PAIN, AUTONOMIC DYSFUNCTION, AND COURSE OF DISEASE IN GUILLAIN-BARRÉ SYNDROME

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Research supported by grant of
GBS/CIDP Foundation International
'Janivo Stichting'

Cover design
ZZESTO
zzesto.com
Layout
Legatron Electronic Publishing, Rotterdam
Printing
Ipskamp Drukkers, Enschede

Financial support for publication

Baxter

Erasmus Universiteit Rotterdam

Pfizer

sanofi aventis
Gezondheid boven alles

Sanquin

Pain, autonomic dysfunction, and course of disease in Guillain-Barré syndrome

2010 Rotterdam
ISBN: 978-90-9025241-4

Pain, Autonomic Dysfunction, and Course of Disease in Guillain-Barré Syndrome

Pijn, autonome dysfunctie en ziektebeloop bij het Guillain-Barré syndroom

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de rector magnificus

Prof.dr. H.G. Schmidt

en volgens het besluit van het College voor Promoties

De openbare verdediging zal plaatsvinden op
donderdag 17 juni 2010 om 11:30 uur

door

Liselotte Ruts
geboren te Schiedam

PROMOTIECOMMISSIE

Promotor
Prof.dr. P.A. van Doorn

Overige leden
Prof.dr. J.G. van Dijk
Prof.dr. P.A.E. Sillevis Smitt
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DROOM DINGEN EN VRAAG ‘WAAROM NIET’

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GBS

CHAPTER 1
THE GUILLAIN-BARRÉ SYNDROME, AN INTRODUCTION

Adapted from

Clinical features, pathogenesis, and treatment of Guillain-Barré syndrome
P.A. van Doorn, L.Ruts, B.C. Jacobs
Lancet Neurology 2008;7:939-950 (review)

Autonome dysfunctie bij patiënten met het Guillain-Barré syndroom
L. Ruts, B.C. Jacobs, J.P. Blankevoort, P.A. van Doorn
Tijdschrift Neurologie & Neurochirurgie 2008;109:118-124

Transient hypertrichosis in a patient with Guillain-Barré syndrome
L. Ruts, J.P. Blankevoort, E.P. Prens, P.A. van Doorn
J Peripher Nerv Syst. 2007;12:290-292

AIMS (CASE-ILLUSTRATED)

The Guillain-Barré syndrome (GBS) is an immune-mediated polyneuropathy. Until now, GBS remains a descriptive diagnosis for which there are no specific diagnostic tests. The combination of rapidly progressive symmetrical weakness in arms and legs with or without sensory disturbances, hypo- or areflexia, in the absence of a cerebrospinal fluid (CSF) cellular reaction, remains the hallmark for the clinical diagnosis of GBS (1,2).

In GBS, there is a broad spectrum of clinical symptoms and severity in the acute phase. During the subsequent course of disease, the presence and severity of residual symptoms is highly variable. In most treatment studies only severely affected patients (those being unable to walk without assistance; GBS disability scale grade 3-5) have been included. Because progressive paralysis is the most striking and alarming symptom of GBS, most attention generally is given to the rapid progression and severity of weakness in the acute phase. There are however some underexposed but important issues in GBS like residual findings in particular in patients which limited weakness (mildly affected patients), a fluctuating course after initial improvement (treatment related fluctuations (TRF)), the transition to chronic inflammatory demyelinating polyneuropathy (CIDP) and the frequency and nature of pain and autonomic dysfunction that have been studied limited so far. These issues have formed the basis of the studies described in this thesis.

The following cases illustrate the importance of these underexposed issues.

Case | Residual findings in mildly affected patients

A 52-years-old man, without significant medical history, was admitted because of distal limb weakness, numbness and tingling in his toes. He was diagnosed with GBS. Maximal weakness was reached 12 days after onset. At that moment he was still able to walk unaided, but unable to run ('mildly affected pateint' with GBS disability scale grade 2). Six months later he visited the outpatient clinic. Rather unexpected for the patient and his neurologist, he was still unable to run, suffered from severe fatigue and had burning pain in his feet.

Case | GBS with a fluctuating course

A 60-years-old man, without significant medical history, was admitted with rapidly progressive limb weakness and tingling in the lower limbs. GBS was diagnosed. He was treated with intravenous immunoglobulins (IVIg). Maximal weakness was reached 18 days after onset. At that moment he could walk with support (GBS disability scale grade 3). After nadir, he improved in strength and after one week he was able to walk unaided.

However, at day 25 after onset the patient deteriorated again and needed support to walk again. This raised doubt about the diagnosis GBS. It was considered that (after all) the diagnosis of CIDP with an acute onset (A-CIDP) could also be possible. For treatment strategy and the prognosis it was relevant to distinguish between GBS with treatment related fluctuations (GBS-TRF) and A-CIDP as soon as possible. It was decided to retreat the patient again with IVIg, whereafter the patient improved and was able to walk unaided again. Unexpectedly, the patient deteriorated again at day 42 after onset. The diagnosis A-CIDP was suggested again and the third IVIg treatment course was given. After one year the patient visited the outpatient clinic. He was recovered completely, and he had had no further deteriorations. In retrospect, the diagnosis GBS-TRF was more likely than A-CIDP.

Case | Pain

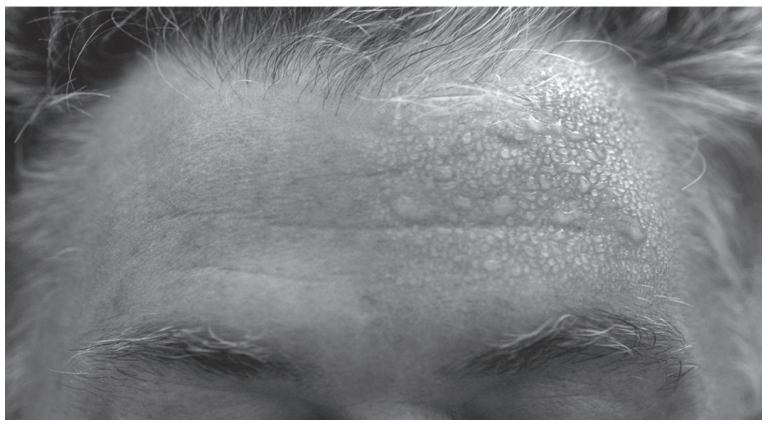
A 25-years-old man, without significant medical history, was admitted because of rapidly progressive limb weakness, numbness and tingling in the lower limbs. GBS was diagnosed. Shortly after admission, he became bedridden and required mechanical ventilation (GBS disability scale grade 5) despite IVIg treatment. During the period at the intensive care unit (ICU), he had severe pain in the extremities. Due to the mechanical ventilation, it was difficult to communicate. After extubation and discharge from the ICU he stressed that the pain he suffered from was one of the most severe symptoms of GBS and a traumatic experience. Three years later, after rehabilitation, he visited the outpatient clinic. He was able to walk unaided and doing his previous job. However, he still suffered from burning pain in his feet.

Cases | Autonomic dysfunction

Autonomic dysfunction occurs in GBS. GBS patients can even die from unpredictable (sudden) autonomic dysfunction (heart rhythm disturbances). Four GBS patients with autonomic dysfunction are described into more detail.

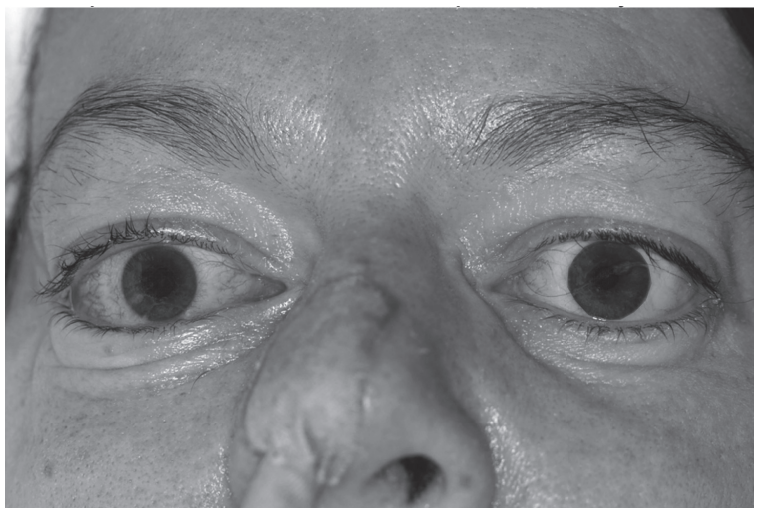
- A 56-years old man with GBS became bedridden and needed artificial ventilation (GBS disability scale grade 5). Besides severe weakness in the extremities and a bilateral facial palsy he developed a ptosis, miosis and anhidrosis on the right side (Horner's syndrome) (figure 1). Also severe blood pressure oscillations and episodic tachycardia did occur (3).

Figure 1 | GBS patient with unilateral anhidrosis (right side) in the acute phase due to autonomic (sympathetic) failure (with permission from the patient)



- A 47-years-old woman with severe GBS, bedridden and ventilated (GBS disability scale grade 5), developed light-reactive dilatation of the right pupil with normal extra-ocular eye movements and without ptosis (figure 2). Also severe blood pressure oscillations and episodic tachycardia did occur (3).

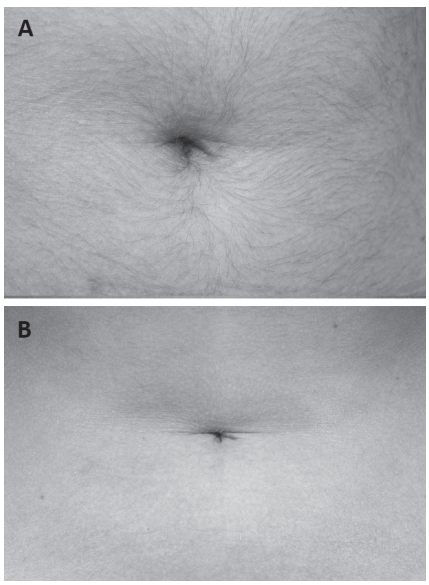
Figure 2 | GBS patient with pupil dilatation (right side) in the acute phase due to failure of the parasympathetic branch of the oculomotor nerve (with permission from the patient).



- A 58-years-old woman with GBS and diabetes and hypertension in medical history became bedridden and needed artificial ventilation (GBS disability scale grade 5). She had three times a cardiac asystole and was reanimated successfully. She later visited the outpatient clinic with very limited residual deficit (3).

- A 20-years-old woman with GBS, without relevant medical history, became bedridden and needed artificial ventilation (GBS disability scale grade 5). She developed excessive hair growth on parts of her body (limbs, trunk, back) defined as hypertrichosis (figure 3a). She also had excessive sweating, blood pressure fluctuations, hypertension, heart rate fluctuations, tachycardia and long-lasting diarrhoea. These findings (including the excessive hair growth) are highly suggestive for widespread autonomic dysfunction. At 6-month follow-up, she had no residual motor or sensory deficits and no further symptoms of autonomic dysfunction. Her hair growth had normalised (figure 3b) (3,4).

Figure 3 | GBS patient (women) with hypertrichosis in the acute phase (A) and normalised hair pattern after 6 months (B) possibly due to involvement of the small nerve fibres in the skin (with permission from the patient)



These cases illustrate the need to study into more detail the outcome in GBS subgroups like mildly and severely affected GBS patients, the distinction between GBS-TRF and A-CIDP and the understanding and treatment of pain and autonomic dysfunction in GBS. These issues were the basis of this thesis.

The aims of this thesis were:

- To provide more insight in the course of disease, the presence and severity of residual findings and the frequency and nature of pain and autonomic dysfunction in GBS;
- To study involvement of small diameter nerve fibres in GBS, because these fibres play a key role in pain conduction and autonomic functions;
- To delineate subgroups of GBS patients having a high chance to develop A-CIDP, pain or autonomic dysfunction;
- To identify possible (new) factors related to outcome in subgroups of GBS.

Before describing the objectives and outline of this thesis, some background information is provided about the clinical manifestations, diagnosis, pathogenesis and treatment of GBS in a general introduction.

GENERAL INTRODUCTION

Diagnosis

GBS is most commonly a post-infectious disorder that usually occurs in otherwise healthy people, not typically associated with an autoimmune or other systemic disorder. The incidence of GBS is reported to be 1.2-2.3/100.000/year (5-11). Most studies found that the incidence increases linearly with age and that men are about 1.5 times more frequently affected than women (6,7,9). The main features of GBS are rapidly progressive bilateral and relatively symmetric weakness of the limbs with or without involvement of respiratory or cranial-nerve-innervated muscles (1,2). Diagnostic criteria for typical GBS are shown in table 1. Weakness might equally affect all limb muscles, or predominantly the distal or proximal muscles in arms or legs. Patients have decreased or absent deep-tendon reflexes, at least in the affected limbs. A lumbar puncture is almost always done in patients suspected to have GBS. CSF examination typically shows an increased protein with normal CSF white-cell count. An increased CSF protein however may be absent especially in the first week after onset of weakness. Electromyography can be helpful to confirm the diagnosis in clinically difficult cases such as in patients who have extreme pain, and in particular is needed for subclassifying GBS into the subgroups of acute inflammatory demyelinating polyneuropathy (AIDP) being the most frequently occurring form of GBS in the Western-world; and in acute motor axonal neuropathy (AMAN) (12). Some features that could raise doubt about a diagnosis of GBS are listed in table 1.

Clinical manifestations of GBS can vary, and an extensive number of other disorders could cause similar features of acute neuromuscular paresis (table 2). The diagnosis of GBS can be difficult, particularly in patients with asymmetric weakness, in those with

weakness initially only in the arms, in patients with rapidly progressive deterioration in pulmonary function with relative preservation of muscle force in the extremities, and in patients with prominent pain or autonomic dysfunction as the presenting symptom (13).

Table 1 | Diagnosis of typical GBS, table adapted from Asbury (1)

Features required for diagnosis
■ Progressive weakness in both arms and both legs (might start with weakness only in the legs)
■ Areflexia (or decreased tendon reflexes)
Features strongly supporting diagnosis
■ Progression of symptoms over days to 4 weeks
■ Relative symmetry of symptoms
■ Mild sensory symptoms or signs
■ Cranial nerve involvement, especially bilateral weakness of facial muscles
■ Autonomic dysfunction
■ Pain (often present)
■ High concentration of protein in CSF
■ Typical electrodiagnostic features
Features that should raise doubt about the diagnosis
■ Severe pulmonary dysfunction with limited limb weakness at onset
■ Severe sensory signs with limited weakness at onset
■ Bladder or bowel dysfuntion at onset
■ Fever at onset
■ Sharp sensory level
■ Slow progression with limited weakness without respiratory involvement (consider subacture inflammatory demyelinating polyneuropathy or CIDP)
■ Marked persistent asymmetry of weakness
■ Persistent bladder or bowel dysfunction
■ Increased number of monouclear cells in CSF (> $50x10^6$/l)
■ Polmorphonuclear cells in CSF

CIDP = chronic inflammatory demyelinating polyneuropathy

About two-third of patients have symptoms of an infection in the three weeks prior to the onset of weakness. One Japanese study found that the most frequent antecedent symptoms in GBS and related disorders were fever (52%), cough (48%), sore throat (39%), nasal discharge (30%), and diarrhoea (27%) (14). In most GBS studies symptoms of a preceding infection of the upper respiratory tract or gastrointestinal tract predominate, although many other types of infections have been reported. Furthermore, an argument for the post-infectious nature of GBS is the usually typical monophasic clinical course of

the disease. The most frequently identified cause of infection is *Campylobacter jejuni*. Other well defined types of infection related to GBS are cytomegalovirus (CMV), Epstein-Barr virus (EBV), *Mycoplasma pneumoniae,* and *Haemophilus influenzae* (15-17).

Table 2 | Differential diagnosis of GBS

Intracranial/spinal cord abnormalities
■ Brain stem encephalitis, meningtis carcinomatosis/lymphomatosis, transverse myelitis, cord compression
Anterior horn cells abnormalities
■ Poliomyelitis, West-Nile virus
Spinal nerve roots
■ Compression, inflammation (e.g. cytomegalovirus), leptomeningeal malignancy
Peripheral nerves abnormalities
■ CIDP, drug-induced neuropathy, porhyria, critical illness polyneuropathy, vasculitis, diphteria, vitamin B1 deficiency (beri-beri), heavy metal or drug intoxication, tick paralysis, metabolic disturbances (hypokalaemia, hypophosphataemia, hypermagnesaemia, hypoglycaemia)
Neuromuscular junction abnormalities
■ Myasthenia gravis, botulism, organophosphate poisoning
Muscular abnormalities
■ Critical illness polyneuromyopathy, polymyositis, dermatomyositis, acute rhabdomyolysis

CIDP = chronic inflammatory demyelinating polyneuropathy

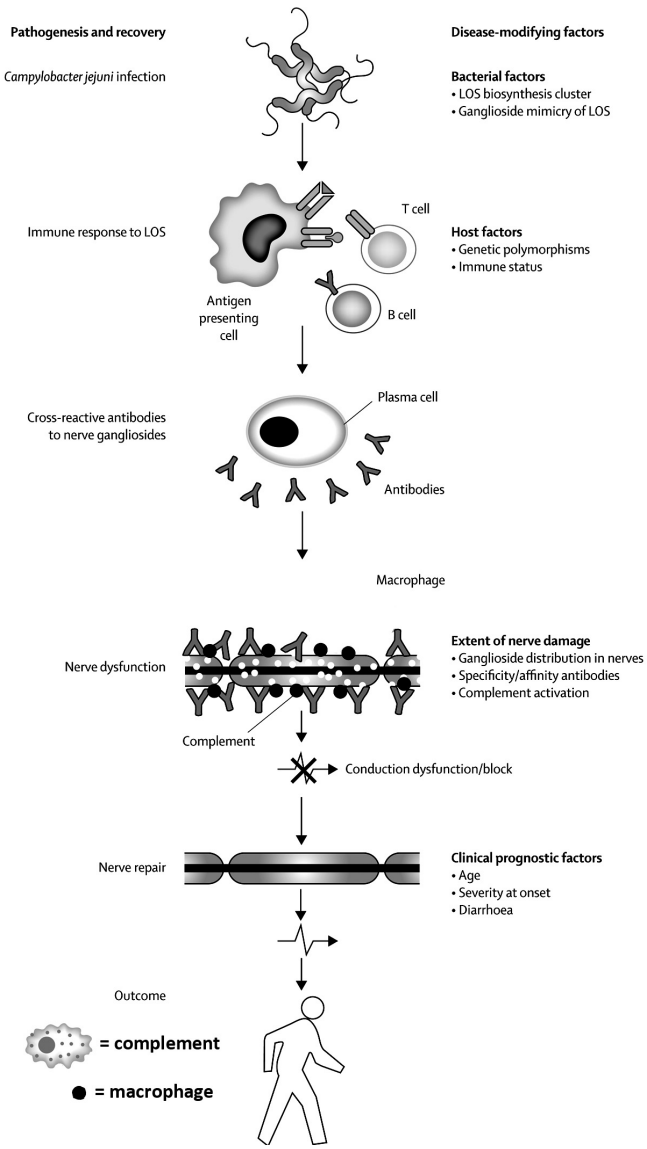
Pathogenesis

Studies in patients and animals have provided convincing evidence that GBS, at least in some cases, is caused by an infection-induced aberrant immune response that damages peripheral nerves (18-25). Four key factors have been identified that control this process (figure 4).

Antiganglioside antibodies

In about half of the patients with GBS, serum antibodies to various gangliosides have be found in human peripheral nerves, including LM1, GM1, GM1b, GM2, GD1a, GalNAc-GD1a, GD1b, GD2, GD3, GT1a, and GQ1b (21,23,26-36). Other antibodies might bind to mixtures or complexes of different gangliosides instead of individual gangliosides (37-40). These gangliosides have a specific tissue distribution in peripheral nerves and are organised in specialised functional microdomains called 'lipid rafts', and play a part in the maintenance of the cell membrane structure (41). Interestingly, most of these antibodies are specific to defined subgroups of GBS. Antibodies to GM1, GM1b, GD1a and GalNAc-GD1a are associated with the pure motor or axonal variants of GBS, whereas antibodies to GD3, GT1a and GQ1b are related to ophthalmoplegia and Miller Fisher syndrome (MFS) (table 3) (6,21,31,42).

Figure 4 | Immunobiology of GBS (with permission from Lancet Neurology)



AP = antigen presenting cell; PC = plasma cell; B = B-cell; T = T-cell

Legend: Infections (eg, with *Campylobacter jejuni)* might induce an immune response that finally leads to GBS. The immune response depends on certain bacterial factors, such as the specificity of lipo-oligosaccharide (LOS), and on the patient-related (host) factors. Genetic polymorphisms in the patient might partially determine the severity of GBS. Antibodies to LOS can cross-react with specific nerve gangliosides and can activate complement. The extent of nerve damage depends on several factors. Nerve dysfunction leads to weakness and might cause sensory disturbances. The outcome in patients with GBS varies. Clinical prognostic factors are: age, severity at onset and diarrhoea.

Table 3 | Spectrum of GBS and serum anti-ganglioside antibodies

GBS subgroup	Antibodies
Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)	Unknown
Acute motor (and sensory) axonal neuropathy (AMAN or AMSAN)	GM1, GM 1b, GD1a, GalNAc-GD1a
Miller Fisher syndrom (MFS) and GBS overlap syndrome	GD3, GT1a, GQ1b

Although there is a relation between the presence of these antibodies and the clinical symptoms and severity of GBS, the pathological significance of some of these antibodies has yet to be established. Antibodies to other glycolipids, and even antibodies and T-cells to peripheral nerve proteins, have also been found in patients with GBS. Despite intensive research over the past two decades, the immune target is still unknown in a substantial group of patients with GBS. This is particularly the case in patients with the sensory-motor AIDP, the most frequent variant in developed countries.

Molecular mimicry and cross-reactivity

Campylobacter jejuni isolates from patients express lipo-oligosaccharides (LOS) that mimic the carbohydrates of gangliosides (43-45). The type of ganglioside mimic in *Campylobacter jejuni* seems to determine the specificity of the antiganglioside antibodies and the associated variant of GBS. *Campylobacter jejuni* isolates from patients with pure motor or axonal GBS frequently express a GM1-like and GD1a-like LOS, whereas those isolated from patients with ophthalmoplegia or MFS usually express a GD3-like, GT1a-like or GD1c-like LOS (40,46,47). Antibodies in these patients are usually cross-reactive, and recognise LOS as well as gangliosides or gangliosides complexes (40). GBS, at least in Campylobacter-associated GM1-related cases, is thought to be a true case of molecular-mimicry-related disease (42,48). Molecular mimicry and cross-reactive immune responses have also been identified after some types of preceding infection, including *Haemophilus influenzae* (49).

Complement activation

Post-mortem studies have shown that local complement activation occurs at the side of nerve damage, such as the axolemma in patients with AMAN and the Schwann-cell membrane in patients with AIDP (50-52).

Host factors

Less than 1 in 1000 patients with a *Campylobacter jejuni* infection will develop GBS (53). Epidemics or outbreaks of GBS have not been reported, not even in families infected with

a gangliosides-mimicking variant of *Campylobacter jejuni* (54). Host factors may influence the susceptibility to GBS, or the extent of nerve damage and outcome.

CLINICAL SPECTRUM AND OUTCOME

The extent and distribution of weakness, sensory involvement and the neurophysiological characteristics varies tremendously between individuals with GBS. The most common subtype of GBS in Europe and North America is the sensory-motor form, AIDP (6). In Europe and North America fewer than 5 to 10% of patients have one of the axonal subtypes – AMAN or acute motor and sensory axonal neuropathy (AMSAN) (12,55-57). Facial nerve palsy is the most common form of cranial nerve involvement in GBS, occurring in at least 70% of patients. Bulbar and oculomotor nerves are less often affected, except in patients with the antiGQ1b antibody syndromes (58). MFS is a cranial nerve variant of GBS. These patients typically have the triad of ophthalmoplegia, ataxia and areflexia (31,42,59)**.** MFS and overlapping syndromes involving cranial nerve dysfunction and limb weakness are probably more common in Japan than in Europe. The GBS varieties have related and sometimes specific antiganglioside antibodies (21,23,26-28,31,32,34,35,42,60,61) (table 3).

Bickerstaff brainstem encephalitis is another overlapping syndrome that generally starts with cranial or peripheral nerve involvement, and can later progress to severe disturbances of consciousness and can even coma (58). Recognition of Bickerstaff brainstem encephalitis is important, because this disorder might improve after plasma exchange (PE), a treatment that despite the absence of a randomised controlled trial (RCT), could be offered in this severe condition (58).

Rapidly progressive weakness is the core clinical feature of GBS. By definition, maximum weakness is reached within four weeks, but most patients have already reached their maximum weakness within two weeks (1,2). Patients then have a plateau phase of varying duration, which ranges from days to several weeks or months. This phase is followed by a usually much slower recovery phase of varying duration. In Europe about a quarter of patients with GBS remain able to walk without aid (mildly affected patients; GBS disability scale grade 1-2) (7,62,63). In patients with GBS who are admitted to hospital and are unable to walk unaided (severe affected patients; GBS disability scale grade 3-5), about 25% need artificial ventilation predominantly because of weakness of the respiratory muscles.

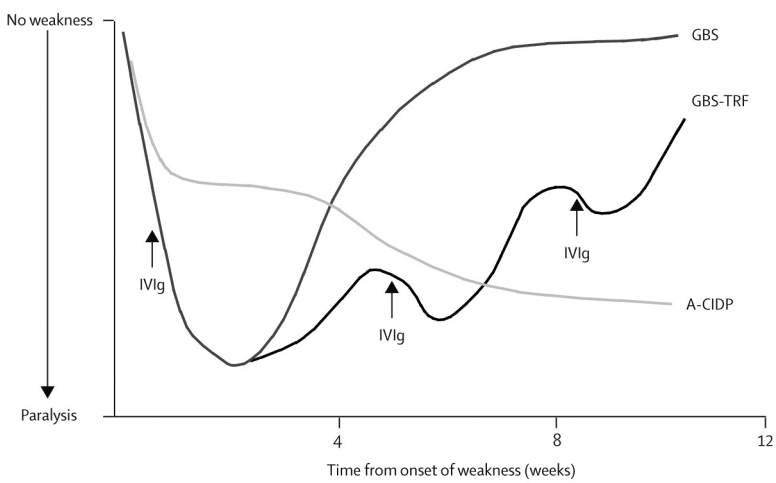
RCTs that have investigated the effect of IVIg or PE in patients who were unable to walk have concluded that about 20% of patients remained unable to walk unaided after 6 months (64). Moreover, many patients remain otherwise disabled or severely fatigued

(65). Even 3-6 years after onset, GBS had great impact on social life and the ability to perform activities (66-68). Therefore, GBS often remains a severe disease for which better treatment is required, at least in a proportion of patients. The severity of GBS seems to be determined already in an early phase of the disease (69).

Detailed information about signs and symptoms in the acute phase, course of disease and outcome in the different GBS subgroups as described above, could be helpful for clinical decision-making like whether and at which point of time there is an indication to start treatment and to guide the prognosis. It also may add to the pathophysiological understanding of GBS and finally to the institution of a better treatment. Different GBS subgroups (MFS, mildly affected, severely affected patients) have been studied and the results are described in chapter 3.

About 5-10% of patients with GBS deteriorate after initial improvement or stabilisation following IVIg treatment, a condition named 'treatment-related fluctuation' (TRF) (figure 5) (70). This often raises the question whether these patients might have CIDP with an acute onset (A-CIDP). The difference between GBS and CIDP is mainly based on the duration of progressive weakness, which is less than 4 weeks in GBS, and, on the basis of research criteria, at least 8 weeks for CIDP (1,2,71). A subacute form between GBS and CIDP has been described (72). Some patients initially have a course like that of GBS, but finally turn out to have CIDP.

Figure 5 | GBS, treatment related fluctuations (TRF) and acute onset CIDP (A-CIDP)



Legend: IVIg=treatment with a course of IVIg (2g/kg bodyweight) over 2-5 days.

Studies that can help to distinguish between GBS-TRF and A-CIDP in the early phase of disease haven been indicated because prognosis and treatment strategy largely differ. We studied this into detail. The results are described in chapter 3.

PAIN

Pain is a common and severe symptom in patients with GBS. Recognition of pain is important, especially in patients unable to communicate due to intubation. Pain as a presenting symptom before the onset of weakness might be confusing and can cause a delay in making a diagnosis of GBS. Pain has been described in up to 89% of patients with GBS (73-75). Different symptoms of pain associated with GBS have been distinguished during different phases of disease: paraesthesia or dysaesthesiae, backache or root pain, meningism, muscle pain, joint pain and visceral pain (76). Pain in GBS can be very severe, and treatment is often far from successful. There are some reports on the effect of medication to relieve pain in GBS (77-83). Corticosteroids, opioids, gabapentin, and carbamazepine are suggested to be effective, although these reports are based on limited numbers of patients, mostly in open studies, and often all types of pain are included together. The likely origin of pain is multifactorial. Pain in the acute phase of GBS might be of nociceptive origin due to inflammation. Small-diameter nerves in the skin, among others responsible for nociception, are affected in GBS. A reduction of intraepidermal nerve fibre density has been found in skin biopsies taken at the ankle from patients with GBS in the acute phase (84). Later in the course of disease, neuropathic pain might result from degeneration and perhaps even regeneration of sensory nerve fibres. Recognition of the presence and type of pain is important because specific treatments can be offered. Skin biopsies may be helpful to elucidate mechanisms that give rise to a painful neuropathy in GBS.

The frequency and nature of the pain in GBS, however, needs to be further defined during the whole course of the disease in relation to the clinical spectrum of GBS. This is of potential benefit for the patient but also for the pathophysiological understanding of pain in GBS. All studies thus far conducted on pain in GBS included only a relatively small number of cases with a limited set of clinical, electrophysiological and serological data. We studied pain in GBS extensively and the results are described in chapter 4**.** Skin biopsies have become an accepted tool for investigating small nerve fibres (85). We studied the number of intraepidermal nerve fibres in skin biopsies from GBS patients in relation pain, autonomic dysfunction and outcome, because small diameter nerve fibres play a key role in pain conduction and autonomic functions. The results are described in chapter 5.

AUTONOMIC DYSFUNCTION

Autonomic dysfunction is a common complication in GBS and occurs in approximately two-thirds of patients (86-89). The extensive distribution of autonomic nerves may result in an array of signs and symptoms due to sympathetic and parasympathetic failure or over-reactivity. Symptoms include various types of cardiac arrhythmias, blood pressure fluctuations, abnormal haemodynamic responses to drugs, sweating abnormalities, pupillary abnormalities, and bladder and bowel dysfunction.

Although autonomic dysfunction is usually of minor clinical importance, life-threatening cardiovascular complications might develop. Three to 10% of patients with GBS die, and in some of these patients the cause is likely to be (sudden) autonomic dysfunction (88). Therefore, recognition of autonomic dysfunction is important. Predicting which patients will develop serious autonomic dysfunction and will therefore need continue monitoring is not yet possible**.** Potentially serious bradyarrhythmias, ranging from bradycardia to asystole, have been found in severely disabled patients, but also in patients who were still able to walk (90). Frequent monitoring of autonomic dysfunction is recommended in all patients with GBS (91). In some cases, application of a transcutaneous pacemaker is indicated or atropine has to be given. In general, vasoactive medication and morphine derivatives should be used with caution. Autonomic nerve fibres can be studied in skin biopsies, and a correlation between reduced intraepidermal nerve fibre density values in skin biopsies from patients with GBS who have clinical autonomic dysfunction has been described once (84).

Detailed information about autonomic functions in relation to the clinical spectrum of GBS needs to be studied into more detail, since this is of potential benefit for the patient but also for the pathophysiological understanding of autonomic dysfunction in GBS. We performed further studies on autonomic functions in different GBS subgroups (MFS, mildly and severely affected patients) and on intraepidermal nerve fibre density values in skin biopsies from GBS patients with or without autonomic dysfunction. The results are described in chapter 3 and 5.

CARE AND TREATMENT

Patients with GBS are in particularly need of excellent multidisciplinary care to prevent and manage potentially fatal complications (91). Thus, patients need careful and regular monitoring of pulmonary function (at least vital capacity and respiration frequency) and possible autonomic dysfunction (heart beat frequency, blood pressure), and infections need to be prevented of (92). Among other issues that need attention already early in the

course of disease are prophylaxis for deep-vein thrombosis, other symptoms of autonomic dysfunction (ilieus, pupil light unresponsiveness), recognition and management of pain, physiotherapy, rehabilitation and psychosocial support (91). Many patients and their relatives benefit from joining a patient organisation (eg, GBS/ Chronic Inflammatory Demyelinating Polyneuropathy [CIDP] Foundation International (www.GBS-CIDP.org), the UK GBS Support Group (www.gbs.org.uk) or the Dutch Association of Muscle Diseases (www.vsn.nl).

The first large trial to show a positive effect of immunotherapy on GBS was the North-American PE study (93). This positive effect was confirmed by a large French PE trial (94,95). PE was beneficial when applied within the first 4 weeks of onset, but the largest effect was seen when started early (within the first two weeks) (93,96). The usual regimen is a five times PE during 2 weeks, with a total exchange of about five plasma volumes. The first RCT on the use of IVIg was published in 1992, and showed that IVIg is as effective as PE (97). Since the publication of these results, IVIg, in a regimen of 0.4 g/kg bodyweight/ day for 5 consecutive days, has replaced PE as the preferred treatment in many centres, mainly because of its greater convenience and availability. The Cochrane review on the use of IVIg in GBS contained four additional trials (98). No difference was found between IVIg and PE with respect to the improvement in disability grade after 4 weeks, the duration of mechanical ventilation, mortality, or residual disability (98). The combination of PE followed by IVIg was not significantly better than PE or IVIg alone (99). Oral steroids or intravenous methylprednisolone (500 mg daily for 5 consecutive days) alone are not beneficial in GBS (100,101). The combination of IVIg and intravenous methylprednisolone was not more effective than IVIg alone, although there might be some indication a short-term effect of this combined treatment when a correction was made for known prognostic factors (64,102,103). The well defined lack of a more obvious effect of corticosteroids remains a puzzling issue in an inflammatory neuropathy disorder such as GBS. Possible explanations could include the minor effect of steroids on the toxicity of antiganglioside antibodies and subsequent complement activation, or an adverse effect on macrophages that clear myelin debris and thus hamper remyelination (104,105). We recently studied the additional effect of a 6-week course of mycophenolate mofetil in GBS. In this pilot-study, there seemed to be no positive effect of mycophenolate mofetil (106). Although there definitely is a positive effect of immunotherapy on the course of GBS, new research into ways to improve the final outcome of GBS are urgently needed (64).

'Mildly affected' is arbitrarily defined as being able to walk without assistance (GBS disability scale ≤ 2) at nadir. A retrospective study showed that these patients often have residual disabilities (69). The RCTs that have assessed the effect of IVIg have not studied the effect in mildly affected patients (64). One large French randomised trial studied the effect of PE also in patients who could walk with or without aid, but not run (62). Onset

of motor recovery was faster in patients who received two PE sessions than in those who received no PE. On the basis of this study, there might be an indication to treat mildly affected patients who have GBS with PE, but it should be kept in mind that no randomised placebo-controlled trials have assessed the effect of PE or IVIg in these mildly affected patients with GBS.

No RCTs have studied the effect of PE or IVIg in patients with MFS (107). Observational studies have suggested that the final outcome in patients with MFS is generally good. In a large Japanese uncontrolled observational study, IVIg slightly hastened the amelioration of ophthalmoplegia and ataxia, but the times to resolution of these symptoms were similar among the IVIg, PE and control groups (108). The investigators concluded that IVIg and PE did not influence the outcome of patients with MFS, presumably because of good natural recovery. Some patients with MFS can be severely affected and could also have swallowing and respiratory problems; they might even have an overlapping syndrome with additional weakness in arms and legs. One could argue that particularly in these patients, or in patients with severe autonomic dysfunction, IVIg treatment might be indicated, although there is no positive evidence of a benefit.

As described before, about five to ten percent of GBS patients deteriorate after initial improvement or stabilisation following IVIg treatment, a condition named 'treatment-related fluctuation' (TRF) (figure 5) (70). Although no RCTs have assessed the effect of a repeated IVIg dose in this condition, it is common practice to give a second IVIg course (2 g/kg in 2-5 days), because these patients are likely to improve after re-initiating this treatment (64). These patients are thought to have a prolonged immune response that causes persistent nerve damage that needs treatment for a longer period of time (109). Some of these patients with GBS might even have several episodes of deterioration. This often raises the question of whether these patients might have CIDP with acute onset (A-CIDP). The differences between GBS-TRF and A-CIDP have been studied and the results are described in chapter 3.

OBJECTIVES AND OUTLINE OF THIS THESIS

The need to study 1) the outcome in GBS subgroups in particular MFS patients and mildly affected GBS patients, 2) the distinction between GBS-TRF and A-CIDP, and 3) pain and autonomic dysfunction, was recognised by the Erasmus MC GBS research group.

As described and case-illustrated, the aims of this thesis were 1) to provide more insight in the course of disease, the presence and severity of residual findings and the frequency and nature of pain and autonomic dysfunction in GBS, 2) to study the presence of small fibre neuropathy in GBS, 3) to delineate subgroups of GBS patients having a high chance to develop A-CIDP, pain or autonomic dysfunction, and 4) to identify possible (new) factors related to outcome in subgroups of GBS.

Overall, the description and recognition of different clinical signs, symptoms, and courses of disease within the broad spectrum of GBS can give more insight into the aetiology, pathogenesis, response to treatment and prognosis of GBS. This eventually could hopefully lead to a better treatment for patients with GBS.

We did several retrospective studies on these topics and designed the GRAPH (GBS Research about Pain and Heterogeneity) study. The GRAPH study is a nationwide prospective GBS follow-up study in an unselected Dutch GBS population that was conducted by the Dutch GBS Studygroup. In this thesis the results of both the retrospective studies and the GRAPH study are described.

An overview of the GRAPH study is given in chapter 2. In Chapter 3 the clinical spectrum of GBS and CIDP and its treatment are described. In chapter 3.1 prospective information about the differences in preceding infections, course of disease and outcome between GBS (non-MFS) versus MFS and mildly versus severely affected GBS patients is presented. In chapter 3.2 the differences between GBS-TRF and A-CIDP are described based on a retrospective study. In chapter 3.3 the differences between GBS-TRF and A-CIDP are described into more detail based on the GRAPH study. In chapter 3.4 a review about the treatment of CIDP is given. Chapter 4 deals with the presence, different locations, types, and intensity of pain in GBS. In chapter 4.1 these aspects of pain, as studied retrospectively in severely affected GBS patients, are described. In chapter 4.2 pain studied retrospectively in pure motor GBS patients is presented. In chapter 4.3 the presence and detailed aspects of pain are described, based on the GRAPH study. These results subsequently are related to other clinical symptoms of GBS. In chapter 5 the presence of small nerve fibre neuropathy in GBS and its subgroups in the acute and chronic phase of disease are described. This has been investigated in skin biopsies by quantification of the intraepidermal nerve fibre density (IENFD). Additionally, the relation between IENFD and pain, autonomic dysfunction and outcome is presented. Finally, in chapter 6 the results of the different studies described in this thesis are summarized and discussed and suggestions for further research are given.

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GBS

CHAPTER 2
GRAPH STUDY

GBS research about pain and heterogeneity

National Dutch prospective one year lasting follow-up study

STUDY DESIGN

The GRAPH (GBS Research about Pain and Heterogeneity) study is a national Dutch prospective one year lasting follow-up study. This study formed the basis for part of the articles included in this thesis. Information was collected from patients with GBS or GBS variants to study pain, autonomic dysfunction, course of disease and outcome. Erasmus MC was the coordinating centre of this multi-centre study conducted by the Dutch GBS study group. The protocol initially was approved by the ethics committee of the Erasmus MC and subsequently by other 55 participating Dutch centres. Patients were included in the GRAPH between February 2005 and October 2008. After obtaining written informed consent, clinical data, biological material and electrophysiological data were collected systematically during one year follow-up (table 1).

Table 1 | Flow-chart GRAPH study

	During hospital stay	**Week 13**	**Week 26**	**Week 39**	**Week 52**
Questionnaires					
■ Medical history	once				
■ Initial symptoms	once				
■ Pain	weekly	x	x	x	x
■ Autonomic (dys)function	weekly		x		
■ Disability	twice a week -weekly	x	x	x	x
■ Course	twice a week -weekly	x	x	x	x
■ Fatigue		x	x	x	x
Neurological exam	twice a week -weekly		x		
Blood	x				
Cerebrospinal fluid (CSF)	x				
Faeces	x				
Sputum	x				
Electromyographic study	x				
For patients admitted in hospital in region of Rotterdam					
Skin biopsy	x		x		
For patients admitted in Erasmus MC					
Second electromyographic study			x		
Autonomic cardiovascular measurement	x		x		

Questionaires about disability, course, and neurological exam were filled in twice a week (in stead of weekly) during the first 3 weeks of hospital stay after inclusion in the GRAPH study and when the patient had a deterioration.

Questionnaires were filled in by the participating neurologist twice a week in the first three weeks after inclusion, weekly during the further hospital stay and once after 26 weeks. The first three weeks after inclusion was determined as the acute phase, because all included patients had their nadir within 3 weeks after inclusion. When the patient was discharged from hospital, additionally questionnaires were filled in by the patient at 13, 26, 39, and 52 weeks after inclusion. If the patient was not able to fill in the questionnaire, relatives were asked for help.

Patients included in the GRAPH study and admitted to one of the hospitals in region of Rotterdam were considered for taking skin biopsies. Patients included in this skin biopsy study (as part of the GRAPH study) and admitted to the Erasmus MC were also asked to participate in a substudy on autonomic functions in GBS. They were considered for autonomic cardiovascular measurements, once in the acute phase and once after 6 months. These patients also had a second EMG after 6 months.

PATIENTS

Patients diagnosed with GBS or a GBS variant could be included in the GRAPH study. Exclusion criteria were: age below twelve and significant co-morbidity with an expected worse prognosis (less than one year survival). In total, 170 patients were included. Table 2 presents a schematic overview of the number of patients included in the GRAPH study performed by the Dutch GBS Studygroup.

We defined patients as GBS or Miller Fisher syndrome (MFS) according to the diagnostic criteria (1,2). Patients finally having a different diagnosis (n=3: hernia nucleus pulposi, Morbus Sjögren, diffuse white matter disease), or accompanying myelitis (n=1), or Bickerstaff encephalitis (n=2) were excluded afterwards. Some patients initially diagnosed and included as having 'GBS', finally revealed to have a chronic relapsing and remitting course (3). These patients were defined as CIDP with an acute onset (A-CIDP). In total 164 patients (138 GBS, 18 MFS, 8 A-CIDP) were included in the studies as described in this thesis.

During one year follow-up some patients died (n=4), were lost to follow-up or refrained further participation (n=5) (figure 1). From 155 patients (95%) all the follow-up questionnaires were sent back. If questionnaires or answers to some questions appeared to be lacking, our research coordinator phoned the patients and asked them to complete and return the questionnaires. If there remained some missing answers, the patients were not excluded from the analyses.

Table 2 | Patients included in the GRAPH study by the Dutch GBS Studygroup, classified by the including hospital and responsible neurologist

Hospital	City	Responsible neurologist	
Erasmus MC	Rotterdam	L. Ruts & Prof.dr.P.A. Doorn (van)	33
Maasstad Ziekenhuis, locatie Clara & Zuider	Rotterdam	H.A.W. Sinnige	12
Academisch Medisch Centrum	Amsterdam	Dr. A.J. Kooi (van der)	10
Canisius-Wilhelmina Ziekenhuis	Nijmegen	Dr. G.W. Dijk (van)	10
Sint Franciscus Gasthuis	Rotterdam	F.H. Vermeij	10
Stichting het van Weel-Bethesda ziekenhuis	Middelharnis	Dr. U.A. Badrising	8
Onze Lieve Vrouwe Gasthuis	Amsterdam	Dr. I.N. Schaik (van)	7
Vlietland Ziekenhuis	Schiedam	J.C.B. Verhey	7
Hofpoort Ziekenhuis	Woerden	J.S. Straver	6
Sint Lucas Andreas Ziekenhuis	Amsterdam	Dr. W.H.J.P. Linssen	5
Ziekenhuis Rijnstate	Arnhem	E.G.J. Zandbergen	4
Catharina Ziekenhuis	Eindhoven	Dr. M.C. Rijk (de)	4
Universitair Medisch Centrum Utrecht	Utrecht	Dr. W.L. Pol (van der)	4
Flevoziekenhuis	Almere	J.P. Blankevoort	3
Wilhelmina Ziekenhuis	Assen	D.G. Oenema	3
St. Lievensberg Ziekenhuis	Bergen op Zoom	B. Feenstra	3
St. Jansdal	Harderwijk	D.J. Hofstee	3
Atrium Medisch Centrum	Heerlen	Dr. R. Beekman	3
Academisch Ziekenhuis Maastricht	Maastricht	Dr. C.G. Faber	3
Jeroen Bosch Ziekenhuis, locatie Groot Ziekengasthuis	Den Bosch	Dr. R.A.J.A.M. Bernsen	3
Meander Medisch Centrum, locatie Elisabeth	Amersfoort	W.G.H. Oerlemans	2
Haga Ziekenhuis, locatie Leyenburg	Den Haag	Dr. R.W.M. Keunen	2
Groene Hart Ziekenhuis	Gouda	G.H.M. Verheul	2
Martini Ziekenhuis	Groningen	Dr. J.W. Snoek	2
Westfries Gasthuis	Hoorn	T.C. Ree (van der)	2
Medisch Centrum Leeuwarden	Leeuwarden	W.J. Schuiling	2
Ruwaard van Putten Ziekenhuis	Spijkenisse	Dr. J.L.M. Jongen	2
Sint Elisabeth Ziekenhuis	Tilburg	Dr. L.H. Visser	2
VieCuri, Medisch Centrum voor Noord-Limburg	Venlo	G.M.J. Lassouw	2
Slotervaartziekenhuis	Amsterdam	Dr. V.I.H. Kwa	1
Delfzicht Ziekenhuis	Delfzijl	J.A. Don	1
Medisch Centrum Haaglanden, locatie Westeinde	Den Haag	Prof. dr. M.J.B. Taphoorn	1
Stichting Oosterscheldeziekenhuizen	Goes	F. Visscher	1
Rijnland Ziekenhuis, locatie Leiderdorp	Leiderdorp	R.J.W. Witteveen	1
Leids Universitair Medisch Centrum	Leiden	Dr. J.J.G.M. Verschuuren	1
IJsselmeerzieuizen, locatie Lelystad	Lelystad	E.M. Leenders	1
Laurentius Ziekenhuis Roermond	Roermond	Dr. P.H.M.F. Domburg (van)	1
Ikazia Ziekenhuis	Rotterdam	D.M.H. Zuidgeest	1
Havenziekenhuis	Rotterdam	H.J. Vroon	1
Lange Land Ziekenhuis	Zoetermeer	R.J. Groen	1
TOTAL			170

Mildly (GBS disability score at nadir ≤ 2, table 6) as well as severely affected patients (GBS disability score at nadir ≥ 3, table 6) were included. At nadir, 4% (7/164) had a GBS disability score 1, 16% (26/164) a GBS disability score 2, 25% (41/164) a GBS disability score 3, 38% (62/164) a GBS disability score 4, and 17% (28/164) a GBS disability score 5. All 164 patients reached nadir of weakness within 29 days after onset of weakness (figure 2).

Figure 1 | Patients included in the GRAPH study and patients who died (n=4) or were lost to follow-up (n=5) during the one year follow-up time

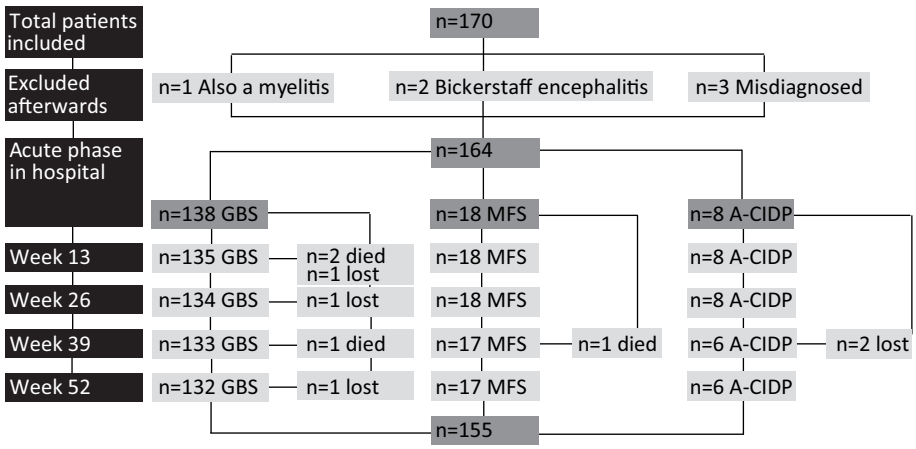
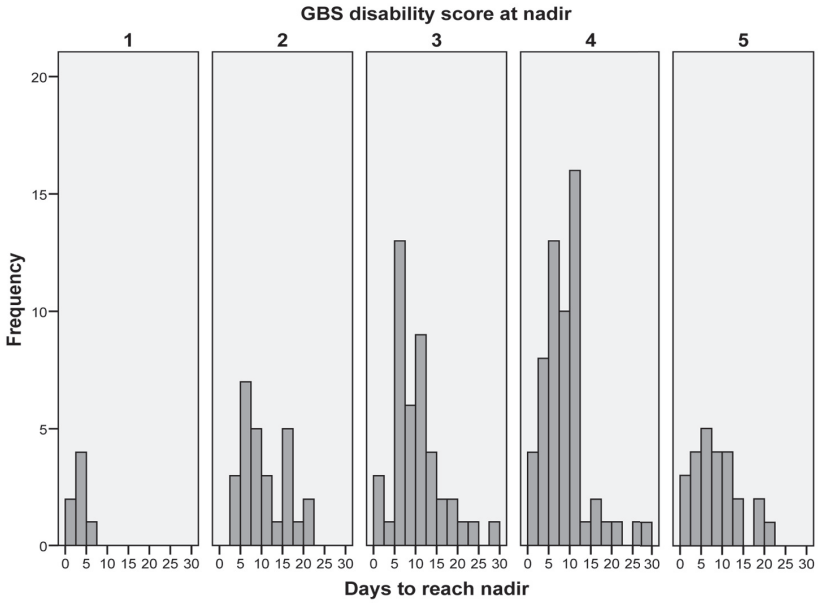


Figure 2 | Frequency histogram displaying the period (in number of days) from onset of weakness to the maximal weakness (nadir) related to the GBS disability score at nadir in 164 patients included in the GRAPH study



QUESTIONNAIRES

The topics addressed in the questionnaires are shown point by point. All topics were asked for in each questionnaire, unless otherwise indicated.

Baseline characteristics and medical history

(only in the first questionnaire)

Pain

For all pain questionnaires it was emphasized that it had to be a newly arisen pain, different from any previous pain in medical history.

To determine the presence of pain we asked for the presence of pain:

- in the previous week
- two weeks before the onset of weakness (only in the first questionnaire)
- in medical history before the onset of GBS (= chronic pain within three months back in time – without 2 weeks before onset of weakness -) (only in the first questionnaire)

To determine the severity of pain at all time-points, we used the 11-point numerical rating scale (NRS, in which 0 represents no pain and 10 represents extreme pain) (4). The following NRS scores were obtained:

- mean NRS of the severest pain in the previous week
- NRS at this moment
- mean NRS in the previous week

The location, character and type of pain were determined.
Options to mark for the location of pain:

- (low)back
- interscapular
- neck
- extremities
- trunk

Character of pain was obtained based on the simplified version of the Dutch McGill Pain Questionnaire (appendix) (5,6).
Options to mark for the type of pain (only filled in by the neurologist) (7):

- radicular pain
- meningism
- painful par/dysaesthesiae
- muscle pain
- joint pain
- other pain (with the possibility to explain)

The use of daily analgesics or co-analgesics was obtained categorized based on the WHO's pain ladder (8):

- none
- paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs)
- opioids
- anti-depressants or anti-convulsants

Neurological symptoms, signs, disability and impairment

Questionnaires only filled in by the neurologist:

- neurological symptoms (only in the first questionnaire)
- impairment scales
  - MRC sumscore, ranging from 0 'paralysis' to 60 'normal strength' (9) (table 4)
  - 'INCAT' sensory sumscore (table 5) (10,11)

- disability scales
  - GBS disability score, ranging from 0 'no symptoms or signs' to 6 'dead' (table 6) (15)
  - overall disability sumscore (ODSS), ranging from 0 'no signs of disability' to 12 'most severe disability score' (table 7) (10,12)
- spinal root and meningeal stretch signs, presence of allodynia, tendon reflexes
- treatment and course of disease (deterioration, improvement or stabilisation)

Questionnaires filled in by the patient after hospital discharge:

- pain symptoms like above
- Fatigue Severity Scale (FSS) ranging from 1 'no signs of fatigue' to 7 'most disabling fatigue' (13;14) (table 8) (FSS in medical history before the onset of GBS = FSS within three months back in time was also obtained (only in the first questionnaire))
- disability scales like above (GBS disability score, ODSS)
- course of disease (deterioration, improvement or stabilisation)

Autonomic (dys)function

Clinical autonomic dysfunction parameters were defined as follows:

- hypertension (systolic blood pressure >140 and/or diastolic blood pressure >90 mmHg)
- hypotension (systolic blood pressure <90 mmHg)
- tachycardia (heart rate >100 bpm)
- bradycardia (heart rate <60 bpm)
- gastrointestinal dysfunction (diarrhoea, constipation, incontinence)
- bladder dysfunction (urine retention, incontinence)
- other symptoms of autonomic dysfunction (for example Horner's syndrome, pupil dilatation, excessive sweating)

We asked for the presence of these items in the previous week.

Table 4 | Medical Research Council sumscore (9)

MRC grades
0 = no movement
1 = palpable contraction, but no visible movement
2 = movement but only with gravity eliminated
3 = movement against gravity (more or less full range)
4 = movement against resistance, but weaker than normal
5 = normal power

Range: 0 'total paralysis' to 60 'normal strength' ; Muscle strength was assessed of six muscle groups (arm abductors, forearm flexors, wrist extensors, hip flexors, knee extensors, foot dorsal flexors) at both sides. The MRC scale was used to score each muscle group and the scores are given in full numbers (0-5) only (4-, 4+, 4½ =4).

Table 5 | INCAT sensory sumscore (10,11)

"INCAT"sensory sumscore				
Pinprick Sensation		**Vibration Sensation**		**2-point discrimination**
Sites of examination + Corresponding grades		Sites of examination + Corresponding grades		Sites of examination + Corresponding grades
Arms	Legs	Arms	Legs	Index fingerK
0 = normal sense at index finger[A]	0 = normal sense at hallux[F]	0 = normal sense at index finger[A]	0 = normal sense at hallux[F]	0 = normal sense (= 4 millimetres)
Abnormal sense	**Abnormal sense**	**Abnormal sense**	**Abnormal sense**	**Abnormal sense**
1= at index finger[B]	1 = at hallux[G]	1= at index finger[B]	1 = at hallux[G]	1 = 5-9 mm
2 = at wrist[C]	2 = at ankle[H]	2 = at wrist[C]	2 = at ankle[H]	2 = 10-14 mm
3 = at elbow[D]	3 = at knee[I]	3 = at elbow[D]	3 = at knee[I]	3 = 15-19 mm
4 = at shoulder[E]	4 = at groin[J]	4 = at shoulder[E]	4 = at groin[J]	4 = 20 mm or more

Pinprick and vibration sense examination took place from distal to proximal and only the highest extension of dysfunction of the most affected arm and leg was recorded separately for both qualities.
Pinprick was tested using the sharp end of a stick. Patients were asked to indicate whether they experienced the pinprick as normal or abnormal. Paraesthesiae, dysaesthesiae or hyperaesthesiae were scored as abnormal. We seek for a normal reference point (e.g. sensation at the face), if a patient was experiencing problems indicating whether the pinprick was abnormal or not.
Vibration was assessed using the RydelSeiffer graduated tuning fork and the obtained values were compared with the published normative vibration threshold values.
ISS composition: pinprick arm grade [range: 0-4] + vibration arm grade [range: 0-4] + pinprick leg grade [range: 0-4] + vibration leg grade [range: 0-4] + 2-point discrimination grade [range: 0-4]. *Sites of examination*: [A & B]=index finger (dorsum distal interphalangeal joint); [C]=ulnar styloid process; [D]=medial humerus epicondyle; [E]=acromio-clavicular joint; [F & G]=hallux (dorsum distal interphalangeal joint); [H]=medial malleolus; [I]=patella; [J]=anterior superior iliac spine; [K]=index finger (ventral side; distal phalanx).
ISS Range: 0 ('no sensory deficit') to 20 ('most severe deficit').

Table 6 | GBS disability score (F-score) (15)

GBS disability score	Definition
0 =	Normal; no symptoms or signs
1 =	Minor symptoms or signs and able to run
2 =	Able to walk at least 10 meters without walker or support, but unable to run
3 =	Able to walk 10 meters with a walker or support
4 =	Bedridden or chair bound (unable to walk 10 meters with a walker or support)
5 =	Requiring artificial ventilation for at least part of the day
6 =	Dead

Table 7 | Overall disability sumscore (ODSS) (10-12)

Overall disability sumscore = Arm disability scale (range: 0-5) + Leg disability scale (range: 0-7)			
Arm disability scale Function checklist	Not affected	Affected but not prevented	Prevented
Dressing upper part of body (excluding buttons/zips)	o	o	o
Washing and brushing hair	o	o	o
Turning a key in a lock	o	o	o
Using knife and fork (spoon: is applicable if the patient never uses knife and fork)	o	o	o
Doing/undoing buttons and zips	o	o	o

Arm grade

0 = Normal

1 = Minor symptoms or signs in one or both arms but not affecting any of the functions listed

2 = Moderate symptoms or signs in one or both arms affecting but not preventing any of the functions listed

3 = Severe symptoms or signs in one or both arms preventing at least one but not all functions listed

4 = Severe symptoms or signs in both arms preventing all functions listed but some purposeful movements still possible

5 = Severe symptoms and signs in both arms preventing all purposeful movements

Leg disability scale - Function checklist	No	Yes	Not applicable
Do you have any problems with your walking	o	o	o
Do you use a walking aid	o	o	o
Ho do you do usually get around for about 10 meters			
Without aid	o	o	o
With one stick or crutch or holding to someone's arm	o	o	o
With two sticks or crutches or one stick or crutch and holding to someone's arm	o	o	o
With a wheelchair	o	o	o
If you use a wheelchair: can you stand and walk a few steps with help	o	o	o
If you are restricted to bed most of the time, are you able to make some purposeful movementso o o	o	o	o

Leg grade

0 = Walking is not affected

1 = Walking is affected but does not look abnormal

2 = Walks independently but gait looks abnormal

3 = Usually uses unilateral support to walk 10 meters (stick, single cutch, one arm -25 yards)

4 = Usually uses bilateral support to walk 10 meters (sticks, cutches, two arm - 25 yards)

5 = Usually uses wheelchair to travel 10 meters (25 yards)

6 = Restricted to wheelchair, unable to stand and walk few steps with help but able to make some purposeful leg movements

7 = Restricted to wheelchair or bed most of the day, preventing all purposeful movements of the legs (e.g. unable to reposition the legs in bed)

ODSS = Arm disability scale (range: 0-5) + Leg disability scale (range: 0-7)
Range: 0 (no signs of disability) to 12 (maximum disability)
For the arm disability scale: Allocate one arm grade only by completing the Function checklist. Indicate whether each function is 'affected', 'affected but not prevented' or 'prevented'. For the leg disability scale: Allocate one leg grade only by completing the Functional questions.

Table 8 | The Fatigue Severity Scale (FSS) (13,14)

Fatigue Severity Scale (FSS)							
1=strongly disagree; 2=mainly disagree; 3= partially disagree; 4=do not agree / disagree; 5=partially agree; 6= mainly agree; 7=strongly agree (circle one answer per question)							
1. My motivation is lower when I am fatigued	1	2	3	4	5	6	7
2. Exercise brings on my fatigue	1	2	3	4	5	6	7
3. I am easily fatigued	1	2	3	4	5	6	7
4. Fatigue interferes whith my physical functioning	1	2	3	4	5	6	7
5. Fatigue causes frequent problems for me	1	2	3	4	5	6	7
6. My fatigue prevents sustained physical functioning	1	2	3	4	5	6	7
7. Fatigue interferes with carrying out certain duties and responsibilities	1	2	3	4	5	6	7
8. Fatigue is among mythree most disabling symptoms	1	2	3	4	5	6	7
9. Fatigue interferes with my work, family, or social life	1	2	3	4	5	6	7

The mean score of the 9 inquiries ranges from 1 (no signs of fatigue) to 7 (most disabling fatigue)

Treatment related fluctuations or exacerbations

To determine nadir, improvement, deterioration or stabilisation during one year follow-up, the GBS disability score (table 6) (15) and MRC sumscore (table 4) (9) were used. By definition**,** the first progressive phase needs to have its nadir within four weeks, in accordance with the criteria for GBS (1,16). After the first nadir, treatment related fluctuations (TRFs) (in case of GBS-TRF) and exacerbations (in case of A-CIDP) could occur with their own nadir. Because only part of the exacerbations in A-CIDP is treatment related (especially during the later phase of disease), here we used the term exacerbations in stead of TRFs.

A TRF or exacerbation was defined as: 1) Improvement in GBS disability score of at least one grade or improvement in MRC sumscore of more than five points after completion of therapy, followed by a worsening in GBS disability score of at least one grade or a decrease in MRC sumscore of more than five points within the first months after onset of disease or 2) Stabilisation of the clinical course for more than one week after completion of therapy, followed by a worsening of at least one grade of the GBS disability score or more than five points on the MRC sumscore (3,17).

Clinical subgroup definitions

We defined the following subgroups:

- pure motor: when pinprick and vibration sense were both normal
- having sensory disturbances: when pinprick or vibration sense were abnormal
- mildly affected: able to walk unaided at nadir = GBS disability score ≤ 2
- severely affected: unable to walk unaided at nadir = GBS disability score ≥3

PRECEDING INFECTIONS

Clinically

The following preceding infections, judged clinically, were scored: respiratory tract infection or influenza (-like) and gastro-enteritis or diarrhoea (18). These were considered positive when patients reported symptoms meeting the criteria for these infections according to the Centre of Disease Control (CDC) definitions for nosocomial infections (18) and when they occurred within four weeks before onset of weakness.

Serology

From 156 patients (95%) pre-treatment serum samples could be obtained. Serum samples were tested to determine recent infection with *Campylobacter jejuni*, human adenoviruses, respiratory syncytial virus (RSV), influenza A virus, influenza B virus, parainfluenza virus 1, 2, and 3, cytomegalovirus (CMV), Epstein-Barr virus (EBV) and *Mycoplasma pneumoniae* using a standard assay (19-21).

Cultures

Bacteriological and virological examination of the stool and throat specimens was performed by (cell) culture and PCR. From 110 patients (67%) stool and throat samples were obtained.

Campylobacter jejuni was cultured from the stools and *Haemophilus influenzae* was cultured from the throat specimens using a standard assay (22,23). Stool samples were analysed for the presence of human adenoviruses and enteroviruses by cell culture (24). Respiratory viruses were isolated by centrifuge-enhanced culture (20). All samples were tested for RSV, influenza viruses type A and B, parainfluenza viruses 1, 2, 3, and 4, human adenoviruses, rhinovirus, and human metapneumovirus (HMPV) by routine diagnostic immunofluorescence (IF) assays 48 hr after inoculation.

Nucleic acid extraction and real time amplification (PCR)

The stool swabs were tested by means of real-time PCR for human adenoviruses, norovirus, enterovirus, parechovirus using a standard assay (24,25). The throat swabs were tested by real-time PCR for RSV types A and B, influenza virus types A and B, human adenoviruses, parainfluenza virus types 1, 2, and 3, rhinovirus, herpes simplex virus (HSV) types 1 and 2, human metapneumovirus (hMPV), and human coronavirus (hCoV) types 229E, OC43 and NL63. Total nucleic acids were routinely isolated at the MagnaPureLC Isolation Station (Roche Applied Science, Penzberg, Germany). A universal internal control virus was used to monitor the whole process from nucleic acid isolation until real-time detection (20,26).

ANTI-GANGLIOSIDE ANTIBODIES AND ROUTINE DIAGNOSTIC TESTS

Serum and cerebrospinal fluid (CSF) were obtained before start of treatment. From 156 patients (95%) pre-treatment serum samples could be obtained. Sera were screened for the presence of IgG and IgM antibodies against GM1, GM2, GD1a and GQ1b using ELISA using standard techniques (27,28). Standard serological diagnostic tests, serum creatine kinase (CK) and the CSF number of cells and protein were determined according to routine laboratory procedures.

ELECTROMYOGRAPHIC STUDIES

Electrophysiological investigations were obtained from 148 patients (90%). According to the protocol, electrophysiological investigations were scheduled within three weeks after inclusion. The electrophysiological investigations were executed according to local settings of the participating hospitals. The nerves were stimulated at the conventional stimulation points (29).

Motor nerve conduction (orthodromic) from the ulnar, peroneal, and optionally the median and tibial nerve. In these nerves the distal and proximal compound muscle action potential (dCMAP and pCMAP) amplitude, distal motor latency (DML), motor nerve conduction velocity (mNCV), and F-wave latencies were measured.

Sensory nerve conduction studies (antidromic) from the median, ulnar, and optionally the sural nerves. The sensory nerve action potential (SNAP) amplitude and sensory nerve conduction velocity (sNCV) were measured.

Needle EMG performed optionally. Patients were classified as demyelinating, axonal, equivocal or normal according to the published classification (30). Reference values were derived from Buschbacher and Pralow (29).

SKIN BIOPSIES

Patients included in the GRAPH study and admitted to one of the hospitals in region of Rotterdam were considered for taking skin biopsies. Exclusion criteria for taking skin biopsies were age below 18 years, already known with signs or symptoms of a polyneuropathy or the presence of diabetes mellitus in medical history. Finally 35 patients were included in the skin biopsy analysis.

Skin biopsies were taken using a disposable 3-mm punch, after local anaesthesia with 2% lidocaine, from:

- the lateral side of the distal leg, 10 cm above the malleolus within the territory of the sural nerve
- the back, 3 cm besides the third/fourth lumbar vertebrae

No suture was used.

Patients underwent skin biopsies:

- in the acute phase
- 6 months after inclusion close to the scar of the former skin biopsy

For comparison, distal leg (n=24) and lumbar site (n=23; 1 lost) skin biopsies from aged and gender-matched control subjects were performed after obtaining a written informed consent. Exclusion criteria were age below 18 years, already known with signs or symptoms of a polyneuropathy or the presence of diabetes mellitus in medical history.

All biopsies were fixed for 24 hours, cryoprotected, coded at Erasmus MC, and shipped to the Skin Biopsy laboratory at the Neurological Institute 'Carlo Besta' of Milan to be processed. Skin biopsy examiners were blinded for the biopsy site and the clinical condition. Three sections randomly chosen from each biopsy were immunoassayed with polyclonal anti-PGP 9.5 antibodies (Biogenesis Ltd, Poole, UK; 1:1000) using the free-floating protocol for bright-field immunohistochemistry previously described (31). The intraepidermal nerve fibre density (IENFD) was derived from the linear quantification of PGP 9.5 positive nerves. The IENFD was determined and reported according to the guidelines of the European Federation of Neurological Societies (32).

AUTONOMIC CARDIOVASCULAR MEASUREMENT

Patients included in this skin biopsy study and admitted to the Erasmus MC (main study centre in the GRAPH study) were also evaluated for an autonomic cardiovascular measurement. The autonomic cardiovascular measurement was done in 19 patients. Spectral analysis of heart rate (HR) and blood pressure (BP) variability was applied to investigate details of cardiovascular control mechanisms (33-36).

- HR variability in the high frequency band (HF: 0.15-0.50 Hz) is related to respiratory variations (respiratory sinusarrythmia) and reflects vagal (parasympathetic) modulation.
- HR variability in the low frequency band (LF: 0.07-0.14 Hz) represents changes in baroreflex response and similarly reflects sympathetic activity, although an influence of vagal modulation has been suggested.

- BP variability in the low frequency band (LF: 0.07-0.14 Hz) reflects alterations in peripheral vasomotor resistance due to baroreflex-mediated sympathetic control.
- Baroreflex sensitivity (BRS) can be provided by the transfer functions between systolic BP (SBP) and R-R interval of the ECG, called interbeat interval (IBI) time series (37).

ECG, BP (using a 2300 Finapres TM blood pressure monitor; Ohmeda, Englewood CO, USA) and respiration were continuously recorded during a 10 minute period of supine rest. R-R intervals in the ECG were transposed to HR series and SBP and DBP were defined per R-R interval of the ECG. Periods of stationary signals with a length of 5 minutes were selected from the 10 minute recording period and corrected for technical and physiological artefacts in the HR, SBP, DBP and respiration time series. Isolated extra-systolic contractions within a time segment were corrected by a linear interpolation procedure. If more than 5% of the total number of IBI's and BP pulses in a time segment needed correction, the period was excluded from further analyses.

HR and BP time series of the 5 minute time segments were subjected to a Fourier transformation (38), to yield power spectra of the rhythmic oscillations over a frequency range of 0.02 to 0.50 Hz. The following cardiovascular parameters were calculated: mean HR, mean SBP and mean DBP, power of the LF band of HR and SBP, and power of the HF band of HR. The spectral power data were transformed to natural logarithmic values to obtain a normal distribution of data. Per time segment the gain in the LF band between SBP and IBI time series was computed as an index of BRS, based on frequency points within the frequency range with a coherence higher than or equal to 0.35 (37). Finally, samples of the respiratory signals were obtained per time segment at each incidence of the R-wave. Respiratory time series were subjected to spectral analysis in the same way as the HR and BP time series, to assess the dominant respiratory frequency within the 5 minute time period, as a control for regularity of breathing.

For comparison spectral analyses of cardiovascular variability, autonomic measurements from 25 age and gender-matched healthy control subjects were used. The controls were recruited by means of advertisements. Specific inclusion criteria for the control group were: medication-free for at least 3 months, absence of any medical illness, in particular cardiovascular and neurological illnesses, and the absence of any mental illness.

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GBS

CHAPTER 3

COURSE OF DISEASE AND TREATMENT OF GBS AND CIDP

3.1 Infections, autonomic dysfunction, disease course, and outcome within the spectrum of Guillain-Barré syndrome

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Manuscript in preparation

3.2 Distinguishing Acute onset CIDP from Guillain-Barré syndrome with treatment related fluctuations

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Neurology 2005;65(1):138-40

3.3 Distinguishing Acute onset CIDP from fluctuating Guillain-Barré syndrome; a prospective study

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Neurology, accepted for publication

CHAPTER 3.1

INFECTIONS, AUTONOMIC DYSFUNCTION, DISEASE COURSE, AND OUTCOME WITHIN THE SPECTRUM OF GUILLAIN-BARRÉ SYNDROME

A nationwide prospective study

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Manuscript in preparation

ABSTRACT

Background: It is unknown why symptoms of the Guillain-Barré syndrome (GBS) remain limited in some patients. Detailed information about preceding infections, autonomic dysfunction, course of disease, and outcome within the whole spectrum of GBS including patients with the Miller Fisher syndrome (MFS) could be helpful to elucidate this important issue.

Objectives: The aim of this study was to obtain detailed information about infections, autonomic dysfunction, course of disease and outcome in MFS patients and mildly affected GBS patients and to compare this with non-MFS patients and severely affected GBS patients. This information may improve knowledge about the relation between infections, symptoms, and severity of GBS and may help to guide the needs to be investigated in new treatment trials.

Methods: A Dutch prospective cohort study in patients with GBS. Eighteen of the 156 patients included, presented with MFS. Of the 138 other patients, 114 were severely (not able to walk unaided) affected and 24 were mildly (able to walk unaided) affected. We compared the 138 GBS (non-MFS) patients with 18 cases with MFS; and 24 mildly versus 114 severely affected GBS (non-MFS) patients. Clinical signs and symptoms, signs of autonomic dysfunction, preceding infections, electrophysiological, and immunological data were collected during one year follow-up.

Results: Mildly affected GBS patients more often showed a preceding virological infection compared to severely affected GBS patients (65% versus 43%; p=0.05). Severely affected GBS patients more often showed tachycardia ($p<0.05$), hypertension ($p<0.05$), gastro-intestinal ($p<0.001$) and bladder dysfunction ($p<0.05$) compared to mildly affected patients. After one year, 59% of MFS patients still had disability (GBS disability score ≥1), 31% had severe fatigue, and 25% reported pain. In the mildly affected GBS group, 46% still had disability, 29% had severe fatigue, and 17% reported pain after one year.

Conclusions: Preceding infections may at least partially determine symptoms and severity of disease. A substantial proportion of MFS and mildly affected GBS patients appeared to have residual deficit after one year.

INTRODUCTION

The extent and distribution of weakness, sensory involvement, presence of pain and autonomic dysfunction, but also the course of disease vary largely between individuals with Guillain-Barré syndrome (GBS). Most treatment trials and the majority of other larger studies have focussed on severely disabled GBS patients that are unable to walk. In the western world, these GBS patients most frequently have acute inflammatory demyelinating polyneuropathy (AIDP). The aim of our prospective study was to provide detailed information about symptoms and signs not only in the acute phase, but also during the course of disease within the whole GBS spectrum, including mildly affected and Miller Fisher syndrome (MFS) patients. We additionally aimed to study preceding infections into detail. This information potentionally is not only of benefit for determining the prognosis and helpful in clinical decision-making, but it may also add to the pathophysiological understanding of GBS. Additionally this information may help to guide current medical treatment and helps to design new treatment trials.

The best known subgroups of GBS based on clinical and electrophysiological characteristics are AIDP, acute motor axonal neuropathy (AMAN) and MFS (1). Besides these well known subgroups, GBS patients can also be classified according to the level of severity in the acute phase, to the course of disease or in relation to outcome. Examples of GBS patients with a less usual course are patients with one or more deteriorations after initial improvement or stabilisation following treatment (plasma exchange (PE) or intravenous immunoglobulin (IVIg)), classified as GBS with 'treatment related fluctuations' (GBS-TRF) (2-6) and patients initially diagnosed as GBS who finally develop CIDP, known as acute onset CIDP (A-CIDP) (7).

In Europe, about 20% of patients with GBS remain mildly affected (being able to walk unaided at nadir) (8-10). There is one prospective study assessing differences in the acute phase between mildly (n=19) and severely affected patients (n=120) (11). It was shown that in the acute phase more females, patients under 50 years of age, and pure motor patients were within the mildly affected group. In severely affected patients, it has been shown that, despite treatment, about 20% remain unable to walk after 6 months (12). It has also been observed that many patients remain otherwise disabled, having pain or are severely fatigued even after many years (13-15). Cross-sectional studies showed that even 3-6 years after onset, GBS has a large impact on social life and the ability to perform activities (16-18). There is one longitudinal two years follow-up study in 42 GBS patients concluding that motor and sensory impairment were each still detectable in a majority of GBS patients after 2 years (19). From one retrospective study, there is some indication that a considerable proportion of mildly patients had residual disabilities after 6 months (11). In a randomised PE trial from France, about one third of the mildly affected

GBS group showed residual signs after one year (8). As far as we know, there is no study that prospectively investigated various symptoms (other than onset of motor recovery) and residual signs at regular time-points in the first year after onset of disease in mildly affected patients.

In severely affected patients, standard treatment with PE or IVIg shortens the acute phase, however it does not, or not substantionally, influence the long-term outcome of the disease (20). Randomised placebo-controlled trials (RCTs) that have assessed the effect of IVIg have not studied the effect in mildly affected patients (12). One trial studied the effect of PE in patients in mildly affected patients (8). Onset of motor recovery was faster in mildly affected patients who received two PE sessions compared to those who received no PE.

RCTs on the effect of PE or IVIg in patients with MFS have not been performed so far (21). From a Japanese uncontrolled retrospective observational study of 92 MFS patients, it was concluded that it is likely that IVIg and PE do not influence the outcome of patients with MFS (22). Oculomotor disturbances and ataxia however tended to improve faster in the IVIg treated group. The same group published an observational retrospective study about 28 untreated MFS patients and concluded that all patients are almost free from ataxia and ophthalmoplegia and are returned to their normal activities after 6 months (23). There is one other retrospective study in 19 patients concluding that MFS is characterized by an excellent recovery (24).

Mildly affected patients and MFS patients potentially could benefit from IVIg treatment, but treatment trials are lacking. However, before indicating the need for a new treatment trial, further studies about the course of disease and the presence of residual signs especially in mildly affected GBS and MFS patients would be very helpful. Here we report the results of a nationwide prospective follow-up study examining the whole spectrum of GBS, including mildly affected and MFS patients. We studied the course of disease and outcome over a follow-up period of one year. In addition, detailed clinical, electrophysiological and serological data were obtained to be able to study differences between subgroups of GBS. Knowledge of factors limiting the severity of disease could also be of importance in unravelling the pathogenesis of GBS and may help to identify and to design new treatment trials in these immune-mediated neuropathies.

MATERIALS AND METHODS

Patients

Patients diagnosed with GBS were eligible to be included in the GRAPH (GBS Research about Pain and Heterogeneity) study. Exclusion criteria were: age below twelve and significant

co-morbidity with an expected worse prognosis (less than 1 year survival) (25;26). In total, 170 patients were included. Patients with Bickerstaff brainstem encephalitis and patients who developed A-CIDP were excluded.

Study design

Patients admitted in the 55 participating Dutch centres could be included in the GRAPH study in the period from February 2005 until October 2008. The protocol was approved by the ethics committee of the participating centres. Clinical data, biological material, and electrophysiological data were collected systematically during 1 year follow-up, after obtaining written informed consent.

Questionnaires were filled in by the participating neurologist twice a week in the first three weeks after inclusion, weekly during the further hospital stay, and once after 26 weeks. The first three weeks after inclusion were determined as the acute phase, because all included patients had their nadir within 3 weeks after inclusion. When the patient was discharged from hospital, additionally questionnaires were filled in by the patient at 13, 26, 39, and 52 weeks after inclusion. If the patient was not able to fill in the questionnaire, relatives were asked for help.

Questionnaires

Baseline characteristics and data about medical history were obtained. Neurological symptoms and signs, disability scales (GBS disability score -ranging from 0 ‘no symptoms or signs’ to 6 ‘dead’- (27), overall disability sumscore (ODSS) -ranging from 0 ‘no signs of disability’ to 12 ‘most severe disability score’- (28,29), MRC sumscore -ranging from 0 ‘paralysis’ to 60 ‘normal strength’-(28,31)), treatment, and course of disease were obtained.

Additionally we asked for the presence and intensity of pain in the past week. To determine the intensity of pain we used the 11-point numerical rating scale (NRS), in which 0 represents no pain and 10 represents extreme pain (32). After hospital discharge we asked the patient for the presence of fatigue. To determine the severity of fatigue we used the Fatigue Severity Scale (FSS, ranging from 1 ‘no signs of fatigue’ to 7 ‘most disabling fatigue’) (32,33).

Clinical autonomic functions were assessed and reflected the last 7 days. Clinical autonomic dysfunction parameters were defined prior to study onset: hypertension (systolic >140 and/or diastolic >90 mmHg), hypotension (systolic <90 mmHg), tachycardia (heart rate >100 bpm), bradycardia (heart rate <60 bpm), gastrointestinal dysfunction (diarrhoea, constipation, or incontinence) bladder dysfunction (urine retention or incontinence) or other symptoms of autonomic dysfunction (for example excessive sweating, Horner’s syndrome, and pupil dilatation).

We used the GBS disability score to indicate the severity of disease during different phases of disease. Mildly affected = able to walk unaided = GBS disability score ≤ 2; severely affected = unable to walk unaided = GBS disability score ≥ 3. Disability = GBS disability score ≥ 1. We defined patients as clinically 'pure motor' when pinprick and vibration sense were normal in the first three weeks after inclusion (acute phase). We defined 'severe fatigue' when mean FSS was ≥ 5 (33).

Recent infections

Clinically

The following recently preceding infections were judged clinically: respiratory tract infection or influenza(-like) symptoms, and gastro-enteritis or diarrhoea. These were considered positive when patients reported symptoms meeting the criteria for these infections according to the Centre of Disease Control (CDC) definitions for nosocomial infections (34) and when they occurred within four weeks before onset of weakness.

Serology

Serum samples obtained in the acute phase of disease and before start of treatment. Serum samples were stored at -80°C. The sera were tested in the co-ordinating centre and the Delft Diagnostic Laboratory to determine recent infection with *Campylobacter jejuni*, human adenoviruses, respiratory syncytial virus (RSV), influenza A virus, influenza B virus, parainfluenza virus 1, 2, and 3, cytomegalovirus (CMV), Epstein-Barr virus (EBV) and *Mycoplasma pneumoniae* using standard assays detecting specific IgG, IgM of IgA antibodies (35-37). Serum examiners were blinded for clinical data.

Culture

In the co-ordinating centre we cultured stools for *Campylobacter jejuni* and throat specimen for *Haemophilus influenzae* using a standard assay (38-40). Additionally stool samples were analysed for the presence of human adenoviruses and enteroviruses by cell culture. Throat specimens were analysed for the presence of respiratory viruses using rapid cell culture with centrifugation and immunofluorescence (IF). All throat specimens were tested for RSV, influenza viruses type A and B, parainfluenza viruses 1, 2, 3, and 4, herpes simplex virus (HSV) types 1 and 2, human adenoviruses, rhinovirus, and human metapneumovirus (hMPV)).

Nucleic acid extraction and real time amplification (PCR)

The stool swabs were tested by means of real-time PCR for human adenoviruses, norovirus, enterovirus, parechovirus using a standard assay (41,42). The throat specimens were tested by real-time PCR for the presence of RSV types A and B, influenza virus types

A and B, human adenoviruses, parainfluenza virus types 1, 2, and 3, rhinovirus, herpes simplex virus (HSV) types 1 and 2, hMPV, and human coronavirus (hCoV) types 229E, OC43 and NL63. Total nucleic acids were routinely isolated at the MagnaPureLC Isolation Station (Roche Applied Science, Penzberg, Germany). A universal internal control virus was used to monitor the whole process from nucleic acid isolation until real-time detection (36,43).

Anti-gangliosides

Pre-treatment sera obtained after inclusion were tested for the presence of IgG and IgM antibody reactivity against GM1, GM2, GD1a, and GQ1b using ELISA (44-45).

Cerebrospinal fluid

In the acute phase of disease, number of cells and protein level in the pre-treatment cerebrospinal fluid (CSF) was determined according to routine laboratory procedures.

Electromyographic studies

Electrophysiological investigations were scheduled within three weeks after inclusion. These investigations were performed according to the standard protocol for the GRAPH study, when necessary adapted to the local settings of the participating hospitals. Age and sex matched reference values were used (46). The electrophysiological investigations were re-examined in the co-ordinating centre (JD and GHV) classified as demyelinating, axonal, inexcitable, equivocal or normal (47).

Statistics

The population of patients was divided into different GBS subgroups. We distinguished GBS (non-MFS) versus MFS and mildly versus severely affected GBS patients. To compare characteristics between GBS subgroups an unpaired t-test or χ^2 tests were performed. If appropriate, the Fisher exact test or the Mann-Whitney U test was used. Data are presented with mean +/- Standard Deviation (SD) or median + IQR.

Longitudinal analysis of disability, impairment, pain intensity, and fatigue scores allowing for occasional missing data at some time points, was performed using repeated-measurement-analysis of variance in the total group and in subgroups using data from the acute phase and from the chronic phase (week 13, 26, 39, and 52 after inclusion). When there was no significant difference in the profile of mean values of the different scores between the subgroups, we calculated the mean difference + 95% CI between the subgroups. For the acute phase we used the data from the questionnaires up to and including week 3, because all patients had their nadir within 3 weeks after inclusion. For reason of comparability between mildly and severely affected GBS patients, patients with MFS were excluded. All calculations were performed using SPSS for Windows 2000 (version 15.0 SPSS, Chicago). A p-value <0.05 was considered to be significant.

RESULTS

Patients

Between February 2005 and October 2008, 170 patients with GBS were enrolled in the GRAPH study (figure 1). During follow-up some initially diagnosed and included 'GBS' patients finally revealed to have another diagnosis (n=3: herniated nucleus pulposus, Sjögren syndrome, diffuse white matter disease), Bickerstaff encephalitis (n=2), an accompanying myelitis (n=1) or A-CIDP (n=8). These 14 patients were excluded from analysis. Of the remaining 156 patients, 138 (88%) fulfilled the diagnostic criteria for GBS (non-MFS) and 18 (12%) had MFS (25;48). These patients were followed for one year. All 156 patients reached nadir of weakness within 29 days after onset of disease (figure 2). After inclusion in the GRAPH study all patients reached nadir of weakness within 3 weeks. During follow-up 3 patients were lost to follow-up and 4 patients died. Of the 138 GBS (non-MFS) patients, 17% (24/138) was mildly affected at nadir.

Figure 1 | Study profile GRAPH study

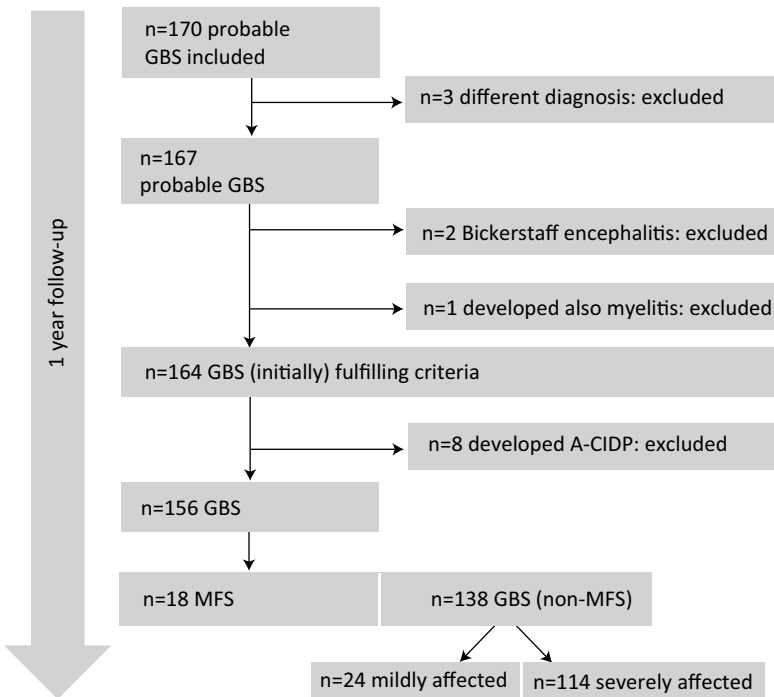
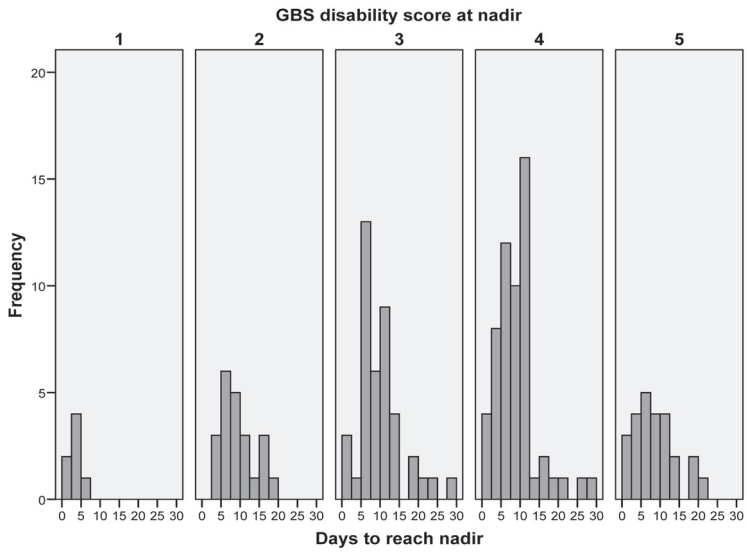


Figure 2 | Frequency histogram displaying the period (in number of days) from onset of weakness to the maximal weakness (nadir) related to the GBS disability score (table 6) at nadir in 156 GBS patients (eight A-CIDP patients were excluded from the total group of 164 patients initially diagnosed with GBS)



Baseline and clinical characteristics in the acute phase

Baseline and clinical characteristics in the acute phase are presented in table 1.

GBS (non-MFS) versus MFS

Besides the finding that patients with MFS more often had cranial nerve involvement which is explained by the definition of MFS, we found that symptoms of pain were significantly different in the acute phase (69%, GBS versus 44 %, MFS ($p<0.05$)).

Mildly versus severely affected GBS (non-MFS) patients

The median age was significantly lower in the mildly affected patients compared to the severely affected patients (36 y versus 53 y; $p<0.01$). Furthermore, the pure motor form was more frequently found in the mildly affected group (54% versus 28 %; $p<0.05$). Abnormal autonomic functions (tachycardia, hypertension, gastro-intestinal and bladder dysfunction) occurred in a significantly lower percentage in the mildly affected patients compared to the severely affected patients.

Electrophysiological data

Table 2 shows the electrophysiological data.

Table 1 | Baseline and clinical characteristics acute phase

	GBS (non-MFS) (n=138)	**MFS** (n=18)	**P Value** GBS versus MFS	**Mild GBS** (non-MFS) (n=24)	**Severe GBS** (non-MFS) (n=114)	**p Value** Severe versus mild
Male, n (%)	82 (59)	13 (72)	0.30	18 (75)	64 (56)	0.11
Age at onset, median (IQR), y	50 (35-66)	53 (39-57)	0.73	36 (26-49)	53 (38-66)	<0.01
GBS/MFS in medical history	‡ 7 (5)	2 (11)	0.28	1 (4)	±6 (5)	0.28
Cranial nerve involvement, n (%)	63 (47)	18 (100)	<0.001	10 (42)	†† 53 (48)	0.66
Clinically Pure motor variant, n (%)	§ 43 (33)	9 (50)	0.19	13 (54)	++ 30 (28)	<0.05
Time to reach nadir, median (IQR), d	* 9 (5-12)	7 (4-10)	0.22	7 (4-12)	9 (6-12)	0.26
Ventilated at nadir, n (%)	27 (20)	1 (6)	0.20	0 (0)	27 (24)	<0.001
At least 1 TRF, n (%)	16 (12)	0 (0)	0.22	0 (0)	16 (14)	0.07
Pain, n (%)						
■ Acute phase	** 92 (69)	8 (44)	<0.05	Δ 16 (70)	†† 76 (69)	0.92
Autonomic function acute phase, n (%)						
■ Tachycardia	54 (39)	6 (33)	0.63	5 (21)	39 (43)	<0.05
■ Bradycardia	13 (9)	1 (6)	1.00	0 (0)	13 (11)	0.12
■ Hypertension	93 (67)	14 (78)	0.43	12 (50)	81 (71)	<0.05
■ Hypotension)	15 (11)	2 (11)	1.00	0 (0)	15 (13)	0.07
■ Gastro-intestinal dysfunction	63 (46)	7 (39)	0.55	1 (4)	63 (55)	<0.001
■ Bladder dysfunction)	28 (20)	2 (11)	0.53	1 (4)	27 (24)	<0.05
GBS Medical treatment, n (%)	‡		<0.001		±	<0.001
■ IVIg	77 (56)	10 (56)		7 (29)	70 (62)	
■ IVIg + methylprednisolon	40 (29)	0		4 (17)	36 (32)	
■ None	20 (15)	8 (44)		13 (54)	7 (6)	

Δ n=23, ++ n=108, †† n=111, ± n=113, ‡ n=137, § n=132, * n=135, ** n=134; Pure motor = normal pinprick and vibration sense in the acute phase; TRF = Treatment related fluctuation; IVIg = Intravenous immunoglobulin ; Gastro-intestinal dysfunction = diarrhoea, constipation or incontinence; Bladder dysfunction = urine retention or incontinence

Mildly versus severely affected GBS (non-MFS) patients

A demyelinating electrophysiological investigation was more frequently found in the severely affected group compared to the mildly affected group (56% versus 32 %, $p<0.05$). Number of patients that had needed artificial respiration was not significantly different between GBS patients with a demyelinating or non-demyelinating electrophysiological investigation (25% versus 13%; $p=0.1$).

Recent infections

From 147 patients (94%) pre-treatment serum samples and from 105 patients (67%) stool and throat specimen samples could be obtained to determine a recent infection. The clinical infections and serological results are indicated in table 2.

GBS (non-MFS) versus MFS

There were no significant differences in preceding clinical infections and serological screening of a recent infection between these two groups (table 2).

In two GBS and none of the MFS patients *Haemophilus influenzae* was cultured. In two other GBS patients and none of the MFS patients *Campylobacter jejuni* was cultured.

In GBS rapid cell culture with immunofluorescence of throat samples yielded in the following positive results: one CMV, three HSV1, one HSV2, one hMPV, one human adenovirus. In MFS rapid cell culture with immunofluorescence of throat samples revealed no positive results. PCR of throat swabs from GBS patients as well as MFS patients resulted in one hCoV and one rhinovirus positive sample. In GBS rapid cell culture of faeces samples resulted in the following positive numbers: one picornavirus, one human adenovirus. PCR of faeces swabs from GBS patients resulted in the following positive results: five noroviruses, two enteroviruses and one parechovirus. In MFS rapid cell culture with immunofluorescence of faeces samples did not reveal positive samples.

Mildly versus severely affected GBS (non-MFS) patients

The results of the serological screening showed a difference in the percentage of preceding recent infections of human adenoviruses (35% in the mild group and 14% in the severe group, $p<0.05$) (table 2). There were no other differences in preceding clinical infections

Table 2 | Electrophysiological and immunological data and preceding infections

	GBS (non-MFS) (n=138)	**MFS** (n=18)	**p Value** GBS versus MFS	**Severe GBS** (non-MFS) (n=114)	**Mild GBS** (non-MFS) (n=24)	**P Value** Severe versus mild
Electrophysiological classification, n (%)	(n=126)	(n=14)	<0.001	(n=104)	(n=22)	<0.05
■ Demyelinating	65 (52)	0(0)		58 (56)	7 (32)	
■ Not demyelinating	61 (48)	14 (100)		46 (44)	15 (68)	
■ Axonal	8 (6)	0 (0)		5 (5)	3 (14)	
■ Equivocal	51 (40)	10 (71)		39 (38)	12 (55)	
■ Inexitable	2 (2)	0 (0)		2 (2)	0 (0)	
■ Normal	0 (0)	4 (29)		0 (0'	0 (0)	
CSF	(n=135)	(n=17)		(n=112)	(n=23)	
■ Cells, (median, IQR), 10^6/l	3 (2- 6)	2 (1-5)	0.12	3 (1-6)	2 (1-5)	0.50
■ Increased protein, >0.55 g/L	81 (60)	5 (29)	<0.05	66 (59)	15 (65)	0.58
Preceding infection clinically, n (%)						
■ Respiratory tract / Influenza(-like)	(n=134) 48 (36)	8 (44)	0.48	(n=110) 39 (36)	9 (38)	0.81
■ Gastro-enteritis/Diarrhoea	(n=135) 49 (36)	3 (17)	0.12	(n=111) 42 (38)	7 (29)	0.49
Infections serology, n (%)	(n=130)	(n=17)		(n=108)	(n=23)	
Positive virological infection	61 (47)	5 (29)	0.20	46 (43)	15 (65)	0.05
■ Human adenovirus	23 (18)	2 (12)	0.74	15 (14)	8 (35)	<0.05
■ CMV	6 (5)	0	1.0	5 (5)	1 (4)	1.0
■ EBV	3 (2)	0	1.0	1(1)	2 (9)	0.08
■ Influenza A	15 (12)	1 (6)	0.70	14 (13)	1 (4)	0.47
■ Influenza B	9 (7)	0	0.60	6 (6)	3 (13)	0.20
■ *Mycoplasma pneumoniae*	4 (3)	0	1.0	3 (3)	1 (4)	0.55
■ Parainfluenza	4 (3)	0	1.0	2 (2)	2 (9)	0.14
■ RSV	15 (12)	3 (18)	0.44	12 (11)	3 (13)	0.73
Positive bacteriological infection						
■ Campylobacter jejuni	30 (23)	3 (18)	0.76	27 (25)	3 (13)	0.28

	GBS (non-MFS) (n=138)	**MFS** (n=18)	**p Value** GBS versus MFS	**Severe GBS (non-MFS)** (n=114)	**Mild GBS (non-MFS)** (n=24)	**P Value** Severe versus mild
Anti-ganglioside antibodies, n (%)	(n=130)			(n=107)	(n=23)	
■ GM1 IgM	12 (9)	0 (0)	0.36	10 (9)	2 (9)	1.0
■ GM1 IgG	14 (11)	1 (6)	0.70	12 (11)	2 (9)	1.0
■ GM2 IgM	7 (5)	0 (0)	0.60	6 (6)	1 (4)	1.0
■ GM2 IgG	6 (5)	0 (0)	1.0	5 (5)	1 (4)	1.0
■ GD1a IgM	1 (1)	0 (0)	1.0	1 (1)	0 (0)	1.0
■ GD1a IgG	5 (4)	1 (6)	0.55	4 (4)	1 (4)	1.0
■ GD1b IgM	6 (5)	0 (0)	1.0	5 (5)	1 (4)	1.0
■ GD1b IgG	19 (15)	1 (6)	0.47	17 (16)	2 (9)	0.52
■ GQ1b IgM	2 (2)	8 (44)	<0.001	1 (1)	1 (4)	0.32
■ GQ1b IgG	4 (3)	17 (94)	<0.001	3 (3)	1 (4)	0.55
■ IgM reactivity against GM1, GM2, GD1a, GD1b or GQ1b	16 (12)	8 (44)	<0.001	13 (12)	3 (13)	0.57
■ IgG reactivity against GM1, GM2, GD1a, GD1b or GQ1b	27 (20)	17 (94)	<0.001	24 (22)	3 (13)	0.31
■ IgM or IgG reactivity against GM1, GM2, GD1a, GD1b or GQ1b	33 (25)	17 (94)	<0.001	29 (27)	4 (17)	0.31

and serological screening of a recent infection between the two groups (table 2). Fourteen GBS patients with a positive campylobacter serology (n=30) also had a positive virus serology (n=3 had a positive human adenovirus serology).

In two severely affected patients *Haemophilus influenzae* was cultured and in one mildy as well as one severely affected patient *Campylobacter jejuni* was cultured.

Regarding the rapid cell culture with immunofluorescence and PCR results described above in the GBS (non-MFS) versus MFS part, there was only one mildy affected GBS patient with a positive PCR for enterovirus; the other positive results were obtained in severely affected patients.

Antiganglioside antibodies

GBS (non-MFS) versus MFS

MFS patients had significantly more frequent GQ1b antibodies, compared to GBS ($p<0.001$). The other anti-ganglioside antibodies did not show any differences (table 2).

Mildly versus severely affected GBS (non-MFS) patients

No differences were found in the presence of anti-ganglioside antibodies (table 2).

Residual symptoms and signs

Table 3 shows the residual signs and symptoms from the GBS (non-MFS) versus MFS, and mildly versus severely affected GBS (non-MFS) patients.

GBS (non-MFS) versus MFS

When we compared GBS (non-MFS) with MFS, there were no significant differences in the presence of disability, fatigue, and pain after one year. Even 59% of the MFS patients still had disability (GBS disability score ≥1) after one year. After 6 months, three MFS patients still had ophthalmoplegia and one MFS patient still had facial weakness.

Mildly versus severely affected GBS (non-MFS) patients

After one year, 46% in the mildly affected GBS (non-MFS) group still had disability (33% GBS disability score 1, 13% GBS disability score 2), 29% had severe fatigue and 17% had pain. After 1 year, all GBS patients classified as axonal had functional disability (GBS disability score>1) compared to 70% of GBS patients classified as demyelinating ($p=0.07$).

In the entire GBS (non-MFS and MFS) group, no significant correlations were found between the level of fatigue (FSS) during follow-up and severity of disease as measured with the MRC sumscore and disability scores at nadir. However, there was a significant ($p<0.001$) correlation between the level of fatigue (FSS) versus disability at all other time-

points from week 13 to 52 (GBS disability score: week 13: r_s=0.40; week 26: r_s =0.39; week 39: r_s =0.47; week 52: r_s =0.45; ODSS: week 13: r_s=0.48; week 26: r_s =0.45; week 39: r_s =0.50; week 52: r_s =0.42).

Table 3 | Residual signs and symptoms

n/N (%)	**GBS (non-MFS)** (n=138)	**MFS** (n=18)	**p Value** GBS versus MFS	**Severe GBS (non-MFS)** (n=114)	**Mild GBS (non-MFS)** (n=24)	**p Value** Severe versus mild
After 3 months						
Residual disability						
■ GBS disability score ≥1	117/133 (88)	12/18 (67)	<0.05	101/109 (93)	16/24 (67)	<0.01
■ Unable to walk without aid	26/133 (20)	2/18 (11)	0.53	26/109 (24)	0/24 (0)	<0.01
Severe fatigue	70/126 (56)	12/18 (67)	0.37	59/102 (58)	11/24 (46)	0.29
Pain	74/130 (57)	10/18 (56)	0.91	63/107 (59)	11/23 (48)	0.33
After 6 months						
Residual disability						
■ GBS disability score ≥1	110/136 (81)	11/18 (61)	0.07	97/112 (87)	13/24 (54)	<0.01
■ Unable to walk without aid	16/136 (12)	1/18 (6)	0.70	16/112 (14)	0/24 (0)	0.07
Residual impairment						
■ Weakness	39/125 (31)	0/18 (0)	<0.05	36/101 (36)	3/24 (13)	<0.05
■ Sensory disturbances	51/115 (44)	4/13 (31)	0.35	48/92 (52)	3/23 (13)	<0.01
Severe fatigue	61/129 (47)	8/17 (47)	0.99	54/105 (51)	7/24 (29)	<0.05
Pain	68/132 (52)	6/18 (33)	0.15	61/109 (56)	7/23 (30)	<0.05
After 9 months						
Residual disability						
■ GBS disability score ≥1	97/135 (72)	11/18 (61)	0.35	85/110 (77)	11/24 (46)	<0.01
Unable to walk without aid	13/135 (10)	1/18 (6)	1.0	12/110 (11)	0/24 (0)	0.12
Severe fatigue	55/130 (42)	7/17 (41)	0.93	51/106 (48)	4/24 (17)	<0.01
Pain	55/131 (42)	3/17 (18)	0.05	51/108 (47)	4/23 (17)	<0.01
After 12 months						
Residual disability						
■ GBS disability score ≥1	96/136 (71)	10/17 (59)	0.32	85/114 (76)	11/24 (46)	<0.01
■ Unable to walk without aid	11/136 (8)	1/18 (6)	1.0	10/111 (9)	0/24 (0)	0.21
Severe fatigue	59/132 (45)	5/16 (31)	0.31	52/108 (48)	7/24 (29)	0.09
Pain	51/130 (39)	4/16 (25)	0.27	47/107 (44)	4/23 (17)	<0.05

Any disability = GBS disability score > 0
Unable to walk without aid = GBS disability score ≥ 3
Severe fatigue = mean FSS≥5

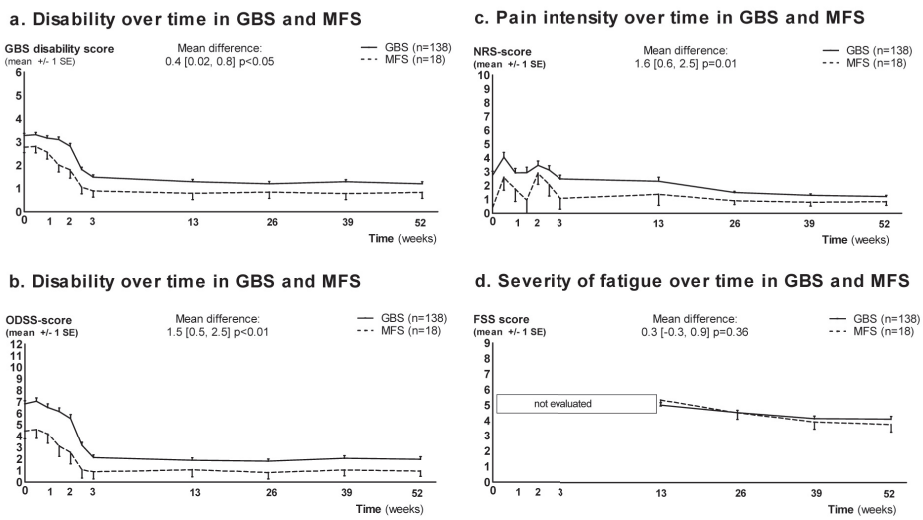
Course of disease

GBS (non-MFS) versus MFS

Figure 3 shows the 1 year follow-up for GBS (non-MFS) and MFS patients expressed by the course of GBS disability score, ODSS, NRS score and FSS score. During the entire 1 year follow-up, MFS patients had a significant lower mean difference in the GBS disability

score, ODSS score and pain as measured with the NRS score. The mean FSS score was not significantly different between the two groups.

Figure 3 | Mean GBS disability score (a.), overall disability sum (ODSS) score (b.), pain intensity (NRS) score (c.) and fatigue severity scale (FSS) score (d.) over time in GBS (non-MFS) (n=138) and MFS (n=18)

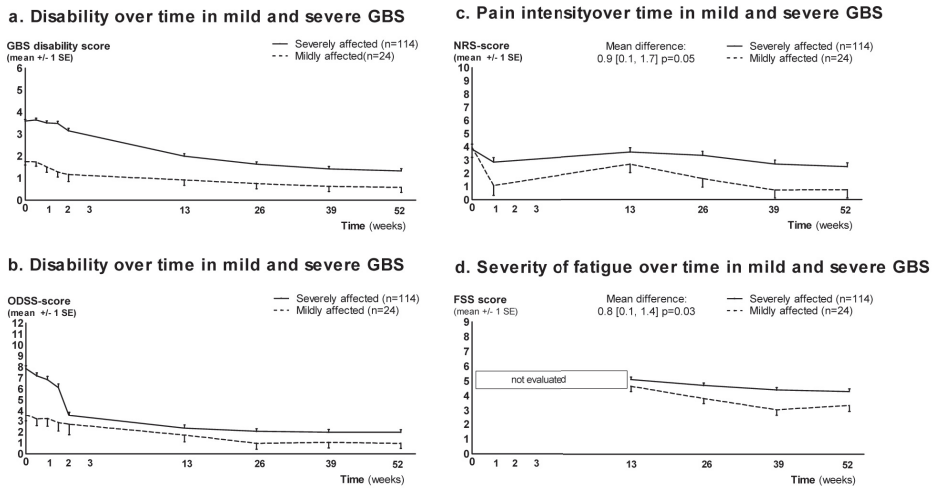


Legend: Data shown are means (+/-SE) from ANOVA. Mean differences (solid minus dotted line) from inclusion day to 52 weeks after onset of weakness between the different groups with 95% CI and p-value are indicated when there was no significant difference in the profile of mean values of the pain intensity score during the whole follow-up between the subgroups.

Mildly versus severely affected GBS (non-MFS) patients

Figure 4 shows the follow-up during one year for mildly and severely affected GBS (non-MFS) patients expressed by the course of the GBS disability score, ODSS, NRS score and FSS score. For disability a difference between mildly and severely affected already can be observed at the day of inclusion. Time to reach nadir was not significantly different between the two groups. The rate of improvement of disability in the acute phase is faster in the severely affected group; where after the mean difference between both groups remained identical during follow-up. The mean NRS and FSS score during the entire course was significantly lower in the mildly affected patients, compared to the severely affected patients.

Figure 4 | Mean GBS disability score (a.), overall disability sum (ODSS) score (b.), pain intensity (NRS) score (c.) and fatigue severity scale (FSS) score (d.) over time in mildly (GBS disability score at nadir ≤2) and severely (GBS disability score at nadir ≥3) affected GBS (non-MFS) patients



Legend: Data shown are means (+/-SE) from ANOVA. Mean differences (solid minus dotted line) from inclusion day to 52 weeks after onset of weakness between the different groups with 95% CI and p-value are indicated when there was no significant difference in the profile of mean values of the pain intensity score during the whole follow-up between the subgroups.

DISCUSSION

This is the first large prospective follow-up study on different infections, course of disease and outcome in mildly affected GBS patients and MFS patients when compared with severely affected GBS patients and GBS (non-MFS) patients. As shown in this study, mildly affected GBS patients more often had serological evidence of a preceding virological infection compared to severely affected GBS patients. Severely affected GBS patients more often had abnormal autonomic functions. Residual symptoms after 6-12 months appeared to be very common, also in mildly affected GBS and in MFS patients.

It is important to discuss whether the study population is representative. Based on the incidence rate of GBS in the Netherlands (1.18/100.000) (49), the 170 patients that entered the study cover about 25% of the total number of expected patients. 12% of the included GBS patients had the MFS subtype, which is higher than the 5% published in the literature, but lower when compared to studies from Asian countries (10,50). A plausible explanation could be that participating centres more often contacted our centre, for testing of anti-ganglioside antibodies (anti-GQ1b) or for asking advice how to handle

in case of a MFS suspected patient. When excluding the MFS patients, we found 17% (24/138) of the GBS patients to be mildly affected being comparable with the 14% in our former study (11). Other percentages of baseline characteristics in the acute phase in our study are similar to percentages reported in earlier studies (20). Taken together, we consider this study population to be representative for a study executed in Western-Europe. We did not include a non-GBS group or healthy controls in our study because we want to compare differences between GBS subgroups.

Based on serology, we found a preceding virological infection more frequently in the mildly affected GBS patients compared to the severely affected GBS group. This difference was especially found for the human adenoviruses. Additionally, although not statistically significant, EBV infections were more frequently found in the mildly affected group. In our former study (that has not studied the occurrence of such a large number of virological infections into depth) this difference in preceding EBV infection was significantly different (11). Base on these findings, our study suggests that an infection with human adenovirus and possibly also EBV more frequently is related with the mild form of GBS. A previous study has reported a low percentage of patients with a positive infection with human adenovirus, probably mainly because only severely affected patients were included (51). Clinically, no difference was found in symptoms of preceding infections between mildy and severely affected patients. This suggests that subclinical virological infections may play a role in the induction of mild forms of GBS. Because virological infections predominantly occur in cases not related to GBS, we tried to substantiate this further by culturing stools and throat specimens. Possibly due to a prolonged period of time between taking the specimen until culturing, the numbers of culture positive infections were very limited, making it impossible to draw meaningful conclusions.

In about one third of our patients we found serum antibodies to various anti-gangliosides, a bit lower than described in the literature (20). As expected, IgG and IgM activity against GQ1b was predominantly present in MFS and activity against GM1 was mostly found in pure motor patients. We found no significant differences in the presence of anti-ganglioside antibodies between mildly and severely affected patients. In our previous studies, a significantly higher percentage of anti-ganglioside antibodies was found in severely affected patients (11,52). We do not have a good explanation for this as there were no differences in the methods or assays used. Differences can possibly be explained by subclass distribution of anti-ganglioside antibodies and the relative limited number of mildly affected patients included in the GRAPH study. This study suggests that the presence of anti-ganglioside antibodies is not directly related to the severity of disease.

Clinically autonomic dysfunction described in GBS is highly variable (53). This already suggests the difficulty in assessing autonomic neuropathy in clinical setting. It has

already been described that autonomic dysfunction can occur both in MFS and in mildy affected GBS patients (54-56). However, this is likely to be the first time that autonomic functions like blood-pressure, heart rate, gastro-intestinal, and bladder function were systematically obtained and were compared between GBS subgroups. We found no differences in abnormal autonomic functions between GBS (non-MFS) and MFS patients. However, severely affected GBS patients more often had tachycardia, hypertension, gastro-intestinal and bladder dysfunction in the acute phase compared to mildly affected patients. Some remarks about our assessment of abnormal autonomic functions must be made. Information about possible abnormal autonomic functions already present in medical history was not obtained and factors resulting in cardiovascular dysfunction like abnormal stress, infection and sepsis were not noted. We did not include a non-GBS control group. Therefore, it cannot be concluded from this study whether the patients had abnormal autonomic functions due to autonomic neuropathy caused by GBS. However, assuming the same hospital conditions for both groups, the results of our study suggest that autonomic dysfunction in the acute phase occurs more often in the severely affected compared to the mildly affected patients. Fortunately none of the patients in this study died due to autonomic dysfunction.

We showed that after one year most of the patients still had residual symptoms. Even half of the MFS and mildly affected GBS patients still experienced disability after one year. Also pain and severe fatigue were frequently present in MFS and GBS patients. In two retrospective studies, it has been described that MFS patients have a fast excellent recovery (24,49). The GBS disability score, although not validated for patients with MFS, but also the presence of pain and fatigue were not studied in these studies. This might partially explain the difference in conclusion about residual signs that can be found in patients with MFS. In our study 4 of the 18 MFS patients still had cranial nerve deficit after 6 months. This difference possibly implicates some slower recovery in Dutch MFS patients compared to MFS patients from Japan. While considering residual symptoms and course of disease it is important to realise that a substantional proportion of MFS patients included in our study received treatment while most mildly GBS patients were not treated and most other GBS patients did receive treatment which may have influenced the results that we have found over time. On the other hand, this reflects daily practice in many neurological institutes.

Our study confirmed our previous cross-sectional published data about the high percentage of severe fatigue after GBS (57). We also confirmed that impaired muscle strength and disability in the initial phase of GBS were not significantly related to fatigue in the later stage of disease (57). However, as shown in this study, residual disability was associated with the level of fatigue during follow-up. This is in line with the results of a study showing a relation between fatigue, pain, and muscle weakness years after GBS

(58). Whether fatigue causes part of disability or disability contributes to fatigue cannot be concluded from our study.

There are no prospective controlled trials of immunotherapy in MFS and IVIg treatment has never been evaluated in a RCT in mildly affected patients (21). One RCT showed the effectiveness of PE in mildly affected patients (8,49). In our study, the vast majority of mildly affected GBS patients were not treated with IVIg. Because a large proportion of mildly affected GBS patients do have functional deficit and disability at least for a period of one year after onset of disease, new treatment trials should at least consider to include also mildly affected GBS patients. Although most MFS patients are in a relative good condition one year after onset, a proportion of patients do have functional deficit, and fatigue but also pain may be present for a long period of time. When considering studying the effect of immunotherapy, it is important to study not only the effect of immunotherapy after 4 weeks from inclusion in a trial, but also to look for residual signs after a longer period of follow-up since not only functional disability, but also residual fatigue and pain may persist for years.

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CHAPTER 3.2

DISTINGUISHING ACUTE ONSET CIDP FROM GUILLAIN-BARRÉ SYNDROME WITH TREATMENT RELATED FLUCTUATIONS

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Neurology 2005;65(1):138-40

ABSTRACT

Guillain-Barré syndrome (GBS) patients may worsen following initial treatment (treatment related fluctuation (TRF)). It is difficult to distinguish GBS-TRF from chronic inflammatory demyelinating polyneuropathy with acute onset (A-CIDP). The authors compared 13 patients with A-CIDP with 11 patients with GBS-TRF and concluded that A-CIDP should be suspected when a patient with GBS deteriorates after 9 weeks from onset or when deterioration occurs three times or more. Maintenance treatment should then be considered.

INTRODUCTION

The spectrum of inflammatory demyelinating polyneuropathy ranges from the acute variant, Guillain-Barré syndrome (GBS), to a slowly progressive form, chronic inflammatory demyelinating polyneuropathy (CIDP). Differences between these variants are, among others, the time to reach maximum severity (nadir) and the following course of the disease. By definition, the time to reach nadir in GBS is within 4 weeks; thereafter the course is monophasic (1). According to the research criteria for CIDP, progression develops during a period of at least 2 months. Thereafter the course may be relapsing-remitting, steadily progressive, or monophasic (2).

Despite these, somewhat artificially, defined time points, it may be difficult to distinguish CIDP from GBS, especially during the early phase of disease. Patients, who initially have a course of disease compatible with that of GBS later on may develop exacerbations and remissions and ultimately are diagnosed as CIDP (3,4).

Additionally, it has been reported that 16 to 20% of patients with CIDP have rapid, progressive weakness with a nadir of the first episode of weakness within 8 weeks from onset of disease and a consecutive chronic course suffer from acute-onset CIDP (A-CIDP) (5,6). Conversely, 8 to 16% of patients with GBS have one or more deteriorations after initial improvement or stabilisation after treatment (plasma exchange or immunoglobulins), described as treatment related fluctuations (TRFs) (7-9).

In clinical practice, it may be difficult to distinguish a patient with GBS having a secondary deterioration after initial improvement or stabilisation within the first weeks or months after onset of disease (GBS-TRF) from a patient having a second episode of weakness due to A-CIDP. It is relevant to distinguish between these two variants as soon as possible because treatment strategy and prognosis differ considerably.

In this study we investigated characteristics and course of the disease in patients with GBS-TRF and A-CIDP and aimed to provide clinical factors that can help to distinguish between these two variants of inflammatory polyneuropathy in the early phase of disease.

METHODS

Clinical data were obtained from medical records of consecutive patients with GBS and CIDP hospitalized or assessed in the Erasmus MC during the period 1987 to 2003. All patients fulfilled the criteria for GBS or CIDP (1). Patients with Miller-Fisher syndrome were excluded. A GBS-TRF case was defined as a patient with GBS with one or more TRFs after the first episode of weakness, eventually followed by a monophasic course.

To determine the severity of weakness, nadir, and improvement or deterioration, the Medical Research Council (MRC) sum score and the GBS disability scale were used (7,10). A TRF was defined as 1) improvement in GBS disability score of at least one grade or improvement in the MRC sum score of more than 5 points after completion of therapy, followed by a worsening in GBS disability score of at least one grade or a decrease in the MRC sum score of more than 5 points within the first months after onset of disease or 2) stabilisation of the clinical course for more than 1 week after completion of therapy, followed by a worsening of at least one grade of the GBS disability score or more than 5 points on the MRC sum score (7).

An A-CIDP case was defined as a patient with CIDP in whom the nadir of the first episode of weakness was within 8 weeks from onset of disease and the consecutive course was chronic, like CIDP (2). Exacerbation in A-CIDP was defined as deterioration after the first episode of weakness, using the same criteria as for TRFs, with the exception that completion of therapy and occurrence within the first months after onset of disease are not requirements.

Because only part of the exacerbations in CIDP is treatment related, we use the term exacerbations in stead of treatment-related deteriorations. For both groups, follow-up data were obtained for a 2-year period after onset of disease. Onset of disease was defined as onset of initial weakness.

For differences in characteristics, symptoms, GBS disability score, and number of days to TRF or exacerbation, the c^2 test was used or the exact two-sample test of Wilcoxon-Mann-Whitney when appropriate. All calculations were performed using Stata/SE 8.2 for Windows 2000 (Stata Statistical Software, College Station, TX). A p value < 0.05 was considered to be significant.

RESULTS

Eleven of 190 patients with GBS (6%) had at least one TRF. Thirteen of 100 CIDP patients had A-CIDP.

Baseline characteristics, clinical features, and initial treatment are listed in table 1. In the patients with A-CIDP, a fixed intermittent treatment regimen was started after three exacerbations. There was a difference in the median time to reach nadir between the GBS-TRF and A-CIDP group (table 2). At nadir, there was a significant difference in GBS disability score. All patients with GBS-TRF had their first TRF within 11 weeks (median 17 days; range 7 to 74 days). The median time to reach the first exacerbation in patients with A-CIDP was higher (74 days, range 17 to 125). Of the patients with GBS-TRF, 27% had a second TRF. Only one patient with GBS (9%) had also a third TRF. Of the patients with A-CIDP, 54% had at least three exacerbations in the first 2 years. Of the patients with

GBS-TRF, 82% had their TRF(s) within 9 weeks from onset of disease, whereas 92% of the patients with A-CIDP had their exacerbation(s) after 9 weeks from onset of disease. The relationship between the course of the disease, TRFs in GBS-TRF, and exacerbations in A-CIDP is expressed in the figure.

Table 1 | Baseline characteristics

	GBS-TRF (n=11)	**A-CIDP** (n=13)
Sex distribution, n (%)		
■ Male	4 (36)	7 (54)
■ Female	7 (64)	6 (46)
Median age at onset, y (90% intercentile range)	44.8 (14.1-71.6)	32.1 (7.1-58.6)
Cranial nerve involvement, n (%)	5 (45)	3 (23)
Pure motor variant, n (%)	1 (9)	2 (15)
Initial treatment, n (%)		
■ PE	0 (0)	1 (8)
■ IVIg	7 (64)	8 (62)
■ IVIg + corticosteroids	4 (36)	1 (8)
■ None	0 (0)	3 (23)

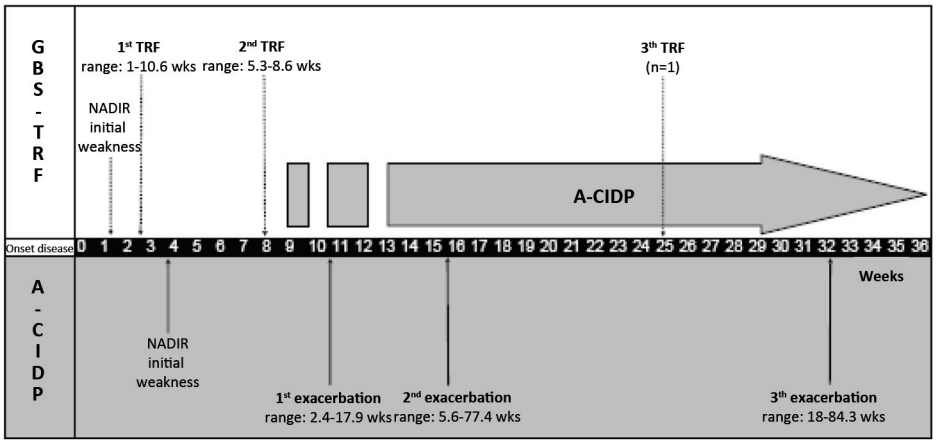
GBS-TRF = Guillan-Barré syndrome with treatment-related fluctuation(s), A-CDIP = chronic inflammatory demyelinating polyneuropathy with acute onset, PE = plasma exchange, IVIg = intravenous immuno-globulins

Table 2 | Clinical information on course of disease

	GBS-TRF (n=11)	**A-CIDP** (n=13)	p Value
Time to reach nadir, median (90% intercentile range), d	8 (2-28)	26 (3-52)	0.02
Nadir, n (%)			
■ ≤ 4 weeks	11 (100)	8 (62)	0.03
■ 4 - 8 weeks	0 (0)	5 (38)	
GBS disability score at nadir, n (%)			
■ ≤ 2	0 (0)	6 (46)	0.02
■ ≥ 3	11 (100)	7 (54)	
Time to reach 1st TRF/exacerbation from onset of disease, median (90% intercentile range), d	17 (7-74)	74 (17-125)	0.01
Number of TRFs (GBS-TRF) or exacerbations (A-CIDP) within two years from onset of disease, n (%)			
■ ≤ 2	10 (91)	6 (46)	0.03
■ ≥ 3	1 (9)	7 (54)	
Number of weeks from onset of disease TRFs (GBS-TRF) or exacerbations (A-CIDP) occur, n (%)			
■ ≤ 9	9 (82)	1 (8)	0.03
■ > 9	2 (18)	12 (92)	

TRF = Treatment related fluctuation, GBS disability score ≤ 2 = able to walk unaided, GBS disability score ≥ 3 = not able to walk unaided or bed bound

Figure 1 | Comparison between TRFs in GBS and exacerbations in A-CIDP patients



Legend: TRF = Treatment related fluctuation, GBS-TRF = GBS patient with one or more TRFs after the first episode of weakness, A-CIDP = CIDP patient in which the nadir of the first episode of weakness is within eight weeks from onset of disease and the consecutive course is chronic like CIDP

Nadir, TRFs and exacerbations (median) in GBS-TRF (upper part) and A-CIDP (lower part). Only the first three exacerbations are indicated and the time-axis ands at 36 weeks. When a 'GBS-patient' deteriorates, the suspicion of A-CIDP should rise when this occurs three times or more, or deterioration takes place after nine weeks from onset of disease (indicated with arrow in the upper part)

DISCUSSION

Because prognosis and treatment strategy in patients with GBS-TRF and those with A-CIDP differ, it is important to distinguish these two entities in an early phase of disease. TRFs have been reported in 8 to 16% of patients with GBS (7-9). In our study, 6% had TRFs; differences may be explained by the definition and numbers of patients studied . Of the patients with CIDP, 13% had an acute onset, which is comparable with another study (5).

The median time to reach nadir was significantly shorter in the GBS-TRF group compared with the A-CIDP group. Becuase 62% of the patients with A-CIDP reached their nadir already within 4 weeks, this underscores the difficulty in distinguishing a patient withA-CIDP one with GBS-TRF early in the course of disease. All patients with GBS-TRF at nadir were unable to walk unaided compared with 54% in the A-CIDP group (p = 0.02). Here, selection bias has to be taken into account, because we only treated GBS patients unable to walk unaided.

In counting the number of and time to TRFs and exacerbations, it should be considered that therapy is a confounder. A TRF is by definition related to therapy. The number and severity of exacerbations in CIDP may also largely be influenced by therapy. However, the

fluctuations in severity of disease in CIDP, irrespective the use of therapy, closely resembles clinical practice.

Our experience suggests that the diagnosis of A-CIDP should be considered when a patient with GBS deteriorates after 9 weeks from onset or when deterioration occurs three times or more. Maintenance treatment should then be considered. A prospective study is needed to help to distinguish patients with GBS-TRF from those with A-CIDP even more accurately early in the course of disease.

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CHAPTER 3.3

DISTINGUISHING ACUTE ONSET CIDP FROM FLUCTUATING GUILLAIN-BARRÉ SYNDROME; A PROSPECTIVE STUDY

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Neurology, accepted for publication

ABSTRACT

Background: The distinction between GBS with fluctuations shortly after start of treatment (treatment related fluctuations or GBS-TRF) and chronic inflammatory demyelinating polyneuropathy with acute onset (A-CIDP) is difficult but important because prognosis and treatment strategy largely differ.

Objectives: The aim of the study was to provide criteria that can help to distinguish between GBS-TRF and A-CIDP already in the early phase of disease.

Methods: GBS patients (n=170) were included in a prospective longitudinal study. GBS-TRF (n=16) and A-CIDP patients (n=8) were analysed and compared. Extended clinical data, biological material and electrophysiological data were collected during 1 year follow-up.

Results: The first TRF in the GBS-TRF group always occurred within 8 weeks (median 18 days; range 10-54 days) from onset of weakness. In the GBS-TRF group five (31%) patients had a 2nd TRF, none had more TRFs. At all time-points, patients in the A-CIDP group were less severely affected than the patients with GBS-TRF, did not need artificial ventilation, rarely have cranial nerve dysfunction and tended to have more 'CIDP-like' electrophysiological abnormalities. More GBS-TRF patients were severely affected and more patients had sensory disturbances when compared to the GBS group without fluctuations.

Conclusions: The diagnosis of A-CIDP should be considered when 'a patient with GBS' deteriorates again after eight weeks from onset or when deterioration occurs three times or more. Especially when the patient remains able to walk independently, has no cranial nerve dysfunction and electrophysiological features likely to be compatible with CIDP, maintenance treatment for CIDP should be considered.

INTRODUCTION

Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP) are immune-mediated neuropathies, sharing many symptoms and signs in the acute phase of disease (1-3). To differentiate between GBS and CIDP in the early phase of disease, clinicians primarily use the time to reach maximum severity (nadir) and the subsequent course of the disease. GBS is a monophasic disease in which the time to reach nadir by definition is within four weeks (4,5). In CIDP, the initial progressive phase lasts more than two months, whereafter the course may be relapsing-remitting, steadily progressive or monophasic (6).

However, not all patients fulfil all diagnostic criteria for either GBS or CIDP. It has been reported that 16% of patients with CIDP have rapidly progressive weakness, with a nadir within eight weeks from onset of disease which is followed by a chronic course. These patients are considered to suffer from acute onset CIDP (A-CIDP) (7). On the other hand, 8-16% of patients with GBS have one or more deteriorations shortly after initial improvement or stabilisation following plasma exchange or intravenous immunoglobulin (IVIg), described as “treatment related fluctuations” (TRF) (8-11). Additionally a group of patients with a progressive phase of 4-8 weeks and a monophasic course has been described as subacute inflammatory demyelinating polyneuropathy (SIDP) (13,14). In clinical practice, it may be very difficult to distinguish a GBS patient having a secondary deterioration after initial improvement or stabilisation within the first weeks or months after onset of disease (GBS-TRF) from a patient having a second episode of weakness due to A-CIDP (15,16).

Because treatment strategy and prognosis for GBS-TRF and A-CIDP differ considerably, it is relevant to distinguish between these two variants early in the course of disease. A patient with GBS-TRF generally requires a repeated IVIg course or plasma exchanges, whereas A-CIDP patients require long-term maintenance treatment with steroids, IVIg or plasma exchange with or without immunosuppressive agents. In a retrospective study, we suggested that the diagnosis A-CIDP should be considered when ‘a patient with GBS’ deteriorates after nine weeks from onset, or when deterioration occurs three times or more (11). There currently is no prospective study that provides robust criteria that can help to distinguish between GBS-TRF and A-CIDP already in the early phase of disease.

Regarding electrophysiological patterns, a direct comparison between GBS-TRF and A-CIDP in the literature is also lacking. However, A-CIDP patients seem to have some distinct electrophysiological features when compared to CIDP patients with a more chronic onset of disease (17). GBS-TRF patients more frequently have sensory disturbances, but otherwise no distinct electrophysiological characteristics when compared to GBS patients (12).

In this study we prospectively investigated a large number of patients initially diagnosed as GBS. Detailed clinical, biological and electrophysiological characteristics were analysed into more detail. We aimed to provide more criteria that can help to distinguish between GBS-TRF and A-CIDP patients already in the early phase of disease.

METHODS

Patients

170 patients diagnosed with GBS or MFS were prospectively included in the GRAPH study (GBS Research about Pain and Heterogeneity) (4,18). During follow-up, part of the patients showed one or more TRFs. Some patients initially diagnosed and included in the GRAPH study as having "GBS", finally revealed to have a chronic relapsing and remitting course. These patients were re-classified as A-CIDP (11). Because we aimed to differentiate between GBS-TRF and A-CIDP, we only analysed these two groups of patients.

Study design

Between February 2005 and October 2008 patients admitted in one of the 55 participating Dutch centres were included in the GRAPH study. Exclusion criteria were: age below twelve and significant co-morbidity with a worse prognosis (less than 1 year survival). The protocol was approved by the ethics committee of the Erasmus MC and subsequently by the other participating centers. Clinical data, biological material and electrophysiological data were collected systematically during 1 year follow-up after obtaining written informed consent for participating the study.

Questionnaires were filled in by the neurologist twice a week during hospital stay and once after 6 months. If the patient, due to deterioration after hospital discharge, visited the hospital again during one year follow-up, an additional questionnaire was filled in by the neurologist.

When the patient was discharged from hospital, additionally questionnaires were filled in by the patient or relatives at 3, 6, 9 and 12 months after inclusion. After receiving the questionnaires back, the research coordinator phoned the patient when questions were not filled in.

Questionaires

Baseline characteristics and data about medical history were obtained. Neurological symptoms and signs, disability scale (GBS disability scale -ranging from 0 "no symptoms or signs" to 6 "dead" (19)), impairment scale (MRC sumscore -ranging from 0 "paralysis" to 60 "normal strength" (20,21)), treatment and course of disease were obtained from the

questionnaire filled in by neurologist. After hospital discharge, the GBS disability score and course of disease were obtained from the questionnaire filled in by patient.

To determine nadir, improvement, deterioration or stabilisation during 1 year follow-up, the GBS disability score (19) and MRC sumscore (20,21) were used. The first progressive phase needs to have its nadir within four weeks, in accordance with the criteria for GBS. Thereafter, TRFs (in case of GBS-TRF) and exacerbations (in case of A-CIDP) occurred with their own nadir. Because only part of the exacerbations in A-CIDP is treatment related (especially during the later phase of disease), here we used the term exacerbations in stead of TRFs. In every questionnaire, information on improvement, stabilisation or deterioration was obtained and we questioned if there was a new hospital visit or any re-treatment. A TRF or exacerbation was defined as: 1) Improvement in GBS disability score of at least one grade or improvement in MRC sumscore of more than five points after completion of therapy, followed by a worsening in GBS disability score of at least one grade or a decrease in MRC sumscore of more than five points within the first months after onset of disease or: 2) Stabilisation of the clinical course for more than one week after completion of therapy, followed by a worsening of at least one grade of the GBS disability score or more than five points on the MRC sumscore (8,11). For both groups, follow-up was 1 year after inclusion. However for counting the number of exacerbations in case of A-CDIP we only used the period before maintenance treatment with IVIg or steroids was started. Time to TRF or exacerbation is defined as the number of days from onset of first weakness until nadir of the TRF or exacerbation.

We defined patients as 'pure motor' when pinprick and vibration sense, were normal. We used the MRC sumscore and the GBS disability scale to indicate the severity of disease (mildly affected = able to walk unaided = GBS disability scale ≤ 2; severely affected = unable to walk unaided = GBS disability scale > 2).

Preceding infections

The following preceding infections were scored within four weeks of onset of GBS: respiratory tract infection or influenza(-like) illness and gastro-enteritis or diarrhoea. These patients were considered to have a clinically defined infection when these symptoms met the criteria for these infections according to the Center of Disease Control (CDC) definitions for nosocomial infections (22). Acute phase serum samples were tested to determine recent infection with *Campylobacter jejuni* using the assay described before (23).

Anti-ganglioside antibodies

We screened for the presence of IgG and IgM antibodies against GM1, GM2, GD1a, GD1b and GQ1b in ELISA, according to methods described earlier (24,25).

Cerebrospinal fluid examination

In the acute phase of disease, number of cells and protein level in the cerebrospinal fluid (CSF) was determined.

Electrophysiology

According to the protocol, electrophysiological investigations were scheduled within three weeks after inclusion in the GRAPH study. Patients were analysed whether they fulfilled the electrophysiological criteria for CIDP (26). The electrophysiological investigations were executed according to local settings of the participating hospitals. Motor nerve conduction studies were performed orthodromically in the ulnar, peroneal, and optionally in the median and tibial nerve. In these nerves the distal and proximal compound muscle action potential (dCMAP and pCMAP) amplitude, distal motor latency (DML), motor nerve conduction velocity (mNCV), and F-wave latencies were measured. Antidromic sensory nerve conduction studies were performed in the median, ulnar, and optionally in the sural nerves. The sensory nerve action potential (SNAP) amplitude and sensory nerve conduction velocity (sNCV) were measured. The nerves were stimulated at the conventional stimulation points (27). Needle EMG was performed optionally. Patients were classified as demyelinating, axonal, equivocal or normal according to the published classification (28). Reference values were derived from Buschbacher and Pralow (27). In 6 A-CIDP patients, also a second electrophysiological investigation was performed.

Statistics

To compare characteristics of GBS patients and controls an unpaired t-test or c^2 test was performed tested two sided. If appropriate, the Mann-Whitney U test or the Fisher exact test was used. Data are cited with mean +/- Standard Deviation (SD), median + 95% confidence interval (95% CI) for the median. For categorical variables, frequencies and percentages are given. All calculations were performed using SPSS for Windows 2000 (version 15.0 SPSS, Chicago). A p-value < 0.05 was considered to be significant.

RESULTS

Patients

Between February 2005 and October 2008, 170 patients with GBS or MFS were enrolled in the GRAPH study. Three misdiagnosed patients were excluded. Three other patients were excluded because they had Bickerstaff encephalitis (n=2) or myelitis (n=1). Of the remaining 164 patients (146 GBS and 18 MFS), there were 16 patients (10%) with at least one TRF, and 8 patients (5%) that turned out to have A-CIDP. None of these 24 patients were included in our previous retrospective study (11). There were no SIDP patients.

Clinical characteristics, preceding infections and laboratory findings in GBS-TRF (n=16) and A-CIDP patients (n=8) in the acute phase are listed in table 1. Patients with A-CIDP had significant less cranial nerve dysfunction compared to GBS-TRF (13% versus 69%, p=0.03). One A-CIDP and no GBS-TRF patients had a preceding vaccination. The same items listed in table 1 were also compared between GBS (n=140) and GBS-TRF (n=16) patients. The only significant difference we found was a lower percentage of pure motor patients in the GBS-TRF group compared to the GBS group without fluctuations (6% versus 39%; p<0.05).

Table 1 | Clinical characteristics, preceding infections and laboratory findings in the acute phase in GBS-TRF and A-CIDP patients

	GBS-TRF (n=16)	**A-CIDP** (n=8)	p Value
Male, n (%)	12 (75)	6 (75)	1.0
Age at onset, mean ± SD	54 ± 17	47 ± 18	0.37
Previous GBS-like episode in medical history, n (%)	1 (6)	1 (13)	1.0
Paresthetic / hypesthetic sensations, n (%)	14 (88)	8 (100)	0.54
■ Pure motor	1 (6)	2 (25)	0.25
■ Pain before onset of weakness	6 (38)	4 (50)	0.67
■ Pain in acute phase	13 (81)	5 (71)*	0.62
Cranial nerve dysfunction, n (%)	11 (69)	1 (13)	0.03
■ III, IV or VI	6 (38)	0	
■ VII	10 (63)	1 (13)	
■ IX, X or XII	4 (25)	0	
Clinical preceding infections, n (%)			
■ Respiratory tract / Influenza(-like)	5 (31)	2 (25)	1.0
■ Gastro-enteritis / Diarrhea	4 (25)	2 (25)	1.0
CSF			
■ Cells, 10^6/l, median (95%CI)	2 (2-4)+	2 (0-5)‡	0.30
■ Protein, g/L, median (95%CI)	0.9 (0.4-1.8)	0.7 (0.5-1.6)*	0.68
■ Increased protein, >0,55 g/L, n (%)	10 (63)	4 (57)*	1.0
Anti-ganglioside antibodies, n (%)			
■ IgM reactivity against GM1, GM2, GD1a, GD1b or GQ1b	2 (13)	1 (13)	1.0
■ IgG reactivity against GM1, GM2, GD1a, GD1b or GQ1b	3 (19)	0	0.53

‡ n=6, *n=7, + n=15, GBS-TRF= GBS with treatment related fluctuations, A-CIDP= acute onset chronic inflammatory demyelinating polyneuropathy

TRFs and exacerbations

The course of disease during follow-up is indicated in table 2. There was a significant difference in the median time to reach nadir, 1st TRF / exacerbation and 2nd TRF / exacerbation between GBS-TRF and A-CIDP. All GBS-TRF patients had their nadir within 16

days and the A-CIDP patients within 22 days. The median time to reach nadir in the GBS group without fluctuations was 8 days which was very much comparable with GBS-TRF group.

The first TRF in the GBS-TRF group was always within 8 weeks (median 18 days; range 10-54 days), and 14 of the 16 GBS-TRF patients had their first TRF within 4 weeks. Five (31%) GBS-TRF patients had also a 2nd TRF and none of these patients had more than 2 TRFs. All A-CIDP patients had their exacerbations after 4.5 weeks (median 51 days; range first exacerbation: 31-63 days). The A-CIDP patients had 2 to 5 exacerbations until intermittent treatment was started. At all time-points there was a significant difference in level of weakness and severity between GBS-TRF and A-CIDP (table 2). The GBS-TRF group, in comparison with the GBS group without fluctuations, was more severely affected (100% versus 79%; p<0.05) and contained more ventilated patients (44% versus 15%; p<0.05) at nadir.

Table 2 | Course, number and severity of TRFs in GBS-TRF and exacerbations in A-CIDP

	GBS-TRF (n=16)	**A-CIDP** (n=8)	p Value
Course			
■ Days to reach nadir+, median (95%CI)	8,5 (6-11)	16,5 (5-22)	0.03
■ Days to reach 1st TRF/exacerbation+, median (95%CI)	18 (15-27)	51 (31-63)	0.00
■ Days to reach 2nd TRF/exacerbation+, median (95%CI)	38 (31-46)*	105 (52-116)*	0.01
■ Days from onset of weakness till inclusion	5 (2-10)	14.5 (5-26)	0.01
■ Days from onset of paresthesia till inclusion	8 (5-17)∞	12.5 (7-24)	0.04
■ Days from onset of hypesthesia till inclusion	6.5 (3-12)≈	10 (7-21)Δ	0.12
Number, n (%)			
■ >2 TRFs /exacerbations ‡	0	4 (50)	0.01
Severity			
■ GBS disability score ≤2 at nadir, n (%)	0	5 (63)	0.00
■ MRC sumscore at nadir, median (95%CI)	42 (26-48)	49 (46-54)	0.01
■ GBS disability score ≤2 at 1st TRF / exacerbation	0	4 (50)	0.01
■ MRC sumscore at 1st TRF / exacerbation, median (95%CI)	31 (10-40)∞	50 (45-52)**	0.00
■ Ventilatory support after onset of disease	7 (44)	0	0.05

* n=5, Δ n=6, ** n=7, ≈ n=10, ∞ n=14, + from onset of disease, ‡ until intermittent treatment was started, TRF = treatment related fluctuation, GBS-TRF = GBS with treatment related fluctuations, A-CIDP = acute onset chronic inflammatory demyelinating polyneuropathy, GBS disability score ≤2 = able to walk independently = mildly affected

Laboratory findings

Table 1 shows the results from the laboratory findings. There were no differences in CSF protein level and number of cells in CSF between GBS-TRF and A-CIDP. In one GBS-TRF patient (6%) and none of the A-CIDP patients, serological evidence was found for a recent infection with *Campylobacter jejuni*. One GBS-TRF patient had IgG and IgM reactivity

against GM1 and GD1b. In one GBS-TRF patient IgG reactivity against GD1b and GQ1b was found, in another GBS-TRF patient IgG reactivity against GD1b was found. In one GBS-TRF and one A-CIDP patient IgM reactivity against GM1 was found.

Electrophysiologic findings

Electrophysiological investigations of 14 GBS-TRF patients and 8 A-CIDP patients were performed after 13 days (median; 95% CI: 0-16 days). Of 18 patients the electrophysiological investigations were performed within 3 weeks after inclusion (as was formulated in the protocol). Due to clinical conditions, 4 patients had their electrophysiological investigation 1 or 2 weeks later. In 6 A-CIDP patients, also a second electrophysiological investigation was performed (median 67 days, 95% CI: 15-187 days). Of 2 GBS-TRF patients, the electrophysiological investigations could not be retrieved. The A-CIDP group tended to have more “CIDP-like” abnormalities (table 3). A higher percentage of A-CIDP patients showed decreased mNCVs compared to the GBS-TRF group (p=0.04). The A-CIDP group showed a higher percentage of other demyelinating features, more sensory abnormalities and a lower percentage of patients showed active denervation. However, these differences did not reach statistical significance. Only 2 patients in the A-CIDP group fulfilled the electrophysiological criteria for CIDP (26). Yet, also in the GBS-TRF group 2 patients fulfilled these criteria. In the second EMG the demyelinating features of the A-CIDP group were more pronounced, though still only 2 patients fulfilled the strict electrophysiological criteria for CIDP (26).

DISCUSSION

Because prognosis and treatment strategy in GBS-TRF and A-CIDP patients differ, it is important to distinguish these two entities already in an early phase of disease. We prospectively investigated the differences between GBS-TRF and A-CIDP patients

In the current study, 5% of the patients initially diagnosed as GBS revealed to have A-CIDP. This is the first study that prospectively investigated the development of A-CIDP in a large group of patients initially diagnosed as GBS. By definition CIDP patients should have their nadir beyond eight weeks. In this study all A-CIDP patients had their nadir already within four weeks, being the reason that they initially were diagnosed as GBS, however active disease exceeded 8 weeks in all A-CIDP patients (4,5). In our retrospective study on this issue for which we used our CIDP database, it appeared that over half of the A-CIDP patients already reached their nadir within four weeks (11). The fact that nadir for A-CIDP often already is reached within four weeks underscores the diagnostic difficulties between

GBS-TRF and A-CIDP. In this study, 10% of the GBS patients had at least one TRF. This percentage is comparable with the percentages described before (9,11,12).

Table 3 | Elelectrophysiological findings in GBS-TRF and A-CIDP patients

	GBS-TRF (n=14)	**A-CIDP** (n=8)	p Value[$]	**A-CIDP 2nd EMG** (n=6)
Demyelinating features, n (%)				
■ Prolonged DML	9 (64)	6 (75)	0.86	6 (100)
■ Decreased mNCV	4 (29)	6 (75)	0.04	4 (67)
■ Conduction block and/or temporal dispersion	4 (29)	3 (38)	0.67	2 (33)
■ Increased latency F-wave	5 (50)[+]	5 (83)[‡]	0.18	5 (100)[§]
Axonal features, n (%)				
■ Denervation potentials	7 (54)[#]	6 (75)	0.06	1 (20)[§]
■ Sensory abnormality arms	7 (50)	0 (0)	0.08	5 (83)
Classification, n (%)			0.53	
■ Demyelinating	9 (64)	6 (75)		5 (83)
■ Axonal	2 (14)	0		0
■ Equivocal	3 (21)	2 (25)		1 (17)
■ Normal	0	0		0
CIDP criteria fulfilled, n (%)	2 (14)	2 (25)	0.90	2 (33)

§ n=5, ‡ n=6, [+] n=10, # n=13, GBS-TRF= GBS with treatment related fluctuations, A-CIDP= acute onset chronic inflammatory demyelinating polyneuropathy, Prolonged DML: DML >110% of upper limit of normal (ULN) (120% if dCMAP < 100% of lower limit of normal (LLN)), Decreased mNCV: mNCV <90% LLN (85% if dCMAP <50%LLN), F-wave abnormality: F-wave latency >120% ULN or absent F-wave, Conduction block or temporal dispersion: with pCMAP/dCMAP ratio of ≤50% (dCMAP≥ 20% LLN), Sensory abnormality: SNAP < 50% LLN or absent, [$] p-value of differences between first EMGs of GBS-TRF group and A-CIDP group

This prospective study showed different clinical, biological and electrophysiological characteristics of A-CIDP patients compared to GBS-TRF patients. The median time to reach nadir, 1st exacerbation and 2nd exacerbation was significantly longer in the A-CIDP group compared to the GBS-TRF group. In contrast to A-CIDP patients, none of the GBS-TRF patients deteriorated after 8 weeks. Most GBS-TRF patients had their 1st deterioration within 4 weeks and none of the GBS-TRF patients had more than 2 TRFs. At least half of the A-CIDP patients were able to walk independently at nadir of the different deteriorations and none of the A-CIDP patients needed artificial ventilation. This is significantly different from the GBS-TRF patients were none of the patients were able to walk independently and 44% needed artificial ventilation at nadir of the different deteriorations. In line with the differences in severity based on the GBS disability score, the MRC sumscore was

significantly lower in the GBS-TRF group compared to A-CIDP group. In counting the number of, time to and severity during the deteriorations it should be considered that therapy is a confounder in both groups. Therefore, we only counted the exacerbations in the A-CIDP group before the start of intermittent treatment.

A-CIDP patients had significantly less cranial nerve dysfunction compared with the group of patients having GBS-TRF, which is in line with our previous retrospective study (11). The percentage of patients with cranial nerve involvement and the level of disability and weakness in the A-CIDP group are in line with the clinical characteristics usually found in CIDP (7). There were no differences in preceding infections between the GBS-TRF and A-CIDP group. In GBS-TRF, preceding infections have been described before in a similar percentage (12). There are no studies known about preceding infections in A-CIDP, however the percentage of preceding infections found in the group of A-CIDP patients are comparable with the preceding infections found in CIDP (7). None of the A-CIDP patients had a positive *Campylobacter Jejuni* serology. In the GBS-TRF group there was only one patient with a positive *Campylobacter Jejuni* serology and the pure motor form. In a previous study none of the GBS-TRF patients had the pure motor form (12).

While not significant, GBS-TRF patients more frequently had IgM and IgG reactivity against anti-gangliosides as compared to the A-CIDP patients. IgM anti-GM1 reactivity has been described before in CIDP and other chronic neuropathies, but in lower percentages than in GBS, comparable with our previous findings (25).

Although for most individual electrophysiological variables there was no statistical significance, the A-CIDP group displayed a trend towards a more “CIDP-like” electrophysiological investigation (26). Signs of axonal damage (denervation potentials) are rare in the A-CIDP group, while more than half of the GBS-TRF patients showed signs of axonal damage in the acute phase. Probably the numbers of patients per group were too small to reach statistical significance.

None of the 18 Miller Fisher syndrome (MFS) patients enrolled in this study developed TRFs. This is a remarkable observation because recurrences of MFS, are more frequent compared to GBS (29).

Compared to the group of GBS patients without TRFs, this study additionally showed that the more severely affected GBS patients with sensory disturbances are at risk for developing TRFs.

This prospective study confirmed the results of our retrospective study and added more robust factors and refined the results that can help to distinguish more accurate between these variants of inflammatory polyneuropathy already in the early phase of disease (11). These results and our experience indicate that the diagnosis of A-CIDP should be considered when ‘a patient with GBS’ deteriorates again beyond eight weeks from onset or when deterioration occurs three times or more. A-CIDP patients generally

are less severely disabled compared to GBS-TRF patients. Patients remaining able to walk independently at nadir of different deteriorations, having no cranial dysfunction and showing electrophysiological features likely to be compatible with CIDP, are more likely to have A-CIDP. In these patients maintenance treatment should be considered.

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CHAPTER 3.4

TREATMENT OF CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

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Curr Opin Neurol. 2004;17(5):607-13 (review)

ABSTRACT

Purpose of the review: Chronic inflammatory demyelinating poly(radiculo)neuropathy (CIDP) is a treatable disorder. There are three proven effective treatments available. Randomised controlled trials have only focussed on short-term effects, but most patients need long-term therapy. The most up-to-date treatment options are discussed. Attention is also paid to the use of appropriate assessment scales and treatment of residual findings.
Recent findings: A Cochrane review is available indicating that intravenous immunoglobulin is an effective treatment. Equal efficacy of intravenous immunoglobulin and steroids was shown during a 6-week treatment period. New open studies indicated possible efficacy for mycophenolate, interferon-β and etanercept. Combinations of treatment are scarcely studied yet. Some Patients with CIDP may have a more acute onset of disease since maximum severity is reached within 4–8 weeks, resulting in confusion about the diagnosis. It was shown that severe fatigue can be a major complaint in Patients with CIDP, a training regimen might partially resolve these problems.
Summary: CIDP is a treatable disorder, but most patients need long-term treatment. Intravenous immunoglobulin, steroids and plasma exchange are shown to be effective. It is suggested that other immunomodulatory agents can also be effective, but randomised trials are needed to confirm these benefits. General measures to rehabilitate patients and to manage symptoms like fatigue and other residual findings are important.

INTRODUCTION

Chronic inflammatory demyelinating poly(radiculo)neuropathy (CIDP) is generally considered being the chronic variety of the Guillain-Barré syndrome (GBS), although there are obvious clinical and immunological differences (1). Criteria for GBS and CIDP are mainly based upon research purposes (2,3). From a clinical prospective, the main difference is the duration of clinical deterioration, which should be less then 4 weeks in GBS and more then 8 weeks in CIDP. The course of CIDP may be one with gradual progression, with steps of progression or with spontaneous relapses and remissions. Most patients with GBS reach their maximum severity of weakness within 2 or 3 weeks from onset. In general there will be no confusion with the course of CIDP; however some patients with CIDP may have a rather acute onset resulting in confusion with GBS. This is important because the prognosis and treatment differ considerably. In CIDP it has been shown that intravenous immunoglobulin and plasma exchange are effective (4,5). Although only one trial with a reasonable number of patients showed efficacy of steroids, it is generally accepted that steroids are effective in CIDP (6). As the name already indicates, CIDP is a chronic disorder and many patients need treatment for years. The fear for side effects of long-term steroid treatment, the high costs of intravenous immunoglobulin and plasma exchange, but also the necessity for specialized equipment and the invasive nature of plasma exchange, are important factors determining the choice for one of these treatments. Another disabling problem for patients is the high incidence of fatigue, which may persist for years. These issues, and the fact that not all patients improve dramatically and others need treatment for a very long period of time, led to roundtable meetings on 'Current Opinions on the Management of CIDP' and discussions about new frontiers in therapy (7). Additionally, the Medical Advisory Committee of the Neuropathy Association proposed new guidelines for the diagnosis and treatment of CIDP (8). Treatment of CIDP is an actual issue which is reflected by the publication of several very useful reviews on treatment for CIDP (5,9-13,14-16).

What is considered to be chronic inflammatory demyelinating poly(radiculo) neuropathy?

The diagnosis of CIDP may be difficult to make; an approach to the evaluation of peripheral neuropathies was recently proposed (17). Classical clinical features of CIDP consist of a progressive (at least for 8 weeks), symmetrical sensory-motor neuropathy with demyelinating features on electromyography and an increased cerebrospinal fluid protein, in the absence of another explanation for the neuropathy. CIDP, however, is not a homogeneous disorder. Not only does the extent of neurological involvement vary; the minimal requirements to meet the electrophysiological diagnosis are also a matter of

debate (18,19). A helpful new set of electrodiagnostic criteria for CIDP has been proposed, giving 75% sensitivity and a 100% specificity with regard to diabetic neuropathy (20). The minimal duration of initial progression in CIDP is another issue. Some patients with rapid progressive weakness like GBS may subsequently follow the otherwise typical clinical course of CIDP (21,22,23-25). Within the group of chronic demyelinating neuropathies that comprise CIDP, several subgroups can be distinguished like the sensory ataxic group, a (sub)-acute motor-sensory demyelinating neuropathy, a chronic motor-sensory demyelinating neuropathy, multifocal motor-sensory neuropathy and a symmetric motor demyelinating neuropathy (26). Based on clinical and neurophysiological characteristics the terms multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) and distal acquired demyelinating symmetric neuropathy (DADS) have been proposed (27). Whether these variants need specific treatment is yet largely unknown. An exception is pure motor neuropathy in which intravenous immunoglobulin is effective and steroids may induce clear deterioration; a feature that previously has been described in multifocal motor neuropathy (MMN) (26).

Treatment trials

CIDP is a treatable disorder, but most patients need long-term treatment. Previous trials showed that patients with CIDP might improve after steroids, intravenous immunoglobulin or plasma exchange. Treatment trials are described and the most up-to-date treatment options are discussed.

Corticosteroids

Dyck et al. (28) have conducted the only randomised controlled open study of prednison, and concluded that steroids are effective in CIDP. Several non-randomised studies suggest that steroids are beneficial in CIDP. A Cochrane review concluded that the single randomised controlled trial provided weak evidence to support the common opinion from non-randomised studies that oral corticosteroids reduce impairment in CIDP (6). The advantages of steroids are their availability and low initial costs, but side effects can be very serious. The best steroid regimen to start with is not known. If we start with prednison, we generally start with 60 mg daily. Others start oral prednison 1.5 mg/kg on alternate days in a single morning dose (5). Since most patients will need steroids for a long-term it is advocated to start osteoporosis prophylaxes at the same time, especially in elderly patients (5). Patients with a pure motor form may deteriorate within days after treatment with steroids (29) (table 1 and 2).

Plasma exchange

Plasma exchange is shown to be effective in CIDP (30,31). A clear disadvantage of plasma exchange is its availability, high costs and the relative invasiveness of the procedure. Patients treated with plasma exchange may improve rapidly, but need regular treatment to avoid clinical deterioration (table 1 and 2).

Table 1 | Proven effective treatment for CIDP

Treatment	Cochrane review	effect	side-effects (potential)	availability	direct-costs
prednison (28,41)	(6)	+	severe	very good	low
PE (30,31)	-	+	minor	rather good	high
IVIg (32-35)	(4)	+	minor/none	good	high

Table 2 | Therapeutic regimes for CIDP

Proven effective treatments	**Regimen**
Prednison	Induction: 60 mg prednison daily or 1.5 mg/kg on alternate days in a single morning dose Maintenance: slowly tapering over months-years
Intravenous immunoglobulin (IVIg)	Induction: 2 g/kg, divided over 2/5 days Maintenance: 0.4/1 g/kg each 2/6 weeks
Plasma exchange (PE)	Induction: 3/5 PE sessions (2/2.5 l/session) Maintenance: 1 PE session/ 1/3 weeks
Not-proven effective treatments	
IV Methylprednisolon	Induction: 500 mg daily for 5 days, or 1 g daily for 3 days Maintenance: not determined
Azathioprine	1.5/3 mg/kg/day
Mycophenolate mofetil	1.0/2.0 g/day divided into 2 doses PO
Cyclosporin	2.5/5.0 mg/kg/day divided into 2 doses PO
Methotrexate	7.5/15 mg once a week PO; see (11*)
Other treatments	see (13*)

Intravenous immunoglobulin

In placebo-controlled studies it was found that intravenous immunoglobulin is an effective treatment for CIDP (31,32-34). A recent Cochrane study confirmed the favourable effect of intravenous immunoglobulin (4,36). If patients improve after intravenous immunoglobulin, the improvement starts within 2 weeks. The majority of patients need intermittent treatment during many months or several years to maintain the improved condition (37). This is a problem because intravenous immunoglobulin is very expensive (table 1 and 2).

Intravenous immunoglobulin in general is well tolerated and has no or few mild infusion-related reactions. Serious adverse effects are rare and can include thromboembolic events, renal failure (mainly in patients with pre-existing renal failure), anaphylaxis (especially in patients with IgA deficiency), or aseptic meningitis (38). A very useful paper on the use and working mechanisms of intravenous immunoglobulin in autoimmune neuromuscular diseases was published recently (39).

Comparison between steroids, plasma exchange and intravenous immuno-globulin

Intravenous immunoglobulin was equal to plasma exchange in a single-blind, controlled crossover trial of Patients with CIDP assigned to a 6-week course of plasma exchange or intravenous immunoglobulin, 0.2-0.4 g/kg administered weekly (40). A randomised double-blind crossover trial showed that intravenous immunoglobulin (2 g/kg given over 1 or 2 days) is not significantly better compared to oral prednisolon during a treatment period of 6 weeks (tapered from 60 to 10 mg daily during that period) (41). This is the only trial comparing intravenous immunoglobulin with steroids, but the treatment duration was too short to judge any differences in side-effects.

New randomised controlled trials

No randomised controlled trial on treatment of CIDP has been published over the last year.

New potentially effective agents, non-randomised trials

Over the years smaller non-controlled studies reported a positive effect of immuno-suppressive agents, such as azathioprine, cyclosporin or mycophenolate. The problem is not only the open fashion, but also the selection of patients since most are refractory to standard treatments. Such a negative selected population makes it even more difficult to judge about possible efficacy of a new potentially effective drug.

Mycophenolate

This drug is successfully applied in organ transplantation patients. Recently, favourable results of mycophenolate have been reported in a small series of immune-mediated neuromuscular disorders including in two patients with CIDP (42). Another study reported on five consecutive treatment-resistant patients with CIDP or MMN who were treated with mycophenolate. None showed clinical significant benefit and two of them had side effects severe enough to stop mycophenolate (43). Another report expresses personal experience with mycophenolate, that are not that encouraging (10). We have treated a few patients with CIDP who did not extremely well on intravenous immunoglobulin or other immunosuppressive treatment, in which it is suggested that mycophenolate might be of help (P.A. van Doorn, unpublished observations). Whether mycophenolate is an attractive

low-toxicity immunosuppressive agent for treatment of CIDP needs to be evaluated in a randomised controlled trial.

Azathioprine

One parallel group open study of azathioprine for 9 months involving 27 participants did not show a positive effect (44). The drug, however, is frequently prescribed because it might reduce the steroid dosage.

Etanercept

Etanercept is a tumour necrosis factor-α antagonist that has demonstrated efficacy in rheumatoid and psoriatic arthritis. Ten CIDP and/or variant patients who were refractory or intolerant of standard therapies were treated with etanercept, subcutaneously, 25 mg twice a week. From this uncontrolled, retrospective study it was concluded that three patients had clear improvement and three others had possible improvement. None of the patients had adverse effects. It was suggested from this study that anti- tumour necrosis factor-α agents might be useful in the treatment of some patients with CIDP, particularly in those who are refractory to or are intolerant of standard therapies (45*).

Interferon-β

Interferons are naturally occurring cytokines. A recent prospective, open-label study described 20 treatment-resistant (at least a failure of intravenous immunoglobulin) patients with CIDP who were treated with intramuscular interferon-β-1a 30 µg once a week for 6 months. Seven patients (35%) showed clinical improvement, 10 (50%) had stable disease, the other three patients continued to deteriorate. This study indicates that some patients with CIDP may benefit of this treatment (46). Another study in ten patients with CIDP failed to demonstrate clinical improvement after subcutaneous interferon-*β*-1a (47). Until we have no results from a randomised controlled trial no further conclusions about the efficacy of interferon-β can be drawn.

Interferon-β has been tried in CIDP presumably because efficacy has been shown in multiple sclerosis. The effect of interferon-β however could be different in patients with demyelination of the central or the peripheral nervous system. This was illustrated by a publication on three children with multiple sclerosis who were treated with interferon-β and who developed CIDP, suggesting that interferon-β did not prevent development of CIDP. In these patients, intravenous immunoglobulin improved the features of CIDP, but not of the central demyelinating disease (48). A recent overview on the pathogenesis CIDP makes comparisons between CIDP and multiple sclerosis and discusses a rationale to use interferon-β in CIDP (49).

Cochrane review on cytotoxic drugs and interferons

Since there are only limited studies, it was concluded in a recent Cochrane review that the evidence is inadequate to decide whether azathioprine, interferon-β or any other immunosuppressive drug is beneficial in CIDP (50).

Combination of treatments

No new trials appeared that studied combinations of treatment that may act synergistically in CIDP. One case-report described two patients with CIDP who initially improved after intravenous immunoglobulin but thereafter deteriorated despite regular intravenous immunoglobulin infusions. Various other immunosuppressive drugs did not improve these patients. However, treatment with plasma exchange immediately followed by intravenous immunoglobulin treatment induced a rapid reduction of weakness (51). Intravenous immunoglobulin and steroids are both effective in CIDP. The combination of intravenous immunoglobulin and steroids has not been studied systematically in CIDP, but is has in GBS. Recently the second randomised controlled trial of the Dutch GBS study group was published (52). This trial compares one course of intravenous immunoglobulin (0.4 g/kg for 5 days) and methylprednisolon (500 mg/day for 5 days) with intravenous immunoglobulin and placebo. There were borderline significant results that became significant after adjustment for well-known (not study-driven) prognostic factors favouring the combination of intravenous immunoglobulin and steroids. Whether a combination of intravenous immunoglobulin and steroids can be helpful in the treatment of patients with CIDP has not been investigated systematically .

Chronic inflammatory demyelinating poly(radiculo)neuropathy and diabetes

Reports indicate that 12-18% of patients with diabetes meet the electrophysiological criteria for CIDP, and that the risk of CIDP is 11 times greater in patients with type 2 diabetes than in those without (53). One study showed that patients with diabetes and electrophysiological features compatible with demyelination might improve after immunomodulatory treatment (54). It is not completely clear from this study whether these patients had a clinical course of progression like idiopathic CIDP. The study indicates that patients with diabetes having an unexpected course of their neuropathy should be evaluated for whether this is CIDP. A controlled trial is needed to establish the safety and efficacy of intravenous immunoglobulin in diabetes-associated CIDP (39).

Chronic inflammatory demyelinating poly(radiculo)neuropathy with lesions of the central nervous system

The combination of CIDP and central nervous system white matter lesions has been described before (48). A recent study reported that resolution of clinical and radiographic findings of central-nervous-system lesions after intravenous immunoglobulin treatment (55).

Chronic inflammatory demyelinating poly(radiculo)neuropathy and hereditary neuropathy

Seven patients with Charcot-Marie-Tooth type 1A (CMT1A) and one with X-linked disease (CMTX) were described who had acute or subacute deterioration (56). Seven had neuropathic pain. The five patients who were treated with steroids and/or intravenous immunoglobulin had a variable response. It was estimated that the association was more frequent than would be expected by chance, suggesting that CMT patients are predisposed to superimposed inflammation. The study stressed the importance of looking out for unexpected clinical deterioration in CMT1A patients, because immunotherapy may relieve these exacerbations (56).

Assessment of the effect of treatment

Improvement can be assessed at various levels: impairment, disability, handicap and quality of life. In order to assess a relevant effect of treatment in immune-mediated neuropathies, appropriate scales should be applied. An outcome measure needs to be relatively simple, valid and reliable. Additionally, a scale needs to be responsive which makes it suitable to study the effect of treatment during the course of disease. Thirteen patients with CIDP on treatment were regularly examined during a period of 52 weeks. In order to detect clinical relevant changes over time, a wide range of assessment scales was applied during this period. The inflammatory neuropathy cause and treatment (INCAT) disability sumscore, the Medical Research Council (MRC) sumscore, and the Vigori hand-held dynamometer were among the best responsive scales. It was suggested to use these measurements in studies of immune-mediated polyneuropathies (57).

Prognostic factors related to improvement

A better outcome is reported to be related with younger age at onset, relapsing-remitting course and absence of axonal damage (16). We have recently reviewed our series of over 90 patients with CIDP and found that all patients with a relapsing course improved after intravenous immunoglobulin treatment (P.A. van Doorn, unpublished observations). As has been described previously, patients with pure motor weakness, irrespective of whether

they have MMN or pure motor demyelinating neuropathy with symmetric involvement, may deteriorate after treatment with steroids (26).

When should one start treatment?

Once the diagnosis of CIDP is clear, treatment should be initiated when the patient exceeds a certain level of disability. Some patients only have minor symptoms, and especially in those patients a spontaneous improvement might be awaited since steroids can induce severe side effects and intravenous immunoglobulin and plasma exchange are very expensive. Most studies suggest that axonal degeneration is a worse prognostic factor for improvement after immunomodulatory treatment. It has not been studied whether intravenous immunoglobulin or steroids can mitigate the long-term axonal degeneration that typically accompanies disease progression.

Cost-utility analysis

Intravenous immunoglobulin is a very expensive therapy and steroids may induce severe side effects. Cost-utility analysis studies would be very helpful for making decisions. A recent study was executed to calculate cost-utility for the patients with CIDP who were randomised in the intravenous immunoglobulin/steroids trial (41,58). The main outcome measure in the economic evaluation was the number of quality-adjusted life years gained, using an 11-point disability scale to measure clinical outcome. As expected during a 6-week period no economic differences could be detected favouring intravenous immunoglobulin. The methods and data reported in this study could be used in future studies aiming to compare various costs, side effects and quality of life during long-term treatment.

Managing of residual symptoms

Over recent years, more attention has been paid to rehabilitation of patients including management of symptoms such as foot drop, but also fatigue and pain (59,60). A recent study indicates that a well-structured physical training programme, three times weekly for 12 consecutive weeks can help to reduce severe fatigue and improve quality of life (61).

CONCLUSION

Intravenous immunoglobulin, steroids and plasma exchange are all effective in about 70-80% of patients with CIDP. Recent studies indicate that CIDP is a heterogeneous disorder, which could be a reason why not all patients improve after one of these treatments. At present there is inadequate evidence to decide whether azathioprine, interferon-β or any other immunosuppressive drug is beneficial in CIDP. Because CIDP is a chronic

disorder, new studies should in particular evaluate long-term treatment with intravenous immunoglobulin and steroids. Many patients with CIDP have residual symptoms like fatigue, and although their nature is presently obscure it seems that a structured training program can be helpful.

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GBS

CHAPTER 4
GBS AND PAIN

4.1 Determination of pain and response to methylprednisolone in Guillain-Barré syndrome

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Journal of Neurology 2007;254(10):1318-1322

4.2 Pain accompanies pure motor Guillain-Barré syndrome

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J Peripher Nerv Syst. 2008;13(4):305-306

4.3 Pain in Guillain-Barré syndrome: a long-term follow-up study

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Submitted for publication

CHAPTER 4.1

DETERMINATION OF PAIN AND RESPONSE TO METHYLPREDNISOLONE IN GUILLAIN-BARRÉ SYNDROME

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Journal of Neurology 2007;254(10):1318-1322

ABSTRACT

Introduction: Pain can be a serious problem in patients with Guillain-Barré syndrome (GBS). Different pain symptoms and the effect of methylprednisolone on pain are evaluated.

Methods: GBS patients were recruited from a randomised placebo-controlled study comparing intravenous immunoglobulin (IVIg) + methylprednisolone (500 mg for 5 days) versus IVIg + placebo. Presence and severity of pain were prospectively scored at randomization and after 4 weeks. Efficacy of methylprednisolone was evaluated using endpoints: percentage of patients with pain and percentage of patients improving in pain-severity level. Medical records of the subgroup of patients treated in the Erasmus MC were screened retrospectively for different pain symptoms and course. Pain was scored at different time intervals: within 4 weeks before randomization and 0-2, 2-4, 4-24, 24-52 weeks after randomization.

Results: 123 *(*55%) of 223 patients had pain at randomization. In 70%, pain already started before onset of weakness. Methylprednisolone did not show a positive effect on the presence and reduction of pain. In the subgroup of 39 patients, backache (33%), interscapular (28%), muscle (24%), radicular pain (18%) and painful par-/dysaesthesiae (18%) were most frequently present within the period of 4 weeks before randomization. Twenty-six percent had extreme pain 0-2 weeks after randomization. Most symptoms of pain decreased after this period, but painful par-/dysaesthesiae and muscle pain often remained present during at least 6 months.

Conclusions: Pain frequently occurs, often starts before onset of weakness and may cause severe complaints. Especially painful par-/dysaesthesiae and muscle pain may persist for months. Methylprednisolone seems to have no significant effect on the presence and intensity of pain.

INTRODUCTION

The most striking and alarming feature in patients with Guillain-Barré Syndrome (GBS) is progressive paralysis. Generally, less attention has been paid to pain, which may be a common and severe symptom in patients with GBS. Recognition of pain is very important, especially in patients unable to communicate due to intubation, because treatment against pain can be offered. Pain as a presenting symptom of GBS before the onset of weakness may be misleading in making the diagnosis of GBS and therefore can cause a delay in starting treatment for GBS.

Pain has been described in 3-89% of patients with GBS (1,6,9,14). Different symptoms of pain associated with GBS have been distinguished: par-/dysaesthesiae, backache / root pain, meningism, muscle pain, joint pain, visceral pain and other types (12). One larger study in 55 GBS patients subdivided the different symptoms of pain as reported on admission into the following: low back pain with radiation (67.3%), dysaesthetic extremity pain (20%) and myalgic-rheumatic extremity pain (9.1%) (9). During the further non subdivided period of six months, low back pain with radiation (61.8%), dysaesthetic extremity pain (49.1%) and myalgic-rheumatic extremity pain (34.5%) were noted (9). As far as we know, there are no publications on the more detailed course and level of severity of the different pain symptoms during the first year after onset of GBS.

Pain in GBS can be very severe, and treatment is often far from successful. In some cases however a positive effect of treatment of pain in the acute phase has been described using corticosteroids (8, 16). The pathophysiology of pain is likely multifactorial. Increased endoneurial fluid pressure in nerve trunks possessing the epi- and perineurium may play a role (2). A possible cause of a salutary effect of corticosteroids could be a reduction of the perineurial and endoneurial inflammatory reaction in GBS.

Most reports on the effect of medication to relieve pain in GBS are based on limited numbers of patients. When measuring a treatment effect, often all types of pain are lumped together (4,8,10,11,15-17). Because it is likely that different pathophysiological mechanisms are related to these symptoms, a more detailed classification of different pain symptoms associated with GBS can be of help to study the effect of drugs.

This study focuses on the frequency, characteristics, severity and course of various symptoms of pain during the course of GBS and on the effect of methylprednisolone as was administered in a large placebo-controlled study.

METHODS

Prospective study

All GBS patients were recruited from a double-blind, randomised placebo-controlled, multicentre study comparing IVIg + methylprednisolone (500 mg for five days) versus IVIg + placebo (18). A patient was eligible for this trial when the onset of weakness was within 2 weeks before the date of randomization and the patient was unable to walk 10 meters across an open space without assistance (GBS disability score ≥. 3). Presence and severity of pain were collected prospectively at randomization and after 4 weeks. Pain severity was judged as: none, mild (pain but no real complaints), moderate (complaints, but no analgesics necessary) or severe (analgesics necessary).

Retrospective study

Medical records of the subgroup of GBS patients who entered the trial and were admitted to the Erasmus MC (the coordinating centre) were retrospectively screened for different pain symptoms. These symptoms were divided in nine different pain symptoms as described before (12). In this subgroup of patients, severity of pain was judged as: none, severe (analgesics necessary in a way the complaints were acceptable) or extreme (severe complaints despite analgesics; defined as feeling uncomfortable due to pain, not well sleeping due to pain). In the Erasmus MC, treatment of pain in the acute phase of GBS is standardized following the WHO's pain ladder. When a GBS patient after a few weeks suffers from pain resembling neuropathic pain, we generally start amitriptyline followed by anti-convulsants. The different pain syndromes and their severity were scored at different time-intervals: within 4 weeks before randomization and 0-2, 2-4, 4-24, 24-52 weeks after randomization. The time points 0 and 4 weeks were fixed visits, during the other intervals we asked the patient at least once for pain at that moment and pain since the last visit. Three patients had to be excluded from the analysis for the time-interval 24-52 weeks after randomization because of lost to follow-up after 24 weeks.

Statistics

Percentage of patients with pain and percentage of patients improving in level of pain-severity in independent groups were compared by the χ^2 test. All calculations were performed using Stata/SE 8.2 for Windows 2000 (Stata Statistical Software, College Station, TX 77845, USA). A p-value <. 0.05 was considered to be significant.

RESULTS

Prospective study

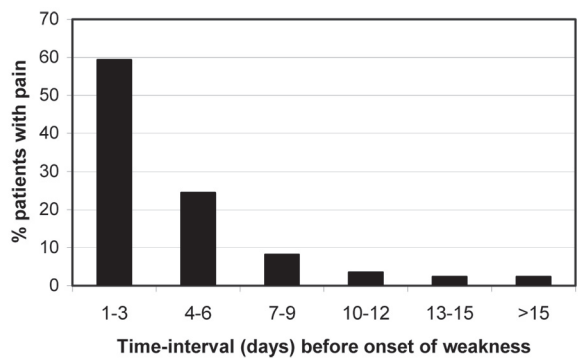
225 GBS patients were included in the prospective study, 2 patients were excluded due to missing data on the presence of pain. Base-line characteristics, including the presence of pain at randomization between the two treatment groups, was not significantly different (table 1). Pain was reported by 123 (55%) of the 223 patients at randomization, 48 (22%) of these patients had severe pain. Of the 123 patients with pain, 86 (70%) indicated that the pain preceded the onset of weakness (median 3 days, range 1–36 days). In 84% of the patients starting with pain, weakness started within one week after the onset of pain (figure 1).

Table 1 | Baseline characteristics of treatment groups at randomization

	IVIg/Placebo group (n=112)	**IVIg/MP group** (n=111)
Sex distribution, n (%)		
■ Male	56 (50)	73 (66)
Age, median	50	51
F-score, n (%)		
■ 3	32 (29)	26 (23)
■ 4	80 (71)	76 (68)
■ 5	0 (0)	9 (8)
Pain, n (%)		
■ No	45 (40)	55 (50)
■ Yes	67 (60)	56 (50)
■ Mild	24 (21)	17 (15)
■ Moderate	17 (15)	17 (15)
■ Severe	26 (23)	22 (20)

MP = methylprednisolone

Figure 1 | Occurrence of pain before onset of weakness in 86 GBS patients



Legend: Pain = one or more pain symptoms, 86/223 GBS patients started with pain before onset of weakness

4 weeks after randomization, 58 patients (57%) in the IVIg/placebo group and 51 (49%) in the IVIg/methylprednisolone group reported pain (no significant difference). In individual patients with pain, there also was no significant difference between the IVIg/methylprednisolone and IVIg/placebo group in decrease or increase of pain severity 4 weeks after randomization (Table 2).

Table 2 | Presence and severity of pain at randomization and 4 weeks later

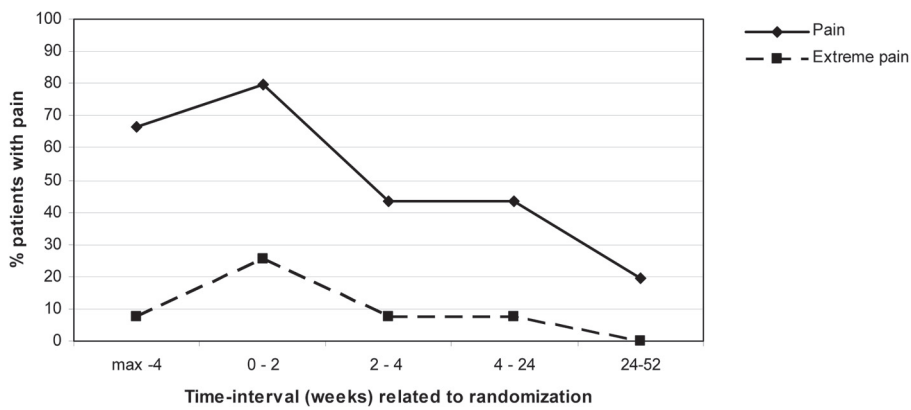
	IVIg/Placebo group (n=112)	**IVIg/MP group** (n=111)
Patients with pain, n (%)		
■ Randomization	67 (60)	56 (50)
■ 4 weeks after randomization	58 (57)	51 (49)
Patients with a decrease in pain severity, n (%)		
■ 4 weeks after randomization	34 (34)	32 (31)
Patients with an increase in pain severity, n (%)		
■ 4 weeks after randomization	26 (26)	22 (21)

MP = methylprednisolone

Retrospective study

Of the 39 retrospectively analysed patients, 26 patients (67%) described one or more symptoms of pain within the 4 weeks before randomization (figure 2). 0-2 weeks after randomization, the prevalence rate increased to 79%, where after it decreased. Within the first 2 weeks after randomization, 26% had extreme pain.

Figure 2 | Prevalence rate of pain over time in 39 patients with GBS



Legend: Pain = one or more pain symptoms, Extreme pain = severe complaints due to one or more pain symptoms despite analgesics; defined as feeling uncomfortable due to pain, not well sleeping due to pain; Time-interval 24-52: n=36 patients

Backache, radicular, interscapular painful par-/dysaesthesiae and muscle pain most frequently occurred in the beginning of the disease (table 3). Most pain symptoms decreased within 2 weeks. However, painful par-/dysaesthesiae and muscle pain remained rather constantly present during at least 6 months.

Table 3 | Prevalence of pain symptoms during course of GBS in 39 patients

	Number of weeks related to randomization				
Pain symptoms [12]	**Before**	**After**			
	(-4-0) n (%)	**0-2** n (%)	**2-4** n (%)	**4-24** n (%)	**24-52*** n (%)
■ Backache	13 (33)	11 (28)	1 (3)	2 (5)	0 (0)
■ Interscapular pain	11 (28)	5 (13)	0 (0)	0 (0)	0 (0)
■ Muscle pain / cramps	9 (24)	6 (15)	6 (15)	6 (15)	1 (3)
■ Painful par-/dysaesthesiae	7 (18)	7 (18)	8 (21)	11 (28)	5 (14)
■ Radicular pain	7 (18)	8 (21)	1 (3)	2 (5)	1 (3)
■ Others	6 (15)	12 (31)	7 (18)	3 (8)	0 (0)
■ Joint pain	2 (5)	2 (5)	2 (5)	5 (13)	0 (0)
■ Visceral pain	2 (5)	4 (10)	4 (10)	3 (8)	0 (0)
■ Meningism	0 (0)	2 (5)	0 (0)	0 (0)	0 (0)

* n=36 patients

DISCUSSION

In this study, we prospectively investigated the frequency of pain and the effect of methylprednisolone on pain in a large group of GBS patients included in a randomised controlled trial. Retrospectively we investigated the frequency and course of the different symptoms of pain in more detail in a subgroup admitted to the coordinating center.

Pain appeared to be highly prevalent in this large, well documented group of GBS patients. 55% of these patients had pain at randomization. In other studies, the incidence of pain during the acute phase varies between 3% and 86% (median value 50%) (1,5-7,9, 13,14,19,20). This variation mainly seems to be caused by the rather limited number of patients included in most studies.

It is remarkable that 70% of the patients reporting pain at randomization already had this pain prior to the onset of weakness. Pain as presenting symptom can lead to diagnostic difficulties (3). When pain initially is the only symptom, considering GBS as a possible diagnosis is not always so likely. So pain in the early phase can be confusing and

later on may cause a delay in diagnosing and starting specific treatment for GBS. This is important to realize, because a delay in diagnosing GBS is potentially life threatening and may hamper recovery.

In the subgroup of patients that we investigated retrospectively in more detail, a somewhat higher percentage of patients (79%) reported pain in the acute phase compared to the whole group (55%). This is most likely due to the use of a time-interval of 2 weeks after randomization in stead of the fixed point in time at randomization.

In the randomised controlled trial, methylprednisolone was primarily evaluated in relation to the effect on disability of GBS (18). We did not use a clinimetrically validated scale to assess the level of severity of pain. Therefore the results of the effect of methylprednisolone on pain have to be interpreted with some caution. In the retrospective part of the study, we were able to assess the level of pain in more detail. We did this in relation to the use of analgesics. Because both treatment of GBS patients and treatment of pain is standardized in our center, it is likely that the prescription of analgesics is rather uniform and reported in a standardized way. This makes it rather well possible to judge about pain severity at a very global level in a retrospective way. It appeared that approximately a quarter of the GBS patients in this study reported extreme pain in the acute phase indicating that pain is not only a common but also a severe symptom.

Backache, interscapular and radicular pain were most frequently present in the acute phase. However, painful par-/dysaesthesiae remained rather constantly present during at least one year (Table 3). This trend is comparable to findings in another larger study in which the different pain symptoms were noted on admission and during one further non subdivided period of 24 weeks (9). The pathophysiological explanation of pain in GBS is diverse. It seems that pain in the acute phase is predominantly nociceptive pain, due to inflammation of the nerve roots and peripheral nerves which may activate nociceptors. Later on, many GBS patients have neuropathic pain. This neuropathic pain is a non-nociceptive pain that doesn't arise from pain receptors but results from degeneration and perhaps even regeneration of nerves and is often encountered in patients with chronic neuropathies. The persistence of muscle pain on the other hand may be related to more mechanical factors due to limitation of physical activities.

Previous case-reports suggest that corticosteroids might be an effective treatment for pain, possibly due to its anti-inflammatory effect (8,16). This is the first study that evaluated the effect of methylprednisolone on pain in a placebo-controlled way. We did not find a significant decrease in the presence and severity of pain in the methylprednisolone treated group. This indicates that methylprednisolone for pain in general does not seem to have a positive effect. However, there are many symptoms of pain. In previous case reports, corticosteroids were reported to have a positive effect on radicular pain. In our series 10 out of 39 patients had radicular pain. All 5 patients treated with methylprednisolone, but

also 4 out of 5 patients treated with placebo, had a decrease in severity of radicular pain after 4 weeks. The number of patients with radicular pain is too small to conclude about a possible favourable effect of methylprednisolone on this type of pain in GBS.

In conclusion, pain frequently occurs and may cause severe complaints in patients with GBS. It often starts before onset of weakness and therefore can lead to diagnostic difficulties. Most pain symptoms decrease within 2 weeks, but painful par-/dysaesthesiae and muscle pain may persist for months. Methylprednisolone seems to have no positive effect on the development and reduction of pain during the acute phase of GBS.

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CHAPTER 4.2

PAIN ACCOMPANIES PURE MOTOR GUILLAIN-BARRÉ SYNDROME

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J Peripher Nerv Syst. 2008;13(4):305-306

INTRODUCTION

In Guillain-Barré Syndrome (GBS), pain is frequently present and can even be misleading in making the diagnosis (1-4). Clinicians generally associate pain with affected sensory nerves and not with a pure motor neuropathy. We investigated whether pain also occurs in the pure motor variant of GBS in a large group of GBS patients from Europe and Curaçao because this could increase awareness and ultimately improve insight into mechanisms of pain in GBS.

METHODS

The European patients with GBS (predominantly Dutch; GBS disability score ≥3) were recruited from a double-blind, placebo-controlled randomised, multicentre study between 1994 and 2000 (5). The presence and severity of pain were prospectively collected. In Curaçao, where we previously described the predominant occurrence of pure motor GBS, we retrospectively screened the medical records of all GBS cases that had been admitted to the island's only neurological department between 1987 and 2006 (6). In all cases, the presence of pain had been collected from the period ranging from hospital admission until 4 weeks later. The clinical differentiation between the motor and sensory-motor variant was made on the presence of sensory signs or symptoms by standard neurological examination. On the basis of electromyographic (EMG) studies, performed within 4 weeks after admission, we also tried to classify the patients as demyelinating [acute inflammatory demyelinating polyneuropathy (AIDP)] or axonal [acute motor axonal neuropathy (AMAN)] (7,8). When the EMG was not conclusive, the patient was classified as 'not conclusive'. Because we were primarily interested whether pain occurs in patients with GBS with pure motor neuropathy, only the clinical pure motor and AMAN patients were further specified in this study.

RESULTS

We studied 225 European and 83 GBS patients from Curaçao. Age, sex, maximum GBS disability score, and the percentage of patients reporting pain were not significantly different between the two groups (table 1). The percentage of patients with a clinically pure motor neuropathy (72% vs. 8%) and AMAN based on the available EMG data (16% vs. 2%) was higher in the GBS population from Curaçao comparable with an earlier study, suggesting a probable relationship with an increased percentage of preceding

gastroenteritis (6). Also in the present study, the percentage of preceding diarrhea was higher in the patients with GBS from Curaçao. Of the total group of 77 patients from Europe and Curaçao with a clinically pure motor neuropathy, 38 (49%) reported to have pain, which was mostly located in the extremities. Some of these patients even reported to have severe pain. Unfortunately, no specific scale has been used to further specify the precise intensity of pain. There was no clear relation between the presence of pain and the severity of disease. However, all patients studied, except 6 patients with GBS from Curaçao, had a severe variety of GBS with a maximum GBS disability score ≥3. Two out of these six mildly affected patients, all with a maximum GBS disability score of 2, reported pain. The pure motor GBS patients from Europe reported a higher percentage of pain compared to the pure motor GBS patients from Curaçao, which could probably be explained by the different way of collecting the data.

Table 1 | Characteristics of GBS patients from Europe and from Curaçao

	GBS patients form Europe (n=225)	**GBS patients from Curaçao** (n=83)
Sex distribution, n (%)		
■ Male	130 (58)	50 (60)
Age, median (90% intercentile range), y	55 (20-74)	44 (6-71)
Max GBS disability score, n (%)**		
■ ≥ 3 (able to walk 10 meters with a walker or support)	100 (100)*	70 (92)
Pain, n (%)**		
■ Admission / randomization	123 (55)	
■ In the first 2 weeks after admission		39 (47)
■ 4 weeks after randomization	109 (53)	
Diarrhoea, n (%)	60 (27)	40 (48)
Pure motor, n (%)		
Clinically	17 (8)	60 (72)
■ Pain (n)	12	26
■ Diarrhoea	9	30
EMG (AMAN)**	4 (2)	12 (16)
■ Pain (n)	2	8

Clinical pure motor = no sensory signs or symptoms, GBS = Guillain-Barré syndrome, EMG = Electromyogram, AIDP = Acute inflammatory demyelinating polyneuropathy, AMAN = Acute motor axonal neuropathy, * GBS disability score ≥3 was an inclusion criterion in the IVIg/MP study [9], ** data not available from all patients

We found that a high percentage of GBS patients with pure motor neuropathy reported pain. Although not all EMG data could be classified as AMAN or AIDP, due to missing or non-conclusive data, this study shows that pain during the initial phase of GBS seems not to be dependent on the presence of sensory symptoms or electrophysiological signs of

demyelination. Neuropathic pain is not expected to be relevant in pure motor GBS because this type of pain results from degeneration or regeneration of sensory nerve fibres, and these patients did not have clinical or electrophysiological signs or symptoms of sensory nerve involvement. Therefore, pain in the acute phase of pure motor GBS is likely to be of nociceptive origin, probably due to activation of the nervi nervorum by inflammation or inflammatory mediators, but this needs further exploration (9).

CONCLUSION

Pain can also accompany pure motor GBS. Recognition of pain is important because treatment can be offered. Further studies are necessary to give more detailed clinical information about the character and intensity of the pain in GBS subgroups.

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CHAPTER 4.3

PAIN IN GUILLAIN-BARRÉ SYNDROME: A LONG-TERM FOLLOW-UP STUDY

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Submitted for publication

ABSTRACT

Background: Pain in GBS may be pronounced and is often overlooked.

Objectives: To obtain detailed information about pain in GBS and its clinical variants.

Methods: Prospective cohort study in 156 patients with GBS (including 18 cases with MFS). Assessment of the location, type, and intensity of pain using questionnaires at standard time points during a one year follow-up. Pain data were compared to other clinical features and serology.

Results: Pain was reported in the two weeks preceding weakness in 36% of patients, 66% reported pain in the acute phase (first 3 weeks after inclusion) and 38% after one year. In the majority of patients the intensity of pain was moderate to severe. Longitudinal analysis showed high mean pain intensity scores during entire follow-up. Pain occurred in the whole spectrum of GBS. The mean pain intensity was predominantly high in GBS patients (non-MFS), patients with sensory disturbances and in severely affected patients. Only during later stages of disease, severity of weakness and disability were significantly correlated with intensity of pain.

Conclusions: Pain is a common and often severe symptom in the whole spectrum of GBS (including MFS, mildly affected and pure motor patients). As it frequently occurs as first symptom, but may even last for at least one year, also pain in GBS requires full attention. It is likely that sensory nerve fibre involvement results in more severe pain.

INTRODUCTION

Guillain-Barré syndrome (GBS) is an acute immune-mediated polyradiculoneuropathy comprising a broad spectrum of clinical variants (1). Pain is often overlooked because most attention is given to progression of weakness. Various types of pain have been described in GBS (2). The pathophysiology of pain is poorly understood. The reported frequency of pain in GBS is highly variable, and most studies determined pain only in the acute phase of GBS (table 1) (3-11). Two studies performed a longer follow-up and reported an increase of pain intensity in time, and one-third of patient may even have pain after two years (4,8). Previously we showed that the character of pain may change during the clinical course of GBS (10). Pain has also been reported in patients with the Miller Fisher syndrome (MFS), acute motor axonal neuropathy (AMAN) and even mild forms of GBS (12-14). Pain may therefore be a severe and chronic problem in a considerable proportion of GBS patients.

The frequency and nature of the pain in GBS, however, needs to be further defined. All studies conducted so far included only a relatively small number of cases with a limited set of clinical, electrophysiological and serological data. Moreover, neither the different types nor the different locations of pain were systematically analysed. Here we report a prospective study defining the character, location, and intensity of pain in GBS during a follow-up of one year. In addition, detailed information regarding the clinical, electrophysiological and serological phenotype was obtained to be able to relate the pain to the spectrum of GBS variants.

MATERIALS AND METHODS

Patients

170 patients fulfilling the diagnostic criteria for GBS were prospectively included in the GRAPH study (GBS Research about Pain and Heterogeneity) (15,16). Exclusion criteria were: age below twelve and significant co-morbidity with a worse prognosis (predicted survival less than 1 year). Patients with Bickerstaff encephalitis and patients who developed A-CIDP (acute onset chronic inflammatory demyelinating polyneuropathy) were also excluded.

Study design

Patients were included in the GRAPH study in 55 participating Dutch centres between February 2005 and October 2008. The protocol was approved by the ethics committee of the participating centres. Clinical data, biological materials and electrophysiological data were collected systematically during 1 year follow-up, after obtaining written informed consent.

Table 1 | Prospective and cross-sectional studies to pain in GBS

Ref.	n	Pain, n (%)	Phase of disease	Overview pain intensity	Overview different locations and types of pain	Mildly or severely affected patients	Pain related to other signs or symptoms
Prospective studies to pain in GBS							
(6)	29	7 (24)	Initial symptom	No	No	Severely	No
(9)	29	16 (55)	Acute phase	No	Yes	Severely	Yes (relation between pain and elevated creatine kinase (CK) level)
(11)	100	50 (50)	Admission	No	No	Both	No
(3)	60	2 (3)	Initial symptom	No	Back and limb pain	Both	No
(3)	60	10 (17)	Follow-up not subdivided	No	Neuralgic pain	Both	No
(5)	24	14 (58)	Acute phase	Yes	Back and leg pain	Both	Yes (relation between pain and nerve root enhancement)
(8)	55	49 (89)	Acute phase and follow-up of 24 weeks	Yes	Yes (admission and non subdivided period of 24 weeks)	Both	Yes (no relation between pain intensity and disability on admission and during follow-up)
(4)	42	30 (71)	Acute phase and follow-up of 2 years	No	No	Both	No
(10)	225	123 (55)	Acute phase	Yes *	No	Severely	No
(7)	95Δ	32 (34)	Acute phase and variable follow-up	Yes	Neuropathic pain	Both	Yes (relation between pain and disability scores acute phase)
Cross-sectional studies on pain several years after onset of GBS							
(37)	120	59 (48)	3-6 years after onset GBS	No	Muscle pain and cramp	Severely	Yes (muscle aches and cramps especially occur when there are residual sensory disturbances)
(36)	50	34 (69)	Median time of 10 years after GBS	No	No	Both	Yes (relation between fatigue, pain and residual weakness)

* based on use of pain medication (not validated pain scale), Δ only children

Questionnaires were filled in by the neurologist weekly during hospital stay and once after 6 months. The first three weeks after inclusion was determined as the acute phase, because all included patients had their nadir of weakness within 3 weeks after inclusion. When the patient was discharged from hospital, additionally questionnaires were filled in by the patient at 3, 6, 9 and 12 months after inclusion. If questionnaires or answers to some questions appeared to be lacking one week, our research coordinator phoned the patients and asked the patient to complete and return the questionnaires if possible. If the patient was not able to fill in the questionnaires, we asked relatives for help. Patients who have sent back their questionnaires where some answers were missing were not excluded from the analyses.

Questionnaires

Baseline characteristics and data about medical history were obtained. Medical history also included questions about the presence of chronic pain within 3 months before onset of GBS. If so, we asked for the type of pain and the daily use of analgesics. The first questionnaire also contained identical questions about pain in the two weeks period before onset of weakness and pain since the onset of weakness. In all subsequent questionnaires we asked about the presence of pain in the past week. Data about location ((low)back, interscapular, neck, extremities, trunk) and type of pain (radicular pain, painful par- and dysaesthesiae, joint pain, muscle pain, meningism and 'other' type of pain (2)) were also obtained. The reported pain had to be new or different from the pain felt in medical history. Intensity of pain was determined using an 11-point numerical rating scale (NRS), in which 0 represents no pain and 10 represents extreme pain (17). The character of pain was obtained based on the simplified version of the Dutch McGill Pain Questionnaire (18,19). The mean NRS of the severest pain in the past week was questioned. Additionally, pain intensity was classified into mild (NRS 0-4), moderate (NRS 5-7), and severe pain (NRS 8-10) (20,21). The use of daily analgesics was obtained and categorized based on the WHO's pain ladder in: none; paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs); opioids; anti-depressants or anti-convulsants.

Besides information about pain, neurological symptoms and signs, impairment scales (MRC sumscore -ranging from 0 'quadriplegic' to 60 'normal strength'(22)) and 'INCAT' sensory sumscore (23,24)) and disability scales (GBS disability score -ranging from 0 'no symptoms or signs' to 6 'dead'- (25) and overall disability sumscore (ODSS) -ranging from 0 'no signs of disability' to 12 'most severe disability score'- (24,26)), treatment and course of disease were obtained from the questionnaires filled in by neurologist during hospital stay and after 6 months. Regarding the INCAT sensory sumscore we used the pinprick sensation score and vibration sensation score without the 2-point discrimination score, because this score was often missing (23,24).

After hospital discharge, pain symptoms, Fatigue Severity Scale (FSS, ranging from 1 'no signs of fatigue' to 7 'most disabling fatigue') (27,28), disability scales (GBS disability score, ODSS) and course of disease were obtained from the questionnaires filled in by patient.

Clinical autonomic functions were obtained over the period of the last 7 days. Clinical autonomic dysfunction parameters were defined prior to study onset: hypertension (systolic >140 and/or diastolic >90 mmHg), hypotension (systolic <90 mmHg), tachycardia (heart rate >100 bpm), bradycardia (heart rate <60 bpm), gastrointestinal dysfunction (diarrhoea, constipation, or incontinence) and bladder dysfunction (urine retention or incontinence).

We defined patients as GBS (non-MFS) or MFS when they fulfilled the diagnostic criteria (15,16). The 'pure motor' variant was defined as having GBS without sensory deficits (normal pinprick and vibration sense). The GBS disability scale was used to indicate the severity of disease at nadir: mildly affected = able to walk unaided = GBS disability score ≤ 2; severely affected = unable to walk unaided = GBS disability score ≥ 3.

Preceding infections

Clinical manifestations of infections within three weeks of onset of weakness were classified as: influenza-, influenza-like illness or respiratory tract infection and gastro-enteritis or diarrhoea when these met the criteria of the Center of Disease Control (CDC) definitions for nosocomial infections (29). Baseline serum samples were tested to determine recent infection with *Campylobacter jejuni* as described (30).

Anti-ganglioside antibodies

Pre-treatment sera obtained after inclusion were tested for the presence of IgG and IgM antibodies against the gangliosides GM1, GM2, GD1a and GQ1b using ELISA as described (31,32).

Electromyographic studies

Electrophysiological investigations were scheduled within three weeks after inclusion. Investigations were executed according to local settings of the participating hospitals. Age and sex matched reference values were used (33). Electrophysiological investigations were classified as demyelinating, axonal, inexcitable, equivocal or normal (34).

Statistics

Percentages were compared between groups using the chi-square test or Fisher's exact test if appropriate. Longitudinal analysis of pain intensity scores, allowing for occasional missing data at some time points, was performed using repeated-measurement-analysis of variance in the total group and in subgroups using data from 2 weeks before onset

weakness, the acute phase (inclusion day, 1, 2 and 3 weeks after inclusion) and from the chronic phase (week 13, 26, 39, and 52 after inclusion). For the acute phase we used the weekly data from the questionnaires until 3 weeks, because all patients had their nadir within 3 weeks after inclusion and after 3 weeks many patients had been discharged from hospital resulting in too small number of patients. The population of patients was divided into different subgroups like GBS (non-MFS) or MFS and by age (using the median value as cut-off), sex, severity according to GBS disability scale (mildly or severely affected), sensory signs (ab)normal pinprick and vibration sense, being treated with intravenous immunoglobulin (IVIg) with or without methylprednisolone (MP), electrophysiological classification (demyelinating or axonal) and by different infections. When there was no significant difference in the profile of mean values of the pain intensity score during the whole follow-up between the subgroups, we calculated the mean difference with 95% CI between the subgroups from time before weakness till 52 weeks. Correlation between impairment (MRC sumscore, INCAT sensory sumscore), disability (GBS disability score, ODSS) and fatigue (FSS) versus pain intensity (NRS) was analysed using Spearman's Rank correlation test (r_s). For the relation between fatigue (FSS) and pain intensity (NRS), changes from the previous measurement were also evaluated using r_s. All calculations were performed using SPSS for Windows 2000 (version 15.0 SPSS, Chicago). A two-sided p-value < 0.05 was considered to be significant.

RESULTS

Patients

Between February 2005 and October 2008, 170 patients with GBS were enrolled in the GRAPH study. During follow-up some patients finally turned out to have another diagnosis (n=3), Bickerstaff encephalitis (n=2), an accompanying myelitis (n=1) or A-CIDP (n=8) (35). These 14 patients were excluded from the analysis. Of the remaining 156 patients (61% male), 138 (88%) fulfilled the diagnostic criteria for GBS (non-MFS) and 18 (12%) had MFS (15,16).

Patient characteristics

Baseline and clinical characteristics, electrophysiological classification, infections and results of laboratory tests in the acute phase are listed in table 2. All patients had their nadir of weakness within three weeks after inclusion, and within four weeks after onset of weakness. At nadir, 81% of the patients (83% of GBS (non-MFS) and 67% of MFS) were unable to walk independently (severely affected). After 6 months 11% of patients (12% of GBS (non-MFS) and 6% of MFS) were still unable to walk independently.

Table 2 | Baseline and clinical characteristics, electrophysiological classification, infections and anti-ganglioside antibodies in the acute phase in 156 patients

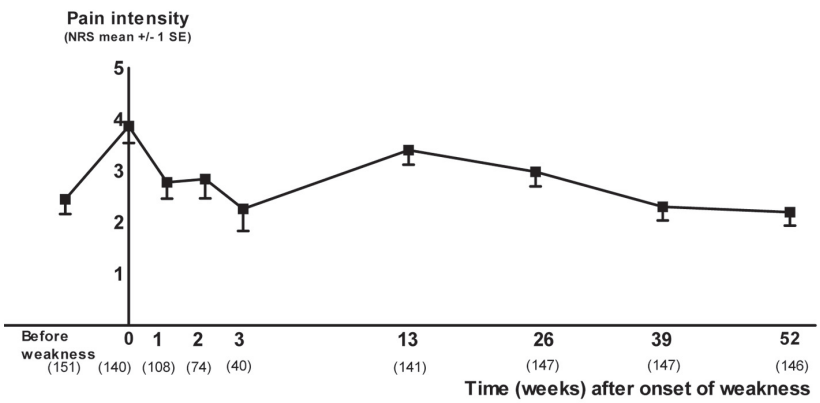
Baseline, n (%)	
■ Male	95 (61)
■ Age, median (IQR), y	50 (35 - 63)
■ GBS (non-MFS)	138 (88)
■ MFS	18 (12)
Acute phase,* n (%)	
■ Signs & symptoms, n (%)	
■ Cranial nerve involvement (n=153)	81 (53)
■ Sensory symptoms (n=152)	132 (87)
■ Sensory disturbances (n=150)	98 (65)
Severity at nadir, n (%)	
■ Severely affected (unable to walk unaided)	126 (81)
■ Respiratory support	28 (18)
Autonomic functions, n (%)	
■ Tachycardia	60 (38)
■ Bradycardia	14 (9)
■ Hypertension	107 (69)
■ Hypotension	17 (11)
■ Gastro-intestinal dysfunction	70 (45)
■ Bladder dysfunction	30 (19)
GBS medical treatment, n (%)	
■ IVIg only	91 (58)
■ IVIg + methylprednisolone	39 (25)
■ None	26 (17)
Electrophysiological classification (n=140), n (%)	
■ Demyelinating	65 (46)
■ Axonal	8 (6)
■ Equivocal	61 (44)
■ Inexcitable	2 (1)
■ Normal	4 (3)
Infections, n (%)	
■ Clinical gastro-enteritis / diarrhoea (n=153)	52 (34)
■ Clinical respiratory tract / influenza (-like) (n=152)	56 (37)
■ Positive C serology (n=148)	33 (22)
Anti-ganglioside antibodies (n=148), n (%)	
■ IgM reactivity against GM1, GM2, GD1a, GD1b or GQ1b	24 (16)
■ IgG reactivity against GM1, GM2, GD1a, GD1b or GQ1b	44 (30)

Given percentages are based on number of patients with returned, filled in questionnaires, serum or electrophysiological data. When the number of patients differs from 156, it is indicated between brackets, GBS=Guillain-Barré syndrome, MFS=Miller Fisher syndrome, Sensory disturbances=abnormal vibration sense / pinprick, Severely affected = Unable to walk unaided = GBS disability scale ≥ 3, IVIg=Intravenous immunoglobulin, * = First 3 weeks after inclusion

Pain

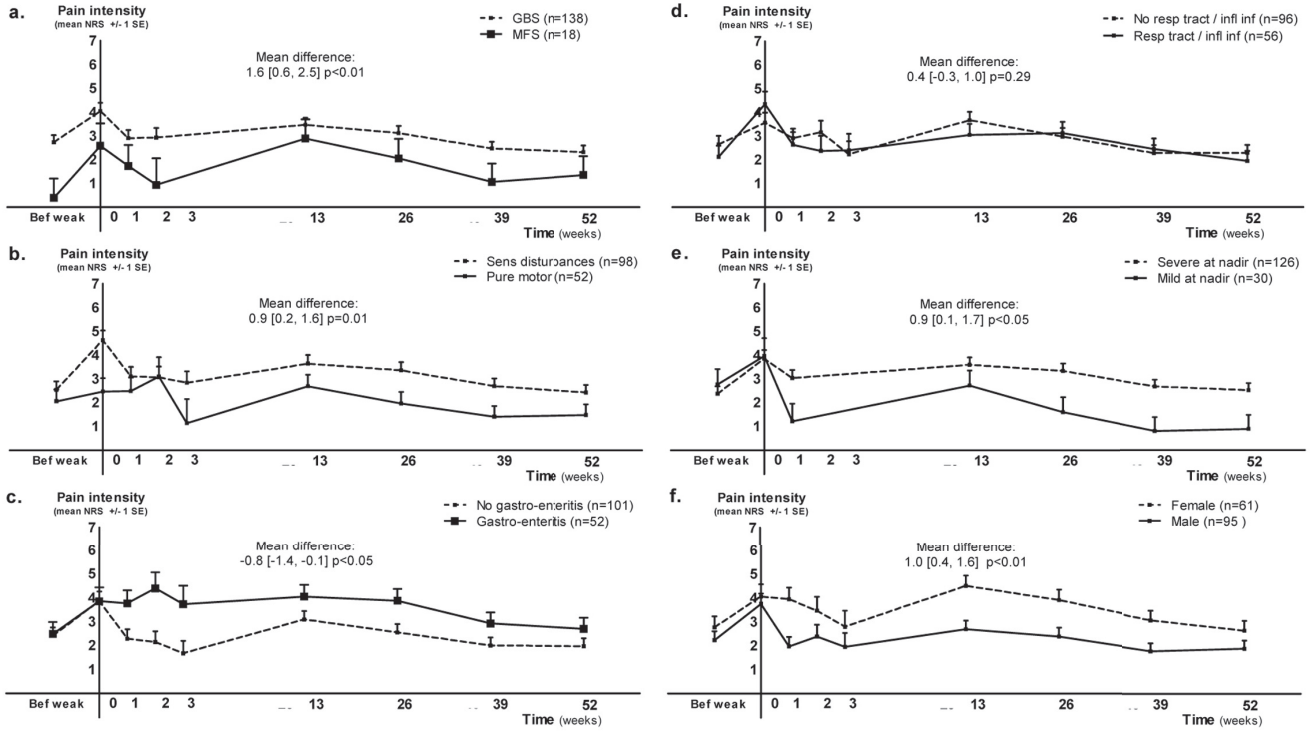
Prevalence, location, type and intensity of pain in the acute phase and during follow-up are listed in table 3. 22% of patients had chronic pain in medical history (mostly joint and backache, both 35%; nearly half of them (47%) used daily analgesics). 66% of patients (69% of GBS (non-MFS) and 44% of MFS; p<0.05) had pain in the acute phase. After the acute phase, the prevalence of pain between GBS (non-MFS) and MFS was not significantly different. 36% of patients already had pain in the two weeks before the onset of weakness (40% of GBS (non-MFS) and 6% of MFS; p<0.01; median 5 days, IQR 1 – 13). The prevalence of pain during the entire follow-up was significantly higher in patients with sensory disturbances compared to patients with the clinical pure motor form (t=0: 62% versus 43%; t=6months: 56% versus 34%; p<0.05). In the first six months the prevalence of pain in mildly and severely affected patients was comparable; hereafter the prevalence of pain was significantly higher in the severely affected patients (t=39 weeks: 45% versus 17%, p<0.01; t=52 weeks: 42% versus 21%, p=<0.05). For the entire group, the prevalence of patients with pain after 3, 6 and 9 months was significantly higher in patients with pain in the acute phase compared to patients without pain in the acute phase (p<0.05). There was no significant difference in the prevalence of pain during the whole follow-up between the patients with or without chronic pain in medical history. From the patients having pain in the acute phase, 86% reported a moderate to severe pain despite using analgesics. Mean pain intensity is shown in figure 1.

Figure 1 | Mean pain intensity over time for the entire group of GBS patients (n=156)



Legend: Data shown are means (+/-SE) from ANOVA. The means are based on number of patients (indicated between brackets) with returned questionnaires and filled in NRS (numerical rating scale) score. Before weakness = maximum of 2 weeks before onset of weakness

Figure 2 | Mean pain intensity over time in GBS subgroups



Legend: Data shown are means (+/-SE) from ANOVA. Mean differences (dotted minus solid line) in pain intensity (NRS) with 95% CI and p-value; from time before onset of weakness to 52 weeks after onset of weakness between the different groups are indicated; a. GBS (non-MFS) (n= 138) & MFS (n=18); b. Weakness and sensory disturbances (n= 98) & pure motor (n=52) (n=6 unknown). Same analysis without MFS: mean difference in pain intensity = 0.9 [0.2, 1.7] p<0.05; c. Gastro-enteritis or diarrhoea (n=52) & no gastro-enteritis or diarrhoea (n=101) (n=3 unknown). Same analysis without MFS: mean difference in pain intensity = -0.8 [-1.4, -0.1] p<0.05; d. Respiratory tract or influenza (-like) infection (n=56) & no respiratory tract or influenza (-like) infection (n=96) (n=4 unknown). Same analysis without MFS: mean difference in pain intensity =0.4 [-0.3, 1.1] p=0.23; e. Severely affected at nadir (n=126) & Mildly affected at nadir (n=30). Same analysis without MFS: mean difference in pain intensity =1.1 [0.2, 1.9] p=<0.05; f. Female (n=61) & Male (n=95). Same analysis without MFS: mean difference in pain intensity =0.9 [0.3, 1.6] p=<0.01.

Table 3 | Presence, location, severity and interpretation of pain in GBS (n=156) and the use of daily (co-)analgesics

	Max 2 wks before onset of weakness	Acute phase*	13 wks	26 wks	39 wks	52 wks
Pain, n/N (%)	54/151(36)	100/152 (66)	84/148 (57)	74/150 (49)	58/148 (39)	55/146 (38)
Location(s) of pain, n/n with pain (%)						
■ (Low)back	19/54 (35)	50/100 (50)	26/84 (31)	31/74 (42)	22/58 (38)	20/55 (36)
■ Interscapular	15/54 (28)	34/100 (34)	24/84 (29)	18/74 (24)	18/58 (31)	18/55 (33)
■ Extremities	38/54 (70)	76/100 (76)	68/84 (81)	65/74 (88)	48/58 (83)	45/55 (82)
■ Neck	15/54 (28)	34/100 (34)	24/84 (29)	21/74 (28)	16/58 (28)	16/55 (29)
■ Trunk	6/54 (11)	12/100 (12)	14/84 (17)	9/74 (12)	10/58 (17)	10/55 (18)
Severity of pain, n/n with pain (%)						
■ NRS 1-4	8/54 (15)	9/100 (9)	19/84 (23)	17/74 (23)	17/58 (29)	16/55 (29)
■ NRS 5-7	25/54 (46)	36/100 (36)	30/84 (36)	28/74 (38)	22/58 (38)	20/55 (36)
■ NRS 8-10	21/54 (39)	50/100 (50)	28/84 (33)	26/74 (35)	18/58 (31)	19/55 (35)
■ Unknown	0	5/100 (5)	7/84 (8)	3/74 (4)	1/58 (2)	0
Interpreation(s) of pain, n/n with pain (%)						
■ Radicular pain	12/54 (22)	31/100 (31)	n.e.	5/74 (7)	n.e.	n.e.
■ Meningism	1/54 (3)	4/100 (4)	n.e.	0	n.e.	n.e.
■ Painful par/dysaesthesiae	16/54 (30)	43/100 (43)	n.e.	23/74 (31)	n.e.	n.e.
■ Muscle pain	28/54 (52)	62/100 (62)	n.e.	32/74 (43)	n.e.	n.e.
■ Arthralgia	3/54 (6)	14/100 (14)	n.e.	16/74 (22)	n.e.	n.e.
■ Unknown	4/54 (7)	7/100 (7)	n.e.	16/74 (22)	n.e.	n.e.
Use of daily (co-)analgesics, n/n with pain (%)						
■ Non-opiods (PCM, NSAID)	20/54 (37)	70/100 (70)	30/84 (36)	25/74 (34)	21/58 (36)	13/55 (24)
■ Opioids (mild – strong)	5/54 (9)	39/100 (39)	13/84 (15)	11/74 (15)	7/58 (12)	4/55 (7)
■ Amitriptyline / ant-epileptic drugs	1/54 (2)	24/100 (24)	18/84 (21)	16/74 (22)	10/58 (17)	7/55 (13)
■ None	33/54 (61)	25/100 (25)	48/84 (57)	41/74 (55)	31/58 (53)	39/55 (71)

The percentages for the location, severity, interpretation and analgesic use are for those GBS patients who had pain at that time-point (n/n with pain). The interpretation about the nature of the pain is only filled in by the neurologist. NRS = numerical rating scale, PCM = paracetamol, NSAID = non-steroidal anti-inflammatory drugs, Before weakness = maximum of two weeks before onset weakness, * = First 3 weeks after inclusion, n.e. = not evaluated

In the acute phase and during the entire period of follow-up, pain was most frequently present in the extremities. (Low-)back pain was notably present in the acute phase. Often, the patient indicated different types of pain at more than one location and the neurologist often indicated more than one interpretation (from the patients having pain, 61% reported pain at more than one location in the acute phase and 51% after 6 months; 53% had more than one interpretation for the pain in the acute phase and 31% after 6 months).

The mean pain intensity was higher in the acute and follow-up phase in females and GBS (non-MFS) patients, in patients with sensory disturbances, preceding gastro-enteritis or diarrhoea and in severely affected patients (figure 2). No association was found between pain intensity and age, additional treatment with MP, the presence of anti-gangliosides and demyelinating versus axonal GBS. When we excluded the MFS patients to evaluate differences in the mean pain intensity between subgroups, the results were comparable (see legend figure 2). Patients without pain before onset of weakness and patients without pain in the acute phase (n=43) had a lower mean pain intensity in the beginning of the follow-up (week 13: mean difference -1.4 [-2.6, -0.2] $p<0.05$; week 26: mean difference -1.3 [-2.6, -0.1] $p<0.05$) compared to patients with pain during that period. This significant difference disappeared after 26 weeks.

The correlation between disability, impairment and fatigue versus pain intensity is listed in table 4. Summarized, pain intensity is associated with level of weakness, functional disability and fatigue, not in the acute but during later stages of GBS. Sensory involvement is associated with the intensity of pain during the acute and later stage of GBS.

DISCUSSION

This is the first large prospective follow-up study on the different aspects of pain in GBS in relation to the spectrum of GBS. As shown in this study, pain appeared to be a very common symptom in the acute phase and during the later stage of GBS and it also occurs in the whole spectrum of GBS variants, like MFS, pure motor and mildly affected patients. By far the most frequent location of pain during the entire follow-up was in the extremities, followed by (low)-back pain and often more than one location was indicated. In MFS patients, neck pain occurred most frequent in the acute phase and also headache was regularly reported as 'other' type of pain, which is also described in another study (13). This indicates that pain in GBS may affect various parts of the body. And comparing GBS (non-MFS) with MFS, the distribution of weakness seems to contribute to the distribution of pain.

Despite the use of analgesics, nearly half of the patients with pain reported moderate and one third even severe pain. This emphasizes the magnitude of the clinical problem of

pain in GBS. In a study in 55 GBS patients, a similar mean pain intensity was found in the acute phase, but a lower mean pain intensity was found in the period until 24 weeks (8).

Table 4 | Correlations between impairment, disability, and fatigue versus pain intensity.

	t=0	Week 13	Week 26	Week 39	Week 52
Impairment					
■ Muscle strength (MRCsumscore)	-0.06 (n=131)	n.e.	-0.25** (n=136)	n.e.	n.e.
■ Sensory involvement	0.28* (n=128)	n.e.	0.41*** (n=125)	n.e.	n.e.
Disability					
■ Disability (GBS disability score)	0.00 (n=138)	0.40 *** (n=141)	045*** (n=147)	0.51*** (n=146)	0.43*** (n=146)
■ Disability score (ODSS score)	-0.04 (n=135)	0.55 *** (n=140)	0.51*** (n=147)	0.54*** (n=147)	0.46*** (n=143)
Fatigue (FSS score)	n.e.	0.43*** (n=137)	0.52*** (n=142)	0.51*** (n=144)	0.37*** (n=145)

Data given are spearmen correlation coefficients (r_s) between disability, impairment and fatigue on one hand versus pain intensity (NRS score) on the other hand for the entire group. For the relation between fatigue and pain intensity, changes from the previous measurement were also evaluated (week 13-26: r_s=0.14; week 26-39: r_s =0.30***; week 39-52: r_s =0.23**). ***p<0.001; **p<0.01; *p<0.05; n.e.= not evaluated

We have asked for the presence of pain within three months before onset of weakness retrospectively, therefore recall bias may have affected this part of the results of our study. In the questionnaires, we emphasized that the reported pain during GBS had to be new or different from the pain felt in medical history. We have to mention however that it can be difficult for patients to differentiate between pre-existent and new pain.

To identify factors that are associated with pain, we related pain to clinical features. As shown in this study, pain intensity is associated with level of weakness, functional disability and fatigue, not in the acute but during later stages of GBS. Whether pain causes part of disability or disability contributes to pain cannot be concluded from our study. In another follow-up study, no significant correlation between disability and pain intensity was found (8). However several years after GBS, an interaction between fatigue, pain, and muscle weakness has been described (36). In this study, they found a higher risk of pain and muscle weakness in individuals with pronounced fatigue. Both symptoms may influence each other and need to be registered. Depression or anxiety may also influence pain in GBS. Depression or anxiety was not specifically assessed in our study and needs further attention in forthcoming studies. Our results indicate that involvement of sensory nerves does play a role in the occurrence and intensity of pain during the acute and later

stage of GBS. It has been described that years after GBS muscle aches and cramps occur especially in patients with residual sensory disturbances (37). It was remarkable that in our study patients with previous diarrhoea had a significantly higher mean pain intensity score compared to patients without diarrhoea. The fact that in this study the number of pure motor patients or severely affected patients was not significantly different in the group with and without diarrhoea does not explain the difference. Possibly different immunological factors generated by an infection may play a role in pain.

The pathophysiology of pain in GBS is largely unknown and this study indicates the complexicity of studying pain in GBS. Affected nerve roots may explain the occurrence of radicular nociceptive nerve pain affecting (low-) back with radiation to extremities or trunk (5). Inflammatory factors generating pain via the nervi nervorum may also play a role in the pathophysiology of pain, but has not been studied yet. In our study, the prevalence of back pain was higher than the prevalence of radicular pain, indicating that other types of pain like muscle pain or arthralgia possibly due to immobilisation may also contribute to back pain in GBS. Neuropathic pain due to spontaneous or abnormal activity from large myelinated sensory afferents may explain the occurrence of painful paraesthesias and dysaesthesias in the extremities. However, considering the high prevalence of pain in the extremities also other types of pain may play a role. Small nerve fibres can also be affected in GBS (38). Affected small nerve fibres in GBS may play a role in pain and autonomic dysfunction and needs additional studies.

Nevertheless, two different combinations of pain symptoms may be distinguished. One combination starts before onset of weakness until hospital discharge, is mostly located in the extremities and contains especially radicular pain, painful paraesthesiae and muscle pain; the other combination is predominantly present after hospital discharge during rehabilitation, is also mostly located in the extremities and contains especially painful paraesthesiae, muscle pain and arthralgia. The intensity of pain is severe during the course of disease, but is most severe in the acute phase. Pain symptoms are associated with sensory disturbances and severe pain symptoms later in the stage of disease are associated with a higher level of weakness and disability. Patients suffering from acute pain symptoms have a higher change on the occurrence of the pain symptoms in the later stage. In case reports, the analgesic effect of corticosteroids for lumbar and leg pain has been described (39,40). In this study there appeared to be no difference in pain between patients treated with MP or not, which is in line with a previous study on the additional effect of MP in GBS (10).

In conclusion, pain is very common and severe in the whole spectrum of GBS during the acute and later stages of disease. Therefore it requires full attention. Sensory nerve fibre involvement is associated with severe pain, but this seems no prerequisite, because patients with pure motor symptoms may also have pain. It is important to realize that only

in the later stage of disease the intensity of pain is related to the extent of weakness and disability.

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GBS

CHAPTER 5

GBS AND SMALL FIBRE NEUROPATHY

Guillain-Barré syndrome: a correlation study of skin biopsy and clinical features

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Submitted for publication

ABSTRACT

Objective: To correlate skin biopsy findings, clinical features, and outcome in patients with Guillain-Barré (GBS) and its variants.

Methods: A cohort of patients included into the 'GBS Research about Pain and Heterogeneity' Study underwent skin biopsy at distal leg and lumbar site, pain, and autonomic assessment. Data were collected in the acute phase and at 6-month follow-up. Intraepidermal nerve fibre density (IENFD) was compared to age and gender-matched healthy subjects and normative reference values. Quality and intensity of pain were evaluated using a questionnaire and the 11-point numerical rating scale. Severity of GBS and outcome were assessed using the GBS disability scale.

Results: Prospective data were available from 32 patients. IENFD declined in the first three weeks from onset (rs -0.389; p=0.027) and was lower at distal leg (median 3.9, IQR 2.4-6.3; p=0.004) and lumbar site (median 10.5, IQR 7.4-16.1; p=0.004) compared to controls (distal leg: median 5.6, IQR 4.9-7.2; lumbar site: median 15.2, IQR 12.0-19.5) and normative values. Distal leg IENFD correlated with pain (p=0.003) and NRS score (p=0.003), but did not predict pain at 6 months. Worse outcome at 6 months correlated with lower lumbar IENFD (p=0.04), GBS score at nadir (p=0.03), and clinically probable dysautonomia (p=0.004). At 6 months, patients had significantly lower IENFD at both sites.

Interpretation: Small nerve fibres are affected in GBS patients since the early phase of disease. Their loss in the first three weeks from onset is associated with the severity of pain and autonomic dysfunction, and may predict long term disability.

INTRODUCTION

Guillain-Barré syndrome (GBS) is an acute immune-mediated disorder of the peripheral nervous system. Its clinical spectrum in the acute phase as well as its outcome is highly variable. GBS mainly affects large diameter fibres carrying motor functions, vibratory, and touch sensation. Their dysfunction reflect the main clinical features, namely rapidly progressive weakness of the limbs, with or without involvement of respiratory or cranial nerve innervated muscles and sensory disturbances (1,2).

Dysautonomia occurs in approximately two-third of GBS patients (3) and can lead to life threatening dysfunctions (4). Dysautonomia has been described also in Miller-Fisher syndrome (MFS), the cranial nerve variant of GBS (5,6).

Pain symptoms have been described in up to 89% of patients with GBS and MFS (7-13). Pain intensity can be very severe, particularly in the acute phase of the disease. We recently observed that 49% of patients with acute motor axonal neuropathy (AMAN) also complain of pain (14). The pathophysiological processes causing and maintaining pain in GBS patients are uncertain and probably more complex than in chronic painful neuropathies. Damage to small nerve fibres has been suggested to play a role (15).

Skin biopsy is an accepted tool to investigate small nerve fibres (16,17). Intraepidermal nerve fibres (IENF) are unmyelinated axons with functions of thermal and nociceptive transducers (18). Their density is a measure of axonal degeneration in painful and non-painful neuropathies (14,15,19-28). Studies in peripheral neuropathies of different etiology suggested that reduced intraepidermal nerve fibre density (IENFD) increases the risk to develop neuropathic pain (29) , whereas its recovery corresponds to decreased pain intensity (30-33).

The only previous study in GBS, based on a cross-sectional design, reported a inverse correlation between IENFD, dysautonomia, and poor outcome. The observation that IENFD may be used as a predictive biomarker in GBS needed to be confirmed by a prospective study. We addressed this issue through a prospective, multiple location study designed to investigate the relationship between IENF loss, dysautonomia, pain, and poor outcome in patients with GBS and its variants, with the aim to identify subgroups of patients at higher risk to develop these complications.

MATERIALS AND METHODS

Patients

Between February 2005 and October 2008, 170 patients diagnosed with GBS or MFS and admitted to one of the participating Dutch centers were evaluated for inclusion into the

GRAPH study (GBS Research about Pain and Heterogeneity). Data were systematically collected over a 6-month follow-up after written informed consent was obtained. Only patients admitted to one of the hospitals in the region of Rotterdam were considered for undergoing skin biopsies. Exclusion criteria for skin biopsy study were age below 18 years, previous diagnosis of neuropathy, diabetes mellitus, or other conditions at risk for neuropathy. Patients included in the skin biopsy study and admitted to the Erasmus MC underwent also autonomic cardiovascular evaluation. The protocol was approved by the Ethic Committee of every participating centre.

GBS was diagnosed according to published criteria (1). During follow-up, some patients initially diagnosed with GBS eventually turned to have relapsing and remitting course and were defined as acute onset chronic inflammatory polyneuropathy (A-CIDP) (34). MFS was defined according to diagnostic criteria (35). Patients were diagnosed with the pure motor variant when they had weakness without sensory symptoms and signs (normal light touch, pinprick, and vibratory sensation).

Timing of assessments

The first 3 weeks after inclusion were considered the acute phase (as all patients had reached their maximal weakness). During this period, we obtained the skin biopsies and assessed pain, autonomic functions, and severity of GBS.

The visit at 6-month follow-up was considered as the chronic phase. At that time we obtained skin biopsies, and assessed pain and residual disability.

Severity and disability assessment

The GBS disability scale score (range 0 ‘no symptoms or signs’ to 6 ‘dead’) (36) was obtained weekly during the acute phase and at 6-month follow-up to indicate the severity of disease and the outcome. Score was dichotomized as follows: mildly affected = able to walk unaided = GBS score ≤ 2; severely affected = unable to walk unaided = GBS score ≥ 3.

Pain assessment

Pain was assessed using a questionnaire that included questions about type(s) of pain (options to mark: radicular pain, paraesthesiae, dysaesthesiae, joint pain, muscle pain, meningism, and other pain) and site of pain (options to mark: back, lowback, interscapular, neck, extremities, and trunk) (10).

All patients were asked to report on the presence of pain in the past week after inclusion. It was emphasized that it had to be a newly developed pain. Patients complaining of muscle or joint pain alone were excluded. The intensity of pain was assessed using the 11-point numerical rating scale (NRS), with 0 representing no pain and 10 the worst pain (37). Patients were asked to report weekly the mean NRS score in the last 7 days. The

intensity of pain in the acute phase was defined as the highest mean NRS score reported in the first 3 weeks after inclusion.

Skin biopsies

Skin biopsies were taken using a 3-mm disposable punch, after local anesthesia with 2% lidocaine under sterile technique, from the distal leg (10 cm above the lateral malleolus) and lumbar site (3 cm besides the third/fourth lumbar vertebra) in the acute phase and at 6-month visit. Follow-up biopsies were performed close to the scars of the former ones. For comparison, distal leg (n=24) and lumbar site (n=23; 1 lost) skin biopsies from age and gender-matched healthy subjects were performed after obtaining written informed consent.

All biopsies were fixed for 24 hours at 4°C, cryoprotected, coded, and shipped to the Skin Biopsy Laboratory at the 'Carlo Besta' Neurological Institute of Milan to be processed. Skin biopsy examiners (R.L., F.C., G.L.) received only the coded specimens and were blinded to subject condition (diseased or healthy subjects) and site of biopsy. Three sections randomly chosen from each biopsy were immunoassayed with polyclonal anti-PGP 9.5 antibodies (Biogenesis Ltd, Poole, UK; 1:1000) using the free-floating protocol for bright-field immunohistochemistry previously described (38). The linear density of IENF (IENFD=IENF/mm) was calculated following the rules reported by the guidelines of the European Federation of the Neurological Societies (39).

IENFD values at distal leg in patients were compared with healthy controls recruited in the present study and with available age and gender stratified normative reference values (40). Similar normative reference values are not available for the lumbar site, therefore we sampled age and gender stratified skin biopsies from normal individuals at this site.

Autonomic functions assessment

Clinical autonomic functions were assessed weekly in the acute period and defined as follows: hypertension (systolic >140 and/or diastolic >90 mmHg), hypotension (systolic <90 mmHg), tachycardia (>100 bpm), bradycardia (<60 bpm), gastrointestinal dysfunction, bladder dysfunction or other symptoms of autonomic dysfunction (e.g., excessive sweating, Horner's syndrome, pupil dilatation). Clinical autonomic dysfunction was considered 'definite' in the presence of at least three abnormal parameters, and 'probable' when two abnormal parameters were scored in at least two of the weekly questionnaires.

Autonomic cardiovascular measurement

Spectral analysis of heart rate (HR) and blood pressure (BP) variability (41-44) was applied the same day of skin biopsy. HR variability in the high frequency band (HF: 0.15-0.50 Hz) is related to respiratory variations (respiratory sinus arrhythmia) and reflects vagal

(parasympathetic) modulation. BP variability in the low frequency band (LF: 0.07-0.14 Hz) reflects alterations in peripheral vasomotor tone related to baroreflex-mediated and predominantly sympathetic control. The interbeat interval (IBI) time series (transfer function between LF-systolic BP [SBP] and LF-R-R interval), is a measure of baroreflex sensitivity (BRS) (45).

Electrocardiogram (ECG), BP (2300 Finapres TM blood pressure monitor; Ohmeda, Englewood CO, USA), and respiration were continuously recorded during a 10-minute period of supine rest. R-R intervals were transposed to HR series and SBP and DBP were defined per R-R interval of ECG. Periods of stationary signals with a length of 5 minutes were selected from the 10 minute recording period and corrected for technical and physiological artefacts in the HR, SBP, DBP and respiration time series.

Fourier transformation was applied to 5-minute HR and BP time series segments (46), to yield power spectra of the oscillations over a frequency range of 0.02 to 0.50 Hz. Spectral power data were transformed into natural logarithmic values to obtain normal distribution. The BRS index (gain in the LF band between SBP and IBI time series) was computed based on frequency points within the frequency range with a coherence ≥ 0.35 (47).Twenty-five age and gender-matched healthy subjects were recorded.

Statistics

Normality was examined using Shapiro-Wilk test. Patients and controls were compared using unpaired t-tests or χ^2 tests. Fisher exact test or the Mann-Whitney U test was used when appropriate. IENFD was compared within the same patient using the paired t-test. Data were expressed as mean±SD or median and interquantile range (IQR). The correlation between GBS disability score at 6 months, IENFD, presence and intensity of pain, GBS disability score at onset, and clinical dysautonomia was analysed using the Spearman's Rank correlation test. IENFD in acute and chronic phase, and autonomic measurements were analysed using the Pearson correlation test. Analysis of variance (ANOVA) and linear multiple regression analysis were used to assess the predictive value of variables. Analyses were performed using the SPSS for Windows 2000 (version 15.0 SPSS, Chicago). P values <0.05 were considered significant.

RESULTS

Patients

Between February 2005 and October 2008, 138 patients with GBS, 18 patients with MFS, and 8 patients with A-CIDP (n=8) were enrolled in the GRAPH study. The skin biopsy study involved patients admitted to the hospitals in the region of Rotterdam. Three patients

younger than 18 years and 4 patients with significant comorbidity were excluded. Nine patients did not give their consent to the study. One patient died one month after inclusion due to severe sepsis. Eventually, 32 patients (26 GBS and 6 MFS) were included, along with 3 patients later diagnosed with A-CIDP (all males, mean age 62 years). Their clinical features are presented in table 1.

Table 1 | Baseline characteristics, signs, symptoms and severity during the acute phase and after 6 months in GBS (non-MFS) and MFS patients included in the skin biopsy study

	GBS (non-MFS) n=26	**MFS** n=6
Age at onset, mean, (SD), y	52 (15)	54 (17)
Male, n (%)	14 (54)	5 (83)
Cranial nerve dysfunction, n (%)	10 (39)	6 (100)
Pure motor, n (%)	7 (27)	3 (50)
Neuropathic pain, n (%)		
■ Acute phase	13 (50)	1(17)
■ After 6 months	6 (23)	0 (0)
Autonomic function acute phase, n (%)		
■ Tachycardia	16 (62)	3 (50)
■ Bradycardia	2 (8)	1 (17)
■ Hypertension	19 (73)	6 (100)
■ Hypotension	4 (15)	1 (17)
■ Gastro-intestinal dysfunction	13 (50)	3 (50)
■ Bladder dysfunction	3 (12)	1 (17)
■ Other	2 (8)	1 (17)
Definite clinical dysautonomia	7 (27)	1 (17)
Probable clinical dysautonomia	12 (46)	2 (33)
Severity, n (%)		
■ Mild at nadir (able to walk independently)	5 (19)	2 (33)
■ Need for artificial respiration	9 (35)	1 (17)
■ Worse outcome after 6 months (unable to walk independently)	4 (15)	1 (17)

In the acute phase, skin biopsies were obtained within one week from onset in 44% of patients, within two weeks in 34% of patients, and within 3 weeks in 22% of patients. Two patients had only distal skin biopsies. Five patients were not available for 6-month follow-up biopsies.

Autonomic cardiovascular measurement was performed in 19 patients (13 GBS, 5 MFS, and 1 A-CIDP). Eight patients were excluded from the analyses (2 patients for unreliable BP recording, 3 patients for arrhythmia, and 3 patients because SBP-IBI time series was <0.35).

Skin biopsy findings

In the acute phase, IENFD at distal leg significantly declined over the first three weeks from onset (rs -0.389; p=0.027), whereas there was no correlation between timing of the biopsy and IENFD at lumbar site. Compared to normative reference values stratified per age decade and gender (40), IENFD in the acute phase was reduced in 15 (40.6%) patients (13 GBS, 2 MFS) at distal leg and in 22 (73.3%) patients (18 GBS, 4 MFS) at lumbar site. Compared to controls recruited in the study (distal leg: median 5.6, IQR 4.9-7.2; lumbar site: median 15.2, IQR 12.0-19.5) IENFD was significantly lower both at distal leg (median 3.9, IQR 2.4 -6.3; p=0.004) and lumbar site (median 10.5, IQR 7.4-16.1; p=0.004) (figure 1 and table 2). Notably, 3 of 7 patients with the pure motor form of GBS had lower IENFD values at the distal leg compared both to controls and stratified normative value (40) whereas 5 of them had reduced values at the lumbar site.

At 6-month follow-up, IENFD remained significantly lower both at distal leg (median 4.3, IQR 3.2-6.7; p 0.024) and lumbar site (median 10.4, IQR 8.7-15.7; p=0.005) compared to controls (figure 1 and table 2). Nine of 15 (60%) patients with reduced distal leg IENFD and 13 of 21 (61.9%) patients with reduced lumbar IENFD in the acute phase showed values lower than stratified normative values (40) at 6-month follow-up (table 2).

Patients with A-CIDP showed significantly lower IENFD at distal leg in the acute (median 3.3; p=0.021) and chronic phase (median 2.5; p=0.005), whereas we did not find significant differences at the lumbar site (figure 1).

Correlation between skin biopsy, neuropathic pain, autonomic dysfunction, severity and outcome

Neuropathic pain

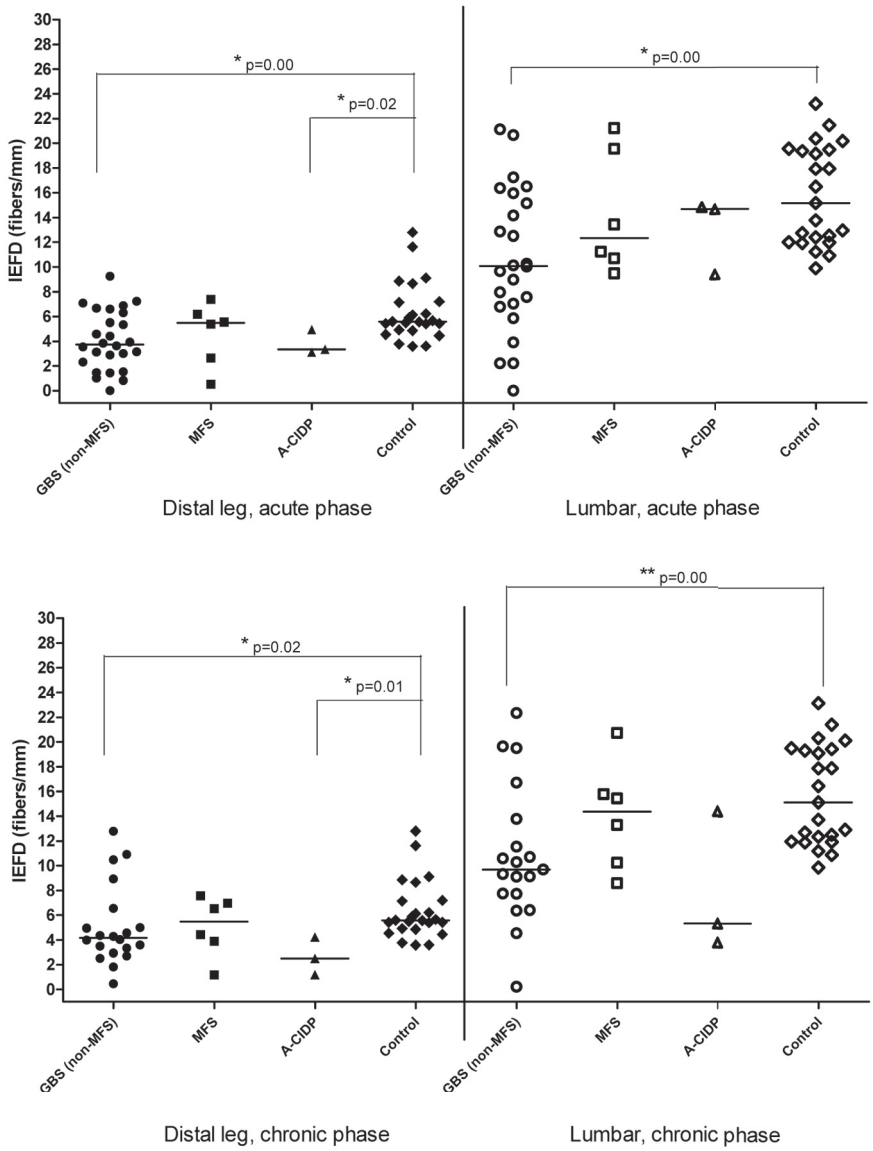
In the acute phase, patients with neuropathic pain showed a significantly lower distal leg IENFD than those without neuropathic pain (median 2.8, IQR 1.5-3.8 versus median 5.5, IQR 3.7-6.9; p<0.001). Moreover, distal leg IENFD was inversely correlated with pain intensity (rs -0.506; p=0.003), whereas IENFD at lumbar site did not. Distal leg and lumbar site IENFD in the acute phase did not predict either occurrence or intensity of pain at 6 months.

Autonomic dysfunction

Definite clinical dysautonomia was present in 8 GBS (25%) and 1 MFS (16%) patients, and probable dysautonomia in 14 GBS (44%) and 2 MFS (33%) patients (table 2). IENFD at any site was not related with clinically definite or probable autonomic dysfunction at onset and 6-month follow-up. However, GBS patients showed significantly higher mean levels of HR, SBP, and lower levels of LFHR power and BRS index compared to controls (table 3).

There was a positive correlation between distal leg IENFD in the acute phase and HFHR (r=0.52; p<0.05) and with BRS (r=0.61; p<0.05).

Figure 1 | Distal leg and lumbar site IENFD of GBS (non-MFS), MFS and A-CIDP patients in the acute and chronic (6-month follow-up) phase compared to healthy controls



Legend: Bars are median values. Differences were tested with the Mann-Whitney U test. P-values <0.05 are shown.

Table 2 | IENFD in the acute phase and at 6 months follow-up, and correlation with time of biopsy, pain, dysautonomia, and severity of disease.

Diagnosis	Age at first skin biopsy	Sex	Skin biopsy (IENFD)					Pain				Dysautonomia		Severity		Pure motor
			Acute phase			After 6 months		Acute phase		After 6 months		Acute phase		Nadir	After 6 months	
			Weeks from onset	Distal leg	Lumbar site	Distal leg	Lumbar site	Presence	Intensity (NRS)	Presence	Intensity (NRS)	Definite	Probable	GBS disability score	GBS disability score	
GBS																
1	65	F	3	**0.0**	**8.0**	†	†	+	8	†		+	+	5	6	
2	38	F	2	**0.8**	21.1	8.9	19.6	+	4		0			2	0	
3	71	M	2	**1.0**	**3.9**	n.e.	n.e.		0		0	+	+	5	1	
4	39	M	2	**1.4**	**9.7**	**2.7**	**6.4**	+	4		0			1	0	+
5	39	F	3	**1.5**	**10.3**	**3.5**	**11.5**	+	6		0			4	2	+
6	50	M	2	**1.5**	n.e.	**1.8**	n.e.	+	8		0			4	0	
7	53	F	2	**2.3**	16.5	5.0	**4.5**	+	9		0	+	+	5	0	
8	52	F	3	**2.9**	**6.8**	**4.3**	**7.8**		0	+	1			3	1	
9	69	M	2	**3.0**	**15.2**	3.6	**9.3**	+	8		0		+	5	2	
10	44	M	2	**3.1**	n.e.	**3.3**	n.e.		0	+	4		+	5	2	
11	57	F	1	**3.1**	**10.0**	4.9	**9.7**	+	8		0			4	0	+
12	56	M	1	**3.5**	**7.1**	**0.4**	**6.4**	+	6		0	+	+	5	5	
13	74	M	2	3.6	**10.1**	2.5	**10.7**	+	4	+	8	+	+	4	3	
14	56	M	3	3.8	**12.5**	4.4	16.7		0		0			4	2	
15	60	M	2	3.9	**0.0**	4.0	**0.2**		0		0			4	2	

16	62	F	1	4.4	**14.2**	4.0	**10.6**	+	7	+	4	+	+	5	3	
Diagnosis	**Age at first skin biopsy**	**Sex**	**Skin biopsy (IENFD)**					**Pain**				**Dysautonomia**		**Severity**		**Pure motor**
			Acute phase			After 6 months		Acute phase		After 6 months		Acute phase		Nadir	After 6 months	
			Weeks from onset	Distal leg	Lumbar site	Distal leg	Lumbar site	Presence	Intensity (NRS)	Presence	Intensity (NRS)	Definite	Probable	GBS disability score	GBS disability score	
17	54	F	3	4.6	**9.0**	n.e.	n.e.		0		0			3	2	
18	67	M	1	5.3	16.0	4.6	**9.1**	+	7		0			2	0	+
19	33	M	1	5.5	**2.2**	n.e.	n.e.		0		0			1	1	
20	24	M	3	**6.3**	20.7	**2.9**	19.5		0		0			3	1	
21	44	F	1	6.6	**5.9**	10.9	**10.3**	+	6	+	2	+	+	5	1	
22	72	M	3	6.7	**2.2**	n.e.	n.e.		0	+	4		+	3	2	
23	59	F	1	6.9	16.4	6.6	**13.8**		0		0		+	4	1	
24	22	M	1	7.0	17.2	n.e.	n.e.		0		0			4	1	+
25	44	F	1	7.2	**7.6**	10.5	**9.1**		0		0		+	5	2	+
26	31	F	2	9.3	**12.9**	12.8	22.3		0		0			2	2	+
MFS																
27	59	M	1	**0.5**	**11.2**	**1.2**	**13.3**		0		0			3	1	+
28	56	F	2	**2.6**	**9.5**	3.9	**8.6**	+	9		0	+	+	3	1	
29	79	M	1	5.4	**10.7**	4.4	**10.2**		0		0		+	5	4	
30	40	M	1	5.6	**13.4**	6.5	15.8		0		0			1	0	
31	60	M	1	6.2	21.2	7.6	15.5		0		0			3	0	+
32	29	M	1	7.4	19.6	7.0	20.7		0		0			1	1	+

In two patients (no. 6 and 10) only distal leg skin biopsies were obtained. Five patients (no. 3, 17, 19, 22, 24) were not available for follow-up biopsies. One patient (no.1) died one month after inclusion due to severe sepsis. In grey, highlighted the values lower than normative values stratified per decade and gender,[40] IENFD = intraepidermal nerve fibre density (IENF/mm); n.e. = not evaluated; NRS = numerical rate scale

Table 3 | Autonomic cardiovascular measurements in GBS patients (n=13 GBS (non-MFS) and n=5 MFS) and controls

	GBS (n=18)	Controls (n=26)	p
Male, n (%)	11 (61)	14 (54)	0.76
Age, mean (SD), y	55 (14)	52 (4)	0.22
Autonomic measures acute phase			
■ SBP, mmHg	139 (124-155)‡	122 (109-139)	0.04
■ DBP, mmHg	62 (58-85)‡	66(60-72)	0.83
■ HR, beats/minute	80 (77-93)	66 (60-73)	0.00
■ LFSBP, ln values	5.5 (4.7-6.5)*	5.5 (4.9-6.1)	0.80
■ LFHR, ln values	4.6 (4.3-6.3)§	6.1 (5.6-6.8)	0.02
■ HFHR, ln values	5.1 (4.2-6.1)§	5.8 (5.3-6.2)	0.19
■ BRS, ms/mmHg	4 (1.8-7.6)*	9.1 (5.8-12.1)	0.00

Shown are data (median + IQR) from the autonomic function test. Due to technical problems, BP data of 2 patients were rejected. In addition, spectral data of 3 patients were excluded from further analyses because of frequently occurring cardiac arrhythmia's, and the BRS could not be computed in 3 patients because the coherence between the SBP and IBI time series was below 0.35 (‡ n=16, § n=15, * n=13)

Table 4 | Correlation between IENFD and severity of disease in the acute phase and after 6 months in 32 GBS patients (n=26 GBS (non-MFS) and n=6 MFS)

	GBS including MFS				GBS (non-MFS)			
	GBS disability score				GBS disability score			
IEFD	**rs**	**p**	**rs**	**p**	**rs**	**p**	**rs**	**p**
Acute phase	**Nadir**		**After 6 months**		**Nadir**		**After 6 months**	
■ Distal leg	-0.19	0.31	0.08	0.67	-0.16	0.42	0.14	0.51
■ Lumbar site	-0.20*	0.29	-0.38*	0.04	-0.09**	0.69	-0.30**	0.16
After 6 months			**After 6 months**				**After 6 months**	
■ Distal leg			-0.26‡	0.21			-0.26	0.28Δ
■ Lumbar site			0.04**	0.84			0.11	0.67**

Data given are spearmen correlation coefficients (rs) between distal leg and lumbar site IENFD versus GBS disability score at nadir and after 6 months (8 n=18, Δ n=20, * n=30, ** n=24, ‡ n=26). For the relation between IENFD and severity of GBS, the regeneration of IENFD (difference in IEFD between the acute phase and after 6 months) versus recovery in GBS disability score was also evaluated.

Severity and outcome

Poor GBS disability score at 6 months correlated with lower lumbar IENFD in the acute phase (rs -0.376; p=0.04), GBS score at nadir (rs -0.50; p=0.03), and clinically probable dysautonomia (rs 0.491; p=0.004). Linear multiple regression analysis, including age, diarrhea, GBS disability score (T0=onset, T1=one week after inclusion, T2=two weeks at

nadir), distal leg and lumbar IENFD in the acute phase, demonstrated that age (p=0.022) and lumbar IENFD (p=0.034) were the best predictor of worse outcome (GBS disability score ≥3) at 6 months (table 4).

DISCUSSION

Our prospective study confirmed that small nerve fibres are affected in patients with GBS and MFS since the acute phase of the disease. We showed that the decrease of IENFD is associated with a higher risk and severity of pain and in part with cardiovascular autonomic dysfunction, and that it may predict a poorer outcome at 6 months.

Small fibre neuropathy in the course of GBS

IENFD at distal leg and lumbar site was significantly reduced, in a non length-dependent pattern, in the acute phase of GBS and MFS, as well as in A-CIDP patients, confirming previous findings (15,48). Intriguingly, we found that IENF can be affected also in patients with the pure motor form of GBS.

The course of small fibre neuropathy and the ability of IENF to regenerate has been previously described in patients with pure small fibre neuropathy and diabetic neuropathy (20,30,32,49), but it has never been investigated in immune-mediated neuropathies. Most patients showed a further decrease of lumbar IENFD over time, suggesting either a slower regeneration rate of IENF at proximal than distal sites or, more likely, a relationship with the timing of skin biopsy. Indeed, the decrease of IENFD at the distal leg correlated with the timing of skin biopsy in the first three weeks after the onset. Since most biopsies were taken in the first week after onset and most patients showed a further decrease of lumbar IENFD at 6 months follow-up, we speculate that the degeneration of IENF continued with a course corresponding to the ascending character of GBS.

Small fibre neuropathy and neuropathic pain

We demonstrated that lower values of IENFD at distal leg were associated with the occurrence of pain. Conversely, Pan and colleagues did not find any difference in distal IENFD values between GBS patients with and without painful symptoms (15). This difference could be related to the definition of pain used. Indeed, we strived to select only those patients with neuropathic pain. We also observed that distal leg IENFD inversely correlated with the severity of pain, differently from what has been recently observed in small fibre neuropathy (20).

Small fibre neuropathy and autonomic dysfunction

IENF are unmyelinated axons with exclusive somatic function. The previous observation that reduced IENFD at distal leg was associated with dysautonomia (15) was not completely confirmed by our results. Indeed, we did not find a correlation between IENFD at any site and clinical features of dysautonomia. However, there was a correlation between IENFD at distal leg, BRS, and HF power of HR, reflecting changes in parasympathetic cardiac vagal tone. Like for pain, results could be influenced by the relative small number of patients and events.

Small fibre neuropathy, disability, and outcome

We did not confirm the correlation between IENFD and disability at nadir as previously reported (15). Conversely, our findings suggest that lumbar IENFD in the acute phase, along with age, may be an independent predictor of worse outcome at 6 months in GBS and MFS. However, this issue needs further investigations before being considered a prognostic factor.

CONCLUSIONS

We demonstrated that somatic IENF can be affected in the whole spectrum of GBS, including in patients with the pure motor variant. The density of IENF inversely correlated with occurrence and intensity of pain, and with measures of autonomic dysfunction in the early phase of the disease. Lower IENFD at lumbar site predicted a worse outcome at 6 months follow-up. The pathophysiology of IENF degeneration in GBS and its variants remains unaddressed. Possibly, the immune-mediated process causes a diffuse damage to peripheral nerves, including small nerve fibres. Whether this is caused by specific antibodies, complement activation, inflammatory cytokines or other factors need focused studies.

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GBS

CHAPTER 6
GENERAL DISCUSSION

GENERAL DISCUSSION

According to the general accepted criteria, rapidly progressive symmetrical weakness is the main clinical symptom for the Guillain-Barré syndrome (GBS) and the course is monophasic (1). Time to reach nadir is within four weeks whereafter the patient improves. However, the extent and distribution of clinical symptoms, course of disease and outcome largely varies between individuals with GBS. Some GBS patients have fluctuating course. This often raises doubt about the diagnosis. Some 'GBS patients' eventually may develop chronic inflammatory demyelinating polyneuropathy (CIDP) with acute onset (A-CIDP). For the treatment strategy and prognosis it is relevant to distinguish between GBS with a fluctuating course and A-CIDP as soon as possible. Besides weakness, pain can be a prominent symptom and is often overlooked, because progressive paralysis is the most striking and alarming symptom of GBS. Autonomic dysfunction also frequently occurs and this can be life threatening. In the studies described in my thesis I have focused on the aforementioned issues. The aim was to provide more insight in the course of disease, the presence and severity of residual findings and the frequency and nature of pain and autonomic dysfunction in GBS and finally to delineate factors that are related to a fluctuating course, pain and autonomic dysfunction. In this chapter, the main findings of the retrospective studies and the results of the prospective GRAPH (GBS Research about Pain and Heterogeneity) study will be discussed. Clinical practical suggestions will be provided and suggestions for future studies are made.

RESIDUAL FINDINGS AND COURSE OF DISEASE

In the GRAPH cohort we found that even one year after onset of GBS, residual symptoms appear to be very common, also in mildly affected as well as in patients with Miller Fisher syndrome (MFS) (chapter 3.1). Besides functional disability, fatigue and pain are also frequently present in the whole spectrum of GBS even after one year (chapter 3.1). Residual findings, especially arm-hand function and mobility in mildly affected patients are comparable with those in a retrospective Dutch study describing that a considerable proportion of mildly patients do have residual disabilities after 6 months (2). Randomised controlled trials (RCTs) that have assessed the effect of intravenous immunoglobulins (IVIg) have not studied the effect in mildly affected patients (3). One trial has described a positive effect of plasma exchange (PE) in mildly affected patients (4).

The presence of residual in patients with MFS (chapter 3.1) are not fully in line with other studies describing fast and excellent recovery (5,6). The GBS disability score – findings not validated for patients with MFS –, the presence of pain and the level of fatigue have not been evaluated in these studies. Additionally it was not mentioned that symptoms of

prolonged double vision or ataxia for several months could clearly limit patient's activity and social life. This might explain the difference in conclusion about residual signs in MFS. No RCTs have studied the effect of PE or IVIg in patients with MFS (7).

Clinical practical suggestions

- Inform also mildly affected GBS patients and MFS patients and their caregivers about possible long-term residual symptoms (functional disability, pain, fatigue) when they are discharged from the hospital (based on this thesis).
- When GBS patients (including mildly affected and MFS patients) are admitted to a rehabilitation centre or visit the outpatient clinic after hospital discharge, pay serious attention to residual symptoms (functional disability, pain, fatigue) (based on this thesis).
- In expectation of a possible RCT to the effect of IVIg in mildly affected patients, and based upon this thesis and the results and outcome of our additional studies evaluating mildly affected GBS patients, treat also mildly affected GBS patients with IVIg, especially 1) when they have considerable deficit otherwise (such as severe cranial nerve dysfunction, autonomic dysfunction or severe pain) especially when this can not be fully substantiated using the GBS disability scale (patient is still able to walk); or 2) when the patient shows rapid clinical deterioration and it is to be expected that walking will be impossible or artificial ventilation will be needed shortly (based on this thesis).
- In expectation of a possible RCT to the effect of IVIg in patients with MFS, it is suggested to treat at least MFS patients having severe opthalmoplegia and/or ataxia, especially when there is a GBS-MFS overlap syndrome (general suggestion).

In the literature the following variants in course of disease are described: subacute inflammatory demyelinating polyneuropathy (SIDP) (8,9), GBS with treatment related fluctuations (GBS-TRF) (10-12), A-CIDP (13), and recurrent GBS (14,15). The distinction between these different types of inflammatory polyradiculoneuropathy perhaps is arbitrary, and these variants likely form a spectrum. However, because treatment strategies and prognosis differ, it is important to have early indicators to distinct between these different types of inflammatory polyradiculoneuropathy.

GBS and CIDP are both immune-mediated disorders for which criteria are defined (1,16), however their precise pathogenesis is still unclear. GBS and CIDP are mainly distinguished based on the severity and duration of progressive weakness. There are currently no specific biomarkers known to distinguish between GBS and CIDP. The pathogenesis of GBS and CIDP variants or overlap syndromes is therefore even more speculative. In this thesis we have provided criteria that help to distinguish between GBS-TRF and A-CIDP in individual patients already in the early phase of disease (chapter 3.2 and 3.3).

Our studies are the first in which GBS-TRF and A-CIDP are compared. These results are helpful in clinical practice for guiding treatment and to determine the course of disease. Because treatment strategy and prognosis for GBS-TRF and A-CIDP differ considerably, it is relevant to distinguish between these two variants early in the course of disease.

Based on the criteria described in our studies, A-CIDP now can be diagnosed earlier. It is to be expected that this will lead to a better and more efficient patient tailored treatment.

Clinical practical suggestion

- The diagnosis of A-CIDP has to be considered when 'a patient with GBS' deteriorates again after eight weeks from onset, or when deterioration occurs three times or more. Especially when the patient remains able to walk independently, has no cranial nerve dysfunction, and electrophysiological features are more likely to be compatible with demyelination, maintenance treatment for CIDP has to be considered (based on this thesis).

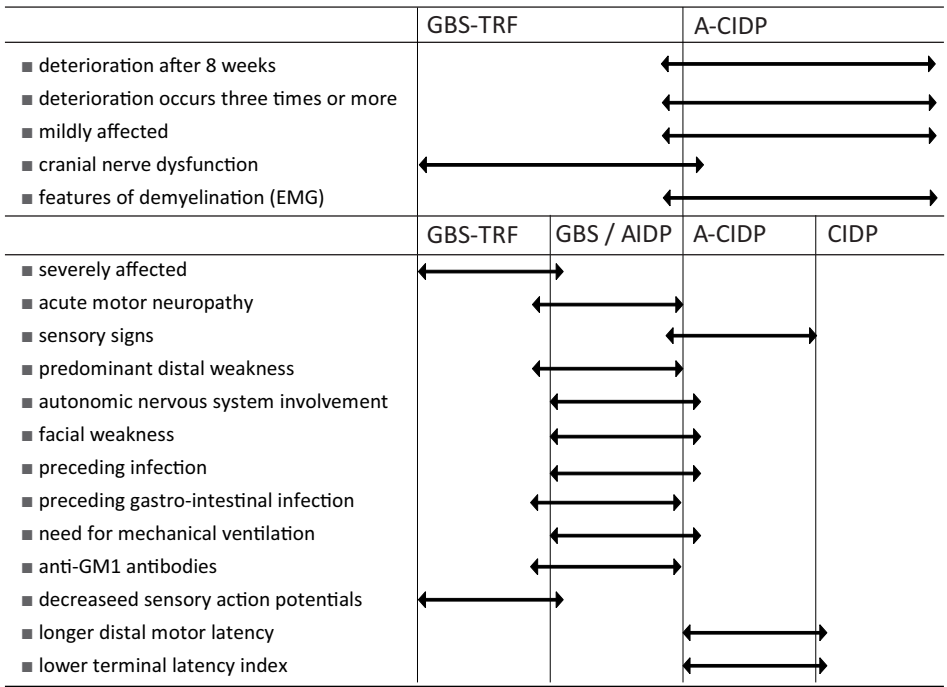
In chapter 3.2 the results of a retrospective study are described. Chapter 3.3 focusses on part of the results of the GRAPH study. In this study patients were prospectively followed. Classifying into GBS-TRF or A-CIDP was done retrospectively based on the clinical course over a period of time. Although the relatively small number of GBS-TRF and A-CIDP patients in both studies, the time to reach deterioration(s) and the number of deteriorations in GBS-TRF and A-CIDP are significantly different. The results from both studies are very much comparable. In our prospective study comparing GBS-TRF and A-CIDP, additional factors about preceding infections and immunological data have been added (chapter 3.3). We have not found differences in preceding infections and anti-ganglioside antibodies. However, the small number of patients with GBS-TRF and A-CIDP makes it difficult to be conclusive about these topics. It is recommended using the provided criteria from now on in individual patients with a fluctuating course to distinguish as soon as possible between GBS-TRF and A-CIDP. This will result in the right treatment as soon as possible and the right indication of the prognosis.

We have also described some clinical differences between GBS patients with and without TRFs to better understand the pathogenesis of TRFs. It appeared that especially the more severely affected GBS patients with sensory disturbances are at risk for developing TRFs (chapter 3.3). A more severe or prolonged immune-attack in individual patients, inducing the need for prolonged- or repeated IVIg treatment, could possibly form the basis of these TRF's.

Several other studies have been published comparing A-CIDP versus acute inflammatory demyelinating polyneuropathy (AIDP) (17), GBS versus GBS-TRF (18), A-CIDP versus CIDP (19), and GBS versus recurrent GBS (20) to generate indicators to differentiate and to better understand the pathogenesis (figure 1). Summarised the following differences are known: 1) A retrospective study has compared A-CIDP versus AIDP (17). More sensory signs in A-CIDP and less autonomic nervous system involvement, facial weakness, preceding infectious illnesses, or need for mechanical ventilation were observed in the A-CIDP group compared to AIDP patients. No electrophysiological differences were found.

2) Another study has compared GBS without TRFs and with TRFs (18). None of the GBS patients with preceding gastro-intestinal illness, initial predominant distal weakness, acute motor neuropathy, or anti-GM1 antibodies showed TRFs. EMG data showed significantly lower sensory nerve action potentials in the TRF group. 3) In a electrophysiological study, A-CIDP patients were reported to show a longer distal motor latency and a lower terminal latency index (TLi), when compared to CIDP patients with a more chronic onset of disease (19), suggesting accentuated pathology in the distal nerve segments in A-CIDP patients. 4) A retrospective study has compared GBS with patients experiencing recurrent GBS (20). Recurrent GBS patients were younger, and more often had MFS or milder symptoms compared to the patients without recurrent GBS. Genetic and immunological host factors seem to play a role in recurrences, since similar neurological symptoms can occur during a recurrence after different infections.

Figure 1 | Differences between A-CIDP, GBS, GBS-TRF and CIDP (studies described in this thesis, 17-19)



So, both GBS and CIDP comprise several subtypes in course of disease and these syndromes may partial overlap and probably form a continuum. The differences between the subtypes suggest a variation of the pathogenesis. In the literature until now, especially clinical and electrophysiological differences between GBS, GBS-TRF, recurrent GBS, AIDP,

A-CIDP, and CIDP are described. In clinical practice this can be used to guide treatment. At this time the pathogenic mechanism underlying these different courses is largely unknown. A relatively prolonged immune response as an explanation for TRFs has been suggested (18). Since more severely affected GBS patients are at risk for developing TRFs (chapter 3.3) this seems in line with this possible explanation. Pathogenic cellular or humoral immune reactions can continue beyond the duration of the effect of IVIg treatment. Antibodies to different gangliosides have been found in about half of GBS patients (21). Antibodies to gangliosides have been reported in fewer than 10% in CIDP patients (22;23). Titers of anti-ganglioside antibodies have been studied in a GBS-TRF patient (24). The conclusion was that the clinical TRF was not due to changes in the titers of anti-ganglioside antibodies. In the same case a long-lasting elevation of cerebrospinal fluid (CSF) protein was found which could possibly be related with long-term inflammation of nerve roots. A recent study showed that GBS patients with limited increase in serum IgG levels after IVIg treatment had a more severe clinical course and poor outcome (25). A possible explanation for the occurrence of TRFs could be explained by a too low dosage of IVIg for these individual patients. In our study GBS-TRF also had a worse prognosis at 6 months compared to GBS without TRFs. It is likely that further research will allow us to design tailor-made treatments for individual patients or groups of patients.

Direction for future research

Studying residual signs and courses of disease in subgroups of patients may determine clues about recovery which can help to design new treatment studies. Since mildly affected GBS patients also had considerable residual symptoms after one-year follow-up (chapter 3.1), new treatment studies should focus on IVIg treatment in mildly affected patients. Also part of the MFS had considerable residual symptoms during follow-up (chapter 3.1). Therefore, investigation of the effect of IVIg in MFS patients is also indicated.

Overall, most of the GBS patients experienced residual symptoms, like functional disability, pain and fatigue after one year. IVIg studies mainly have focussed on the effect of disability (GBS disability scale) after 4 weeks. Therefore it is important that new treatment studies include a long-term follow-up in order to evaluate the treatment effect in the acute phase but also in the chronic phase, one or maybe two years after onset of disease. New treatment studies should also focus on the additional therapeutic benefit of a higher dosage or second course of IVIg on disability but also on artificial respiration and the just mentioned residual findings. However, it needs to be stressed that residual findings could also be due to axonal degeneration in the early phase of disease. In this case, a higher dosage or second course of IVIg would likely not benefit the patient, unless

it will be applied very early in the course of disease when nerve degeneration is still likely to be reversible.

It is evident that some GBS or CIDP patients respond better to immunotherapy than others. Different responses to standard therapy might also suggest that not only humoral factors but also other mechanisms or other factors are relevant. These factors could be the occurrence and extent of complement activation, ongoing and specific infections, variation in IVIg kinetics, the extent of axonal degeneration otherwise or a variation in genetic background (immune response gene polymorphisms). Additional detailed information about preceding and ongoing infections before any deterioration and titers of anti-gangliosides antibodies during the entire course of disease could give more detailed information about the role of infections and anti-gangliosides antibodies in these subgroups of patients.

Measuring of IgG levels in GBS-TRF patients pre-treatment and regularly during the course of disease (for example every two days) could possibly answer the question if the dosage of IVIg for these individual patients is too low. A controlled trial is needed to demonstrate the additional therapeutic benefit of a higher dosage or second course of IVIg in these GBS-TRF patients. A new RCT investigating the effect of a second dose IVIg versus placebo in GBS patients (SID-GBS study) with a poor prognosis is now carried out in the Netherlands by the Dutch GBS studygroup. An international-SID GBS study is expected to start soon.

PAIN AND SMALL FIBRE NEUROPATHY

In chapter 4 we extensively describe the frequency, intensity, location and interpretation of pain in the first year after onset of GBS and we have related these aspects of pain to the spectrum of GBS variants. We have shown that pain is a common and severe problem in about two thirds of the GBS patients and that it also occurs in mildly affected, MFS and pure motor patients. For some patients pain can be a very traumatic experience and one of the most severe symptoms of GBS. Even after one year, one third of the GBS patients has to deal with pain. Probably the results in chapter 4 are underestimated, because most of the GBS patients included in our studies used analgesics. This underscores the problem of pain even more. It also indicates the difficulty of treating pain in GBS.

Clinical practical suggestions

- Pain can be severe in the various phases of GBS. Daily ask for the presence and intensity of pain in every GBS patient during hospital stay (based on this thesis).
- Be aware that pain can also be severe during the rehabilitation phase (based on this thesis).
- The NRS scale can easily be used to evaluate the severity of pain (27) (general suggestion).
- For patients who are intubated, it is essential to create a uniform manner for communication and to ask for pain (general suggestion).

We did not include a control group in our studies on pain in GBS. It is known from the literature that pain is a common problem in mechanically ventilated critical ill patients in general (26). 18% from the GBS patients included in the GRAPH study had to be ventilated. Especially procedures like mobilisation or endotracheal suctioning are described to be very painful in mechanically ventilated critical ill patients (26). Therefore, also pain symptoms, likely not primary GBS related, have influenced our results. For the practical approach dealing with pain in GBS, the cause of the pain doesn't really matter, for the pathophysiology of pain in GBS it does.

The pathophysiology of pain in GBS is largely unknown. In general two types of pain can be distinguished: nociceptive and neuropathic pain. Stimulation of a nociceptor may cause nociceptive pain. Damage to the nervous system itself may cause neuropathic pain (27). In chapter 4.3 we describe the interpretation of pain filled in on the questionnaires by the neurologists. In one third of the patients with pain in the acute phase, the nature was interpretated as radicular pain. Affected nerve roots in the acute phase may likely explain the occurrence of nociceptive nerve pain affecting (low-)back with radiation to extremities or trunk. The origin of radicular pain is unclear. Root enhancement in GBS patients with pain has been described in a prospective MRI study (28). Probably inflammatory factors or peripheral nerve ischemia generate radicular pain via the nervi nervorum (nociceptive neuropathic pain). In our study, the prevalence of (low-)back pain was higher than the prevalence of radicular pain, this suggests that other factors like muscle or facet joint pain also contribute to (low-)back with radiation in the acute phase of GBS. About one third of the pain in the acute and chronic phase was interpreted as painful paraesthesias and dysaesthesias. Pain due to spontaneous or abnormal activity from the affected large myelinated sensory afferents in GBS may explain the occurrence of this neuropathic pain. This is in line with the result that sensory nerve fibre involvement is related with more severe pain during the entire follow-up (chapter 4.3). A small number of patients with pain in the acute phase, had meningism and some of these patients had an increased cell count in the CSF. CSF pleiocytosis suggests meningeal irritation due to inflammatory factors in these GBS patients. CSF pleiocytosis and meningeal inflammation have been described before (29). One retrospective study showed that pain in the neck, usually with

meningism, occurred in around one third of severely affected patients (30). The prevalence of neck pain was higher than the prevalence of meningism, suggesting that other factors like muscle or facet joint pain may contribute to neck pain in the acute phase of GBS. The most common type of pain during the entire follow-up in our study was muscle pain (chapter 4.3). This suggests overuse of (weak) muscles. Due to overuse, muscle lesions can occur which results in activation of the muscle nociceptor, local oedema and ischemia. Possibly muscle nociceptors can also be stimulated otherwise in GBS, a mechanism we don't know yet. In our study an elevated CK level, a measure for muscle lysis, was found in a quarter of the GBS patients in the acute phase. In a previous report, elevated CK levels in GBS were associated with the presence, but not the severity of pain (31). We have not found an association with neither the presence, nor the intensity of (muscle) pain and CK levels. Also within the GBS patients with muscle pain, where an elevated CK could be expected, we have not found a higher CK level compared to patients without muscle pain suggesting that muscle lysis in GBS is not the main factor in muscle pain in GBS. The presence of joint pain increased during follow-up (chapter 4.3). This suggests that joint stiffness and contractures due to immobilisation (32,33), but possibly also too intensive passive stretch movements, result in local joint problems which results in nociceptive joint pain. Damage to small nerve fibres, which has been already shown in one study in GBS patients (34) and which is also described in chapter 5, could also trigger pain in GBS. We demonstrated in chapter 5 that lower values of distal leg IENFD were associated with the presence of neuropathic pain and correlated with its intensity.

Taking these results together, it can be concluded that the pathophysiological processes causing the initiation and the maintenance of pain in GBS patients are likely more complex than in other chronic and painful polyneuropathies (35). In chapter 4.3 we also describe that often a combination of different types and locations of pain is present. Distribution and characteristics of pain in GBS reflect the presence of both nociceptive pain, and neuropathic pain, during different phases of disease. It seems that pain in the acute phase is predominantly nociceptive pain, due to inflammation of the nerve roots and peripheral nerves which may activate nociceptors. Later on, many GBS patients have neuropathic pain. This neuropathic pain is a non-nociceptive pain that doesn't arise from pain receptors but results from degeneration and perhaps even regeneration of nerves, often encountered in patients with chronic neuropathies. Which analgesics are most effective in the whole spectrum of GBS is not known. In chapter 4.1 we describe that methylprednisolone did not show a positive effect on the presence and reduction of pain in 225 severely affected GBS patients (36). Previous case-reports suggest that corticosteroids might be an effective treatment for pain, possibly due to its anti-inflammatory effect (37,38). However, there are many symptoms of pain. In previous case reports, corticosteroids were reported to have a positive effect on radicular pain. Theoretically, methylprednisolone could be

effective because it could reduce swelling of the nerve roots. In our study, the number of patients with radicular pain was too small to conclude about a possible favourable effect of methylprednisolone on this type of pain in GBS.

Besides this study there are some other studies about pain treatment in GBS, however most are based on limited numbers of severely affected patients. Summarised there is: 1) A randomised, double-blind, cross-over trial involving 18 GBS patients admitted to the intensive care unit (ICU) who required assisted ventilation. Gabapentin or placebo was given for 7 days before switching to the alternate treatment (39). There was a significant relief of pain intensity and reduction in the need for rescue medication in the gabapentin group. 2) In a similar study of 12 patients, a significant relief of pain intensity and reduction in the need for rescue medication was obtained from carbamazepine for 3 days compared to placebo (40). 3) In a randomised, double-blind study in 36 GBS patients admitted to the ICU who required assisted ventilation, the effects of gabapentin and carbamazepine were compared (41). The patients in the gabapentin group had significantly lower pain intensity scores. 4) Relief of severe pain by epidural infusions of opioids has been reported in two case-reports about mechanically ventilated GBS patients (42,43). 5) Pain relief after treatment with corticosteroids via oral or intravenous routes has also been described in a few cases (37,38).

In conclusion, only small and mostly non-controlled studies about pain treatment in GBS are available. In the small randomised trials only ICU admitted ventilated patients are included and the effect on pain is only studied for a very short period. Further studies, how to treat pain in GBS are needed. Herefore it is important to assess pain in the right way. Assessment of pain in patients with GBS can be regarded as a time-consuming process, especially when patients are nearly unable to express themselves because they are paralysed and intubated.

As described above, the origin of pain just after onset of disease will likely to be nociceptive. In the course of time, spontaneous or abnormal activity from sensory afferents may explain the occurrence of neuropathic pain. Although not validated for GBS patients separately, the Neuropathic Pain Symptom Inventory (NPSI) can be used to diagnose neuropathic pain (44).

Clinical practical suggestions

- Because of the limited studies about pain treatment in GBS and the probable nociceptive origin in the acute phase, treat pain in the acute phase according the WHO pain ladder (non opioids (aspirin, paracetamol); then, if necessary, mild opioids (codeine); then strong opioids such as morphine, until the patient is free of pain). Be aware of constipation as side-effect of opiods which can be more severe due to autonomic dysfunction. To calm fears and anxiety, additional drugs, adjuvants like antidepressants, anticonvulsants, steroids, muscle relaxants, exercise and psychological support could be used (general suggestion).
- Try to make a distinction between pain during procedures or activities and pain in rest. In the first situation a pain treatment can be given before the procedure or activity, in the other situation analgesics have to be given 'by the clock' (that is e.g. every 3-6 hours) to maintain freedom from pain in stead of as-need basis (general suggestion).
- The effect of pain treatment in the acute phase should be evaluated every day (general suggestion).
- Treat neuropathic pain with tricyclic antidepressant (TCA), gabapentin, pregabalin or other anti-epileptic agents according studies to neuropathic pain in general and the CBO guideline 'Polyneuropthie' (45,46) (general suggestion).

Direction for future research

As described in this thesis, pain is major problem in GBS. The cause of pain in GBS is largely unknown. Only limited studies about pain treatment are done. Probably various subtypes and causes of pain exist in GBS. Clinical discrimination between the different types of pain like radicular pain, meningism, painful par/dysaesthesiae, muscle pain and joint pain is rather possible. However, studying the course of the different types of pain and the effect of pain treatment is difficult especially because different types of pain often occur simultaneously. Therefore it is recommended to focus future research on exploring the pathophysiological processes of different types of pain in GBS (47). Finally, this might guide the development of new therapeutic strategies. Inflammation likely plays an important role in the origin of pain in the acute phase of GBS. Pain is mediated by several different classes of nociceptive afferent fibres. Numerous chemical substances play a part in generating nociceptive impulses (e.g. histamine, serotonin, prostaglandins) and the pathogenetic role of inflammatory cytokines such as TNF-α and neuropeptides such as CGRP and substance P are interesting to explore in relation to pain. Pharmacological and physiological studies argue that pro-inflammatory cytokines such as TNF- α are strongly involved in the generation and maintenance of neuropathic pain (48). Elevated serum concentrations of TNF- α show a positive correlation with severity of neuropathy in patients with GBS (49). Furthermore, the role of neuropeptides, such as CGRP and substance P, has clearly been demonstrated in the activation of early neurogenic inflammation. In diabetic neuropathy, where nociceptive afferent fibres could also be affected, a marked reduction of CGRP and substance P immunoreactivity has been described (50;51). TRPV1

is expressed in the central and the peripheral nervous system and is essential for selective modalities of pain sensation and for thermal hyperalgesia induced by tissue inflammation (52). Whether TRPV1 has a role in maintaining pain in GBS is not known. Notably, previous studies in painful diabetic neuropathy have shown a diffuse loss of TPRV1 positive axons both in the sural nerve and in the skin (53). Moreover, intraepidermal nerve fibres express TPRV1, which shows that they are nociceptors (53). To further investigate pain in the acute phase of GBS and during recovery, antibodies against 1) neuropeptides and 2) pain receptors as indicated above should be used in further studies. For this, skin biopsies can be used.

AUTONOMIC DYSFUNCTION AND SMALL FIBRE NEUROPATHY

Abnormal autonomic functions frequently occur in GBS, including in MFS and mildly affected patients (chapter 3.1). Severely affected GBS patients more often showed abnormal autonomic functions (tachycardia, hypertension, gastro-intestinal, and bladder dysfunction) than in the mildly affected group (chapter 3.1). The frequency of clinical autonomic dysfunction described in GBS is highly variable (54). This already suggests the difficulty in assessing autonomic neuropathy in clinical setting.

Some remarks about our assessment of abnormal autonomic functions must be made. A control group was lacking, and we were not well informed about autonomic functions in medical history, therefore we could not assess autonomic dysfunction purely due to GBS. Unlike severely affected patients, serious bradycardias did not occur in the acute phase in mildly affected patients (chapter 3.1). In the literature it has been described in a small study that serious bradyarrhythmias spontaneously or after eyeball pressure testing was also present in mild-to-moderately disabled patients (55-56). On the other hand, it has been described that mechanically ventilated patients have the greatest risk of developing serious bradyarrhythmias (57). In our study bradycardias did not occur more frequently in mechanically ventilated patients compared to not mechanically ventilated patients.

Several techniques have been devised for assessment of autonomic functions. Examples available to assess the sympathetic and parasympathetic nervous system are: cardiovascular reflex testing by Valsalva manoeuvre, blood pressure response to standing or tilt and measuring the heart rate variation during deep breathing and during the Valsalva manoeuvre. However, at least part of the severely affected GBS patients are unable to perform standardised tests of autonomic function in an appropriate fashion (57). Therefore we choose a non-invasive and easy applicable autonomic cardiovascular measurement (blood pressure (BP), heart rate (HR), and spectral analysis of their variability measured during 10 minutes supine rest) in a subgroup of GBS patients in the first week

after inclusion under uniform circumstances (chapter 5). We did realise that these measurements are not always related to clinically autonomic dysfunction. GBS patients showed significantly higher mean levels of HR, systolic blood pressure (SBP), and lower levels of low frequency heart rate (LFHR) power and baroreflex sensitivity (BRS) index as compared to controls. A high GBS disability score (severely affected) was associated with a high HR. It is likely that associated problems that may occur especially in severely affected patients, like ICU related stress and pneumoniae, may also play a role in this association. For all the other autonomic parameters there was no correlation with severity of disease.

AIDP patients (based on the electrophysiological classification) more frequently showed abnormal autonomic functions in the acute phase compared to acute motor axonal neuropathy (AMAN), however this was, except for the gastro-intestinal dysfunction, not significant and could be related to the relative small number of AMAN patients included in the GRAPH study. In one other study it was concluded that AMAN was not necessarily associated with marked autonomic dysfunction except for the sudomotor hypofunction seen in patients with severe neurological deficits (58).

Clinical practical suggestions

- Be aware that abnormal autonomic functions frequently occur in GBS, including in mildly affected and MFS patients (based on this thesis).
- Regularly (every 3 to 4 hours) assess the autonomic functions in the acute phase in the whole spectrum of GBS including MFS and mildy affected GBS patients. Especially cardiovascular autonomic functions (BP and HR) have to be asessed, because those can be life-treathening (general suggestion).

Direction for future research

In a further study to autonomic dysfunction in GBS, discrimination between differences in abnormal autonomic functions and autonomic neuropathy due to GBS needs to be made. To make conclusions about clinical abnormal autonomic functions, a control group needs to be included. However, defining and finding an otherwise comparable (non-GBS) control group admitted to a hospital or ICU that is not likely to develop abnormal autonomic functions is difficult. Regarding autonomic function tests, part of the severely affected patients are unable to perform tests of autonomic function in an appropriate fashion (57). The non-invasive and early applicable autonomic cardiovascular measurement (BP, HR, and spectral analysis of their variability) measured during 10 minutes is a usable tool, however it does not always correlate with clinical autonomic dysfunction. Additionally spectral analysis is not always and everywhere available and the interpretation might be difficult. Before using this measurement clinically, further study is needed in a large group of GBS patients to interpretate the clinical relevance for the individual GBS patient.

Another way to further study autonomic dysfunction in GBS is to obtain information about the involvement of autonomic nerve fibres in GBS. With PGP 9.5, the non-specific panaxonal marker, we studied the unmyelinated small fibres in the epidermis. Distal leg density of the unmyelinated small fibres in the epidermis in the acute phase showed a significantly positive correlation with part of the cardiovascular autonomic functions (chapter 5). To investigate autonomic nerve fibre involvement during the acute phase and during recovery, antibodies against cholinergic sympathetic receptors on sudomotor fibres innervating sweat glands and adrenergic sympathetic receptors on non-sudomotor fibres like antibodies against vaso intestinal peptide (VIP), neuropeptide Y and tyrosine hydroxylase can be used. Immunohistochemical analysis could identify the type of fibres predominatly involved in autonomic dysfunction in GBS.

OUTCOME OF DISEASE AND SMALL FIBRE NEUROPATHY

Small nerve fibres are affected in the whole spectrum of GBS at distal but also lumbar sites already from the early phase of the disease and their loss is associated with the occurrence of acute neuropathic pain and autonomic dysfunction but may also have a relation with outcome (chapter 5).

Clinical practical suggestion

- Skin biopsy and determination of intradermal nerve fibre density (IENFD) often shows reduced number of fibres not only in severe but also in mildly affected GBS patients. Reduced fibre numbers are related with pain and autonomic dysfunction. Whether skin biopsies are helpful to determine the prognosis in GBS needs further studies. Currently skin biopsy investigation in GBS has to be considered as a research tool and is not indicated in clinical practice (based on this thesis).

Direction for future research

Long-term morbidity from GBS is presumably predominantly caused by axonal damage. Motor impairment dominates the clinical pictures also during the chronic phase of recovery, but there are some data on potential biomarkers useful to indicate an active regenerating process at the neuropathological level. This information could be important for the overall prognosis of patients. A prospective study demonstrated that the concentration of neurofilaments in the CSF was of prognostic value in GBS. Pathologically high CSF neurofilament levels predicted worse motor and functional outcome (59). As far as we know there are no studies available yet on cytoskeleton elements in skin biopsies from GBS patients. To investigate the axonal structure during the acute phase of the disease

and during recovery, antibodies against cytoskeleton elements like monoclonal antibodies against unique β-tubulin (TuJ1), nonphosphorylated microtubule associated protein-1B (MAP1B), neurofilament (NF) and phosphorylated neurofilament (SMI 312) could be used.

Myelinated nerve fibres, a primary target of disease in GBS (AIDP), can be investigated in the skin using specific antibodies against myelin basic protein (MBP) and peripheral myelin protein (PMP 22). Myelinated fibres of the skin haven't been studied before in GBS patients. It seems possible to study it in GBS since it is possible to quantitate and to study morphology of myelinated fibres in other immune-mediated demyelinating neuropathies (60). It would be interesting to study whether the demyelinating proces and/or axonal damage present in large fibres is reflected in the small fibres, and whether skin biopsies can act as a model to study the disease process.

Finally, GBS is associated with antibodies to several gangliosides or ganglioside complexes (61), and complement activation and membrane attack complexes (MAC) play a prominent role (62). Therefore it would be interesting to study these factors also in skin biopsies.

GENERAL CONCLUSION

GBS is a heterogeneous disorder regarding the severity, course of disease, residual symptoms, the presence and severity of pain, and autonomic dysfunction. Infections, cross-reactive anti-ganglioside antibodies, and electrophysiological findings may at least partially determine the severity of disease. The studies described in this thesis have provided more insights in the course of disease and the presence of residual findings. These studies have also contributed to delineate factors that play a role in a fluctuating course that eventually may lead to CIDP, the presence and severity of pain and the presence of autonomic dysfunction within the spectrum of GBS. The 'clinical practical suggestions' are expected to be helpful to optimize medical treatment and care for patients with GBS.

The prognosis of individual GBS patients is still difficult to determine. Recently our GBS study group has published two prognostic models based upon severely affected GBS patients (63,64). These models, in combination with the results of this thesis, may help to determine additional prognostic factors that may be relevant for a broad spectrum of GBS patients. It would be helpful not only to identify factors that predict functional disability, but also to add factors that predict pain or autonomic dysfunction, which needs further research.

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GBS

CHAPTER 7

SUMMARY / SAMENVATTING

SUMMARY

In this thesis, studies concerning the heterogeneity in clinical symptoms and course of disease of the Guillain-Barré syndrome (GBS) are presented. GBS is an acute immune-mediated polyneuropathy characterised by rapidly progressive and relatively symmetrical limb muscle weakness and loss of tendon reflexes with or without sensory disturbances, cranial nerve involvement and respiratory dysfunction. In most patients, GBS is a post-infectious disorder with a monophasic course of disease. Time to reach nadir is within four weeks where after the patient gradually improves. There are some underexposed issues in GBS that we have studied and discussed in this thesis: 1) **Residual findings.** The presence and severity of residual findings in GBS largely varies between individuals. Most treatment trials and the majority of other larger studies have focussed on severely disabled GBS patients (patients who are unable to walk). In this thesis, we have also focussed on the presence and severity of residual findings in subgroups of GBS patients, in particular mildly affected patients and patients with Miller Fisher syndrome (MFS). This information may help to guide whether these GBS subgroups also require medical treatment already during the progressive phase of disease. 2) **Fluctuating course of disease**. Some GBS patients have a fluctuating course instead of a monophasic course. This often raises doubt about the diagnosis. Some 'GBS patients' eventually may develop chronic inflammatory demyelinating polyneuropathy with acute onset (A-CIDP). For the optimal treatment strategy and prognosis, it is relevant to distinguish between GBS with a fluctuating course and A-CIDP as soon as possible. 3) **Pain**. Besides weakness and sensory disturbances, pain can be a prominent symptom. Because progressive paralysis is the most striking and alarming symptom of GBS, pain is often overlooked. 4) **Autonomic dysfunction**. Autonomic dysfunction also frequently occurs and can be life threatening. In the studies presented in this thesis, we have focussed on the aforementioned underexposed but important issues in GBS. The aim was to provide more insight in the presence and severity of residual findings, course of disease, and the frequency and nature of pain and autonomic dysfunction, and finally to delineate factors that relate to a fluctuating course, pain and autonomic dysfunction in GBS. To study these issues we have set up the Dutch prospective 'GBS Research about Pain and Heterogeneity' (GRAPH) study.

Chapter 1 is the general introduction of this thesis. Background information about clinical features, pathogenesis, and treatment of GBS is reviewed to provide an overview of the current knowledge about GBS. Additionally, the rationale for this thesis is described in relation to several cases that illustrate some difficulties physicians may be faced with when taking care for patients suffering from GBS. The cases that are described are: 1) a mildly affected GBS patient having residual symptoms, 2) a patient with GBS having a fluctuating course, 3) a patient having severe pain during the course of GBS, and 4) GBS patients with severe autonomic dysfunction.

In **chapter 2** an overview of the GRAPH study design is given. The GRAPH study is a prospective observational follow-up study with 55 participating Dutch centres. In total 170 patients were included. Clinical data, biological material (serum, CSF, throat and stool specimens, skin biopsies), an electromyographic study, and autonomic parameters were collected at standard time points during one-year follow-up. The results of the GRAPH study are described in chapter 3 to 5.

In **chapter 3,** the clinical spectrum and the treatment of GBS and CIDP are described. **Chapter 3.1** provides prospective collected information about the differences in preceding infections, autonomic dysfunction, course of disease and residual findings in GBS (non-MFS) versus MFS, and mildly versus severely affected GBS patients. We found that mildly affected GBS patients more often showed a preceding virological infection compared to severely affected GBS patients. This suggests that preceding infections may at least partially determine symptoms and severity of disease. Severely affected GBS patients more often showed autonomic dysfunction compared to mildy affected patients. Residual symptoms like functional disability, pain and fatigue appeared to be very common, not only in severely affected GBS patients, but also in MFS and in mildly affected GBS patients. This raises the question if patients with MFS and mildly affected GBS patients also require treatment with intravenous immunoglobulin (IVIg). In **chapter 3.2,** the differences between GBS with treatment related fluctuations (GBS-TRF) and A-CIDP are described based on a retrospective study. It is relevant to distinguish between these two variants as soon as possible because treatment strategy and prognosis differ considerably. We compared thirteen A-CIDP patients with eleven GBS-TRF patients and for the first time we identified factors that help to distinguish between GBS-TRF and A-CIDP. In **chapter 3.3**, the differences between GBS-TRF and A-CIDP are described into more detail based on the GRAPH study. The diagnosis of A-CIDP indeed should be considered when ‘a patient with GBS’ deteriorates again after eight weeks from onset, or when deterioration occurs three times or more. Especially when the patient remains able to walk independently during the most severe phase of disease, has no cranial nerve dysfunction and electrophysiological examination shows features of demyelination, it is likely that the patient has A-CIDP. In this case, maintenance treatment for CIDP should be considered. **Chapter 3.4** reviews treatment of CIDP. IVIg, steroids and plasma exchange (PE) are shown to be effective. It is suggested that some other immunomodulatory agents can also be effective, but that randomised trials are needed to confirm these benefits. Residual symptoms in CIDP, including pain and fatigue are also discussed (with the suggestion to pay attention and manage these residual symptoms). Based upon the studies as described in this thesis, and at least from the more clinical point of view, it is likely that GBS, A-CIDP, and CIDP are all within one spectrum ranging from very acute GBS on one side to a slowly progressive form of CIDP on the other side.

In **chapter 4**, the focus is on the occurrence, the different types and locations, and the intensity of pain in GBS. In **chapter 4.1**, the presence of pain and the effect of methylprednisolone on pain is described in 225 severely affected GBS patients enrolled in a randomised controlled trial (RCT) studying the additional effect of methylprednisolone when added to standard treatment with IVIg with the aim to improve disability. Pain was reported by 55% of patients at randomisation, 22% of these patients had severe pain. Of the patients with pain, surprisingly 70% indicated that the pain preceded the onset of weakness. Although this RCT was not designed to study the effect of methylprednisolone on pain reduction in GBS, it could be concluded that there was no indication that methylprednisolone has a positive effect on the presence and reduction of pain in GBS patients. A retrospective analysis in a subgroup of patients showed that backache, interscapular -, muscle -, and radicular pain, together with painful par-/dysaesthesiae were most frequently present in the acute phase of disease. Most symptoms of pain decreased after this period, but painful par-/dysaesthesiae and muscle pain appeared to be present in a large number of patients even after 6 months. In **chapter 4.2**, we describe that pain rather surprisingly can also occur in patients with the pure motor form of GBS. Of a group of 77 GBS patients from Europe and Curaçao with a clinically pure motor neuropathy that we studied retrospectively, it appeared that 49% of the patients reported to have pain, which was mostly located in the extremities. Some of these patients even reported to have severe pain. In **chapter 4.3**, the presence and detailed aspects of pain are described based on the results of the GRAPH study in an unselected GBS population. Here we related pain symptoms also to other clinical symptoms of GBS. Pain was reported to occur already in the two weeks preceding weakness in 35% of the patients. In the acute phase 64% of the patients reported pain and 35% even had pain after one year. In the majority of patients, the intensity of pain was moderate to severe. The mean pain intensity in the whole cohort of GBS patients slowly decreased over time. Pain occurred in the whole spectrum of GBS (also pure motor, mildly affected and MFS patients). Pain symptoms were associated with sensory disturbances, and the presence of severe pain symptoms later in the stage of disease was associated with a higher level of weakness, disability and fatigue at that moment. Mainly radicular pain, painful par-/dysaesthesiae and muscle pain were described in the acute phase. After 6 months, painful par-/dysaesthesiae and muscle pain were predominantly present. It could be concluded that pain is a common and often severe symptom in the whole spectrum of GBS and it is likely that sensory nerve fibre involvement results in more severe pain. Overall, it can be concluded that pain in GBS requires full attention.

Small diameter nerve fibres play a key role in pain conduction and autonomic functions. These fibres can easily be investigated in skin biopsies by quantification of the intraepidermal nerve fibre density (IENFD). With the aim to get more information on

the presence and ultimately also on pathophysiology of pain and autonomic dysfunction in GBS, we performed a skin biopsy study in part of the GBS patients enrolled in the GRAPH study. The results are described in **chapter 5**. In this chapter we investigated the number of small diameter fibres within the whole spectrum of GBS over time in both distal (ankle) and proximal (lumbar paraspinal) sites of the body. In GBS patients, distal and lumbar IENFD values were lower in the acute phase as compared to controls. IENFD remained lower also at 6-month follow-up. Loss of small nerve fibres was associated with the presence and intensity of neuropathic pain, autonomic dysfunction, and – to some extent – with worse outcome. It could be concluded from this study that small diameter nerve fibres are affected in the various subgroups of GBS at different locations and over time. Furthermore, that research using skin biopsies may lead to more insight into the pathophysiology of features leading to pain and autonomic dysfunction in GBS.

Finally, in **chapter 6** the results of the different studies described in this thesis are discussed and suggestions for further research are given.

SAMENVATTING

In dit proefschrift is het onderzoek naar de heterogeniteit van klinische symptomen en het beloop van het Guillain-Barré syndroom (GBS) beschreven. GBS is een acute immuun-gemedieerde polyneuropathie. Klinisch wordt GBS gekenmerkt door een snel progressieve symmetrische zwakte van de armen en benen, verlaagde of afwezige spierrekkingsreflexen, al dan niet gepaard gaand met gevoelsstoornissen, uitval van de hersenzenuwen en zwakte van de ademhalingsspieren. Bij de meeste patiënten is er een voorafgaande infectie geweest en heeft de ziekte een monofasisch beloop. Het dieptepunt van de zwakte wordt bereikt binnen vier weken, waarna de patiënt geleidelijk aan weer verbetert. In de klinische praktijk, is een aantal onderwerpen rondom GBS onderbelicht. De volgende onderwerpen zijn bestudeerd in dit proefschrift: 1) **Restverschijnselen**. De aanwezigheid en de ernst van restverschijnselen van GBS varieert sterk tussen individuele patiënten. De meeste gerandomiseerde trials en andere grotere studies zijn gericht op ernstig aangedane GBS patiënten (patiënten die niet in staat zijn om te lopen). In dit proefschrift, hebben we ons gericht op de aanwezigheid en de ernst van restverschijnselen in subgroepen van GBS patiënten, in het bijzonder de relatief mild aangedane patiënten en patiënten met het Miller Fisher syndroom (MFS). Informatie over restverschijnselen kan meehelpen in de beslissing of deze GBS subgroepen wel of niet behandeld moeten worden met intraveneus immunoglobuline (IVIg). 2) **Fluctuerend ziektebeloop**. Sommige GBS patiënten hebben een fluctuerend ziektebeloop, in plaats van een monofasisch beloop. Dit resulteert vaak in twijfel over de juiste diagnose. Sommige 'GBS patiënten' ontwikkelen namelijk uiteindelijk chronische inflammatoire demyeliniserende polyneuropathie met een acuut begin (A-CIDP). Voor de juiste behandeling en de prognose, is het van belang om zo vroeg mogelijk onderscheid te maken tussen GBS met een fluctuerend beloop en A-CIDP. 3) **Pijn**. Behalve zwakte en gevoelsstoornissen, kan pijn een belangrijke klacht zijn. Omdat de aandacht meestal uitgaat naar de progressie van de zwakte, wordt pijn vaak over het hoofd gezien. 4) **Autonome dysfunctie**. Autonome dysfunctie, wat ook vaak voorkomt bij GBS, kan levensbedreigend zijn. In het onderzoek wat beschreven is in dit proefschrift hebben we ons gericht op de bovengenoemde onderbelichte, maar belangrijke onderwerpen bij GBS. Het doel was om meer inzicht te krijgen in de aanwezigheid en ernst van de restverschijnselen, het beloop van de ziekte en in de frequentie en de aard van pijn en autonome dysfunctie om vervolgens factoren te identificeren die bij GBS patiënten van invloed zijn op een fluctuerend verloop, pijn en autonome dysfunctie. Om dit te onderzoeken hebben wij de Nederlandse prospectieve GRAPH studie opgezet. GRAPH staat voor 'GBS Research about Pain and Heterogeneity'.

Hoofdstuk 1 is de algemene inleiding van dit proefschrift. Hierin wordt een overzicht gegeven van de huidige kennis over de klinische symptomen, pathogenese en behandeling

van GBS. Daarnaast wordt het doel van dit proefschrift beschreven aan de hand van enkele patiënten casussen die de moeilijkheden illustreren waar artsen mee te maken hebben tijdens de zorg voor patiënten die lijden aan GBS. De voorbeelden die worden beschreven zijn: 1) een mild aangedane GBS patiënt met restverschijnselen, 2) een patiënt met GBS met een fluctuerend beloop, 3) een patiënt met ernstige pijn tijdens het doormaken van GBS, en 4) GBS patiënten met ernstige autonome dysfunctie.

In **hoofdstuk 2** wordt de onderzoeksopzet van de GRAPH studie beschreven. De GRAPH studie is een prospectieve observationele follow-up studie waaraan 55 Nederlandse centra deelnamen. In totaal zijn er 170 patiënten geïncludeerd. Klinische gegevens, biologisch materiaal (serum, liquor, faeces, sputum, huidbiopten), een EMG en autonome parameters werden verzameld op standaard tijdstippen gedurende één jaar follow-up. De resultaten van de GRAPH studie worden beschreven in hoofdstuk 3 tot en met 5.

In **hoofdstuk 3** wordt het klinische spectrum en de behandeling van GBS en CIDP beschreven. **Hoofdstuk 3.1** bevat prospectief verzamelde informatie over de verschillen in voorafgaande infecties, autonome dysfunctie, beloop van de ziekte en restverschijnselen in GBS (zonder MFS) versus patiënten met MFS en mild aangedane versus ernstig aangedane GBS patiënten. We vonden dat mild aangedane patiënten vaker een voorafgaande virologische infectie hadden doorgemaakt in vergelijking met ernstig aangedane GBS patiënten. Dit suggereert dat een voorafgaande infectie deels bepalend kan zijn voor de symptomen en de ernst van de ziekte. Ernstig aangedane GBS patiënten bleken vaker autonome dysfunctie te vertonen in vergelijking met mild aangedane patiënten. Restklachten zoals functionele handicap, pijn en vermoeidheid kwamen frequent voor, niet alleen bij ernstig aangedane GBS patiënten, maar ook bij MFS en mild aangedane GBS patiënten. Dit resulteert in de vraag of MFS en mild aangedane GBS patiënten ook behandeld zouden moeten worden met IVIg. In **hoofdstuk 3.2** zijn de verschillen tussen GBS patiënten met treatment related fluctuation (GBS-TRF) en A-CIDP beschreven op basis van een retrospectieve studie. Het is van belang om zo spoedig mogelijk onderscheid te maken tussen deze twee varianten, omdat de behandeling en de prognose aanzienlijk verschillen. We vergeleken dertien A-CIDP patiënten met elf GBS-TRF patiënten en voor het eerst identificeerden we factoren die helpen onderscheid te maken tussen GBS-TRF en A-CIDP. In **hoofdstuk 3.3** zijn de verschillen tussen GBS patienten met treatment related fluctuatGBS-TRF en A-CIDP beschreven in meer detail, gebaseerd op de GRAPH studie. De waarschijnlijkheidsdiagnose A-CIDP moet worden gesteld als ‘een patiënt met GBS’ opnieuw verslechtert na acht weken na het begin van GBS, of wanneer er drie keer of meer een verslechtering optreedt. Vooral wanneer de patiënt nog zelfstandig kan lopen tijdens het dieptepunt van de ziekte, geen hersenzenuw uitval heeft en het elektrofysiologische onderzoek kenmerken toont van demyelinisatie, is het waarschijnlijk dat de patiënt A-CIDP heeft. In dat geval moet onderhoudsbehandeling voor CIDP worden overwogen.

Hoofdstuk 3.4 beschrijft de behandeling van CIDP. IVIg, steroïden en plasmaferese zijn effectief gebleken. Gesuggereerd wordt dat sommige andere immunomodulerende middelen ook effectief zouden kunnen zijn. Gerandomiseerde studies zijn nodig om dit te bevestigen. Restklachten in CIDP, zoals pijn en vermoeidheid, zijn eveneens beschreven met de opmerking om aandacht te besteden aan restverschijnselen bij deze patiënten. Op basis van de studies zoals beschreven in dit proefschrift en vanuit klinisch oogpunt, is het waarschijnlijk dat GBS, A-CIDP en CIDP allemaal onderdeel uitmaken van een spectrum met aan de ene kant de zeer acuut vorm, GBS en aan de andere kant de langzaam progressieve vorm, CIDP.

In **hoofdstuk 4** ligt de nadruk op pijn bij GBS. De prevalentie, de verschillende soorten, lokalisaties en intensiteit van pijn worden beschreven. In **hoofdstuk 4.1**, is de aanwezigheid van pijn en het effect van methylprednisolon op de pijn beschreven onder 225 ernstig aangedane GBS patiënten die geïncludeerd waren in een gerandomiseerde gecontroleerde trial (RCT) naar het additionele effect van methylprednisolon op de snelheid van het verbeteren van de functionele handicap wanneer dit toegevoegd werd aan de standaardbehandeling met IVIg. Pijn werd gerapporteerd door 55% van de patiënten bij randomisatie, 22% van deze patiënten had ernstige pijn. Van de patiënten met pijn gaf 70% aan dat de pijn vóór aanvang van zwakte al was begonnen. Hoewel deze RCT niet was ontworpen om het effect van methylprednisolon op pijn in GBS te bestuderen, kan er worden geconcludeerd dat er geen aanwijzingen waren dat methylprednisolon een positief effect heeft op de aanwezigheid en de vermindering van pijn bij GBS patiënten. Uit een retrospectieve analyse van een subgroep van patiënten bleek dat rugpijn, interscapulaire -, spier -, en radiculaire pijn, samen met pijnlijke par-/dysaesthesieën het meest aanwezig waren in de acute fase van de ziekte. De meeste pijnsymptomen namen af na deze periode, maar vooral pijnlijke par-/dysaesthesieën en spierpijn bleken in een groot aantal van de patiënten zelfs na 6 maanden nog aanwezig te zijn. In **hoofdstuk 4.2** wordt beschreven dat pijn opvallenderwijs ook kan optreden bij patiënten met de puur motore vorm van GBS. In een groep van 77 GBS patiënten uit Europa en Curaçao met de klinisch puur motore vorm die we retrospectief bestudeerd hebben, bleek dat 49% van de patiënten pijn had, die voornamelijk was gelokaliseerd in de extremiteiten. Sommige van deze patiënten gaven ook aan ernstige pijn te hebben. In **hoofdstuk 4.3** wordt pijn bij GBS gedetailleerd beschreven in een niet-geselecteerde GBS populatie van het cohort van de GRAPH studie. Daarnaast is pijn gerelateerd aan andere klinische symptomen van GBS. 35% van de patiënten had al pijn in de twee weken voorafgaand aan de zwakte. In de acute fase gaf 64% van de patiënten aan pijn te hebben en 35% had zelfs pijn na één jaar. Bij de meerderheid van de patiënten was de intensiteit van de pijn matig tot ernstig. De gemiddelde pijn intensiteit van het gehele GBS cohort nam langzaam af in de tijd. Pijn kwam voor in het gehele spectrum van GBS (dus ook bij

de puur motore vorm, de mild aangedane en MFS patiënten). De aanwezigheid van pijn was geassocieerd met de aanwezigheid van gevoelsstoornissen. Na de acute fase was de ernst van de pijn geassocieerd met de ernst van de zwakte, de ernst van de handicap en de ernst van vermoeidheid op dat moment. In de acute fase werden vooral radiculaire pijn, pijnlijke par-/dysaesthesieën en spierpijn beschreven. Na 6 maanden waren voornamelijk pijnlijke par-/dysaesthesieën en spierpijn aanwezig. Geconcludeerd kan worden dat pijn een veel voorkomend en vaak ernstig symptoom is in het hele spectrum van GBS. Het is waarschijnlijk dat betrokkenheid van de sensibele zenuwvezels leidt tot ernstigere pijn. Over het algemeen kan worden geconcludeerd dat pijn bij GBS veel aandacht behoeft.

Dunne zenuwvezels spelen een belangrijke rol in pijngeleiding en autonome functies. Deze vezels kunnen eenvoudig worden onderzocht in huidbiopten door kwantificering van de intraepidermale zenuwvezel dichtheid (IENFD). Met als doel om meer inzicht te krijgen in de pathophysiologie van pijn en autonome dysfunctie bij GBS hebben we bij een deel van de GBS patiënten geïncludeerd in de GRAPH studie huidbiopten afgenomen. De resultaten zijn beschreven in **hoofdstuk 5**. In dit hoofdstuk onderzochten we het aantal dunne zenuwvezels binnen het gehele spectrum van GBS na verloop van tijd in distale (enkel) en proximale (paraspinaal lumbaal) delen van het lichaam. Bij GBS patiënten waren de distale en lumbale IENFD waardes lager in de acute fase in vergelijking met de controle groep. IENFD was ook lager na 6 maanden follow-up. Verlies van kleine zenuwvezels was geassocieerd met de aanwezigheid van neuropathische pijn, autonome dysfunctie, en – tot op zekere hoogte – met een slechter herstel van de zwakte. Uit deze studie kan worden geconcludeerd dat de dunne zenuwvezels in de verschillende subgroepen van GBS op verschillende locaties en op verschillende tijdstippen zijn aangedaan. Onderzoek van huidbiopten kan leiden tot een beter inzicht in de pathofysiologie van pijn en autonome dysfunctie bij GBS.

Tenslotte worden in **hoofdstuk 6** de resultaten van de verschillende studies die in dit proefschrift zijn beschreven besproken en worden er suggesties voor verder onderzoek gegeven.


GBS

LIST OF ABBREVIATIONS
APPENDIX

LIST OF ABBREVIATIONS

A-CIDP	= acute onset chronic inflammatory demyelinating polyneuropathy
AIDP	= acute inflammatory demyelinating polyneuropathy
AMAN	= acute motor axonal neuropathy
AMSAN	= acute motor and sensory axonal neuropathy
BP	= blood pressure
BRS	= baroreflex sensitivity
CIDP	= chronic inflammatory demyelinating polyneuropathy
CMV	= cytomegalovirus
CSF	= cerebrospinal fluid
dCMAP	= distal compound muscle action potential
DML	= distal motor latency
DBP	= diastolic blood pressure
DRG	= dorsal root ganglion
EBV	= Epstein-Barr virus
EMG	= electromyography
GBS	= Guillain-Barré syndrome
GBS-TRF	= Guillain-Barré syndrome with treatment related fluctuations
GRAPH	= GBS Research about Pain and Heterogeneity
hCoV	= human coronavirus
HF	= high-frequency
HR	= heart rate
hMPV	= human metapneumovirus
HSV	= herpes simplex virus
IBI	= interbit interval
ICU	= intensive care unit
IENFD	= intra epidermal nerve fibre density
IENF	= intra epidermal nerve fibre
IF	= immunofluorescence
IVIg	= intravenous immunoglobulin
LF	= low-frequency
LOS	= lipo-oligosaccharide
MFS	= Miller Fisher syndrome
mNCV	= motor nerve conduction velocity
MP	= methylprednisolone
pCMAP	= proximal compound muscle action potential
PE	= plasma exchange

PGP 9.5	= protein gene product 9.5
RCT	= randomised controlled trial
RSV	= respiratory syncytial virus
TRF	= treatment related fluctuation
SBP	= systolic blood pressure
SIDP	= subacute inflammatory demyelinating polyneuropathy
SNAP	= sensory nerve action potential
sNCV	= sensory nerve conduction velocity
TLi	= terminal latency index
TRF	= treatment related fluctuation

Appendix

PAIN QUESTIONNAIRE GRAPH STUDY

Erasmus MC — GRAPH studie — 1 / 2

s.v.p. faxen naar 0031-10-4087984

Pijn formulier
(vanaf zwakte)

Week: 0 | Studienummer: 202

Heeft patiënt sinds
[1] het vorige tijdstip van vragenlijsten invullen of (indien dit de eerste keer is)
[2] het begin van de zwakte t/m nu
pijn geleden, waar hij/zij voordat het GBS begon niet mee bekend was.

O Onbekend
O Nee
O Ja

Vul datum en initialen in aan de onderkant van het formulier en ga verder met het formulier neurologisch onderzoek.

1. Pijn eigenschappen

Indien pijn in het kader van GBS nieuw is voor de patiënt:
Wanneer is de pijn dan begonnen?

Datum (dd - mm - yyyy): ☐☐ - ☐☐ - ☐☐☐☐

LOCATIE (Meerdere antwoorden zijn mogelijk)	(laag) in de rug	tussen de schouder-bladen	nek	extremi-teiten	romp
TYPE (Meerdere antwoorden zijn mogelijk)	☐ indien aangevinkt onderstaande kolom invullen	☐ indien aangevinkt onderstaande kolom invullen	☐ indien aangevinkt onderstaande kolom invullen	☐ indien aangevinkt onderstaande kolom invullen	☐ indien aangevinkt onderstaande kolom invullen
De pijn is...					
...kloppend	☐	☐	☐	☐	☐
...schietend / flitsend	☐	☐	☐	☐	☐
...stekend	☐	☐	☐	☐	☐
...snijdend	☐	☐	☐	☐	☐
...drukkend	☐	☐	☐	☐	☐
...trekkend / scheurend	☐	☐	☐	☐	☐
...branderig	☐	☐	☐	☐	☐
...gloeiend	☐	☐	☐	☐	☐
...koud	☐	☐	☐	☐	☐
...tintelend	☐	☐	☐	☐	☐
...krampend / stijf	☐	☐	☐	☐	☐
...zeurend	☐	☐	☐	☐	☐
PATROON					
De pijn...					
...zit steeds op dezelfde plaats	☐	☐	☐	☐	☐
...schiet van ene naar andere plaats	☐	☐	☐	☐	☐
...straalt uit naar andere plaatsen	☐	☐	☐	☐	☐
TIJDSBELOOP					
De pijn is...					
...continue even erg	☐	☐	☐	☐	☐
...wisselend qua ernst	☐	☐	☐	☐	☐
...aanvalsgewijs (tussendoor dus weg)	☐	☐	☐	☐	☐
De pijn is uitlokbaar door...					
...beweging	☐	☐	☐	☐	☐
...aanraking	☐	☐	☐	☐	☐

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s.v.p. faxen naar 0031-10-4087984

Pijn formulier

(vanaf zwakte)

Week 0

Studienummer 202

(vervolg indien pijn)

INTENSITEIT

Hoeveel totale pijn heeft patiënt gemiddeld...

...als deze op zijn ergst is? ☐☐

...op dit moment? ☐☐

...gemiddeld de afgelopen week? ☐☐

0 = geen pijn
10 = ergst denkbare pijn die patiënt zich kan voorstellen

INTERPRETATIE DOOR DE ARTS

Anamnese en neurologisch onderzoek samen genomen, lijkt patiënt last te hebben van...
(Meerdere antwoorden zijn mogelijk)

- ☐ *...radiculaire pijn*
- ☐ *...pijnlijke paraesthesieën / dysaesthesieën*
- ☐ *...gewrichtspijn*
- ☐ *...spierpijn*
- ☐ *...anders, namelijk*

2. Pijnmedicatie

Gebruikt patiënt dagelijks corticosteroid-medicatie? O Nee O Ja O Onbekend

Gebruikt patiënt dagelijks pijnmedicatie? O Nee O Ja O Onbekend

Wat voor soort pijnmedicatie? (meerdere antwoorden zijn mogelijk)

- ☐ Paracetamol en/of NSAID (zoals naproxen, diclofenac, ibuprofen, vioxx)
- ☐ Zwak opioid (zoals codeine en tramadol)
- ☐ Sterk opiod (zoals morfine, oxycodone, fentanyl dermaal)
- ☐ Invasieve pijnbestrijding (zoals morfine im/sc/iv of fentanyl sc/iv)
- ☐ Anti-depressivum (zoals amitryptiline, norriptyline)
- ☐ Anti-epilepticum (zoals carbamazepine, gabapentine)

Met bovenstaande medicatie is de pijn in grote lijnen:

- O afgenomen
- O toegenomen
- O gelijk gebleven
- O onbekend

Als u bij één bepaald medicijn het gevoel heeft, dit werkt uitstekend tegen de pijn, dan mag u dat hier invullen

Medicijn ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐ *dd* ☐☐ *mg* ☐☐☐☐☐☐

Datum van invullen (dd - mm - yyyy) ☐☐ - ☐☐ - ☐☐☐☐ *Initialen invullend arts* ☐☐☐☐☐☐☐☐

49755


GBS

EPILOGUE

ACKNOWLEDGEMENTS / DANKWOORD

Februari 2002, ik weet het nog goed, mijn begin als arts-assistent Neurologie op de afdeling 6 Noord in het Erasmus MC in Rotterdam. Naast Neuroloog worden, wilde ik ook graag onderzoek doen. Al snel had ik een goed gevoel bij de GBS onderzoeksgroep en het onderzoek wat daar mogelijk was. Dat gevoel bleek wederzijds. Nu, acht jaar later heb ik mijn promotieonderzoek afgerond. In het vaak meest gelezen onderdeel van het proefschrift wil ik vele patiënten, familieleden, vrienden en collega's bedanken. Want zonder hen was het niet mogelijk geweest het promotieonderzoek tot een goed einde te brengen. Ik kan niet genoeg benadrukken hoe dankbaar ik hiervoor ben. Een aantal mensen wil ik graag persoonlijk noemen, waarbij ik me besef nooit volledig te kunnen zijn.

Deelnemende Guillain-Barré patiënten en controlepersonen
Op de eerste plaats wil ik alle patiënten en controlepersonen bedanken voor hun deelname aan het GBS onderzoek. Dankzij hen is het mogelijk geweest het GBS onderzoek weer een stapje verder te brengen. Bij heel veel Rotterdamse GBS patiënten heb ik wekelijks aan het bed gestaan om onder andere de vragenlijsten voor de GRAPH studie af te nemen. De plotselinge afhankelijkheid, het machteloze gevoel, de pijn, de angst hoe het verdere beloop zou zijn, het verdriet en de frustraties maakte ik hierdoor van dichtbij mee. Meer en meer respect kreeg ik voor jullie doorzettingsvermogen. Jullie motiveerden me om meer te weten te komen over deze plotseling optredende ziekte met zijn diversiteit aan klachten en beloop. Dank jullie wel, jullie verhalen zullen me altijd bijblijven!

Deelnemende centra GRAPH studie
Zonder de neurologen en arts-assistenten uit de 55 deelnemende ziekenhuizen was de GRAPH studie nooit een succes geworden. Bedankt voor jullie inzet de afgelopen jaren. Daarnaast wil ik alle onderzoeksassistenten, verpleegkundigen en secretaressen die ons hierin hebben bijgestaan bedanken voor hun hulp.

Prof. dr. Pieter A. van Doorn | Promotor
Beste Pieter, in 2001 zat je in m'n sollicitatiecommissie, in 2010 ben je de promotor van m'n promotiecommissie. Kort nadat ik deel uitmaakte van de GBS onderzoeksgroep, gingen we met de gehele GBS onderzoeksgroep op congres in Canada. Tijdens dat congres hebben we elkaar direct goed leren kennen. Het was voor mij een bevestiging dat ik de juiste keus had gemaakt te starten met promotieonderzoek onder jouw begeleiding. Jouw enthousiasme en betrokkenheid bij het GBS onderzoek hebben voor mij altijd zeer motiverend gewerkt. Op wetenschappelijk gebied heb ik erg veel van je geleerd. Ook heb je me heel veel bijgebracht van de neurologie en in het bijzonder van de neuromusculaire

ziekten. Je stond steeds open voor ideeën en verleende ook altijd alle medewerking, ondanks je vaak overvolle agenda. Naast promotor ben ik je enorm gaan waarderen als mens. Elke keer toon je oprechte interesse ook in het leven buiten het onderzoek. Het is erg prettig om op een informele en open manier met je te kunnen praten. We hebben ook veel gelachen. Eén van die hilarische momenten was dat we samen op krukken langs de patiënten gingen. Je kracht om aan de ene kant wetenschappelijk het maximale uit me te halen en aan de andere kant even bij te praten over van alles en nog wat, maken jou in mijn ogen een hele unieke 'baas'. Daarnaast heb ik bijzonder veel waardering voor de manier waarop jij meewerkt aan het groepsgevoel binnen de GBS onderzoeksgroep. Wat er ook ondernomen wordt binnen de groep, jij bent van de partij. Sterker nog, jij neemt vaak ook het initiatief om er wederom een geslaagde dag, avond of nacht van te maken tijdens congressen, 'vergaderingen te water' of andere uitjes. Bedankt en ik hoop je nog vaak te zien!

Bart Jacobs, Pieter van Doorn, Judith Drenthen, Marcel Garssen, Karin Geleijns, Rinske van Koningsveld, Mark Kuijf, Krista Kuitwaard, Ellen Maathuis, Sonia van Nes, Christa Walgaard, Martine Bos Eyssen | GBS onderzoeksgroep

GBS onderzoekers, jullie input en suggesties bij de vele besprekingen en de gezamenlijke artikelen die we hebben geschreven, hebben mede geleid tot dit proefschrift. Bart, jou wil ik hiervoor in het bijzonder bedanken. Jij wist elke keer weer tot de kern van te zaak te komen. Dat er met jou ook andere discussies te voeren waren, bijvoorbeeld over 'een berenbel', was een plezierige afwisseling. Ik waardeer het zeer dat jij deel uitmaakt van m'n promotiecommissie. Judith, Rinske, Mark, Krista, Sonia en Christa, tijdens m'n vakanties waren jullie altijd bereid de GBS telefoon over te nemen en GBS patiënten te includeren in de GRAPH studie, dank je wel. De koffie, taart, lunch en borrel-breaks op de 22e, zorgden altijd voor de benodigde ontspanning. De congressen die we met elkaar bezocht hebben zal ik nooit vergeten. In het bijzonder heb ik mooie herinneringen aan de gletsjerbeklimming en het kanogevecht in Canada. In Barcelona zal ik de Carpe Diem Lounge Club nooit vergeten. Pisa, in het mooie Italië, wat hebben we gelachen. Na het congres in Utah gingen Karin, Sonia, Pieter en ik op pad richting de Rocky Mountains. De liedjes van Bruce onderweg, de zware beklimming in Bryce en de welverdiende afkoeling in Zion, stuk voor stuk onvergetelijke herinneringen. En tot slot niet te vergeten onze diverse avontuurlijke, culinaire zeiltochten. Bedankt voor alles en ik hoop jullie nog vaak tegen te komen!

Dr. Giuseppe Lauria, Francesca Camozzi, Raffaella Lombardi | National Neurological Institute 'Carlo Besta' (Italië)

Dear Giuseppe, in 2005 we met at the PNS congress in Pisa and started to talk about Milan. What a coincidence that you knew some people I worked with during my training period in Milan in 1997. In Pisa the skin biopsy project for the GRAPH study started. As 'skin-biopsy hero', you provided the knowledge and all facilities to set up the skin biopsy part in Rotterdam. Also you supported me with the article and thesis. After the congress in Pisa, many congresses followed. We have had a lot of fun and I greatly appreciate that you are member of my PhD committee. In 2006, I visited your lab in Milan. Francesca and Raffaella, you showed me the whole work-up from biopsy to density. Thanks for your explanation, counting, fun and lovely espressos! Recent years, many frozen biopsies have travelled the road Rotterdam – Milano. After visiting the lab and meeting you all, I know the biopsies are in good hands. Grazie!

Prof. dr. Gert J. van Dijk, Prof. dr. Rogier Q. Hintzen, Prof. dr. Peter A.E. Sillevis Smitt | Leden van de promotiecommissie

Beste professor van Dijk, hartelijk dank voor het kritisch doorlezen van mijn manuscript en het plaatsnemen in de kleine commissie. Beste Rogier, als MS-goeroe had jij vanuit een andere hoek input op de neuro-immunologie besprekingen. Dat zorgde vaak voor net weer even een andere kijk op de zaak. Daarnaast was het gewoon altijd erg gezellig! Dank je wel dat je deel uitmaakt van m'n promotiecommissie. Beste Peter, het grootste deel van m'n neurologie opleiding ben jij de opleider geweest. Ik heb veel van je geleerd in de kliniek waarvoor ik je wil bedanken. Eén van onze eerste en ook onze laatste gesprekken in het Erasmus MC gingen onder andere over een wereldreis. Ik ben je meer dan dankbaar dat je openstond om de mogelijkheden hiervoor te bekijken. Ook wil ik je bedanken voor de betrokkenheid bij m'n nieuwe baan in het Havenziekenhuis. Ik waardeer het zeer dat je deel uitmaakt van m'n promotiecommissie, en dank dat je ook de secretaris wilde zijn van de kleine commissie.

Rita de Kimpe | Research coördinator

Het opzetten en draaiende houden van de GRAPH studie was een hele klus. Mede dankzij jouw hulp liep de logistiek uiteindelijk gesmeerd. Jij had het overzicht en zorgde ervoor dat alle gegevens binnenkwamen. Ik ben je heel erg dankbaar voor al het werk dat je me uit handen hebt genomen. Als jij ergens je tanden in zette, ging je er ook voor. Ik zal nooit vergeten dat we onze, in jaren verzamelde, huidbiopten op luchttransport naar Milaan hadden gezet via Nederlands grootste postbedrijf. Wat bleek…, de doos met de ingevroren huidbiopten had het vliegtuig gemist. Waar ze nu dan waren en of ze niet

zouden ontdooien, was onbekend. Jij pakte de telefoon en zocht alles piekfijn uit. Eind goed, al goed, bedankt!

Cisca Peters | Neuromusculair vepleegkundige
Lieve Cisca, samen hebben we vele GBS patiënten op de poli gezien. Het afnemen van de huidbiopten, de bloeddrukmetingen, jij stond altijd klaar om te helpen en bleef vooral ook rustig als we de bloeddrukmeter weer eens niet aan de praat kregen. Hiervoor wil ik je bedanken. Ook ben ik je dankbaar voor de mooie gesprekken die we hadden. Ik heb respect voor datgene wat je allemaal doet binnen, maar zeker ook buiten het Erasmus MC!

Anne Tio, Wouter van Rijs | Afdeling Immunologie
Beste Anne en Wouter, jullie wil ik bedanken voor de bepalingen en opslag van de honderden bloed- en liquormonsters. Jullie waren altijd bereid mee te denken en de terugkoppeling wanneer er monsters misten, liep gesmeerd. Mede dankzij jullie was er zo'n hoge opbrengst, dank jullie wel!

Dr. Joost L. Jongen, Elize Haasdijk, Dr. Joan C. Holstege, Prof. dr. Chris I. de Zeeuw | Afdeling Neurologie en Neurowetenschappen
Beste Joost, met het pijnonderzoek had jij al heel wat ervaring op de afdeling Neurowetenschappen. Met veel enthousiasme was je altijd bereid mee te denken over en input te leveren aan het pijnonderzoek bij GBS. Naast een goede 'pijnraadgever', vind ik je een fantastisch skiër. We hebben veel plezier gehad tijdens de vele Babinski-reisjes. In 2005 maakten Pieter en ik een afspraak met Chris en Joan, met de vraag of we konden samenwerken op het gebied van pijn en huidbiopten. Hartelijk dank dat dit mogelijk was. Elize, jij was de reddende engel toen we het huidbiopten project daadwerkelijk wilden gaan starten in het Erasmus MC. Wij hadden de wens, jij de spullen en de techniek. Door jouw hulp is het gelukt. Altijd was je vrolijk, behulpzaam en bereid medium klaar te zetten en de biopten op te slaan. Voor de diverse transporten naar Milaan, was jij degene die zorgde voor een goede verzendbox met alle biopten op droogijs. Bedankt voor alles!

Dr. Roelie J. Hempel, Dr. Hugo G. van Steenis, Dr. Joke H.M. Tulen | Afdeling Psychiatrie
Beste Joke, Hugo en Roelie, de bloeddrukmeting en de spectraal analyse, voor jullie dagelijkse kost, voor mij in het begin één groot raadsel. Jullie hebben me de afgelopen jaren op een zeer prettige manier geholpen. Allereerst, de spullen die nodig waren voor de autonome metingen. Hartelijk dank voor het lenen. Daarnaast de uitleg en de hulp als ik het apparaat weer eens niet aan de praat kreeg. Jullie waren altijd bereid mee te helpen en mee te denken. Tenslotte de analyses, Roelie heel erg bedankt dat je dit wilde doen.

Dr. Anton H. van den Meiracker, Arnold Birkenhager | Afdeling Interne
Beste Ton, dank je wel voor de mogelijkheid om de spullen voor de bloeddrukmeting te lenen en mij op weg te helpen in de autonome wereld. Je manier van uitleggen was erg prettig en verhelderend. Ik waardeer het zeer dat jij deel uitmaakt van m'n promotiecommissie. Beste Arnold, ik hoefde maar te bellen of te mailen en ik kon de spullen voor de bloeddrukmeting ophalen. Heel erg fijn. Ik vond het jammer te horen dat je uiteindelijk een andere weg bent ingeslagen. Ik hoop dat het goed met je gaat!

Dr. Gerhard H. Visser, Judith Drenthen, Ellen Maathuis, Jannie en Michiel de KNF laboranten, Magda en Monique van het secretariaat, Dr. Joseph C. Perumpillichira, Dr. Joleen H. Blok, Ruud Veldhuizen | Afdeling KNF
Beste Gerhard, hartelijk dank voor het mede mogelijk maken van de vele EMG's op de afdeling KNF en de verhelderende overlegmomenten. Het bouwen van een EMG database was een hele klus, zeker als er ijs lag, maar het is gelukt! Gerhard, Joseph, Ellen en Judith, heel wat studiepatiënten hebben jullie gemeten, dank je wel. Judith in het bijzonder wil ik bedanken voor het (her)beoordelen van alle GRAPH EMGs en de prettige samenwerking. De KNF laboranten, Jannie en Michiel, wil ik bedanken voor de gezellige meetsessies en het invoeren van de EMG data in de database. Het secretariaat van de KNF en Ruud wil ik bedanken voor het kunnen plannen (en vaak weer verzetten) van de GRAPH patiënten.

Prof. dr. Gerard J.J. van Doornum, Dr. Hubert P. Endtz, Dr. Peggy C.R. Godschalk, Rogier Louwen, Ad Luijendijk, Machteld van Rede, Cobi Kerkhof, Sandra Scherbeijn | Afdeling Medische Microbiologie en Virologie
De baliemedewerkers van de afdeling Medische Microbiologie en Virologie wil ik bedanken voor het in ontvangst nemen en verwerken van de honderden kweekmonsters. Beste Gerard, jij zorgde er samen met Sandra voor dat de virologische bepalingen en interpretaties op tijd af waren, dank je wel! Je rustige manier van uitleggen, waardeerde ik zeer. Veel dank dat je deel uitmaakt van m'n promotiecommissie. Beste Hubert, Peggy en Rogier, ook voor de GRAPH studie werd er weer gezocht naar de campy. Bedankt voor de prettige samenwerking. Ad, bedankt voor het verzorgen van de talloze studiemapjes.

Dr. Wim C.J. Hop | Statisticus
Beste Wim, met behulp van de repeated measurements wist jij alle data van de GRAPH studie te gebruiken. Hartelijk dank voor de prettige overlegmomenten, je hulp en je uitleg.

Dr. Ingemar S.J. Merkies | Spaarne Ziekenhuis
Roberto E. Rico, Juan David Botero, secretariaat| Sint Elisabeth Hospitaal (Curaçao)
Izzy Gerstenbluth | GGD (Curaçao)
Beste Ingemar, dankzij jou was het mogelijk naar Curaçao te gaan voor het GBS onderzoek. Hier ben ik je erg dankbaar voor. Je lieve familie zorgde voor een warm welkom en onderkomen. Ook wil ik je bedanken voor je begeleiding in de begintijd van m'n onderzoek. Beste Roberto, dank voor de mogelijkheid langs te komen en me opweg te helpen in het Sint Elisabeth Hospitaal om het GBS onderzoek voort te zetten. Het secretariaat hielp me de statussen bij elkaar te zoeken, hartelijk dank. Beste Juan, bedankt voor het meehelpen en nasturen van de GBS gegevens. Beste Izzy, bedankt voor je uitleg over de regenstatistieken van het eiland en het nuttige werk wat je doet bij de GGD. Later heb je me nog allerlei GBS gegevens toegestuurd, dank je wel. Twee weken Curaçao waren twee onvergetelijke weken.

Patricia Blomkwist, Eimbert van de Oet | Vereniging Spierziekten Nederland
Beste Patricia en Eimbert, als geen ander weten jullie wat GBS patiënten doormaken en hoe ze een hart onder de riem te steken. Patricia, ik ben je heel erg dankbaar dat ik je elke keer weer kon bellen om de GBS patiënten in het Eramus MC te bezoeken. Daarnaast heb ik grote waardering voor de jaarlijkse organisatie van de GBS patiëntendag.

Lourens van Briemen, Kris Sieradzan | Computerhelden
Beste Lourens, dankzij jouw hulp werkte mijn computer en had ik die programma's die ik nodig had. Je was altijd bereid om een handje te helpen, dank je wel! Beste Kris, uren en uren zijn erin gaan zitten om al die vragenlijsten voor de GRAPH te ontwerpen in teleform. Heel wat discussies hebben we gevoerd of het nu zus of zo moest. Gelukkig was er altijd die heerlijke espresso. Dank je wel.

Arjenne, Betty, Caroline, Claudia, Elles, Erna, Isabel, Jacqueline, Joram, Legisa, Marja, Minah | Secretariaat
Beste Arjenne, jou wil ik bedanken voor allerlei regeldingen. Je was elke keer bereid om even te helpen. Bij jou was het papierwerk in goede handen. Het ga je goed. Betty wil ik bedanken voor het inplannen (en regelmatig ook weer verzetten) van de afspraken voor de GBS patiënten. Even binnenlopen voor een vraag of een praatje, het kon altijd. Beste Minah, jij deed altijd weer de moeite om wensen voor onderzoekstijd, congresbezoek en niet te vergeten vakanties in te plannen. Dank je wel. Beste Erna, dank je wel voor je interesse en het doorsturen van de post. De secretaresses van de polikliniek neurologie wil ik bedanken voor het klaarzetten van de benodigde spullen, het opzoeken van de statussen en de prettige werksfeer op de poli.

Alcidia, Alja, Chantale, Joyce, Magda, Marjolein, Nathalie | Doktersassistenten
De doktersassistenten wil ik bedanken voor het afnemen en wegbrengen van de vele buisjes bloed, het aanvullen van de benodigde spullen en de prettige samenwerking.

Verpleging van de afdeling Neurologie en Intensive Care
De verpleging wil ik bedanken voor de goede zorg voor de patiënten, het afnemen en wegbrengen van de kweken en de fijne werksfeer op de afdeling.

Nadine van der Beek, Janet de Beukelaar, Eric van Breda, Maaike Dirks, Laura Donker Kaat, Puck Franssen, Mary-Lou van Goor, Marloes Hagemans, Heleen den Hartog, Ilse Hoppenbrouwers, Nagmeh Jafari, Immy Ketelslegers, Ladbon Khajeh, Alex Korsten, Lisette Maasland, Bas ter Meulen, Karin ter Meulen, Rinze Neuteboom, Niels Prins, Sonia Rosso, Maaike Schuur, Harro Seelaar, Juna de Vries, Annemarie Wijnhoud, Marie-Claire de Wit | Overige collega's uit 'de witte toren'
Alle collega's van de hoogbouw wil ik hartelijk bedanken voor de goede tijd op de 22e. Naast jullie interesse wil ik jullie bedanken voor de ontspannende koffie-breaks. Nadine, Janet, Ilse, Naghmeh, Immy, Rinze en Juna, heel wat nuttige, maar zeker ook gezellige neuro-immunologie besprekingen of avondjes hebben we de afgelopen jaren gehad samen met de GBS onderzoekers, dank jullie wel. Bas, samen begonnen we in 2002 op afdeling 6 Noord en later ook op de 22e. Je was een fijne collega. Niels, de salsa lessen zorgden voor een swingende ontspanning. Juna en Ladbon, wat leuk dat jullie uiteindelijk toch in Rotterdam zijn komen werken. Ilse en Bregje, ik hoop dat onze etentjes nog lang door blijven gaan. Harro, m'n kleine buurjongen van vroeger, leuk je weer te ontmoeten op de 22e. Iedereen van de boekenclub, het waren mooie avonden. Marloes, jij hebt me wegwijs gemaakt in de repeated measurements, hartelijk dank hiervoor. Alle arts-assistenten en neurologen van de afdeling Neurologie die ik niet persoonlijk heb genoemd, bedankt voor de prettige samenwerking en alles wat ik van jullie heb geleerd!

Maarten Liedorp, Sonia Rosso, Annemarie Wijnhoud en alle andere collega's | Havenziekenhuis
1-1-2010 ben ik begonnen als Neuroloog in het Havenziekenhuis. Johan Dorresteijn en Ineke Leenders, dank voor jullie overtuigingskracht en aanstekelijk enthousiasme. Maarten en Sonia, het is toch heel bijzonder dat we allemaal zo ongeveer tegelijk gestart zijn in het Havenziekenhuis, we maken er iets moois van! Annemarie, heel veel succes in het IJsselland Ziekenhuis, we komen elkaar vast weer tegen. Collega's van de poli, KNF en afdeling Neurologie, eerste hulp en alle andere afdelingen, dank voor de nu al prettige samenwerking. Ik hoop nog vele jaren te werken in dit prettige, patiëntgerichte, zorgzame ziekenhuis!

Van Rotterdam tot Milaan | Mijn vrienden

Lieve vrienden, bedankt voor jullie vriendschap! Ook al hebben we elkaar niet veel gezien het afgelopen jaar, ik wist dat jullie er waren. Jullie zijn voor mij zeer waardevol! Iederéén bedanken is helaas niet mogelijk, toch ook een paar persoonlijke woorden van dank.

Ingrid, Lianne, Mirella, Saskia en Willeke, ieder via haar eigen weg begonnen we uiteindelijk samen aan de studie Geneeskunde in Utrecht. Onze gesprekken begonnen bij de koffieautomaat in het voormalige AZU. Door de jaren heen is onze band sterker en sterker geworden. Dank voor jullie vriendschap. Dat de bijzondere momenten met z'n allen nog heel lang mogen doorgaan! Lieve Lianne, we waren ook huisgenoten en zijn ongeveer tegelijk het promotietraject ingestapt. Heel wat hebben we de afgelopen jaren gedeeld met elkaar. Samen door de dalen en samen naar 'de top'. Dat we dit jaar elkaars paranimf zijn, vind ik erg bijzonder. Bedankt voor alles en 'to be continued'! Annemieke, Els, Evelien, Ingrid en Janneke, deels op dezelfde middelbare school en vervolgens samen gaan studeren. Wat heerlijk dat jullie niet in de medische hoek zijn beland. Bedankt voor de mooie vriendschap. Dear Veronica, I will never forget our very special times in Milano. Stefan en Kathalijne, onze vriendschap begon in Rotterdam, inmiddels zijn jullie verhuisd en wonen jullie helaas niet meer in de buurt. Dank voor de mooie gesprekken over het leven en hoe deze zijn weg kan gaan. Stefan, fantastisch dat je met ZZESTO mee wilde denken en werken aan het ontwerp voor de kaft van dit boekje samen met je collega Hendrik. Het is prachtig geworden, dank jullie wel! Elise, Ilse en Bregje, met jullie heb ik heel wat gesport en vooral ook heerlijk gegeten. Dank voor de gezellige, relativerende ontspanning! Amanda, het is toch een giller hoe parallel onze levens lopen en onze wegen elkaar elke keer weer kruisen, leuk! Vrienden uit Brabant, ook al zal ik nooit een echte Brabander worden, het is altijd erg gezellig om 'onder de rivieren' te zijn, bedankt!

Hennie, Toon, Meike, Jasper en Karin | Mijn 'schoonfamilie'

Hennie en Toon, bedankt voor het altijd welkom zijn op de Kivitslaan, jullie goede hulp om alles draaiende te houden in drukke tijden en jullie inspanning om met regelmaat er op uit te gaan met z'n allen, erg fijn! Meike, bedankt voor je gezelligheid, je vrolijkheid, je attentheid en je warmte. Te grappig dat jij mee ging helpen om Babinski te organiseren en dat ik samen met jou en m'n collega's heb geskied. Dat skiën hebben we sowieso heel wat jaren gedaan. Jij ging altijd sneller, maar dat mocht de pret niet drukken. Jasper en Karin, tijdens de weekendjes en etentjes hebben we het altijd erg naar ons zin, bedankt hiervoor.

Papa, mama, Jan Willem en Charlotte | Mijn familie

Lieve papa en mama, Wat ben ik een gelukkig mens dat jullie mijn ouders zijn. Met onbeschrijfbaar veel liefde, geborgenheid, zorgzaamheid en vertouwen ben ik opgegroeid.

Altijd hebben jullie mij gesteund in de keuzes die ik in mijn leven maakte. De adviezen die jullie mij daarin gaven waren: doe datgene waar je hart ligt en waar je lol in hebt. Dat heeft mij gebracht tot waar ik nu sta in mijn werk, maar zeker ook privé. Jullie bevonden je niet altijd naast de deur. Maar waar ook ter wereld, voor mijn gevoel waren jullie altijd dichtbij. Sowieso, en het laatste jaar in het bijzonder, hebben jullie klaar gestaan om te helpen. Zonder jullie hulp was het niet mogelijk de afronding van mijn proefschrift, mijn nieuwe baan als Neuroloog en het moeder zijn te combineren. Dank, dank, dank!

Lieve Jan Willem, je bent een kanjer van een broer, van wie ik ongelofelijk veel hou. Ik vind het dan ook geweldig dat je mij terzijde wil staan tijdens m'n promotie. Ook ben je nauw betrokken geweest bij het Guillain-Barré onderzoek. Dagen heb je op de 22e vragenlijsten geprint voor de GRAPH studie. Toen ik voor het Guillain-Barré onderzoek naar Curaçao ging, kwam jij me opzoeken. Jij was 5, ik 15, toen we al het plan hadden gemaakt om ooit een keer samen naar Curaçao te gaan. Toen Pieter mij in 2005 vertelde dat ik voor het Guillain-Barré onderzoek naar Curaçao mocht gaan, was jij dan ook de eerste die ik belde om mee te gaan. Jij bent zelfs verknocht geraakt aan het eiland en woont er nu. Ook hebben we samen de huidbiopten naar Milaan gebracht. Op de terugweg sloegen we nog even rechtsaf om een weekendje te kunnen skiën. De weg Rotterdam – Milaan heb jij nog meerdere keren gereden met een box bevroren huidbiopten in de achterbak. Onder andere een keer met Charlotte, inmiddels je grote liefde. Lieve Charlotte, ik ben heel erg blij dat jij bij onze familie bent gekomen. Bedankt voor je gezelligheid, warmte en heerlijke koken. Nu samen met Jan Willem op Curaçao, fantastisch dat jullie dit samen hebben ondernomen!

Lieve familie, we go far, we see the world, but we don't forget where we come from! Ik hou van jullie, grenzeloos veel.

Remko Sanders | Mijn grote liefde

Allerliefste Remko, ik ben je zo ongelofelijk dankbaar voor alles wat jij het afgelopen jaar op je hebt genomen om het promoveren te laten slagen. Kort nadat ons prachtig, lieve mannetje Abe geboren werd, begon de 'eindsprint' voor het proefschrift. Alles combineren leek een onmogelijke klus. Maar het was juist de combinatie die ervoor zorgde dat de wil er was de klus te klaren. Jij hebt hier een heel belangrijke rol in gespeeld. Ik heb heel veel bewondering voor hoe jij elke keer weer met je enthousiasme, zorgzaamheid, energie en liefde alles draaiende hield. Jij creëerde thuis enerzijds de rust en tijd om te kunnen werken in de avonduren en weekenden, anderzijds zorgde je voor de 'quality time' met Abe en elkaar waardoor het lukte om 'het schema' vol te houden. Hiervoor heb je heel veel opzij gezet en gegeven. Ook fietste je tussendoor nog even zes keer de Alpe d'Huez op

en neer in één dag voor het goede doel. Een klein voorbeeld om aan te geven hoe uniek ik je vind. Jij staat ergens voor, gaat ergens voor en leeft bewust het leven! Jouw 'zijn', geeft ons balans. Onze balans, geeft onze dromen. Onze dromen, geven ons leven. Lief, de reis door het leven met jou is prachtig mooi, en die mag van mij oneindig lang duren. Vanaf nu ook weer buiten de Wilhelminalaan!

ABE | Mijn alles

Lieve Abe, zo klein als je bent, zo groot is jouw rol geweest bij de afronding van dit proefschrift. Op de dag dat ik de inclusie voor de GRAPH studie stopzette, vond jij het tijd worden om geboren te worden. De clichés zijn waar: een wonder, een verrijking, een onvoorwaardelijk gevoel van liefde! Jouw tevredenheid, rust en regelmaat, zorgden voor mijn tevredenheid, rust en regelmaat. Je bent een heerlijk mannetje, voor wie ik de omvang van 'houden van' niet in woorden kan omschrijven. Wat is het toch fijn dat jij er bent!

ABOUT THE AUTHOR

Liselotte Ruts was born on November 3rd, 1974 in Schiedam, The Netherlands. In 1993 Liselotte passed her secondary school exam (Atheneum) at the Odulphus Lyceum in Tilburg.

In 1993 she started the study Medical Biology at Utrecht University. During this study she conducted research in the area of 'glutamate receptor modification in the brain of diabetic rats' (Institute of Pharmacological Sciences, Milan, Italy), and in the area of 'receptor modification in the brain of epileptic patients' (Rudolf Magnus Institute for Neuroscience, Utrecht). In 1997, Liselotte also started Medical School, at the same university. She obtained her Medical Biology degree in August 1999 and her Medical degree in January 2002.

From 2002 to 2009 Liselotte was resident in Neurology at Erasmus MC in Rotterdam (head Prof. dr. P.A.E. Sillvis Smitt). During this period she combined her residency with research underlying this thesis at the Department of Neuro-Immunology/Neuromuscular disorders of Erasmus MC under supervision of Prof. dr. P.A. van Doorn. She set-up and coordinated the nationwide GRAPH (GBS research about pain and heterogeneity) study and obtained part of her research material from Curaçao (Sint Elisabeth Hospitaal, Willemstad). For the skin biopsy part of her study Liselotte collaborated with the 'Carlo Besta' Neurological Institute in Milan (Italy). In 2008 she received a grant from the GBS/CIDP foundation and the 'Janivo Stichting' supported her research.

From January 2010 onwards, Liselotte works as a neurologist in the Havenziekenhuis / Harbour Hospital – Institute for Tropical Diseases – in Rotterdam

Liselotte lives in Rotterdam, together with her boyfriend Remko Sanders and their son Abe (2008).

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01. Di Luca M, **Ruts L**, Gardoni F, Cattabeni F, Biessels GJ, Gispen WH. NMDA receptor subunits are modified transcriptionally and post-translationally in the brain of streptozotocin-diabetic rats. Diabetologia 1999;42:693-701

02. van Doorn PA, **Ruts L**. Treatment of chronic inflammatory demyelinating polyneuropathy. Curr Opin Neurol 2004;17:607-613

03. **Ruts L**, van Koningsveld R, van Doorn PA. Distinguishing acute-onset CIDP from Guillain-Barré syndrome with treatment related fluctuations. Neurology 2005;65:138-140

04. **Ruts L**, van Koningsveld R, Jacobs BC, Van Doorn PA. Determination of pain and response to methylprednisolone in Guillain-Barré syndrome. J Neurol 2007;254:1318-1322

05. **Ruts L**, van Doorn PA, Blankevoort JP, Prens EP. Transient hypertrichosis in a patient with Guillain-Barré syndrome. J Peripher Nerv Syst 2007;12:290-292

06. **Ruts L**, Rico R, van Koningsveld R, Botero JD, Meulstee J, Gerstenbluth I, Merkies ISJ, van Doorn PA. Pain accompanies pure motor Guillain-Barré syndrome. J Peripher Nerv Syst 2008;13:305-306

07. van Doorn PA, **Ruts L**, Jacobs BC. Clinical features, pathogenesis, and treatment of Guillain-Barré syndrome. Lancet Neurol 2008;7:939-950

08. **Ruts L**, Jacobs BC, Blankevoort J, van Doorn PA. Autonome dysfunctie bij patiënten met het Guillain-Barré syndroom. Tijdschrift Neurologie & Neurochirurgie 2008;109:118-124

09. Dekker MJ, van den Akker EL, Koper JW, Manenschijn L, Geleijns K, **Ruts L**, van Rijs W, Tio-Gillen AP, van Doorn PA, Lamberts SW, Jacobs BC. Effect of glucocorticoid receptor gene polymorphisms in Guillain-Barré syndrome. J Peripher Nerv Syst 2009;14:75-83

10. Kuitwaard K, **Ruts L**, van der Pol WL, van Doorn PA. Individual patients who experienced both Guillain-Barré syndrome and CIDP. J Peripher Nerv Syst 2009;14:66-68

11. Kuitwaard K, van Koningsveld R, **Ruts L**, Jacobs BC, van Doorn PA. Recurrent Guillain-Barré syndrome. J Neurol Neurosurg Psychiatry 2009;80:56-59

12. Kuijf M, **Ruts L**, van Doorn PA, Koudstaal PJ, Jacobs BC. Diagnostic value of anti-GQ1b antibodies in a patient with relapsing dysarthria and ataxia. BMJ Case Reports 2009 [doi:10.1136/bcr.08.2008.0783]

13. **Ruts L**, Drenthen J, Jacobs BC, van Doorn PA. Distinguishing Acute onset CIDP from fluctuating Guillain-Barré syndrome; a prospective study. Accepted for publication in Neurology.

14. Walgaard C, Lingsma HF, **Ruts L**, Drenthen J, van Koningsveld R, Garssen MJP, van Doorn PA, Steyerberg EW, Jacobs BC. Prediction of respiratory insufficiency in Guillain-Barré syndrome. Accepted for publication in Annals of Neurology.

15. van Doorn PA, Kuitwaard K, Walgaard C, van Koningsveld R, **Ruts L**, Jacobs BC. IVIg treatment and prognosis in Guillain-Barré syndrome. Accepted for publication in J Clin Immunology.

16. **Ruts L**, Drenthen J, Jongen JLM, Hop WCJ, Visser GH, Jacobs BC, van Doorn PA. Pain in Guillain-Barré syndrome, a long-term follow-up study. Submitted for publication.

17. **Ruts L**, van Doorn PA, Lombardi R, Haasdijk ED, Camozzi F, Tulen JHM, Hempel RJ, van den Meiracker AH, Lauria G. Guillain-Barré syndrome: correlation study of skin biopsy and clinical features. Submitted for publication.

18. **Ruts L**, Drenthen J, van Doornum GJJ, Jacobs BC, Visser GH, Tio-Gillen AP, Herbrink P, Endtz HP, van Doorn PA. Infections, course of disease and outcome within the spectrum of Guillain-Barré syndrome, a prospective follow-up study. Manuscript in preparation.

PhD PORTFOLIO

General courses		
2006	Modern statistical methods, NIHES, Rotterdam, NL	4.3
2007	Biomedical English Writing, Rotterdam, NL	4
International conferences and presentations		
2003	International Congress (PNS, Banff, Canada) (poster presentation)	1
2004	European Congress (ENS, Barcelona, Spain) (oral presentation)	2
2005	International Congress (PNS, Pisa, Italy) (poster presentation)	1
2007	International Congress (PNS, Utah, USA) (2 poster presentations)	1
2008	International Congress (PNS, Paris, France) (poster presentation)	1
2009	International Congress (PNS, Würzburg, Germany) (oral + poster presentation)	2
National conferences and presentations		
2006	Neuromuscular study club, Utrecht, NL (oral presentation)	1
Seminars		
2002-2009	Department seminars	2
TOTAL		**19.3**