General introduction

Immune-mediated polyneuropathies cover a spectrum of potentially treatable disorders of the peripheral nervous system leading to variable levels of weakness and sensory disturbances. Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) are important disorders in this spectrum. Both GBS and CIDP show a diversity in clinical symptoms, response to treatment and outcome. In the papers in this thesis we investigate what determines this variation in disease course and treatment response. The focus of the first part of this thesis is on the spectrum of GBS and CIDP as well as its subtypes such as recurrent GBS, acute-onset CIDP (A-CIDP), and GBS with treatment-related fluctuations (GBS-TRF). The second part of the thesis focusses on the treatment of GBS and CIDP with IV immunoglobulins (IVIg).

GUILLAIN-BARRÉ SYNDROME

In 1916, two French soldiers with acute flaccid paralysis and a high cerebrospinal fluid (CSF) protein level with a normal cell count were described by Guillain, Barré and Strohl.[1] This syndrome became known as the Guillain-Barré syndrome (GBS) and nowadays it is the most common severe acute paralytic neuropathy worldwide.[2] The diagnosis of GBS is based mainly on the clinical characteristics of progressive symmetric muscle weakness with reduced or absent tendon reflexes of the arms and legs.[3, 4] Other common symptoms are cranial nerve dysfunction (resulting in facial palsy, double vision or swallowing difficulties), sensory symptoms and pain. Important symptoms to recognise and monitor closely are weakness of respiratory muscles and autonomic dysfunction which may require ICU admittance and artificial ventilation. GBS is often a severe disease, and about 25% of patients require artificial ventilation for some period of time.[2] A variant of GBS is the Miller Fisher syndrome (MFS), characterised by ophthalmoplegia, ataxia and areflexia.[5] MFS patients in general show a milder disease course than GBS, but progression to GBS can occur (GBS-MFS overlap syndrome).[6] GBS is often preceded by an infection such as a respiratory tract - or gastrointestinal infection, and sometimes by a vaccination, which may induce an autoimmune response attacking the peripheral nerves and spinal roots. Whether vaccinations can lead to recurrences of GBS is unknown. Preceding infections of GBS are *Campylobacter jejuni (C. jejuni)*, cytomegalovirus, Epstein-Barr virus, *Mycoplasma pneumoniae*, *Haemophilus influenza*, hepatitis E virus, and recently Zika virus has also been suggested to be associated with GBS as well.[7, 8-11] Molecular mimicry between microbial agents and peripheral nerve antigens (gangliosides) play an important role in the pathogenesis of GBS after infection with *C. jejuni*.[12] Although *C. jejuni* infections are common, only one in 2000-5000 individuals with a *C. jejuni* infection will eventually develop GBS.[13] Since only a small subset of individuals develops this post-infectious polyneuropathy, host susceptibility factors are likely to play an important role

as well in the development of the disease.[14] A key factor in the development of GBS after *C. jejuni*-infection in many patients is the production of antibodies to gangliosides that cross-react against neural antigens. These antibodies are neurotoxic and their fine specificity is associated with the type of clinical deficits: antibodies to GM1 are associated with pure motor GBS and antibodies to GQ1b are related to MFS or oculomotor dysfunction in GBS, which is in accordance with the spatial distribution of these gangliosides in the peripheral nervous system.[15]

On a yearly basis, about 200-250 individuals in the Netherlands develop GBS, which can occur at all ages, although the frequency increases with age. The annual incidence rate of GBS in Europe and North America is 1-2 per 100.000.[13] The main clinical symptom of GBS is rapidly developing limb weakness which should by definition reach its maximum within 4 weeks of onset, but most patients already reach their maximum weakness within 2 weeks.[7] This is followed by a plateau phase of variable duration (generally weeks to months), followed by a recovery phase which can take years (Figure 1).[2] Patients often have an increased CSF protein level but this is not mandatory for the diagnosis. The CSF protein level might be normal especially in the early phase of the disease.[16] CSF examination is more important to rule out an increased cell count which should lead to further investigation for other diseases that can mimic GBS such as Lyme's disease, cytomegalovirus or HIV-infection, or leptomeningeal malignancies.

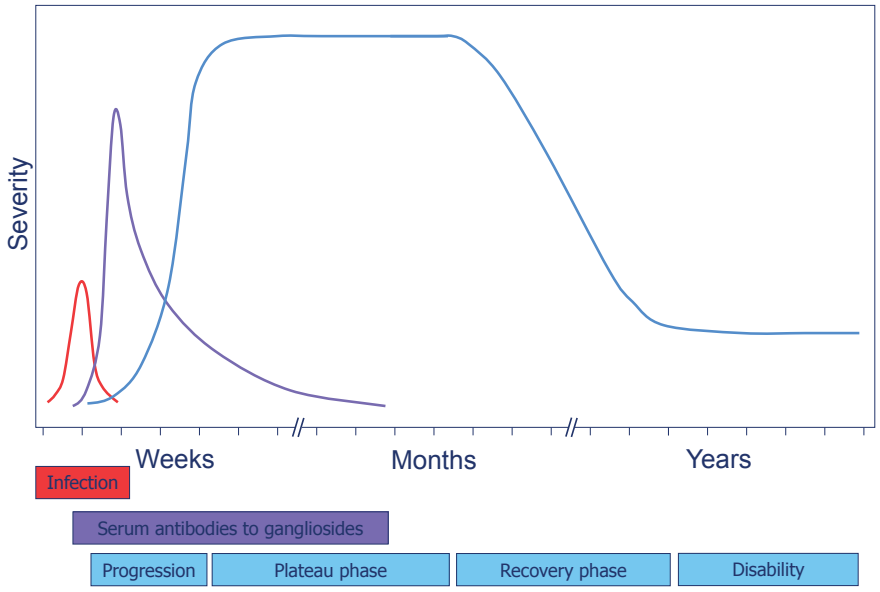

Figure 1. Guillain-Barré syndrome time course[2]

Electromyography (EMG) can be helpful to confirm the diagnosis and to distinguish the demyelinating subtype from the pure axonal form. Currently, the distinction between an axonal and a demyelinating subtype of GBS is of predominant importance for research purposes. In Europe and North America the demyelinating form (acute inflammatory demyelinating polyradiculoneuropathy or AIDP) is the most common form whereas the axonal form (acute motor axonal neuropathy or AMAN or acute motor and sensory axonal neuropathy or AMSAN) is more common in China and Japan.[17, 18] It is important to recognise that the results of EMG in GBS can be normal in the early phase of the disease, and therefore the usefulness of EMG is often limited in the acute phase. EMG however can be helpful, especially when there are abnormalities indicating a polyneuropathy, or when there is doubt about the diagnosis. Criteria supporting the diagnosis of GBS as well as criteria that function as a "red flag" for the diagnosis are listed in Table 1. Table 2 shows differential diagnostic possibilities of GBS.

Table 1. Diagnostic criteria for Guillain-Barré syndrome[3, 21]

Features required for the diagnosis
Progressive motor weakness of arms and legs
Reduced or absent tendon reflexes
Features strongly supportive of the diagnosis
Progression of symptoms over days till maximum of 4 weeks
Relative symmetry
Mild sensory symptoms or signs
Cranial nerve involvement
Autonomic dysfunction
Pain
Increased CSF protein level
Typical electro diagnostic features
No other identifiable cause
Features that should raise doubt about the diagnosis
Fever at onset
Bladder or bowel dysfunction at onset
Sharp sensory level
Increased CSF cell count (>50×10^6/L) or polymorph nuclear cells in CSF
Marked persistent asymmetry
Sensory signs with limited weakness at onset
Severe pulmonary dysfunction at onset
Slow progression with limited weakness and no respiratory involvement
Another identifiable cause of acute polyneuropathy

Table 2. Differential diagnosis of GBS [2, 22, 23]

Metabolic
Diabetic polyradiculopathy/plexopathy
Vitamin deficiency (B1, B12)
Hypophosphatemia
Hypermagnesaemia
Hypokalaemia
Inflammatory or autoimmune
A-CIDP
Myasthenia Gravis
LEMS[1]
Poly- or dermatomyositis
Vasculitis
Transverse myelitis
ADEM[2]
Infectious
Lyme's disease
HIV
Poliomyelitis
West-Nile virus myelitis
Diphtheria
Botulism
Rabies
Cytomegalovirus
Neoplastic
Leptomeningeal carcinomatosis/malignancies
Drug induced
Disulfiram
Nitrofurantoin
Chemotherapeutic drugs
Hereditary
Porphyria
Intoxication
Arsenic neuropathy
Thallium
Shell fish or puffer fish poisoning
Tick paralysis
Alcoholic neuropathy
Spinal cord or brainstem injury
Spinal stenosis or disc prolapse
Epidural abscess or haematoma

Table 2. Differential diagnosis of GBS [2, 22, 23] (continued)

Anterior spinal artery occlusion
Atlantoaxial dislocation
Brain stem stroke
Other
ICU-acquired weakness
Acute rhabdomyolysis

[1] Lambert-Eaton myasthenic syndrome
[2] Acute disseminated encephalomyelitis

Even after full recovery of muscle strength, many patients are bothered, even years later, by severe fatigue interfering with their daily activities.[19, 20] A multidisciplinary practical guideline has been published in 2010 in the Netherlands that covers many aspects of GBS; regarding its diagnosis and treatment, including physiotherapy and revalidation. This guideline (multidisciplinaire richtlijn Guillain-Barré syndrome) can be downloaded at www.vsn.nl. It also contains information about long-term symptoms such as pain and fatigue. We evaluated the levels of pain and fatigue experienced by patients long after the initial phase of their disease.

CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

The first case of chronic and recurrent neuritis was probably already described in 1890, but the concept of steroid-responsive chronic or relapsing neuritis followed much later in 1958.[24, 25] Various names have been used since then until in 1982 the term chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) was given to the disorder and this description has been used ever since.[26] The features of CIDP are in many ways similar to those in GBS, but weakness is usually less severe in CIDP. Patients with CIDP have limb muscle weakness, most often with clear proximal involvement, and decreased or absent reflexes.[27] Most patients have sensory involvement as well, but CIDP can manifest as a pure motor neuropathy.[28] Although pain is present in many GBS patients, not much is known about the occurrence of pain in CIDP.[29-31]

In CIDP about one third of patients report a preceding infection or vaccination as a trigger which is considerably lower than in GBS where two-third reports such a trigger.[32] Not much is known regarding the safety of vaccinations in CIDP patients. CIDP is a chronic polyradiculoneuropathy that develops by definition over more than 8 weeks, distinguishing this disorder from its acute counterpart: GBS. The disease course of CIDP can be either monophasic, chronic or relapsing. The diagnosis of CIDP is based on clinical characteristics combined with electro diagnostic findings.[33] EMG examination is

essential and must display features of demyelination to establish the diagnosis of CIDP.[33] Similar to GBS, the CSF protein level is most often increased in CIDP and an increased CSF protein level supports the diagnosis.[33] A normal CSF protein level can occur in CIDP but an increased cell count should raise the suspicion for other diagnostic possibilities. Criteria supporting the diagnosis of CIDP as well as criteria that function as a "red flag" for the diagnosis are listed in Table 3. CIDP can be difficult to diagnose and has a very broad differential diagnosis (Table 4). In difficult diagnostic cases, a MRI scan of the brachial plexus or a nerve ultrasound can be helpful.[34-37] A nerve biopsy can be used to exclude another diagnosis such as amyloidosis or vasculitis, but is rarely needed.[33, 38] Diabetes or the presence of another autoimmune disease or a monoclonal gammopathy

Table 3. Diagnostic criteria for chronic inflammatory demyelinating polyradiculoneuropathy[3]

Features required for the diagnosis
Progressive motor weakness of arms and legs
Reduced or absent tendon reflexes
Electro diagnostic criteria for primary demyelination
Features strongly supportive of the diagnosis
Progression of symptoms over more than 8 weeks
Sensory symptoms or signs
Increased CSF protein level
Proximal muscle weakness
Features that should raise doubt about the diagnosis
Respiratory muscle weakness
Bladder or bowel dysfunction at onset
Sharp sensory level
Increased CSF cell count (>50×10^6/L) or polymorph nuclear cells in CSF
Marked persistent asymmetry
Autonomic dysfunction
Severe ataxia or tremor at onset
Family history of (hereditary) neuropathies or clear muscle atrophy at onset
Systemic complaints (weight loss, lymphadenopathy, skin changes)
Another identifiable cause of chronic polyneuropathy
Features that rule out the diagnosis
IgM paraprotein with anti-MAG antibodies[1]
Paraprotein related haematological disorders such as POEMS syndrome[2] (often increased VEGF[3]), Waldenström's macroglobulinemia, multiple myeloma, lymphoma
Alternative diagnosis; such as MMN[4], amyloidosis, hereditary neuropathy

[1] Myelin-Associated Glycoprotein
[2] Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, Skin changes
[3] Vascular Endothelial Growth Factor
[4] Multifocal Motor Neuropathy

Table 4. Differential diagnosis of CIDP

Metabolic
Diabetic polyradiculopathy/plexopathy
Uremic polyneuropathy
Hepatic polyneuropathy
Vitamin deficiency (B1, B6, B12)
Tangier disease
Inflammatory
Recurrent GBS
GBS-TRF
MMN[1]
Paraprotein with anti-MAG antibodies
POEMS[2] syndrome
CANOMAD[3]
Sarcoidosis
SLE[4]
Sjögren's syndrome
Amyloidosis
Vasculitis
Infectious
Lyme's disease
Syphilis
HIV
Hepatitis C
Varicella zoster virus
Cytomegalovirus
Neoplastic
Multiple myeloma or osteosclerotic myeloma
Leptomeningeal carcinomatosis
Lymphoma
Leukaemia
Cryoglobulinemia
Drug induced
Amiodarone
Intrathecal methotrexate
Tacrolimus
Hereditary
CMT[5] type 1A, B, C, CMTX
HNPP[6]
Metachromatic leucodystrophy or adrenomyeloneuropathy
Porphyria

Table 4. Differential diagnosis of CIDP (continued)

Refsum's disease
Intoxication
Lead or arsenic neuropathy
Idiopathic
CIAP[7]

[1] Multifocal Motor Neuropathy
[2] Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, Skin changes.
[3] Chronic sensory Ataxic Neuropathy, Opthalmoplegia, IgM paraprotein, cold Agglutinins, Disialosyl antibodies
[4] Systemic Lupus Erythematosus
[5] Charcot-Marie-Tooth
[6] Hereditary Neuropathy with susceptibility to Pressure Palsies
[7] Chronic Idiopathic Axonal Polyneuropathy

of undetermined significance (MGUS) does not exclude the diagnosis of CIDP as long as the clinical and EMG features are compatible with CIDP. It is unknown whether CIDP patients more often have other autoimmune disorders. In case of an IgM paraprotein, the presence of anti-MAG (myelin-associated glycoprotein) antibodies should be examined. If a patient has a more slowly progressive disease with predominantly distal weakness and sensory symptoms, the presence of anti-MAG antibodies rule out the diagnosis of CIDP. These patients should be classified as an IgM anti-MAG related polyneuropathy and treated accordingly.

This differential diagnosis list as presented represents the most common differential diagnostic possibilities. It should be noted that some disorders are probably associated with CIDP (mainly in case reports) such as HIV, hepatitis, SLE, connective tissue disease, sarcoidosis, thyroid gland disorders, inflammatory bowel disease, glomerulonephritis and bone marrow transplantation and therefore do not rule out the diagnosis of CIDP.

THE SPECTRUM OF GBS AND CIDP

GBS has traditionally been separated from its chronic counterpart CIDP by the duration of progressive weakness.[4] Preceding infections, involvement of cranial nerves or weakness of respiratory muscles are more often encountered in GBS than in CIDP, but can occur in both. Several subforms of GBS and CIDP exist; such as recurrent GBS, GBS with treatment-related fluctuations (GBS-TRF) and acute-onset CIDP (A-CIDP). Although GBS is generally a monophasic disorder, TRFs and recurrences can occur. How often GBS patients show a recurrence and what predisposes them for a recurrent GBS is currently unknown. CIDP usually runs a progressive or relapsing course but may be monophasic resembling GBS, and requiring only a single course of treatment. How often this happens

is unknown. Additionally, CIDP patients with an acute or subacute onset, resembling GBS, do exist. Although it can sometimes be difficult to distinguish GBS from CIDP it is important to do so because treatment and prognosis can be different.

CASE 1
"A 42-year-old woman complained of severe pain and soon thereafter she developed progressive weakness and sensory disturbances, which reached their nadir in less than 4 weeks. She showed a near complete recovery. Seven years later, after a flu, she had similar symptoms that peaked in less than 2 weeks. Sixteen years later she had another episode of progressive weakness after a flu-like infection that developed in one week. Five years after the previous episode, she developed a 4th episode after a bout of diarrhoea of progressive weakness that developed over a few hours.
Despite treatment with IVIg, she needed artificial ventilation and had severe autonomic dysfunction complicated by an asystole. She was successfully resuscitated and eventually discharged to a rehabilitation centre. A year later she was using a walker but was independent in her daily life activities. "

Although GBS is most often a monophasic disorder, recurrences like in case 1 can occur. Five patients who fully recovered from an initial episode of GBS have been described who had another acute episode years later. [39] The clinical features of rapid progressive weakness, return of normal reflexes as well as the long asymptomatic intervals distinguished them from CIDP. [39] All had similar antecedent infections as well as similar symptoms over time. [39] Another 12 patients with recurrent GBS have been reported with a total of 32 episodes (1-6 recurrences). [40] Vaccinations may be associated with the recurrence of GBS as well.[41] It is unknown why only some patients develop a recurrence of GBS and whether symptoms and triggers may differ between episodes.

CASE 2
"A twenty-year-old man complained of muscle aches after a flu infection. Two days later he had tingling in his limbs. Whilst at the general practitioner he fell off the examination couch and could not get up by himself. At hospital admission a few hours later he had a tetraparesis and areflexia. CSF showed a normal protein level. He was treated with IVIg and over the following week his muscle strength of arms and legs improved quickly. Just a few days later he developed bilateral facial palsy and progressive weakness, and he was successfully re-treated with another IVIg course."

Most often GBS follows a monophasic course but some patients like the one described in case 2, experience a worsening after an initial improvement to treatment; the so called treatment-related fluctuations (TRFs).[42] Ten out of 95 GBS patients who had been treated with a course of plasma exchange (PE) showed worsening after an initial improvement. [43] Eight of these patients were treated with a repeated course of PE which was then followed by a clinical improvement, and during follow-up none of these patients developed CIDP. [43] Similar worsening after treatment was seen in GBS patients treated with IVIg.[42] Re-treating these TRF patients with another IVIg course also led to an improvement. [42] The prospective GRAPH study showed that a diagnosis of A-CIDP is more likely than GBS-TRF if a patient deteriorates after ≥ 8 weeks of onset or ≥ 3 times. [44]

CASE 3

"A 52-year-old woman developed sensory disturbances after a flu infection. Two days later she was unable to walk. Maximum disability was reached in 6 days. Over the next few months she had several exacerbations needing IVIg treatment, and she was treated subsequently with IVIg once every month for the next 7 years."

Case 3 describes a patient who was diagnosed initially with GBS due to the onset phase of less than 4 weeks but who turned out to have acute-onset CIDP (A-CIDP). A prospective study found that 5% of patients initially diagnosed with GBS actually had A-CIDP, all with an onset phase of < 4 weeks.[44] Seven patients with a monophasic episode of progressive weakness over the course of 4-8 weeks have been classified as subacute idiopathic demyelinating polyneuropathy (SIDP).[45] These patients had predominantly motor dysfunction and were relatively mildly affected, none needed artificial ventilation.[45] All patients clearly responded to prednisone or had a spontaneous recovery.[45] An acute-onset has been reported in 15% of CIDP patients.[32] It can be difficult to distinguish GBS-TRF from A-CIDP, but a diagnosis of A-CIDP is more likely when a patients deteriorates after 8 weeks from onset or 3 times or more.[44] Whether GBS and CIDP can co-occur in the same patient has not been determined yet. The whole spectrum of GBS and CIDP including its overlap or sub forms including some of our research questions of this thesis are shown in Figure 2.

TREATMENT OF GBS AND CIDP

In GBS, both PE and IVIg are proven to be beneficial, but in recent years most patients are treated with IVIg.[46, 47, 48, 49] IVIg contains a huge number of different human immunoglobulins (IgG antibodies) derived from pooled blood of several thousands of blood donors and is given by IV infusion. The exact working mechanism is unknown but probably multifactorial. IVIg has only proven its benefit so far when given within two weeks from onset of weakness in GBS patients who are unable to walk independently.[47, 50] IVIg is usually the first treatment choice; it is readily available and had a better side-effect profile and because of its convenience patients are more likely to complete the course.[47] Despite the clinical variation between GBS patients, all are treated with one standard IVIg course (2 g/kg over 5 days). Not all GBS patients however respond in a similar way and it is unknown whether this standard course is appropriate for all, irrespective of their clinical course, severity or prognosis.

It has not yet been investigated whether mildly affected patients or patients with MFS may benefit from IVIg treatment.[51] Despite the absence of proof from RCTs, and more based upon expert opinion, it has been recommended to treat severely affected MFS patients and MFS patients who develop a GBS-MFS overlap syndrome with IVIg.[52] The same has been advocated for mildly affected GBS patients who show fast progression

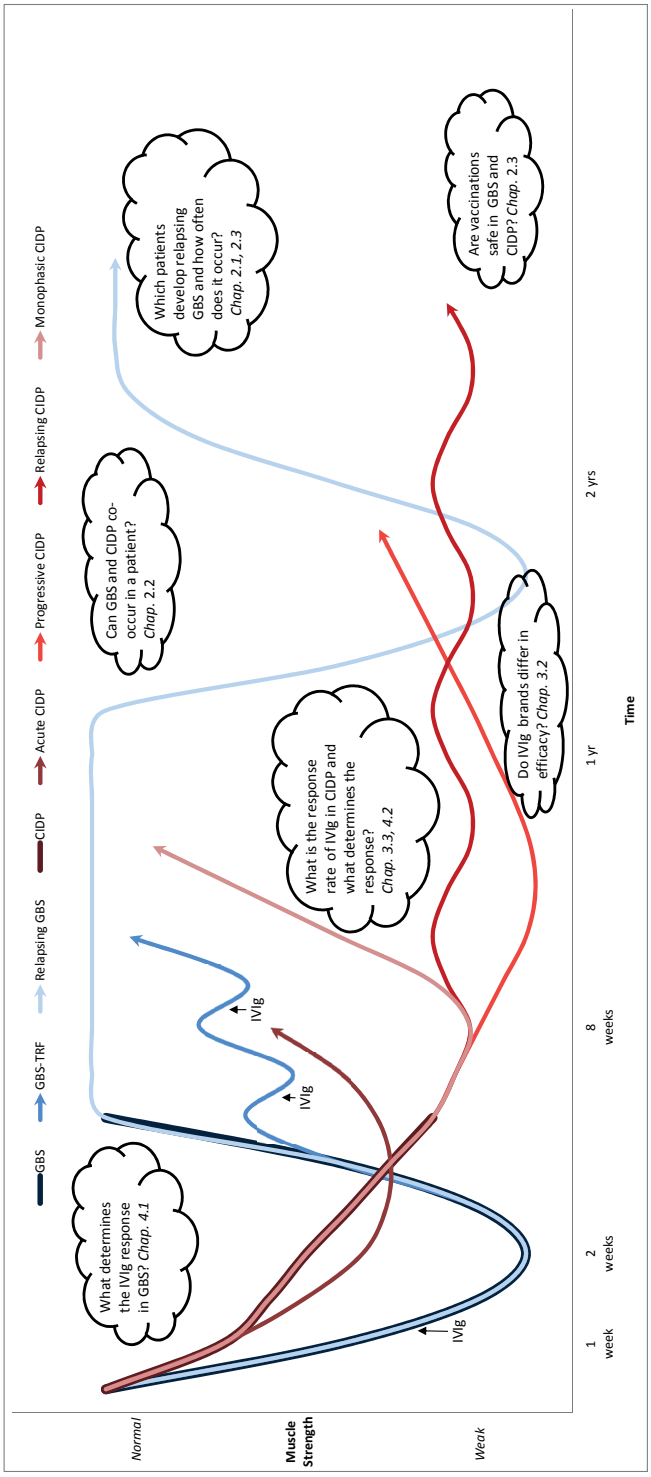

Figure 2. The spectrum of GBS and CIDP

within the first two weeks or who develop severe autonomic dysfunction, bulbar or facial weakness.[52] When GBS patients develop a TRF, another full IVIg course (2 g/kg) is recommended (expert opinion). Despite IVIg treatment, GBS has a high morbidity, with 25% of patients needing artificial ventilation and 20% of patients remaining severely disabled after half a year, and a mortality rate of about 3-5%. [53] Surprisingly, steroids alone are ineffective in GBS. When added to IVIg, intravenous methylprednisolone might have a small positive effect on the short-term outcome compared to IVIg alone.[54]

In CIDP, IVIg, PE and corticosteroids are proven to be effective; although the evidence for a positive treatment effect of corticosteroids is less strong.[55-59] It is currently unknown why some patients do not respond to IVIg and if various IVIg brands differ in clinical efficacy. CIDP patients are treated initially with a loading course of IVIg (2 g/kg) but most patients need intermittent IVIg treatment for several years, for a median duration of about 5 years, ranging up to even more than 30 years (P.A. van Doorn, personal communication). In contrast to GBS, monotherapy with corticosteroids can be effective in CIDP. IVIg is the first choice of treatment in many hospitals because of its convenience and better side-effects profile. IVIg however is an expensive treatment and the time to reach a clinical remission (without treatment) might be longer with IVIg compared to IV corticosteroid treatment.[60] As most CIDP patients improve after IVIg, steroids or PE, the diagnosis should be reconsidered in a patient that does not respond to one of these treatments.[61] CIDP patients who become unresponsive to therapy should be checked again for the appearance of a monoclonal protein or signs of malignancy.[62] Effective dosages and the frequency of IVIg administration required seem to vary largely between patients and it is not known what determines this variation. Variation in the required dose and interval of IVIg in CIDP might be due to differences in IVIg catabolism. It is unknown if high peak serum IgG levels are needed, or if more constant serum IgG levels are preferable.

OBJECTIVES

The research described in this thesis focusses on GBS and CIDP including its overlapping variants.

The aims of this thesis are:

1. To gain a better understanding of the spectrum of GBS and CIDP
2. To obtain more information about the presence of (other) autoimmune diseases and the risk of vaccinations in GBS and CIDP
3. To study the efficacy of IVIg in GBS and CIDP in more detail
4. To improve treatment options in GBS and CIDP

In order to study questions related to these objectives we use GBS and CIDP cohorts (Dutch GBS study group, the Erasmus MC cohort of inflammatory neuropathies, and a Canadian CIDP cohort), as well as a survey of GBS and CIDP members of the Dutch society of neuromuscular disorders.

The studies in this thesis are intended to answer the following questions (related to aim 1 and 2):

1) Can GBS and CIDP co-occur in a single patient?
2) How often does GBS reoccur, and why do some patients have recurrences? Do patients with recurrences show the same symptoms and triggers each time?
3) What is the chance of developing a recurrence of GBS or an increase of symptoms of CIDP after a vaccination?
4) Do (other) autoimmune diseases occur more frequently in GBS and CIDP?

Although treatment with IVIg is relatively successful in most GBS and CIDP patients, many questions remain (related to aim 3 and 4):

1) How often is IVIg effective as a first treatment in CIDP? What is the chance that an IVIg non-responder improves after a second or third treatment modality? Why do not all GBS and CIDP patients improve after a standard course of IVIg?
2) Is one brand of IVIg more effective than another product?
3) Is the standard IVIg dose (2 g/kg) suitable for all GBS patients, or do some patients need a higher dosage or another course?
4) What determines the variation in dosage and frequency of IVIg maintenance treatment required and how should maintenance IVIg treatment be given? How can the efficacy of IVIg maintenance treatment in CIDP be improved?
5) What is the variation in serum IgG levels before and after IVIg in GBS and CIDP? Are serum IgG levels useful to monitor or predict the treatment response?

These questions are investigated in the following studies as described in this thesis.

OUTLINE

Chapter 2 covers the spectrum of GBS and CIDP. In **Chapter 2.1** the clinical characteristics of 32 recurrent GBS patients are described and compared with those of 476 non-recurrent patients. Four patients who had separate episodes of both GBS and CIDP that fulfilled the clinical and diagnostic criteria of these disorders are presented in **Chapter 2.2**. In **Chapter 2.3** the results of a survey of 461 members of the Dutch society of neuromuscular disorders with the diagnosis of GBS or CIDP are described. Recurrences, vaccinations and long-term symptoms such as pain, fatigue and quality of life are described.

Chapter 3 covers the treatment of CIDP. An overview of different treatment options in CIDP is given in **Chapter 3.1**. In **Chapter 3.2** the results of a RCT comparing two different brands of immunoglobulins in CIDP is given (CIC study). In **Chapter 3.3** the results of a retrospective study in 281 patients from two large university hospitals (Erasmus MC, University Medical Centre Rotterdam, the Netherlands and London Health Sciences Centre London Ontario, Canada) being treated with IVIg as a first treatment modality are described. The response to IVIg as well as the response to second or even third treatment modalities was studied. In addition, clinical factors that were associated with a good response to IVIg were assessed. **Chapter 3.4** contains a review regarding maintenance treatment of IVIg in CIDP. The rationale and outline of a dose response trial of IVIg in CIDP (DRIP study) that we are currently performing is described in **Chapter 3.5**. This multi-centre randomised placebo-controlled trial investigates whether high frequency low dosage IVIg treatment is more effective than low frequency high dosage as maintenance treatment for CIDP.

Chapter 4 describes serum IgG levels in IVIg-treated GBS and CIDP. **Chapter 4.1** shows the results of a study of serum IgG levels in 174 GBS patients treated with a standard course of IVIg (2 g/kg). We investigated whether serum IgG levels are related to the outcome. The variability of serum IgG levels in clinically stable but IVIg-dependent CIDP patients receiving maintenance treatment of IVIg is described in **Chapter 4.2**.

In **Chapter 5**, the results of these chapters are discussed in a broader perspective and in relation to the current literature, and suggestions for further research are given.

In **Chapter 6** the observations from the studies, as described in **Chapter 2-4**, are summarised.

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Chapter 2