Diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy in clinical practice: A survey among Dutch neurologists

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Abstract
The diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is often a challenge. The clinical presentation is diverse, accurate biomarkers are lacking, and the best strategy to initiate and maintain treatment is unclear. The aim of this study was to determine how neurologists diagnose and treat CIDP. We conducted a cross-sectional survey on diagnostic and treatment practices among Dutch neurologists involved in the clinical care of CIDP patients. Forty-four neurologists completed the survey (44/71; 62%). The respondents indicated to use the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) 2010 CIDP guideline for the diagnosis in 77% and for treatment in 50%. Only 57% of respondents indicated that the presence of demyelinating electrophysiological findings was mandatory to confirm the diagnosis of CIDP. Most neurologists used intravenous immunoglobulins (IVIg) as first choice treatment, but the indications to start, optimize, or withdraw IVIg, and the use of other immune-modulatory therapies varied. University-affiliated respondents used the EFNS/PNS 2010 diagnostic criteria, nerve imaging tools, and immunosuppressive drugs more often. Despite the existence of an international guideline, there is considerable variation among neurologists in the strategies employed to diagnose and treat CIDP. More specific recommendations regarding: (a) the minimal set of electrophysiological requirements to diagnose CIDP, (b) the possible added value of nerve imaging, especially in patients not meeting the electrodiagnostic criteria, (c) the most relevant serological examinations, and (d) the clear treatment advice, in the new EFNS/PNS guideline, would likely support its implementation in clinical practice.

KEYWORDS
chronic inflammatory demyelinating polyradiculoneuropathy, corticosteroid, guideline, immunoglobulin, survey
INTRODUCTION

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a rare, treatable immune-mediated neuropathy that typically presents as a symmetric chronic progressive or relapsing sensorimotor polyneuropathy of all extremities, often with clear involvement of proximal muscles.\(^1\)\(^,\)\(^2\) Despite the published European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) 2010 diagnostic criteria for CIDP, the diagnosis can be challenging, leading to both over- and underdiagnosis.\(^3\)\(^-\)\(^8\) The extent to which patients can differ in clinical presentation has become more visible in the last decade, resulting in an extended group of atypical CIDP variants, such as distal predominant and asymmetric, for which clear definitions are lacking.\(^9\)\(^-\)\(^1\)\(^9\) In addition, not all patients with a clinical suspicion of CIDP completely fulfill the EFNS/PNS 2010 (electro) diagnostic criteria for CIDP.\(^1\) Moreover, there is a broad differential diagnosis where accurate diagnostic biomarkers for CIDP are lacking.\(^1\)\(^,\)\(^1\)\(^0\) Intravenous (IVIg) and subcutaneous (SCIg) immunoglobulins, corticosteroids, and plasma-exchange (PE) are all proven effective treatments for CIDP.\(^1\)\(^1\)\(^-\)\(^1\)\(^5\) The best strategy to initiate and maintain treatment, however, is not known, largely due to a lack of head to head and long-term treatment comparisons.\(^1\)\(^5\) Furthermore, the best approach to manage wear-off signs and withdrawal of IVIg is unclear.\(^1\)\(^6\)\(^-\)\(^1\)\(^7\) Because of these challenges, we expect that both the diagnostic workup and treatment strategies for CIDP patients are highly variable.

Insight in current clinical practice and potential diagnostic and therapeutic pitfalls is needed to improve current CIDP guidelines and could help for educational purposes. Therefore, the aim of this study is to determine how Dutch neurologists diagnose and treat patients with CIDP, and their use of existing CIDP guidelines.

MATERIALS AND METHODS

Study design

A cross-sectional questionnaire study was conducted among neurologists who diagnose and/or treat CIDP patients. We approached all university hospitals in The Netherlands (n = 7), and all non-university hospitals in South Holland (n = 14), the province where the Erasmus MC is located, to participate. We included non-university hospitals in only one Dutch province due to logistic reasons and because we expected that, our regional network would maximize the participation rate of the neurologists. We approached: (a) neurologists who had referred patients with CIDP to the Erasmus MC, (b) neurologists who indicated on their hospital website that they had expertise in neuromuscular diseases, (c) neurologists that were part of our (CIDP) network, and (d) eurologists who were participating in our ongoing research projects on Guillain-Barré syndrome (GBS) or CIDP. This study was approved by the medical ethical committee of the Erasmus University Medical Center in Rotterdam (MEC-2018-1569).

Development survey

Based on the current literature and clinical experience, M. C. B. and B. C. J. developed an online survey with multiple-choice (multi-select and single-select) and open-ended questions. The full set of questions could be filled out in 20 minutes, and included the following topics: (a) diagnostic workup of CIDP, (b) treatment of CIDP, and (c) profile of the neurologist. In several questions, we asked for quantitative estimations. The respondents could indicate how often they used a particular diagnostic or treatment strategy (never = 0%, rarely = 1-10%, sometimes = 10-50%, most of the time = 50-90%, and always = 90-100%). We defined ‘most of the time’ and ‘always’ as essential in the diagnostic workup or representative of the general policy of the responding neurologist. The survey was reviewed by an expert in medical decision-making (H. F. L.) and four neurologists from both university (P. A. D., F. E.) and non-university hospitals (K. K., P. W. W.) who regularly diagnose and/or treat CIDP patients. A pilot version of the survey was tested by the GBS/CIDP research team at Erasmus MC to ensure that all questions were clear. Several strategies were used to increase the response rate.\(^1\)\(^8\)\(^-\)\(^2\)\(^0\) The survey was developed in English, with the aim of facilitating and extending its use and to enable future comparison in an international setting. The survey is available on request.

Data collection

We used the GemsTracker Software for web-based data collection.\(^2\)\(^1\) Neurologists were invited by email with a personal link to access the online survey. Neurologists were asked to provide information based on their own individual strategy of preference (eg, not necessarily according to their local departmental policies) regarding the diagnosis and treatment of CIDP. No specific information regarding individual patients was collected.

Statistical analyses

We presented continuous data as means and SD or medians with full ranges. Frequencies and proportions were calculated for dichotomized and categorical variables related to the number of respondents for that variable. We examined factors associated with diagnostic and treatment practice, including (a) university affiliation, (b) expertise in neuromuscular diseases, (c) more than 5 CIDP diagnosed patients per year, and (d) more than 10 CIDP patients in follow-up, with the \(\chi^2\) test and Fisher’s exact test. A two-sided \(P\)-value < .05 was considered significant. We used Statistical Package for Social Sciences (SPSS) version 25 for data analysis.
TABLE 1  Profile of participating neurologists (n = 44)

| Age, y, n (%)        |        |
|----------------------|--------|
| ≤40                  | 12 (27)|
| 41-50                | 17 (39)|
| 51-60                | 11 (25)|
| >60                  | 4 (9)  |

| Hospital type, n (%) |        |
|----------------------|--------|
| University           | 25 (57)|
| Non-university        | 19 (43)|

| Years practicing as neurologist, median (range) | 11 (1-36) |

| Field of interest or expertise in neuromuscular diseases*, n (%) | 31 (71) |

| Completion fellowship neuromuscular diseases, n (%) | 15 (34) |

| CIDP patients diagnosed per year, n (%) |        |
|----------------------------------------|--------|
| <1                                     | 16 (36)|
| 1-5                                    | 18 (41)|
| 6-10                                   | 6 (14) |
| 11-20                                  | 4 (9)  |

| CIDP patients currently treated or under follow-up, n (%) |        |
|----------------------------------------------------------|--------|
| 0                                                        | 10 (23)|
| 1-10                                                     | 26 (60)|
| 11-25                                                    | 5 (11) |
| 26-50                                                    | 1 (2)  |
| >50                                                      | 2 (5)  |

Abbreviation: CIDP, chronic inflammatory demyelinating polyradiculoneuropathy.
*Expertise in neuromuscular diseases (64%), immune-mediated diseases of the peripheral nervous system (32%), and/or clinical neurophysiology (16%).

3  | RESULTS

3.1  | Participating neurologists

The survey was sent to 81 neurologists between June 2018 and September 2018. Ten neurologists were excluded, because they no longer diagnosed or treated CIDP patients (n = 7) or were no longer employed at one of the included centers (n = 3). Forty-four neurologists completed the survey (response rate 62%). The respondents varied regarding age and experience as a neurologist (Table 1). Twenty-five respondents worked in a university hospital and 19 respondents in a non-university hospital. The majority of respondents (71%) reported neuromuscular diseases as field of interest or expertise. Ten respondents (23%) diagnosed more than 5 CIDP patients yearly and eight (18%) had more than 10 CIDP patients under follow-up.

3.2  | Diagnosis of CIDP

Most respondents (77%) indicated that they used the EFNS/PNS 2010 diagnostic criteria for CIDP (Table 2). Various laboratory tests were performed in the diagnostic workup of CIDP to exclude other diagnoses (Figure A1). Of all respondents, 91% screened for the presence of paraproteinemia. Almost all respondents indicated that nerve conduction studies (NCS) were essential in the diagnostic workup of CIDP; however, only 57% indicated that demyelinating findings on NCS were mandatory.

Abbreviations: CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CSF, cerebrospinal fluid; EFNS, European Federation of Neurological Societies; MRI, magnetic resonance imaging; NCS, nerve conduction studies; NUS, nerve ultrasound; PNS, Peripheral Nerve Society.
to confirm a CIDP diagnosis. Cerebrospinal fluid (CSF) testing was considered mandatory for the diagnostic workup of CIDP in only 55% of respondents. This may be explained by the fact that majority of respondents considered an elevated CSF protein level not a prerequisite to confirm CIDP diagnosis. Thirty-four percent of respondents indicated that nerve ultrasound (NUS) was generally used to support or confirm CIDP diagnosis, while only 7% indicated using magnetic resonance imaging (MRI) as diagnostic tool. The minority of respondents with a non-university affiliation (42%) indicated that their general policy was to refer patients to a center of expertise to confirm CIDP diagnosis.
3.2.1 | Factors associated with diagnostic practice

The EFNS/PNS 2010 diagnostic criteria was used more often by university-affiliated respondents ($P = .07$), neuromuscular experts ($P < .01$), and respondents diagnosing more than five CIDP patients yearly ($P = .09$). Respondents who indicated that electrophysiological demyelinating features support a CIDP diagnosis but were not mandatory to confirm the diagnosis of CIDP performed NUS more often (44% vs 24%; $P = .16$), although this was not significantly associated. NUS was more often performed by university-affiliated respondents ($P < .01$), neuromuscular experts ($P < .01$), and respondents who diagnose more CIDP patients (>5) yearly ($P = .02$). A similar correlation was seen for MRI and university-affiliated respondents (3 vs 0 respondents; $P = .25$) and neuromuscular experts (3 vs 0 respondents; $P = 0.54$), although this was not significantly associated.

3.3 | Treatment of CIDP

3.3.1 | General

Thirty-four (77%) respondents indicated that they were treating CIDP patients, and half of them indicated that they used the EFNS/PNS 2010 treatment guideline. Almost all respondents indicated that fulfillment of diagnostic criteria was required to start therapy, with the exception of patients with a high clinical suspicion that did not completely fulfill these diagnostic criteria. Thirteen (68%) respondents with a non-university affiliation treated CIDP patients, of which the minority (31%) indicated that their general policy was to refer patients to a center of expertise for a treatment-related second opinion.

3.3.2 | Initial therapy

The majority of respondents (68%) indicated that they only started (induction) therapy in patients with severe signs or symptoms that interfered with daily life activities, while 32% of respondents indicated that they started therapy in all diagnosed CIDP cases. Most respondents reported IVIg as first treatment choice (82%) and corticosteroids as second choice (71%) (Figure 1), with the rapid improvement following IVIg treatment as the most important reason (54%). Of the 28 respondents who started with IVIg as initial treatment, 25 reported to start with an IVIg loading dose of 2 g/kg over two to five consecutive days.

3.3.3 | Long-term therapy

Three respondents did not divide CIDP treatment into induction and maintenance therapy and three respondents referred all patients who required maintenance treatment, leaving 28 respondents with data for specific analysis on maintenance treatment. The majority of respondents reported IVIg as first choice of maintenance treatment (96%) and corticosteroids as second choice (71%) (Figure 1), with the low risk of side effects related with IVIg treatment as the most important reason (54%).
important reason (67%). Fifty-two percent of the respondents (14/27) reported giving a dosage of 0.4 g/kg varying between once every 2 and 4 weeks, while four respondents reported giving a dosage of 1 g/kg varying between once every 3 and 4 weeks. Timing of initiation and optimizing of maintenance therapy varied. In the case of clinical deterioration, most respondents (45%) would increase the IVIg dose, whereas almost all respondents (90%) would increase the frequency in the case of wear-off signs. If a patient was clinically stable on IVIg treatment, most respondents would reduce IVIg dosage or frequency, while 10% would stop IVIg immediately. IVIg maintenance treatment was reported as given at home most of the time/always by 71% of respondents. The majority of respondents used one or more second line treatment options of which 14 respondents (11 university affiliated vs 3 non-university affiliated) reported using immunosuppressive treatments, including azathioprine, mycophenolate mofetil, rituximab, methotrexate, ciclosporine, and cyclophosphamide (Figure 2).

3.3.4 Factors associated with treatment practice

Non-university-affiliated respondents were more likely to prefer IVIg as initial therapy compared to university-affiliated respondents (71% university- vs 100% non-university-affiliated; P = .06), although this was not significantly different. Immunosuppressive drugs were more often used by university-affiliated respondents (55% university- vs 25% non-university-affiliated; P = .10) and neuromuscular experts (52% neuromuscular vs 14% non-neuromuscular experts; P = 0.10), although this was not significantly different.

4 DISCUSSION

Although the majority of Dutch neurologists used the EFNS/PNS 2010 guideline, we found considerable variation in the strategy to diagnose and treat CIDP. While most neurologists consider NCS essential in the diagnostic workup of CIDP, only 57% indicated that the presence of demyelinating electrophysiological findings was mandatory to confirm the diagnosis of CIDP. IVIg was most often used as first choice therapy and corticosteroids as second choice in the treatment of CIDP. Variation in treatment of CIDP was found when considering when to start treatment, when and how to withdraw IVIg, what to do in case of clinical deterioration during treatment, and the use of immunosuppressive treatment options. University-affiliated respondents used the EFNS/PNS 2010 diagnostic criteria, nerve ultrasound, and immunosuppressive drugs more often compared to non-university-affiliated respondents.

A cross-sectional survey was conducted recently to evaluate how neurologists from the United States diagnosed and treated CIDP.22 Corresponding with our findings, these authors reported IVIg as first choice treatment and corticosteroids as second choice in CIDP but also found variation in the neurologists’ strategy of when and how to withdraw IVIg treatment. In contrast to our study, the US study showed that the respondents were less familiar with the EFNS/PNS diagnostic criteria and only 55% of respondents reported using the EFNS/PNS recommended loading dose of 2.0 g/kg, possibly due to the lower percentage (22%) of neuromuscular experts.3

Two studies were performed to investigate adherence of the EFNS/PNS guideline for CIDP and multifocal motor neuropathy (MMN).23,24 The European study group on guidelines for neuropathy conducted a survey on compliance with the EFNS/PNS 2010 guidelines on CIDP and MMN in eight European countries and the state of Kerala in India. This study found that nearly 60% of non-neuromuscular neurologists use the EFNS/PNS guidelines to treat CIDP and MMN.23 However, the response rate of this study was low (4.2%) and a selection bias is likely to have occurred. A survey conducted among French neurologists studied the daily practice of IVIg treatment for CIDP and MMN in relation to the EFNS/PNS 2010 guideline.24 The authors of this French study concluded that these guidelines were followed. However, several discrepancies concerning IVIg treatment compared to the EFNS/PNS 2010 guideline were observed, specifically the number of induction courses without dose modification (approximately 45% >3 courses of 2 g/kg), maximum frequency of long-term treatment (76% >6 weeks), and the use of immunosuppressive drugs (40%). Furthermore, the response rate of this French study was low (17%).

In the current study, the minority of respondents diagnosed more than five patients per year. Some respondents did not screen for the presence of paraproteinemia, despite the consensus that the diagnosis CIDP cannot be made in patients with IgM anti-MAG antibodies.3 Surprisingly most respondents otherwise excluded various rare causes of a (axonal) polyneuropathy, such as beriberi or syphilis. Although the frequency of examining CSF in patients varied among neurologists, there was consensus on the interpretation of the CSF protein level. The majority of neurologists indicated that an elevated CSF protein level without pleiocytosis supported, but was not mandatory to confirm the diagnosis of CIDP, and only a few respondents mentioned diagnostic doubts in the case of a normal CSF protein level. These results may suggest that neurologists examine CSF in particular in cases of diagnostic doubts. Although demyelinating findings on NCS are considered essential for a CIDP diagnosis,3 surprisingly only 57% indicated that the presence of demyelinating findings on NCS were mandatory for a CIDP diagnosis. Apparently, many neurologists considered that the EFNS/PNS 2010 electrodiagnostic criteria are not sensitive enough to identify all CIDP patients. We did not collect information regarding the outcome measures and the definition of treatment response used in practice. Such information is important as the diagnosis of CIDP needs to be reconsidered in absence of a treatment response, especially if the electrodiagnostic requirement is not fulfilled. It would be helpful if the new EFNS/PNS guideline could specify a definition of treatment response. The availability of NUS as additional diagnostic tool in CIDP patients may also play a role. Although NUS is not considered supportive according to the current EFNS/PNS guideline, this diagnostic tool was often used, while the use of MRI was limited in our study. Results of NUS and MRI can support the diagnosis and might be particularly useful in patients with a strong clinical suspicion of CIDP that do not fulfill the full EFNS/PNS
2010 electrodiagnostic criteria.\textsuperscript{1,3,25} However, interpretation of NUS and MRI findings both require neurophysiological and radiological expertise and standardized protocols with specified reference and cutoff values are scarce.\textsuperscript{1,26–28} These limitations may explain why these modalities are less often used in non-university hospitals. Importantly, specificity of NUS and especially MRI are not optimal, thus reliance on these tools without other supportive evidence might lead to false positive CIDP diagnosis and overtreatment of patients.\textsuperscript{28}

We found variation in treatment practices that are not specifically addressed in the EFNS/PNS 2010 guideline. This guideline states that an IVIg maintenance dose of 1.0 g/kg over 1 to 2 days every 3 weeks has been shown to be efficacious, but the appropriate dose needs to be individualized (usually 0.4–1.2 g/kg every 2–6 weeks). Furthermore, it is advised to reduce the dose or frequency of IVIg if a patient becomes stable on a regimen of intermittent IVIg. However, the EFNS/PNS 2010 guideline is not fully clear about the indications to start maintenance therapy, how to optimize and reduce IVIg, and how to manage wear-off symptoms. The lack of these specific recommendations might explain some of the variation in treatment practices. A few studies on how to dose maintenance treatment for CIDP have recently been published or are currently ongoing, and may be helpful in the next version of the EFNS/PNS guideline on treatment.\textsuperscript{16,17,29–32}

About one-third of respondents indicated that they would start initial therapy in all CIDP patients irrespective of the severity of symptoms and the interference with daily life activities, while the EFNS/PNS 2010 guideline recommends only to treat patients with moderate or severe disability. Although 5% to 30% of CIDP patients only needs one IVIg course (2 g/kg) to induce remission, almost one-third of the respondents indicated starting maintenance therapy after improvement on the first IVIg induction course without subsequent deterioration.\textsuperscript{3,33} All non-university-affiliated respondents preferred IVIg as treatment. This may be biased by the fact that these centers are located in the area near the Erasmus MC and therefore may have consulted this center, where IVIg usually is preferred as a first choice treatment for CIDP. Nevertheless, most respondents indicated that their IVIg preference is due to the rapid improvement following IVIg and the low risk of side effects. Despite the absence of evidence that immunomodulatory drugs than IVIg, SCiG, corticosteroids, and PE work in CIDP, nearly half of the respondents indicated that they also use second line therapy, such as mycophenolate mofetil and rituximab.\textsuperscript{11–15}

Our study has several strengths. First, the survey was developed by experts in the field. Second, data were collected from both university and non-university affiliated neurologists to optimize generalizability of our findings. A limitation of our study was the relatively small number of respondents, although the response rate was 62%. Our study probably underestimates the variation in clinical practice as we included all non-university hospitals from a single province only, as these centers likely collaborate with one or a few neuromuscular expertise centers. Nevertheless, we think that this effect is limited, because the majority of non-university affiliated neurologists do not refer to a center of expertise. Furthermore, experienced neurologists are probably more likely to respond. In addition, we asked for general policies. However, in clinical practice, diagnostic and treatment strategies could be different and might depend on patient characteristics or CIDP variants. Finally, we realize that the use of SCiG is likely increasing since the publication of the PATH trial and that our results could be an underestimation of the current use of SCiG.\textsuperscript{12}

Despite the fact that the majority of respondents indicated to use the EFNS/PNS 2010 CIDP guideline, we found substantial variation in the diagnostic and treatment practice of CIDP among Dutch neurologists. Our findings suggest that it would be helpful if the EFNS/PNS guideline, which is currently undergoing revision, could be more specific about: (a) the minimal set of electrophysiological requirements to diagnose CIDP, (b) the possible added value of NUS and MRI in the diagnostic workup of CIDP, especially in patients not meeting the electrodiagnostic criteria, (c) the most relevant serological examinations, and (d) a clear treatment advice. In addition, strategies for implementing the guideline should be considered. We encourage to refer patients to CIDP expertise centers if they do not fulfil the diagnostic criteria, or respond poorly or not at all to proven effective treatments for CIDP, in order to reevaluate the diagnosis before further treatment options may be tried.

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FIGURE A1  Laboratory tests generally performed in the diagnostic work-up of CIDP to exclude other disorders (n = 44). ANA, antinuclear antibodies; CK, creatine kinase; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; LDH, lactate dehydrogenase; TSH, thyroid-stimulating hormone.