Atypical CIDP: diagnostic criteria, progression, and treatment response. Data from the Italian CIDP Database

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ABSTRACT

Objectives A few variants of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) have been described but their frequency and evolution to typical CIDP remain unclear. To determine the frequency and characteristics of the CIDP variants, their possible evolution to typical CIDP, and treatment response.

Methods We applied a set of diagnostic criteria to 460 patients included in a database of Italian CIDP patients. Clinical characteristics and treatment response were reviewed for each patient. The Kaplan-Meier curve was used to estimate the progression rate from atypical to typical CIDP.

Results At the time of inclusion 376 (82%) patients had a diagnosis of typical CIDP while 84 (18%) had atypical CIDP, including 34 (7%) with distal acquired demyelinating symmetric neuropathy (DADS), 17 (4%) with purely motor, 17 (4%) with Lewis-Sumner syndrome (LSS), and 16 (3.5%) with purely sensory CIDP. Based on retrospective review of the symptoms and signs

present at onset and for at least one year, 180 (39%) patients had an initial diagnosis compatible with atypical CIDP that in 96 (53%) patients evolved to typical CIDP. Mean disease duration was longer in patients evolving to typical CIDP than in those not evolving (p=0.0016). Patients with DADS and LSS had a less frequent response to immunoglobulin than those with typical CIDP, while patients with purely motor and sensory CIDP had a similar treatment response.

Conclusions The proportion of patients with atypical CIDP varies during the disease course. DADS and LSS have a less frequent response to intravenous immunoglobulin compared to typical CIDP, raising the possibility of a different underlying pathogenetic mechanism.

Keywords: chronic inflammatory demyelinating polyradiculoneuropathy, Lewis–Sumner syndrome; distal acquired demyelinating symmetric neuropathy; CIDP; diagnostic criteria

INTRODUCTION

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a chronic and disabling immune-mediated polyradiculoneuropathy.[1] Several clinical variants of CIDP have been reported widening the spectrum of this neuropathy. These variants have been defined by the Joint Task Force of the European Federation of Neurological Societies and the Peripheral Nerve Society (EFNS/PNS) as ‘atypical CIDP’, and include distal acquired demyelinating symmetric neuropathy (DADS), purely motor or sensory CIDP, Lewis-Sumner syndrome (LSS) and focal CIDP.[1] The diagnostic criteria for these forms are however not well defined possibly explaining their variable frequency ranging from 1 to 49% in different series[2,3] and the reported differences in their treatment response.[4-7] It is also unclear the frequency and time to their possible evolution to typical CIDP.[5,8]

We established a set of diagnostic criteria for the CIDP variants derived from a revision of the literature and applied it to a large series of patients with CIDP included in a web-based database on

Italian CIDP patients, to determine the frequency and characteristics of the CIDP variants, their possible evolution to typical CIDP, and their treatment response.

PATIENTS AND METHODS

Database and study population

From January 2015 to April 2018 we included data from 500 patients with a diagnosis of CIDP or one of its variants followed by 22 Italian Centers with expertise in immune-mediated neuropathies. The diagnosis of CIDP was made by the treating neurologist and reviewed by the coordinating Centre (PED and ENO) and classified according to the EFNS/PNS diagnostic criteria.[1] The reasons for suspecting CIDP when nerve conduction studies were not diagnostic were also reported by the treating neurologist and included, beside a clinical history and presentation consistent with CIDP, abnormality of the supportive tests[1] (CSF analysis, ultrasound or magnetic resonance imaging –MRI- of the nerves and plexus, sensory conduction studies or somatosensory evoked potentials, nerve biopsy and response to previous therapy) and a relapsing course of the disease. All the data were included by the treating neurologist in a web-based electronic database expressly prepared by CINECA, Bologna, Italy. Informed consent was obtained from all participants at enrollment.

Diagnosis of atypical CIDP

We reviewed the literature on the diagnostic criteria used for atypical CIDP [4-29] (supplementary table 1), and defined a set of clinical diagnostic criteria for all the patients included in our study (table 1). Our criteria include mandatory and exclusion criteria for each atypical CIDP form while symptoms and signs not essential for the diagnosis (but that may be part of the clinical picture) were defined as ‘other possible symptoms and signs’. We also decided that a minimum of one-year duration of symptoms and signs specific to each atypical form was necessary to establish a

diagnosis of atypical CIDP. This because even typical CIDP may initially present with purely sensory or motor symptoms evolving over few months to a typical sensorimotor form. We defined purely sensory CIDP as a non-length dependent sensory neuropathy, DADS as a length-dependent sensory or sensorimotor neuropathy. Since however some authors included length-dependent purely sensory neuropathy as sensory CIDP we also separately analyzed the data of patients with sensory or sensorimotor DADS. We defined LSS as a sensory or sensorimotor multifocal neuropathy or in the presence of a clearly distinct degree of impairment among contiguous nerves. We included under this form focal CIDP where symptoms were homogeneously restricted to the nerves of one limb or two limbs (ipsilateral upper and lower limb). For chronic immune sensory polyradiculopathy (CISP) we used the criteria proposed by Sinnreich M. and coworkers.[9] Depending on the distribution of symptoms, patients with only sensory impairment were therefore split in our study into pure sensory CIDP including CISP, pure sensory DADS or pure sensory LSS. We adhered to the criteria of the EFNS/PNS[1] for the diagnosis of typical CIDP but we also included under this diagnosis patients with bilateral, although asymmetric, but not multifocal, motor and sensory impairment (at least one MRC point difference between the two sides).

Table 1 Proposed clinical diagnostic criteria for atypical CIDP

DADS
Mandatory criteria
A) with or B) without increased distal motor latency
1. Symmetric, sensory or sensorimotor symptoms and signs starting distally in the lower limbs, without proximal limb – trunk - face involvement (length-dependent fashion) ¥
Other possible symptoms
1. Ataxia, neuropathic pain, cramps, fatigue, autonomic symptoms, tremor
2. Upper-limb distal sensory or sensorimotor symptoms and signs occurring later ~~(at least after one year from onset)~~
Exclusion criteria
1. Cranial nerve involvement
2. Proximal limbs, trunk, face involvement
3. Weakness without sensory symptoms
4. Symptoms and signs starting in the upper limbs
PURE SENSORY CIDP
Mandatory criteria
A) with or B) without abnormal motor nerve conduction studies
1. Sensory symptoms (including ataxia), without weakness, in a polineuropathic distribution, symmetric or asymmetric ¥
2. Symptoms may start anywhere in the body excluding a *length-dependent pattern* (included under DADS)
Other possible symptoms
1. Neuropathic pain, fatigue, tremor
2. Facial sensory symptoms
Exclusion criteria
1. Motor symptoms/signs including cramps and motor cranial nerve palsy
2. Multifocal distribution
3. Autonomic dysfunction
CISP
Mandatory criteria

1. Sensory symptoms with a polyneuropathic distribution without weakness ¥
2. Normal motor and sensory nerve conduction and EMG studies
- *PLUS at least two of the following:*
3. Abnormal SSEP not due to CNS involvement
4. MRI showing gadolinium enhancement and/or hypertrophy of the cauda equina, lumbosacral or cervical nerve roots, or the brachial or lumbosacral plexuses
5. Elevated CSF protein level with normal cells

Exclusion criteria and other possible symptoms

1. As in pure sensory CIDP

PURE MOTOR CIDP

Mandatory criteria

A) with or B) without abnormal sensory nerve conduction studies

1. Weakness, without sensory symptoms or signs, in a polineuropathic distribution, symmetric or asymmetric. ¥
2. Symptoms may start anywhere in the body

Other possible symptoms

1. Cramps, fatigue, tremor
2. Motor cranial nerve palsy

Exclusion criteria

1. Sensory symptoms/signs including sensory ataxia
2. Autonomic dysfunction
3. Neuropathic pain
4. Multifocal distribution

LSS

Mandatory criteria

A) with or B) without motor conduction block

1. Sensory symptoms, with or without weakness, in a multifocal distribution (unilateral focal[Ω] CIDP included) ¥
2. Symptoms may start anywhere in the body

Other possible symptoms

1. Cramps, fatigue, autonomic symptoms, ataxia, neuropathic pain
2. Motor and/or sensory cranial nerve palsy

Exclusion criteria

1. Weakness in isolation, without sensory symptoms
2. Symptoms/signs in a polyneuropathic distribution

¥ Clinical phenotype must have lasted at least one year (temporal criterion).

Ω Focal CIDP defined as the presence of symptoms homogeneously restricted to the nerves of one limb or two limbs (ipsilateral upper and lower limb).

CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; CISP = chronic immune sensory polyradiculopathy; DADS = distal acquired demyelinating symmetric neuropathy; LSS = Lewis-Sumner syndrome; SSEP = somatosensory evoked potentials

Some authors also included additional specific electrodiagnostic parameters for the diagnosis of atypical CIDP (supplementary table 1) even if these were not considered in the EFNS/PNS Guidelines for CIDP. These parameters include abnormally increased motor distal latency (DL) in patients with DADS, normal sensory nerve conduction studies in patients with purely motor CIDP, normal motor nerve conduction studies in sensory CIDP, and presence of conduction blocks (CBs) in LSS. In our study, we used the electrodiagnostic criteria of the EFNS/PNS for the diagnosis of CIDP and its variants [1] but we restricted the diagnosis of atypical CIDP to clinical criteria to allow a retrospective analysis of the diagnosis at onset and of its evolution during the course of the disease. We compared however the data of patients within each group who fulfilled or not the additional electrodiagnostic parameters for the diagnosis of atypical CIDP at the time of inclusion in

the study. Since the data on distal distance were not available, we did not calculate the terminal latency index in patients with DADS.

Clinical assessment and ancillary tests

At enrollment, all patients underwent a detailed clinical history including time of clinical onset, presence - distribution and date of onset of motor and sensory symptoms, ataxia, pain, tremor, cramps, fatigue, autonomic dysfunction, and cranial nerve involvement. This information was integrated with the data reported in the medical records. Disease course was defined as progressive, relapsing or monophasic by the treating neurologist. Response to previously performed therapy were reported by the treating neurologist as ‘improved’, ‘stable’ or ‘worsened’. Since the number of patients with atypical CIDP treated with other therapies besides steroids and intravenous immunoglobulin (IVIg) was relatively small, we focused our analysis on these two therapies. The clinical evaluation at enrollment included assessment of muscle strength using the Medical Research Council (MRC) sumscore on 12 muscles (range 0-60). Neurological disability was evaluated at enrollment with the Inflammatory-Rash Overall Built Disability Scale (I-RODS)(range 1-48), and the Inflammatory Neuropathy Cause and Treatment (INCAT) disability scale (range 0-10), while Quality of life (QoL) was assessed with the EuroQol-5D-3L scale (five items, each with a score from 1 -best- to 3 -worst). Results of previously performed examinations including CSF analysis, nerve ultrasound or brachial/lumbosacral plexus MR examination and sural nerve biopsy, were reported when available. The results of nerve conduction studies performed during the course of the disease were included. Sensory nerve conduction studies were performed bilaterally in median, ulnar and sural nerves and included evaluation of sensory nerve action potential (SNAP) amplitude, distal latency (DL) and sensory conduction velocity (SCV). Motor nerve conduction studies were also performed bilaterally in median, ulnar, common peroneal and tibial nerves and included distal and proximal compound muscle action potential (cMAP) amplitude (onset to peak) and duration, motor conduction velocity (MCV), distal and proximal motor latency and in most

patients F-wave latency. Abnormalities of motor and sensory nerve conduction studies consistent with demyelination were defined according to the EFNS/PNS criteria.[1] Some patients also underwent somatosensory evoked potentials (SSEP). At the time of inclusion, patients with an alternative diagnosis for the neuropathy or high titers of anti-MAG (myelin-associated glycoprotein) antibodies (over 7000 [BTU] by Bühlman method) or without available nerve conduction studies were excluded. In all the patients, the diagnosis at entry was revised by the coordinating Center according to the above-mentioned diagnostic criteria (table 1). These criteria were also applied at clinical presentation based on symptoms present at onset and for at least one year. Progression of atypical to typical CIDP was based on the time of appearance of symptoms before the inclusion in the study. CIDP diagnosis was classified in 'definite', 'probable' or 'possible' according to the EFNS\PNS criteria.[1]

Statistical analysis

Descriptive statistics were reported for the entire sample of patients with CIDP, and for typical and the atypical CIDP forms separately. Categorical variables were described using frequencies and percentages, while continuous variables using mean, medians, and ranges. Demographic, clinical and neurophysiological features, treatment response, strength deficit, 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 or the Wilcoxon-Mann-Whitney test for continuous variables. For patients with atypical CIDP at onset, the progression rate from atypical to typical CIDP was calculated using Kaplan-Meier survival curves, considering the different atypical forms separately. All tests were two-tailed and the significance level was set to 0.05. Analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Frequency and clinical course of atypical CIDP

By April 2018, 500 patients were enrolled in the database. Twenty-three patients were excluded from the analysis for the presence of an alternative diagnosis (18 patients with anti-MAG titers ranging from 9,300 to over 70,000 BTU, median 41,191 BTU), one with Charcot-Marie Tooth 1A, three with amyloidosis, and one with only cranial nerve palsy), and 17 for the absence of available nerve conduction studies or incomplete data. A total 460 patients were included in the study (293 men; 167 women), aged 11-92 years, (mean 58; median 60 years), with mean disease duration of 8.3 years (range 0.5-60 years, median 6 years).

At study entry, 376 (82%) patients had a diagnosis of typical CIDP and 84 (18%) of atypical CIDP. The diagnosis fulfilled the EFNS/PNS diagnostic criteria for CIDP in 82% of the patients with typical CIDP and in 76% of those with atypical CIDP (p= 0.2149). Among the patients with atypical CIDP, 34 (7% of total CIDP patients) had DADS, 17 (4%) had purely motor CIDP, 17 (4 %) had LSS including three with focal CIDP, and 16 (3.5%) had purely sensory CIDP including two (0.5%) with CISP (figure 1B). When we retrospectively reviewed the symptoms and signs at disease onset, we found that 180 (39%) patients fulfilled the diagnosis of atypical CIDP. This included 59 (13%) patients with DADS, 49 (11%) with purely sensory CIDP including two with CISP, 40 (9%) with purely motor CIDP, 29 (6%) with LSS, and three (1%) with CIDP clinically restricted to cranial nerves (cranial CIDP) (figure 1A). Ninety-six (53%) patients with atypical CIDP at onset progressed to typical CIDP after mean disease duration of 5.5 years (range 1-38; median 3) including 25/59 (42%) with DADS, 33/49 (67%) with purely sensory CIDP, 23/40 (57.5%) with purely motor CIDP, 12/29 (41%) with LSS, and 3 with cranial CIDP. Figure 2 shows the yearly progression rate to typical CIDP for patients with different atypical CIDP forms at onset. The clinical form with the highest progression rate was pure sensory CIDP, while DADS showed the lowest rate. Within 5 years, 48% of sensory CIDP patients, 32% of pure motor, 36% of LSS and 24% of DADS had progressed to typical CIDP; the corresponding values at 10 years were 77%, 64%, 63% and 39% (figure 2). Patients with atypical CIDP who progressed to typical CIDP had longer disease duration compared to patients who did not progress (mean, 11 vs 7 years; p=0.0016).

Clinical and electrophysiological features of the different forms of atypical CIDP

In table 2 are summarized the clinical features and treatment response of the patients with different forms of atypical CIDP in comparison to patients with typical CIDP.

Table 2 Comparison of clinical features and treatment response in atypical and typical CIDP

	DADS (n. 34)	Pure sensory (n. 16)	Pure motor (n. 17)	LSS (n. 17)	Typical CIDP (n. 376)	P value
Gender (M:F)	24:10	10:6	8:9	16:1	235:141	0.0079****
Age at onset; years; mean (range)	58 (20-79)	57 (31-75)	53 (11-82)	48 (27-75)	49 (5-86)	0.0032*
Disease duration; years; mean (range)	8 (0.5-26)	5 (0.5-17)	10 (0.5-28)	7 (0.5-24)	8.5 (0.5-60)	NS
Fulfillment of EFNS/PNS criteria	24 (70.5%)	12 (75%)	15 (88%)	13 (76%)	310 (82%)	NS
Increased CSF proteins; positive/tested	26/29 (90%)	10/15 (67%)	7/9 (78%)	5/13 (38%)	243/284 (85.5%)	0.0002****
Mean CSF proteins; mg/dL (range)	93 (52-379)	86 (46-193)	171 (47-679)	82 (61-146)	123 (46-1000)	NS
Nerve imaging; positive/tested	7/7	5/5	0/0	6/7 (86%)	26/36 (72%)	NS
Nerve biopsy; positive/tested	2/4 (50%)	1/4 (25%)	0/0	0/1	21/36 (58%)	NS
MRC sum score; mean (range)	58 (48-60)	60 (60-60)	51 (36-60)	57 (49-60)	53.5 (26-60)	0.0003*
I-RODS score; mean (range)	39 (16-48)	38 (23-47)	31 (11-48)	40 (26-47)	33 (1-48)	0.0027*; 0.0301****
INCAT disability score; mean (range)	1.5 (0-6)	1.7 (0-3)	3.5 (0-10)	2 (0-6)	2.7 (0-10)	0.0005*
Quality of life score; mean (range)	7 (1-9)	7 (5-9)	8 (5-13)	7 (5-9)	8 (5-14)	0.0030*
Overall treatment response	16/25 (64%)	9/10 (90%)	15/17 (88%)	9/14 (64%)	299/344 (87%)	0.0050*; 0.0326****
EFNS/PNS only	9/15 (60%)	8/8 (100%)	14/15 (93%)	7/11 (63%)	191/216 (88%)	0.0107* 0.0075****
Corticosteroids	9/16 (56%)	4/6 (67%)	3/7 (43%)	3/7 (43%)	110/215 (51%)	NS
Intravenous immunoglobulin	9/18 (50%)	6/7 (86%)	14/17 (82%)	5/12 (42%)	233/299 (78%)	0.0178*; 0.0086****
EFNS/PNS only	6/12(50%)	4/5 (80%)	13/16 (82%)	2/7 (29%)	139/185 (75%)	0.0852* 0.0151****

* Typical CIDP vs DADS, **Typical CIDP vs Pure sensory, *** Typical CIDP vs Pure motor, **** Typical CIDP vs LSS.

CIDP = chronic inflammatory demyelinating polyradiculoneuropathy ; DADS = distal acquired demyelinating symmetric neuropathy; F = female; INCAT = Inflammatory Neuropathy Cause and Treatment ; I-RODS = Inflammatory Rasch Overall Disability Scale ; LSS = Lewis-Sumner syndrome ; M = male ; MRC = Medical Research Council ; NS = not significant

DADS. Thirty-four patients had a diagnosis of DADS at study entry including 22 with only sensory symptoms without weakness. All patients had a symmetric presentation of symptoms and signs distally in the lower limbs. Compared to typical CIDP, patients with DADS had an older age at onset (mean 58 vs 49 years; p= 0.0032). At onset, 26 (76%) patients presented with purely sensory symptoms while eight (24%) also had ankle weakness at presentation. After a mean disease duration of 8 years (range 0.5-26 years), sensory symptoms had progressed to involve also distal upper limbs in 12 (35%) patients, while 12 (35%) patients had distal weakness that in eight was restricted to the lower limbs. Ataxia was present in 16 (47%) patients, five (15%) had postural and intention tremor in the arms, and 14 (41%) patients had pain. Disease course was chronic-progressive in 18 (53%) patients, relapsing in 14 (41%) patients and monophasic in two patients.

Twenty-four (70.5%) patients met the EFNS/PNS diagnostic criteria for CIDP (21 definite, three probable). Seven of them had increased motor DL. Even if there were some differences between patients with (7 patients) or without (17 patients) increased motor DL in terms of frequency of upper-limb involvement (28.5% vs 47% patients; p= 0.6921) and presence of weakness (14% vs 41% patients; p= 0.6417), none of the differences was significant.

Compared with typical CIDP, DADS patients had higher MRC sumscore (mean 58 vs 53.5; p= 0.0003), lower disability levels measured with INCAT (mean 1.5 vs 2.7; p= 0.0005) and I-RODS (mean 39 vs 33; p= 0.0027), and better QoL (mean 7 vs 8; p= 0.0030).

PURELY SENSORY CIDP. Sixteen patients had a diagnosis of purely sensory CIDP at study entry including two with CISP. In three patients sensory symptoms were confined to the upper limbs, in three patients to the proximal and distal areas of the lower limbs, in nine patients to the four limbs, and in one patient to the face - trunk and the four limbs. Strength was normal in all patients. Ataxia

and fatigue were reported by three (19%) and four (25%) patients, respectively. The clinical course was relapsing in seven (44%) patients, progressive in eight (50%) patients and monophasic in one. Twelve (75%) patients met the EFNS/PNS diagnostic criteria for CIDP (11 definite, one probable) with demyelinating features on motor conduction studies despite the absence of motor symptoms and signs.

No significant difference between purely sensory and typical CIDP was found in terms of severity assessed with INCAT (mean, 1.7 vs 2.7; p= 0.0532) and I-RODS (mean, 38 vs 33; p= 0.0799), and QoL (mean, 7 vs 8; p= 0.1310).

PURELY MOTOR CIDP. Seventeen patients had a diagnosis of purely motor CIDP at study entry. All patients presented with weakness without sensory symptoms, initially distributed in the upper limbs in two (12%) patients, in the lower limbs in nine (53%) patients and in the four limbs in six (35%) patients. After mean disease duration of 10 years (0.5-28 years), 12 (70.5%) patients had weakness in the proximal and distal muscles of the four limbs while clinical involvement remained confined to the upper limbs in one (6%) patient and to the lower limbs in four (23.5%) patients. In four (23.5%) patients, clinical manifestations were asymmetric without a multifocal distribution. Sensory examination was normal in all patients. Disease course was relapsing in seven (41%) patients and chronic progressive in 10 (59%) patients.

Fifteen (88%) patients met the EFNS/PNS criteria of CIDP (14 definite, one possible). The most common electrophysiological findings in these patients were CBs (11 patients) and reduced MCV (nine patients). Sensory nerve conduction studies were normal in only five patients despite the absence of sensory symptoms. There was no significant clinical difference between patients with or without abnormal sensory conduction studies.

No significant difference between purely motor and typical CIDP was found in terms of severity of motor impairment measured with MRC sumscore (mean, 51 vs 53.5; p= 0.1792), disability by the

INCAT (mean, 3.5 vs 2.7; p= 0.0972) and I-RODS (mean, 31 vs 33; p= 0.7017), and QoL (mean 8 vs 8; p= 0.9260).

LSS. Seventeen patients had a diagnosis of LSS at study entry. Compared with typical CIDP, LSS patients more frequently were males (p= 0.0079). Initial symptoms were exclusively sensory in three (18%) patients and sensorimotor in 14 (82%), with symptoms and signs predominantly confined to one upper limb in four (23.5%), one lower limb in six (35%), and one upper plus one lower limb in four (24%) patients. Three (18)% patients had focal CIDP, with symptoms in only one limb. All but two patients developed sensorimotor disturbances after a mean of 7 years (range 0.5-24 years). The clinical course was relapsing in eight (47%) patients, progressive in six (35%) patients and monophasic in three (18%) patients.

Thirteen patients (76%) met the EFNS/PNS criteria for CIDP (11 definite, one probable, one possible) including eleven with CBs in motor nerves. There was no difference between patients with or without CBs in terms of presence of weakness (90% vs 83%; p= 1.0000) and frequency of involvement of upper and lower limbs (44% vs 57%; p= 0.6284).

Patients with LSS had less disability by I-RODS (mean, 40 vs 33; p= 0.0301) but not INCAT (mean, 2 vs 2.7; p= 0.2063) compared to patients with typical CIDP, with similar MRC values (mean, 57 vs 53.5; p= 0.0778) and QoL (mean 7 vs 8; p= 0.2453).

Response to therapy in atypical CIDP

In table 2 is summarized the response to treatment in patients with atypical CIDP. Response to one or more therapy was reported in 16/25 (64%) treated patients with DADS including 9/15 (60%) fulfilling the EFNS\PNS criteria. There was no difference in treatment response between DADS patients with sensory or sensorimotor disturbance and between DADS patients with or without increased motor DL. Response to therapy occurred in 9/10 (90%) treated patients with sensory CIDP including 8/8 (100%) fulfilling the EFNS/PNS criteria. Improvement was also observed in 15/17 (88%) treated patients with purely motor CIDP, including 14/15 (93%) patients fulfilling the EFNS/PNS criteria. There was no difference in the overall response to therapy between patients

with purely motor CIDP with or without abnormal sensory nerve conduction studies. Response to steroids was also observed in 3/7 (43%) patients with purely motor CIDP patients. None of the patients with normal sensory nerve conduction studies improved however after steroid therapy while all improved patients had abnormal sensory conduction studies. Response to therapy was reported in 9/14 (64%) treated patients with LSS, including 7/11 (63%) patients fulfilling the EFNS/PNS criteria. There was no difference between LSS patients with or without CBs.

Compared with typical CIDP, the overall response to treatment was significantly lower in patients with DADS (p= 0.0050) and LSS (p= 0.0326) even when we restricted the analysis to patients fulfilling EFNS/PNS criteria that in all but one patient with LSS and two with typical CIDP were consistent with definite or probable CIDP (table 2). The same occurred for patients with purely sensory DADS (p= 0.0109) but not for patients with purely sensory (p= 1.000) or purely motor CIDP (p= 0.7182). Patients with DADS and LSS also had a less frequent response to IVIg (p= 0.0178 and p= 0.0086) compared to typical CIDP and the same occurred for patients fulfilling EFNS/PNS criteria even if the difference remained significant only for LSS (table 2). A less frequent response to IVIg was also observed in patients with sensory DADS (p= 0.0108) but not in patients with pure motor o pure sensory CIDP. There was no difference among the different groups in the response to steroids. Among the patients with typical CIDP, 235 (62.5%) patients had symmetric CIDP while 141 (37.5%) an asymmetric but not multifocal CIDP ~~(> 1 MRC point difference between the two sides), and 36 (9.5%) patients had slightly asymmetric (but not multifocal) CIDP (1 MRC point difference between the two sides)~~. There was no difference between patients with symmetric or asymmetric CIDP in the overall response to therapy (87% vs 87%; p= 1.0000) or in the response to IVIg (78% vs 78%; p= 1.0000) or steroids (48% vs 56%; p= 0.3533) while the difference in the overall response to treatment (p= 0.0384) and to IVIg (p= 0.01) remained significant between patients with either symmetric or asymmetric typical CIDP and LSS. (Verifica i dati)

DISCUSSION

There is some discrepancy on the frequency of the CIDP variants with numbers ranging from 1 to 49%.[2,3] It is unclear whether this discrepancy reflects the use of different diagnostic criteria in previous studies or a different disease duration at the time of ascertainment. There are indeed some differences in the definition of these phenotypes.[4-29] We applied our set of diagnostic criteria to all our patients and found that the frequency of atypical CIDP at study entry was 18%, similarly to some previous studies (17.8-19.6%).[10,11] When we retrospectively analyzed the symptoms at the time disease onset and for the following year, we found that 39% of the patients had a clinical presentation consistent with atypical CIDP that in 53% of the patients evolved to typical CIDP by the time of inclusion in the study. A similar rate of progression (20-71%) was previously reported in other small series of patients.[5,8,12] In our study, progression to typical CIDP was significantly associated with a longer disease duration. Still, 55% of our patients with atypical CIDP at study entry had a disease duration of at least 5 years and 30% of at least 10 years. This finding supports the idea that progression to typical CIDP is often, though not invariably, associated with the disease duration. Some patients with typical CIDP presented some clinical modifications during the course of the disease leading to a predominantly distal or sensory but not motor or multifocal impairment, even if the previously more diffuse and sensorimotor impairment did not lead to a change in their diagnosis. There are also some differences in the reported frequency of the different forms of atypical CIDP. The relatively small prevalence of LSS in our series (4%) compared to some previous series (0.5-34%)[3,6,10,11,13] may reflect the inclusion in our series of only patients with a multifocal neuropathy and not of those with an asymmetric polyneuropathy. This decision was also supported by the absence of difference in the response to therapy between patients with symmetric or asymmetric typical CIDP~~, and by the finding that almost 40% of the patients with typical CIDP in our cohort had some degree of asymmetry, a figure that is more indicative of a typical form rather than an atypical form~~. Similarly, we found a lower prevalence of sensory CIDP (3.5%) compared to previous series (11-35%).[14,15] This may partly reflect our use of stringent

diagnostic criteria with the proportion of patients raising to 7.8% if we also included patients with purely sensory DADS or LSS. It is also possible that the disease duration explains the difference with a prevalence of sensory CIDP in our series decreasing from 11% at onset to 3.5% at enrollment. DADS was the most common CIDP variant in our study (7%), (2-17% in previous studies),[2,6,10] followed by the purely motor form (4%) (4-10% in previous series).[2,10,13]

Only few studies have compared disability in typical and atypical CIDP.[6,30,31] Two studies found a higher level of disability and impairment in typical CIDP than in LSS and DADS patients.[6,30] Another study did not find difference in terms of disability between typical and atypical CIDP.[31] In our series, patients with typical CIDP had a worse MRC score, higher disability and worse QoL than patients with DADS, confirming that DADS is clinically less disabling than typical CIDP. Patients with LSS had less severe disability than patients with typical CIDP by I-RODS but not by INCAT. This discrepancy may reflect the wider range of item difficulties in the I-RODS than INCAT scale. On the other hand we did not find differences in the degree of motor impairment, disability and QoL between purely motor CIDP patients and typical CIDP patients. Similarly, disability and QoL where similar in sensory and typical CIDP.

There are some differences in the reported response to therapy in patients with atypical CIDP. A better response to IVIg than to steroids was reported in some series of patients with LSS,[4,5,7,16,17] while others[6] reported a reduced response to IVIg but not to steroids compared to typical CIDP. Patients with DADS were reported to have a less satisfactory response to treatment than patients with typical CIDP.[18,19] In our series, patients with LSS and DADS had a less frequent response to therapy ($p= 0.0326$; $p= 0.0050$) and to IVIg ($p= 0.0086$; $p= 0.0178$) compared to patients with typical CIDP and the same occurred for patients with purely sensory DADS, while there was no differences in the response to steroids.

Several reports suggest that purely motor CIDP may not respond to or even worsen after corticosteroids.[20,21] Based on these findings, the EFNS/PNS Guidelines recommend the use of IVIg for motor CIDP.[1] However, response to steroids has been reported in other studies, with

figures up to 20% of treated patients.[13] We found that 43% of our purely motor CIDP patients improved after steroids. All these patients had however a concomitant sensory electrophysiological, although not clinical, impairment. This finding suggest that the diagnosis of motor CIDP and the decision to avoid steroids should be probably restricted to patients without any clinical and electrophysiological involvement of motor nerves. Only few data are available on the response to therapies in patients with purely sensory CIDP with a usually favourable response to both IVIg and steroids.[13,22-24] We also found a similar response rate in comparison to patients with typical CIDP.

In conclusion, our study on a large population of patients classified according to a uniform set of diagnostic criteria, confirms that the proportion of patients with atypical CIDP varies according to the duration of the disease and that response to therapy is different in some of these forms (DADS and LSS). The persistence of an atypical presentation in a consistent proportion of patients for several years together with the different response to therapy in some of these forms, suggest that some difference in the pathogenic mechanisms may underlie some of these variants. An extensive immunological study to investigate the presence of different anti-nerve antibodies is in progress in this cohort of patients to verify whether the different clinical presentations and response to therapy might be associated with specific immunological abnormalities as was recently reported for patients with antibodies to neurofascin 155, contactin 1 and other nodal-paranodal proteins.[32,33] It would be also advisable to verify these data in a prospective study on a large series of newly diagnosed patients in whom a definite set of diagnostic criteria and of diagnostic investigations and assessment would be applied and subsequently periodically verified.[34]

Figure 1A. CIDP type at one year after onset of symptoms; B CIDP type at study entry (mean 8 years after onset).

Graphs show the frequency of the atypical CIDP variants at one year after the onset of symptoms (A) and at study entry (B) in 460 patients.

Figure 2 Probability of progressing from atypical CIDP to typical CIDP.

Graph shows the yearly progression rate to typical CIDP of the individual atypical CIDP forms at onset.

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, AM, GAM, AC, BF, SJ, AMC, MC, AS, ML, GL, GA, TR, GS, GC, GL, LS, EP, ST, MR, SCT, AT, GM, LP, GC, MS contributed to the conception, organization, and execution of the research project, reviewed and commented on the statistical analysis and the report. EB designed and executed the statistical analysis, contributed to the conception, organization, and execution of the research project, reviewed and commented on the statistical analysis and the report. ENO conceived, organized and designed the study, reviewed and commented on the statistical analysis, wrote the first draft of the report, reviewed the report.

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Competing interests

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. Pietro Emiliano Doneddu has received travel grants to attend scientific meetings from CSL Behring and Kedrion. Giuseppe Liberatore 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. Erdita Peci has received travel grants to attend scientific meetings from CSL Behring. 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. Marinella Carpo has received travel grants to attend scientific meetings from Kedrion. Anna Mazzeo has received travel grants from Kedrion and CSL Behring to attend scientific meeting. Chiara Briani has served on scientific advisory boards for Pfizer and 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. Brigida Fierro has received travel grants to attend scientific meetings from CSL Behring and liberal contribution from CSL Behring for the neuromuscular diseases centre, outside the submitted work. 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. Andrea Cortese has received travel grants to

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Patient consent

Obtained

Ethics approval

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

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