Challenges in the diagnosis and treatment of chronic inflammatory demyelinating polyneuropathy

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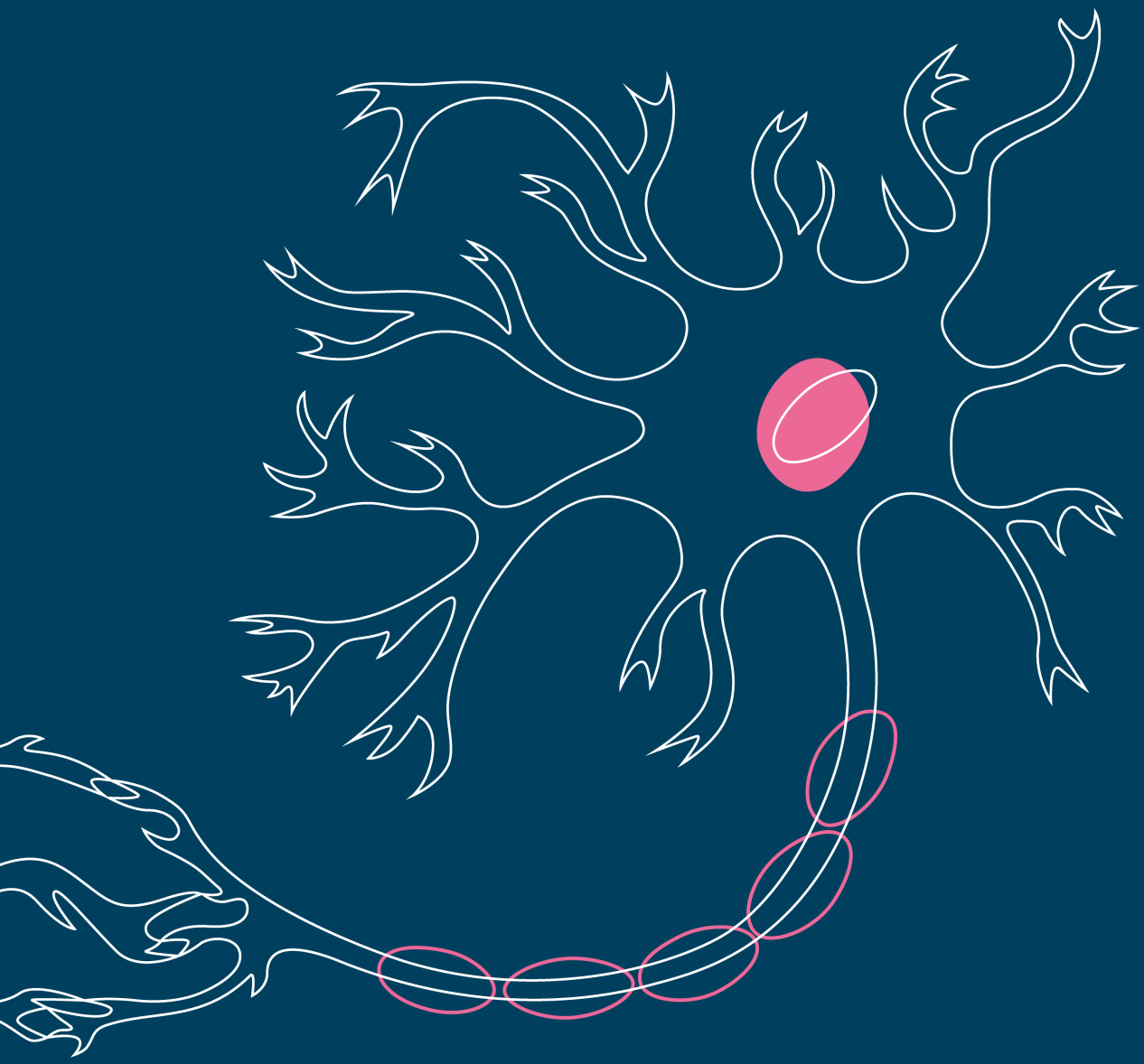

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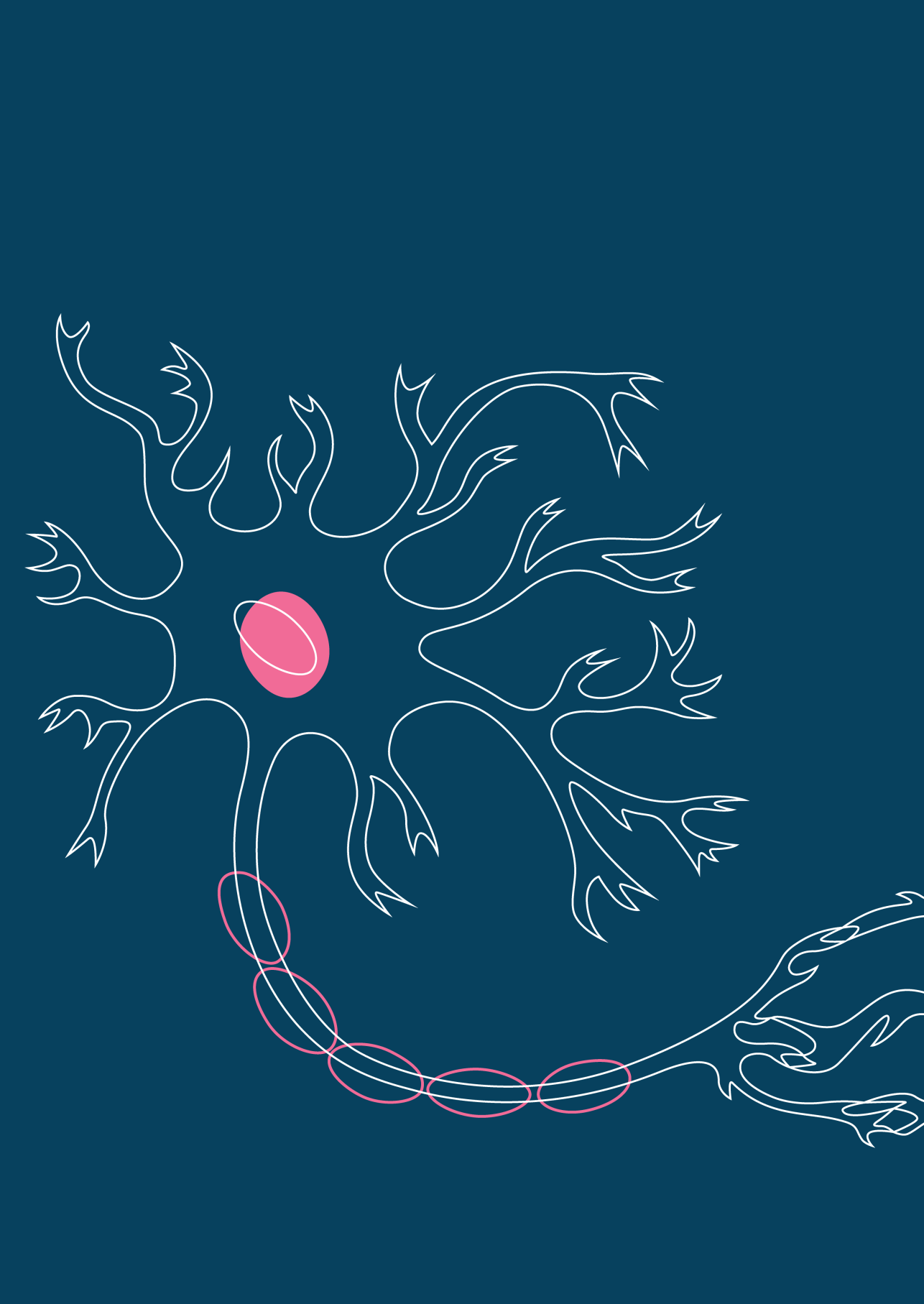
TABLE OF CONTENTS



General introduction and outline of this thesis

Adapted from: Filip Eftimov[1], Ilse M Lucke[1], Luis A Querol[2,3], Yusuf A Rajabally[4], Camiel Verhamme[1]. Diagnostic challenges in chronic inflammatory demyelinating polyradiculoneuropathy.

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Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) consists of a spectrum of immune-mediated neuropathies, causing weakness and sensory symptoms in a progressive, relapsing-remitting or monophasic way.[1] Typical CIDP is defined as proximal and distal symmetric weakness and sensory dysfunction of all extremities, with absent or reduced tendon reflexes in all four limbs. Signs and symptoms typically progress over months. Typical CIDP accounts for more than half of CIDP cases.[2] According to the EFNS/PNS 2010 criteria atypical CIDP may be divided, based on clinical presentation, in an asymmetric, focal, distal, pure motor and pure sensory variant.[1]

CIDP often leads to significant disability. At some point during their illness, 54% of patients is dependent on help for attending bodily needs and walking.[3] Early diagnosis is therefore important, as start of treatment can quickly improve signs and symptoms and relieve disability. Furthermore, early start of treatment prevents development of axonal damage and permanent disability.[3-7] However, arriving quickly at a CIDP diagnosis is often challenging because of the heterogeneous presentation. Currently, clinical presentation and nerve conduction studies (NCS) play a leading role in diagnosing CIDP. These main features may be supplemented with diagnostic tests such as cerebrospinal fluid (CSF) examination, MRI of the brachial plexus, nerve biopsy and somatosensory evoked potentials (SSEP).[1] Recently, nerve ultrasound and testing for autoantibodies were introduced also as potentially helpful in making a diagnosis.[8,9] All diagnostic tests have their pitfalls and should be interpreted in their clinical context, and alternative causes of a demyelinating neuropathy should be considered before making the diagnosis.

Nerve conduction studies

The diagnosis of CIDP relies heavily on identification of demyelinating features on motor NCS. The electrophysiological demyelinating features are markers for functional disruption or slowing of the saltatory conduction of the myelinated axons. Based on the amount and certainty of demyelinating features, this will lead to a definite, probable or possible electrodiagnosis according to the EFNS/PNS 2010 criteria.[1] Recent studies highlighted the importance of correct interpretation of NCS and electrodiagnostic criteria, as interpretation errors were shown to often lead to misdiagnosis.[10,11] One of the main pitfalls is that the electrophysiological criteria are sensitive to diagnose a demyelinating neuropathy, but lack specificity. As such these criteria may also be fulfilled in other diseases. Alternatively, severe axonal loss can

have a profound influence on nerve conduction velocity hampering distinction of demyelinating features, leading to underdiagnosis.

NCS can be time consuming and painful for patients. In clinical practice the order and extensiveness of NCS vary widely. The guideline advises to first test the median and ulnar nerve at one forearm and the fibular and tibial nerve of one lower leg, and then extend the investigation if necessary.[1] The guideline does not distinguish between typical and atypical CIDP and it is unknown whether this advice is also the best strategy for atypical CIDP variants. Additionally, if too few nerve segments are tested, this may lead to underdiagnosis and this may be even more pronounced in the atypical asymmetric cases.

CSF examination

Elevated protein in the CSF with normal leucocytes is found in up to 90% of patients with typical CIDP.[12-14] In atypical CIDP variants such as the asymmetric subtype, protein elevation might be less pronounced, or even absent.[15] It is unclear which amount of leukocytes is still compatible with the diagnosis CIDP and how extensive the diagnostic work-up should be in patients with a demyelinating neuropathy and pleocytosis. Nevertheless, if an elevated leucocyte count (>10/mm3) is found, infections or malignancies should be considered and ruled out.

Imaging

MRI of the brachial plexus and nerve ultrasound can be an addition in the diagnostic work-up, although nerve ultrasound is not part of the EFNS/PNS 2010 guidelines.[1] The advantage of nerve imaging is the ability to assess the proximal part of the brachial plexus and nerve roots, while these regions cannot be studied with NCS. MRI can also asses the lumbosacral plexus. In both techniques, one of the main parameters to be assessed, is nerve size.[16] It is noteworthy that nerve hypertrophy is not an exclusive phenomenon for acquired inflammatory neuropathies and may be seen in other relatively prevalent diseases such as diabetes mellitus, hereditary demyelinating neuropathies and neuralgic amyotrophy.[17-19] A recent study showed that qualitative measures of the typical MRI findings of nerve hypertrophy and signal hyperintensity on MRI were of limited value in diagnosing CIDP, as this was also found in other diseases and healthy controls. Additionally, a high variability of intra observer agreement was shown. On the other hand, more quantitative imaging measures obtained with MRI such as diffusion tension imaging were shown to be

able to discriminate between inflammatory neuropathies and controls.[20] In this study, measuring the cross sectional area of nerves with ultrasound was also able to discriminate between inflammatory neuropathies and controls.[20] The high sensitivity of ultrasound was also highlighted in other studies.[8,21] In addition, limited intra- and interobserver variability was shown for nerve ultrasound.[22] This combination makes ultrasound a promising new diagnostic tool with also the advantage that it is relatively quick, easy and patient-friendly to perform. In addition, a previous study has shown that ultrasound was of additional value in comparison to NCS only in identifying patients with an inflammatory neuropathy. Patients with a high clinical suspicion, that did not meet the electrodiagnostic criteria and responded to treatment could be identified by ultrasound.[21]

Somatosensory evoked potentials

SSEP may be useful in diagnosing CIDP, especially in the sensory (predominant) variants. SSEPs are used to assess the functioning of the whole sensory pathway, including the nerve roots. The evidence that supports the use of SSEP in diagnosing CIDP is limited.[23-26] In clinical practice, SSEP should be considered in patients with predominant sensory ataxia and areflexia, if the electrodiagnostic criteria are not fulfilled.[27,28]

Nerve biopsy

Whether nerve biopsy has additional value in diagnosing CIDP has long been a matter of debate. It was suggested that none of the biopsy findings were specific for CIDP, as these findings were also found in vasculitis, axonal and demyelinating hereditary neuropathies and monoclonal gammopathies.[29] Other studies also showed that nerve biopsies failed to differentiate between CIDP and axonal neuropathies or diabetic neuropathies.[30-32] Some studies suggested that there might be some value in atypical CIDP cases.[28,33] Nerve biopsy is considered invasive and will lead to persisting sensory loss in most patients, while persisting pain, infections and dysesthesias have also been reported in a minority of patients.[34,35] Nerve biopsy should only be considered in very selected cases, in which diagnostic uncertainty remains based on other examinations.

Autoantibodies

The search for pathogenic autoantibodies has always been an important topic of research in CIDP. However, only just recently, subgroups of CIDP patients with

antibodies targeting the nodes of Ranvier and paranodal regions have been described.[9,36] The discovery of these antibodies, associated with antibody-specific clinical features, boosted a renewed interest in the role of antibodies as diagnostic and prognostic biomarkers. In general, antibodies to nodal and paranodal proteins are associated with a subacute onset and more progressive CIDP phenotypes, initially often classified as Guillain-Barré syndrome, and poorer responses to immunoglobulins than patients without these autoantibodies.[9,37] Testing for antibodies is not yet part of the standard diagnostic work-up as this is not widely available yet. At this point antibody testing is mostly considered in treatment unresponsive patients, especially in the presence of atypical symptoms such as a subacute onset, severe ataxia, pain or tremor. In case of a distal phenotype and treatment unresponsiveness, M-protein reanalysis and anti-myelin-associated glycoprotein (MAG) antibodies should be considered.

Challenges in CIDP diagnosis

Despite all these diagnostic tools, CIDP diagnosis remains challenging and in clinical practice both mis- and underdiagnosis are common. Misdiagnosis is reported in up to 50% of patients referred to a tertiary referral center with a CIDP diagnosis,[10] possibly leading to the inappropriate use of expensive and potentially harmful treatment. Underdiagnosis is reported in up to 20% of patients and means that patients may not get effective treatment.[10,28,38,39] In patients with a typical presentation of proximal and distal weakness, diagnosing CIDP is often straightforward. It was even suggested that in such cases a diagnosis could be made based on this typical presentation without further support of nerve conduction studies.[40] However, as various rare diseases can mimic both the clinical and neurophysiological characteristics of CIDP, these diseases should always be considered and ruled out with ancillary investigations, especially if patients do not respond to treatment.[41] Diagnosis becomes more challenging if patients have an atypical presentation and this has been reported as an important factor for both mis- and underdiagnosis.[10,39] However, even in patients with a typical presentation diagnosis can be complicated by inconclusive results of the diagnostic tests, such as NCS showing severe axonal damage, or the incorrect interpretation of diagnostic tests.

Treatment

Intravenous immunoglobulins (IVIg), corticosteroids and plasma exchange are all efficacious first line treatments for CIDP.[5-7] IVIg treatment leads to quick improvement and is often the first choice of treatment in Western countries.

CIDP treatment can be divided into induction treatment and maintenance treatment. The goal of induction treatment is to induce remissions (i.e. sustained improvement after stopping treatment) and if that is not possible to improve impairment and reduce disability as much as possible. In most patients maintenance treatment is necessary to retain the improvement in impairment and disability and prevent deterioration. Most of the treatment studies in CIDP have focused on induction treatment, and studies on maintenance treatment are scarce. A meta-analysis of IVIg trials showed that IVIg reduces disability in 54% of patients with CIDP in the first 6 weeks.[5] In patients who respond to treatment, improvement is usually observed within the first 6 weeks, but further improvement is still possible in the first 6 months.[42] In only 15% of patients, 1 or 2 induction IVIg treatments are sufficient and no maintenance therapy is necessary.[43,44] Induction with steroids can be achieved with both daily prednisolone and pulses of dexamethasone or methylprednisolone.[45,46]

Evidence of IVIg efficacy as maintenance treatment is provided largely by retrospective observational studies. The first trial showing effectiveness of IVIg beyond induction treatment was the extension phase of the ICE trial in which patients previously responding to IVIg were randomized for IVIg treatment or placebo.[47] This study showed that patients on maintenance IVIg dose of 1g/kg per 3 weeks did not deteriorate as often as patients randomized for placebo.[47] However, it was also shown that maintenance therapy is not necessary in all CIDP patients as around half of patients randomized for placebo remained stable during study follow up. Even though maintenance therapy in CIDP has proven to be effective, very little is known about the dose, interval and duration IVIg should be given in. Treatment guidelines provide only rough recommendations on maintenance treatment, without specific instructions on when and how to change or stop treatment. For these reasons, finding the right dose for an individual patients is often a process of trial and error. In the trials a maintenance dose of 1 g/kg every 3 weeks was often used to minimize doubt about efficacy. In practice, the total IVIg dose required (grams IVIg/month) appears to vary greatly between patients.[48,49]

Importantly, CIDP is a disease with a variable course, including spontaneous remissions. There have been several studies comparing different types of treatment for CIDP with placebo in patients who were previously stable on IVIg. Interestingly, up to 40% of patients randomized for placebo remained stable without treatment for the duration of these studies.[47,50,51] Even though these studies were not designed to study overtreatment with IVIg, they suggested that patients might be frequently overtreated. Unfortunately, identifying patients who are no longer dependent on IVIg treatment is difficult as no biomarkers for disease activity are available. Also, both patients and their treating physicians can be reluctant to stop treatment because of the risk of deterioration as much is still unknown about how soon patients recover after a withdrawal attempt.

OUTLINE OF THIS THESIS

Following the general introduction, **chapter 2** contains a retrospective study on patients with the asymmetric CIDP variant. The diagnostic value of testing clinically affected and unaffected limbs was assessed and a NCS strategy to diagnose the asymmetric CIDP variant was proposed. Also, treatment response and long-term outcome in these patients was described. In **chapter 3,** we describe a series of patients diagnosed with CIDP according to the EFNS/PNS 2010 diagnostic criteria, in whom an elevated CSF leukocyte count was found. In **chapter 4,** blood samples of patients before and after IVIg treatment were examined to determine how often IVIg treatment leads to apparent seroconversion for Borrelia Burgdorferi antibodies. In **chapter 5,** we describe patients who had a high clinical suspicion of an inflammatory neuropathy but did not meet the EFNS/PNS 2010 diagnostic criteria and were treated with IVIg. We evaluate which diagnostic results led to the decision to start treatment and we describe the treatment response in these patients.

To identify how often CIDP patients are overtreated and if IVIg withdrawal is safe, we compare IVIg withdrawal to continuing IVIg treatment in a double blinded randomized controlled non-inferiority trial (IOC trial) in **chapter 6.** In **chapter 7,** the findings of these thesis, the implications on current practice and recommendations for future research are discussed.

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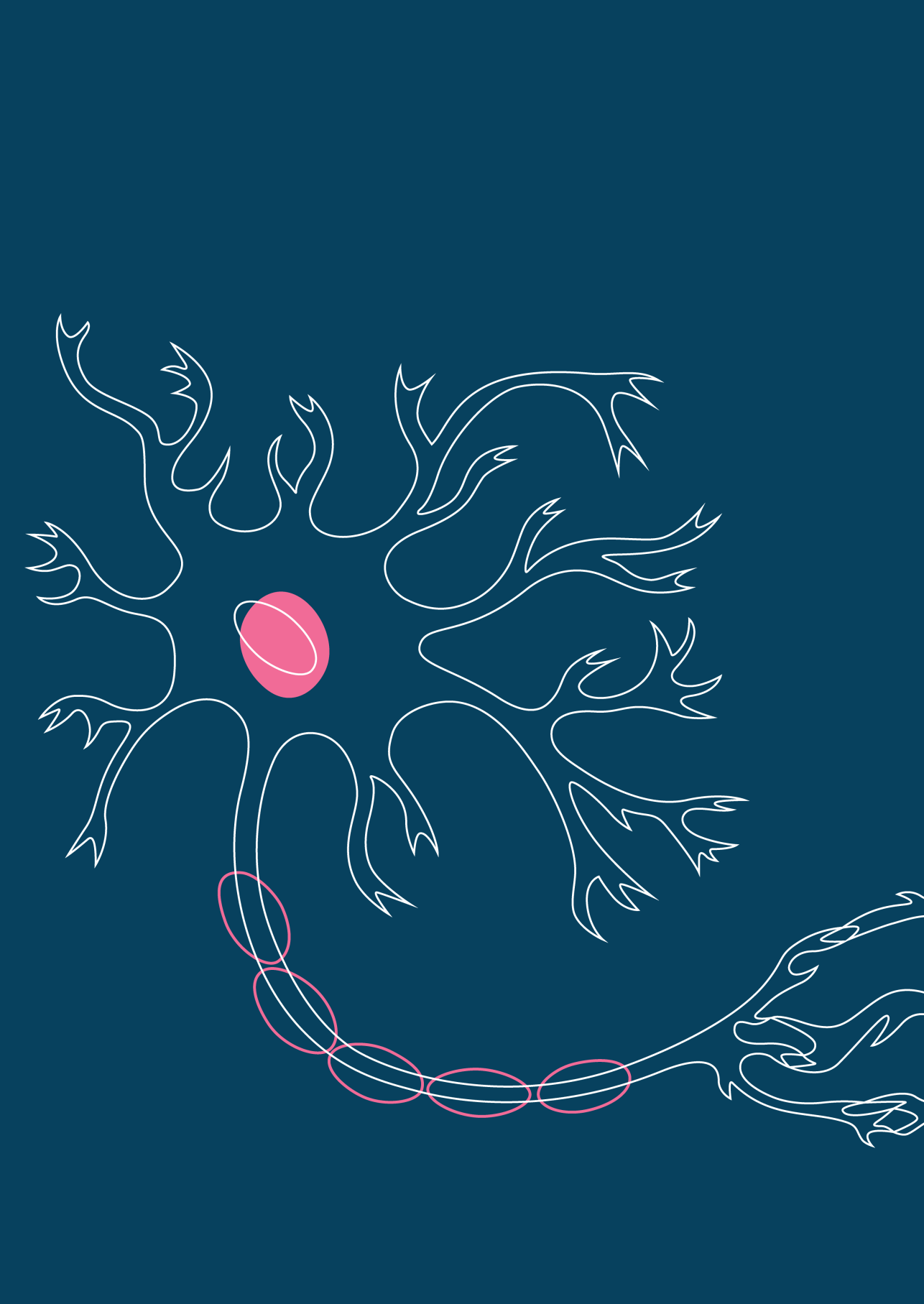

Diagnosis and treatment response in the asymmetric variant of chronic inflammatory demyelinating polyneuropathy

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ABSTRACT

Objectives: To 1) assess the diagnostic value of testing clinically affected and unaffected limbs with nerve conduction studies (NCS) in patients with the asymmetric CIDP variant and to define the most useful strategy for diagnosis, and 2) describe treatment response and long-term outcome.

Methods: We performed a retrospective study and included patients with a multifocal distribution of symptoms and signs, who met the probable or definite EFNS/PNS diagnostic categories for CIDP.

Results: We included 34 patients and 32 NCS datasets were available. Of these 32 patients, 25 (78%) met the electrodiagnostic criteria for definite or probable CIDP and seven (22%) for possible CIDP. Patients fulfilling the possible electrodiagnostic criteria and a supportive criterion were considered as probable CIDP. NCS of the clinically affected forearm and leg led to a probable or definite diagnosis in 13 patients (41%). Measuring both arms up to Erb's point led to a probable or definite diagnosis in 25 patients (78%), after which NCS of both legs did not contribute to additional probable or definite diagnoses.

In total, 30% of patients treated with dexamethasone and 94% of patients treated with intravenous immunoglobulins (IVIg) responded. IVIg withdrawal attempts were successful in 21% of patients.

Conclusion: After measuring the clinically affected arm up to Erb's point, NCS of the unaffected arm to Erb's point has the highest additional diagnostic yield in patients with asymmetric CIDP. Patients seem to respond better to IVIg than to corticosteroids and long-term treatment is often required, although IVIg withdrawal was successful in 21%.

INTRODUCTION

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a heterogeneous disorder with multiple phenotypes, including an asymmetric variant. Due to its asymmetric presentation, diagnosis can be more difficult than the diagnosis of typical CIDP.[1] The EFNS/PNS guideline for CIDP is the most widely used set of diagnostic criteria, focusing mainly on nerve conduction studies (NCS) abnormalities suggestive of demyelination.[2,3] The guideline recommends to initially test the forearm and lower leg on one side. If the criteria are not met, NCS can be extended.[2] However, since the guideline does not distinguish between typical and atypical CIDP, it is unknown whether this is also the best strategy to diagnose patients with an asymmetric distribution of symptoms and signs. Furthermore, in daily practice often all four limbs are tested, including clinically unaffected limbs. It is unclear how often NCS of the clinically affected limbs are sufficient, and whether testing clinically unaffected limbs is of additional diagnostic value.

Both typical and atypical CIDP patients can be treated with intravenous immunoglobulins (IVIg) or corticosteroids.[4,5] While multiple studies were done to evaluate treatment response in CIDP, they rarely focused on the asymmetric variant.[6]

The objectives of this study were 1) to assess the diagnostic value of testing clinically affected and unaffected limbs and to define a useful NCS strategy to diagnose the asymmetric CIDP variant, and 2) to describe treatment response and long-term outcome.

METHODS

We retrospectively screened medical files from all CIDP patients seen at our neuromuscular referral clinic between 1992 and 2017. Patients were selected if they were diagnosed with atypical CIDP - asymmetric variant, including similar diagnoses such as multifocal acquired demyelinating sensory and motor neuropathy (MADSAM), Lewis-Sumner syndrome, and multifocal inflammatory demyelinating neuropathy (MIDN).[7-9] All patients fulfilled the EFNS/PNS diagnostic categories for probable or definite CIDP.[2] According to the diagnostic categories, patients fulfilling the clinical

criteria, the possible electrodiagnostic criteria and at least one supportive criterion were also considered as probable CIDP.

The diagnosis was clinically defined as chronic asymmetric weakness and sensory symptoms with involvement of multiple individual nerves (multiple mononeuropathy). Signs and symptoms at first presentation, ancillary investigations, treatment and follow up data were extracted from medical charts. Motor strength was assessed with the Medical Research Council (MRC) sum score and included shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension and ankle dorsiflexion (range: 0 – 60).

Our extensive NCS protocol included testing of the 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. All nerve conduction studies were performed at time of diagnosis. NCS data were reanalyzed for this study by a neurophysiologist (CV) who was blinded to the clinical distribution of symptoms. Analysis was done on the table of results and if necessary, verified on the wave forms. Following the recommendation of the EFNS/PNS guideline,[2] we first assessed NCS results of the median and ulnar nerve in the clinically most affected forearm and the peroneal and tibial nerve of the clinically most affected lower leg. In case only one limb was affected, we assessed the other ipsilateral upper or lower limb. According to the guideline, NCS can be extended in two ways: extending to the other forearm and lower leg, followed by extension to Erb's point at both sides (protocol A) or first extending to Erb's point at the most affected side, followed by the forearm and lower leg at the other side and ultimately to Erb's point at the other side (protocol B). Both protocols were analyzed. In addition to the guideline, we assessed the NCS results of the musculocutaneous and the radial nerves in both arms. In case the electrodiagnostic criteria for probable or definite CIDP were met in a patient at a certain step, it was concluded that extra measurements were not of additional diagnostic value in that patient.

Patients were initially treated with pulsed dexamethasone, IVIg or a combination of IVIg and intravenous methylprednisolone according to the local treatment protocol at presentation. Dexamethasone was the first choice of treatment. IVIg was the preferred choice of treatment in patients with contraindication for corticosteroids

or those with clinically minimal sensory involvement. In addition, IVIg was continued if patients responded to IVIg administered previously in the referring hospital. From 2014 onwards, patients were treated with the combination of IVIg and intravenous methylprednisolone, a regimen that is currently studied in our center. The dexamethasone was given in courses of 40 mg per day during four days per month for the duration of 6 months.[10,11] IVIg was given in a loading dose of 2gr/kg followed by maintenance treatment of 1gr/kg every three weeks. Patients who received the combination therapy were treated with one course of methylprednisolone 1 gram every three weeks, for 18 weeks in total. Treatment response was defined as any improvement on motor or sensory impairment as captured by the treating neurologist. Remission was defined as a stable or improving neurological condition, without further need of treatment.[12]

RESULTS

According to the medical files a total of 189 patients was diagnosed with CIDP between 1992 and 2017. Thirty-eight patients were diagnosed with an asymmetric CIDP variant. Four of these patients did not meet the EFNS/PNS diagnostic categories for probable or definite CIDP and were excluded. Thirty-four patients were included.

Patient characteristics are summarized in table 1. Fifteen patients (44%) presented with arm symptoms only, seven patients (21%) with leg symptoms only and 12 patients (35%) with symptoms in both arms and legs.

Nerve conduction studies

Thirty-two extensive NCS datasets were available for analysis. In three patients only arm nerves were tested. For two patients only NCS summary and conclusions were available. Table 2 summarizes the number and type of demyelinating features per nerve. Based on extensive NCS, fifteen patients (47%) met the electrodiagnostic criteria for definite CIDP, ten patients (31%) met the electrodiagnostic criteria for probable CIDP and seven patients (22%) met the electrodiagnostic criteria for possible CIDP. These seven patients met the diagnostic category of probable CIDP, based on the presence of at least one supportive criterion.

Table 1. Patiënt characteristics

N=34	
Gender	
Male	23 (68%)
Female	11 (32%)
Median age at presentation	53 (28-79)
Symptom duration	36m (1-180 months)
Comorbid diseases	
Diabetes Mellitus	2 (6%)
Other auto immune diseases	7 (21%)
Symptoms at presentation:	
Upper limb	15 (44%)
Lower Limb	7 (21%)
Upper and lower limb	12 (35%)
Muscle Atrophy	22 (65%)
Fasciculations	3 (9%)
Pain	10 (29%)
Cranial nerve involvement	3 (8%)
Median MRC sum score	58 (43-60)
Lumbar puncture	17
Elevated protein	9 (53%)
Median protein (g/L)	0.54 (0.21-2.33)

Abbreviations: MRC: medical research council, g: grams, L: liter

Table 3 shows the cumulative diagnostic yield of the different NCS steps as suggested by the EFNS/PNS guideline. NCS of the clinically (most) affected forearm and lower leg led to the diagnosis in thirteen patients (41%). Both extending to Erb's point in the (most) affected arm and extending to the contralateral forearm and leg led to the diagnosis in an additional six patients (total 59%, table 3). Combining both strategies led to the diagnosis in another six patients (total 78%). Additionally, testing the radial and the musculocutaneous nerve did not contribute to a definite or probable diagnosis, but led to a possible fulfillment of the electrodiagnostic criteria in one patient.

Table 2. Number and type of demyelinating findings[1] per nerve[2]

	Median	Ulnar	Radial	Musculo-cutaneous	Peroneal	Tibial	Total
Motor conduction block	27	26	2	3	5	8	71
Reduction of motor conduction velocity	15	22	1	4	3	-	45
Abnormal temporal dispersion	15	8	-	-	-	3	26
Motor distal latency prolongation	4	2	-	1	-	-	7
Distal CMAP duration increase	4	1	-	-	2	2	9
Prolongation of F-wave latency	6	8	-	-	-	3	17
Absent F-wave	10	6	-	-	8	2	26
Total	81	73	3	8	18	18	201

1: According to the EFNS/PNS criteria 2010, 2: Left and right nerve combined
Abbreviations: CMAP: Compound muscle action potential

In twelve patients out of 32 patients (38%) demyelinating features were found between the axilla and Erb's point. In three patients demyelinating conduction velocities between axilla and Erb's point were the only demyelinating features, leading to a possible diagnosis in two patients and a definite diagnosis in one patient.

Demyelinating features in the legs were found in twelve patients (38%). In two out of the seven patients (29%) who presented with lower limb symptoms only, demyelinating features were found in the legs.

Findings in the legs never contributed to a definite or probable diagnosis, but contributed to a possible diagnosis in two patients.

Table 3. Cumulative electrodiagnostic yield of nerve conduction study protocols

N=32	Diagnosis[1] %(N)	Possible %(N)	No DF %(N)
EFNS/PNS protocol A			
Forearm + lower leg[2] AS	41%(13)	28%(9)	31%(10)
Forearm + lower leg[2] OS	59%(19)	31%(10)	9%(3)
Arms to Erb[3]	78%(25)	19%(6)	3%(1)
Radial and Musculocutaneous nerve	78%(25)	22%(7)	0
EFNS/PNS Protocol B			
Forearm + lower leg[2] AS	41%(13)	28%(9)	31%(10)
To Erb AS[3]	59%(19)	25%(8)	16%(5)
Forearm + lower leg[2] OS	78%(25)	19%(6)	3%(1)
To Erb OS[3]	78%(25)	19%(6)	3%(1)
Radial and Musculocutaneous nerve	78%(25)	22%(7)	0
Alternative protocol			
To Erb AS[3]	53%(17)	25%(8)	22%(7)
To Erb OS[3]	78%(25)	13%(4)	9%(3)
Legs[4]	78%(25)	19%(6)	3%(1)
Radial and Musculocutaneous nerve	78%(25)	22%(7)	0

Cumulative electrodiagnostic yield in 32 MADSAM patients consecutively following the steps as described in the EFNS/PNS criteria (van den Bergh et al. 2010) split in protocol A and B, and a proposed alternative protocol.
1: fulfilling definite or probable electrodiagnostic criteria, 2: Median, ulnar, peroneal and tibial nerves,
3: Median and ulnar nerves 4: Peroneal and tibial nerves on both sides
Abbreviations: DF: demyelinating features, AS: (most) affected side, OS: other side

Table 3 shows the diagnostic yield of an alternative NCS protocol, starting with testing the arms. Measuring the arm at the clinically most affected side up to Erb's point led to the diagnosis in 17 patients (53%). Extending the NCS to the other arm up to Erb's point led to the diagnosis in an additional eight patients (total 78%). Extending the NCS to the legs and the musculocutaneous and radial nerves did not contribute to a definite or probable diagnosis in the remaining seven patients.

Treatment

Ten patients were initially treated with dexamethasone, of whom three patients (30%) responded. Fifteen patients were initially treated with IVIg, of whom 14 patients responded to therapy (93%). Five patients received a combination therapy of IVIg and methylprednisolone, of whom four patients (80%) responded. In the patients who responded to treatment, the median MRC sum score before treatment was 56 (range 50-60) and after treatment 59 (range 54-60). In non-responders the median MRC sum score before treatment was 57 (range: 43-60) and after treatment 56 (range: 35-60). Due to mild symptoms, four patients (12%) were not treated.

Long term follow up

The median duration of follow up was 39 months (range 1-151). During follow up all three patients who responded to dexamethasone treatment remained in remission. At last known follow up, the total duration of remission was between 14 and 83 months. The total response to one of the three treatment regimens was 94%.

In total 26 patients received IVIg maintenance therapy at some point during follow up, with a median treatment duration of 50 months (1-144 months). Eight patients (31%) showed progression of symptoms during treatment requiring higher IVIg doses or at shorter interval. IVIg withdrawal was attempted in fourteen patients, but was only successful in three patients (21%).

DISCUSSION

NCS of the clinically affected forearm and lower leg led to a definite or probable fulfillment of the electrodiagnostic criteria[2] in less than half of patients with the asymmetric CIDP variant, meaning these measurements would not be sufficient in an important portion of patients. Most demyelinating features were found in the arms, especially when measured to Erb's point, even if patients presented with lower limb symptoms only.

The first description of an asymmetric CIDP variant was a report of the Lewis-Sumner syndrome, which described five patients with a chronic asymmetric sensorimotor neuropathy with focal involvement of individual nerves, with persistent conduction block at NCS.[8] Since this first report, multiple other terms have been introduced,

such as MADSAM and MIDN.[7,9] Because no official criteria have been published, definitions that are being used vary greatly, making different studies difficult to compare. Because of the ambiguous definitions, these terms were replaced in the EFNS/PNS criteria for the term atypical CIDP, asymmetric variant.[2] This study showed that the additional value of performing NCS in the arm at the clinically unaffected side in patients with an asymmetric CIDP variant is high, while the diagnostic value of measuring the legs is low, even if the leg is clinically affected. For the upcoming update of the EFNS/PNS diagnostic guideline we suggest a different NCS strategy for patients with an asymmetric distribution of symptoms specifically, starting with the arm at the clinically most affected side up to Erb's point or to the axilla, as we recognize that NCS until Erb's point may not be possible in every center. If criteria are not met, the NCS can be extended to the other arm first, and, ultimately, to the legs. This will lead to less extensive NCS in most patients.

Demyelinating features are often not limited to the clinically affected limbs in both typical and atypical CIDP.[13,14] A study in mixed typical and atypical CIDP showed that the specificity and sensitivity of the diagnostic criteria increased when testing three instead of two limbs.[15] In contrast to our findings, the number of demyelinating features was higher in the legs and testing another leg as the third limb had the most diagnostic value. However, this study included only few patients with asymmetric CIDP, in which arm involvement is relatively more prominent compared to other CIDP subtypes. In addition, proximal upper limb stimulation at the axilla and Erb's point was not performed.[15] Another study also found that the total number of demyelinating features, might be higher in the arms than in the legs.[14] Possible explanations for this could be the difficulty to detect demyelinating features in leg nerves due to severe axonal damage[14,16] and more stringent demyelinating criteria for leg nerves, while the proximal parts of the leg nerves are not accessible for NCS.[17]

In this study, patients responded better to IVIg than to corticosteroids, with an overall treatment response over 90%. However, in 31% of patients symptoms progressed despite treatment. Response to immunomodulatory treatment (IVIg, corticosteroids or plasmapheresis) has been reported in 60-88% of patients with the asymmetric variant of CIDP.[7,18-21] Sample sizes of these studies were often small and results were difficult to compare due to differences in patient inclusion, treatment and outcome measurements. Although studies have shown that IVIg is an effective treatment in patients with the asymmetric CIDP variant,[6,20] the literature is still inconclusive about

the treatment effect of corticosteroids. An overview of multiple studies showed an overall treatment response of 64% to corticosteroids, similar to the response to IVIg in asymmetric CIDP,[6] and to the response to corticosteroids in typical CIDP patients.[5,22] However, response rates to corticosteroids in patients with an asymmetric CIDP varied greatly throughout literature.[18,21,23] In our study, response rate to dexamethasone was low, but most patients had predominantly motor involvement which has previously been described a predictor of poor response or even deterioration to corticosteroids.[24-26] In our study, most patients needed long term IVIg maintenance therapy and IVIg withdrawal attempts were succesfull in only 21% of patients, which is in line with other studies in asymmetric CIDP variants.[27-29] In a large retrospective study, including typical and atypical CIDP, 40% of IVIg responsive patients were in remission after a mean follow up of 5 years,[30] suggesting that patients with an asymmetric CIDP variant might be more dependent on long term IVIg maintenance treatment than CIDP patients in general.

The strengths of this study are the relatively large number of patients with the asymmetric CIDP variant and the performance of neurophysiological testing according to a predefined and extensive protocol in almost all patients, regardless of the number of demyelinating features found in tested nerves. Limitations should be mentioned. All data were collected retrospectively from the medical files, which might have resulted in cases being missed. Due to the long inclusion period, there was no standardized evaluation and follow up. Our treatment protocol changed during inclusion making the sample size per treatment regimen even smaller. Because treatment response was not assessed in a standardized way we defined treatment response as any improvement on motor or sensory impairment as captured by the treating neurologist. This may have overestimated treatment response as in in randomized trials treatment response is based on predefined cut-off's on disability.

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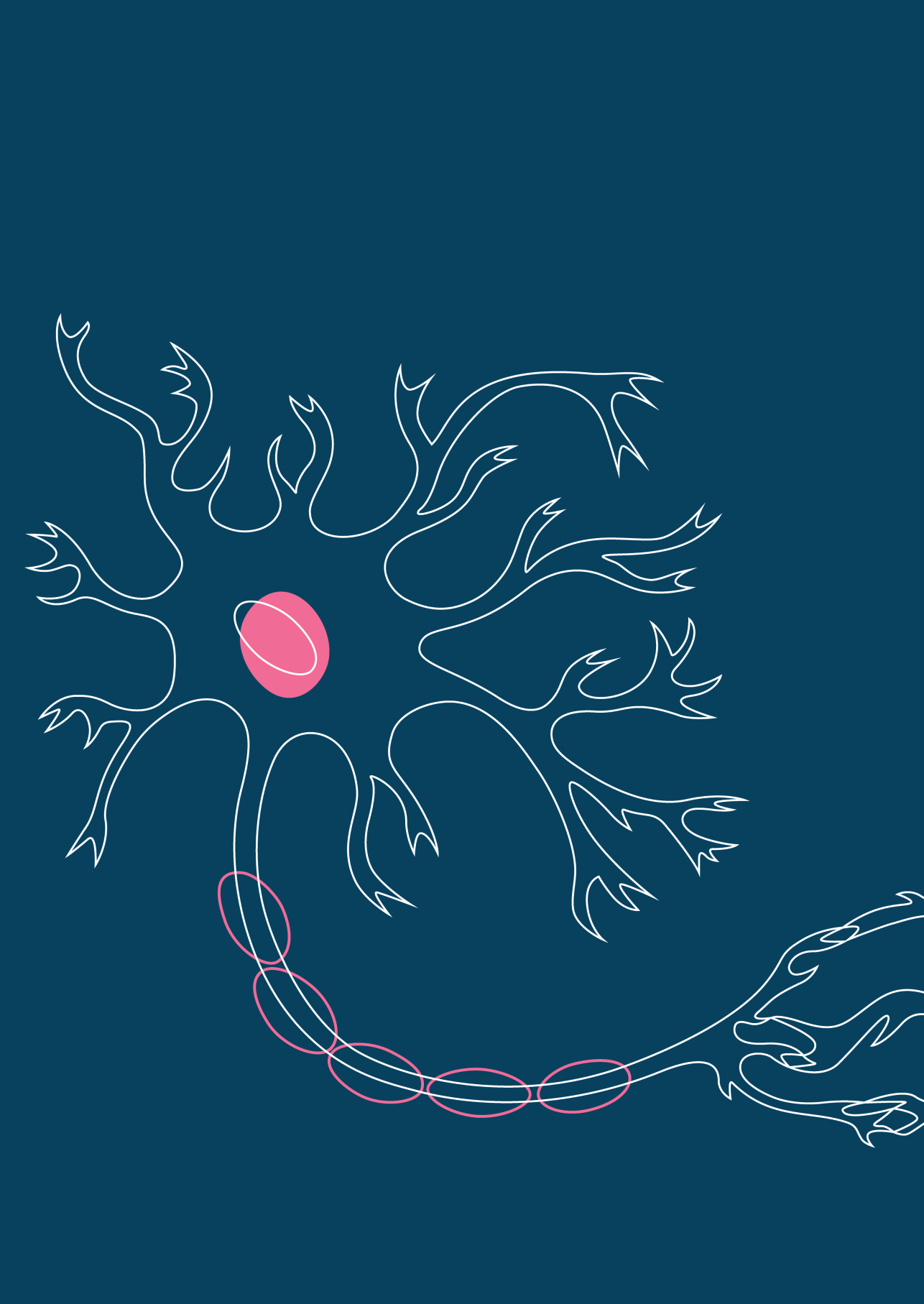
AUTHOR CONTRIBUTIONS

Ilse Lucke: data collection, drafting/revising the manuscript and analysis or interpretation of data. Luuk Wieske: drafting/revising the manuscript. Anneke van der Kooi: drafting/revising the manuscript. Ivo van Schaik: drafting/revising the manuscript. Filip Eftimov: drafting/revising the manuscript, study concept or design and analysis or interpretation of data. Camiel Verhamme: drafting/revising the manuscript, study concept or design and analysis or interpretation of data.



Elevated leukocyte count in cerebrospinal fluid of patients with chronic inflammatory demyelinating polyneuropathy

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ABSTRACT

Objectives: Cerebrospinal fluid (CSF) examination is often part of the diagnostic work-up of a patient suspected of having chronic inflammatory demyelinating polyneuropathy (CIDP). According to the EFNS/PNS criteria, an elevated protein level without pleocytosis (leukocytes <10 cells/µl) is supportive of the diagnosis CIDP. The objective of this study was to identify and describe patients with an elevated leukocyte count, who otherwise fulfill the diagnostic criteria for CIDP.

Methods: We performed a retrospective study at two tertiary neuromuscular referral clinics and included patient who met the EFNS/PNS criteria for definite or probable CIDP and had elevated CSF leukocytes (≥10 cells/µl).

Results: Fourteen out of 273 (6%) patients with CIDP had elevated CSF leukocytes. Eight patients (57%) presented with a subacute onset and four patients with an antecedent infection. Most patients responded well to therapy, and eight patients are currently in remission. In four patients, lumbar puncture was repeated. A spontaneous decrease in leukocytes before start of treatment was found in three patients.

Conclusion: Our data indicate that a mild to moderate pleocytosis in CSF does not exclude the diagnosis of CIDP, especially in patients with a subacute onset of disease.

INTRODUCTION:

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an acquired immune mediated neuropathy with a variable clinical presentation. The EFNS/PNS guideline for diagnosis and treatment of CIDP is the most widely used diagnostic criteria set and is based on clinical criteria and findings in nerve conduction studies (NCS) suggestive of demyelination.[1,2] Supportive criteria can further increase the diagnostic certainty.[1] Examination of the cerebrospinal fluid (CSF) is one of these supportive criteria and is also frequently performed to rule out other diagnoses. An elevated protein without pleocytosis (<10cells/μL) is found in 75-95% of patients[3,4] and is supportive of the diagnosis CIDP.[1] Infections, other inflammatory disorders or malignancies should be considered when an elevated leukocyte count is found. However, the cut-off at nine cells is arbitrary and differs for example from the diagnostic guidelines for Guillain-Barre Syndrome (GBS) where a cut-off of 50 cells is used.[5] We encountered several patients with pleocytosis that otherwise fulfilled the EFNS/PNS criteria for CIDP and who responded well to treatment. Therefore, we hypothesized that the currently used cut-off might be too low and may falsely rule out CIDP as a diagnostic possibility, which could lead to unnecessary additional diagnostic tests and a delay in treatment.

In this retrospective case series we describe 14 patients diagnosed with CIDP according to the current EFNS/PNS criteria with a CSF leukocyte count above the currently used cut-off.[1]

METHODS

We retrospectively screened medical files from all patients fulfilling the diagnostic criteria for definite or probable CIDP[1] at two tertiary neuromuscular referral centers between 1997 and 2017: the Clinical Center of Serbia in Belgrade and the Academic Medical Center in Amsterdam. Patients were selected if they had a leukocyte count greater than, or equal to 10 cells/μL. If erythrocytes were elevated, a subtraction factor of 1 leukocyte per 750 erythrocytes was used. Acute or subacute onset was defined as symptom duration of less than two months prior to presentation.

All patients underwent standard diagnostic work-up. Additional diagnostic work-up in case of pleocytosis varied and was at the discretion of the treating physician.

All demographic, clinical, diagnostic and follow up data was extracted from the medical charts. We used the CIDP Disease Activity Status (CDAS) to categorize clinical outcome, which encompasses disease activity as judged by the treating physician, neurological examination and duration of treatment.[6]

RESULTS

A total of 325 patients with CIDP were identified. Lumbar puncture was performed in 237 patients (73%), and all CSF test results were available for analysis. Elevated leukocyte count was found in fourteen patients (6%). An elevated CSF protein was found in 13 out of those 14 patients (93%).Four patients had CSF leukocytes of more than 50cells/µl. These are described in detail below.

Table 1 summarizes the characteristics of all patients. Thirteen patients met the EFNS/PNS neurophysiological criteria for definite CIDP; one met the criteria for probable CIDP. Ten patients were male (71%) and four patients were female (29%). The median age at presentation was 57 years (range 36-73). There were 11 patients with typical CIDP and symmetric sensory and motor involvement. One patient presented with only sensory symptoms, and two patients had multifocal CIDP.

Eight patients (57%) had an (sub)acute onset of symptoms at presentation, of whom four patients reported a gastrointestinal or respiratory infection in the weeks before onset. In six patients symptoms progressed for more than eight weeks, up to start of treatment. In two cases symptoms progressed for less than eight weeks (cases 7 and 14). Case 7 was treated one month after start of symptoms and improved. However, he had a relapsing remitting course of disease and had multiple relapses during follow-up. In case 14 symptoms progressed up to seven weeks before treatment was started (see below).

Lumbar puncture was performed before start of treatment In 12 patients. In two patients (case 8 and 9) lumbar puncture was performed after one course of IVIg was given in the referring hospital (5 weeks and 3 months earlier respectively).

Lumbar puncture was repeated in four patients. All four had an (sub)acute onset and showed a marked decrease or normalization of leukocyte count. In three patients leukocytes decreased before treatment was started. In one case, one course of IVIg was given 12 weeks before second lumbar puncture was repeated (patient 11).

Magnetic resonance imaging (MRI) was performed in four patients. Minimal nerve root enhancement, without hypertrophy was found in only one patient (case 14). Ultrasound was performed in three patients (case 9,12 and 14). Hypertrophy of multiple nerves was found in all three patients.

Eleven patients were treated with corticosteroids (prednisolone or pulsed dexamethasone); two patients with intravenous immunoglobulins (IVIg), and one patient was treated with a combination of methylprednisolone and IVIg. After six months, all but one patient improved. Patient 2 did not improve and died of an unknown cause one year after start of treatment. The median duration of follow-up was 1 year (range 1- 11 years). At the last available follow-up visit, eight patients were stable without treatment (CDAS 1 and 2) of whom two were considered cured (CDAS 1). Four patients were stable on maintenance therapy (CDAS 3) and one patient was unstable despite treatment (CDAS 5).

Case 11 was a 38-year-old man who presented with progressive symmetric, proximal and distal weakness, sensory symptoms, areflexia, dysarthria and dysphagia for one week. His medical history included Alport syndrome leading to a kidney transplantation one year before presentation. He used low dose prednisolone and tacrolimus. CSF test results showed elevated protein 1.12 g/L and a leukocyte count of 57cells/μL. There were no signs of renal transplant rejection. NCS showed signs of demyelination. Initially, the patient was diagnosed with Guillain Barre Syndrome (GBS) and he was treated with a course of IVIg. The dysphagia and dysarthria improved, but after several weeks the weakness in arms and legs progressed. Ten weeks after the start of symptoms, patient was readmitted due to further increase of limb weakness. The lumbar puncture was repeated and showed 23 cells/μL and a total protein of 3.7g/l. NCS was repeated and fulfilled the EFNS/PNS criteria for definite CIDP. All additional investigations were negative (Table 1). Patient was treated with pulsed dexamethasone (monthly pulses of 40 mg daily for four days during 6 months). He improved and has remained in remission for seven years (CDAS 1).

Table 1. Patient characteristics

Patient	1	2	3	4	5	6
Age at onset	58	73	46	60	55	62
Gender	F	M	M	M	M	F
NCS results according to EFNS/PNS	Definite	Definite	Definite	Definite	Definite	Definite
Duration of symptoms prior to (first) lumbar puncture*	3y	6m	6m	2m	2m	2m
Subtype	Sensory	Typical	Typical	Typical	Typical	Typical
(Sub)acute onset	No	No	No	Yes	Yes	Yes
History of infection	No	No	No	No	No	Yes
CSF WBC (cell/ul)	17	10	19	10	14	19
CSF Protein (g/l)	0.47	1.26	1.00	2.88	0.99	0.55
2nd CSF WBC	-	-	-	-	-	-
Time between 1st and 2nd lumbar puncture	-	-	-	-	-	-
Treatment[1]	P	P	P	P	P	P
Treatment response at 6 months, CDAS[2]	4	5	4	4	4	4
Clinical status at last FU, CDAS[2]	3	-	3	5	2	3
Other diseases investigated	Borrelia, HIV, Lues, Sarcoidosis Hep[3] B, C SCTD[4]	Borrelia HIV Lues Hep B, C SCTD	Borrelia HIV, Lues, Hep B, C SCTD	Borrelia, HIV, Lues, Hep B, C SCTD	Borrelia, HIV, Lues, TBC[5], Sarcoidosis Hep B, C SCTD	Borrelia, HIV, Lues, Sarcoidosis Hep B, C SCTD

1: P: prednisolone, PD: pulsed dexamethasone, MP: methylprednisolone, IVIg: intravenous immunoglobuline.
2. CDAS: 1. Cure (>5y of treatment), 2. Remission (<5y of treatment), 3. Stable active disease (>1y on treatment), 4. Improvement (>3m <1 year on treatment), 5. Unstable active disease
*3: Hep: Hepatitis 4: SCTD: systemic connective tissue disease 5: TBC: Tuberculosis 6: NT: Neurotropic viruses 7: SLE: Systemic lupus erythematosus 8: RA: Rheumatoid arthritis 9: PNA: Paraneoplastic antibodies * Duration of progression of symptoms in subacute cases is described in the results section.*

7	8	9	10	11	12	13	14
59	60	54	69	38	54	36	49
M	M	M	M	M	M	F	F
Definite	Definite	Definite	Definite	Definite	Probable	Definite	Definite
1m	1w	10y	18m	1w	5w	6m	1m
Typical	Typical	Typical	Typical	Typical	Multifocal	Multifocal	Typical
Yes	Yes	No	No	Yes	Yes	No	Yes
Yes	Yes	No	No	Yes	No	No	No
11	11	14	18	57	55	61	120
1.16	1.38	2.50	1.30	1.12	0.77	1.20	1.16
-	2	-	-	23	4	-	50
-	6w	-	-	11w	2w	-	1w
PD	IVIg	PD	PD	PD	PD	IVIg	IVIg + MP
4	4	4	4	4	4	4	4
2	2	2	1	1	2	3	2
Borrelia, Lues, NV[6] CNS Malignancy Hep B, C SCTD	-	Borrelia, HIV, TBC	Borrelia, Lues, Amyloidosis, m. Sjogren, Celiac disease Mercury and Arsenic intox.	Borrelia, Lues, NV, SLE[7], m. Sjogren, RA[8], Multiple myeloma PNA[9]	Borrelia, Lues, NV, SLE, Vasculitis, Amyloidosis Hep B, C	Borrelia, SLE, HIV, Lues, Sarcoidosis	Borrelia, HIV, Lues, TBC, NV, West Nile virus, CMV, PNA, CNS malignancy

Case 12 is a 54-year-old man who presented with a progressive asymmetrical, predominantly distal weakness, sensory symptoms, and moderate neuropathic pain for five weeks. CSF showed an elevated protein of 0.77 g/l and a leukocyte count of 55 cells/µL. NCS showed axonal loss in multiple nerves and a definite conduction block with slowing and an absent F-response in the ulnar nerve. Twelve days after first lumbar puncture, CSF analysis was repeated and showed 4 cells/µL and a total protein of 0.7 g/l. Peroneal nerve biopsy was performed because a vasculitis neuropathy was suspected. Pathological examination showed no signs of vasculitis, but endoneurial lymphocytic infiltrates and demyelination. NCS was repeated after five weeks and confirmed the definite conduction block, without a decrease in the distal CMAP. The patient was diagnosed with CIDP and was treated with intravenous methylprednisolone followed by pulsed oral dexamethasone. The patient improved and treatment was stopped after six monthly pulses, he is currently stable after ten months without treatment (CDAS 2).

Case 13 was a 36-year-old woman who presented with asymmetric distal weakness and sensory symptoms in the last six months. NCS was performed and met the EFNS criteria for definite CIDP. CSF examination showed 61 leukocytes/µl and a total protein of 0.27g/l. Additional diagnostic tests were negative, and she was diagnosed with multifocal CIDP. She was treated with IVIg leading to almost complete recovery after 1 year (CDAS 3).

Case 14 was a 49-year-old woman who presented with symmetric proximal and distal weakness, sensory symptoms and neuropathic pain in the last four weeks. There was no cranial nerve deficit, respiratory insufficiency or autonomic dysregulation. Two months before onset of symptoms she underwent a thyroidectomy because of a thyroid carcinoma. Thyroid hormone was supplemented, and there were no clinical or laboratory signs of hypothyroidism. NCS results met the criteria for definite CIDP. CSF examination showed a leukocyte count of 120 cells/µL and an elevated protein of 1.16 g/l. Extensive additional diagnostic tests showed no alternative cause (Table 1). Lumbar puncture was repeated one week after the first puncture and showed a decrease of leukocytes to 50 cells/µL. Nerve ultrasound showed hypertrophy of the C7 nerve roots and the median, right ulnar and left sural nerves. Symptoms progressed over seven weeks, and a diagnosis of CIDP was considered more likely. She was treated with a combination of three-weekly pulsed methylprednisolone

and IVIg. After 7 treatments, she recovered almost completely and she has been in remission for six months (CDAS 2).

DISCUSSION

In this retrospective study, we describe 14 patients (6% of the total cohort) with a demyelinating neuropathy and CSF pleocytosis, fulfilling the EFNS criteria for CIDP.[1] Only a few small studies have addressed the CSF findings in patients with CIDP. Van Doorn and colleagues found elevated leukocyte counts in six patients in their cohort of 52 patients with CIDP (11%), with leukocyte counts up to 27 cells/μL.[7] Press and colleagues found leukocyte counts between 0 and 33 cells/μL in their cohort of 32 patients with CIDP.[8] In GBS leukocyte counts up to 50 cells/μl are compatible with the diagnosis.[9] In one large study including 494 patients with GBS, 10 or more leukocytes were found in 6% of the patients, similar to the findings in our CIDP population.[5]

We found an acute or subacute onset in more than half of our cases with increased leukocyte count**.** An acute onset has been reported in up to 16% of CIDP patients, making early distinction between CIDP and GBS difficult.[10,11] In this study, we distinguished CIDP from GBS in most cases based on progression of symptoms of more than eight weeks, the occurrence of relapses and/or the need for maintenance therapy. In case 14 one could debate whether the diagnosis was CIDP or a prolonged form of GBS. We found a diagnosis of CIDP more likely as symptoms progressed over seven weeks and because of absence of cranial nerve deficit, respiratory insufficiency or autonomic dysregulation.

Interestingly, four of these eight patients reported an infection before onset. While it is generally accepted that GBS is a post-infectious polyneuropathy, it is unclear whether and how often CIDP is triggered by an antecedent infection. Infectious polyradiculitis was considered in some of our patients with subacute or acute onset, especially in those with higher cell counts. In some of these cases lumbar puncture was repeated and showed a spontaneous decrease in leukocytes. Transient pleocytosis might be even more frequent as most CIDP patients have slowly progressive disease and are usually diagnosed after months or years after start of symptoms.

Some of our patients had an atypical clinical presentation of CIDP or concomitant diseases making additional investigations necessary to exclude other causes of demyelinating neuropathy. Patients 11 had a history of kidney transplantation with associated immunosuppression, while patient 14 was recently treated for thyroid carcinoma. Both organ transplantation and the use of tacrolimus have been associated with developing CIDP.[12-14] Associations of many systemic diseases and malignancies with CIDP have been described, and how these different conditions affect immunological tolerance is largely unclear. The EFNS/PNS guideline recommends to consider these patients as idiopathic CIDP and treat them as such.[1]

Most patients responded well to therapy and improved. Eight patients reached remission at some point during follow-up, of whom two patients were considered cured. In previous literature a remission rate of 26% was found in patients treated with corticosteroids,[15] although a monophasic course of disease and remissions were reported to be more frequent in patients with an acute onset.[16]

The main limitation of this study is that CSF examination was only performed in 73% of our CIDP population. If the clinical presentation and NCS results were conclusive, a lumbar puncture was not always performed. This could have led to a selection bias and therefore to an overestimation of the number of CIDP patients with pleocytosis.

In addition, lumbar puncture was performed in two patients after a course of IVIg. It cannot be excluded that IVIg led to pleocytosis in these patients. Aseptic meningitis is a rare complication of IVIg treatment with an estimated incidence around 0.6%.[17] However, this complication usually develops 24-48 hours after IVIg administration. Both cases had no clinical signs of meningitis and the long interval between IVIg administration and lumbar puncture makes relation between pleocytosis and IVIg treatment unlikely.

In conclusion, evidence from literature and our case series suggest that elevated CSF leukocytes can be present in patients with CIDP. Acknowledging that pleocytosis may occur in CIDP, might lead to an earlier diagnosis and treatment. It remains unclear what the upper limit of pleocytosis in CIDP should be. The higher the number of leukocytes, the more unlikely the diagnosis of CIDP probably is and additional tests will be necessary to exclude other diagnoses first. Based on currently available evidence, CIDP patients with over 50 leukocytes in CSF are probably rare and

therefore we suggest to accept leukocyte counts up to 50 cells/µl in the upcoming update of the EFNS/PNS criteria, similar to the Brighton criteria for GBS, if the clinical presentation and the NCS results are consistent with the diagnosis CIDP. In those with subacute onset of symptoms and a higher number of leucocytes in CSF, one could consider repeating CSF analysis as a spontaneous decrease of leukocyte count might provide an additional argument for CIDP.

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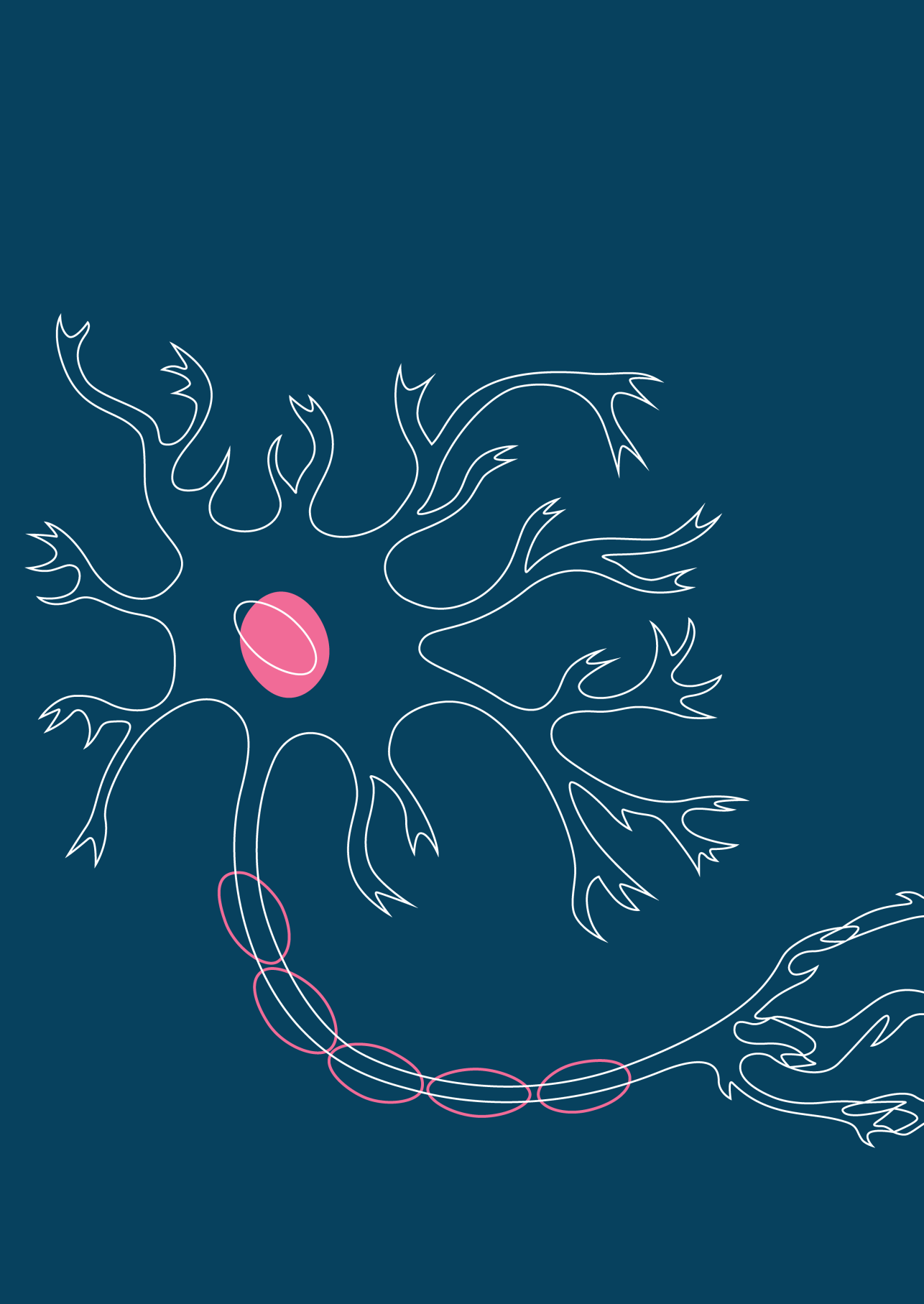
AUTHOR CONTRIBUTIONS

Ilse Lucke: data collection, drafting/revising the manuscript and analysis or interpretation of data. Stojan Peric: data collection, drafting/revising the manuscript. Gwen van Lieverloo: drafting/revising the manuscript. Luuk Wieske: drafting/revising the manuscript. Camiel Verhamme: analysis or interpretation of data and drafting/revising the manuscript. Ivo van Schaik: drafting/revising the manuscript. Ivana Basta: data collection and drafting/revising the manuscript. Filip Eftimov: drafting/revising the manuscript, study concept or design and analysis or interpretation of data.



Borrelia burgdorferi sensu lato seroconversion after intravenous immunoglobulin treatment: a cohort study

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ABSTRACT

Objective: IVIg consists of pooled donor immunoglobulins (IgG), possibly including anti-*Borrelia burgdorferi* (*Bb*sl) antibodies. Apparent IVIg-related *Bb*sl seroconversion could lead to incorrect diagnosis of Lyme borreliosis. This cohort study was designed to determine how often IVIg treatment leads to apparent *Bb*sl seroconversion and whether antibodies disappear post-treatment.

Methods: Sera from chronic inflammatory demyelinating polyneuropathy (CIDP) and myositis patient were analyzed, drawn pre-treatment and 6-12 weeks after start of IVIg. In patients with apparent seroconversion follow-up samples after treatment withdrawal were analyzed, if available. Patients treated with corticosteroids were included as controls. A two-tier protocol was used for serological testing, consisting of the C6 Lyme ELISA (Oxford Immunotec) and confirmation by IgM and IgG immunoblot (Mikrogen).

Results: We included 61 patients: 51 patients were treated with IVIg and 10 with dexamethasone. Of patients treated with IVIg, 42 had CIDP (82%), all were treated with Nanogam® (Sanquin Plasma Products). Nine patients had myositis (18%) and were treated with Privigen® (CSL Behring). Anti-*Bb*sl IgG seroprevalence pre-treatment was 3% (2/61). Apparent seroconversion during IVIg treatment occurred in 39% of patients (20/51), all treated with Nanogam®. Post-treatment seroreversion occurred in 92% of patients (12/13) with available follow up samples; in 78% (7/9) seroreversion was observed within 3 months.

Conclusions: Transient presence of anti-*Bb*sl IgG antibodies after IVIg is regularly observed. This effect appears to be dependent on the IVIg brand, probably reflecting variation in *Bb*sl exposure of plasma donors. Lyme borreliosis serological testing during, and weeks to months after IVIg, is therefore of limited utility.

INTRODUCTION

Intravenous immunoglobulins (IVIg) are used in the treatment of inflammatory neuromuscular disorders, such as chronic inflammatory demyelinating polyneuropathy (CIDP) and myositis.[1,2] IVIg consist of pooled polyclonal IgG immunoglobulins from at least a thousand donors per batch, including antibodies directed to different microorganisms the donors have encountered such as *Borrelia burgdorferi* sensu lato (*Bb*sl).[3] Because Lyme borreliosis is an important differential diagnosis in patients with CIDP, serological testing for *Bb*sl is frequently performed.[4] Lyme borreliosis is especially considered in CIDP patients without improvement or in deterioration of patients with Guillain Barre syndrome after start of IVIg treatment. Even though apparent seroconversion for anti *Bb*sl antibodies after IVIg does not lead to any symptoms or illness in patients, it could lead to confusing results, delay in diagnosis or unnecessary antibiotic treatment.

The main objective of this study was to determine how often IVIg leads to the transient presence of anti-*Bb*sl antibodies in serum of CIDP and myositis patients.

METHODS

Patients and serum samples

In this cohort study, we used consecutive serum samples collected from CIDP and myositis patients seen at our tertiary neuromuscular referral center. Samples were collected in the context of three studies: the Amsterdam UMC inflammatory neuromuscular diseases biobank, the International CIDP Outcome study, a prospective cohort study,[5] and the IMMEDIATE study, a prospective cohort study investigating IVIg in myositis.[2] All studies were approved by the local ethics committee. All patients provided informed consent for storage and use of samples for future studies related to the disease and/or treatments. Patients were eligible if they were not treated with IVIg at baseline and were repeatedly treated with IVIg afterwards. CIDP controls were treated with dexamethasone only. After selection of patients, analysis was performed anonymously, using leftover material from the above mentioned biobank and study cohorts.

We analyzed samples from two different time points: pre-treatment and 6-12 weeks after initiation of treatment. In selected patients that showed apparent seroconversion, we analyzed, if available, follow-up samples up to ten months post-treatment.

Treatment

Two different IVIg brands were used: Nanogam® (Sanquin Plasma Products, The Netherlands) and Privigen® (CSL Behring CSL Behring, King of Prussia, PA, USA). All patients received a loading dose of 2g/kg followed by a maintenance dose of 1g/kg every 3-4 weeks. Dexamethasone was given in a fixed scheme of 40mg per day for four days every month, during six months.[6]

Serological testing

Sera were analyzed according to a standard two-tier testing protocol, consisting of the C6 Lyme ELISA (Oxford Immunotec, Abingdon, Oxfordshire, UK) and, in case of an equivocal or positive Lyme Index, an IgM and IgG immunoblot (Mikrogen®). Cut-off values recommended by the manufactures were used. Immunoblots were assessed by two independent researchers; in case of disagreement, a third opinion was decisive. Equivocal immunoblot results were considered negative and immunoblot results determined the final outcome. In addition, Nanogam® and Privigen® were tested by two-tier testing. Privigen® was 1:2 diluted in dilution buffer, to equalize concentrations. Volumes used were those recommended for serum by the manufacturers.

Statistical methods

Statistical analysis was performed in SPSS (IBM SPSS Statistics 26) using a McNemar test. Statistical significance was determined as a p-value <0.05.

RESULTS

A total of 61 patients were included: 52 CIDP and 9 myositis patients. The median age was 64 years (range: 18-87) and 38 patients (61%) were male. IVIg was administered to 51 patients: 42 patients had CIDP and received Nanogam®, all myositis patients received Privigen®. Dexamethasone was given to 10 CIDP patients. Patients were treated between 2015 and 2019.

Anti-*Bb*sl antibodies pre-treatment (seroprevalence) were found in two out of the 61 patients (3%). Apparent seroconversion detected by the C6 ELISA test occurred in 20 patients (39%) whom were treated with IVIg. In all these patients seroconversion was confirmed by immunoblot (Table 1) (p<0.001). All of these patients were treated with Nanogam®, while apparent seroconversion occurred in none of the patients treated with Privigen®. In addition, no apparent seroconversion was found in patients treated with dexamethasone.

Table 1. Two-tier *Bb*sl testing of cases and controls

	First-tier (C6 ELISA)				Two-tier (C6 ELISA and immunoblot IgM/IgG)			
	IVIg			PD	IVIg			PD
	CIDP (n=42)	Myositis (n=9)	Total (n=51)	CIDP (n=10)	CIDP (n=42)	Myositis (n=9)	Total (n=51)	CIDP (n=10)
Seroprevalence	3 (7)	1 (11)	4 (8)	0 (0)	2 (5)	0 (0)	2 (4)	0 (0)
Seroconversion	20 (48)	0 (0)	20 (39)	0 (0)	20 (48)	0 (0)	20 (39)	0 (0)
Seroreversion	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Seronegative	19 (45)	8 (89)	27 (53)	10 (100)	20 (48)	9 (100)	29 (57)	10 (100)

Abbreviations: PD: pulsed dexamethasone; Bbsl: Borrelia burgdorferi sensu lato; IVIg = intravenous immunoglobulins; CIDP = chronic inflammatory demyelinating polyneuropathy

The C6 Lyme Index increased in 95% of patients (40/42) treated with Nanogam® (Figure 1), reaching the cutoff (Lyme Index 0,90) in 51% of previously seronegative patients (20/39). In patients treated with Privigen® or dexamethasone, the C6 Lyme Index did not increase or only marginally increase, none reaching the cutoff. One Privigen®-treated patient already had a positive C6 Lyme Index before and during IVIg, without immunoblot confirmation, and was therefore considered seronegative.

One Nanogam®-treated patient had also apparent seroconversion for IgM antibodies during IVIg. This patient had a negative C6 Lyme Index pre-treatment; an additionally performed immunoblot was equivocal for IgM and negative for IgG. The follow-up sample of this patient was C6, IgM and IgG negative.

Follow-up samples post-treatment were available for thirteen patients with apparent seroconversion. Median treatment duration was 4 months (range 4-12). Twelve

patients (92%) showed seroreversion. An early follow-up sample (1-3 months) after withdrawal of IVIg was available in nine patients; seven patients (78%) had seroreversion and two patients had an equivocal C6 Lyme Index. Of these two patients, one had negative IgM and IgG immunoblots and the C6 Lyme Index 8 months after withdrawal was negative. In the second patient the IgG immunoblot was positive and no further follow-up samples were available. In later follow-up samples, no equivocal or positive C6 Lyme Indexes were found. The C6 Lyme Index in these patients pre-, during and post-IVIg are also shown as a supplementary figure (appendix A).

Direct testing of IVIg showed a positive C6 Lyme Index (3,25) for Nanogam® and a negative C6-index (0,50) for Privigen®. The immunoblot performed on Nanogam® was highly positive for anti-*Bb*sl IgG antibodies and negative for IgM.

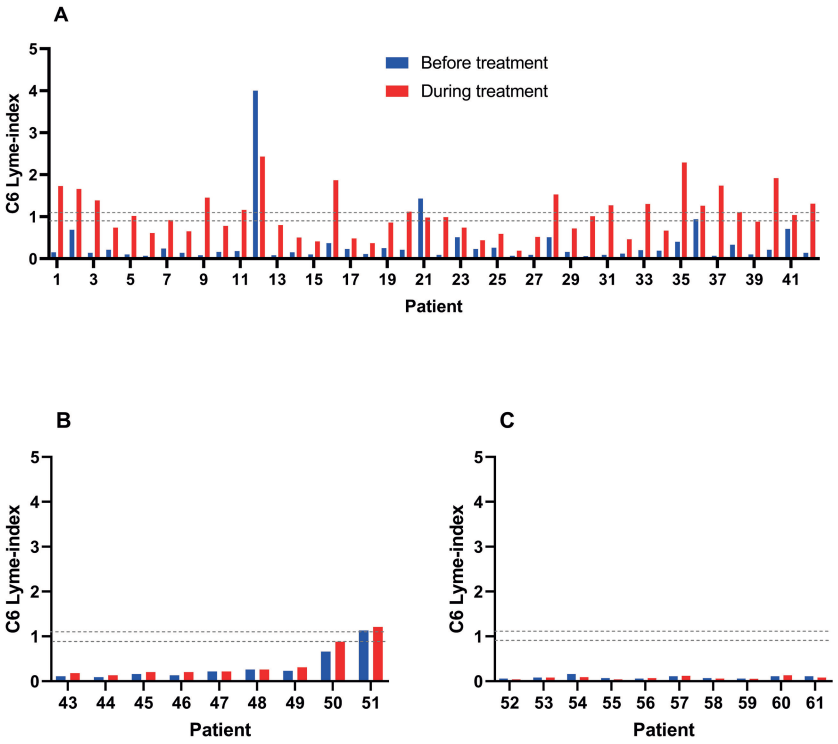

Figure 1. Quantitative C6 Lyme Index in patients treated with IVIg or dexamethasone
(A) Patients treated with Nanogam®. (B) Patients treated with Privigen®. (C) Patients treated with dexamethasone. Cutoff values recommended by the manufacturer are depicted by the dotted lines; C6 Lyme Index ≤0,90 is considered a negative result, 0,90-1,09 equivocal result and ≥1.10 positive result.

DISCUSSION

In this study we observed apparent seroconversion for anti-*Bb*sl antibodies in 48% of patients treated with Nanogam®. None of the patients treated with Privigen® or dexamethasone showed apparent seroconversion. Interestingly, antibodies disappeared in 92% of patients during follow-up after IVIg withdrawal.

We found an anti-*Bb*sl antibody seroprevalence of 3%, comparable with the Dutch population (4-8%).[7] However, the prevalence of anti-*Bb*sl antibodies depends on geographical region,[8] possibly explaining the difference in apparent seroconversion between patients receiving Nanogam®, a Dutch product, and Privigen®, produced in either the USA or Germany. The finding that the C6 Lyme Index was positive in Nanogam® and negative in Privigen®, is in accordance with previous findings.[3]

Interestingly, one patient experienced apparent seroconversion for both IgM and IgG antibodies during IVIg treatment (Nanogam®). IVIg consists of at least 95% of IgG antibodies, and a very small proportion of IgA antibodies (CSL Behring prescribing information on Privigen®; Sanquin product information on Nanogam®). We cannot exclude the presence of a minimal fraction of IgM, although anti-*Bb*sl IgM antibodies were not demonstrated in the Nanogam® batch we tested. Alternatively, the finding in this particular patient that both IgM and IgG were negative during follow-up, without antibiotic treatment, makes Lyme borreliosis unlikely.

All but one patient with 'IVIg-induced apparent seroconversion' returned to a seronegative state within a few months post-treatment. In this patient, anti-*Bb*sl IgG antibodies were still detectable by immunoblot eight weeks post-treatment. This could most likely be explained by the finding that IVIg metabolism differs greatly between patients, with a half-life ranging between18-32 days.[9] Unfortunately, no later follow-up samples were available for this patient. Alternatively, albeit less likely, this could have reflected interim exposure to *Bb*sl.

The strengths of this study include the relatively large sample size. Samples from at least two time points were available for all patients and two different types of IVIg were used. A limitation is that not all follow-up samples were taken at the same time point. Therefore, we are not able to calculate when serological testing for Lyme borreliosis would be reliable again after IVIg treatment . Unfortunately, we did not

test different batches of Nanogam® to see if apparent seroconversion was batch-related. The batch numbers of the Nanogam® the patients were treated with, were not available. Patients were treated over a period of 5 years, meaning that different batches were used. We assume it is not exceptional for a batch of Nanogam® to contain anti-*Bb*sl antibodies, given the high seroprevalence of anti-*Bb*sl antibodies in the Dutch population and the high number of different donor immunoglobulins used in one batch of IVIg.

In conclusion, we show that IVIg can lead to transient presence of anti-*Bb*sl antibodies. Therefore, when patients received IVIg produced in a Lyme borreliosis endemic region, clinicians should be careful interpreting results of *Bb*sl serological assays. When Lyme borreliosis is part of the differential diagnosis, it would be highly recommendable to test for antibodies either before or several months after IVIg administration.

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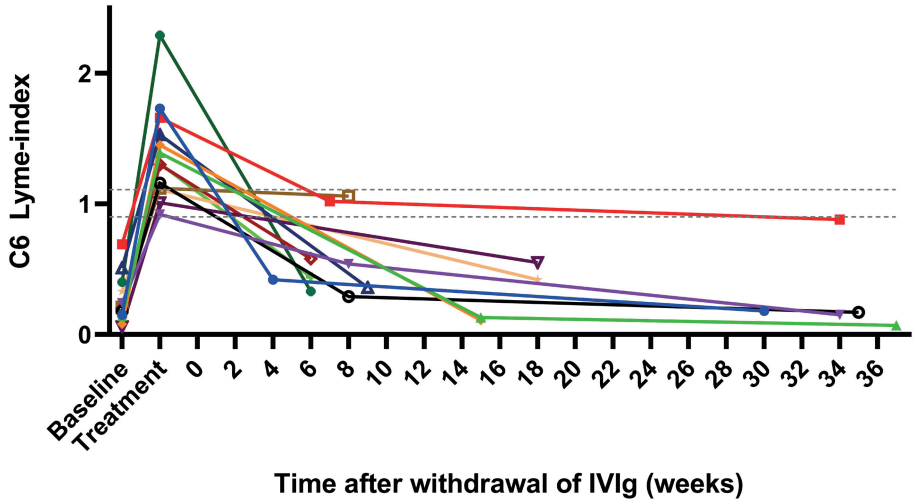
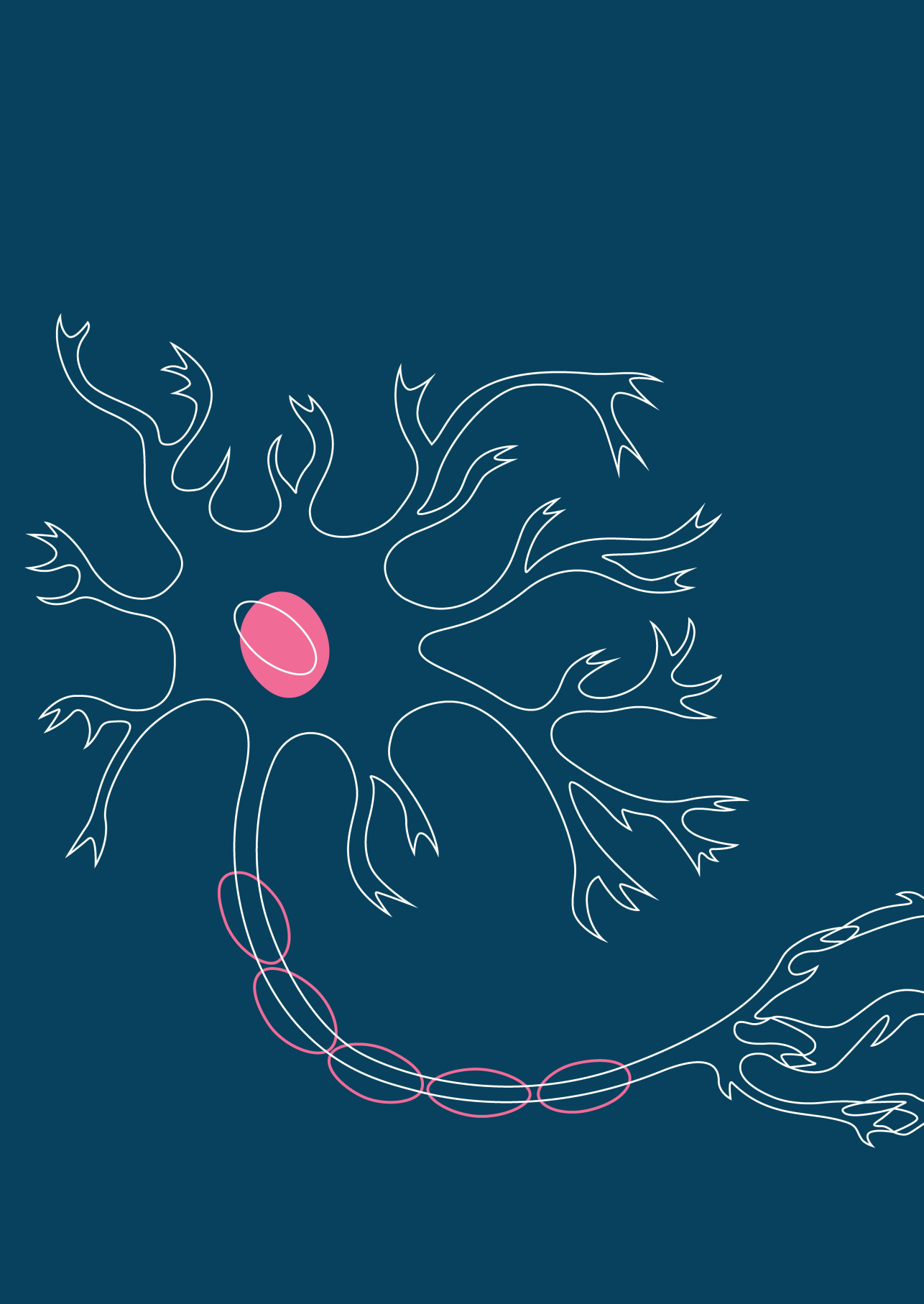
AUTHOR CONTRIBUTIONS

Ilse Lucke: study concept or design, data collection, drafting/revising the manuscript and analysis or interpretation of data. Amber Vrijlandt: data collection, drafting/revising the manuscript and analysis or interpretation of data. Johan Lim: data collection, drafting/revising the manuscript. Anneke van der Kooi: drafting/revising the manuscript. Ivo van Schaik: drafting/revising the manuscript. Hans Zaaijer: drafting/revising the manuscript. Joppe Hovius: drafting/revising the manuscript, study concept or design and analysis or interpretation of data. Filip Eftimov: drafting/revising the manuscript, study concept or design and analysis or interpretation of data.

SUPPLEMENTARY MATERIAL



Appendix A. C6 Lyme Index in 13 patients pre-, during and post-IVIg treatment



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

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ABSTRACT

Objectives: 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.

Methods: 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.

Results: 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.

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.

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.

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 fulfil 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 gr/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 gr/kg and at least one additional IVIg dose of 1 gr/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.

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).

Table 1. Diagnostic test results

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

Abbreviations: CIDP: chronic inflammatory demyelinating polyradiculoneuropathy, MMN: multifocal motor neuropathy, R; responders, NR: non responders, g: grams, L: liters, NCS: nerve conduction studies, MRI: magnetic resonance imaging, N: number

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

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 1mV. 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.

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[1] (range)	55 (42-95)	74 (50-105)	*	*
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[1] (range)	70 (44-105)	54 (40-103)	55 (50-60)	55 (50-60)

*1: Grip strength of most affected hand in kilo Pascal (kPa). *Grip srength was not available*
Abbreviations: CIDP: chronic inflammatory demyelinating polyradiculoneuropathy, MMN: multifocal motor neuropathy, MRC: Medical Research Council; mRS: modified Rankin scale

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 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.

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

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 colleagues 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 presence 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 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 inter-observer 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 useful 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, although elevation was mild (<1gr/l) in the majority of patients. Allen and colleagues found that half of patients who were misdiagnosed with CIDP, had a mild elevated CSF protein (<1g/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 10-78%, 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 less than 10% of patients with a diagnosis of lower motor neuron disease and that there was a relatively low response rate of 31% despite thorough 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 disability 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.

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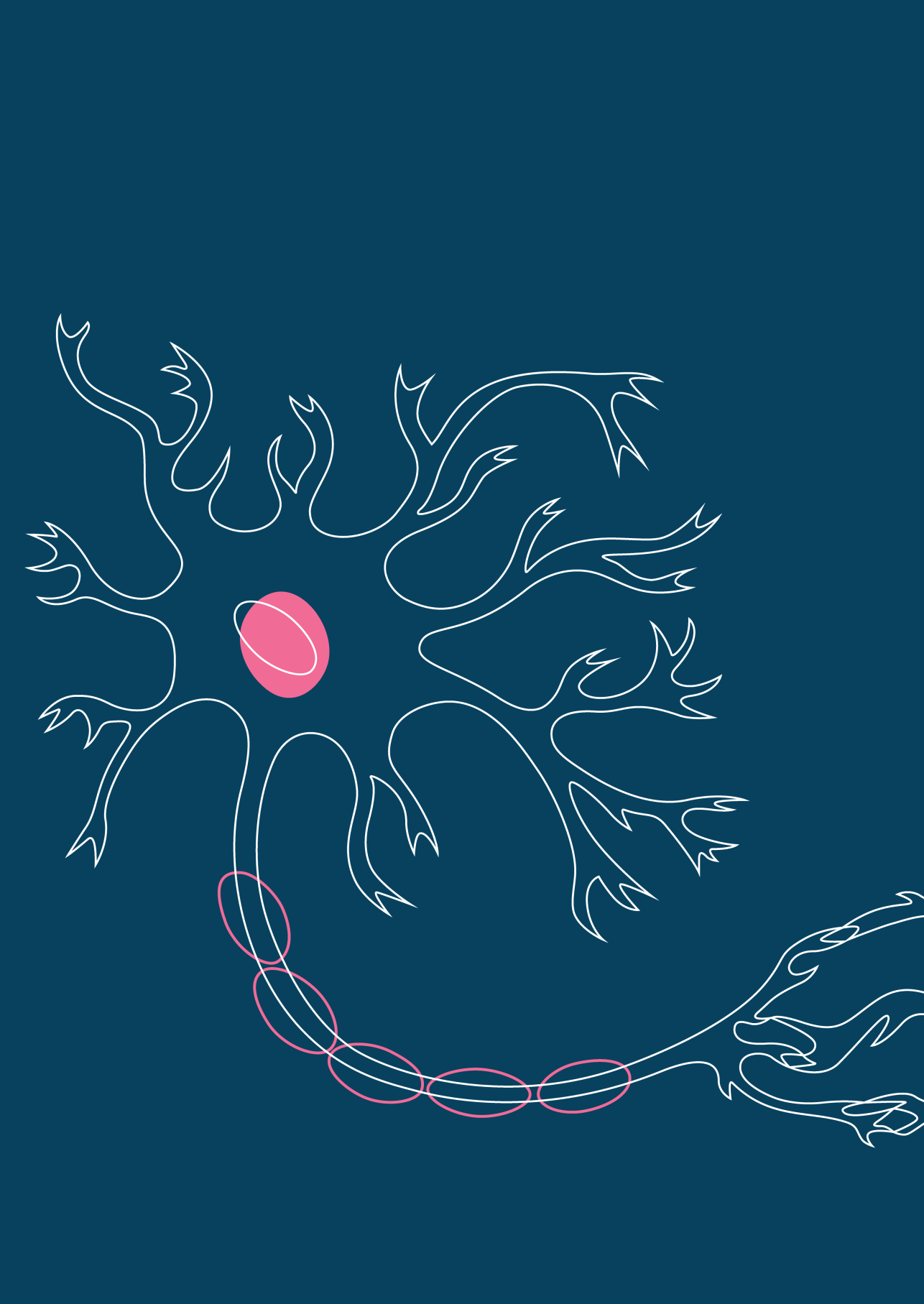

Withdrawal of intravenous immunoglobulin in chronic inflammatory demyelinating polyradiculoneuropathy

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ABSTRACT

Objective: Intravenous immunoglobulins (IVIg) are an efficacious treatment for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Biomarkers for disease activity are lacking, making the need for ongoing treatment difficult to assess, leading to potential overtreatment, and high health care costs. Our objective was to determine whether IVIg withdrawal is non-inferior to continuing IVIg treatment and to determine how often patients are overtreated.

Methods: We performed a randomized, double-blind, IVIg-controlled non-inferiority trial in seven centers in the Netherlands. Adults with clinically stable CIDP using IVIg maintenance treatment for at least 6 months were included. Patients received either IVIg withdrawal (placebo) as investigational treatment or continuation of IVIg treatment (control). The primary outcome was the mean change in logit scores from baseline to 24-weeks follow-up on the patient-reported Inflammatory Rasch-Overall Disability Scale (iRODS). The non-inferiority margin was predefined as between-group difference in mean change scores of -0.65. Patients who deteriorated could reach a relapse endpoint according to predefined criteria. Patients with a relapse endpoint after IVIg withdrawal entered a restabilization phase. All patients from the withdrawal group who remained stable, were included in an open-label extension phase of 52 weeks.

Results: We included 60 patients of whom 29 were randomized to IVIg withdrawal and 31 to continuation of treatment. The mean age was 58 years (SD 14.7) and 67% was male. The between-group difference in mean change iRODS scores was -0.47 (95%CI -1.24 to 0.31), indicating that non-inferiority of IVIg withdrawal could not be established. In the IVIg withdrawal group, 41% remained stable for 24 weeks, compared to 58% in the IVIg continuation group (-17%; 95%CI -39 to 8). Of the IVIg withdrawal group, 28% remained stable at end of the extension phase. Of the patients in the restabilization phase, 94% restabilized within 12 weeks.

Conclusion: It remains inconclusive whether IVIg withdrawal is non-inferior compared to continuing treatment, partly due to larger than expected confidence intervals leading to an underpowered study. Despite these limitations, a considerable proportion of patients could stop treatment and almost all patients who relapsed were restabilized quickly. Unexpectedly, a high proportion of IVIg treated patients

experienced a relapse endpoint, emphasizing the need for more objective measures for disease activity in future trials, as the patient reported outcome measures might not have been able to identify true relapses reliably. Overall, this study suggests that withdrawal attempts are safe and should be performed regularly in clinically stable patients.

INTRODUCTION

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a heterogeneous disease with an unpredictable disease course, which can be progressive, relapsing-remitting and monophasic.[1] Several studies demonstrated short term superiority of treatment with intravenous immunoglobulins (IVIg) over placebo in CIDP.[2] In patients who improve on treatment, maintenance treatment is often started as most patients run a chronic course.[1] However, there is limited evidence on how long maintenance treatment should be given and how IVIg dependency should be assessed. IVIg overtreatment in up to 60% of CIDP patients has been suggested in previous studies, based on lack of clinical deterioration in the patients who were included in placebo arms during a variable period of follow-up.[3-6] However, none of these trials were specifically designed to assess IVIg overtreatment.

Clinical evaluation after tapering or stopping IVIg is currently the only way to assess ongoing need for IVIg. Many patients and physicians are reluctant to perform withdrawal trials because of the risk of deterioration.[7] In practice, this means that many patients receive IVIg for years without verifying whether ongoing treatment is needed. Preventing IVIg overtreatment would reduce healthcare burden, adverse events and health care costs.

The objective of this study was to investigate whether withdrawal of IVIg treatment was non-inferior to continuing IVIg treatment in clinically stable CIDP patients and to determine how often these patients are overtreated with IVIg.

MATERIALS AND METHODS

Study design

We conducted a multicenter randomized, double-blind, non-inferiority trial in clinically stable CIDP patients based on the hypothesis that IVIg withdrawal is non-inferior to continuation of IVIg treatment. IVIg withdrawal was considered as the interventional treatment, while continuation of IVIg treatment was considered as the standard or control treatment. The trial was registered at the ISRCTN registry (ISRCTN13637698). In addition, we performed an open-label prospective follow-up study to provide a better estimate of the risks of IVIg withdrawal by assessing the

number of patients that successfully stopped IVIg for an additional period of 52 weeks, and by assessing the rates and time to full restabilization in patients who deteriorated after IVIg withdrawal.

The study was approved by the ethical committee of the Amsterdam UMC.

Patients

Patients were included in five university hospitals and two regional hospitals in the Netherlands from April 2014 until November 2018 when the last patient was included. Adult patients were eligible if they had been diagnosed with probable or definite CIDP according to the EFNS/PNS 2010 criteria, and had stable disease under IVIg treatment for at least six months with a treatment interval between 2 to 6 weeks.[1] Disease stability was judged by treating physicians; subjective, minor wear-off symptoms were permitted. Patients were excluded if they had experienced deterioration after IVIg withdrawal in the previous 12 months; if there were changes in IVIg dose or interval in the previous six months or changes in additional CIDP treatment (e.g. corticosteroids) in the previous three months; a prolonged period (>6 weeks) of disability increase following an earlier IVIg withdrawal attempt or a history of CIDP related respiratory failure. Written informed consent was obtained from all subjects according to the Declaration of Helsinki.

Randomization and masking

After informed consent, patients were randomly allocated to IVIg withdrawal or continuation of IVIg treatment. The randomization procedure was web-based (TENALEA, https://www.aleaclinical.eu/products/), using the non-deterministic minimization method as described by Pocock and Simon.[8] The method used duration of prior IVIg treatment (6-12 months versus > 12 months) for balancing. We chose the minimization procedure to prevent predictability of upcoming randomizations considering the fact that deblinding took place when a patient reached a study endpoint. After inclusion, the local investigator provided a prescription for IVIg to the trial pharmacist for a total period of 24 weeks. The randomization code and treatment allocations were provided by TENALEA also to the trial pharmacist. The pharmacist prepared investigational medicinal product (IMP). Blinded infusion bags and closure systems, and coated intravenous lines were used to ensure adequate masking. As IVIg/placebo volume ratio changed during tapering, volume and number of infusion bags of IVIg and/or placebo were adjusted to keep these parameters constant during

the first three study treatments in order to maintain blinding. An unblinded nurse prepared the IMP for administration at the central pharmacy site and transported IMP to patients' homes, where a second nurse, blinded for treatment allocation, administered the infusions. Outcome assessors were blinded for treatment allocation. After completion the final visit of each patient, the treating physician contacted the study team who contacted the trial pharmacist. The trial pharmacy disclosed the allocation of the patients to the treating physician. Deblinding during the trial was only possible in case of reaching a relapse endpoint requiring change or addition of treatment.

Procedures

After the baseline visit, patients received an unblinded IVIg treatment at the same dose and interval as prior to the study to measure trough and peak IgG levels. Serum was collected at the same day directly before and after the IVIg treatment. Patients received IMP infusions at the same interval as IVIg prior to the study (Fig. 1A). IVIg withdrawal consisted of an IVIg tapering phase and a placebo only phase. Tapering consisted of three infusions of 75%, 50% and 25% respectively of the patients' individual pre-study IVIg dose combined with placebo, which was followed by 100% placebo infusions. Placebo consisted of a sodium chloride solution (NaCl 0.9%) in identical volume as previous IVIg treatment. Patients allocated to continuation of treatment continued the same IVIg treatment (brand, dose and interval) as prior to the study. Follow-up visits were scheduled every 6 weeks. Patients received a phone call in between visits to monitor a possible relapse.

Patients randomized into the withdrawal group who reached a pre-defined relapse endpoint during follow-up received a rescue IVIg loading dose of 2 g/kg followed by maintenance IVIg treatment (Fig. 1B). A maintenance dose equal to the second last dose prior to first signs of deterioration was advised. For example, a patient who deteriorated after receiving 25% of his/hers baseline IVIg dose received a maintenance dose of 75% of the baseline IVIg dose after their rescue loading dose. We did not restart patients on a lower maintenance dose than 50% of their baseline IVIg dose. Total duration of the restabilization phase was 12 weeks. Visits were scheduled at 3, 6 and 12 weeks after administering the loading dose. There was no fixed restabilization schedule for patients randomized into the IVIg continuation group who reached a relapse endpoint. The treating physician made the decision if a loading dose, an extra dose or just continuation of treatment was necessary.

Patients from the IVIg withdrawal group who remained stable at 24 weeks were included in an open-label 52-week extension phase to assess potential relapses after the trial phase (Fig. 1C). In the extension phase, follow-up visits were scheduled at 12, 24 and 52 weeks, or earlier if a relapse occurred.

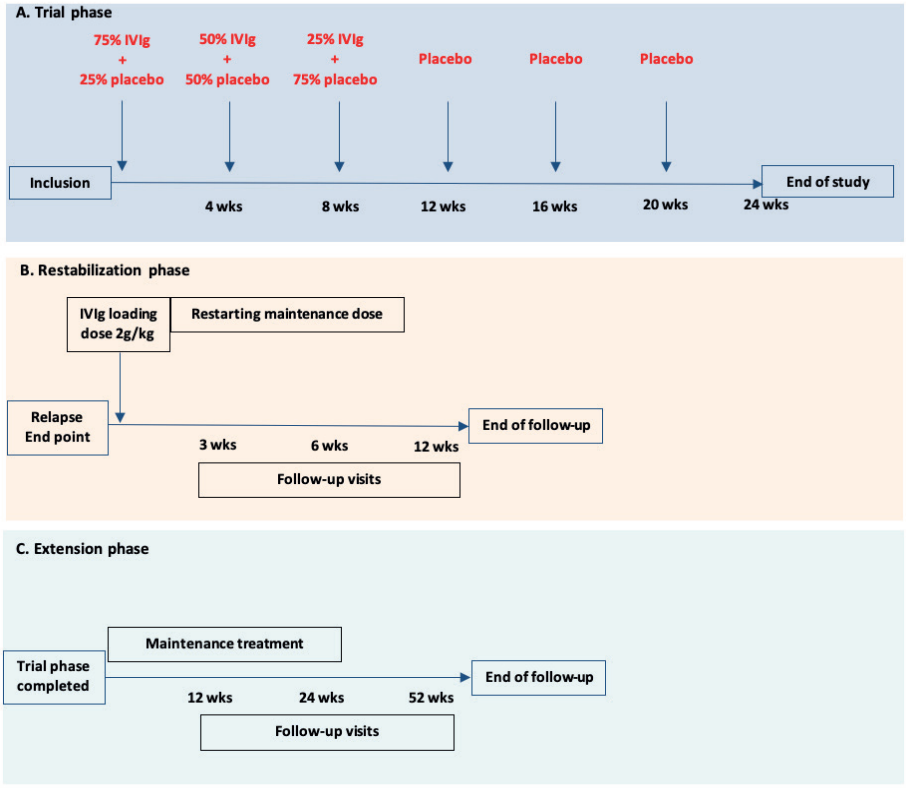


Figure 1. IVIg withdrawal schedule in a patient on a 4-weekly interval

Outcomes

Trial phase

The primary outcome was the mean change score from baseline to final follow-up on the inflammatory Rasch-Overall Disability Scale (iRODS). The iRODS is an interval disability scale based on Rasch methodology (Supplementary Table 1), with the standard unit of measurement expressed in logits.[9] The primary endpoint was reached at 24 weeks after first study treatment or earlier, in case of a relapse. In

the original protocol, a relapse endpoint was defined as a deterioration of >0.65 logits on the iRODS. In addition, deterioration warranting treatment according to the physicians' or patients' judgment was regarded as a relapse endpoint regardless of the iRODS-score.

The main secondary outcome was the proportion of patients who did not meet the criteria for a relapse endpoint and completed the 24-week follow-up. Other secondary outcomes were assessed at 24 weeks, or at a relapse endpoint if appropriate. These included: muscle strength measured using the Medical Research Council (MRC) sum score; grip strength (Martin-Vigorimeter) of the dominant hand or, in case of asymmetric weakness, the most affected hand; sensory impairment using the INCAT-Sensory Sum Score (INCAT-SS)[10]; pain using the Pain Intensity Numerical Rating Scale (PI-NRS); fatigue using a 7-item linear modified Rasch-built fatigue severity scale (FSS)[11]; disability using the generic AMC Linear Disability Score (ALDS)[12]; patient's perception of clinical deterioration or improvement on a 5-point patient global impression of change scale (PGIC), and quality of life using the 36-item Short Form Health Survey (SF-36).[13] Additional information on the outcome measures, including ranges of the scales can be found in Supplementary Table 1. The treating physician blinded for treatment allocation performed muscle strength, grip strength and sensory assessments. The other outcome instruments were based on patient self-reports. Assessments were scheduled every 6 weeks during 24 weeks of follow-up after the first IMP treatment, or earlier if a relapse was suspected. At the end of the study, patients were asked to guess to which treatment group they were allocated.

Restabilization phase

Restabilization was assessed using the individual MCID on the iRODS and grip strength. Additionally, restabilization was assessed using a 5-point patient global impression of change scale (PGIC). Patients and physicians were asked to indicate whether restabilization was reached up to the baseline level before entering the trial at each visit. For iRODS and grip strength, patients were considered restabilized if the score difference between follow-up (before IVIg withdrawal) and baseline) was less than the individual MCID on the iRODS and respectively less than 8 kPa on the grip strength, or if score at follow-up was higher than baseline. On the PGIC and physician's questionnaire, restabilization was defined by scores at follow-up indicating no change or better compared to baseline.

Extension phase

In the extension phase, the proportion of patients stable without the need of treatment 76 weeks after start of treatment withdrawal was assessed. This included the 24-week follow-up of the trial phase and 52-week follow-up of the extension phase. Stable disease was defined as no change or a change less than the MCID on the iRODS compared to baseline, without restart of treatment.

Protocol changes during study

The study protocol was changed twice during the study. After randomization of the first two patients (both received a single IMP), a paper was published that enabled calculation of the Minimally Clinically Important Difference (MCID) based on a change of at least 1.96 standard error, for each individual iRODS score across the iRODS continuum.[14] This MCID is equivalent to a score between 4 and 8 points on the non-linear scale (0-48 points) in clinical practice, depending on the individual baseline iRODS score. The study protocol was amended to define a relapse endpoint as the individual MCID on iRODS rather than a fixed cut-off of -0.65 logits.

Secondly, an explorative iRODS measurement was added just before the last regular IVIg infusion. This was advised by the data safety monitoring board (DSMB) to identify possible wear-off symptoms as a reason for the unexpectedly high number of patients in the IVIg group who reached a preliminary outcome.

Statistical analyses

Sample size calculation

Rationale of the non-inferiority margin

The non-inferiority margin was -0.65 logits. This non-inferiority threshold reflects a deterioration to a functional ability level of (0.35 - 0.65) = -0.30 logit. This means that an 'average' patient could still do shopping, but experience minor difficulties to walk one flight of stairs. This non-inferiority margin was considered clinically acceptable given the given the extremely high cost of IVIg, potential (severe) side effects of IVIG, the patient burden of treatment and possibility to restart IVIg if necessary. The non-inferiority margin corresponds with a deterioration of approximately 3 points on the non-linear iRODS score from 0-48.

Conceptual background of the sample size calculation

For the sample size calculation, we first defined a clinically acceptable deterioration on the iRODS in an average CIDP patient based on the original iRODS paper.[9] The functional ability level of stable patients on the iRODS ranges from -6.95 to 8.11 logits, with a mean logit score of 0.35 (SD 0.84).[9] We considered a non-inferiority margin of -0.65 logit (lower confidence interval of the difference in mean change score) as acceptable given the very high costs and patient-burden of IVIg overtreatment (for clarification see Supplementary Table 1). The null hypothesis being tested is that withdrawal of IVIg is not non-inferior to the treatment continuation. In other words, withdrawal is worse than continuation of treatment. If the null hypothesis is rejected, withdrawal is not worse than continuation. The null hypothesis is rejected, if the lower bound of the 95% confidence interval of the difference between withdrawal and continuation of treatment is higher than -0.65.

When statistical testing the null hypothesis a one-sided 0.025 significance level is used as we are only interested in the lower boundary of the 95% confidence interval.

Sample size calculation

When the sample size in each group is 27, a two group one-sided 0.025 significance level t-test will have 80% power to reject the null hypothesis that withdrawal of IVIg treatment is more than 0.65 logit of mean change scores worse than continuation of IVIg treatment (difference μW minus μC <-0.65) in favour of the alternative hypothesis that the mean change score of withdrawal of IVIg treatment is more alike or even better than the mean change score of continuation of IVIg treatment (difference μW minus μC >-0.65). It was assumed that the expected difference in mean change scores is 0 and the common standard deviation is 0.84. Anticipating a 10% attrition rate, 30 (27/0.90) patients per treatment arm (60 patients in total) were included.

Trial phase

The primary outcome was statistically tested for non-inferiority. based on the intention-to-treat principle. Additionally, the primary outcome was also analyzed on a per-protocol basis. The intention to treat population included all randomized patients, regardless of protocol deviations. The per-protocol population encompassed patients included and treated in accordance with the study protocol. Patients who had been unblinded were excluded from the per-protocol population (supplementary table 3).

Baseline assessments were summarized using simple descriptive statistics. The main analysis focused on the between-group difference in the mean change iRODS (logit) scores. Statistical uncertainty of this difference was expressed in a two-sided 95% Confidence Interval (CI). If the lower limit of the CI crosses the non-inferiority margin of -0.65 logits, non-inferiority of the IVIg withdrawal group cannot be established (for additional explanation, see also the previous text in the subsection 'Sample size calculation'). Inferiority can be established when the upper limit of the CI is below the non-inferiority margin.

Additionally, the non-inferiority of treatment withdrawal was tested using multivariable linear regression with iRODS follow-up scores as the dependent variable, adjusting for both the iRODS baseline scores and the minimization variable (duration of prior IVIg treatment). The linear regression modelling was performed within the context of a non-inferiority design. The coefficient for withdrawal treatment was expressed with its 95% CI.

Regarding the secondary endpoints, baseline, endpoint and group change scores were summarized using descriptive statistics. In all secondary outcomes analyses statistical uncertainty was expressed in two-sided 95% CI. As the MRC scores were not normally distributed we expressed the point estimate and CI were analyzed using the Hodges-Lehmann approach.[15]

Unplanned post-hoc analysis

We described the number of patients experiencing wear off symptoms at start of trial and with a relapse endpoint during the trial phase. Furthermore, the between-group difference in the time to relapse endpoint was analyzed by plotting Kaplan-Meier curves and comparing them using the log-rank test.

Restabilization phase

For the restabilization phase, we described the number of patients who restabilized within 12 weeks on the different scales.

Extension phase

For the extension phase, we described the number of patients from the IVIg withdrawal group with stable disease at end of follow up.

An independent DSMB performed an interim safety analyses after 10 patients reached a relapse endpoint and after the inclusion of 30 patients. No interim efficacy analyses were performed. Sample size calculation and statistical analyses were performed in nQuery (v8.5.1) and IBM SPSS Statistics (v25), respectively.

RESULTS

A total of 96 patients were considered eligible (Figure 2) and 60 patients were included between April 2014 and November 2018. Twenty-nine patients were allocated to the IVIg withdrawal group and 31 to the IVIg continuation group (Figure 2).

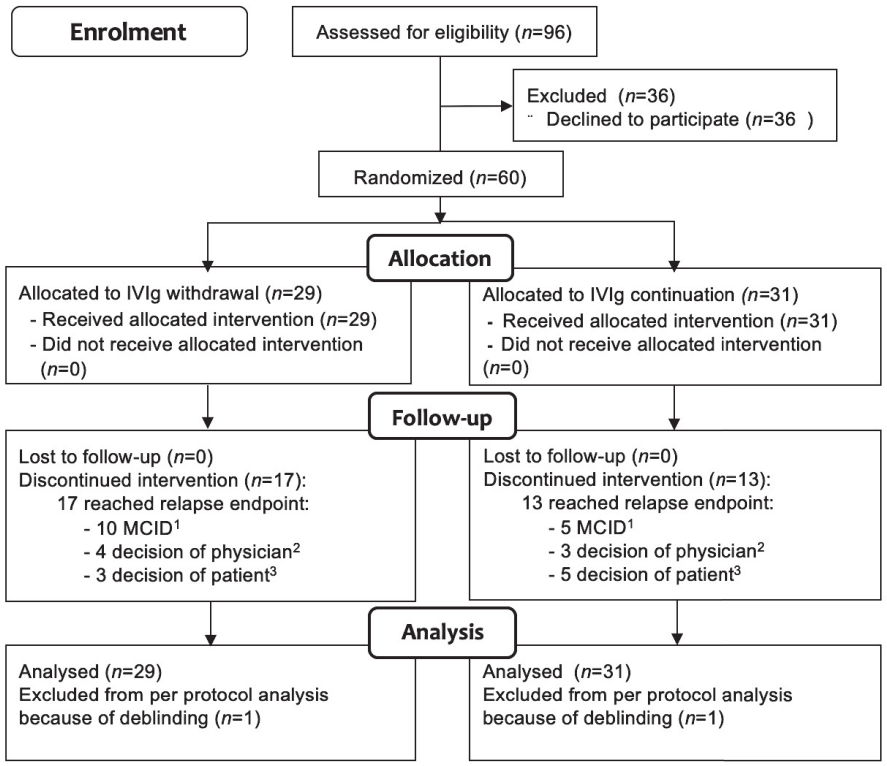


Figure 2. Enrolment and randomization

1: MCID on iRODS, 2: Decision of treating physician: relapse, but not captured on the iRODS, 3: Decision of patient: subjective relapse.

Abbreviations: MCID: individual minimal clinically important difference

Table 1. Baseline demographic and clinical characteristics

	IVIg withdrawal group (29)	IVIg continuation group (31)
Sex Male	21 (72%)	21 (68%)
Age (mean ± SD, (range))	60.1 (13.54, 21-86)	(15.97, 29-81)
CIDP		
Typical	25 (86%)	22 (71%)
Atypical	4 (14%)	9 (29%)
Asymmetric CIDP	2 (7%)	4 (13%)
Pure motor/sensory	2 (7%)	5 (16%)
Disease duration in months (median, range)	64 (7-586)	50 (9-299)
Wear off symptoms	6 (21%)	9 (29%)
MRC sum score (median, range)	58 (38-60)	60 (49-60)
Grip strength (mean ± SD, [range])	84kPa (SD 34.37; 18-145)	79kPa (SD 28.29; 9-155)
Duration of IVIg treatment:		
6-12 months	15 (52%)	16 (51%)
>12 months	14 (48%)	15 (49%)
Patients with previous withdrawal attempts	11 (38%)	54%)
IVIg interval		
2 weeks	3 (10%)	1 (3%)
3 weeks	16 (55%)	16 (52%)
4 weeks	9 (31%)	9 (29%)
5 weeks	-	3 (10%)
6 weeks	1 (3%)	2 (6%)
IVIg dose per infusion (median, range)	45g (10-80)	40g (10-80)
IVIg brand		
Nanogam®	18 (62%)	16 (52%)
Kiovig®	10 (35%)	14 (45%)
Privigen®	1 (3%)	0
Gamunex®	0	1 (3%)
Immunosuppressive treatment besides IVIg[a]	1 (3%)	0 (0%)
Serum IgG level change after last regular IVIg infusion[b] (mean ± SD)	13.19g/l (SD 7.99)	12.80g/l (SD 5.78)
iRODS (mean ± SD) **- Logits**	3.80 (SD 2.86)	4.66 (SD 2.29)

[a]daily oral prednisone 5mg for rheumatic polymyalgia, [b] serum was collected before and after IVIg treatment at the day of the treatment.
Abbreviations: IVIg: intravenous immunoglobulins, SD: standard deviation

Baseline characteristics in both groups were comparable (Table 1). The baseline iRODS logit scores were higher in the IVIg continuation group (mean 4.66 [SD 2.29]) compared to the withdrawal group (3.80 [SD 2.86]). Previous treatment withdrawal attempts had been performed in 11 out of 29 patients (38%) in the IVIg withdrawal group and in 15 out of 31 patients (54%) in the IVIg continuation group. Wear off symptoms were reported in 6 out of 29 patients (21%) in the IVIg withdrawal group and 9 out of 31 patients (29%) in the IVIg continuation group.

Trial phase

In the IVIg withdrawal group, 17 of 29 patients (59%) reached a predefined relapse endpoint compared to 13 of 31 (42%) in the IVIg continuation group. In other words, 12 out of 29 (41%) and 18 out of 31 patients (58%) respectively remained stable during the 24-week follow up in the trial phase (difference -17%; 95% CI -39 to 8) Of the patients with a relapse endpoint, 10 out of 17 patients (59%) in the IVIg withdrawal group worsened by their individual MCID on the iRODS compared to 5 out of 13 (38%) in the IVIg continuation group.

The primary outcome is depicted in Figure 3. Both groups showed a lower mean logit score at endpoint compared to baseline. The between-group difference in mean change scores was -0.47 (95% CI: -1.24 to 0.31). The results from the primairy outcome were inconclusive. As the lower bound of the CI crosses the non-inferiority margin of -0.65, non-inferiority of IVIg withdrawal could not be demonstrated. Alternatively, we could also not demonstrate that IVIg withdrawal was significantly inferior to IVIg continuation, as the upper bound of the CI was not below the non-inferiority margin. Additional multivariable linear regression also fails to demonstrate non-inferiority of IVIg withdrawal. After adjustment, the coefficient for withdrawal treatment was -0.56, with the lower bound of the CI well below the non-inferiority margin of -0.65 (95% CI: -1.35 to 0.23). See Appendix 1 for further details.

In total, 28 patients from the IVIg withdrawal group and 30 patients from the IVIg continuation group were included in the per-protocol analysis. Two patients were excluded because of early unblinding (Supplementary Table 3). In the per-protocol population too, non-inferiority in the withdrawal group could not be demonstrated, with the lower bound of the CI of the between-group difference in mean change scores of -0.47 again well below the non-inferiority margin (95% CI -1.27 to 0.33).

Results of the secondary outcomes are shown in Table 2. In general, variable levels of deterioration were observed in all outcomes in both study arms. However, the deterioration seemed to be more pronounced in the IVIg withdrawal group with regard to grip strength and the PGIC. Figure 4 shows the proportion of patients that reached a relapse endpoint on the different time points in both groups. There was no significant difference in time to relapse between both treatment groups.

IVIg withdrawal group			IVIg continuation group			Treatment comparison		
n	Mean Baseline score	Mean Follow up score	*n*	Mean Baseline score	Mean Follow up score	Mean change score withdrawal group	Mean change score continuation group	Between-group difference in mean change scores (95% CI)
29	3.80 (SD 2.86)	2.81 (SD 3.10)	31	4.66 (SD 2.29)	4.13 (SD 2.55)	-1.00 (SD 1.56)	-0.53 (SD 1.43)	-0.47 (-1.24 to 0.31)

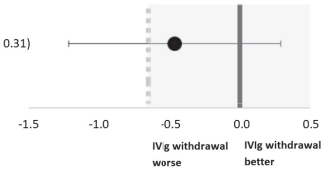


Figure 3. Primary outcome

Between-group comparisons of the primary outcome expressed in mean change logit scores on the iRODS. The dotted line represents the non-inferiority margin of -0.65. The shaded area marks the non-inferiority zone. † Reported mean changes and differences in mean changes may slightly differ from apparent differences due to rounding.

Abbreviations: IVIg: intravenous immunoglobulin; 95% CI: 95% Confidence Interval; SD: standard deviation;

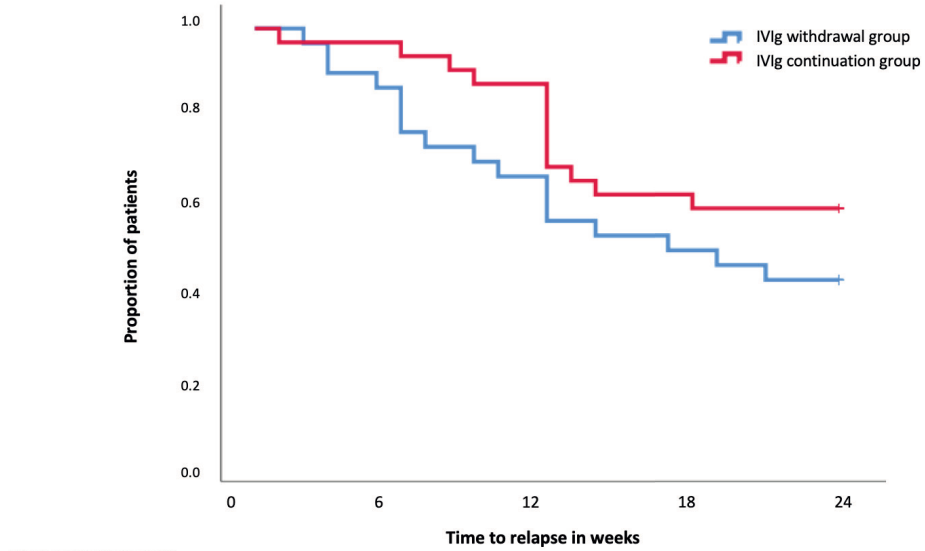
Table 2. Secondary outcomes

	IVIg withdrawal group				IVIg continuation group				Treatment comparison	
	N	Baseline	Endpoint	Mean Change†	N	Baseline	Endpoint	Mean Change†	Difference in mean change scores	95% CI
MRC sum score (median, range)	29	58 (38-60)	58 (41-60)	0* (-10-3)	31	60 (49-60)	59 (42-60)	0* (-7-2)	0**	-1 to 0**
Grip strength (mean ± SD)	29	85.3 kPa (34.4)	73.5 kPa (31.2)	-11.8 kPa (14.2)	31	79.3kPa (29.2)	75.8 kPa (28.9)	-3.5 kPa (17.8)	-8.3	-16.8 to 0.2
INCAT-SS (mean ± SD)	29	5.2 (4.6)	5.6 (4.2)	0.4 (2.4)	31	3.8 (3.7)	3.5 (3.6)	-0.4 (2.3)	0.8	-0.4 to 2.0
PI-NRS (mean ± SD)	28	1.6 (1.9)	2.4 (2.5)	0.8 (2.4)	29	1.8 (2.4)	2.3 (2.5)	0.5 (1.6)	0.2	-0.9 to 1.3
FSS score (mean ± SD)	27	35.0 (10.1)	35.9 (12.1)	0.9 (6.5)	29	31.9 (12.3)	32.9 (12.4)	1.0 (10.8)	-0.1	-6.3 to 4.0
ALDS (mean ± SD)	27	83.2 (10.3)	80.6 (12.5)	-2.6 (7.4)	30	87.4 (6.0)	86.7 (11.7)	-0.7 (5.0)	1.9	-1.5 to 5.3
SF-36 (mean ± SD)	27				29					
Physical component		42.1 (9.9)	37.8 (11.2)	-4.4 (9.4)		45.2 (8.5)	41.2 (10.5)	-4.0 (8.9)	-0.4	-5.3 to 4.5
Mental component		50.9 (10.3)	53.1 (7.9)	2.1 (9.4)		49.7 (11.8)	47.9 (12.4)	-1.8 (13.9)	3.9	-2.4 to 10.4
PGIC scale (n (%))	27				29					
Same or better than prior to study		NA	10 (37%)	NA		NA	17 (59%)	NA	NA	-44 to 4
Worse than prior to the study		NA	17 (63%)	NA		NA	12 (41%)	NA	NA	

† Reported mean changes and differences in mean changes may slightly differ from apparent differences due to rounding.

** Median change scores on the MRC. ** The within-group median change score was calculated as the 50th percentile of all individual differences; ** Between-group difference on the MRC expressed in median difference in change scores; point estimate and 95% CI were analysed using the Hodges-Lehmann approach.*

Abbreviations: IVIg: intravenous immunoglobulin; MRC: Medical Research Council; INCAT-ss: INCAT sensory sum score; SF 36: Short Form 36; ALDS: AMC Linear Disability Score; FSS: Fatigue severity scale; PI-NRS; Pain intensity numeric rating scale; PGIC: patient global impression of change; 95% CI: 95% Confidence Interval



Number of patients at risk					
IVIg withdrawal	29	25	10	14	12
IVIg continuation	31	30	27	19	18

Figure 4. Relapse endpoint during trial phase in both treatment arms
Abbreviations: IVIg: intravenous immunoglobulins

Table 3. Post hoc analyses in patients who reached a relapse endpoint

		IVIg withdrawal group			IVIg continuation group			Treatment comparison	
		N	Baseline	Mean Change	N	Baseline	Mean Change	Difference in mean change scores	95% CI
iRODS(mean ± SD)	Relapse endpoint	17	3.3 (3.1)	-1.9 (1.3)	13	3.9 (2.6)	-1.3 (1.0)	0.54	-0.33 to 1.42*
Logits	MCID Endpoint[a]	10	3.4 (2.4)	-2.5 (1.2)	5	4.3 (2.7)	-2.2 (0.8)	-0.3	-1.6 to 1.01
MRC sum score (median, range)	Relapse endpoint	17	58 (38-60)	0 (-10-3)**	13	60 (49-60)	-1 (-7-0)**	0***	-1.0 to 2.0***
	MCID Endpoint	10	58.5 (52-60)	-2 (-10-0)	5	60 (52-60)	0 (-6-0)	0***	-4.0 to 2.0***
Grip strength (mean ± SD)	Relapse endpoint	17	79.5 kPa (38.1)	-16.4 (15.4)	13	77.6 kPa (32.7)	-11.6 (17.9)	-4.9 kPa	-17.8 to 8.1
	MCID Endpoint	9	87.8 kPa (42.2)	-19.4 (15.2)	5	82.0 kPa (52.8)	-5.6 (9.0)	-13.8	-30.1 to 2.4
INCAT-SS (mean ± SD)	Relapse endpoint	17	5.7 (5.1)	0.8 (2.2)	13	4.2 (3.5)	0.5 (2.9)	0.3	-1.7 to 2.2
	MCID Endpoint	10	5.7 (4.1)	1.1 (2.3)	5	2.8 (3.0)	1.8 (2.2)	-0.7	-3.4 to 2.4
PI-NRS (mean ± SD)	Relapse endpoint	16	1.8 (2.0)	1.8 (2.7)	11	2.0 (2.5)	1.1 (1.7)	0.7	-1.2 to 2.4
	MCID Endpoint	9	1.1 (1.7)	3.1 (2.6)	5	1.2 (2.7)	1.4 (2.2)	1.7	-1.3 to 4.7
FSS score (mean ± SD)	Relapse endpoint	16	31.7 (13.1)	-6.0 (6.5)	11	32.3 (13.0)	-4.4 (8.0)	-1.6	-7. to 1.4
	MCID Endpoint	9	37.0 (7.4)	-6.2 (7.0)	5	33.0 (11.5)	-6.6 (4.6)	0.4	-9.6 to 10.3
ALDS (mean ± SD)	Relapse endpoint	15	81.4 (11.1)	-3.9 (9.6)	13	85.3.8 (9.2)	-2.6 (18.1)	1.4	-5.8 to 8.6
	MCID Endpoint	10	82.9 (7.9)	-7.1 (9.1)	4	79.8 (11.1)	-7.4 (11.3)	-0.2	-12.8 to 12.3

Table 3. (Continued)

		IVIg withdrawal group			IVIg continuation group			Treatment comparison	
		N	Baseline	Mean Change	N	Baseline	Mean Change	Difference in mean change scores	95% CI
SF-36 (mean ± SD)	Relapse endpoint	15	38.8 (10.5)	-7.2 (10.1)	12	42.4 (8.6)	-8.0 (8.4)	0.8	-6.7 to 8.9
Physical component	MCID Endpoint	9	41.2 (9.3)	-10.9 (10.0)	4	41.5 (11.3)	-8.8 (9.8)	-2.1	-15.3 to 11.0
Mental component	Relapse endpoint	15	50.9 (10.1)	0.3 (8.4)	12	47.2 (13.5)	-4.5 (16.6)	4.8	-5.3 to 14.9
	MCID Endpoint	9	51.4 (10.2)	-0.5 (5.8)	4	44.7 (18.9)	-3.8 (23.0)	3.2	-34.2 to 40.7

[a] patients who reached an relapse endpoint based on the minimal clinically important difference on the iRODS. Change of -1,9 logits and -1,3 logits on the iRODS correspond with -12.4 and -8.8 centile points respectively. Difference in mean change score of 0,54 logits corresponds with 3.6 centile points.

** Point estimate and 95% CI were analysed using an independent sample t-test according superiority analysis;*

*** The within-group median change score was calculated as the 50th percentile of all individual differences; *** Between-group difference on the MRC expressed in median difference in change scores; point estimate and 95% CI were analysed using the Hodges-Lehmann approach;*

Abbreviations: IVIg: intravenous immunoglobulins; MRC: Medical Research Council; INCAT-ss: INCAT sensory sum score; SF 36: Short Form 36; ALDS AMC Linear Disability Score; FSS: Fatigue severity scale; PI-NRS; Pain intensity numeric rating scale; 95% CI: 95% Confidence Interval

Restabilization

Patients from the IVIg withdrawal group with a relapse endpoint during the trial phase entered the restabilization protocol. Overall, 16 out of 17 (94%) restabilized within the restabilization phase of 12 weeks on iRODS and grip strength (Table 4). At 12 weeks, 14 out of 15 (93%) restabilized on the PGIC scale, and 15 out of 17 (88%) according to the treating physician. After the loading dose, five patients were restarted on a lower IVIg dose, based on the second to last dose on which they were stable during the trial. All five patients relapsed again during the follow up period.

Of the 13 patients who reached a relapse endpoint in the IVIg continuation group, two patients received a loading dose of IVIg (2g/kg over 5 days), four patients received an extra IVIg dose and in seven patients their maintenance treatment was continued. During the extension phase, three patients needed a higher maintenance dose or shorter interval and in four patients the maintenance dose was not changed. In two patients the maintenance dose was lowered and in two patients the treatment was successfully stopped.

Extension phase

The 12 patients from the IVIg withdrawal group who remained stable during the trial phase entered the extension phase. Four patients relapsed during the additional 52-week follow up, two of whom just prior to their final visit. Overall, 8 out of 29 (28%) patients from the IVIg withdrawal group remained stable during the trial and extension phase (combined duration 76 weeks).

Table 4. Number of restabilized patients on different time points

	Week 3	Week 6	Week 12
iRODS	15/17 (88%)	15/17 (88%)	16/17 (94%)
Grip Strength	12/17 (71%)	14/17(82%)	16/17 (94%)
PGIC scale	9/15 (60%)	13/16 (81%)	14/15 (93%)
Restabilization according to physician	13/16 (81%)	14/17 (82%)	15/17 (88%)

Abbreviations: iRODS: Inflammatory Rasch Overall Disability Scale, PGIC: patient global impression of change

DISCUSSION

We could not demonstrate non-inferiority of withdrawal of IVIg maintenance treatment compared to continuation of treatment in clinically stable CIDP patients, as our study turned out to be underpowered due to much larger than expected confidence intervals. We chose a non-inferiority design as this reflects best the clinical equipoise in patients who are stable on maintenance IVIg treatment. Efficacy of IVIg in CIDP in patients with active disease has been demonstrated in various trials and we expected that a proportion of patients would need ongoing treatment, as also demonstrated in this study. Our hypothesis was that many patients on chronic treatment do not have active disease requiring further treatment, leading to non-inferiority on disability level on a group level and that in these stable patients, withdrawing IVIg will not lead to deterioration in their daily functioning and permanent disability.

As expected, our findings confirm that many CIDP patients included in this trial required IVIg maintenance treatment. Nevertheless, our study also confirms that a large proportion of patients do not need IVIg maintenance treatment as 41% remained clinically stable at 24 weeks after IVIg withdrawal during the trial. Overall, 28% remained stable during 76 weeks after start of IVIg withdrawal. It might be possible that some of these patients experience a relapse after these 76 weeks as reported by Nobile-Orazio et al.[16] However, the majority of relapse endpoints in both groups were reached within 12 weeks, as illustrated by Figure 4. Also in other studies, including the larger FORCIDP trial and the ICE trial, a relapse in most patients occurred within the first months after treatment withdrawal.[4,6] Together with other studies, this suggests that most IVIg-dependent patients can be identified within 3-6 months after IVIg withdrawal.[3,16]

If the main objective of an IVIg treatment withdrawal is to determine whether there is any disease activity, stopping treatment directly is probably the fastest way to determine IVIg dependency. Our experience is that many patients feel more comfortable with slower withdrawal rather than directly stopping treatment. This was the main reason to choose a 3-step withdrawal schedule, in which the initial maintenance dose was lowered with 25% per infusion. Currently, there is no consensus on the optimal way to attempt IVIg withdrawals. This is the first study that uses the three-step withdrawal schedule, while in previous studies IVIg was

often directly stopped. It is not clear whether IVIg dependent patients deteriorate less severely or restabilize more quickly after tapering compared to directly stopping treatment. In the open-label IVIg dependency test of the PATH study, 11% of patients who stopped IVIg treatment and deteriorated could not be restabilized to their baseline disability score during a 12-week follow-up.[17] In this study, all but one patient with a relapse endpoint in our withdrawal group were restabilized within 12 weeks. More importantly, a vast majority of patients were considered restabilized by 3 weeks on the iRODS. As we expected that not all patients with a relapse endpoint would reach their MCID on the iRODS, we also used grip strength and restabilization as perceived by the patient as well as the treating physician to assess restabilization. Similar proportions and speed of restabilization was seen when using these alternative scales. All patients were considered restabilized within 24 weeks. Therefore, the 3-step withdrawal schedule in combination with a loading dose of IVIg, if a patient relapses, used in this study appears to be a safe method to assess IVIg dependency, but given the small numbers of patients and not universally accepted criteria of restabilization, we cannot confirm that complete restabilization will occur in all patients. In addition, although restabilization was fast in the majority of patients, occasionally restabilization can take more time in some patients which will probably also influence future withdrawal attempts.

There is no commonly accepted threshold of a relapse in IVIg withdrawal or IVIg substitution trials. Generally, in CIDP, disability scales are considered the most appropriate outcome scales for both improvement and deterioration, but some have advocated to include impairment scales to determine deterioration.[18] This study was designed to limit deterioration as much as possible to prevent long-term disability. Therefore, we used a broader definition for a relapse endpoint, in which we allowed the judgment of the treating physicians as well as the patients, that probably also mirrors clinical practice. Not allowing severe relapses, might explain why there was no difference on the secondary outcomes between both groups when focusing only on patients who reached a relapse endpoint. Unexpectedly however, 42% of the IVIg continuation group also reached a relapse endpoint. Disease progression despite IVIg treatment is an unlikely cause of the high number of patients with a relapse endpoint, as all were considered to have stable disease at inclusion and because they were treated with the same IVIg brand, dose and interval during the trial. Fluctuations of symptoms might have contributed to this finding, especially when a longer follow-up period is performed. A minority of patients reported wear-

off symptoms at the end of an IVIg cycle prior to the study that might have resulted in patients experiencing deterioration between infusions during the trial. However, wear-off symptoms were not associated with a relapse endpoint nor were they captured by deterioration on the iRODS between baseline and the last pre-trial infusion. Interestingly, of the patients who reached a relapse endpoint, a smaller proportion of patients in the IVIg continuation group reached their MCID on the iRODS compared to the withdrawal group (38% vs. 59%). Similarly, the proportion of patients with a relapse endpoint, whose endpoint was based on subjective deterioration as perceived by the patient, was higher in the IVIg continuation group (38% vs. 18%). These findings emphasize the need to use validated clinical outcome measures, although further studies are needed to determine the clinically relevant differences on these scales. This is illustrated also by the fact that almost half of patients who reached a relapse endpoint in the IVIg continuation group reached commonly accepted MCID criteria for grip strength and MRC sum score.

Finally, as patients can be reluctant to undergo IVIg withdrawal because of fear of increase of symptoms or reduced functioning, the possibility of being randomized to placebo might have led to a nocebo effect in some of our patients. Nocebo effect refers to the phenomenon that negative expectations of patients have a negative effect on the outcome.[19] A clear majority of patients in this study indicated at their final visit that they received placebo, including half of patients from the IVIg continuation group who remained stable during the trial period, both supporting this hypothesis of nocebo effect. This is in line with a recent systematic review showed a considerable nocebo effect in CIDP trials especially when using non-deterioration as the primary endpoint.[20] Importantly, a nocebo effect in this study might also have led to a higher proportion of patients with a relapse endpoint in the withdrawal group, and an underestimate of overtreatment. In addition, entering the trial might have been a negative trigger for patients to report worse than they normally would have (observation bias). Some patients might have been reluctant to take part in the trial as suggested by the 30% of eligible patients that were not willing to participate in the study. This, together with the use of subjective outcome measures might have skewed the results in both treatment groups towards more frequent deterioration.

This study had several limitations. First of all, the results of our primary outcome was inconclusive. We observed higher than expected standard deviations of the

iRODS changes scores in both treatment groups, partly due to the unexpectedly high number of patients in the IVIG continuation group who reached a relapse endpoint. As this lead to an imprecise estimate, this means that our study turned out to be underpowered to address the primary question. Also, the non-inferiority margin was based on an earlier published average patient logit score of 0.35 on the iRODS and the MCID at this position of the scale.[9] In our study, baseline scores in the IVIg withdrawal and continuation group were considerably higher. However, the non-inferiority margin of -0.65 logits remains valid, as the size of the individual MCID based on the expected average score was comparable to the individual MCID based on the (higher) average score found in this study. The non-inferiority margin might also be considered to be large and was based on what we believe is an acceptable clinically relevant deterioration, given the extremely high cost of IVIg, potential (severe) side effects of IVIG and the patient burden of treatment.

Furthermore, a total of 50% of patients reached a relapse endpoint during the trial, of which only half were captured by the predefined MCID on the iRODS. We believe that patients who experience minor deterioration consider this as clinically important when they are on a stable IVIg dose. For these reasons, the use of the patient-reported disability scale, such as the iRODS, as the only primary outcome measure might also be considered as a limitation in this trial. Combining the iRODS with impairment measurements, such as grip strength, could have made reported health changes more objective.[21] On the other hand, a more stringent definition of a relapse endpoint would probably have led to less willingness of patients to participate in the study. More important, it would limit the external validity of the results as we believe that the patient's voice is often leading in the decision to restart IVIg.

The inclusion rate was slow, as over 30% of eligible patients refused to participate in the study. This may have resulted in a selection of patients, limiting external validity. The majority of these patients did not want to taper treatment, although some wanted to stop treatment directly or preferred slower tapering than used in the trial. Additionally, we only included patients who were previously stable. Withdrawal attempts in patients with unstable disease should generally be avoided as it is uncertain whether these patients can be restabilized as well as in our study population.

We did not have any missing data on the primary endpoints and no patients were lost to follow-up. Two patients were unblinded during the trial. Both patients completed the follow-up without experiencing a relapse endpoint and were included in the intention-to-treat analysis, but were excluded in the per protocol analysis. Before deblinding, all patients who deteriorated (both treatment groups) guessed that they received placebo, while similar proportions of patients who remained stable guessed their treatment allocation correctly. For these reasons, we do not have reason to believe that blinding was not maintained in this study.

In conclusion, it remains inconclusive whether IVIg withdrawal is non-inferior compared to continuing treatment, partly due to much larger than expected confidence intervals, leading to an underpowered study. Despite these limitations, we found that a considerable proportion of CIDP patients could stop treatment. This study emphasizes that treatment withdrawal is safe and suggests that attempts should be performed regularly in clinically stable CIDP patients, preferably including objective measurements. In our experience, discussing withdrawal attempts with patients when starting IVIg prevents reluctance in patients when a withdrawal attempt is actually planned in the future. Until we identify biomarkers of disease activity that can identify patients in need of IVIg maintenance treatment, we should probably use at least one objective outcome measure instead of solely relying on patient reported outcomes, both in trials as well as clinical practice. Alternatively, for future withdrawal studies, other approaches such as a causal interference design might be considered, that allow studying the effect of an intervention with adjustment for different confounders, without the need for randomization.[22]

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AUTHOR CONTRIBUTIONS

Ilse Lucke: data collection, drafting/revising the manuscript and analysis or interpretation of data, Max Adrichem: data collection, drafting/revising the manuscript and analysis or interpretation of data, Alexander Vrancken: data collection, drafting/revising the manuscript, Stephan Goedee: data collection, drafting/revising the manuscript, Luuk Wieske: drafting/revising the manuscript and analysis or interpretation of data, Marcel Dijkgraaf: drafting/revising the manuscript, study concept or design and analysis or interpretation of data, Nicol Voermans: data collection, drafting/revising the manuscript, Nicolette Notermans: data collection, drafting/revising the manuscript, Catharina Faber: data collection, drafting/revising the manuscript, Leo Visser: data collection, drafting/revising the manuscript, Krista Kuitwaard: data collection, drafting/revising the manuscript, Pieter van Doorn: data collection, drafting/revising the manuscript, Ingemar Merkies: drafting/revising the manuscript and study concept or design, Rob de Haan: drafting/revising the manuscript, study concept or design and analysis or interpretation of data, Ivo van Schaik: drafting/revising the manuscript, study concept or design and analysis or interpretation of data, Filip Eftimov: drafting/revising the manuscript, study concept or design and analysis or interpretation of data.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Outcome Measures

Outcome	Measure	Description	Range
Primary outcome			
Disability	Inflammatory Rasch-Overall Disability Scale (iRODS)	Patient reported linear disability scale, developed within the frame work of Item Response Theory[1] Unit of measurement expressed in logits Higher scores represent lower levels of disability	Logits: -6.95 - 8.11
Secondary outcomes			
Muscle Strength	Medical research council (MRC) sum score	6 pairs of muscles Shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension and foot dorsiflexion Higher scores represent more muscle strength	0-60
Grip Strength	Martin Vigori meter	Measured in kilo Pascal (kPa) Higher score represents greater grip strength Highest value out of 3 measurements per hand Dominant hand in typical CIDP and most affected hand in multifocal or asymmetric CIDP	0-160
Sensory impairment	Modified INCAT sensory Sum score (INCAT-SS)	Sensory scale including vibration and pinprick sense plus a two-point discrimination value Higher score represents more sensory impairment	0-20
Pain	Pain Intensity Numerical Rating Scale (PI-NRS)	Average pain over the past 4 weeks Higher score represents more pain	0-10
Fatigue	Rasch-built fatigue severity scale (FSS)	7 item scale Higher score represents greater fatigue	0-49
Disability	AMC linear disability score (ALDS)	A calibrated generic item bank to measure the level of physical disability in patients with chronic diseases. Higher scores represent lower levels of disability	0-100
Quality of life	Short form 36 (SF-36)	Divided into physical and mental health components Higher scores represent better quality of life	Normalized to the Dutch population mean score of 50 and a SD of 10
Patient's perception of deterioration or improvement	Patient global impression of change scale	5 point Likert-scale on which patients indicate if their CIDP complaints are much better, better, similar, worse or much worse than before start of the study	NA

Supplementary Table 2. Protocol violations

Patient	Protocol violation	Study action
1	Patient in the withdrawal group refused to stay blinded at 12 weeks due to anxiety of not knowing what the treatment allocation was. This patient agreed to proceed with follow-up assessments and remained stable until last follow-up visit.	- Included in intention-to-treat analysis - Excluded in per-protocol analysis
2	Patient in the IVIg continuation group was unblinded at 3 weeks of follow-up due to an invoice from the insurance company for IVIg treatment; this patient remained stable until last follow-up visit.	- Included in intention-to-treat analysis - Excluded in per-protocol analysis
3	Patient was wrongly allocated during the minimization procedure in terms of duration of treatment. The duration was corrected in the data-analysis.	- Included in intention-to-treat analysis - Included in per-protocol analysis
4	Study treatment was delayed because of one extra regular infusion after randomization.	- Included in intention-to-treat analysis - Included in per-protocol analysis

Supplementary Table 3. Different outcome measures in patients with a relapse endpoint at different time points

N (%)		Week 6		Week 12		Week 18		Week 24	
		Freq.	Cum. Freq.	Freq.	Cum. Freq.	Freq.	Cum. Freq.	Freq.	Cum. Freq.
All relapse endpoints (N=30)									
IVIg withdrawal (N=17)	Total	7 (42)	7 (42)	6 (20)	13 (65)	2 (12)	15 (88)	2 (12)	17 (100)
	iRODS[a]	5/7 (71)	5/7 (71)	2/6 (33)	7/13(54)	1/2 (50)	8/15 (53)	2/2 (100)	10/17 (59)
	GS[b]	5/7 (71)	5/7 (71)	3/6 (50)	8/13(62)	2/2 (100)	10/15 (67)	2/2 (100)	12/17 (71)
	MRC[c]	4/7 (57)	4/7 (57)	1/6 (17)	5/13 (38)	1/2 (50)	6/15 (37)	1/2 (50)	7/17 (41)
	PGIC[d]	7/7 (100)	7/7 (100)	5/5 (100)	12/12 (100)	2/2 (100)	14/14 (100)	2/2 (100)	16/16 (100)
IVIg continuation (N=13)	Total	2 (15)	2 (15)	8 (62)	10 (77)	3 (23)	13 (100)	0	13 (100)
	iRODS	1/2 (50)	1/2 (50)	4/8 (50)	5/10 (50)	0/3	5/13 (38)		5/13 (38)
	GS	2/2 (100)	2/2 (100)	2/8 (25)	4/10 (40)	2/3 (67)	6/13 (46)		6/13 (46)
	MRC	1/2 (50)	1/2 (50)	4/8 (50)	5/10 (50)	1/3 (33)	6/13 (46)		6/13 (46)
	PGIC	1/2 (50)	1/2 (50)	6/6 (100)	7/8 (88)	3/3 (100)	10/11 (91)		10/11 (91)
Relapse according to MCID iRODS									
IVIg withdrawal (N= 10)	Total	5 (50)	5 (50)	2 (20)	7 (70)	1 (10)	8 (80)	2 (20)	10 (100)
	GS	5/5 (100)	5/5 (100)	1/2 (50)	6/7 (86)	1/1 (100)	7/8 (88)	2/2 (100)	9/10 (90)
	MRC	4/5 (80)	4/5 (80)	1/2 (50)	5/7 (71)	0/1 (0)	5/8 (63)	1/2 (50)	6/10 (60)
	PGIC	5/5 (100)	5/5 (100)	1/1 (100)	6/6 (100)	1/1 (100)	7/7 (100)	2/2 (100)	9/9 (100)

Supplementary Table 3. (Continued)

N (%)		Week 6		Week 12		Week 18		Week 24	
		Freq.	Cum. Freq.	Freq.	Cum. Freq.	Freq.	Cum. Freq.	Freq.	Cum. Freq.
IVIg continuation N=5	Total	1 (20)	1 (20)	4 (80)	5 (100)	0 (0)	5 (100)	0	5 (100)
	GS	1/1 (100)	1/1 (100)	2/4 (50)	3/5 (60)		3/5 (60)		3/5 (60)
	MRC	1/1 (100)	1/1 (100)	3/4 (75)	4/5 (80)		4/5 (80)		4/5 (80)
	PGIC	1/1 (100)	1/1 (100)	3/3 (100)	4/4 (100)		4/4 (100)		4/4 (100)
Other relapse									
IVIg withdrawal (N=7)	Total	2 (29)	2 (29)	4 (57)	6 (86)	1 (14)	7 (100)	0 (0)	7 (100)
	GS	2/2 (100)	2/2 (100)	2/4 (50)	4/6 (67)	1/1 (100)	5/7 (71)		5/7 (71)
	MRC	0/2 (0)	0/2 (0)	0/4 (0)	0/6 (0)	1/1(100)	1/7 (14)		1/7 (14)
	PGIC	2/2 (100)	2/2 (100)	4/4 (100)	6/6 (100)	1/1 (100)	7/7 (100)		7/7 (100)
IVIg continuation (N=8)	Total	1 (13)	1 (13)	4 (50)	5 (63)	3 (38)	8 (100)	0 (0)	8 (100)
	GS	1/1 (100)	1/1 (100)	0/4 (0)	1/5 (20)	1/3 (33)	2/8 (25)		2/8 (25)
	MRC	1/1 (100)	1/1 (100)	1/4 (25)	1/5 (20)	1/3 (33)	2/8 (25)		2/8 (25)
	PGIC	0/1 (0)	0/1 (0)	3/3 (100)	3/4 (75)	3/3 (33)	6/7 (86)		6/7 (86)

[a] Minimal clinically important difference on the iRODS;, [b] Relapse on grip strength: deterioration of at least 8kPa; [3] Relapse on MRC: deterioration of at least 2 points on MRC sum score; [d] Relapse on PGIC scale (1-5) was defined as a score of : a little worse or a lot worse than before the study.

Abbreviations: freq: frequency, cum: cumulative, IVIg: intravenous immunoglobulins, GS: grip strength, MRC: MRC sum score, PGIC: patient global impression of change scale.

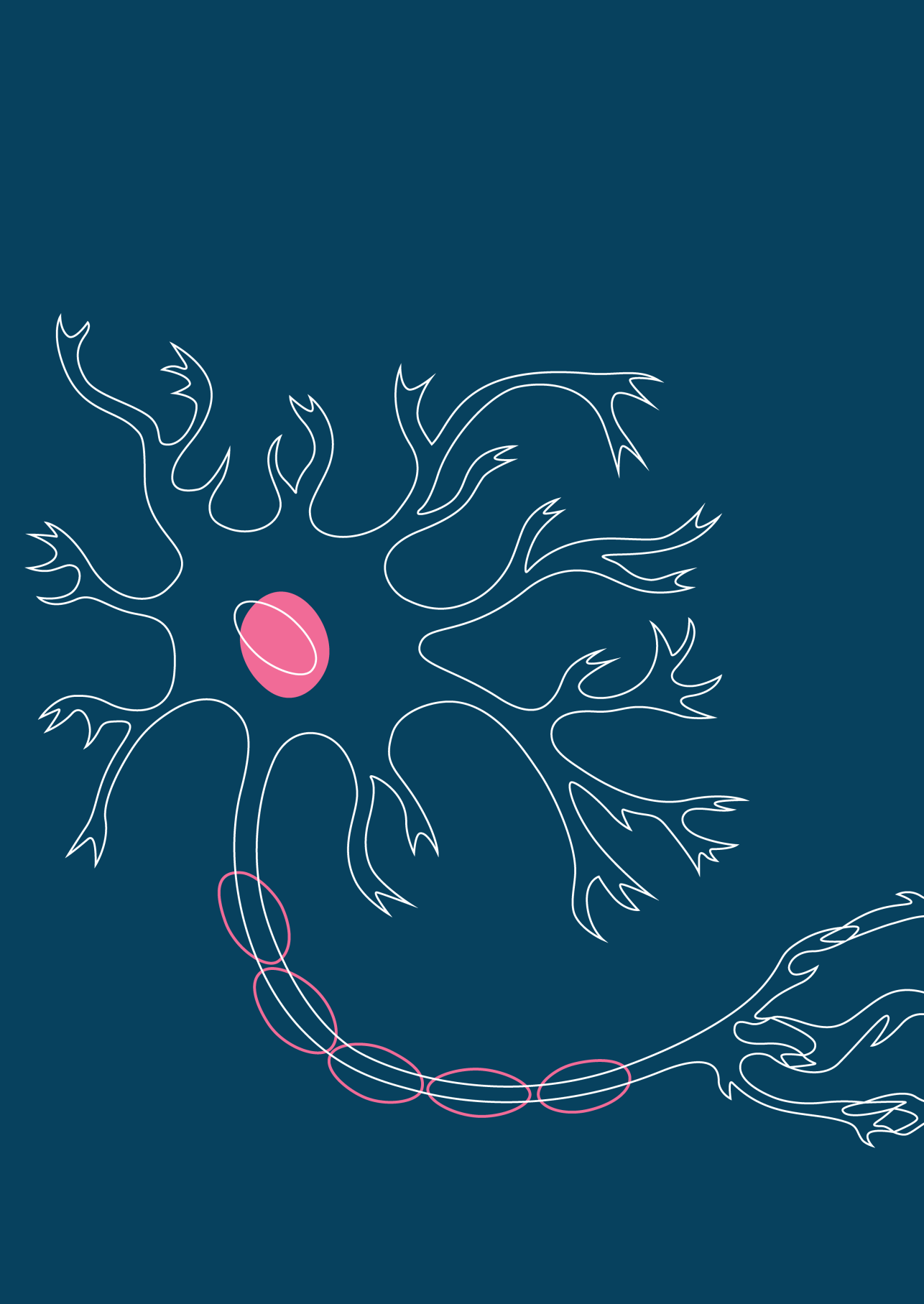
Appendix 1. Linear regression in the context of non-inferiority

We used multivariable linear regression on the iRODS follow-up scores in the context of non-inferiority by comparing the lower bound of the 95% confidence interval of the between group-difference with -0.65 as the margin of non-inferiority, adjusting for both the iRODS baseline scores and duration of prior IVIg. The following results were obtained:

Model Coefficients

			95% confidence interval	
Predictor	**Estimate**	**SE**	**lower bound**	**upper bound**
Intercept	-0.319	0.459	-0.1238	0.600
iRODS baseline	0.921	0.077	0.766	1.076
Duration prior IVIg treatment	0.370	0.395	-0.422	1.163
Withdrawal treatment	-0.558	0.395	-1.348	0.233

After adjustment, the coefficient for withdrawal treatment was -0.558 with a lower bound of -1.348. With the lower bound well below the non-inferiority margin of -0.65, the multivariable approach fails to demonstrate non-inferiority of withdrawal treatment.



General discussion

CHALLENGES IN DIAGNOSIS

Since the first paper describing the most common features of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), various different clinical phenotypes have been identified that all respond to immunomodulatory treatment, but do not necessarily share all the original features.[1] In a typical clinical phenotype with symmetric proximal and distal weakness, sensory symptoms and areflexia, diagnosis can be straightforward.[2] In atypical clinical variants diagnosis is more challenging,[3,4] and with the still expanding spectrum of clinical phenotypes diagnosis will only get more complicated, ultimately further increasing the chances of both over- and underdiagnosis.

There is no gold standard test to diagnose CIDP available which further complicates the quick arrival at a correct diagnosis. Currently, the diagnosis is made based upon fulfillment of diagnostic consensus criteria sets such as the EFNS/PNS 2010 criteria and the recently published EAN/PNS 2021 criteria.[5,6] For the EFNS/PNS 2010 criteria, nerve conduction study (NCS) findings suggestive of demyelination are mandatory, supported by other diagnostic tests, resulting in a possible, probable or definite CIDP diagnosis.[5] Even though the ENFS/PNS 2010 criteria have a higher sensitivity than previous criteria sets, these criteria are still considered suboptimal as both over- and underdiagnosis have been reported.[3,7-9] An update of the EFNS/PNS 2010 criteria was very long awaited and the EAN/PNS 2021 criteria were recently published.[6] Nerve ultrasound and antibody testing are now incorporated in the diagnostic criteria and terminology regarding the different levels of diagnostic certainty has changed. The different atypical CIDP phenotypes are now considered CIDP variants. Several red flags for CIDP diagnosis have been defined and the differential diagnosis for each variant has been specified. However, in essence the criteria did not change much. The NCS criteria are still mandatory for diagnosis, supported by the different additional diagnostic tests. A specific biomarker for CIDP is also still lacking. This means that many of the problems in CIDP diagnosis unfortunately remain unsolved.

The diagnosis of CIDP still relies heavily on identification of demyelinating features on motor NCS.[6] The electrophysiological demyelinating features are not equivalent to classical demyelination as found in nerve biopsies, but rather are markers for functional disruption or slowing of the saltatory conduction of the myelinated axons.[10] Even though NCS are the cornerstone of CIDP diagnosis, the available

evidence regarding the diagnostic value is limited. The available studies do not meet the STARD guidelines on reporting diagnostic accuracy studies and even the EAN/PNS guideline committee considered the certainty of the available evidence to be low. [6,11] Nevertheless, the few available studies have shown high sensitivity and specificity for the NCS criteria to diagnose CIDP.[8,12] The main limitation of these studies is that no relevant control patients were included. Patient with chronic idiopathic axonal polyneuropathies or chronic diabetic polyneuropathies were mainly used as controls.[8,12] This does not reflect the clinical practice, as based on history and physical examination, it is often not difficult to distinguish these patients from patients with an inflammatory neuropathy. Studies including patients with clinically suspected CIDP or other demyelinating polyneuropathies, such as POEMS syndrome, are scarce. Thus NCS findings suggestive of demyelination are not only found in CIDP, but also in other acquired and hereditary demyelinating neuropathies. NCS findings should therefore always be used in the context of the clinical picture. A thorough history and physical examination should be performed and if any alarm symptoms such as extreme pain or systemic involvement is present, additional diagnostic tests should be performed to rule out other diagnoses first. For example, a patient with POEMS syndrome will meet the CIDP NCS criteria perfectly, and without proper further evaluation, will be misdiagnosed and treated as a CIDP patient with possible severe consequences. Additionally, studying the diagnostic value of NCS criteria in CIDP patients in whom diagnosis was already made based on NCS findings suggestive of demyelination, will lead to a self-fulfilling prophecy. In that way, patients that do respond to treatment, but without the characteristic demyelinating NCS features will never be identified.

Even if the most perfect set of diagnostic criteria will be developed, the application in clinical practice will remain challenging. The electrodiagnostic criteria can be interpreted in different ways by different clinicians. Furthermore, the extent, order and reference values of NCS studies do not only differ between countries, but also between different hospitals in one country. Even the settings of the equipment can influence the results.[13] Despite the clinical heterogeneity, there are no specific NCS strategies for the different subtypes. As we have shown in **chapter 2**, the proposed initial NCS protocol of measuring the clinically affected forearm and lower leg as suggested by the EFNS/PNS 2010 criteria was insufficient in around half of patients with asymmetric CIDP. Measuring the most affected arm up to Erb's point, and if necessary, followed by the unaffected arm to Erb's point, had the highest diagnostic

yield. We additionally found that demyelinating features were often not limited to clinically affected limbs. In the recent update of the criteria, there are some additional recommendations regarding the CIDP variants. However, this only pertains to the diagnostic certainty of the NCS findings and not the order and extend of the NCS.[6] It therefor remains difficult to decide how extensive the NCS should be. Measuring both arms up to Erb's point and both legs probably has the highest sensitivity, although this is not specifically studied. Such extensive NCS are not possible in all centers as it is time consuming and therefor costly. Extensive measurements are also painful for patients. Experience with measurements up to Erb's point is also necessary, as this is technically more difficult. However, even if NCS protocols would be standardized, several pitfalls in interpreting NCS results remain and thus experience is essential. Severe axonal loss has an influence on nerve conduction velocity. Demyelinating features in compression or entrapment segments should not be considered supportive for CIDP and interpretation of conduction blocks should be done with care in trajectories of nerves that are adjacent to each other, as co-stimulation and co-registration may occur.[10,14]

Despite all the shortcomings, NCS are still the most reliable diagnostic test in CIDP diagnosis.[10] However, as described in **chapter 5,** there are patients who respond to immunomodulatory treatment, but in whom the mandatory NCS findings suggestive of demyelination are not found. Identifying these patients remains difficult, as none of the other diagnostic tests correlated with treatment response. Although we considered the supportive diagnostic criteria helpful in some case, we also found that supportive findings such as an elevated CSF protein and enlarged nerves on ultrasound can occur in patients in whom another diagnosis than CIDP was ultimately made. This highlights one of the greatest difficulties in the diagnostic process: none of the available diagnostic tests is specific for CIDP. For example, an elevated CSF protein without pleocytosis is considered one of the hallmark features of CIDP.[15] However, a slightly elevated CSF protein level has a poor specificity and is also found in diseases such as diabetes mellitus and hereditary neuropathies.[16,17] On the other hand, normal protein levels do not exclude the diagnosis, especially in atypical CIDP variants as we have shown in **chapter 2**.[16-18] Additionally, in **chapter 3** we showed that mildly elevated CSF leukocytes can be found in CIDP patients and thus do not necessarily exclude the diagnosis. As we only found pleocytosis in a minority of patients, extensive work-up is still probably warranted to exclude other diagnosis such as malignancies or polyradiculitis caused by Borrelia Burgdorferi.

To make matters even more complicated, testing for Borrelia serology should be done with caution when a patient is already treated with IVIg. IVIg treatment can lead to apparent seroconversion for Borrelia Burgdorferi antibodies **(chapter 4)**, dependent of the IVIg brand that is used. When Lyme Borreliosis is part of the differential diagnosis, testing for antibodies should be done either before or several months after IVIg administration.

If imaging is required, nerve ultrasound is probably preferred compared to MRI, as it is easier, less expensive and has a higher diagnostic accuracy.[19] However, enlarged nerves are also found in (more prevalent) diseases such as diabetes mellitus, amyotrophic neuralgia and hereditary neuropathies.[20-22] The role of evoked potentials and nerve biopsy is very limited and should be reserved for selected cases.[9,23-25]

As CIDP is a rare disease, most neurologists only encounter a few patients in their whole career. The atypical CIDP variants are even less prevalent, adding to the chance of misdiagnosis. Studies on diagnostic and treatment practices among neurologist showed that there was variability in the knowledge about the EFNS/PNS 2010 criteria and the adherence to the criteria.[26,27] This, in combination with the experience that is needed for correct interpretation of the NCS results and other supportive test, may lead to the conclusion that CIDP diagnosis and treatment should be limited to specialized centers as much as possible.

Future directions for diagnostic challenges

Considering that inflammation and demyelination as core features are not present in all CIDP patients, while in all patients an autoimmune aetiology is presumed, the term 'chronic autoimmune neuropathies' may be a better fit.[10] Future studies should probably focus on proving auto-immunity, leading to specific immunological test that can be part of the diagnostic work-up. Currently, specific autoantibodies are only found in a minority of patients while nerve biopsy results supporting an autoimmune origin are uncommon.[10] More auto-antibodies are likely to be found in the future, but it is yet unclear if there is an underlying autoantibody-induced pathology in all patients.

Until specific immunological tests for CIDP are available, further improvement of the diagnostic criteria is necessary. As mentioned before, the recent update of the criteria has only led to slight changes, not solving all the challenges in the diagnostic

process. A possible way to improve the diagnostic criteria is to leave the structure of the stringent NCS criteria supported by additional tests, but to examine the diagnostic value of different combinations of clinical characteristics and supportive diagnostic tests. For example, in case of a typical clinical phenotype an elevated CSF protein and enlarged nerves on ultrasound might be enough to diagnose CIDP without the need of extensive NCS. Prospective studies comparing all the available different diagnostic modalities in different clinical phenotypes will be necessary, and the use of clinically relevant control groups will be essential. In absence of a gold standard test, clinical improvement on immunomodulatory treatment such as IVIg can be used as the ultimate proof of an inflammatory origin. However, a minority of CIDP patients meets the current diagnostic criteria, but does not respond to the first line immunomodulatory treatment. Using treatment response as proof for the diagnosis means that these patients might not be identified anymore. On the other hand, this could lead to identification of a higher number of treatment responsive patients that are underdiagnosed with the current criteria. Unfortunately, determining treatment response is still very difficult. Studies on overtreatment have shown that even patients with axonal neuropathies reported improvement after IVIg treatment, especially on subjective outcome measures.[3] At this moment, using treatment response as a gold standard for diagnosis, might lead to overdiagnosis and the overuse of expensive, potentially harmful treatment.

There is a growing attention to machine learning models in medicine. Machine learning is based on efficient computational algorithms that are able to detect complex relationships in enormous data sets, which are not visible to the human eye or simple statistical models.[28] For example, an algorithm used in oncology is able to give a personalized treatment plan based on different clinical parameters.[29] The use of such algorithms might be also helpful in CIDP diagnosis and even yield better performance results in comparison to consensus guidelines. However, one of the pitfalls when training a machine learning model is again to use irrelevant control patients and only CIDP patients that meet the NCS criteria for demyelination. In that case, the algorithm will be trained to identify the same patients we can already diagnose based on the available diagnostic criteria. One study has already shown that an algorithm was capable to differentiate based on NCS findings between different types of neuropathy.[30] For future studies, it would be even more interesting to combine different features such as clinical phenotype, other supportive test results and treatment response. However, the key in machine learning is to

enter data of many patients, which is difficult for a rare disease as CIDP. This is a recurring problem in CIDP research. The total number of CIDP patients per country is low and sharing data internationally is not yet common. If we really want to make progress, international collaboration is essential. Initiatives such as The Inflammatory Neuropathy Consortium Base (INCbase) are a great first step in the right direction.[31]

CHALLENGES IN TREATMENT

Induction treatment for CIDP consists of IVIg, corticosteroids and plasma exchange.[32-34] In clinical practice, most clinicians choose to start with IVIg or corticosteroids. Both treatments have advantages and disadvantages: IVIg works quick and is well tolerated, but is extremely expensive, especially if long-term treatment is required.[34] Corticosteroids have more side effects and improvement usually takes several months. However, long term remission is more often found, while the majority of patients treated with IVIg seems to need long term maintenance treatment.[35,36] Additionally, there is an increasing attention to the possible severe side effects of IVIg.[37] At this point it is still unclear which treatment should be started in which individual patient. Some CIDP variants probably respond less to corticosteroids, such as the pure motor variant and the asymmetric variant, as we have shown in **chapter 2**.[38] However, the choice of treatment is often still based on the preference and experience of the treating clinician. In high income countries clinicians prescribe IVIg more often. So far, attempts to find other, less expensive, treatment options were unsuccessful.[39,40] Currently, a combination treatment of IVIg and corticosteroids is studied, hopefully leading to more patients reaching long term remission.[41] Until then, many CIDP patients are treated with IVIg maintenance treatment, contributing to ever increasing healthcare costs.

Finding the right dose and duration of IVIg maintenance therapy is difficult and is often a process of trial and error. Previous studies already suggested that some patients could stop IVIg treatment, but were not designed specifically to study overtreatment.[40,42-44] We showed in **chapter 6** that around 40% of CIDP patients can, at least temporarily, stop IVIg treatment. Of the patients who deteriorated during the study, more than 90% restabilized within 12 weeks after restart of treatment. This means that IVIg withdrawal attempts are safe and should be part of CIDP practice. Unfortunately, identifying a true relapse remains difficult, as was illustrated by the

unexpected high number of patients in the IVIg continuation group that reported a relapse. Possible reasons for this could be disease fluctuations, wear-off or just deterioration under treatment. However, for several reasons it seems very unlikely that these reasons completely explain the high number of reported relapses in the IVIg continuation group. We included patients that were stable on the same IVIg dose for at least 6 months; some were even stable for years. Additionally, not many patients reported wear-off symptoms before they entered the study. We found that our outcome measures such as the iRODS, grip strength and muscle strength did not capture a deterioration in many patients reporting a relapse. A possible explanation for this is that anxiety and patients' expectations towards treatment withdrawal play an important role in the success of the withdrawal attempt. Before IVIg treatment is started, many patients experience how it is to be disabled or even to be wheelchair bound. Withdrawing IVIg can understandingly lead to anxiety for deterioration and irreversible damage. The phenomenon that negative expectations of patients can have a negative effect on the outcome is called a nocebo effect.[45] However, even if the reported relapse was captured on the iRODS, grip strength or muscle strength, the objectivity of these outcome measures can be questioned. A patient reports his/her own symptoms on the iRODS and has to put in maximum effort when testing the grip strength and muscle strength. If a patient already believes he deteriorated, this will probably be reflected in the outcome measures. Furthermore, these measurements are not specifically measuring deterioration because of CIDP. An intercurrent problem such as an infection will also influence the daily functioning and this will also influence the outcome measures. Additionally, even patients who are in remission for years can still experience slight fluctuations in symptoms. When someone is anxious and experiences a fluctuation, this can easily be interpreted as a relapse and treatment will be restarted. After all, clinicians also do not want to risk causing irreversible damage. Unfortunately, we did not record the patients' expectations regarding the study and IVIg withdrawal or personality characteristics, as this could give some helpful insights. We did ask patients at the last study visit in which group they thought they were randomized. Naturally patients who relapsed all reported that they thought they were randomized for IVIg withdrawal, but also most patients who remained stable reported that they were randomized for IVIg withdrawal. They reported that they experienced more CIDP symptoms and less side effects than before entering the trial. It seems that when entering a trial, patients already have expectations regarding the group they will be randomized to and that they are likely to believe they are randomized for the intervention group. Placebo

and nocebo effects are not limited to our trial solely. One study showed that all CIDP treatment trials had at least some placebo effect.[46] This effect was more pronounced in trials in which relapses or deterioration were the primary outcome and less in studies in which improvement was the primary outcome.[46] The authors suggest that treatment naïve patients are less prone to a placebo effect, as they do not know what to expect from the therapy. Patients who are already used to the treatment, know what effects and side-effects the treatment has. They also found that older patients, with a more severe disease might be more prone to the placebo effect.[46] If we then assume that not all patients who report a relapse experience a true relapse, this will mean that the number of patients in our trial that could have stopped IVIg is even higher. These findings also have implications for new treatment trials. For example, in the Path study IVIg dependency was tested before randomization by stopping treatment and restabilizing those who deteriorated. Despite this 'demonstration' of IVIg dependency, almost 40% of patients who were randomized to placebo remained stable during the study.[43] Because it is unknown if the deterioration a patients reports is a true relapse, it is still likely that despite testing IVIg dependency, patients will be included in a trial that do not need IVIg treatment. When designing a new study, this should be considered especially with the power calculation. This will lead to a higher number of subjects that should be included to prove effect of a treatment.

Future directions for treatment challenges:

Future studies should focus on improving outcome measurements and determine the clinically relevant differences on these scales, but this will only partially overcome the problem. Not all deterioration is measurable in the consultation room. Additionally, it is difficult to determine what a clinical relevant deterioration is for each individual patient. For a patient that used to run marathons who can no longer do so, this can be an unacceptable deterioration, while other patients accept some disability when stopping treatment. It is not easy to determine how much deterioration is still acceptable in individual patients, especially in the context of the very high costs of IVIg. The question remains who has the final say in restarting therapy; the doctor or the patient?

Finding proof of auto-immunity or disease activity is not only a challenge in CIDP diagnosis, but also in treatment. It is still unknown if there is one underlying pathophysiological mechanism, or several different mechanisms sharing similar

clinical features. If this is the case, finding one biomarker for all patients is unlikely. Dividing an already rare disease into even rarer subtypes makes research even more complicated and at this point it is unclear which patients would share the same underlying pathophysiology. The lack of biomarkers for disease activity, makes it difficult to determine whether the disease is still active or if IVIg could be withdrawn. Until we can find proof for disease inactivity with an objective biomarker before treatment withdrawal and proof for (reoccurring) disease activity in case of a reported relapse, treatment withdrawal will remain a process of trial and error. During this process, it is very important to communicate with patients regarding treatment withdrawal and acknowledge that this can cause anxiety. If a patient really does not want to start a withdrawal attempt, such an attempt will probably be unsuccessful. When starting IVIg, treatment withdrawal should directly be discussed. Clinicians should emphasize that spontaneous remissions are part of the disease and treatment withdrawal is safe. In our practice we find that if we do this, many patients are ready to try and stop IVIg after a while, as these infusions and the side effects also have a negative impact on their daily lives.

In conclusion, as a consequence of being a rare and heterogeneous disease many challenges remain in the diagnosis and treatment of CIDP. Until we find markers for diagnosis or disease activity, CIDP remains a clinical diagnosis supported by additional tests. New methods such as machine learning might help improving the diagnosis. Treatment and IVIg withdrawal will continue to be a process of trial and error and communication with patients is key. If possible, patients suspected of CIDP should be referred to specialized centers for diagnosis and treatment. To make progress, larger studies are needed and international collaboration is essential.

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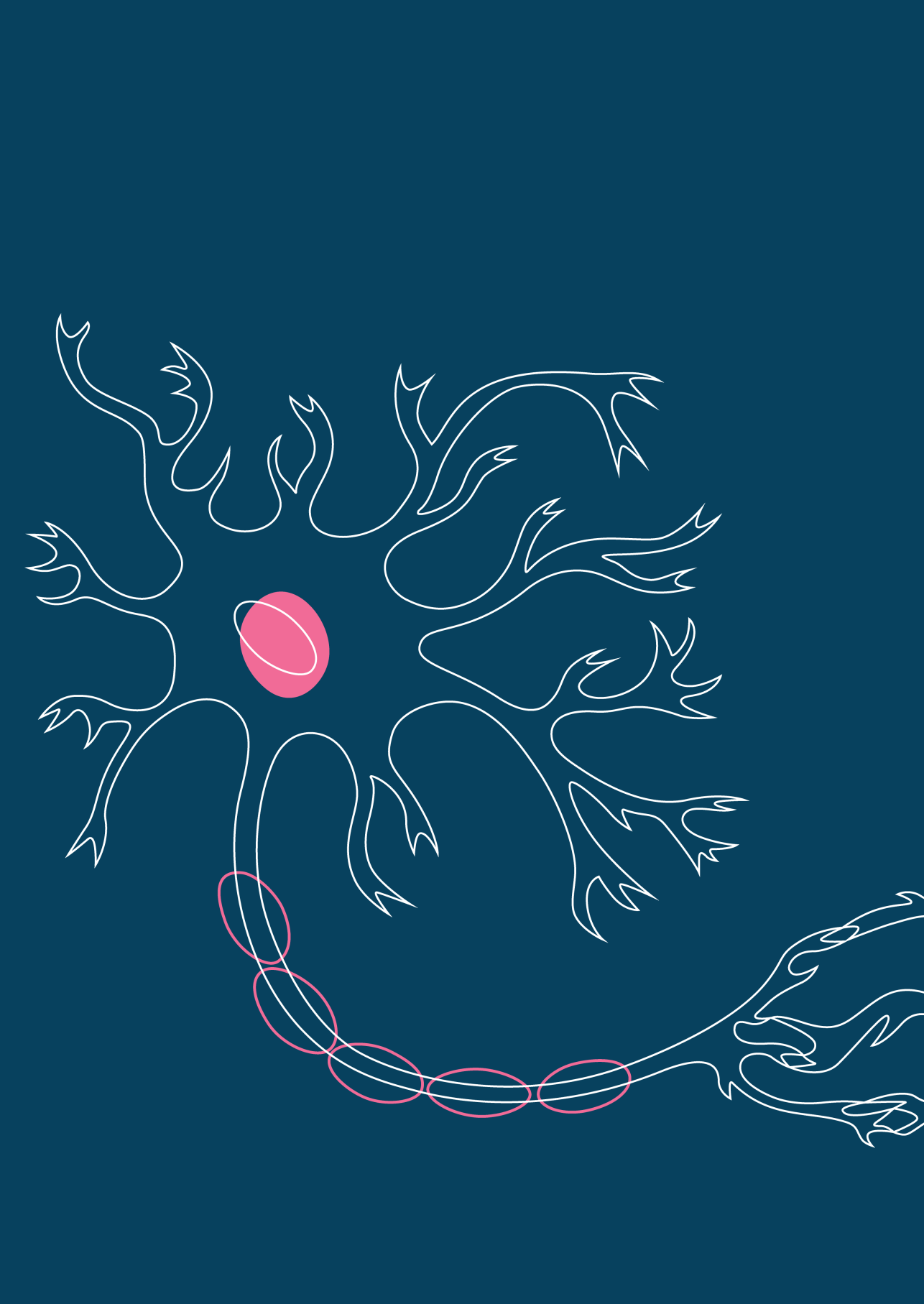

Appendices

ENGLISH SUMMARY

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) consist of a spectrum of autoimmune diseases of the peripheral nerves with a very heterogeneous clinical presentation. A presumable cause is a breach of tolerance leading to auto-immunity against nerve antigens. Different pathophysiological mechanisms have been identified, not always sharing the same clinical features, which makes both diagnosis and choosing the right treatment strategy challenging. In this thesis we aimed to identify some of these challenges in treatment and diagnosis.

Currently, the cornerstone of CIDP diagnosis are nerve conduction studies (NCS). The objective of **chapter 2** was to assess the diagnostic value of testing clinically affected and unaffected limbs with nerve conduction studies in patients with the asymmetric variant of CIDP and to describe treatment response and long term outcome in these patients. We retrospectively included 34 patients. We found that NCS of the clinically affected forearm and lower leg, as suggested by the EFNS/PNS 2010 criteria, led to a definite or probable diagnosis in only less than half of patients. Measuring the most affected arm up to Erb's point, and if necessary, followed by the unaffected arm to Erb's point, had the highest diagnostic yield. Demyelinating features were often not limited to clinically affected limbs. An elevated CSF protein was only found in around half of patients. Patients responded better to IVIg than to corticosteroids. We found that only 30% of patients improved after corticosteroid treatment, while in the literature the response rate to corticosteroids is similar to the response to IVIg. Most patients needed long-term IVIg maintenance treatment and withdrawal attempts were only successful in a minority of patients. These findings suggest that patients with asymmetric variants might be more dependent on long term IVIg maintenance treatment than CIDP patients in general.

The EFNS/PNS 2010 criteria includes an elevated CSF protein without pleocytosis (<10 cells/µl) as a supportive criterion for CIDP. However, in clinical practice we encountered several CIDP patients with pleocytosis that fulfilled the other criteria and responded to treatment. In **chapter 3** we describe CIDP patients with a CSF leukocyte count above the cut off value of 10 cells/µl. In total 14 patients out of 273 (6%) CIDP patients had an increased leukocyte count, of whom four patients had a leukocyte count above 50 cells/µl. Eight patients had a subacute or acute onset and

four patients reported an infection before onset. In some patients, lumbar puncture was repeated and showed a spontaneous decrease in leukocytes prior to treatment. Most patients responded well to treatment and most patients reached remission at some point during follow up. This study showed that a CSF pleocytosis of more than 10 cells/µl does not exclude CIDP, but extensive work-up is warranted in these cases to exclude other diagnosis such as malignancies.

The objective of **chapter 4** was to determine how often IVIg treatment leads to seroconversion for Borrelia Burgdorferi antibodies. IVIg consist of pooled IgG immunoglobulins from different donors. These include antibodies directed to microorganisms the donors have encountered, such as Borrelia Burgdorferi (*BB*sl). Polyradiculitis caused by Borrelia is an important differential diagnosis in CIDP, especially when patients do not respond to IVIg treatment. As a tertiary referral center, we often see patients who are already treated with IVIg, but in whom there is uncertainty about the diagnosis. We included 51 patients with CIDP and myositis who were treated with IVIg. Ten CIDP patients treated with dexamethasone were included as controls. We found apparent seroconversion for anti-*BB*sl in almost 40% of patients. Seroconversion was dependent of the IVIg brand that was used. Nanogam, a product made in the Netherlands where Borrelia is relatively highly prevalent, led to apparent seroconversion of 50% of patients. In none of the patients treated with Privigen (produced in the USA) apparent seroconversion was found. In almost all patients the antibodies disappeared after IVIg withdrawal. This study shows that clinicians should be careful interpreting Borrelia assays after IVIg treatment, dependent on the IVIg brand that was used. When Lyme Borreliosis is part of the differential diagnosis, it would be highly recommendable to test for antibodies either before or several months after IVIg administration.

In **chapter 5** we reported on patients who did not meet the mandatory EFNS/PNS nerve conduction study criteria for CIDP or multifocal motor neuropathy (MMN) and received IVIg treatment. The objective of this study was to evaluate which diagnostic results let to the decision to start IVIg treatment and to describe the treatment response in these patients. We included 35 patients of whom 19 patients were suspected of CIDP and 16 patients were suspected of MMN, based on their clinical picture. More than half of patients with suspected CIDP had a so called atypical clinical phenotype. We found that enlarged nerves on nerve ultrasound and an elevated cerebrospinal fluid (CSF) protein were the most frequent diagnostic

tests to support the diagnosis. There was a higher rate of improvement in patients with a clinical suspicion of CIDP than in patients with a clinical suspicion of MMN (68% versus 31%). The presence of the different supportive criteria did not differ between patients who responded to treatment and patients who did not respond to treatment. Supportive findings such as enlarged nerves on nerve ultrasound and elevated CSF protein were also found in patients in whom another diagnosis was made.

In **chapter 6** we studied IVIg overtreatment in CIDP patients. Biomarkers for disease activity are lacking, making the need for ongoing treatment difficult to assess, leading to potential overtreatment and high health care costs. Our objective was to determine whether IVIg withdrawal is non-inferior to continuing IVIg treatment and to determine how often patients are overtreated. We performed a randomized, double-blind, IVIg-controlled non-inferiority trial. A total of 60 patients who were stable on IVIg maintenance treatment were included, of whom 29 were randomized for IVIg withdrawal and replacement with placebo and 31 patients were randomized for continuation of their own IVIg dose and interval. We could not demonstrate non-inferiority of withdrawal of IVIg maintenance treatment compared to continuation of treatment, as our study turned out to be underpowered due to much larger than expected confidence intervals. However, we found that around 40% of patients randomized for IVIg withdrawal could successfully stop treatment for 24 weeks. Almost all patients who deteriorated restabilized quickly after restart of IVIg treatment. Unexpectedly, a high proportion of patients randomized for IVIg continuation experienced a relapse endpoint, possibly explained by disease fluctuations. However, negative expectations of patients toward treatment withdrawal (nocebo effect) could have played an important role as well. This study emphasizes that treatment withdrawal is safe and suggests that attempts should be performed regularly in clinically stable CIDP patients, preferably including objective measurements.

NEDERLANDSE SAMENVATTING

Chronische inflammatoire demyeliniserende polyradiculoneuropathie (CIDP) bestaat uit een spectrum van auto-immuunziekten van de perifere zenuwen, met een zeer heterogene klinische presentatie. Een vermoedelijke oorzaak is een aantasting van tolerantie, leidend tot auto-immuniteit tegen zenuwantigenen. Er zijn verschillende pathofysiologische mechanismen geïdentificeerd, die niet altijd dezelfde klinische kenmerken hebben. Dit maakt zowel het stellen van de diagnose, als het kiezen van de juiste behandelingsstrategie uitdagend. Het doel van dit proefschrift was om enkele van deze uitdagingen bij de behandeling en diagnosestelling te identificeren.

Op dit moment is zenuwgeleidingsonderzoek (EMG) de hoeksteen van de diagnostiek van CIDP. Het doel van **hoofdstuk 2** was om de diagnostische waarde te bepalen van het EMG bij klinisch aangedane en niet-aangedane ledematen van patiënten met de asymmetrische variant van CIDP. Daarnaast was het doel om de respons op behandeling en de langetermijnuitkomst bij deze patiënten te beschrijven. We includeerden 34 patiënten retrospectief. Het EMG van de klinisch aangedane onderarm en het aangedane onderbeen, zoals de EFNS/PNS 2010 criteria adviseren, leidde bij minder dan de helft van de patiënten tot een definitieve of waarschijnlijke diagnose. Het meten van de meest aangedane arm tot aan het punt van Erb, en indien nodig, gevolgd door de niet aangedane arm, had de hoogste diagnostische opbrengst. Demyeliniserende kenmerken waren vaak niet beperkt tot de klinisch aangedane ledematen. Een verhoogd eiwit in de liquor werd maar bij ongeveer de helft van de patiënten gevonden. Patiënten reageerden beter op intraveneuze immunoglobulinen (IVIg) dan op corticosteroïden. Slechts 30% van de patiënten verbeterde na behandeling met corticosteroïden, terwijl in de literatuur de respons op corticosteroïden vergelijkbaar is met de respons op IVIg. De meeste patiënten hadden langdurige IVIg-onderhoudsbehandeling nodig en afbouwpogingen waren slechts bij een minderheid van de patiënten succesvol. Deze bevindingen suggereren dat patiënten met asymmetrische CIDP-varianten mogelijk vaker afhankelijk zijn van langdurige IVIg- onderhoudsbehandeling dan CIDP patiënten in het algemeen.

In de EFNS/PNS 2010 criteria is een verhoogd eiwit in de liquor zonder pleiocytose (<10 cellen/µl) een ondersteunend criterium voor CIDP. In de klinische praktijk hebben we echter verschillende CIDP patiënten gezien met een pleiocytose in

de liquor, die wel aan de andere diagnostische criteria voldeden en daarnaast reageerden op behandeling. In **hoofdstuk 3** beschrijven we CIDP patiënten met een leukocytenaantal boven de afkapwaarde van 10 cellen/µl. In totaal hadden 14 van de 273 (6%) CIDP patiënten verhoogde leukocyten, van wie 4 patiënten meer dan 50 cellen/µl hadden. Acht patiënten hadden een subacuut of acuut begin van de ziekte en vier patiënten meldden een infectie voor aanvang van de klachten. Bij patiënten bij wie de lumbaalpunctie herhaald werd, toonde deze een spontane daling van het aantal leukocyten voordat behandeling gestart werd. De meerderheid van de patiënten reageerde goed op behandeling en bereikten remissie op enig moment tijdens de follow-up. Deze studie toonde aan dat een pleiocytose van meer dan 10 cellen/µl in de liquor CIDP niet uitsluit, maar uitgebreid aanvullend onderzoek blijft noodzakelijk om andere diagnoses, zoals maligniteiten, uit te sluiten.

Het doel van **hoofdstuk 4** was om te bepalen hoe vaak IVIg-behandeling leidt tot schijnbare seroconversie voor *Borrelia burgdorferi* antilichamen. IVIg bestaat uit gepoolde IgG immunoglobulines van veel verschillende donoren en bevat antilichamen gericht tegen micro-organismen waarmee de donoren in aanraking zijn gekomen, zoals *Borrelia burgdorferi* sensu lato. Polyradiculitis veroorzaakt door *Borrelia* is een belangrijke differentiaal diagnose bij CIDP, vooral wanneer patiënten niet reageren op IVIg-behandeling. Als tertiair verwijzingscentrum zien wij vaak patiënten die reeds met IVIg zijn behandeld, maar bij wie onzekerheid bestaat over de diagnose. Wij includeerden 51 patiënten met CIDP en myositis die werden behandeld met IVIg en tien CIDP patiënten die met dexamethason werden behandeld als controles. We vonden schijnbare seroconversie voor anti-*B*bsl antilichamen bij bijna 40% van de patiënten die met IVIg werden behandeld. De schijnbare seroconversie was afhankelijk van het IVIg merk dat werd gebruikt. Nanogam®, een product dat in Nederland wordt gemaakt waar *Borrelia* relatief veel voorkomt, leidde tot schijnbare seroconversie bij 50% van de patiënten. Bij geen van de patiënten die werden behandeld met Privigen® (geproduceerd in de Verenigde Staten) werd schijnbare seroconversie gevonden. Bij bijna alle patiënten verdwenen de antilichamen na het staken van IVIg. Deze studie toont aan dat clinici voorzichtig moeten zijn met het interpreteren van *Borrelia* testen na IVIg-behandeling, afhankelijk van het IVIg merk dat gebruikt wordt. Wanneer Lyme borreliose deel uitmaakt van de differentiaal diagnose, bevelen we aan om op antistoffen te testen voor- of enkele maanden na IVIg-toediening.

In **hoofdstuk 5** beschrijven we patiënten die niet voldoen aan de verplichte EFNS/PNS EMG-criteria voor CIDP of multifocale motorische neuropathie (MMN) maar wel behandeld werden met IVIg. Het doel van deze studie was om te evalueren welke diagnostische resultaten geleid hebben tot de beslissing om te starten met IVIg-behandeling. Daarnaast beschreven we de respons op de behandeling bij deze patiënten. Wij includeerden 35 patiënten. Op basis van de klinisch presentatie werden 19 patiënten verdacht van CIDP en 16 patiënten van MMN. Meer dan de helft van de patiënten bij wie CIDP werd vermoed, had een zogenaamd atypisch klinisch fenotype. Wij vonden dat vergrote zenuwen bij zenuwechografie en een verhoogd eiwit in de liquor de meeste gebruikte kenmerken waren, om de diagnose te ondersteunen. Meer patiënten met een klinische verdenking op CIDP verbeterden na behandeling, dan patiënten met een klinische verdenking op MMN (68% versus 31%). De aanwezigheid van de verschillende ondersteunende criteria verschilde niet tussen patiënten die reageerden op behandeling en patiënten die niet reageerden op behandeling. Ondersteunende bevindingen, zoals vergrote zenuwen bij zenuwechografie en een verhoogd eiwitgehalte in de liquor, werden ook gevonden bij patiënten bij wie uiteindelijk een andere diagnose werd gesteld.

In **hoofdstuk 6** beschrijven we IVIg-overbehandeling bij CIDP patiënten. Er bestaan geen biomarkers voor ziekteactiviteit, waardoor de noodzaak van onderhoudsbehandeling moeilijk te bepalen is. Dit kan leiden tot overbehandeling en daarmee hoge kosten voor de gezondheidszorg. Ons doel was om te bepalen of afbouw van IVIg niet inferieur is aan doorgaan met IVIg-behandeling en om te bepalen hoe vaak patiënten worden overbehandeld. Wij voerden een gerandomiseerde, dubbelblinde, IVIg-gecontroleerde non-inferioriteitsstudie uit. In totaal werden 60 patiënten geïncludeerd die stabiel waren op IVIg-onderhoudsbehandeling. Hiervan werden 29 patiënten gerandomiseerd voor afbouwen van IVIg met placebo en 31 patiënten werden gerandomiseerd voor het doorgaan van hun eigen IVIg-dosis en

-interval. Non-inferioriteit van de afbouw van IVIg-onderhoudsbehandeling ten opzichte van continueren van de behandeling werd niet aangetoond, omdat onze studie underpowered bleek te zijn als gevolg van veel grotere dan verwachte betrouwbaarheidsintervallen. We stelden echter vast dat ongeveer 40% van de patiënten die gerandomiseerd werden voor IVIg afbouw, de behandeling gedurende 24 weken met succes konden stoppen. Bijna alle patiënten die verslechterden, herstelden snel na herstart van de IVIg-behandeling. Een onverwachte bevinding

was dat een groot deel van de patiënten die de IVIg-behandeling continueerden, achteruitgingen. Dit kan mogelijk worden verklaard door ziektefluctuaties. Negatieve verwachtingen van patiënten ten aanzien van het staken van de behandeling (nocebo-effect) zouden echter ook een belangrijke rol kunnen hebben gespeeld. Deze studie benadrukt dat het staken van IVig behandeling veilig is en adviseert om bij klinisch stabiele CIDP-patiënten regelmatig afbouwpogingen te ondernemen, waarbij bij voorkeur objectieve uitkomstmaten gebruikt worden.

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LIST OF ABBREVIATIONS

µl	microliter
Anti-MAG:	anti myelin-associated glycoprotein
ALDS:	Academic Medical Center linear disability score
ALS:	amyotrophic lateral sclerosis
*Bb*sl:	Borrelia burgdorferi sensu latu
CANOMAD:	chronic ataxic neuropathy, ophthalmoplegia, immunoglobulin M [IgM] paraprotein, cold agglutinins, and disialosyl antibodies
CDAS:	chronic inflammatory demyelinating polyradiculoneuropathy disease activity status
CI:	confidence interval
CIDP:	chronic inflammatory demyelinating polyradiculoneuropathy
CMAP:	compound muscle action potential
CSF:	cerebrospinal fluid
DSMB:	data safety monitoring board
EAN/PNS:	European Academy of Neurology/Peripheral Nerve Society
EFNS/PNS:	European Federation of Neurological Societies/Peripheral Nerve Society
FSS:	fatigue severity scale
G:	grams
GBS:	Guillain-Barré syndrome
IMP:	investigational medicinal product
INCAT-SS:	inflammatory neuropathy cause and treatment sensory sum score
iRODS:	inflammatory rasch-overall disability scale
IVIg:	intravenous immunoglobulins
Kg:	kilograms
MADSAM:	multifocal acquired demyelinating sensory and motor
MCID:	minimally clinically important difference
MGUS:	monoclonal gammopathy of undetermined significance
MIDN:	multifocal inflammatory demyelinating neuropathy
MMN:	multifocal motor neuropathy
MND:	motor neuron disease
MRC:	Medical Research Council sum score
MRI:	magnetic resonance imaging
NCS:	nerve conduction studies
PGIC:	patient global impression of change

POEMS:	polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes
PSMA:	progressive spinal muscular atrophy
PI-NRS	pain intensity numerical rating scale
SSEP:	somato sensory evoked potentials
SF-36:	short form-36

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This thesis

Lucke IM, Peric S, van Lieverloo GGA, Wieske L, Verhamme C, van Schaik IN, Basta I, Eftimov F. Elevated leukocyte count in cerebrospinal fluid of patients with chronic inflammatory demyelinating polyneuropathy. Journal of the peripheral nervous system. 2018;Mar;23(1):49-54

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PHD PORTFOLIO

Name PhD student: Ilse Mariëlle Lucke
PhD period: 2017 - 2022
PhD supervisors: prof. dr. IN van Schaik, dr. F. Eftimov and dr. C. Verhamme

PhD training	Year	ECTS
General courses		
AMC world of science	2017	0.7
Basic Course Regulations and Organization for Clinical Investigators (BROK)	2017	1.5
Practical Biostatistics	2017	1.4
Oral presentation in English	2017	1.0
Scientific writing in English for publication	2018	1.5
Searching for Evidence	2018	0.1
Seminars, workshops and master classes		
Muscles2Meet	2017	0.5
	2019	0.5
Belgian Dutch neuromuscular meeting	2017-2019	0.25
Dutch society for clinical neurophysiologists (NVKNF) winter meeting	2019	0.1
Oral presentations		
Belgian Dutch neuromuscular meeting *Intravenous immunoglobulin withdrawal in chronic inflammatory demyelinating polyneuropathy (IOC trial)*	2019	0.5
Dutch Society for Clinical Neurophysiologists (NVKNF) winter meeting *Diagnosis and treatment response in multifocal acquired demyelinating sensory and motor neuropathy*	2019	0.5
Peripheral Nerve Society annual meeting *Restabilization after intravenous immunoglobulin withdrawal in patients with chronic inflammatory demyelinating polyneuropathy*	2019	0.5
Peripheral Nerve Society annual meeting *Optimizing electrodiagnosis for chronic inflammatory demyelinating polyneuropathy with automated analysis and machine learning.*	2019	0.5
Patient conference for neuromuscular diseases *Intravenous immunoglobulin withdrawal in chronic inflammatory demyelinating polyneuropathy (IOC trial)*	2019	0.5
Dutch Society for Neurologists (NVN) scientific meeting *Intravenous immunoglobulin withdrawal in chronic inflammatory demyelinating polyneuropathy (IOC trial)*	2019	0.5

PhD training	Year	ECTS
Poster presentations		
Patient conference for neuromuscular diseases *Optimal treatment in CIDP (OPTIC protocol): combined intravenous immunoglobulins and methylprednisolone as induction treatment.*	2017	0.5
Dutch Society for Neurologists scientific meeting *Optimal treatment in CIDP (OPTIC protocol): combined intravenous immunoglobulins and methylprednisolone as induction treatment.*	2017	0.5
Peripheral Nerve Society annual meeting *Intravenous immunoglobulins in patients with clinically suspected chronic immune-mediated neuropathy.*	2018	0.5
Peripheral Nerve Society annual meeting *Diagnosis and treatment response in multifocal acquired demyelinating sensory and motor neuropathy.*	2018	0.5
Peripheral Nerve Society annual meeting *Restabilization after intravenous immunoglobulins withdrawal in patients with chronic inflammatory demyelinating polyneuropathy.*	2019	0.5
Peripheral Nerve Society annual meeting *Optimizing electrodiagnosis for chronic inflammatory demyelinating polyneuropathy with automated analysis and machine learning*	2019	0.5
Patient conference for neuromuscular diseases *Intravenous immunoglobulins in patients with clinically suspected chronic immune-mediated neuropathy.*	2019	0.5
(Inter)national conferences		
Dutch Society for Neurologists (NVN) scientific meeting	2017 2019	0.5 0.5
Patient conference for neuromuscular diseases	2017 2019	0.25 0.25
Amsterdam Neuroscience meeting	2017 2018	0.5 0.5
Peripheral Nerve Society annual meeting	2018 2019	1.0 1.0
Teaching	**Year**	**ECTS**
Neurological examination	2017-2019	1.5
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Supervising master thesis Mireille Kamminga	2019	2.0

ABOUT THE AUTHOR

Ilse Lucke was born on June 9th 1990 in Amsterdam. She grew up in Almere with her parents and two sisters. After graduation (cum laude) in 2008 at the Baken Park Lyceum in Almere, she started medical school at the University of Amsterdam.

During a short internship in the second year, she first encountered patients with neurological diseases and the interest for neurology started. This interest was further confirmed during the rest of medical school and the rotations. For a scientific internship, she lived for four months in Baltimore to do an internship at the department of child psychiatry at John Hopkins medical center. She studied the role of attention and inhibitory control in children with obsessive compulsive disorder and tic disorders under supervision of doctor Marco Grados. During her rotations she did an internship at st. Lukes Hospital in Malawi. After graduation in 2016, she started working as a clinical resident at the Neurology department of the OLVG-Oost hospital in Amsterdam. In May 2017, she started as a PhD candidate at the Neurology department of the Amsterdam UMC, location AMC. Under supervision of prof. dr. Ivo van Schaik, dr. Filip Eftimov and dr. Camiel Verhamme, she studied different aspects of the diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy. After working on her PhD thesis for 2,5 years, she started her Neurology residency at the Amsterdam UMC, location AMC under supervision of dr. Vincent Odekerken and prof. dr. Yvo. Roos.

Ilse is engaged to Joost and they live together in Utrecht.

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Verder wil ik alle andere arts-onderzoekers van de afdeling neurologie bedanken, meer specifiek de mede-onderzoekers van H2-235. Het is achteraf echt een wonder dat er met tien man in zo'n kleine ruimte nog gewerkt werd. We hebben zoveel tijd met elkaar doorgebracht dat we onze eigen rituelen ontwikkeld hebben. De lunch was altijd stipt om 12:00 uur en er kon geen thee gehaald worden zonder dat de hele kamer in de 'Tea Train' er achteraankwam. Naast onderzoek heb ik me ook op zoveel andere vlakken kunnen ontwikkelen. Ik weet nu in welke Hogwarts afdeling ik zit en ik was bijna lid geworden van de Scientology kerk. Twan, je begon als enige vaatonderzoeker in de grote kamer en hoorde daardoor toch ook een beetje bij de NMZ-groep. Dank voor de gezelligheid en alle fun-facts over verschillende theesoorten en communistische leiders. Mayte, ik ben er toch nooit helemaal overheen gekomen dat jij uiteindelijk besloot naar de vaatkamer te verhuizen toen daar ruimte vrij kwam. Melanie, het samen sporten vond ik altijd heel gezellig. Jij was bij de grootste doorbraak van mijn onderzoekstijd: het moment dat ik tijdens Pilates eindelijk met mijn vingers de grond kon aanraken.

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