifocal motor neuropathy (MMN). The presence of anti-GM1 IgM antibodies was also reported by Busby and Donaghy in two of seven patients with pure motor CIDP compared to none of 25 patients with typical CIDP.[37] If confirmed, the increased frequency of anti-GM1 antibodies in patients with pure motor CIDP may reinforce the hypothesis raised by the reported deterioration of these patients under steroid therapy[1] that these patients may have a symmetric form of MMN instead of a purely motor CIDP. It is also possible that patients with IgM MGUS have antibodies against other identified (such as GQ1b)[39] or unidentified antigen in nerve. The small difference between patients with IgG or IgA MGUS (older age and more frequent cranial nerve involvement) and patients without support the recommendation of the EFNS/PNS to consider CIDP with MGUS not different from idiopathic CIDP.[1]

The prevalence of other autoimmune disorders (excluding DM) in our cohort (15%) was more than three times the estimated prevalence of autoimmune diseases in the general population in Europe[29] and is similar to what observed in other diseases, such as myasthenia gravis,[40] celiac disease,[41] Graves' disease,[42] and Hashimoto's thyroiditis,[42] all known to be associated with an increased risk of other immune-mediated diseases. Laboratory findings suggestive of concomitant different immune mediated disorders were also previously reported to be relatively

common in CIDP.[43] These findings might suggest that CIDP shares common pathogenic mechanisms with other immune disorders. A possible role of the human leukocyte antigen (HLA) phenotype might be reinforced by the recently reported association of DRB1*15 alleles with the presence of anti-NF155 antibodies in patients with CIDP.[44] No HLA data are however available in our population. A more frequent occurrence of cranial nerve involvement was observed in patients with (33%) than without (19%) other autoimmune disorders. The reason for this increased prevalence remains unclear but may either reflect the longer duration of CIDP in these patients or the presence of a possible concomitant pathogenic mechanism related to the underlying autoimmune disorders or just a casual finding as it might be also the case for this association in patients with a concomitant IgG or IgA MGUS.

A possible association of CIDP with cancer has been previously reported, although there are no epidemiological data consistent with this association.[9] A medical history of solid cancer was present in 9% of our patients, percentage similar to that observed in the general Italian population with the same age.[28] In only 55% of the cases, the diagnosis of cancer preceded the diagnosis of CIDP by a mean of 10 years (mode 8 years, range 1-25), in 29% the diagnosis of CIDP preceded the diagnosis of cancer by a mean of 8.5 years (mode 7 years, range 1-21), while only in 11% of the patients the two diagnoses were made in the same year (table 2). This time discrepancy is not clearly consistent with a possible pathogenetic relationship between CIDP and cancer in most of our patients,[45] as also suggested by the absence of distinguishing demographic or clinical features, including response to therapy, between patients with and without a history of cancer, apart from the older age at symptoms onset in the former group.

Some previous studies reported an association between CIDP and lymphoma. [7-9] We found a low prevalence of lymphoma in our patients with CIDP and did not find difference in demographic and clinical features between patients with and without lymphoma. This data and the lapse of time between CIDP and lymphoma (mean 18 years; range 8-39 years) and vice versa (mean 8 year; range 7-10 years) do not support a possible paraneoplastic mechanism of the neuropathy. It is not

possible, however, to exclude that the immune dysregulation present in lymphoma may somehow influence the appearance of CIDP in these patients.[46]

The main limitation of this study is its retrospective nature with information collected from medical charts and by clinical history using a structured questionnaire, without being confirmed by more precise biological or pathogenic indicators. The presence of selection bias cannot be also excluded as, compared to the general population, patients seen in our centers might be more complex cases and, as such, include patients with comorbidities more frequently than expected. It is also possible that this study is only representative of the Italian population and might not be extended to other populations. A non-homogeneous verification of the response to therapy among the different centers might have also influenced the results of this retrospective study. The use of more stringent criteria to define improvement has been also proposed in patients with CIDP.[25] The same approach was however used in each Center for patients with and without comorbidities limiting the possible bias related to our method of assessment. We think however that the results of our study could be the base for future and possibly prospective studies on the association of CIDP with other diseases.

Figure 1. Frequency of comorbidity combinations in 393 CIDP patients

Abbreviations: MGUS = monoclonal gammopathy of undetermined significance

Figure 2. Frequency of comorbidities potentially influencing treatment choice in 393 CIDP patients

Contributors

PED contributed to the conception of the research project, reviewed and commented on the statistical analysis, wrote the first draft of the report, and reviewed the report. DC, FM, RF, CB, MF, LB, SJ, AM, GA, GC, GAM, AC, AMC, MC, AS, GS, ML, GL, TR, GC, EBeghi, GL, LS, ES, EP, ST, MR, SCP, EPV, LG, LL, GM, LP contributed to the conception, organization, and execution of the research project, reviewed and commented on the statistical analysis and the report. EBianchi designed and executed the statistical analysis, contributed to the conception, organization,

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Competing interests

Pietro Emiliano Doneddu 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. 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. Raffaella Fazio has served on scientific advisory boards for CSL Behring and has received travel grants from Kedrion and CSL Behring to attend scientific meeting. Chiara Briani 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. Massimiliano Filosto has served on scientific advisory boards for CSL Behring and has received travel grants from Kedrion, Baxter and CSL Behring to attend scientific meeting. Stefano Jann has received research grants from Grifols, outside this work, and travel grants from Grifols and Kedrion. Anna Mazzeo has received travel grants from Kedrion and CSL Behring to attend scientific meeting. Giuseppe Cosentino has received travel grants to attend scientific meetings from CSL Behring and Kedrion. Andrea Cortese has received travel grants to attend scientific meetings from Kedrion. Marinella Carpo has received travel grants to attend scientific meetings from Kedrion. Marco Luigetti has received travel grants to attend scientific meetings from Kedrion. Guido Cavaletti has received honoraria for lecturing and travel grants to attend scientific meetings from Kedrion. Ettore Beghi reports grants from UCB-Pharma, grants from Shire, grants from EISAI, personal fees from Viropharma, grants from Italian Ministry of Health, grants from Fondazione Borgonovo, grants from Associazione IDIC 15, grants from European Union, outside the submitted work. Giuseppe Liberatore has received travel grants to attend scientific meetings from CSL Behring and Kedrion. Lucio Santoro reports personal fees for scientific events from CSL Behring and has received travel grants to attend scientific meetings from CSL Behring and Kedrion. Erdita Peci has received travel grants to attend scientific meetings from CSL Behring. Eduardo Nobile Orazio reports personal fees for Advisory or Scientific Board from Kedrion, Italy, Baxter, Italy, Novartis, Switzerland, CSL-Behring, Italy, Astellas, the Netherlands, outside the submitted work and travel grants to attend Scientific Meeting from Baxter, Grifols, Kedrion, and Novartis, Italy. The other authors declare no conflict of interest.

Patient consent

Obtained

Ethics approval

The study was approved by the Ethical Committee of each participating Center.

REFERENCES

1. 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.
2. Sharma KR, Cross J, Farronay O, et al. Demyelinating neuropathy in diabetes mellitus. *Arch Neurol* 2002;59:758-765.
3. Chiò A, Plano F, Calvo A, et al. ; Piemonte and Valle D'Aosta Registry for CIDP (PARCIDP). Comorbidity between CIDP and diabetes mellitus: only a matter of chance? *Eur J Neurol* 2009;16:752-754.
4. Laughlin RS, Dyck PJ, Melton LJ 3rd, et al. Incidence and prevalence of CIDP and the association of diabetes mellitus. *Neurology* 2009;73:39-45.
5. Bril V, Blanchette CM, Noone JM, et al. The dilemma of diabetes in chronic inflammatory demyelinating polyneuropathy. *J Diabetes Complications* 2016;30:1401-1407.
6. Rajabally YA, Stettner M, Kieseier BC, et al. CIDP and other inflammatory neuropathies in diabetes - diagnosis and management. *Nat Rev Neurol* 2017;13:599-611.

7. Viala K, Béhin A, Maisonobe T, et al. Neuropathy in lymphoma: a relationship between the pattern of neuropathy, type of lymphoma and prognosis? *J Neurol Neurosurg Psychiatry* 2008;79:778-782.
8. Tomita M, Koike H, Kawagashira Y, et al. Clinicopathological features of neuropathy associated with lymphoma. *Brain* 2013;136:2563-2578.
9. Rajabally YA, Attarian S. Chronic inflammatory demyelinating polyneuropathy and malignancy: A systematic review. *Muscle Nerve* 2018;57:875-883.
10. Bromberg MB, Feldman EL, Albers JW. Chronic inflammatory demyelinating polyradiculoneuropathy: comparison of patients with and without an associated monoclonal gammopathy. *Neurology* 1992;42:1157-1163.
11. Simmons Z, Albers JW, Bromberg MB, et al. Presentation and initial clinical course in patients with chronic inflammatory demyelinating polyradiculoneuropathy: comparison of patients without and with monoclonal gammopathy. *Neurology* 1993;43:2202-2209.
12. Simmons Z, Albers JW, Bromberg MB, et al. Long-term follow-up of patients with chronic inflammatory demyelinating polyradiculoneuropathy, without and with monoclonal gammopathy. *Brain* 1995;118:359-368.
13. Gorson KC, Allam G, Ropper AH. Chronic inflammatory demyelinating polyneuropathy: clinical features and response to treatment in 67 consecutive patients with and without a monoclonal gammopathy. *Neurology* 1997;48:321-328.
14. Cocito D, Durelli L, Isoardo G. Different clinical, electrophysiological and immunological features of CIDP associated with paraproteinaemia. *Acta Neurol Scand* 2003;108:274-280.
15. Domingos JP, Garrido C, Moreira Silva H, et al. Chronic inflammatory demyelinating polyneuropathy associated with autoimmune hepatitis. *Pediatr Neurol* 2014;51:13-14.

16. Mochan A, Anderson D, Modi G. CIDP in a HIV endemic population: A prospective case series from Johannesburg, South Africa. *J Neurol Sci* 2016;363:39-42.
17. Abraham H, Kuzhively J, Rizvi SW. Chronic Inflammatory Demyelinating Polyneuropathy (CIDP): An Uncommon Manifestation of Systemic Lupus Erythematosus (SLE). *Am J Case Rep* 2017;18:980-983.
18. Suanprasert N, Taylor BV, Klein CJ, et al. Polyneuropathies and chronic inflammatory demyelinating polyradiculoneuropathy in multiple sclerosis. *Mult Scler Relat Disord* 2019;30:284-290.
19. 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*. Italian CIDP Database study group. *J Neurol Neurosurg Psychiatry* 2019;90:125-132.
20. Feinstein AR. Pre-therapeutic classification of co-morbidity in chronic disease. *J Chronic Dis* 1970;23:455-468
21. Istituto Italiano di Statistica. *Annuario Statistico Italiano, Anno 2018*. Roma: ISTAT, 2018.
22. Vernocchi A, Longhi E, Lippi G, et al. Increased Monoclonal Components: Prevalence in an Italian Population of 44 474 Outpatients Detected by Capillary Electrophoresis. *J Med Biochem* 2016;35:50-54.
23. Kyle RA, Therneau TM, Rajkumar SV, et al. Prevalence of monoclonal gammopathy of undetermined significance. *N Engl J Med* 2006;354:1362-1369.
24. Lotan I, Hellman MA, Steiner I. Diagnostic criteria of chronic inflammatory demyelinating polyneuropathy in diabetes mellitus. *Acta Neurol Scand* 2015;132:278-283.
25. Merkies IS, van Nes SI, Hanna K, et al. 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.
26. Doneddu, PE, Mandia, D, Gentile, F, et al. Home monitoring of maintenance intravenous immunoglobulin therapy in patients with chronic inflammatory neuropathy. *J Peripher Nerv Syst* 2020;1–9.
27. Torlasco C, Faini A, Makil E, et al. Nation-wide hypertension screening in Italy: data from May Measurements Month 2017-Europe. *Eur Heart J Suppl* 2019;21:66-70.
28. AIRTUM Working Group. Italian cancer figures, report 2014: Prevalence and cure of cancer in Italy. *Epidemiol Prev* 2014;38:1-122.
29. Eaton WW, Rose NR, Kalaydjian A, et al. Epidemiology of autoimmune diseases in Denmark. *J Autoimmun* 2007;29:1-9.
30. Viala K, Maisonobe T, Stojkovic T, et al. A current view of the diagnosis, clinical variants, response to treatment and prognosis of chronic inflammatory demyelinating polyradiculoneuropathy. *J Peripher Nerv Syst* 2010;15:50-56.
31. Wadwekar V, Kalita J, Misra UK. Does the chronic inflammatory demyelinating polyradiculoneuropathy due to secondary cause differ from primary? *Neurol India* 2011;59:664-668.
32. Abraham A, Alabdali M, Qrimli M, et al. Treatment Responsiveness in CIDP Patients with Diabetes Is Associated with Higher Degrees of Demyelination. *PLoS One* 2015;10:e0139674.
33. Jann S, Bramerio MA, Beretta S, et al. Diagnostic value of sural nerve matrix metalloproteinase-9 in diabetic patients with CIDP. *Neurology* 2003;61:1607–1610
34. Mata S, Betti E, Masotti G, et al. Motor nerve damage is associated with anti-ganglioside antibodies in diabetes. *J Peripher Nerv Syst* 2004;9:138–143.

35. Dunnigan SK, Ebadi H, Breiner A, et al. The characteristics of chronic inflammatory demyelinating polyneuropathy in patients with and without diabetes--an observational study. *PLoS One* 2014;9:e89344.
36. Bida JP, Kyle RA, Therneau TM, et al. Disease associations with monoclonal gammopathy of undetermined significance: a population-based study of 17,398 patients. *Mayo Clin Proc* 2009;84:685-693.
37. Busby M, Donaghy M. Chronic dysimmune neuropathy. A subclassification based upon the clinical features of 102 patients. *J Neurol* 2003;250:714-724.
38. Nobile-Orazio E, Barbieri S, Baldini L, et al. Peripheral neuropathy in monoclonal gammopathy of undetermined significance: prevalence and immunopathogenetic studies. *Acta Neurol Scand* 1992;85:383-390.
39. Willison HJ, Townson K, Veitch J, et al. Synthetic disialylgalactose immunoadsorbents deplete anti-GQ1b antibodies from autoimmune neuropathy sera. *Brain* 2004;127:680-691.
40. Gilhus NE, Nacu A, Andersen JB, et al. Myasthenia gravis and risks for comorbidity. *Eur J Neurol* 2015;22:17-23.
41. Neuhausen SL, Steele L, Ryan S, et al. Co-occurrence of celiac disease and other autoimmune diseases in celiacs and their first-degree relatives. *J Autoimmun* 2008;31:160-165.
42. Boelaert K, Newby PR, Simmonds MJ, et al. Prevalence and relative risk of other autoimmune diseases in subjects with autoimmune thyroid disease. *Am J Med* 2010;123:1-9.
43. Abraham A, Albulaihe H, Alabdali M, et al. Frequent laboratory abnormalities in CIDP patients. *Muscle Nerve* 2016:862-865.

44. Martinez-Martinez L, Lleixà MC, Boera-Carnicero G, et al. Anti- NF155 chronic inflammatory demyelinating polyradiculoneuropathy strongly associates to HLA-DRB15. *J Neuroinflammation* 2017;14:224.
45. Graus F, Delattre JY, Antoine JC, et al. Recommended diagnostic criteria for paraneoplastic neurological syndromes. *J Neurol Neurosurg Psychiatry* 2004;75:1135-1140.
46. Briani C, Visentin A, Campagnolo M, et al. Peripheral nervous system involvement in lymphomas. *J Peripher Nerv Syst* 2019;24:5-18.