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Intravenous immunoglobulins in patients with clinically suspected chronic immune-mediated neuropathy

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ABSTRACT

Intravenous immunoglobulins (IVIg) are an efficacious treatment for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and multifocal motor neuropathy (MMN). IVIg is considered in patients who have a high suspicion of an inflammatory neuropathy, but do not meet diagnostic criteria. The objective of this retrospective study was to assess which diagnostic results led to the decision to administer IVIg and to determine the rate of improvement.

We included consecutive patients suspected of CIDP or MMN who did not meet the electrophysiological EFNS/PNS criteria and received IVIg treatment. Patients were included in a tertiary referral center for inflammatory neuropathies and motor neuron diseases.

Thirty-five patients were included; 19 patients suspected of CIDP and 16 suspected of MMN. Nerve hypertrophy on ultrasound (80% of patients suspected of CIDP and 67% of patients suspected of MMN) and/or elevated cerebrospinal fluid (CSF) protein (53% of patients suspected of CIDP and 45% of patients suspected of MMN) were the most frequent findings that supported the diagnosis. Thirteen patients suspected of CIDP (68%) and five patients suspected of MMN (31%) responded to treatment. There was no association between the presence of the EFNS/PNS supportive criteria, including nerve hypertrophy on ultrasound, and treatment response.

In conclusion, enlarged nerves on ultrasound and elevated CSF protein were the main reasons to start IVIg treatment in our study, although findings did not correlate with treatment response. In tertiary referral clinics, IVIg treatment could be considered in selected patients with a high suspicion of an inflammatory neuropathy, especially in those suspected of CIDP.

1. Introduction

Intravenous immunoglobulins (IVIg) are an effective, widely used treatment for chronic immune-mediated polyneuropathies such as chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN) [1,2]. Several diagnostic criteria have been proposed throughout the years to diagnose CIDP as the disease has a heterogeneous presentation and various phenotypes [3]. The European federation of Neurological societies and the Peripheral Nerve Society (EFNS/PNS) guidelines for CIDP [4] and for MMN [5] are the most widely used sets of criteria [3]. Currently, diagnosis is based on clinical characteristics and nerve conduction study (NCS) abnormalities suggestive of demyelination and conduction blocks. Several diagnostic tests can be added to increase diagnostic certainty (supportive criteria), but the electrophysiological criteria are still considered mandatory to establish the diagnosis. Both diagnostic criteria sets are regarded as suboptimal as several studies have reported patients who do not fulfill current electrophysiological diagnostic criteria, but who do respond to immunosuppressive or immunomodulatory treatment [6–8]. Response to IVIg is also considered a supportive criterion of CIDP or MMN. In clinical practice, IVIg treatment is sometimes given to patients who are suspected of having a chronic inflammatory neuropathy, but do not meet the diagnostic criteria for CIDP or MMN.

In this retrospective study, we report on 35 patients who did not meet the EFNS/PNS diagnostic criteria for CIDP or MMN and received IVIg treatment. The objectives of this study were to evaluate which diagnostic results led to the decision to start treatment, describe the treatment response in these patients, and to explore possible factors that are associated with treatment response.

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2. Methods

We retrospectively screened medical files from consecutive patients who received IVIg treatment in our tertiary referral center between 2012 and 2017. Patients were identified by using the search term IVIg in our prescription database. For technical reasons, we could not identify patients who received IVIg treatment before 2012. Therefore, we additionally performed a database search using the reports of nerve conduction studies according to the 'acquired demyelinating neuropathy' protocol performed at our center between 2006 and 2017. Reports were screened using the search key words: CIDP, MMN, block, demyelination and demyelinating. Patients were included if they had a clinical suspicion of CIDP or MMN, but did not meet the EFNS/PNS electrophysiological criteria for possible, probable or definite CIDP or the electrophysiological criteria for probable or definite conduction block for MMN, and if they received IVIg as treatment.

All clinical, diagnostic, treatment and follow-up data were extracted from medical charts. According to our local protocol, an extensive NCS protocol was performed in all patients with the differential diagnosis of an inflammatory neuropathy (CIDP, MMN of IgM related neuropathy) and/or isolated lower motor neuron disorder. This NCS protocol was not performed if there were bulbar symptoms or pathological reflexes on clinical examination. The NCS protocol included testing of the motor median, ulnar, radial, musculocutaneous, peroneal and tibial nerve at both sides after warming up. The median, ulnar and musculocutaneous nerves were tested up to Erb's point. Sensory testing included the median, ulnar, radial and sural nerve on both sides. An experienced clinical neurophysiologist who was blinded for final diagnosis and treatment outcome reassessed NCS results.

Furthermore, we focused on diagnostic tests that are used to fulfill the supportive criteria according to the EFNS/PNS guidelines and the nerve ultrasound results. We considered the cerebrospinal fluid (CSF) protein to be elevated above 0.5 g/l. For the somatosensory evoked potentials in CIDP patients we used the normative values of our laboratory. An experienced neuropathologist performed pathological examination of nerve tissue and reported whether abnormalities were compatible with the diagnosis of CIDP. Antibodies against GM1 were assessed in a central laboratory (Erasmus Medical Center). Nerve ultrasound is routinely performed in our centre since 2013. For assessment of the nerve ultrasound results of the arm and leg nerves we used the upper range values defined by Kerasnoudis et al. [9] For the brachial plexus we used the normal range values defined by Haun et al. [10] For this study, nerve ultrasound data were reanalyzed based on the upper limits of nerve size in patients with axonal neuropathies as defined by Goedee et al. [11].

All patients received an IVIg loading dose of 2 g/kg and at least one additional IVIg dose of 1 g/kg after three to four weeks. Treatment response was defined as any improvement on impairment or disability scales and the decision of the treating physician to continue IVIg treatment. The impairment scales included the Medical Research Council (MRC) sum score and grip strength (Vigorimeter). The MRC sum score included shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension and ankle dorsiflexion (range: 0–60). Disability was scored using the Modified Ranking Scale (mRS). Treatment response was assessed within three months after start of treatment.

We used descriptive statistics to assess the treatment response in patients with a clinical suspicion of CIDP and patients with a clinical suspicion of MMN. We compared the treatment response between patients suspected of CIDP and MMN. Furthermore, we compared the presence of abnormalities on the diagnostic tests used to fulfill the supportive criteria for CIDP or MMN and on nerve ultrasound between responders and non-responders. For these analyses we used the Fisher's exact test and the Mann-Whitney *U* test, where appropriate. A *P*-value of < 0.05 was considered statistically significant. Analyses were performed using SPSS software version 24.

3. Results

A total of 262 IVIg prescriptions and 686 nerve conduction study reports were found. This led to a total screening of 847 unique patient files. A total of 216 patients presented with lower motor neuron syndromes, of which we excluded 49 patients who met the diagnostic criteria for MMN and 151 patients who were diagnosed with motor neuron disease (i.e. segmental or progressieve spinal muscle atrophy). Of the remaining 631 patients, we excluded 139 patients who met the EFNS/PNS electrophysiological criteria for CIDP and 473 patients who had an alternative diagnosis (i.e. axonal polyneuropathy or demyelinating neuropathy due another cause) or who were treated with IVIg for another reason than a neuropathy.

Thirty-five patients were included in this study, 19 patients (54%) had a clinical suspicion of CIDP and 16 patients (46%) had a clinical suspicion of MMN. Twenty-one patients (60%) were male, and median age was 50 years (range 19–85 years). The median duration of follow up was 31 months (range 3–91).

Seven patients (37%) suspected of CIDP presented with a typical phenotype, seven patients (37%) presented with a multifocal phenotype, four patients (21%) presented with a pure sensory phenotype and one patient (5%) had a pure motor phenotype.

All patients suspected of MMN presented with upper limb weakness. Twelve patients (75%) presented with weakness in one arm. Four patients (25%) presented with weakness in both arms.

In patients suspected of CIDP, enlarged roots or nerves on nerve ultrasound (80%) and an elevated CSF protein (53%) were the most frequent findings that supported the diagnosis (Table 1). In patients suspected of MMN enlarged roots or nerves on nerve ultrasound (67%), elevated CSF protein (45%) and hypertrophy and/or hyperintensity on MRI (44%) were the most frequent found supportive criteria (Table 1).

Using the upper limits for axonal neuropathies [11], nerve ultrasound was supportive of an acquired inflammatory neuropathy in all patients, based on enlargement of (some part of) the brachial plexus.

In two patients suspected of CIDP no supportive criteria were found. The decision to start treatment was made based on NCS abnormalities that just did not meet the electrophysological criteria for demyelinating neuropathy. One patient had a prolonged F-wave latency with a normal compound muscle action potential (CMAP) amplitude and one patient had slow conduction velocities with normal CMAP amplitudes. Both patients responded to therapy.

Three patients suspected of MMN had no supportive criteria. The decision to start treatment was also made based on NCS abnormalities suggestive of demyelination. In one patient abnormal temporal dispersion and an absent F-wave were found, but no conduction blocks. In two patient abnormalities suggestive of a conduction block were found, however CMAP amplitudes were just below 1 mV. None of these three patients responded to therapy.

Thirteen out of 19 patients (68%) with a clinical suspicion of CIDP and five out of 16 patients (31%) with a clinical suspicion of MMN (*p-value 0.04*) responded to treatment. Improvement on impairment and disability is shown in Table 2. There was no difference in clinical CIDP phenotypes between responders and non-responders. Four patients suspected of CIDP (21%) had a relapsing course of disease, all responded to treatment. Diagnostic test results of all patients are summarized in Table 1. There were no differences in the rate of abnormalities on performed diagnostic tests between responders and non-responders in both groups (Table 1). The total number of supportive criteria did not differ between responders and non-responders for both groups. The number of patients with enlargement of the brachial plexus only did not differ between treatment responders and treatment non responders (*p value 0.45*) in both groups.

At last known follow up, the median duration of IVIg treatment was 27 months (range 2–81). IVIg withdrawal was attempted in six patients with clinical CIDP and was successful in three patients. Treatment withdrawal was attempted in two patients with clinical MMN, and was

Table 1
Diagnostic test results.

	CIDP				MMN			
	(N = 19)	R (N = 13)	NR (N = 6)		(N = 16)	R (N = 5)	NR (N = 11)	
	n/N (abnormal/tested (%))[a]			P-value[b]	n/N (abnormal/tested (%))[a]			P-value[b]
Hypertrophy on nerve ultrasound	12/15	7/9(78%)	5/6(83%)	1.0	6/9	3/3(100%)	3/6 (50%)	0.46
Hypertrophy of brachial plexus		3/9 (33%)	2/6 (33%)			3/3 (100%)	1/6 (17%)	
Hypertrophy of median nerve		1/9 (11%)	0/6			0/3	0/6	
Hypertrophy of plexus and nerves		3/9 (33%)	3/6 (50%)	1.0		0/3	2/6 (33%)	0.4
Lumbar Puncture	19/19				11/16			
Median Protein (g/l, range)		0.66 (0.21–1.47)	0.58 (0.18–1.04)	0.80		0.37 (0.28–0.79)	0.45 (0.31–0.90)	0.65
Number of patients with elevated protein (> 0.5 g/l)	10/19	7/13 (54%)	3/6 (50%)	1.0	5/11	1/4 (25%)	4/7 (57%)	0.55
Number of patients with elevated protein (> 1 g/l)	2/10	1/13 (8%)	1/6 (17%)	1.0		NA	NA	
Sensory demyelinating abnormalities on NCS	3/19	1/13 (8%)	2/6 (33%)	0.22		NA	NA	
Hypertrophy and/or hyper intensity on plexus MRI	3/14	2/11 (18%)	1/3 (33%)	1.0	7/16	3/5 (60%)	4/11 (36%)	0.59
Abnormalities on nerve biopsy (supporting diagnosis CIDP)	1/3	1/2 (50%)	0/1 (0%)	NT	–	NA	NA	NA
Prolonged latencies on SSEP	1/3	0/1(0%)	1/2 (50%)	NT	–	NA	NA	NA
Presence of anti GM1 IgM antibodies	–	NA	NA	NA	2/12	2/5 (40%)	0/7 (0%)	NT
N of supportive criteria: Median (range)		1.0 (0–3)	1.5 (1–5)	0.37		2 (1–3)	1 (0–2)	0.09
0		2 (15%)	0			0	3 (27%)	
1		6 (46%)	3 (50%)			2 (40%)	6 (55%)	
≥2		5 (38%)	3 (50%)	0.65		3 (60%)	2 (18%)	0.31

Abbreviations: MRI: Magnetic resonance imaging; N: number; NA: not applicable; NT: not tested; NR: non responder; R: responder; SSEP: somatosensory evoked potential;
[a] Number of abnormal test results/number of tests performed.
[b] Abnormal test results compared between responders and non responders.

Table 2
Clinical outcome in responders and non-responders.

	CIDP (N = 19)		MMN (N = 16)	
	Baseline	After treatment	Baseline	After treatment
Responders	N = 13		N = 5	
Median MRC sum score (range)	56 (48–60)	60 (50–60)	57 (50–59)	60 (57–60)
Modified Ranking Scale				
Median (range):	2 (1–4)	2 (1–3)	2 (1–4)	1 (1–2)
mRS 1–2:	77%	92%	80%	100%
mRS 3–5	23%	8%	20%	0%
Median Grip strength[a] (range)	55 (42–95)	74 (50–105)	[b]	[b]
Non-responders	N = 6		N = 11	
Median MRC sum score (range)	59.5 (54–60)	60 (44–60)	56 (48–60)	52 (38–60)
Modified Ranking Scale				
Median (range):	2.5 (1–34)	3 (1–4)	2 (1–4)	2.5 (1–4)
mRS 1–2:	50%	33%	70%	50%
mRS 3–5:	50%	67%	30%	50%
Median Grip strength[a] (range)	70 (44–105)	54 (40–103)	55 (50–60)	55 (50–60)

Abbreviations: MRC: Medical Research Council; mRS: modified Rankin scale.
[a] Grip strength of most affected hand in kilo Pascal (kPa).
[b] Grip strength was not available.

successful in one patient.

The final diagnosis in patients with a clinical suspicion of CIDP who did not respond to treatment was: chronic ataxic neuropathy ophthalmoplegia M-protein agglutination disialosyl antibodies syndrome (CANOMAD) in one patient and motor neuron disease (MND) in another patient. The diagnosis remained unclear in four patients. All these four patients received additional corticosteroid therapy. None of these patients responded.

The final diagnosis in patients with a clinical suspicion of MMN who did not respond to treatment was MND in eight patients (73%). Of these patients, three patients were diagnosed with amyotrophic lateral sclerosis (ALS), three patients with segmental spinal muscle atrophy, one patient with progressive spinal muscle atrophy (PSMA) and one patient with Hirayama disease. These patients are characterized in Table 3. In one patient spinal leptomeningeal metastases were found and in one patient multiple mononeuropathy possibly associated with IgM MGUS. The latter patient also did not respond to rituximab treatment. The diagnosis remained unclear in one patient who was lost to follow up.

4. Discussion

In this study, enlarged nerves on nerve ultrasound and an elevated CSF protein were the most frequent diagnostic tests that supported the clinically suspected diagnosis of CIDP or MMN leading to the decision to start IVIg treatment. There was a higher rate of improvement in those with a clinical suspicion of CIDP than those with a clinical suspicion of MMN. The number of supportive criteria did not differ between treatment responders and treatment non-responders.

It has been suggested before that CIDP can be diagnosed in the absence of demyelinating features on NCS. Koski and collegues developed a set of criteria to diagnose CIDP based on a typical clinical presentation of symmetric proximal and distal weakness and absent reflexes [12]. However, an important part of CIDP patients present with an atypical presentation limiting sensitivity of these criteria. Alternatively,the EFNS/PNS criteria for CIDP also include these atypical clinical phenotypes but require the precense of at least one demyelinating feature in one nerve for diagnosis. Eventough the EFNS/PNS criteria have a higher sensitivity than previous criteria sets, several reports have emphasized that not all patients who respond to immunosuppressive or immunomodulating treatment are identified by these criteria [3,6]. In particular patients with the pure sensory CIDP phenotype can have normal motor NCS, in which case the diagnostic criteria cannot be met [13]. Similarly, to fulfill the EFNS/PNS electrophysiological criteria for MMN at least a probable block has to be found. Whether conduction blocks should be mandatory for the diagnosis of MMN is subject to debate ever since the first reports of MMN [14]. Other diagnostic criteria have been proposed that are less strict

Table 3
Clinical presentation of patients diagnosed with MND.

Patient	Age	Weakness at presentation	CNS involvement	Supportive criteria	Final diagnosis
1	22	Both arms	No	MRI abnormalities	PSMA
2	19	Right lower arm	No	MRI abnormalities	Hirayama
3	65	Both arms	No	–	ALS
4	38	Right arm	No	MRI abnormalities	Segmental SMA
5	69	Both arms	No	–	ALS
6	71	Left arm	No	CSF protein Nerve ultrasound	ALS
7	74	Right hand	No	–	Segmental SMA
8	40	Right arm	No	CSF protein	Segmental SMA

Abbreviations: CNS: central nervous system, PSMA: progressive spinal muscular atrophy, ALS: amyotrophic lateral sclerosis, SMA: spinal muscular atrophy.

and also included other demyelinating features than conduction blocks [15–17]. The term MMN without conduction blocks has also been introduced [18]. However, it is unlikely that this is a different disease as they share the same clinical presentation, treatment response and long-term prognosis [7].

Recently, nerve ultrasound has shown very promising results in diagnosing CIDP and MMN [10,11,19]. Goedee and colleagues found a sensitivity of 95% and a specificity of a 100%, suggesting that ultrasound of the median nerve and the brachial plexus can reliably detect and distinguish inflammatory neuropathies from other causes such as ALS or axonal polyneuropathy [20]. In our study, a high percentage of patients screened with nerve ultrasound had enlarged nerves, but treatment response did not differ. When using the cut-off values for the brachial plexus from the Goedee criteria, we found that all patients in our cohort had enlarged nerves, suggesting these cut-off values of the brachial plexus might be too low to reliably distinguish between inflammatory neuropathies and other diagnosis in our cohort. When applying more conservative cut-off values for the brachial plexus [10], isolated enlargement of the brachial plexus was found in almost half of our patients. A possible explanation for this high percentage of patients with nerve enlargement might be that the Goedee study included patients with a clear-cut diagnosis of CIDP, MMN, ALS or axonal polyneuropathy, while we included only patients where there was clinical doubt. Furthermore, the Goedee study did not specifically address treatment response. Our results suggest that nerve enlargement has a less than perfect positive predictive value to identify patients responding to IVIg. It is however also important to emphasize that not all patients with CIDP and MMN respond to IVIg, so absence of response does not preclude the diagnosis CIDP and MMN. Currently, nerve ultrasound criteria are being studied in different conditions to better define its diagnostic accuracy. In this regard, it was shown that interobserver variability of nerve ultrasound in peripheral neuropathy is good, although variability was higher for the brachial plexus and nerve roots than for the arm nerves [21]. These findings emphasizes critical interpretation of brachial plexus and nerve roots abnormalities, especially when there are no other abnormalities in the arms.

In three patients with a final diagnosis of MND, IVIg treatment was started because of hypertrophy or hyperinsity of the brachial plexus on MRI. It has been reported that MRI can be useful in distinguishing MMN from MND [22]. However, more recent studies have shown that both hyperintensity and hypertrophy of the brachial plexus was also frequently found in patients with ALS. This suggests that MRI results should be carefully interpreted and might not be very usefull in deciding to start IVIg treatment in these patients.

Cytoalbuliminologic dissociation is often found in CIDP patients [23]. In this study, about half of patients had elevated CSF protein, altough elevation was mild (< 1 g/l) in the majority of patients. Allen and collegues found that half of patients who were misdiagnosed with CIDP, had a mild elevated CSF protein (< 1 g/l). This suggests that clinicians should be careful to put too much weight on slightly elevated CSF protein.

The rate of abnormal tests that are considered as EFNS/PNS supportive criteria did not differ between the treatment responders and non-responders. Furthermore, the number of supportive criteria did not differ between responders and non-responders. Given the low prevalence of MMN and CIDP, and the relatively frequent false positive rate of the supportive criteria and nerve ultrasound, we would also like to emphasize the suboptimal positive predictive value of these parameters. Unfortunately, we were not able to calculate the positive predictive value based on this study, as not all diagnostic tests were performed in all patients in whom an inflammatory neuropathy was considered.

Our data suggest that IVIg treatment can be a potential strategy to identify an IVIg-responsive chronic inflammatory neuropathy in patients in whom diagnostic uncertainty remains after full diagnostic work-up, especially in those patients with a clinical suspicion of CIDP. The rate of improvement in patients with a clinical suspicion of CIDP is similar to the rate of improvement reported in the literature [1,24]. The response rate in patients with a clinical suspicion of MMN is much lower compared to the rate of improvement reported in the literature [2]. Motor neuron disease is the most important differential diagnosis in these patients and it is often difficult to distinguish MMN from MND with pure lower motor neuron involvement. For this reason, some authors have advocated an IVIg test treatment in these patients, as unlike MND, MMN is a treatable disease. Burrell and colleagues even suggested to give an IVIg test treatment to all patients who present with isolated lower motor neuron syndromes, however they also report that treatment response might be associated with predominant upper limb involvement [25]. There is a very large difference in reported response to IVIg treatment in these patients, varying from 10 to 78%, which probably illustrates a different selection of patients [25–27]. In this study we only treated patients with weakness in upper limb(s). It should be emphasized that we treated < 10% of patients with a diagnosis of lower motor neuron disease and that there was a relatively low response rate of 31% despite thourough selection of patients.

Alternatively, CIDP misdiagnosis is a problem, leading to IVIg overuse and increasing costs for patients and society. Allen and colleagues found that almost 50% of patients reffered with a diagnosis of CIDP, were misdiagnosed, but nevertheless received IVIg treatment [28]. Improvement after IVIg treatment was reported in the majority of these patients. The improvement was mainly on subjective scales, which underlines the importance of the use of objective disability and impairment scales when prescribing treatment. Therefore, it should be emphasized that all patients in this study were included in a tertiary referral center for both inflammatory neuropathies and motor neuron disease. In addition to supportive criteria, the choice of administrating treatment of IVIg at the end was primarily based on the a priori clinical suspicion of whether these patients had a chronic inflammatory neuropathy, rather than an alternative diagnosis. Unfortunately, the reasons that led to the clinical suspicion of a chronic inflammatory neuropathy were not systemicially recorded in the medical files. We therefore recognise that the level of clinical suspicion was probably based on poorly defined clinical ‘red flags’ supporting the diagnosis of chronic inflammatory neuropathy, or against the most common alternative diagnoses such as axonal polyneuropathy in case of CIDP, and motor neuron disease in case of MMN. In addition, this study illustrates the suboptimal positive predictive value of the supportive criteria and ultrasound for treatment response. For all these reasons, the results of this study are not generalisable to non-referral clinics for inflammatory neuropathies and motor neuron diseases. If an inflammatory neuropathy is supected, a neuromusculair specialist with expertise in these diseases should be consulted prior to starting IVIg treatment.

Another limitation of this study is the small number of patients, reflecting the low incidence rates of these diseases. Furthermore, data was collected retrospectively and there were no pre-defined criteria for selecting patients that received treatment, which could have led to a selection bias. Inherent to the retrospective design of the study, the number of additional diagnostic tests was at the discretion of the treating physician, as was the evaluation of treatment outcome. As not all tests were performed in all patients, it is difficult to speculate on the additive value of the particular diagnostic tests and the number of abnormal tests that are needed to make the choice whether to start treatment. Finally, there was no standardized evaluation of treatment outcome. By defining treatment response as any improvement on an objective impairment or disability scale, this study may have overestimated treatment response, especially compared to treatment response rates found in randomized trials that are based on predefined cut-off's on disability scales. For this reason, we included also the physicians' judgement to continue IVIg treatment, hopefully reflecting improved functioning and participation of patients rather than only improvement on impairment scales. Because there was no standardized follow up of these patients, no validated disability scales for CIDP and MMN such as the inflammatory Rasch Overall Disability scale were available. Nevertheless, the improvement on the mRS suggests that improvement was not limited to impairment only.

In conclusion, in patients with a clinical suspicion of CIDP or MMN, who do not meet the EFNS/PNS electrodiagnostic criteria for CIDP or MMN, but were treated with IVIg, enlarged nerves on ultrasound and an elevated CSF protein were the most frequent found supportive criteria for the diagnosis of an inflammatory polyneuropathy. In this highly selected population, two thirds of patients with clinical suspicion of CIDP and almost one third of patients with clinical suspicion of MMN, showed improvement on impairment and/or disabilitiy after IVIg treatment. The presence of supportive criteria including enlarged nerves on ultrasound did not differ between treatment responders and non-responders, illustrating its suboptimal predictive value for treatment response to IVIg. More specifically, this study highlights the need of higher sensitivity of the diagnostic criteria for CIDP and MMN and confirmation of the specificity of nerve ultrasound, especially of the brachial plexus. Awaiting improvement of these diagnostic criteria, we believe that IVIg might be considered in patients who have a high clinical suspicion of an inflammatory neuropathy and fulfill only supportive criteria but not the current electrophysiological criteria. Given the setting of this study, the decision to start an IVIg treatment should be made by a neuromuscular expert, and follow-up should include objective outcome measures to evaluate treatment response.

Disclosure of conflict of interest

Ilse M. Lucke has nothing to disclose, Max E. Adrichem has nothing to disclose, Luuk Wieske has nothing to disclose, Anneke J. van der Kooi reports grants from CSL Behring, outside the submitted work, Camiel Verhamme has nothing to disclose. Ivo N. van Schaik reports departmental honoraria from CSL-Behring and from UCB, outside the submitted work; He received departmental research support from The Netherlands Organization for Scientific Research and from the Dutch Prinses Beatrix Spierfonds. Filip Eftimov reports grants from Prinses Beatrix Spierfonds, Netherlands Organization for Health Research and Development, and a consulting fee from CSL Behring, UCB Pharma and Aserta Pharma that was paid to Institution, outside the submitted work.

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