Treatment in chronic immune-mediated neuropathies

A time to start and a time to stop

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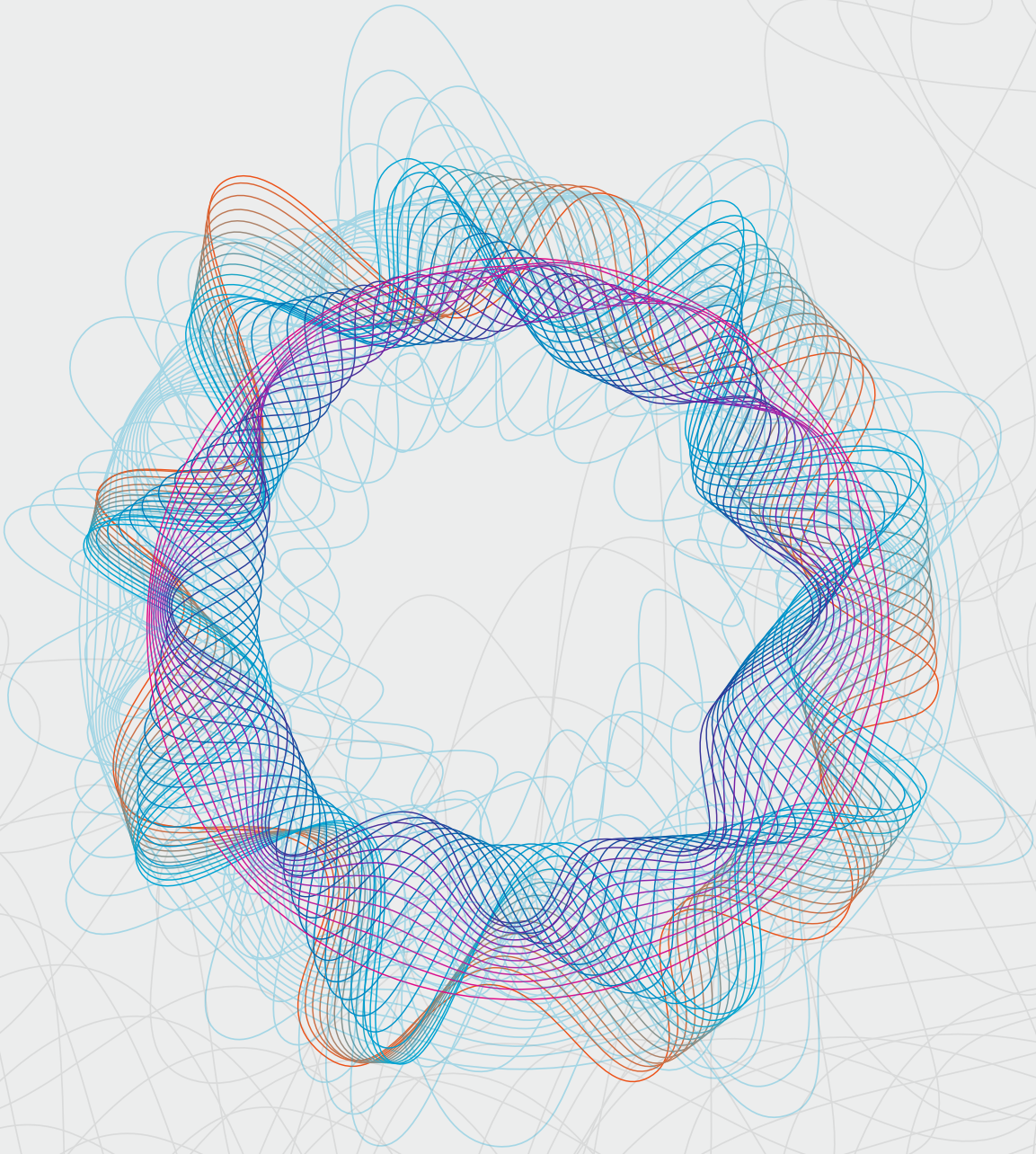

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General introduction and outline of the thesis

Both chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and multifocal motor neuropathy (MMN) are immune-mediated polyneuropathies and both are potentially treatable conditions. Although CIDP and MMN share demyelinating features in nerve conduction studies (NCS), the clinical symptoms differ. CIDP may run a chronic, relapsing-remitting or monophasic course causing muscle weakness and sensory deficits in the arms and legs (*Van den Bergh et al., 2021*) . MMN is characterized by slowly progressive, asymmetric, predominantly distal weakness of one or more limbs without sensory loss (*Beadon et al., 2018*).

CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

CIDP is a heterogeneous disease causing muscle weakness and sensory deficits in the arms and legs, which develop over at least two months (*Van den Bergh et al., 2021*). The prevalence varies greatly with a crude estimate between 1 - 8.9 / 100:000 (*Broers et al., 2019; Laughlin et al., 2009; Lunn et al., 1999*). The disease course can be relapsing-remitting, monophasic or chronic progressive, which makes it difficult to predict the eventual clinical outcome and consequences for patients suffering from this condition. CIDP was initially described as a recurrent polyneuropathy in early literature. The general disease course of 32 of these cases was described as a symmetrical polyneuropathy with both motor and sensory deficits that involved both arms and legs (*AUSTIN, 1958*). Maximal disability was reached after an average of 5 months. Interestingly, this study reported that most patients reached complete recovery after corticosteroid treatment. Recurrence of the disease took place months to years after recovery. These cases of polyneuropathies with a sub-acute onset and relapsing remitting course have been granted many names over the years like recurrent and chronic relapsing Guillain-Barre polyneuritis; chronic relapsing polyneuritis; steroid responsive recurrent polyneuropathy and recurrent demyelinating neuropathy. It was until 1975 that the term chronic inflammatory polyradiculoneuropathy was introduced (*Dyck et al., 1975*). This term covered the recurrent polyneuropathy as well as the monophasic or chronic progressive course of this disease. Finally, the currently used term 'chronic inflammatory demyelinating polyradiculoneuropathy' was introduced in 1982 (*Dyck et al., 1982*).

Establishing the diagnosis of CIDP is mainly based on clinical criteria and specific nerve conduction studies (NCS) features. Many criteria-sets have been proposed over the years. A review of 15 different sets of criteria showed that the EFNS/PNS

2010 criteria had the highest sensitivity and good specificity in diagnosing CIDP (*Breiner and Brannagan, 2014*). Based on this high diagnostic accuracy and broad consensus among experts to use a uniform set to make the diagnosis, the EFNS/PNS criteria became the diagnostic standard in the past decade. Recently, the EAN/PNS published updated criteria (*Van den Bergh et al., 2021*). A diagnosis of CIDP requires, apart from the (mandatory) clinical criteria, at least two demyelinating features in two different motor nerves on sites other than typical nerve entrapment. If these demyelinating features are not fully met, a diagnosis of CIDP can still be made using several supportive criteria namely: response to treatment, abnormal findings in imaging (enlarged nerves on MRI or ultrasound), elevated cerebrospinal fluid (CSF), or demyelinating features in nerve biopsy**.** The diagnosis can be challenging especially in atypical CIDP. The diagnostic test are not specific for CIDP and a variety of pitfalls in interpreting the results have been described (*Eftimov et al., 2020*). Therefore, mis- and underdiagnoses are common (*Allen and Lewis, 2015*).

Several treatments have shown to be successful in treating CIDP including corticosteroids, intravenous immunoglobulins and plasma exchange. In contrast to the earlier described case series by Austin et al., response to corticosteroids was shown in up to 60% in more recent studies (*Eftimov et al., 2012; van Lieverloo et al., 2018*). The broad experience with the use of corticosteroids and its effectiveness makes it a first line treatment of CIDP (*Hughes and Mehndiratta, 2012*). It was in the early 80' that IVIg was introduced as a possible treatment (*Vermeulen et al., 1985*). Several studies showed the effectiveness of IVIg (*Oaklander et al., 2017*). High doses of as much as 2g/kg every three weeks are given as maintenance therapy. A recent trial showed no beneficial effects in maintenance treatment response comparing 2g/kg or 1g/kg every three weeks in the first 6 months of treatment (*Cornblath et al., 2022*). However, it is unclear whether lower maintenance dosages might be sufficient, especially in the long-term. The use of plasma exchange is recommended in refractory disease to IVIg and corticosteroids. The choice of first line therapy remains arbitrary. IVIg induces relatively quickly remissions with little side effects (*Latov et al., 2010*). On the contrary, corticosteroids seem to induce remission over a longer period of time (*Eftimov et al., 2012*). By the introduction of immunotherapy in the early 20th century, the disease course is altered which makes it difficult to identify how the disease would have behaved in a specific patient. Nevertheless, early reports describe a relapsing-remitting course in about a third of CIDP patients with relapses occurring months to years after the initial onset (*McCombe et al., 1987*). Long-term treatment might be beneficial in progressive disease but not necessarily in the relapsing-remit-

ting type. Biomarkers for disease activity are not available which makes it challenging to determine if patients are in need for ongoing treatment. Withdrawing treatment to observe deterioration is the only option to monitor ongoing disease activity. CIDP patients withdrawing IVIg maintenance treatment during several trials did not deteriorate in 11-55% (*Hughes et al., 2008; Mielke et al., 2019; Nobile-Orazio et al., 2015*). This might warrant regular withdrawal attempts to evaluate the necessity of maintenance treatment. However, the safety of these withdrawal attempts was not well investigated and the possible deterioration and disability makes patients and physicians reluctant to withdraw treatment.

MULTIFOCAL MOTOR NEUROPATHY

Multifocal motor neuropathy (MMN) classically presents with an asymmetrical, slowly progressive, pure motor neuropathy with prominent muscle atrophy. MMN is a rare disease with a prevalence of 0,5 - 0,6 per 100.000 (*Cats et al., 2010; Matsui, 2012*). The mean age of onset is 40 years, although there is a considerable range in age of onset (*Cats et al., 2010*). Men are more frequently affected than women. Patients with the clinical phenotype of MMN with conduction blocks on NCS were first described in 1986 (*Chad et al., 1986; Roth et al., 1986*). The term multifocal motor neuropathy was introduced in 1988 and an association of MMN with anti-ganglioside antibodies was found (*Pestronk et al., 1988*).

The hallmark of diagnosing MMN is the presence of conduction blocks in nerve conduction studies. The clinical and electrophysiological criteria published by the EFNS/PNS are considered the reference standard for diagnosing MMN (*van Schaik In, 2010*). However, not all patients with the clinical picture of MMN have conduction blocks making it challenging to distinguish MMN from an untreatable condition like lower motor neuron disease or other immune neuropathies, such as multifocal CIDP. The presence of IgM anti-GM1 antibodies is considered as a supportive criterion for MMN. However, IgM anti-GM1 antibodies are not specific for MMN and might also be present, although infrequently, in patients with other immune neuropathies or lower motor neuron disease (*Kuijf et al., 2005*). Despite attempts to standardize methods to determine the IgM anti-GM1 antibodies using Enzyme-linked immunosorbent assay (ELISA), there is a wide variety in local ELISA protocols in defining positive results (*van Schaik et al., 1995; Willison et al., 1999*).

Next to IgM anti-GM1 antibodies, increased CSF protein, MRI abnormalities in the brachial plexus and a response to IVIg treatment are considered supportive

criteria for the diagnosis of MMN. More recently, high diagnostic accuracies were shown for nerve ultrasound in distinguishing MMN from MND (*Loewenbruck et al., 2016; Oudeman et al., 2020*). Additionally, nerve ultrasound might identify treatment responsive patients suspected of having a chronic immune neuropathy (*Herraets et al., 2020*). Despite all these diagnostic tools, it is not always clear when to start treatment in MMN patients.

IVIg is the only proven successful treatment in MMN and is recommended as first-line treatment (*Keddie et al., 2022*). In contrast to CIDP, corticosteroids and plasma exchange seem not effective in MMN and might even worsen symptoms (*Claus et al., 2000; Donaghy et al., 1994; Lehmann et al., 2008*). There is a lack of high-quality evidence supporting other immunomodulatory or immunosuppressive treatments such as cyclophosphamide, cyclosporine, azathioprine, interferon beta-1a or rituximab. Due to the potential serious side effects it is therefore recommended to only use these treatments in case IVIg is not effective (*Umapathi et al., 2015*).

OUTLINE OF THE THESIS

This thesis is divided in two parts. The first part of this thesis focuses on patients suspected of having CIDP or MMN. In **Chapter 2,** we assessed which diagnostic results led to the decision to start IVIg treatment in patients clinically suspected of having CIDP or MMN but not meeting the NCS criteria. Furthermore, we evaluated the response-rate to IVIg treatment in these patients. **Chapter 3** reports a meta-analyses of the diagnostic test accuracy (DTA) of IgM anti-GM1 antibodies in MMN. We focused on the role of IgM anti-GM1 antibodies in patients suspected of having MMN but not meeting the criteria. Diagnosis in these patients is challenging and these patients might benefit from IVIg treatment.

The second part explores the improvement of the existing induction treatment schedule and potential overtreatment in CIDP. In **Chapter 4,** we describe an extensive literature review on long-term treatment in CIDP, focusing on the possible overtreatment with IVIg. **Chapter 5** reports a prospective pilot study in which we investigated the combination of IVIg and IVMP as induction treatment in CIDP patients. We wanted to explore whether remission was more often reached using this treatment combination. To evaluate the safety and feasibility of a phase-3 trial, we first performed this pilot study. In **Chapter 6,** we describe a case series of six patients with cutaneous lupus erythematosus (cLE) as an adverse effect of IVIg maintenance treatment. This recurrent adverse effect might warrant withdrawing IVIg

treatment. In **Chapter 7,** we report the results of the IOC trial. In this randomized, double-blind non-inferiority trial, we investigated IVIg withdrawal in clinically stable CIDP patients who were on maintenance treatment. We evaluated the safety of withdrawal attempts and wanted to find out whether patients could be restabilized after a relapse by restarting IVIg treatment. Furthermore, we wanted to investigate the expense of overtreatment with IVIg maintenance treatment. We also wanted to explore possible clinical predictors for disease activity. Finally, the main findings of this and implications for future research are summarized and discussed in **Chapter 8**.

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