Treatment of Guillain-Barré syndrome and causes and treatment of residual fatigue

Marcel P.J. Garssen

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Treatment of Guillain-Barré syndrome and causes and treatment of residual fatigue

Behandeling van het Guillain-Barré syndroom
en oorzaken en behandeling van vermoeidheid

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Promotor:	Prof.dr. P.A. van Doorn
Overige leden:	Prof.dr. P.A.E. Sillevis Smitt
	Prof.dr. M.J. Zwarts
	Prof.dr. H.J. Stam
	Prof.dr. F.G.A. van der Meché
	Prof.dr. L.H. van den Berg
	Prof.dr. P. van den Bergh
	Dr. I.S.J. Merkies
Paranimfen:	M. Brinkhuijsen
	F.P. Garssen

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To my parents
For Nancy and the boys

CONTENTS

CHAPTER 1

Introduction

1.1 GENERAL INTRODUCTION

The Guillain-Barré syndrome (GBS) is an acute immune-mediated poly(radiculo)neuropathy, a disease of the peripheral nervous system, with a broad clinical spectrum and specific pathophysiological and electrophysiological features.[1,2] The incidence is fairly uniform ranging between 0.8 and 2 cases per 100.000 throughout the world.[3-5] In a retrospective study in the Southwest of the Netherlands, the overall incidence rate was 1.18 per 100.000 inhabitants, corresponding with about 200 cases yearly diagnosed in the Netherlands.[5] GBS is not restricted to a specific race, age group, or gender. However, most studies report that GBS affects males more than females, and that incidence increases linear with age.[3,5] About two-third of GBS patients report symptoms of an antecedent infection, mostly being a gastro-enteritis or respiratory infection, within three weeks prior to the onset of disease.[6-8] Neurological sequellae depend on localization and severity of involvement of nerve roots, motor, sensory and autonomic nerves during the disease process.

GBS is characterized by rapidly progressive, symmetrical limb weakness and reduction or loss of myotatic reflexes. Muscle weakness reaches its maximal severity (nadir), by an arbitrarily definition, within 4, but in the majority within 2 weeks.[9] Sensory deficits, autonomic dysfunction, and respiratory insufficiency may occur. The acute phase is followed by a plateau phase of variable duration, subsequently followed by spontaneous resolution of paralyses, resulting in variable degrees of recovery.[1] Recovery can be hastened with plasma-exchange (PE) and intravenous treatment with immune-globulins (IVIg) (see paragraph 1.4).

GBS was first described by J.B.O. Landry in 1859, however, the syndrome was named after G. Guillain, and J.A. Barré, two French army neurologists, who together with A.Strohl described the typical findings of 'dissociation albumino-cytologique' in the cerebrospinal fluid already in 1916.[10] To date, GBS is no longer considered as one single disease entity, but as a continuous spectrum, ranging from a pure motor form to a combination of motor and sensory nervous system disturbances with or without cranial nerve involvement. Electrophysiological studies are of additional value in further subdividing GBS in a demyelinating polyneuropathy, a pure axonal polyneuropathy, or a combination of these entities.[11,12] Presently, GBS is mostly divided in 4 subgroups, according to their clinical and electrophysiological features and disease course.[2,12-15] These include the classic acute inflammatory demyelinating polyneuropathy (AIDP), the most common subtype in the USA, Canada and Europe,[3,5,16] acute motor axonal neuropathy (AMAN), the most prevalent form in China and Japan, and probably also in some other regions (e.g. Curacao),[17-20] acute motor and sensory axonal neuropathy (AMSAN),[18,21] and the Miller Fisher syndrome (MFS),[22] which is characterized by ophthalmoplegia, ataxia and absence of myotatic reflexes. A transition or progression of MFS into generalized GBS is observed in a proportion of patients.[23] In addition, a number of uncommon regional variants may occur,[24] like pure ataxic GBS,[25] isolated bulbar palsy,[26,27] and pharyngeal-cervical-brachial GBS.[28,29]

The disease course may be so mild that medical attention is never sought. The proportion of GBS patients who remain able to walk, which is generally considered to be 'mild' GBS, ranges from 4.7% in a retrospective single hospital based study conducted in 254 patients,[30] to 14% in a population based prospective nationwide survey including 139 patients, and almost 30% in a retrospective epidemiological survey in the Netherlands.[5,31] However, the majority of patients suffer from a moderate or severe course of disease, defined as patients who are unable to walk unaided. For these patients a prolonged admission to a hospital will be necessary. Mechanical ventilation for days to months is needed for a prolonged period in 20 - 30% of patients with a severe course of disease.[32-35]

The cornerstone of therapy is supportive treatment.[36,37] Additionally, based on the immune-mediated and inflammatory character of GBS, several therapeutic regimens have been investigated. To date, IVIg is the preferred treatment for patients in the acute phase of GBS.[36-40] Despite these treatments and the general opinion that the majority of patients recover neurologically rather well, mortality and morbidity are still considerable. About 20% of the patients is still not able to walk unaided six months after onset.[5,8,40,41] In addition, up to 80% of all patients suffers from severe residual fatigue.[42]

In conclusion, GBS is nowadays recognized as an acute post-infectious immune-mediated polyneuropathy, with diversity in pathogenesis, clinical and electrophysiological features, functional outcome, and residual complaints. A majority of patients remains severely fatigued and restricted in their daily and social activities. To date, fatigue is considered one of the most disabling residual symptoms, seriously affecting quality of life.[42] The considerable percentages of mortality and morbidity, as well as the persisting residual neurological complaints including severe fatigue, were the most important reasons to initiate this study; 'treatment of GBS and causes and treatment of residual fatigue'.

1.2 DIAGNOSIS

The first diagnostic criteria for GBS were published in 1978 at the request of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS).[43] The reason for developing diagnostic criteria was related to an increasing incidence of GBS during the swine flu vaccination period in 1976 and 1977. In 1990, the criteria for the diagnosis of GBS were reaffirmed, and the electrodiagnostic criteria were expanded. These new and simple diagnostic criteria seem appropriate to clinically define GBS.[9] The diagnostic criteria include progressive weakness in two or more limbs reaching a maximum within 4 weeks, reduced or absent tendon reflexes in the weak limbs, and exclusion of alternative causes. Cerebrospinal fluid examination is performed especially to exclude other diagnoses (see table 1). Electrophysiological investigation is performed to support the clinical diagnosis of a polyneuropathy, and is of additional value in classifying the different disease varieties of GBS. The sensitivity of confirming a polyneuropathy

with electrophysiological measurements in GBS patients reaches 85% at admission and 93% at the nadir of disease. Specificity reaches 100% in GBS patients unable to walk without support (see table 2).[16]

As described before, GBS is generally divided in 4 subgroups. One of the clinical differences between these subgroups is the different pattern in speed of progression between AMAN and AIDP. AMAN mostly has a very rapid progression, whereas patients with AIDP in most cases have a somewhat longer evolution of increasing deficiency.[44] Therefore, new diagnostic and classification criteria have been proposed, based on the different clinical findings.[11] However, to date the NINCDS criteria are still most frequently used.

Table 1. Diagnostic Criteria for GBS[9]

Features required for diagnosis
- Progressive motor weakness of more than one limb
- Areflexia or marked hyporeflexia in very weak muscles (<grade 3 MRC)

Features strongly supportive of the diagnosis
- Progression over days to a maximum of 4 weeks
- Relative symmetry
- Mild sensory signs or symptoms
- Cranial nerve involvement
- Onset of recovery 2-4 weeks after progression stops
- Autonomic dysfunction
- Initial absence of fever at onset of symptoms
- Elevated CSF protein after the first week of symptoms
- CSF cell counts of 10 or fewer mononuclear leucocytes/mm^3 ($\leq 30 \times 10^6$)
- Abnormal electro diagnostics with conduction slowing or conduction block
- No other identifiable cause

Features casting doubt on the diagnosis
- Marked, persistent asymmetry of weakness
- Persistent bladder or bowel dysfunction
- Bladder or bowel dysfunction at onset
- More than 50 mononuclear leucocytes/ mm^3 in CSF ($>150 \times 10^6$)
- Presence of polymorphonuclear leucocytes in CSF
- Sharp sensory level

Features that rule out the diagnosis
- A current history of hexacarbon use
- Abnormal porphyrin metabolism
- A history or culture evidence of recent diphtheric infection
- Lead intoxication
- The occurrence of a purely sensory syndrome
- Diagnosis of poliomyelitis, botulism, toxic neuropathy (e.g. nitrofurantoin, dapsone, or organophosphorus compounds), tick paralysis, or hysterical paralysis

Table 2. Electrodiagnostic Criteria for GBS[16]

At least 3 of the following abnormalities should be demonstrated per nerve in at least 2 individual nerves

- Distal motor latency > ULN*
- Motor nerve conduction velocity < LLN*
- F-wave latency (given a normal distal motor conduction velocity) > ULN
- Sensory nerve conduction velocity < LLN
- Distal compound muscle action potential (CMAP)-amplitude < LLN
- Abnormal reduction of the CMAP-amplitude: CMAP-amplitude reduction exceeding ULN if distal CMAP > 5mV. If distal CMAP after distal stimulation < 5mV (measured peak to peak), abnormal CMAP-amplitude reduction if difference between distal and proximal stimulation at least 1mV
- Distal CMAP-duration > ULN (proximal versus distal stimulation)
- Increase of CMAP-duration > ULN
- Distal compound sensory nerve action potential (CSNAP)-amplitude < LLN
- Recruitment pattern: either absent or 'single pattern'
- Presence of denervation potentials (spontaneous muscle fiber activity)

*ULN = upper limit of normal
*LLN = lower limit of normal

1.3 PATHOGENESIS

GBS is the prototype of a post infectious immune-mediated illness; about 70% of all patients reports a preceding infection, the disease course is generally monophasic and recovery can be hastened using immune-modulating therapies. Antibodies against gangliosides (major constituents of the nerve cell membrane) are frequently present. There is evidence that molecular mimicry plays an important role (see figure 1 and 2). In molecular mimicry the host generates an immune response to an infectious agent that shares epitopic determinants present in the host's affected tissue.[6,45-47] Shared epitopes between *Campylobacter jejuni*, *Heamophilus influenzae*, cytomegalovirus (CMV), *Mycoplasma pneumoniae*, and nerve fibers have been identified as targets for aberrant cross-reactive immune-responses.[47,48] The immunological attack consists of deposits of immunoglobulins and complement on the axon and Schwann cell surface, accompanied by macrophage and T-cell infiltration of the nerve.[45,47,49-51] The majority of lesions are detectable along the ventral roots, proximal spinal nerves, and lower cranial nerves.[46] The spectrum of these pathological changes can range from focal or extensive demyelination in the presence or absence of cellular infiltration (i.e. AIDP), to axonal degeneration with or without demyelination or inflammatory infiltrates (i.e. AMAN or AMSAN).[1,46] The distinctive histopathological features mirror these clinical diversities of GBS. Whereas AIDP is characterized by macrophage-mediated demyelination with disruption of the myelin lamellae and some cellular infiltration, AMAN and AMSAN exhibit a macrophage-mediated axonal neuropathy, with scarce lymphocytic infiltrates, and macrophages entering the nerves via the nodes of Ranvier.[20,21,46]

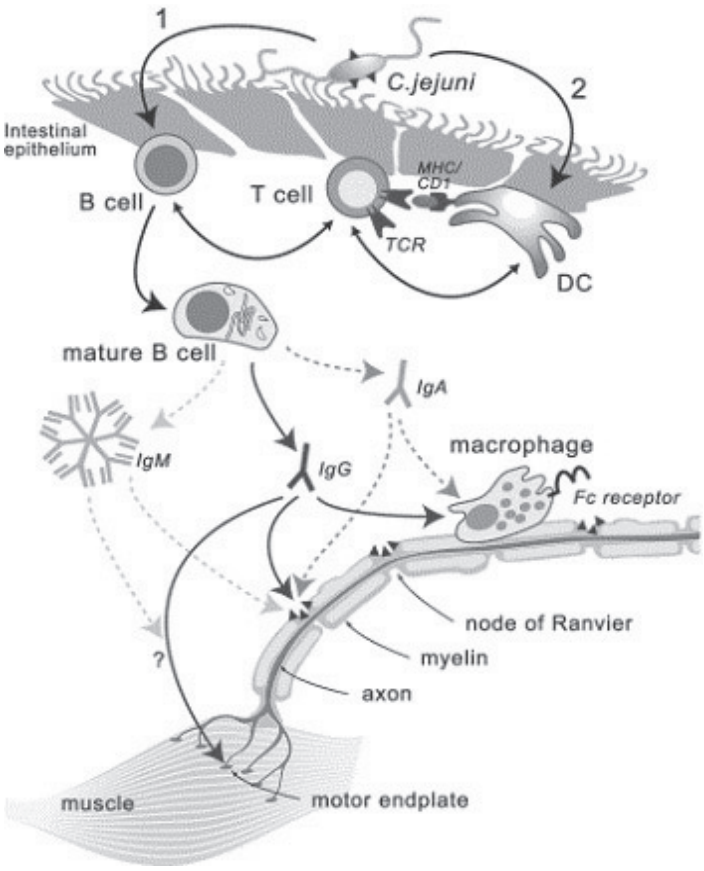

Figure 1. Schematic illustration of immune system involvement in GBS (From: N.M. van Sorge et al. Autoimmune reviews 3 (2004) 61-68).

The delay between a preceding infection and onset of symptoms suggests that not the infection itself but the remote effects or induced immune response to that infectious agent must play a role in the pathogenesis of GBS. Presently, there is evidence that both humoral immunity (auto-antibodies), and cellular immunity (T cells) play different and interactive roles in the different stages and histopathological subtypes of GBS.[46,51-56] It is likely that genetic factors also contribute, at least to the severity of GBS.[57,58]

Humoral immunity

Various observations suggest that humoral factors play a role in the pathogenesis of GBS. Anti-ganglioside antibodies are present in the acute phase sera in a proportion of patients with GBS, PE and IVIg treatment result in clinical improvement, and depositions of immune-globulins and complement has been demonstrated on myelinated fibers in nerve biopsies of GBS patients.[45] Furthermore, anti-gangliosides are able to fix complement,[59] immune-globulins can inhibit

pathophysiological effects at least through inhibition of antibody binding,[60] and immunisation with gangliosides induces an immune-mediated polyneuropathy in rabbits and mice.[51,61,62]

Cellular immunity

In experimental autoimmune neuritis (EAN), the combination of adoptive transfer of T cells with antibodies to antigenic epitopes expressed on the surface of Schwann cells, elicits more severe disease with more demyelination than adoptive transfer of T cells alone.[63,64] The role of T cells in the pathogenesis of disease is further supported by observations that EAN is not inducible in T cell deficient rats.[65] Additionally, although the effect and working mechanism of IVIg is complex, possible mechanisms of action of IVIg in GBS include, besides antibody binding and interference with the complement cascade, regulatory effects on T cells.[66-68] However, to date it remains largely unresolved to which extent T cells are involved in roles other than providing T cell help to antibody production.[45]

Genetic factors

Different observations favor a contribution of genetic or host factors related to the susceptibility to develop GBS. This is partly based on the fact that in the Netherlands at least 12 families have been identified in which more than one family member suffered from GBS, and that GBS occurred slightly more frequent within siblings.[69] At least one individual patient developed GBS at 4 different occasions. Additionally, in the general population, GBS rarely occurs after an infection with one of the common infectious agents frequently reported in GBS. Only about 1 out of 1000 patients suffering from Campylobacter jejuni enteritis develops GBS.[70] In one family suffering from Campylobacter jejuni enteritis, only one member, the one with high titers anti-ganglioside antibodies, developed GBS.[71] Additionally, when a person suffered from GBS, it was calculated that this patient has a 10-50 fold increased risk to develop GBS for a second time.[72] Finally, there is evidence that some single nucleotide polymorphisms (SNPs) in genes encoding molecules involved in nerve damage are associated with the severity of disease and outcome.[58] Although all mentioned observations suggest the involvement of genetic factors, it is difficult to identify general genetic factors related to disease susceptibility, since susceptibility genes may be so numerous, their interactions so divers and dependent on the type of antecedent infections.[58,73]

Although novel insights in immunology and advances in biotechnology have contributed to an increased understanding of the different underlying pathological mechanisms, many aspects of disease still have to be elucidated. To date, GBS is considered an organ-specific immune mediated disorder, emerged from a synergistic interaction of humoral and cell-mediated immune responses to still incompletely characterized peripheral nerve antigens, in which genetic/host factors are likely to play a role.[46]

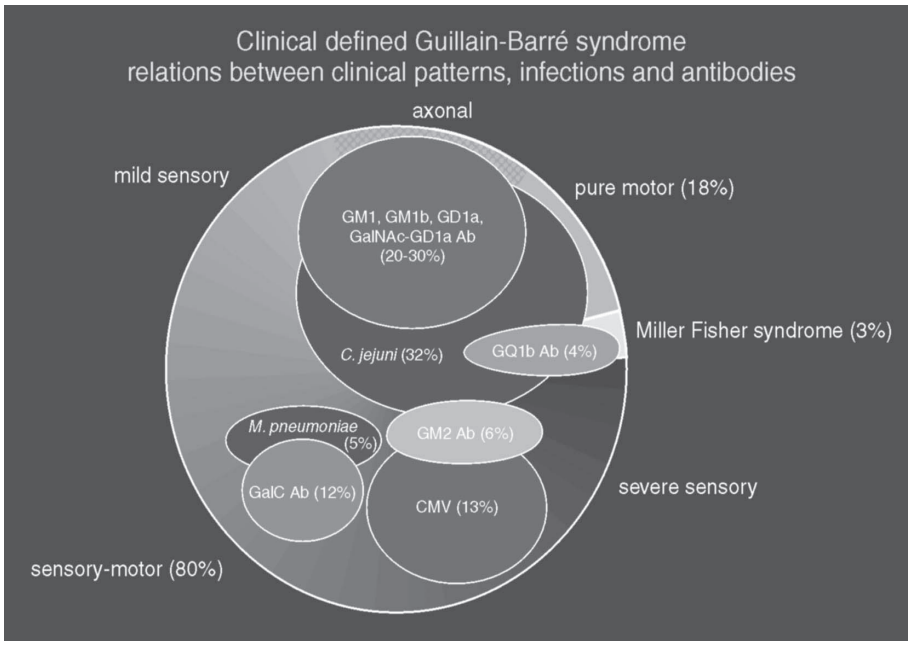

Figure 2. Diagram presenting in a semi-quantitative way the relation between clinical characteristics, infections and antibodies.

1.4 TREATMENT

Although specific therapeutic interventions are available nowadays, the cornerstone of therapy is supportive treatment.[1,37] Patients with GBS need to be admitted to a hospital for close observation.[36,74] GBS may cause, in addition to paralysis and respiratory failure, many general medical problems that could have great bearing on outcome. General medical care requires special attention in paralysed patients. Progression to mechanical ventilation is highly likely in patients with rapid disease progression, bilateral facial weakness, dysautonomia, impaired vital capacity (less than 20 ml/kg), and in patients with low maximal inspiratory and expiratory pressures.[75] It can happen with alarming speed of progression that intubation and mechanical ventilation may be necessary within 24-48 hours from onset of symptoms.[1] Problems with swallowing and progressive weakness may cause aspiration and respiratory tract infections. Prevention of respiratory infection, deep vein thrombosis, and pulmonary embolism should have attention, especially in paralysed and immobilized patients. Dysautonomic problems such as blood pressure instability (hyper- and hypotension), cardiac arrhythmias, or ileus may occur. Patients need to be checked regularly for urinary tract infections, gastrointestinal dysfunction, and hyponatremia. Many patients suffer from serious pain, varying from severe back pain, radicular pain or dys- and paresthesias.[76] Throughout the illness, psychological aberrations and communication problems must be addressed.[32,77]

Based on the immune-mediated and inflammatory character of GBS, several treatment regimens have been studied.[36,39] In most treatment trials only patients were included who were within 2 weeks after onset of symptoms and unable to walk independently. Outcome measures were mostly based on the GBS-disability scale (or f-score).[78,79] The score from this seven point functional scale ranges from f=0 representing healthy, or f=1; minor symptoms and capable of running, to f=5; requiring assisted ventilation for at least part of the day, or f=6; dead (table 3).[78,79]

Table 3. The GBS disability scale (F-score)[79]

F-score	Definition
0	Healthy
1	Minor signs or symptoms of neuropathy but capable of running
2	Able to walk without support or a stick but incapable of running
3*	Able to walk with a stick, appliance, or support
4*	Confined to bed or chair bound
5*	Requiring artificial ventilation
6	Dead

** GBS patients with F-scores of 3, 4, or 5 are generally considered for participation in randomized controlled treatment trials. GBS patients with F-scores of 1 or 2 are considered as mild patients.*

It has been shown that GBS-patients unable to walk independently (f-score of 3 or worse), benefit from PE or IVIg, when started within two weeks from onset of weakness (see table 4).[34,80-84] PE reduced the median time to regain the ability to walk unaided from 85 to 53 days (table 5).

Treatment with IVIg is at least equally effective as PE, but more convenient to administer, with less side effects.[83] Randomised trials on the effect of PE and IVIg show a median time towards independent walking ranging between 49 and 70 days (see table 4 and 5).[34,80,83,84] PE followed by IVIg is not significantly superior to one of these treatments alone.[84] In one study comparing 3 or 6 days of 0.4g/kg/day IVIg in patients with contra-indications for PE, there was a trend toward a better outcome in the group receiving 6 treatments. Outcome was significantly improved only when ventilated patients were considered.[85] In a recent study in children unable to walk unaided, there was no significant difference in the effectiveness of 2 g/kg IVIg administered over 2 days versus 5 days, although early "relapses" occurred more frequently after the shorter treatment regimen.[86] Presently, IVIg, in a dosage of 0.4g/kg/day for 5 consecutive days, or in a dosage of 1g/kg/day for 2 consecutive days remains the preferred treatment for patients with GBS.[1,36,84,87] It is known from different trials that corticosteroids administered alone are not of benefit.[78,88-90] Recently, a randomised controlled trial was published, in which the additional effect of methylprednisolone (500 mg intravenously/day for 5 consecutive days) when added to IVIg was investigated.[91] In contrast to an earlier conducted pilot study,[92] the primary endpoint in patients treated with the combination of IVIg and MP was not statistically significant

different. However, after adjustment for various non-study driven factors, there appeared to be a favourable short-term effect of the combined treatment, only for the primary outcome measurement four weeks after onset of treatment.[91]

Table 4. Randomized controlled trials in GBS

Year	Investigators	N	Therapy	Primary endpoint	Result
1978	Hughes et al.[78]	40	Low dose prednisone vs placebo	Improvement of ≥1 grade on the GBS disability scale at 4 weeks	Prednisone not effective
1985	North American GBS study group[80]	245	PE vs supportive care	Improvement of ≥1 grade on the GBS disability scale at 4 weeks	PE effective
1987	French Cooperative group[83]	220	PE vs supportive care	The time to recover walking with Assistance	PE effective
1992	The Dutch GBS study group[34]	150	IVIg vs PE	Equal improvement on the GBS disability scale at 4 weeks	IVIg = PE
1993	GBS steroid trial group[88]	242	High dose prednisone vs placebo	Improvement of 0.5 grade on the GBS disability scale at 4 weeks	Prednisone not effective
1997	French Cooperative group[82]	556	0 vs 2 PE in mild, 2 vs 4 PE in moderate, and 4 vs 6 PE in severe patients	Time to onset of motor recovery in mild group Time to reach GBS disability grade 3 in moderate and severe group	2 PE effective in mild, 4 PE effective in moderate, 4 PE = 6 PE in severe group
1997	PE /Sandoglobulin GBS trial group[84]	379	IVIg vs PE vs IVIg + PE	Difference in mean improvement in disability grade after 4 weeks, < 0.5 GBS disability grade for equivalence.	IVIg = PE = IVIg + PE
2000	The Dutch GBS study group[91]	225	IVIg + MP vs IVIg + placebo	Improvement of ≥1 grade on the GBS disability scale at 4 weeks	IVIg + MP = IVIg + placebo. IVIg + MP effective after correction known prognostic factors

Table 5. Median time in days to independent walking in RCT's in GBS

Study	Treatment	Placebo	PE	IVIg	IVIg + PE	MP	IVIg + MP
North American GBS study group[80]	PE	85	53				
French Cooperative Group[83]	PE		70				
Dutch GBS study Group[34]	IVIg vs PE		69	55			
PE/Sandoglobulin GBS trial group[84]	IVIg vs PE vs IVIg + PE		49	51	40		
GBS steroid trial group[88]	MP	50				38	
Dutch GBS study Group[91]	IVIg vs IVIg + MP			56			28

It is presently not well known whether mildly affected patients should be treated with IVIg. Only one trial evaluated the effect of PE in patients still able to walk without aid at time of randomisation. It was argued that early treatment in these patients might be helpful.[93] In another study in 72 children with GBS, there was a trend that treatment with IVIg before loss of unaided walking did not give rise to a less severe course, but recovery occurred somewhat faster.[86] Despite these findings, it is still debatable whether mild patients should be treated with immune-modulating therapy besides supportive care. Trials investigating this important issue are urgently needed.

In 2003 the Quality Standards Subcommittee of the American Academy of Neurology published the practice parameter of immunotherapy for GBS, to provide an evidence-based statement to guide physicians in the management of immunotherapy in GBS. It was stated that treatment with PE or IVIg hastens recovery, but that the combination of IVIg and MP, and steroid treatment given alone is not beneficial. It was recommended that non-ambulant adult patients with GBS within 2 or possibly 4 weeks of the onset of neuropathic symptoms should be considered for treatment with IVIg. PE was recommended for non-ambulant adult patients with GBS who seek treatment within 4 weeks of the onset of neuropathic symptoms. PE should also be considered for ambulant patients examined within 2 weeks of the onset of neuropathic symptoms. The effects of PE and IVIg were considered to be equivalent. Corticosteroids were not recommended for the management of GBS. Sequential treatment with PE followed by IVIg, or immune-absorption followed by IVIg was not recommended for patients with GBS, and PE and IVIg were both considered treatment options for children with severe GBS.[36]

Despite all above-mentioned treatments, mortality is 3-13%, and about 20% of the severely affected GBS patients randomised in the treatment trials is still not able to walk unaided after six months.[8,40,41] Additionally, a majority of patients remain severely fatigued, restricted in their daily and social activities, and is known with a significantly decreased quality of life. These complaints may persist for many years.[41,42,94,95]

1.5 PROGNOSIS / OUTCOME

Although it is not systematically studied, it seems to be a general believe that most patients suffering from a mild course of disease may show a neurologically good recovery. However, in one study it was found that also patients with a mild course of disease may suffer from residual morbidity.[31] In patients with severe course of disease, about 25% need mechanical ventilation for a prolonged period.[32-35] Prognosis ranges from complete neurological recovery with or without fatigue,[42] to wheelchair dependency or dead. Mortality rates range from 2 to 13%.[3,14,34,80,83,84,96,97] The most common causes of death after GBS are respiratory failure, cardiovascular and autonomic disturbances, and thrombo-embolisms.[1,36,74]

The considerable differences in outcome were one of the reasons to study prognostic factors. Another important reason to explore prognostic factors was development of new treatment strategies for those with a poor prognosis. Additionally, the prediction of the clinical course and residual outcome might be helpful to improve information and support to the individual patient. To date it is known that different, mainly clinical factors are the main predictors of outcome in GBS. These worse prognostic factors include older age, severe and rapid onset of weakness, a preceding gastrointestinal illness or recent CMV infection, severely reduced compound muscle action potential amplitude, and a low MRC-sumscore at randomisation.[14,33,41,96,98-104] This MRC sumscore is a score assessed in six bilateral muscles of arms and legs: upper arm abductors, elbow flexors, wrist extensors, hip flexors, knee extensors, and dorsal foot flexors. Scores are mostly given in full numbers, yielding a sumscore ranging from 60 (normal) to 0 (quadriplegic).[78] A recent interesting study aiming to identify clinical factors present at admission related to outcome showed that a lower MRC sumscore, a higher age and the presence of diarrhea are the main predictors of poor neurological outcome.[105] One study found that poor recovery is present in 86% of 71 patients who required ventilation and who failed to improve to independent breathing within 3 weeks.[106] Another study on 114 patients admitted to the intensive care unit, reported that 79% out of 60 GBS patients who initially needed mechanical ventilation improved to independent walking.[41] Although recovery from severe GBS may be prolonged, most survivors regain independent ambulation.

Long-term outcome of motor dysfunction / ambulation

Most studies about long-term follow-up studies determined functional outcome using a disability scale, predominantly based on motor function of the legs.[78] Because this functional scale, the GBS disability scale (table 3), does not provide information regarding the arms, a new overall disability scale in immune-mediated polyneuropathies was evaluated and demonstrated all clinimetric requirements for adequately monitoring impairment disturbances leading to disability.[107] However, to date most studies are still based on the GBS disability scale.

The time of follow-up in studies evaluating functional outcome generally range from 1-2 years.[3,14,35,41,96,97,108] These studies revealed 'poor' functional outcome in 17-30%, mild

handicap / functional outcome in up to 35% of patients, and complete recovery in 35-71%. One epidemiological study reported that 8% had died, 4% remained bed bound or ventilator dependent, and 9% was unable to walk unaided after 1 year.[3] A retrospectively conducted study in 223 patients, showed that 60% of all patients had normal muscular force in limbs and no cranial nerves deficit, 2 years after disease.[108] Only a few studies showed data after a follow-up time ranging from 3 to 24 years.[94,95,109-111] In these studies, complete recovery was found in 35-90%, and (minimal) residual motor signs were found in 21-35%.[94,110] In 30% of patients a moderate or severe residual paresis was found after a period up to 24 years of follow-up.[94] The most serious residual neurological deficits were localized distally, in the lower limbs, and in muscles innervated by nerves running along entrapment sites.[94,110]

Long-term outcome of sensory dysfunction

Besides the residual motor phenomena and functional outcome scales described in many follow-up studies in GBS, sensory dysfunction generally receives little attention. However, it is reported that 38% of patients still suffers from sensory deficits in the arms and 66% of patients still suffers from these deficits in the legs, 3 to 6 years after GBS.[112] A considerable number of patients considers these complaints as moderately to seriously disruptive. Muscle pain and cramps seemed to be related more to sensory rather than motor dysfunction.[112] Sensory changes like decreased sensation or positive sensory complaints have been reported in 20 to 69% of cases.[35,94,108,110,112] Disturbed sensation of vibration is the most common finding, although light touch, joint position, and pinprick can also be found at long-term follow-up.[112]

Long-term electrophysiological outcome

Recovery from GBS mainly depends on remyelination and compensatory reinnervation, as is known from electrophysiological studies the first year after onset of disease.[11,16] However, only few studies about long-term electrophysiological outcome have been reported.

It was shown in a long-term follow-up study (up to 9 ½ years) in 10 GBS patients that initial decrease in motor unit numbers is followed by a progressive increase with the passage of time from onset of disease.[113] Others confirmed these acute changes in evaluating motor unit number estimation.[114] It was found in other long-term follow-up studies that persisting signs of demyelination (prolonged distal latencies and slowed conduction velocities) were occasionally noticeable, even many years after the acute phase of the syndrome, and even in completely symptom free patients.[115] Spontaneous muscle activity and abnormal nerve conduction were also described, without having a strong relationships with residual paresis, 11 years after GBS.[116]

One of the best electrophysiological studies in GBS was recently published. It was shown that reinnervation takes place in 76% of all patients. Axonal loss was noticed in a substantial number of GBS patients and was associated with permanent muscle weakness caused by insufficient reinnervation.[117] In a long term follow-up study in 40 GBS patients, features of a residual

polyneuropathy (clinical or electrophysiological) was present in almost half of all patients. It leads to motor and sensory dysfunction, and showed a trend toward an impaired self-reported physical health status.[118]

Long-term psychosocial outcome

Many patients suffer from psychosocial problems after GBS. Psychosocial functioning remains seriously affected, even when patients showed physical recovery or only suffered from (mild) residual signs in a substantial number of patients.[119] In about 30-70% of patients, GBS caused alterations in work, ranging from ending working career to work at a lower level.[94,95,109] It was found that up to 63% of patients, initially unable to walk independently more than 10 meters (F-score ≥ 3), showed one or more changes in lifestyle, work, leisure activities, or in life with partners, 3 to 6 years after onset of GBS. Changes were influenced by impaired final functional outcome along with poor physical condition, although some physically well-recovered patients showed these changes as well.[95,111,119] Finally, also long-term fatigue is present in up to 80% of patients, irrespective of the presence of residual signs or good neurological recovery (see paragraph 1.6)[42]

1.6 FATIGUE

Merkies and co-workers noticed that, despite relatively good neurological recovery after GBS, many patients remained restricted in daily and social activities.[42] These patients addressed fatigue as one of the most important causes of their dysfunction. Although fatigue and endurance intolerance already have been mentioned as a residual complaint in the past, these complaints were only described sparsely and never studied systematically.[32,95,120-122] For example, it was already known that soldiers, who were clinically recovered from GBS, might exhibit a deficit during strenuous exercises requiring maximal effort and muscular endurance.[122] Others mentioned that physical fatigue often occurred, mainly in the first year after onset of GBS.[32] In a follow-up study it was found that more than half of GBS patients showed loss of power and poor condition, 3-6 years after GBS. These complaints were partly influenced by an impaired final functional outcome, although physically recovered patients showed these changes as well.[95] Until the above-mentioned study by Merkies et al, it seemed that fatigue after GBS remained under-recognized by neurologists and rehabilitation physicians.[42]

Merkies determined the prevalence and severity of ongoing fatigue in 113 patients suffering from immune-mediated polyneuropathies, using a controlled, cross-sectional study design. Eighty-two of these patients had experienced GBS in the past, mean 5.2 years ago.[42] Fatigue severity was evaluated using the Fatigue Severity Scale (FSS), a brief and self-assessed 9-item questionnaire, with answers ranging from 1 ("strongly disagree") to 7 ("strongly agree") for each inquiry (see table 6).[42,123] The mean score of the 9 inquiries ranges from 1 ("no signs of fatigue")

to 7 ("most disabling fatigue"). Severe fatigue, arbitrarily defined as a FSS score ≥ than the 95th percentile (FSS score ≥5.0) in healthy controls, was demonstrated in 80% of all patients with immune-mediated polyneuropathies. Fatigue, distinguishable from the transient and mild fatigue many healthy persons experience, was significantly associated with a reduced quality of life, and the majority of patients rated their complaints about fatigue among one of their three most disabling symptoms. Fatigue appeared to be independent of muscle strength, sensory deficits, functional ability, and duration of symptoms.[42] It was noticed that fatigue is a long-term, prominent and highly disabling symptom in the majority of patients with immune-mediated polyneuropathies. Additionally, the FSS seemed appropriate for assessing fatigue in these patients, based on good internal consistency, test-retest reliability, and validity.

Table 6. The Fatigue Severity Scale (FSS)[42,123]

FATIGUE SEVERITY SCALE							
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 with 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 my three 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

Legend to Table 6. The mean score of the 9 inquiries ranges from 1 ("no signs of fatigue") to 7 ("most disabling fatigue"). Severe fatigue was defined as a mean FSS score ≥5.0.

Although recently more attention is paid to fatigue as a residual complaint, its underlying pathophysiological mechanisms remain unknown.[42] Clear treatment strategies to relieve fatigue were lacking, although a few small studies reported possible benefits of physical exercise training. Only one study reported that physical exercise might lead to further impairment of muscle function[124]. The other reports described positive effects of low-intensity training interventions on fatigue, fitness, and quality of life in a limited number GBS patients.[125-127] One patient, still suffering from residual symptoms following GBS, was able to improve his cardiopulmonary and work capacity, isokinetic strength of his legs, and activities of daily living after a 16 week during supervised training program.[125] Others described positive effects of low-intensity aerobic exercise programs in a limited number of patients with immune-mediated polyneuropathies and chronic peripheral neuropathies.[126,127] As far as we know, no further

exercise studies or pharmacological intervention studies aiming to treat fatigue, have been performed, before we started our studies.

1.7 OUTLINE OF THIS THESIS

Since GBS - despite all different treatment regimens - remains a disease that results in considerable co-morbidity and mortality and because it is associated with long-lasting residual neurological deficits - in particular severe residual fatigue - we initiated the studies described in this thesis. The aim of this thesis was threefold; firstly, to develop a new treatment strategy for the acute phase of GBS, secondly to develop treatment strategies for severe residual fatigue and finally to increase insight in the underlying causes of this invalidating complaint.

Chapter 2 focuses on treatment of immune-mediated polyneuropathies. In **chapter 2.1** an overview of different treatment strategies in patients with immune-mediated polyneuropathies is described. **Chapter 2.2** is about an open-label study, in which the additional effect of mycophenolate mofetil (Cellcept®), administered together with IVIg and MP, was studied in 26 GBS patients. The aim of this pilot was studying whether this treatment combination was safe to administer and whether this combination seemed more effective than treatment with the combination of IVIg and MP.

Chapter 3 focuses on treatment of residual fatigue after GBS. **Chapter 3.1** is about a double blind, placebo controlled, randomized, cross-over trial studying amantadine. This study aimed to reduce severe fatigue in 80 GBS patients. In **chapter 3.2** the effects of a 12-week during bicycle exercise training on fatigue, physical fitness and quality of life are described. Twenty severely fatigued GBS and CIDP patients participated. In **chapter 3.3** the long-term changes in fatigue, fitness, and quality of life are studied, mean more than 2 years after the training intervention as described in chapter 3.2.

Chapter 4 mainly focuses on residual fatigue and its possible underlying pathophysiological mechanisms. In **chapter 4.1** the relation between severe fatigue in GBS and clinical characteristics, disease course, and antecedent events is described, in a cross-sectional study within a prospective nationwide survey in the Netherlands. **Chapter 4.2** is about conventional nerve conduction studies in relation to residual fatigue in GBS and CIDP. In **chapter 4.3** changes in nerve conduction velocity distribution are described. This was studied in the motor median nerve, in neurologically well-recovered but fatigued GBS and CIDP patients. In **chapter 4.4** the results of a study on the relative contributions of central and peripheral factors during a fatiguing 2-minutes maximal voluntary contraction are discussed in relation to residual fatigue in GBS. In **chapter 4.5** the favourable effects of physical exercise training in fatigued GBS and CIDP patients is discussed related to physical fitness, fatigue and physical and mental functioning.

Finally, in **chapter 5** the results of the different studies are discussed and future perspectives are given.

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CHAPTER 2

Studies on treatment of Guillain-Barré syndrome

CHAPTER 2.1

Treatment of immune neuropathies

Van Doorn, P.A., and Garssen, M.P.J.

From the Department of Neurology; Erasmus Medical Center, Rotterdam, The Netherlands

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ABSTRACT

Purpose of the review Guillain-Barré syndrome (GBS), chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN) are potentially treatable disorders. The use of appropriate assessment scales to evaluate the effects of treatment is essential. Recent therapeutic trials and the question of whether patients with mild disease or other variants of these disorders need to be treated are discussed.

Recent findings Recent clinical trials and Cochrane reviews give new information on the effect of various treatments in patients with GBS, CIDP and MMN. Intravenous immunoglobulin remains the only treatment proven to be effective in MMN. Combinations of treatment may be even more effective in GBS. Studies on prognostic factors related to improvement have been reported. Whether patients with Miller Fisher syndrome or those with mild GBS should also be treated is still debated. New assessment scales at the disability and handicap level have now been evaluated for GBS and CIDP, and are ready for use. Results of studies in experimental models contribute to our understanding of the mechanism of action of intravenous immunoglobulin.

Summary Recent new information on the use of intravenous immunoglobulin and steroids indicate that the former should remain the cornerstone of treatment for GBS and MMN, and probably also for CIDP. Whether steroids not only suppress disease activity in CIDP but also eradicate the disease remains to be established. Some GBS patients have secondary deterioration or finally turn out to have CIDP; additional information in this group of patients may lead to more appropriate disease management. Most patients with CIDP and those with MMN need long-term treatment. New treatment strategies should now focus also on the effect and the costs of treatment over long-term follow up.

INTRODUCTION

Immune-mediated neuropathies are associated with a broad range of symptoms, severity and duration of progression. These disorders may share immunological mechanisms following antecedent infections in some patients but not in all, and are potentially treatable [1]. Most studies have been conducted in patients with Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). These disorders appear to be variants of one disorder, with very acute GBS patients at one end of the clinical spectrum and slowly progressive CIDP patients at the other.

Treatment trials have investigated whether prednisone, plasma exchange, or intravenous immunoglobulin (IVIg) are effective. Over the past few years more anecdotal reports on other immune modulatory drugs were published. Recent trials evaluated different dosage schedules of one single treatment or combinations of treatments. New potential effective treatments such as cerebrospinal fluid (CSF)-pheresis were also evaluated. IVIg presently remains a cornerstone of treatment for GBS, multifocal motor neuropathy (MMN) and, in many centres, for CIDP. Studies on the mechanisms of action of these various treatments remain scarce. GBS is a disorder in which infections, antiganglioside antibodies and molecular mimicry may cause or at least contribute to development of the disorder [2**,3**,4*,5*,6]. It is expected that plasma exchange at least removes possible pathogenic antibodies or other circulating agents, and that IVIg interferes with either antibody production or function. The present review discusses clinical indications and the effects of various treatments for GBS [including Miller Fisher syndrome (MFS)], CIDP and MMN.

Assessment of the effect of treatment

Improvement following treatment can be determined at various levels, including impairment, disability, handicap and quality of life. In order to assess a particular effect of treatment in immune mediated neuropathies, appropriate scales should be applied. An outcome measure needs to be relatively simple, valid and reliable. In addition, a scale needs to be responsive, so that it will permit study of the effects of treatment during the course of disease. In GBS, the seven-point Hughes' disability scale is most widely used. In CIDP the modified Rankin disability scale has been used. Merkies and the Immune-mediated Neuropathy Cause and Treatment group [7,8*,9*] have clinimetrically evaluated various (pre-existing but also newly developed) assessment scales in patients with GBS, CIDP and monoclonal gammopathy of undetermined significance (MGUS) neuropathies. A selection of these scales may be used to evaluate the effects of treatment in patients with immune mediated polyneuropathies. A trial comparing the effect of steroids and IVIg in patients with CIDP [10**] was the first to use these outcome measurements.

GUILLAIN-BARRÉ SYNDROME

Most important in the treatment of GBS is excellent general and intensive care facilities, including respiratory care, monitoring and early treatment of autonomic disturbances, anticoagulation and good nursing care [11]. Chalela [12] evaluated the 'pearls and pitfalls' of intensive care treatment of GBS. When to admit a patient to the intensive care unit is an important issue. Progression to mechanical ventilation was highly likely in GBS patients with rapid disease progression, bulbar dysfunction, bilateral facial weakness or dysautonomia; in patients with vital capacity less than 20 ml/kg; and in patients with low maximal inspiratory and expiratory pressures [13*]. These data may be used in deciding whether to admit a patient to the intensive care unit and whether to prepare for elective intubation. Pain can be a serious problem in GBS. Enhancement of the cauda equina on magnetic resonance imaging has been found in children presenting with lower limb and back pain [14]. Carbamazepine or treatment with steroids was reported to relieve the pain. Whether pain in general decreases rapidly or occurs less frequently in the adult population after treatment with methylprednisolone will be resolved following analysis of data from a recently completed trial of IVIg combined with methylprednisolone (see Corticosteroids alone and in combination with intravenous immunoglobulin, below).

GBS may be subdivided into the most common form, namely acute immune-mediated demyelinating polyneuropathy, and the generally more rarely occurring varieties: acute motor axonal neuropathy, and acute motor and sensory axonal neuropathy [15]. Because treatment studies are generally conducted in the whole group of severely affected GBS patients, further subclassification is not made here. The cranial nerve variant MFS is discussed separately because it occurs more frequently, because it is related to the presence of anti-GQ_{1b} immunoglobulin G antibodies, and because recently developed research models (using MFS serum or anti-GQ_{1b} antibodies) can be used to study the mechanism of action of IVIg and guide the search for possible even more effective treatments in GBS (see Miller Fisher syndrome and other variants of Guillain-Barré syndrome, below).

Intravenous immunoglobulin and plasma exchange

Plasma exchange is the first and only treatment in GBS that has been proven to be superior to supportive treatment alone [16*]. It reduces the time to independent locomotion by approximately 1 month (45-83 days) when applied within the first 2 weeks of disease [17,18]. IVIg is an effective treatment for patients with GBS who are unable to walk unaided and are still within the first 2 weeks from onset of disease. IVIg and plasma exchange have a similar ability to hasten recovery from GBS [19,20,21*]. The largest GBS trial ever conducted [20] did not show significant differences between IVIg, plasma exchange, or plasma exchange followed by IVIg. The referral pattern and outcome of GBS patients was studied in The Netherlands [22*]. It was found that, following the introduction of IVIg as an effective treatment, fewer GBS patients were transferred from small to large hospitals and that this did not result in a worse outcome

in those patients treated in small centres. It was concluded that the introduction of IVIg has led to better use of different levels of health care facilities. For reasons of convenience and safety, and particularly in children and in patients with autonomic instability, IVIg is used as standard treatment in most centres [23]. Kazatchkine and Kaveri [24**] recently reviewed the general proposed mechanisms of action of IVIg.

Intravenous immunoglobulin dosage

The best dosage of IVIg in GBS is not known. IVIg is usually administered at a dosage of 0.4 g/kg body weight for 5 consecutive days. However, a total dose of 2 g IVIg/kg applied over 2 days may act more rapidly, but may result in higher rates of adverse effects. A study that compared different total doses of IVIg was conducted in a selected group of GBS patients [25*]. That randomized, double-blind, phase II trial was conducted in 39 GBS patients who required artificial respiration and had contraindications for plasma exchange. It showed that patients treated with 6 days IVIg at a dosage of 0.4 g/kg per day improved more rapidly as compared with patients who received only 3 days of IVIg at 0.4 g/kg per day (P =0.04). In the whole group of GBS patients who were unable to walk, there was a tendency toward faster recovery with the 6-day schedule (P =0.08). Thus, that small study indicated that 6 days of IVIg at a standard dosage of 0.4 g/kg per day may be more beneficial than 3 days.

Corticosteroids alone and the combination with intravenous immunoglobulin

Treatment with intravenous methylprednisolone alone did not result in a significant difference in terms of disability-related outcome as compared with a placebo group [26]. It was concluded that corticosteroids alone should not be used in GBS [27*]. A pilot study [28] reported a positive effect of combined treatment with IVIg and methylprednisolone in 25 GBS patients. The effect of combined treatment with IVIg and methylprednisolone has now been evaluated in a randomized controlled study conducted by the Dutch GBS study group. All 225 GBS patients unable to walk unaided and within the first 2 weeks of disease were treated with IVIg 0.4 g/kg per day for 5 days. They were randomly assigned to intravenous methylprednisolone 500 mg/day or placebo for 5 consecutive days. We presented data from that study at scientific meetings, and the final results are expected to be published this year.

Cerebrospinal fluid filtration

CSF filtration is a new, potentially effective treatment for patients with GBS. In a recent study conducted in 37 patients with GBS who were unable to walk unassisted [29*], functional improvement on the standard seven-point GBS scale was assessed at 28 days after randomization. The patients received standard plasma exchange or 14 days of CSF filtration. The results appeared almost identical. After 2 months there appeared to be a slight advantage conferred by CSF filtration, but after 6 months there was no difference between treatments. It was concluded that both therapies are equally efficacious. However, an editorial [30]

summarized a number of concerns, mainly related to the design and conduct of the trial. It concluded that the study was almost certainly under-powered to establish equivalence, and that its utility needs to be established. It has been suggested [31] that removal of elevated concentrations of a variety of inflammatory mediators, such as the sodium channel blocking pentapeptide QYNAD, from the CSF may play a role. Whether this is of clinical importance is unclear because relevant postforaminal nerve trunk pathology is beyond the region at which CSF filtration is alleged to act [32]. On the other hand, significantly increased levels of interferon-gamma-inducible protein were found in the CSF of patients with GBS and CIDP [33], suggesting a potential clinical role for CSF filtration.

Potentially interesting treatments

Several small studies have addressed the issue of whether immune adsorption is effective in GBS. One recent study conducted in 76 GBS patients [34] reported approximately equal efficacies of immune adsorption and plasma exchange. That study was planned to randomize 279 patients but was terminated because of a low inclusion rate. A possible favourable effect of the combination of IVIg with interferon-β-1a was reported in a single GBS patient [35]. A therapeutic benefit from interferon-β in GBS was suggested because it was found that interferon-β inhibited in-vitro lymphocyte adhesion to recombinant vascular adhesion molecule-1 and recombinant intercellular adhesion molecule-1 [36]. In experimental allergic neuritis (a model of GBS), it was found that two new cyclo-oxygenase-2 inhibitors significantly inhibited clinical and histological features [37], indicating that new cyclo-oxygenase-2 inhibitors might be useful as additional therapeutic agents in GBS.

Guillain-Barré syndrome patients with mild disease

Most treatment trials in GBS only consider patients who are unable to walk unaided. More attention has recently been paid to GBS patients who remain able to walk during the course of disease, so-called 'mild patients'. One question is whether these patients need to be treated with IVIg or plasma exchange at all. The proportion of GBS patients who remained able to walk was 4.7% in a retrospective, single hospital based study conducted in 254 patients [38]. Van Koningsveld *et al*. [39] reported that 14% of GBS patients remained mildly affected, based on a prospective nationwide survey, including 139 patients. The results of the French Cooperative Group on Plasma Exchange in GBS study [40] argue for early treatment (with two plasma exchange sessions) in patients who are still able to walk. Despite the findings of that study, the question of whether one should treat GBS patients with minimal disease is still not fully resolved, and more information on the course of disease would be helpful.

The severity of weakness between patients who ultimately remained 'mild' and those who became 'severely' affected appeared to differ on the day of admission [39]. Thereafter, both groups show a remarkably similar rate of progression. The patients with mild GBS reached a maximal degree of weakness after approximately 8 days, leading to the conclusion that

treatment may be unnecessary in patients who remain able to walk during the second week of illness [38]. On the other hand Van Koningsveld *et al*. [39] reported that 38% of mildly affected patients had problems in hand function and an inability to run at 3 and 6 months. Therefore it appears appropriate that new trials also consider treatment of mildly affected patients. In general, it is important not only to study the effects of IVIg or plasma exchange after 4 weeks but also to assess functional disability after a longer period of follow up. Residual fatigue and severely restricted endurance, as well as pure functional disability, may persist for years after the onset of GBS, even in patients who appear to have recovered well [41].

Guillain-Barré syndrome patients with secondary deterioration

Approximately 10% of GBS patients deteriorate after initial improvement or stabilization following IVIg or plasma exchange [42]. In such patients it is recommended that the same treatment be repeated, and it can be anticipated that these patients will again improve. Some patients who initially have a course of disease that is compatible with GBS later develop relapses and remissions, and are ultimately found to have CIDP [43*]. When it is clear that a patient does indeed have CIDP, then treatment according to the diagnosis of CIDP must be applied. In such patients, corticosteroids or intermittent IVIg infusions should be given in order to prevent repeated deterioration.

Miller Fisher syndrome and other variants of Guillain-Barré syndrome

MFS may be considered a variant of GBS (Fig. 1) [44**]. Yuan *et al*. [45] reported that 18% of patients with GBS had MFS. Mori *et al*. [46*] reviewed 50 consecutive MFS patients, including 28 patients who had received no immunotherapy. It was found that patients with MFS usually had a good recovery. Almost all patients with MFS have immunoglobulin G anti-GQ_{1b} antibodies. There is now evidence that both presynaptic and postsynaptic mechanisms play a role in in-vitro/ex-vivo models [47,48**,49]. There is also experimental evidence that a complement-dependent mechanism plays a role [50,51*], indicating that complement-blocking agents may have a potential role in the treatment of these patients. Recent experiments [48**] clearly demonstrated that IVIg, but also $F(ab)_2$ and post-treatment GBS serum, inhibit impulse blocking. Dalakas [52] reviewed the mechanism of action of IVIg in GBS. Rapid reduction in nerve conduction blocks after plasma exchange has also been described in patients with GBS [53].

At present, it appears that most of our understanding of the pathogenesis of GBS originates from studies in MFS and the acute motor axonal variety, and not from the most frequent form, namely acute immune-mediated demyelinating polyneuropathy [54].

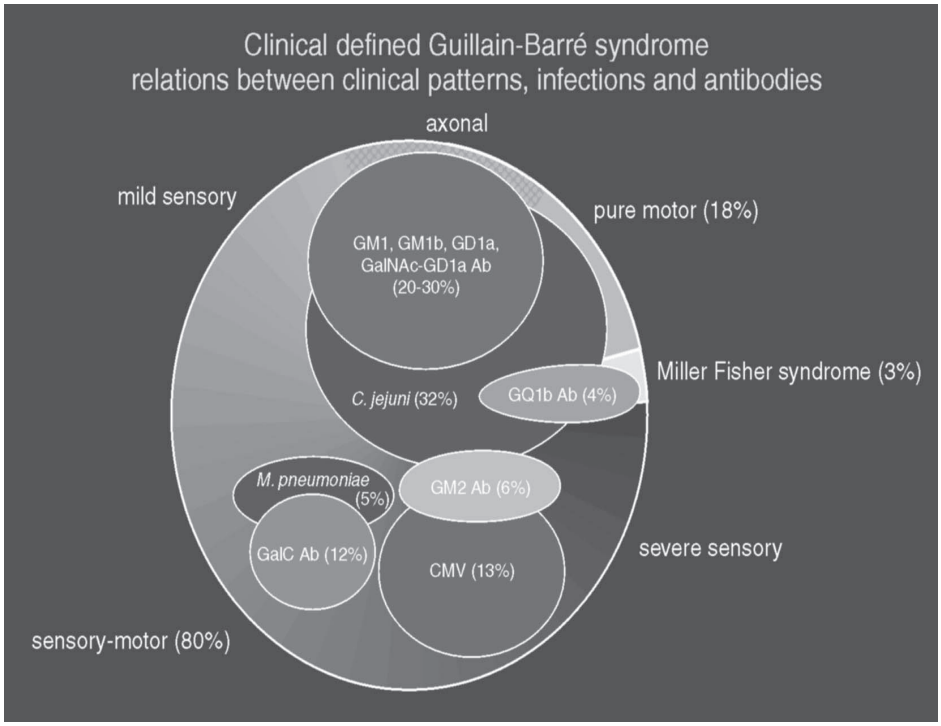

Figure 1. Diagram presenting in a semi-quantitative way the relation between clinical characteristics, infections and antibodies.

CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

CIDP may be considered a chronic variety of GBS, although there certainly are clear clinical and immunological differences [55,56]. The course of CIDP may be one of gradual progression, with steps of progression, or one of spontaneous relapses and remissions [57*,58*]. According to generally accepted criteria, the duration of progression in CIDP exceeds the duration of progression in GBS. New criteria for CIDP were recently published [59,60*]. It is sometimes difficult to distinguish between relapsing GBS and CIDP. In particular, difficulties arise when patients initially have a course that resembles that of GBS [43*].

All patients with a possible CIDP should be screened for the presence of a monoclonal gammopathy. Whether the presence of a serum monoclonal gammopathy rules out the diagnosis of CIDP is still a matter of debate. In particular, the presence of immunoglobulin M MGUS with anti-MAG antibodies should not be considered CIDP [61]. Patients suspected of having CIDP but who do not respond to conventional treatment or who show dramatic progression of weakness despite regular treatment should be checked again for the presence of a monoclonal gammopathy. Patients with a demyelinating polyneuropathy in association with a MGUS generally have a slowly progressive course, with predominant sensory involvement

[62]. If patients with CIDP and an MGUS deteriorate very rapidly and treatment is less effective, then this should raise suspicion of the development of a haematological malignancy [63].

There are several variants of CIDP, termed multifocal inflammatory demyelinating neuropathy [64,65], pure motor CIDP [66], multifocal acquired demyelinating sensory and motor neuropathy, distal acquired demyelinating symmetric neuropathy [60] and ataxic CIDP [67]. Whether these variants require specific treatments is as yet largely unknown.

Corticosteroids

Dyck *et al*. [68] conducted the only randomized, controlled, open study of prednisone, and concluded that steroids are effective in CIDP. Several large nonrandomized studies suggest that steroids are beneficial in CIDP. A recent Cochrane review [69*] concluded that the single randomized controlled trial provided weak evidence to support the commonly held opinion from nonrandomized studies that oral corticosteroids reduce impairment in CIDP (Table 1). An advantage of steroids is their availability and low initial costs, but side effects can be very serious. Patients with CIDP may have a pure motor form. It has been reported that these patients do not respond, or may even deteriorate shortly after treatment with steroids [66].

Plasma exchange

Plasma exchange has been shown to be effective in CIDP (Table 1) [70,71]. A clear disadvantage of plasma exchange is its availability, high costs and the relatively invasive nature of the procedure. Patients treated with plasma exchange may improve rapidly but need regular treatment to avoid clinical deterioration. A single patient study [77] concluded that immunoadsorption was inferior to plasma exchange in CIDP.

Table 1. Proven effective treatment for chronic inflammatory demyelinating polyneuropathy

Treatment	Cochrane review	Effect	Side effects (potential)	Availability	Direct costs
Prednisone [10**,68]	[69*]	+	Severe	Very good	Low
Plasma exchange [70-72]	--	+	Minor	Rather good	High
IVIg [10**,72-74,75**]	[76*]	+	Minor/none	Good	High

Intravenous immunoglobulin

In placebo-controlled studies it was found that IVIg is an effective treatment for CIDP [73,74,75**] (Table 1). In the study conducted by Mendell *et al.* [75**], 76% of patients improved in strength but improvement on a disability scale was found in only one-third of the patients. A recent Cochrane review [76*] confirmed the favourable effect of IVIg. If patients improve after IVIg, then improvement starts within 2 weeks. The majority of patients need intermittent treatment during many months or several years to maintain the improved condition, which is a problem because IVIg is very expensive [78].

Comparison between steroids, plasma exchange and intravenous immunoglobulin

One study [72] did not show a difference in treatment effect between plasma exchange and IVIg. In a recent randomized, double-blind, cross-over trial [10**], over a treatment period of 6 weeks IVIg (2 g/kg given over 1 or 2 days) tended to be superior to oral prednisolone (tapered from 60 to 10 mg/day over the study period). This is the first trial to compare IVIg with steroids, but the duration of treatment was relatively short for a chronic disorder that generally requires treatment for many months or years. An editorial by Van den Bergh [79*] provides a good overview.

Other potentially effective treatments

Over the years, smaller noncontrolled studies have reported the effects of immunosuppressive agents. Favourable results were recently reported following long-term use of mycophenolate in a small series of immune-mediated neuromuscular disorders, including two patients with CIDP [80*]. Whether mycophenolate is indeed an effective, low-toxicity, immunosuppressive agent for the treatment of CIDP needs to be evaluated in a randomized controlled trial. Autologous stem cell transplantation was successfully applied in a single CIDP patient who had a chronic course without spontaneous remissions [81]. At present, such treatments should be regarded as options only when standard treatment fails.

Prognostic factors related to improvement

Better outcomes are reported to be associated with younger age at onset, a relapsing-remitting course and absence of axonal damage [82,83]. From a study conducted in 16 CIDP patients [84], it was found that those with histopathological axonal lesions in sural nerve biopsies responded less well to treatment with IVIg, plasma exchange, or steroids. Interestingly, improvement in such patients with axonal pathology could be achieved with cyclophosphamide. In general, patients with a progressive course, central nervous system involvement, and active signs of demyelination and axonal loss had greater disability [85]. The electrophysiological distribution pattern of demyelination along the course of the nerve was found to correlate with clinical profile and response to treatment in a group of 42 CIDP patients [86].

MULTIFOCAL MOTOR NEUROPATHY

Patients with MMN have a progressive predominantly distal, asymmetric limb weakness, with minimal or no sensory impairment. It predominantly affects the upper limbs. Electromyography reveals multifocal motor conduction blocks without sensory deficit. Contrary to CIDP, patients with MMN do not have spontaneous remissions. In a series of 38 MMN patients with a disease duration ranging from 6 months to 34 years [87*], weakness and disability became significantly more severe with longer disease duration. Reduction in distal and proximal compound muscle

action potential amplitudes and an increasing number of conduction blocks was more frequently found in patients with longer duration of disease. MMN patients may have high-titre anti-GM_1 immunoglobulin M antibodies and generally improve after IVIg treatment, which strongly suggests that the disease has an immunological background. No randomized controlled trials are available to indicate whether immunosuppressive agents are beneficial in MMN [88*]. A summary of the available evidence for the effectiveness of treatments is presented in Table 2.

Table 2. Proven effective treatment for multifocal motor neuropathy

Treatment	Cochrane review	Effect	Side effects	Availability	Costs
IVIg [89,90*,91*]	--	+	Minor/none	Good	High
Immunosuppressive agents	[88*]	TBD	Minor/severe	Good	Depends on treatment

TBD = to be determined (no randomized controlled trials yet available).

IVIg is the only treatment that has been shown to be effective in controlled trials (Table 2) [89,90*,91*,92,93]. In a recent study [87*] it was shown that 30 out of 34 patients improved after IVIg treatment, and that IVIg can induce and maintain improvement in most MMN patients but it does not eradicate the disease. Criteria have been formulated that predict response to IVIg [94]. The following were found significantly more often in nonresponders: older age at onset, a greater number of affected limb regions, and a creatine kinase level greater than 180 U/l. Anti-GM_1 antibodies and definitive conduction blocks were found significantly more often in responders to IVIg. Because of the favourable response to IVIg, even in MMN patients with severe and prolonged disease, the progression of weakness is suggested to be the result of an ongoing, immune mediated process. This implies that early treatment may prevent future progression of weakness and disability in patients with MMN [87*]. Nobile-Orazio [95*] studied 23 consecutive patients with clinically typical MMN and demonstrated that patients with possible conduction blocks may also improve after IVIg treatment. It was suggested that failure to fulfil the American Association of Electrodiagnostic Medicine criteria for conduction blocks in patients with otherwise clinically typical MMN should not preclude the diagnosis, which consequently warrants a trials of treatment with IVIg.

CONCLUSION

Recent studies have provided new information regarding the effect of treatment in patients with GBS, CIDP and MMN. IVIg may clearly be of benefit in these disorders. Whether patients with MFS or those with mild GBS also need plasma exchange or IVIg warrants further study. Surprisingly, corticosteroids are highly likely not to be of benefit in MMN and pure motor CIDP. Treatment with IVIg or plasma exchange is certainly not the final answer to GBS because a significant

proportion of patients has slow recovery or remains disabled or fatigued, even after many months or years. Combinations of treatments may reduce deterioration and improve recovery. The final results of a trial conducted to evaluate the additional effect of methylprednisolone over that of standard treatment with IVIg in patients with GBS are expected to be published this year. The mechanisms of action of IVIg are complex but recent experiments have further elucidated some of these mechanisms, at least in a subgroup of patients with GBS.

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CHAPTER 2.2

Treatment of Guillain-Barré syndrome with intravenous immune globulins and methylprednisolone, combined with mycophenolate mofetil, a pilot study

Garssen M.P.J., van Koningsveld R., and van Doorn P.A., for the Dutch GBS study group*

From the Departement of Neurology; Erasmus Medical Center, Rotterdam, The Netherlands

* listed at the end of this chapter

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ABSTRACT

Introduction Despite different treatment regimens, Guillain-Barré syndrome (GBS) remains associated with considerable co-morbidity, mortality, and long-lasting residual deficits. We conducted an open-label study on the additional effect of Mycophenolate Mofetil (MM) when added to the combination of intravenous immune globulins (IVIg) and intravenous methylprednisolone (MP). The aims of this pilot study were to investigate the safety of this treatment combination and to study the potential additional effect of MM on outcome in patients with GBS.

Patients and methods GBS patients, within two weeks from onset of weakness and unable to walk unaided, were treated for 6 consecutive weeks with MM in a dosage of 2g daily, and for 5 days with 0.4 g IVIg/kg of body weight and 500 mg MP daily. The IVIg-MP treatment group from the Dutch IVIg-MP trial served as control group. The primary endpoint was improvement at four weeks by at least one grade on the GBS-disability scale.

Results Twenty-six patients were included in the analysis. The primary endpoint was reached in 62% in the group of patients treated with IVIg-MP-MM, and in 68% in the group treated with IVIg-MP (OR 1.3, 95% CI 0.6-3.2, p=0.54). Secondary endpoints did not show any significant differences either. Complications and adverse events were comparable in both groups.

Conclusions The combination of Mycophenolate Mofetil with intravenous immune globulins and methylprednisolone was well tolerated. There was no significant improved outcome in the group of patients additionally treated with MM. New treatment studies are warranted.

INTRODUCTION

Guillain-Barré syndrome (GBS) is a severe, (sub)acute, generally monophasic immune-mediated polyneuropathy, affecting 1-1.5 per 100.000 inhabitants per year.[1,2] Based on the immune-mediated and inflammatory character of GBS, several treatment regimes have been studied. It has been shown that GBS-patients unable to walk independently, improve after plasma-exchange (PE) and intravenous immune globulin therapy (IVIg).[3-6] IVIg is nowadays the preferred treatment for patients with GBS.[7-9] There is no beneficial effect of corticosteroids alone.[10,11] Also the combination of methylprednisolone (MP) and IVIg does not result in significant better improvement after four weeks if not adjusted for important prognostic factors.[12]

Despite these different treatments, GBS remains associated with many long-lasting residual deficits; about 20% of the patients is still unable to walk unaided after six months, and mortality ranges between 3-5%.[8,13] The majority of patients remains severely fatigued, restricted in daily and social activities, and has a significantly decreased quality of life, supporting the need for other therapeutic options.[14] New treatments should preferentially focus on rapid suppressing of disease activity in order to prevent demyelination and (secondary) axonal damage, and to hasten recovery.

Both autoantibodies, and B and T cells are likely to play a role in different stages of GBS.[15-19] It seems important to use fast acting immune-modulating drugs early in the active phase of disease. Mycophenolate Mofetil (MM) is a relatively new, fast acting immune-suppressive agent that mainly suppresses B and T lymphocyte activity, induces apoptosis of activated T cells and interferes with adhesion molecules and cytokines.[20] MM has been widely and successfully used in preventing rejection of renal, heart, and liver transplants. Recent studies in patients with chronic immune-mediated neurological disorders, including chronic inflammatory demyelinating polyneuropathy (CIDP), suggested clinical improvement in some patients after administration of MM.[21,22-25] The combination of MM with other immune-modulatory agents does not seem to result in major side effects.[21,24]

The aim of this study was twofold; to investigate whether the combined treatment of MM with IVIg and MP is safe, and secondly, whether there is a tendency for an improved outcome compared to treatment with IVIg and MP alone.

PATIENTS AND METHODS

Patients

All patients admitted in the 10 participating centres, who fulfilled the National Institute of Neurological Disorders and Stroke criteria for GBS,[26] were considered for inclusion. Patients who used IVIg and the combination of IVIg and MP in the previously performed Dutch GBS-trial were

used as historical controls.[12] The ethics committee of every participating centre approved the protocol (see list of participants).

In- and exclusion criteria

A patient was eligible when the onset of weakness was within two weeks before inclusion, the patient was unable to walk independently for ten meters (GBS-disability score ≥ 3) and had signed informed consent.[27,28]

Exclusion criteria were age below 18 years, suffering from GBS before, a previous severe allergic reaction to properly matched blood products, a known selective IgA deficiency, pregnancy or breast feeding, steroid or other immunosuppressive treatment, antacids treatment containing magnesium or aluminium, treatment with drugs interfering the enterohepatic recirculation (e.g. cholestyramine), contraindications for steroid treatment, suffering from an immune-mediated disease other than well regulated diabetes mellitus, suffering from severe concurrent disease, clinical evidence of a pre-existing polyneuropathy (caused by e.g. diabetes, alcoholism, severe vitamin deficiency, heavy metal intoxication or porphyry), or an expected inability to follow-up.

Treatment

All patients were simultaneously treated with 0.4g IVIg (Gammagard SD®, Baxter) per kilogram bodyweight per day and 500mg intravenous MP, for five consecutive days. Additionally, patients were treated with MM (Cellcept®, Roche), orally administered in a dosage of 2 times 1000mg per day, for 6 consecutive weeks. Treatment with MM had to start within two weeks after onset of weakness and within 72 hours after the start of the combined treatment with IVIg and MP.

Outcome measures

Outcome measures were identical to the outcome measures used in the Dutch IVIg-MP trial.[12] The primary endpoint was defined as the percentage of patients that improved one or more grades on the GBS-disability scale four weeks after inclusion, as compared with the score at time of entry. Secondary endpoints were the percentage of patients able to walk independently after eight weeks, time required to improve at least one grade on the GBS-disability scale, time required to improve until independent walking, difference in grade on the GBS-disability scale at six months, and difference in need and duration of artificial respiration. In order to investigate the overall disability scale (ODSS) as outcome measure, the time required to improve at least two grades on the overall disability sumscore (ODSS) and difference in grades on the ODSS six months after inclusion, was additionally assessed in the IVIg-MP-MM group.[29]

Assessments

Cranial nerve dysfunction, the GBS-disability score, the ODSS, and the MRC sumscore were assessed every week during the first eight weeks after entry, once at week 10, and every four weeks during week 10-26, or until the patient reached a GBS-disability score of one or less.

The GBS disability scale is a seven point functional scale, mainly focussing on mobility and previously used in most GBS treatment trials[27,28]

The ODSS is a composed arm and leg disability scale with a total score ranging from 0; no signs of disability, to 12; most severe disability score. Five daily arm activities are scored as being "not affected", "affected but prevented", or "prevented". The leg scale highlights problems regarding walking taking into account the use of a device. Subsequently, these results are translated into an arm grade (0 [normal arm abilities] to 5 [severe symptoms and signs in both arms preventing all purposeful movements]) and leg grade (0 [walking not affected] to 7 [restricted to wheelchair or bed most of the day, preventing all purposeful movements of the legs]).[29] This questionnaire was added to the GBS disability score because it also evaluates functional problems with daily arm activities. It has been shown that muscle weakness and sensory deficits leading to disability could be better monitored by the ODSS, compared with the GBS disability score.[29]

The MRC sumscore was assessed in six bilateral muscles of arms and legs, ranging from 60 (normal) to 0 (quadriplegic).[28]

Sensory symptoms were scored at entry, at 4, 8, 14 and 26 weeks after inclusion. Sensory examinations included tactile, pinprick, vibration, and position sense, and static 2-points discrimination at the index finger.

Additional studies included routine testing of blood, urine and cerebrospinal fluid; serological tests for IgM and IgG antibodies against anti-GM1; and serological screening for preceding infections with *Campylobacter jejuni*.

Adverse events

Adverse events were monitored daily and evaluated every next visit. These included: respiratory and urinary tract infection, intravenous catheter sepsis, gastrointestinal bleeding, deep venous embolism, pulmonary embolism, serum glucose level >10 mmol/l, renal failure, delirium, hematological complications (defined as leucopenia or anaemia in accordance to the criteria of the local participating center), or other complications. Every major adverse event was reported as soon as possible to the coordination center at the Erasmus Medical Center Rotterdam.

Statistical analysis

Percentages in the group of patients treated with IVIg-MP-MM were compared with the group of 112 patients treated with IVIg-MP in the previously performed trial by the chi-square test (without correction for continuity). The time to reach an endpoint was analyzed by the method of Kaplan and Meier and the log-rank test. Additionally, two important secondary endpoints (the time to improve 1 grade or more on the GBS disability score, and the time to independent walking) were also compared with the group of 113 patients treated with IVIg alone in the Dutch IVIg-MP trial.[12] All analyses were performed using STATA version 8.0.

RESULTS

Between July 2002 and January 2005, 31 GBS patients were considered for inclusion (figure 1). One patient did not meet the eligibility criteria. Four patients had to be excluded from analysis. One of these patients received MM for only one week due to a medication prescription failure. Three patients were included, but unfortunately no further data were collected and no endpoints were available due to local inappropriate follow-up, resulting in 26 patients included in the analysis. Baseline characteristics for both treatment groups are shown in table 1. No significant differences between these groups were found.

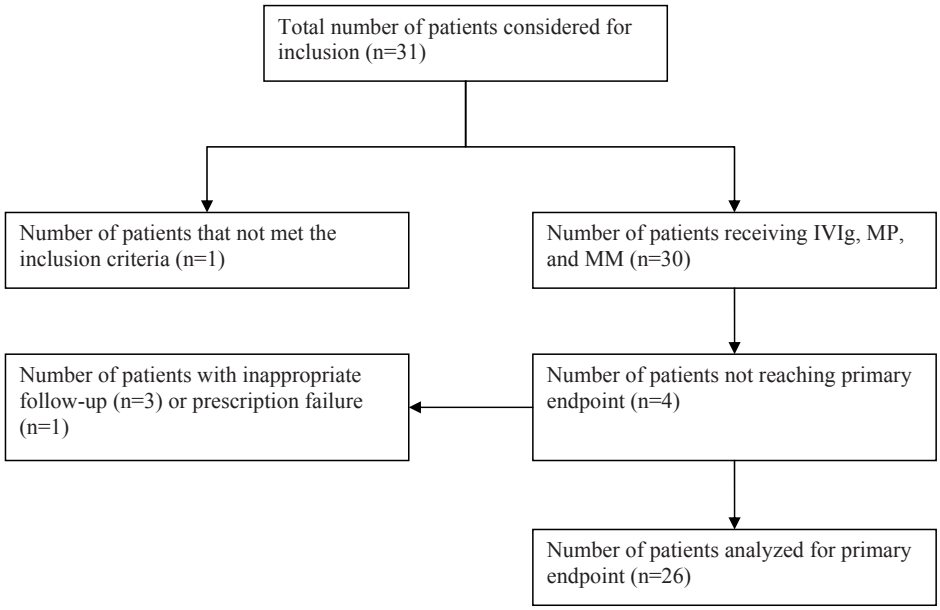

Figure 1. Study profile.

Primary endpoint

In the IVIg-MP-MM treatment group 16 (62%) of the 26 patients improved by one or more grades on the GBS disability score after 4 weeks, compared to 76 (68%) of the 112 control patients treated with IVIg-MP (OR 1.3, 95% CI 0.6-3.2, p=0.54).[12]

Table 1. Baseline characteristics

Characteristics	IVIg + MP + MM (n=26)	IVIg + MP [12] (n=112)
Male (%)	19 (73%)	73 (65%)
Median age in years (95% CI) **age ≥ 50 years (%)**	46 (23-76) 12 (46%)	58 (50-61) 68 (61%)
GBS-disability score (F-score) at baseline (%) **F=3** **F=4** **F=5**	 4 (15%) 21 (81%) 1 (4%)	 26 (23%) 77 (69%) 9 (8%)
Onset weakness-randomisation ≤ 4 days	13 (50%)	64 (57%)
Diarrhoea (%)	10 (39%)	30 (27%)
Upper respiratory tract infection (%)	7 (27%)	39 (35%)
Positive *C jejuni* serology (%)	6 (23%)	29 (28%)

Secondary endpoints

Secondary endpoints are listed in table 2 and show no significant differences between groups.

Figure 2 shows the Kaplan-Meier survival estimate curve of time to improve at least 1 grade on the GBS disability score, and figure 3 shows the time to independent walking (GBS disability score ≤ 2). To further compare possible differences in treatment modalities, these graphs also show the results of the group of 113 patients who received IVIg only in the Dutch IVIg-MP trial.[12] No significant differences between the three groups were found for both endpoints. A comparison of the differences in MRC sumscores and sensory scores (as described in the patients and methods section) between the groups did not show significant differences either.

Table 2. Secondary endpoints

Endpoint	IVIg/MP/MM[12] (n=26)	IVIg/MP [12] (n=112)	P-value
Percentage of patients able to walk independently after 8 weeks (GBS disability score ≤2)	12 (52%)	78 (70%)	P=0.12
Median time to independent walking (GBS disability score ≤2) *	70 days	28 days	P=0.22
Median time to improve ≥1 grade on GBS disability scale *	28 days	21 days	P=0.08
Improvement ≥1 grade on GBS disability scale after 6 months (%)	21 (84%)	90 (93%)	P=0.17
Need for artificial respiration	4 (15%)	22 (21%)	P=0.5

* see also figure 2 and 3.

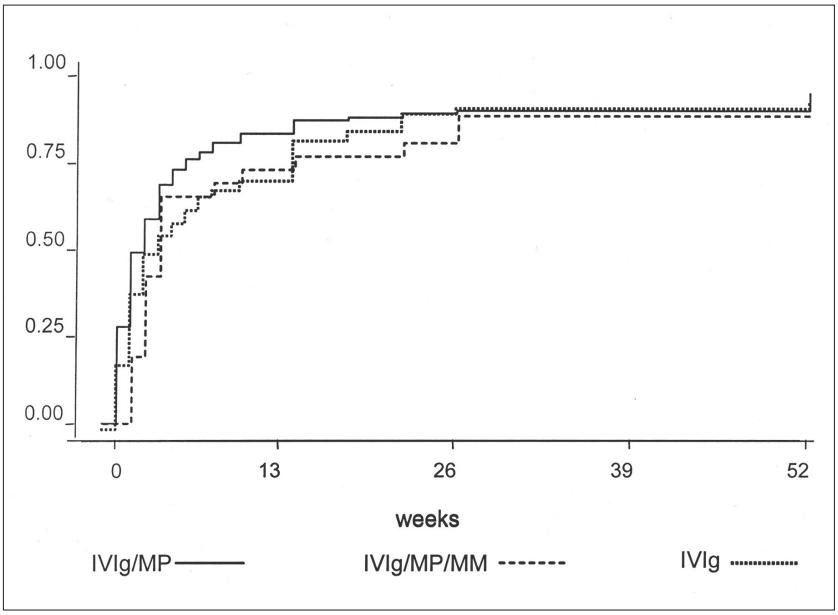

Figure 2. Kaplan-Meier curves indicating the proportion of patients that has improved 1 or more grades on the GBS disability score during 52 weeks of follow-up.

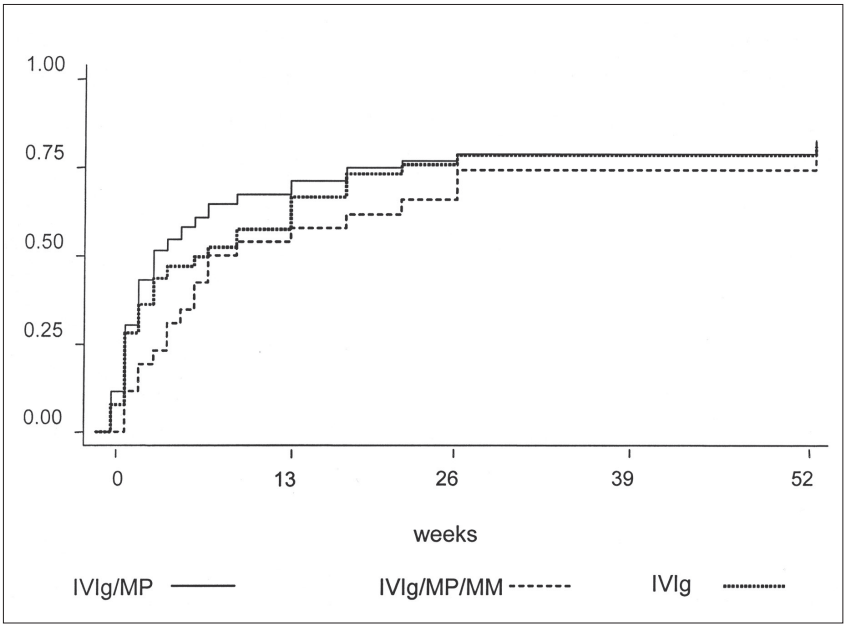

Figure 3. Kaplan-Meier survival estimates for the proportion of patients that has improved to independent walking (GBS disability ≤ 2) during 52 weeks of follow-up.

ODSS versus GBS-disability score

The ODSS was only available for the IVIg-MP-MM treatment group. In this group 59% improved at least two points on the ODSS. This is comparable with the 62% of patients that improved on the GBS disability scale. At six months 87% improved at least 2 points on the ODSS scale and 81% improved at least one grade on the GBS disability score.

Adverse events

Side effects are listed in table 3. None of the reported side effects differed significantly between both groups. Only 1 patient interrupted MM treatment because of abdominal complaints, without the presence of diarrhoea or constipation. Two (8%) of 26 patients treated with IVIG-MP-MM died, compared to 6 (5%) of 112 patients treated with the combination IVIG and MP. The first patient, a 76-year-old female patient suffered from bulbar dysfunction, and died 7 weeks after inclusion due to severe aspiration pneumonia while admitted at a nursery home. Blood studies showed an elevated ESR with leucocytosis. During the use of MM no haematological side effects occurred. The second patient, a 73-year-old male patient, died almost 15 weeks after inclusion, 9 weeks after finishing MM treatment. This patient had recurrent respiratory distress and difficulties with swallowing, due to a combination of Parkinson disease and bulbar dysfunction after GBS. The patient did not have relevant laboratory abnormalities, needed intermittently mechanical ventilation and died at the intensive care unit due to respiratory dysfunction after extubation.

Table 3. Adverse events

Event	IVIg + MP + MM			IVIg + MP
	0 - 6 weeks (n=26)	7-26 weeks (n=26)	overall (n=26)	overall (n=112)
Urinary tract infection	19%	4%	23%	18%
Respiratory tract infection	15%	4%	19%	32%
Glucose > 10 mmol/l	19%	0%	19%	21%
Haematological complication*	8%	0%	8%	n. a.
Renal failure	4%	0%	4%	3%
Deep venous thrombosis	0%	8%	8%	5%
Pulmonary embolism	0%	4%	4%	4%
Delirium	0%	4%	4%	5%
Gastro-intestinal bleeding	0%	4%	4%	3%

* leucopenia or anaemia.

DISCUSSION

In this pilotstudy GBS patients were treated with the combination of IVIg, MP and MM. There was no tendency for improved outcome at four weeks compared to the historical IVIg-MP control group from the Dutch IVIg-MP trial.[12] Side effects did not significantly differ between groups of patients treated with the combination IVIg-MP-MM or IVIg-MP only. Side effects were generally mild, confirming earlier reported data that MM is safe to administer in combination with IVIg or MP.[21,24] Two out of 26 patients died (8%), which is comparable with data from previous studies.[1,8,12] A direct relation between these serious adverse events and the use of MM was unlikely. Secondary outcome measures, mainly concerning long-term effects, did not show significant differences between groups. We additionally performed Kaplan-Meier survival analyses to compare the time to independent walking and the time to improve at least one grade on the GBS disability scale. Because we also wanted to exclude a negative effect of the combination of MM with MP and IVIg, we also included the IVIg treatment group from the Dutch IVIg-MP trial in the analyses. Also this comparison did not reveal any significant difference, favouring one of the treatment combinations (figure 2 and 3).

Although patients were recruited from the same geographic region as the historical control patients, and the methodological approach was similar to the previous studies,[12] our results have to be interpreted carefully. The chosen study design in which data of a small group of non-randomised patients were compared with historical data from a large group of patients is mainly useful in detecting major differences between groups. Additionally, although the dosage of MM is a standard dosage, a late start of MM or an inadequate duration of therapy might contribute to the lack of efficacy. In different studies aiming to treat patients with immune mediated diseases, MM was administered for at least 5 months up to 3 years.[22-24,30-32] However, these studies all evaluated patients with chronic neurological disorders like CIDP and myasthenia gravis. Since GBS is a disease with rapid onset and progression to nadir within two to four weeks, this seems to justify the decision to continue MM for a total period of 6 weeks. It is arguable whether the treatment regimen presently studied is administered to late after onset of GBS. It might be better to start treatment as early as practically possible. Also the timing, dosage and frequency of IVIg administration can be discussed, however these treatment-related topics have never been studied systematically.

Besides these methodological considerations, different hypotheses can be suggested why the addition of MM did not reveal major differences between groups. Maybe MM does not interfere with the crucial immunopathological pathways in GBS, or nerve damage already took place even before MM was administered and lymphocyte proliferation was inhibited. Another explanation could be that many activated circulating lymphocytes remain active, also after MM administration. To date there is accumulating evidence from pathological studies that early changes in nerve fibers are accompanied by the presence of anti-ganglioside antibodies, macrophage recruitment, and complement deposits. This suggests that an antibody-mediated

attack on the nerve, rather than a T cell mediated disease, seems most relevant in GBS.[19,33-35] In mouse models, it has been shown that inhibition of auto-reactive antibodies is important in preventing activation of complement and macrophages.[19] Treatment with IVIg or PE interferes with auto-reactive immune globulins and complement activation.[36] Although MM strongly inhibits T cell proliferation, a possible contributor to the pathogenesis of GBS, it seems that it does not play a major role in inhibition of important auto-reactive antibodies and does not interfere with complement activation.[20]

This was the first GBS treatment study in which the ODSS was used additionally to the GBS disability scale. Besides evaluation of the leg function (as the GBS disability score assesses) it also evaluates arm function and is therefore a potentially more accurate scale to consider overall disability in GBS. However, the percentages of patients improving on both assessment scales were comparable. Future studies must further show the place of the ODSS in the assessment of treatment trials in GBS.

In conclusion, despite different immune-modulating treatments and combinations of treatments, morbidity and mortality in GBS are still frequent. The results of this study in combination with recent insights in the pathophysiological mechanisms contributing to GBS are not encouraging to conduct a randomized controlled trial studying the additional value of MM in combination with IVIg and MP.

APPENDIX

The following investigators participated in the study:

The Netherlands: J.A. van Leusden, Medisch Centrum Alkmaar, Alkmaar; I.N. van Schaik, Academisch Medisch Centrum, Amsterdam; W.H.J.P. Linssen, Sint Lucas Andreas Ziekenhuis, Amsterdam; F. Visscher and A.M. Boon, Stichting Oosterscheldeziekenhuizen, Goes; C.G. Faber, Academisch Ziekenhuis Maastricht, Maastricht; J.Meulstee and M.J.J. Prick, Nijmeegs Interkonfessioneel Ziekenhuis Canisius-Wilhelmina, Nijmegen; M.P.J. Garssen and P.A. van Doorn, ErasmusMC, Rotterdam; L.H. van den Berg and H. Franssen, Universitair Medisch Centrum Utrecht, Utrecht; J.A.P. Hiel, Sint Joseph Ziekenhuis, Veldhoven.

Belgium: P.Y.K. van den Bergh and C.J.M. Sindic, Clinique Universitaire St.Luc, Brussels.

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CHAPTER 3

Studies on treatment of residual fatigue

CHAPTER 3.1

Amantadine for treatment of fatigue in Guillain-Barré syndrome: a randomized, double blind, placebo controlled, crossover trial

Garssen M.P.J.[1], Schmitz P.I.M.[2], Merkies I.S.J.[3], Jacobs B.C.[1,4], van der Meché F.G.A[1], and van Doorn P.A.[1]

From the Departments of Neurology[1] (Garssen, Jacobs, van der Meché, van Doorn), Statistics[2] (Schmitz), and Immunology[4] (Jacobs): Erasmus Medical Center, Rotterdam; from the Department of Neurology[3] (Merkies): Spaarne Hospital, Haarlem, The Netherlands

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ABSTRACT

Objective Fatigue is a major complaint in patients with immune-mediated polyneuropathies. Despite apparently good physical recovery after Guillain-Barré syndrome (GBS), many patients remain restricted in daily and social activities and have a decreased quality of life. In this trial the effect of Amantadine on severe fatigue related to GBS was studied.

Methods During a pre-treatment phase, all patients were monitored for two weeks. Only patients with severe fatigue, defined as a mean fatigue score of 5.0 or more on the fatigue severity scale (FSS), were randomized for this double blind, placebo controlled, crossover study. Primary outcome measure was improvement of at least 1 point on the FSS. Secondary outcome measures were impact of fatigue, anxiety and depression, handicap, and quality of life.

Results Eighty GBS-patients were randomized. Seventy-four patients were included for analysis. Fatigue appeared to be reduced already during the pre-treatment phase (p=0.05), likely due to increased attention provided to the patients. No significant differences in any of the primary and secondary outcome measures were found.

Conclusions Amantadine was not superior to placebo. Because fatigue remains a serious complaint, other studies evaluating new treatment options are strongly recommended.

INTRODUCTION

Guillain-Barré syndrome (GBS), an immune-mediated disease of the peripheral nervous system, is characterized by acute symmetrical limb weakness and reduction or loss of myotatic reflexes. Sensory deficits and respiratory insufficiency may occur.[1] Approximately three-quarters of the GBS-patients experience good neurological recovery after adequate therapy.[2] However, severe fatigue turns out to be a major residual complaint in the majority of patients with immune-mediated polyneuropathies. Fatigue, which cause is still unknown, is significantly associated with a reduced quality of life.[3] It appears to be independent of muscle strength, sensory deficits, functional ability, and duration of symptoms.

A systematic literature review was conducted evaluating the therapeutic options of fatigue in other immune-mediated (neurological) disorders. Treatment options turned out to be limited. Besides training intervention studies[4], various pharmacological agents as Pemoline, Modafinil, and Amantadine were studied for treating fatigue in multiple sclerosis (MS)[5-9] Four short-term studies demonstrated the efficacy of Amantadine in treating fatigue in patients with mild to moderate MS.[5-8] Amantadine, a NMDA receptor antagonist, blocks pre-synaptic dopamine reuptake and stimulates postsynaptic receptors. However, its working mechanism in fatigued MS patients is still poorly understood. To our knowledge to date no pharmacological intervention studies, aiming to treat fatigue, have been performed in GBS. Although GBS and MS are certainly not fully comparable, both diseases are immune-mediated demyelinating disorders in which relapses may be triggered by infections.[10 11] Prompted by these observations, we conducted a randomized, double blind, placebo controlled, single center crossover trial using Amantadine, in apparently 'good recovered' but severely fatigued GBS-patients.

METHODS

Patients

Eighty neurologically stable patients with GBS in the past and meeting the international NINCDS-criteria were included in the current study.[1] Patients were recruited from the Dutch GBS databank at the Erasmus Medical Center Rotterdam or the Dutch GBS patients association. Many patients participated in an earlier study on assessment scales by Merkies et al.[3] The study was approved by the Ethics Committee of Erasmus Medical Center in May 2000. Informed consent was obtained.

Patients fulfilling criteria for "severe fatigue", defined as a mean fatigue severity scale score (FSS) of 5.0 or more, were eligible for inclusion.[3 12] A stable neurological clinical condition was defined as no apparent changes in GBS disability score within 3 months before the start of this study, as declared by the patients to their best knowledge.[13] The onset of GBS was more than 6

months and less than 15 years ago. Patients were at least 18 years old, and had a GBS disability score of 3 or less (at least able to walk 10 meters with or without aid).[13]

Patients were excluded if they experienced severe fatigue before GBS or if they were suffering from concomitant conditions that might cause fatigue (e.g., malignancy, chronic infections, anemia, hypothyroidism, renal and liver disease, chronic fatigue syndrome, human immunodeficiency virus, chronic obstructive pulmonary disease, cardiovascular disease, diabetes, or other immune-mediated disorders). Patients with medication inducing fatigue (within 4 weeks before onset study) were excluded. To avoid a possible confounding effect of depressive symptoms, patients with depression, as defined by a score of more than 10 points on the depression subscale of the Hospital Anxiety and Depression scale (HAD), were excluded.[14] Also pregnancy, breast-feeding, and known contra-indications for the use of Amantadine (e.g., renal dysfunction and known allergy) were exclusion criteria.

Blood values examined were: erythrocyte sedimentation rate, hemoglobin, hematocrit, aspartate transaminase, alanine aminotransferase, γ-glutamyltransferase, lactic dehydrogenase, alkaline phosphatase, total bilirubin, urea, creatinine, sodium, potassium, glucose, thyroid-stimulating hormone, and creatine phosphokinase. If necessary, ß-HCG was evaluated to exclude pregnancy.

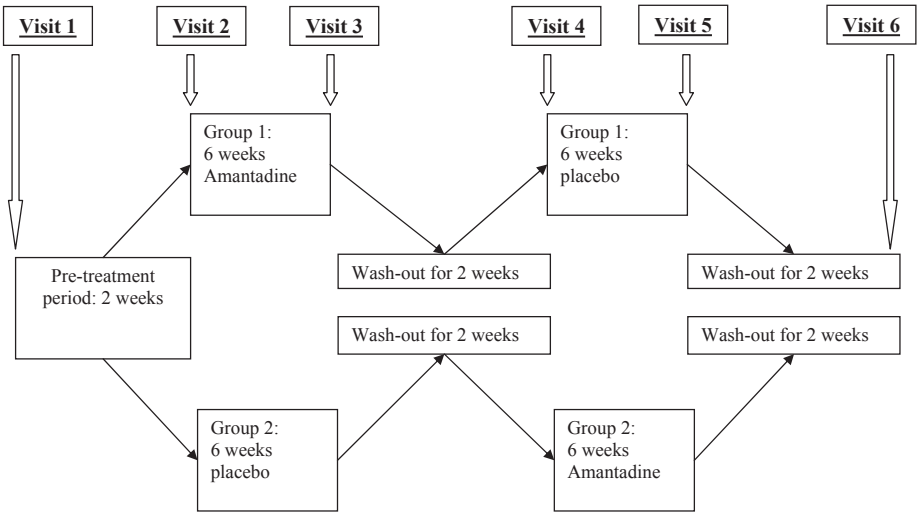
Endpoints

The primary endpoint was reduction of severe fatigue, defined as improvement of at least 1 point on the FSS.[3 12] Secondary efficacy variables were changes at the level of *impact of fatigue* (Fatigue Impact Scale / FIS)[15]; *anxiety and depression* (Hospital Anxiety en Depression Scale / HAD)[14 16]; *handicap* (Rotterdam Handicap Scale / RHS)[17]; and *quality of life* (Short Form-36 / SF-36,[18 19] and Euroqol Health Questionnaire / EHQ).[20]

Study design

All patients enrolled in this single center, randomized, double-blind, placebo controlled, 2 x 2 crossover trial (figure 1) initially received a letter, including the FSS, requesting their participation. Possible eligible patients visited our outpatient clinic (baseline-visit). If a patient met the eligibility criteria, a neurological and physical examination (including Medical Research Council sumscore, Vigorimeter dynamometry and GBS disability score)[13 21] was performed, assessment scales were completed, and blood samples were drawn. Only severely fatigued (defined as FFS-score 5.0 or more) and non-depressed (defined as HAD-depression subscale score 10.0 or less) patients with normal blood values were randomized (at visit 2).

Figure 1. Flow diagram of treatment schedule



Legend to Figure 1. Visit 1 (baseline visit) was followed by a pre-treatment period of two weeks. At visit 2, patients were randomized and started with the first intervention period, Amantadine or placebo. All data were obtained on 6 consecutive visits; pre-treatment (baseline) visit, start, and finish of each intervention period, and post-treatment, two weeks after finishing the second intervention period. Each intervention period was followed by a wash-out period of two weeks.

Treatment

To determine the effect of extra attention for fatigue, 1 extra visit was scheduled 2 weeks before the start of medication. After this pre-treatment period, patients started the first medication period at follow-up visit 2. Amantadine (100 mg tablets) and indistinguishable (taste / color / size) placebo tablets were supplied to the investigators by the Pharmacy department of the Erasmus Medical Center Rotterdam. Patients received Amantadine or placebo for 6 weeks. The dosing schedule was 1 tablet daily taken in the morning during the first week, a second tablet was added in the afternoon in week 2 until week 6. After a washout period of 2 weeks, patients received the crossover treatment for another 6 weeks. All data were obtained on 6 follow-up visits; pre-treatment, start, and finish of each intervention period, and post-treatment, two weeks after finishing the second intervention period (figure 2). Investigators and patients were blinded to treatment group assignment. Only the pharmacologist was unblinded.

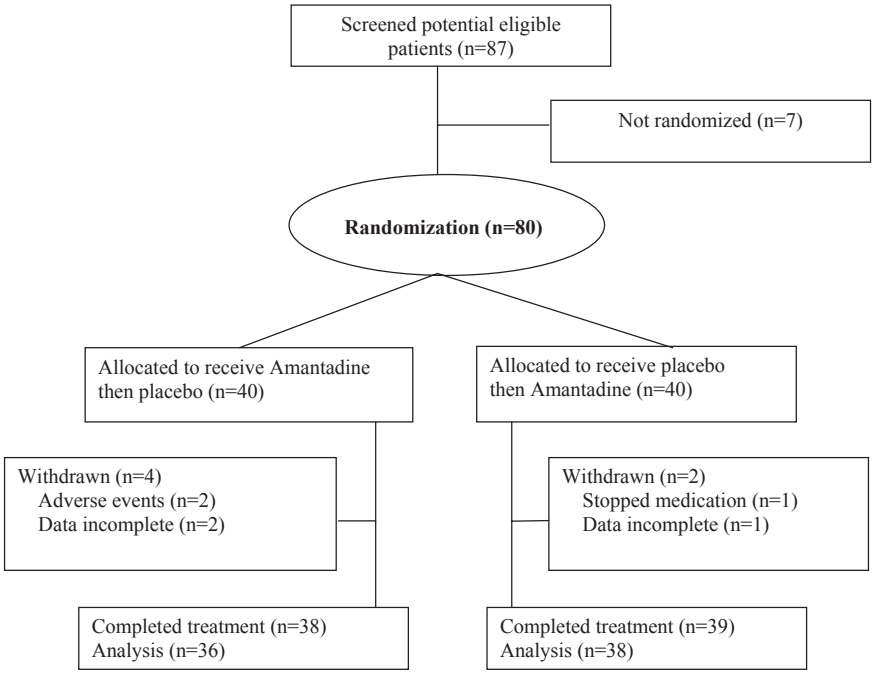


Figure 2. Flow diagram of patient groups.

Adverse events

If serious toxicity occurred, the treatment was discontinued and the patient was dropped from the study. Patients were withdrawn if 1) they failed to take the study medication for more than one day; 2) there were persisting adverse events like lightheadedness, insomnia, and loss of appetite in combination with nausea for more then 3 consecutive days, hallucinations, convulsions, rash or ataxia. After each treatment period, the patients were asked whether they had experienced adverse events.

Statistical Methods

Based on data of a small pilot study on the effect of Amantadine on fatigue in 5 GBS and 2 chronic inflammatory demyelinating polyneuropathy (CIDP) patients, a reduction of one point on the FSS seemed clinically relevant. We assumed that 25% of the patients would improve at least 1 grade on the FSS during treatment with placebo, while the percentage of patients improving after Amantadine was estimated at 65% (data not published). Using a two-sided alpha of 5%, and a power of 90%, the sample size should be 2 x 36, rounded up to 2 x 40 patients.[22] Because fatigue may vary considerably between patients, a crossover design was chosen, to adjust for individual differences.

Randomization

The allocation sequence was generated by block randomization, with a block size of 6 patients. Each block included 3 patients starting with Amantadine and 3 patients starting with placebo, randomly distributed in each block. Before starting this trial, the statistician has sent the allocation sequence list to the pharmacy department. Every consecutive eligible patient seen at the outpatient clinic was given a number, starting with 1 till 80 (assigned in sequence of entering the study). The allocated medication was supplied blinded by an independent pharmacy assistant.

Analyses

Baseline comparison within treatment groups was performed. The primary endpoint was analyzed by comparing paired proportions using the McNemar test. Period and treatment effects were analyzed using a one-sample t-test, and an analysis of variance (ANOVA), treating the FSS as a continuous variable. Additional crossover analyses on secondary (continuous) variables were also analyzed using ANOVA. Analysis of the patients' opinion in which period they thought they used Amantadine or placebo was performed using Pearson's chi square test. All calculations were carried out in Stata version 8.0 for Windows (Stata Statistical Software: Release 8.0. 702 University Drive East, College Station, TX: Stata Corporation 2003) and Excel (Microsoft Office 2000).

RESULTS

Baseline characteristics

Baseline characteristics are listed in table 1. From 87 potential eligible patients (see figure 2), 7 patients were not eligible: 5 patients initially known with an eligible FSS-score, had a pre-entry FSS-score less than 5.0, 1 patient was suffering from severe cardiovascular disease, another patient from hypothyroidism, anemia and depression. Three randomized patients were withdrawn in the first treatment phase; two while using Amantadine for the following reasons: one patient was admitted to another hospital due to an acute cholangitis, the other patient developed severe complaints of dizziness and strange feelings in his head, persisting for more than 3 consecutive days. The patient withdrawn from the placebo-starting group thought she was pregnant and decided to stop directly. Seventy-seven patients (96%) completed this trial. Besides these 3 dropouts, 3 patients did not correctly fill in all FSS-items at respectively visit 2, 3 and 5. Analysis was performed in 74 patients.

Table 1. Baseline characteristics for all 80 randomized patients

Characteristics			
		Sequence	
		first Amantadine then placebo	first placebo then Amantadine
Sex, n	Female	19	21
	Male	21	19
Median age at start of the study, years (range)		47.5 (19-77)	52 (24-82)
Median duration after diagnosis, years (range)		3.8 (0.5-13.1)	2.6 (0.5-15)
MRC-sumscore distribution, range 0-60, n (%)			
48-57		4 (5%)	8 (10%)
58-59		12 (15%)	7 (9%)
60		24 (30%)	25 (31%)
GBS-disability score distribution, range 0-6, n (%)			
1		30 (38%)	26 (33%)
2		7 (9%)	13 (16%)
3		3 (3%)	1 (1%)
FSS-score, median (range 1-7)		5.9 (5.1-7.0)	6.0 (5.0-7.0)

Legend to Table 1. MRC = Medical Research Counsil, GBS = Guillain-Barré syndrome, FSS = Fatigue Severity Scale. All baseline characteristics were measured at visit 1.

Pre-treatment response

Based on 74 patients, fatigue reduction almost reached significance when comparing visit 1 with visit 2 (p=0.05, Wilcoxon signed-rank). Despite this pre-treatment decrease of fatigue, fatigue was still sufficiently disabling at visit 2, with a median FSS-score of 5.9 in both groups. Seven patients (9%) had a FSS score less than 5.0 at the end of this pre-treatment phase.

Primary endpoint

The responses to Amantadine and placebo for all individual patients are shown in table 2. From the patients responding to one treatment only 6 of 11 (55%) patients in the Amantadine-placebo group improved after Amantadine treatment (OR 1.20 [95% CI 0.31-4.97], p=0.76, McNemar test). In the placebo-Amantadine group this proportion was 3 of 14 (21%) patients (OR 0.27 [95% CI 0.05-1.03], p=0.03), indicating a more favorable outcome for placebo treated patients in this subgroup. However, combined for both groups of patients this proportion was 9 of 25 (36%) patients (OR 0.56 [95% CI 0.22-1.35], p=0.16), indicating no difference between responses after placebo or Amantadine. The overall mean difference between the Amantadine and Placebo period changes in FSS scores is -0.45 [95% CI -0.94-0.04; t = -1.80, df = 73, p = 0.076] which does not quite reach significance, although it favors Amantadine since that treatment period leads to the greater decreases in FSS scores.

To check for order and carry-over effects, which could cause biases, we compared the different treatment period responses in a different way. The mean improvement in FSS scores in the Amantadine-placebo sequence group was 0.46 (SD1.29) in the Amantadine treatment period and 0.08 (SD 1.44) in the placebo treatment period. The mean improvement in FSS scores in the

placebo-Amantadine sequence group was –0.03 (SD 1.35) in the Amantadine treatment period and 0.4 (SD 1.27) in the placebo treatment period. The additional two group t test analysis did not show a significant period effect (p=0.078 [95% CI –0.92-0.05]) and carry-over effect (p=0.28 [95% CI –1.24-0.44]).

Table 2. Reaching primary endpoint during the different treatment sequences

		Amantadine-Placebo group			Placebo-Amantadine group			Both groups		
		≥ 1 point improvement during placebo treatment			≥ 1 point improvement during placebo treatment			≥ 1 point improvement during placebo treatment		
≥ 1 point improvement during Amantadine treatment		Yes	No	Total	Yes	No	Total	Yes	No	Total
	Yes	2	6	8	1	3	4	3	9	12
	No	5	23	28	11	23	34	16	46	62
	Total	7	29	36	12	26	38	19	55	74

Legend to Table 2. Reaching the primary endpoint is defined as reduction of at least one point on the FSS. Amantadine-Placebo group = changes in period 1 and 2 for the group of patients with sequence Amantadine-placebo; Placebo-Amantadine group = changes in period 1 and 2 for the group of patients with sequence placebo-Amantadine; Both groups = changes in period 1 and 2, combined for both treatment groups.

Secondary endpoints

FIS: no significant differences between the treatment periods within individual patients comparing mean FIS and its subscale scores at the end of treatment period 1 (visit 3) and period 2 (visit 5) were observed (one-sample t-test, p=0.77). The FIS showed the same trends in the different treatment periods as were noticed in the FSS.

HAD: Comparing mean HAD-scores at the end of treatment period 1 and treatment period 2 did not reveal any difference; regarding anxiety (p=0.06) and depression (p=0.11), a slight tendency in favor of the placebo-treated group was observed (one-sample t-test).

Handicap / Quality of Life: The RHS and the EHQ did not show significant differences between the two groups (one-sample t-test, p=0.54 and p=0.21). No significant differences were seen comparing mean SF-36 subscale scores in both groups, although the subscales of role-physical functioning and mental health perception increased significantly in the placebo treated group (t-test, both p=0.008).

Allocation concealment

If patients used Amantadine in allocation period one, 49% thought they used active medication in this period, 31% thought in the second period and 20% did not observe any difference. If patients used Amantadine in period two, 44% thought they used active medication in this treatment period, and 44% thought they used it in the first period. Twelve percent had no opinion. No correlation was found in what patients really used and what they thought they used (p=0.46). By verbal report at the end of the study, patients believed in a slight benefit of 'the study drug', without knowing the allocation sequence. Two weeks after the last treatment

period, and before unblinding the study, 75% of patients wanted to continue with open treatment of Amantadine as compared with no treatment.

Adverse effects

In 40% of patients mild and transient side effects were noticed; in twenty-two patients (28%) during Amantadine treatment and in 10 patients (13%) during placebo treatment. Anticholinergic complaints (i.e. dry mouth, dizziness) occurred in 6 patients (8%) and were equally divided between both treatment groups. Dizziness, generally mild and transient within 2 or 3 days, was reported directly after starting medication or increasing the dose. Gastro-intestinal complaints were noticed in 7 placebo (9%) and in 3 Amantadine treated patients (4%). Most striking differences were noticed in complaints about sleep. Nine patients (11%) reported some sleep disturbances when treated with Amantadine, and 1 patient (1%) while using placebo. These disturbances sometimes persisted for days, although not that severe to interrupt trial participation. Other low frequent side effects included headache, nervous feelings and vividly dreaming. One patient complained about transient blurred vision directly after starting Amantadine.

DISCUSSION

This is the first study evaluating Amantadine as treatment of severe fatigue after GBS. Amantadine was not effective. No significant differences were seen on the FSS between treatment groups. Nevertheless, a certain reduction of fatigue was observed seen both during the pre-treatment period (visit 1 to visit 2), and during the consecutive visits. A possible explanation may be the increased attention for fatigue provided by this study and its corresponding ameliorating influence on fatigue. A similar phenomenon was observed in the fatigue treatment studies of Krupp et al. and the Canadian MS Research Group.[7] Krupp et al. noticed a decline of fatigue severity for all patients between their first and second study visits, even before starting treatment.[6] In our study, Amantadine did not significantly change levels of anxiety and depression, impact of fatigue, functional disability, handicap scores, and quality of life. Amantadine was generally well tolerated and side effects were mild and transient (only one patient withdrew because of side effects).

In four short-term multiple sclerosis (MS) studies it was indicated that fatigue was reduced in 20-40% of patients using Amantadine. The mechanism for the positive response on Amantadine in MS is not known. Patients participating in these MS studies were mild to moderate disabled, which seems to be worse compared to the neurological mildly affected GBS-patients in our trial. Despite comparable methods (equivalent dosage of Amantadine and duration of treatment periods), differences in underlying pathophysiological mechanisms and in disease course may be explanatory factors for the negative effect of Amantadine in our study population. In

contrary to MS, GBS generally is a monophasic disease without further relapses. Therefore, it may be indicated to study the effect of Amantadine in patients with a more chronic and still active immune-mediated polyneuropathy (e.g., CIDP during the long-term treatment phase). Regarding the primary outcome measurement, the FSS seemed an adequate questionnaire, as described by Merkies et al.[3] Although some authors criticized the FSS for assessing a combination of very general and very specific aspects of the patients' experience of fatigue and for its limited utility in examining the ways in which fatigue affects patients' lives, assessment of fatigue using the FSS and the FIS showed the same results and trends in this study.[15,23] Both severity as well as impact of fatigue on cognitive, physical, and social functioning showed corresponding changes on both assessment scales.

Fatigue has been briefly addressed as a residual complaint in a few cases of GBS in the past.[24-26] It was mentioned that physical fatigue often occurred in the first year after onset of GBS, and that fatigue rarely disabled patients.[27] However, Merkies et al. showed that complaints about fatigue and endurance intolerance may persist for many years. It was noticed that fatigue, distinguishable from the transient and mild fatigue many healthy persons experience, is still under-recognized by neurologists and rehabilitation physicians. Fatigue remains a severe problem and one of the most important reasons for decrement of quality of life, social life and physical functioning for years.[3] Besides studies reporting positive effects of training intervention on fatigue in GBS and CIDP, to date no adequate drug therapy exists.[28-31]

Amantadine did not show a positive effect in this trial. At least attention for fatigue seems to be important. Because of the persistence and severity of the complaints, further studies evaluating pathophysiological mechanisms and evaluating other drugs or physical training for 'post-GBS-fatigueness' are indicated.

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CHAPTER 3.2

Physical training and fatigue, fitness, and quality of life in Guillain-Barré syndrome and CIDP

Garssen M.P.J.[1], Bussmann J.B.J.[2], Schmitz P.I.M.[3], Zandbergen A.[2], Welter[2] T.G., Merkies I.S.J.[4], Stam H.J.[2], and van Doorn P.A.[1]

From the Departments of Neurology[1] (Garssen, van Doorn), Rehabilitation[2] (Bussmann, Zandbergen, Stam), and Statistics[3] (Schmitz); Erasmus Medical Center, Rotterdam; from the Department of Neurology[4] (Merkies); Spaarne Hospital, Haarlem, The Netherlands

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ABSTRACT

Many Guillain-Barré syndrome (GBS) and Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) patients suffer from excessive fatigue, which may persist for years and reduce quality of life. We performed a 12-week during bicycle exercise training in 20 severely fatigued patients, 16 relatively good recovered from GBS and 4 with stable CIDP. Training seemed well-tolerated and self-reported fatigue scores decreased 20% (p=0.001). Physical fitness, functional outcome, and quality of life were improved.

INTRODUCTION

Guillain-Barré syndrome (GBS) and Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) are immune-mediated polyneuropathies.[1] Despite relatively good neurological recovery, the majority of GBS or CIDP patients remain severely fatigued.[2] Fatigue, different from the transient and mild fatigue healthy persons can experience, seems independent of muscle strength and present disability score, and is one of the most disabling symptoms.[2]

Aerobic training decreases fatigue and improves physical fitness and quality of life in patients with multiple sclerosis.[3] It is unknown whether 'neurologically recovered' GBS patients or stable CIDP patients are able to perform a training program. Training may not be tolerated because of the initial complaints of severe fatigue or residual neurological deficits.[4] However, some positive effects of low-intensity training interventions on fatigue, fitness, and quality of life are reported.[5] We determined the feasibility and effect on fatigue severity of a structured 12-week during bicycle exercise training program. Additionally, we evaluated the effect on physical fitness, muscle strength, functional outcome, anxiety and depression, handicap, and quality of life.

PATIENTS AND METHODS

Sixteen 'neurologically relatively good recovered' GBS-patients and 4 neurologically stable CIDP-patients, fulfilling the diagnostic criteria, participated in this prospective observational study. Two CIDP-patients needed intermittent intravenous immunoglobulins. Patients were recruited from the GBS/CIDP databank at the Erasmus Medical Center Rotterdam or the Dutch GBS patients association. Ten sex and age (maximum 5 years difference) matched healthy subjects (not known with any disease or use of medication) were recruited from patients' surrounding. The Ethics Committee of Erasmus Medical Center approved the study.

Inclusion criteria

Severe fatigue, defined as mean fatigue severity score (FSS) at least 5.0 out of 7.0[2,6], and neurologically stable (no changes in GBS-disability score within 3 months before baseline). Onset of GBS/CIDP more than 6 months and less than 15 years ago, age at least 18 years, and a GBS-disability score of 3 or less (able to walk 10 meters).

Exclusion criteria

Severe fatigue before GBS or CIDP. Concomitant conditions (e.g. malignancy, chronic infections, hypothyroidism, anemia, renal and liver disease, chronic pulmonary and cardiovascular disease, chronic fatigue syndrome, diabetes) or use of medication (<4 weeks before onset study) that

might cause or influence fatigue (e.g. benzodiazepines, antidepressants and immunotherapy). Depression, hypertension, and β-blocking drugs.

Withdrawal criteria

Not able to train for 3 consecutive sessions; persisting and disabling adverse events like severe muscle cramps, weakness or increasing sensory deficits; development of new co-morbidity interfering with training procedures.

Study design

Patients registered in the database received a letter and FSS-form, requesting participation. Patients meeting the eligibility criteria, underwent a neurological/physical examination (including electrocardiogram), assessment scales were completed, and blood samples drawn (to exclude other reasons for fatigue). Severely fatigued (mean FSS score of 5.0 or more) and non-depressed (Hospital Anxiety and Depression Scale / depression subscale score of 10 or less) patients with normal blood values were included and returned for a cardio-respiratory fitness test, isokinetic muscle strength measurements, and ambulatory activity measurement. Thereafter patients started a 12-week during bicycle exercise training, with a short evaluation after 6 weeks. Afterwards, all assessments and measurements performed at baseline were repeated. Healthy subjects underwent all baseline measurements, but did not participate in the training intervention.

Outcome measures

Primary outcome measures were the training feasibility and reduction of fatigue (improvement of at least 1 mean point on the FSS).[2,6] Secondary outcome measures were changes at the level of cardio-respiratory fitness and isokinetic muscle strength; functional outcome - daily physical activity (e.g., duration and distribution of standing, sitting, walking, cycling and transitions from positions measured by the Rotterdam Activity Monitor/RAM)[7], fatigue impact scale[8], and GBS-disability score; hospital anxiety and depression scale[9]; rotterdam handicap scale; and quality of life (SF-36).

Training program

Training consisted of 3 supervised training sessions, every week, for 12 weeks. Each session consisted of 5 minutes warm-up (65% of maximum heart rate as measured by the cycle ergometer test), and 30 minutes of cycling. The first weeks, training intensity increased from 70% to a maximum of 90% of maximal heart rate. After the third week, the load of the home trainer was weekly increased from 0 to 10 or 20 Watt, depending on patients' physical ability. Each training session was finished with 5-10 minutes of cool-down cycling. Exercise heart rates were monitored continuously.

Statistics

Primary analysis was performed using the two-sample t-test with equal variances. Treatment effects were analyzed after 6 and 12 weeks, using the paired t-test, two-sample t-test with equal variances, Wilcoxon signed-rank test, and two-sample Wilcoxon rank-sum (Mann-Whitney) test.

RESULTS

Baseline characteristics are listed in table 1. Of the 22 potential participants, two were non-eligible; one patient suffered from cardiovascular diseases, one patient was not able to adhere all training sessions. Two included patients stopped training after 2 and 3 weeks; one patients' partner died; the other developed a cholecystitis.

Table 1. Baseline characteristics

	Patients	Healthy individuals
	(n=20)	(n=10)
Characteristics		
GBS (n)	16	-
CIDP (n)	4	-
Sex (F/M)	14 / 6	6 / 4
Median age at start of the study, yr (range)	49 (22-66)	51 (23-64)
Mean duration since diagnosis, yr (range)	4.1 (0.5-15)	-
MRC sumscore distribution, n (score range: 0-60)		
52-57	2	-
58-59	4	-
60	14	10
GBS-disability distribution, n (score range: 0-6)		
F = 0	-	10
F = 1	15	-
F = 2	5	-
FSS-score, mean (range)	6.1 (5.8-6.4)	2.2 (1.6-2.8)

Legend to Table 1. GBS = Guillain-Barré syndrome; CIDP = Chronic Inflammatory Demyelinating Polyneuropathy; MRC = Medical Research Counsil. Sumscore distribution ranges from 0 (paralysis) to 60 (normal strength), examined in 6 muscle pairs; GBS-disability score: F = 0 (healthy, no symptoms or signs), F = 1 (minor symptoms or signs, capable of running), F = 2 (able to walk at least 10 meters across an open space without assistance, walking frame, or stick, but unable to run), F = 3 (able to walk 10 meters with walking frame, sticks or support); FSS = Fatigue Severity Scale, scores ranging from FSS = 1 (no signs of fatigue), to FSS = 7 (most disabling fatigue).

Primary outcomes

Feasibility. Side effects, occurring in 5 patients (25%), consisted of muscle cramps, paresthesias, pain, and burning sensations in legs. Side effects were experienced as mild and transient within 2 to 6 weeks, and were no reason to interrupt the training.

FSS. Training resulted in a 20% fatigue severity reduction (see table 2). Both GBS and CIDP patients showed comparable changes on the FSS.

Table 2. Severity of fatigue, impact of fatigue, anxiety, depression, handicap and quality of life scores

		Exercise group			Healthy individuals
Variable		baseline (n=20)	6 week (n=17)	12 week (n=18)	baseline (n=10)
FSS		6.1 (0.65)	5.1 (1.35)[1]	4.8 (1.53)[1]	2.2 (0.88)[3]
FIS	Cognitive (n=10)	1.37 (0.98)	1.05 (0.77)	0.81 (0.96)[1]	0.25 (0.34)[3]
	Physical (n=10)	2.18 (0.81)	1.39 (0.76)[1]	1.13 (0.89)[1]	0.23 (0.30)[3]
	Social (n=20)	1.35 (0.75)	0.97 (0.68)[2]	0.81 (0.81)[1]	0.21 (0.23)[3]
HAD	Anxiety	1.89 (0.48)	1.71 (0.36)	1.59 (0.30)[2]	1.44 (0.32)[3]
	Depression	1.71 (0.37)	1.55 (0.44)	1.39 (0.28)[1]	1.26 (0.32)[3]
RHS*		3.56	3.78[1]	3.89[1]	4[3]
SF-36	PCS	44.0	45.6	50.1[2]	58.4[3]
	MCS	51.6	52.7	55.9	55.7

Legend to Table 2. [1] Significant change from baseline, $p<0.01$. [2] Significant change from baseline, $p<0.05$. [3] Significant difference compared to baseline values of exercise group, $p<0.01$. All data are mean values (SD). FIS = Fatigue Impact Scale; HAD = Hospital Anxiety and Depression Scale; RHS = Rotterdam Handicap Scale, * RHS data are centiles and were available in 17 patients; SF-36 = Short Form-36 Health Questionnaire, PCS = Physical Component Summary, MCS = Mental Component Summary.

Secondary outcomes

Changes in fatigue severity, impact of fatigue, anxiety, depression, handicap and quality of life are listed in table 2. Changes in physical fitness, muscle strength and activity pattern are listed in table 3. Two patients improved in GBS-disability score after training. Initially both were unable to run, after training one was able to run, the other improved to score 0 (no symptoms).

Table 3. Cardio-respiratory cycle ergometer test, maximum isokinetic muscle strength variables, and activity percentages

	Exercise group		Healthy individuals
Variable	baseline (n=20)	12 week (n=18)	baseline (n=10)
K4b² physical condition			
VO2max (ml/kg/min)	25 (8)	30 (10)[1] (+20%)	33 (7) [2]
POmax (Watt)	133 (38)	172 (53)[1] (+29%)	190 (54) [2]
HRmax (bpm)	163 (17)	172 (12)[1] (+6%)	172 (15)
Isokinetic muscle strength			
Elbow flexion (Watt)	27.7 (13.2)	31.4 (14.9) [1]	34.5 (15,3)
Elbow extension (Watt)	27.5 (14)	32.7 (16.7) [1]	33.9 (10.3)
Knee flexion (Watt)	39.3 (17.6)	43.2 (19.7)	52.3 (16.3) [2]
Knee extension (Watt)	74.4 (30.3)	84.8 (33.8) [1]	85.7 (22.4)
Σ Strength elbow	27.6 (13.3)	32 (15.6) [1]	34.2 (12.5)
Σ Strength knee	56.8 (23.4)	64 (25.4) [1]	69 (18.4)
RAM			
Percentage activity	10.7	11.2	12.2

Legend to Table 3. [1] Significant change from baseline, $p<0.01$. [2] Significant difference compared to baseline values of exercise group, $p<0.05$. All data are mean values (SD). VO2max = peak oxygen uptake; POmax = maximal power output; HRmax = maximal heart rate; bpm = beats per minute; Σ Strength = sum of all tested muscle groups; RAM = Rotterdam Activity Monitor, measuring percentages of activity during 24 hours.

DISCUSSION

Despite our intensive training protocol, only 5 patients had mild and transient side effects and training seemed to be feasible. After training, we found a 20% reduction of self-reported fatigue. Both severity as well as impact of fatigue showed corresponding improvements. VO2max increased with 20%, consistent with effects of aerobic exercise training in healthy sedentary individuals (15%), and in patients with multiple sclerosis (22%).[3,10] Also functional outcome and quality of life improved. Most patients (80%) were motivated to continue with regular training activities.

The patients reported that increased physical activity in the past often resulted in increased neurological complaints, resembling the initial phase of GBS or CIDP, which resulted in threatening and anxious feelings of getting a relapse. This medical supervised training showed the opposite, patients became confident, and a negative circle seemed to be broken. Depression and anxiety scores improved significantly, supporting the former explanation. Especially the physically focused domains of the SF-36 showed improvement, suggesting being a result of improved physical fitness and muscle strength.

In contrast with most physiological and subjective variables, objectively measured daily physical activity using the RAM did not show any significant increase in activity. This may suggest that changing the level of daily physical activity is not an important adaptation strategy in these fatigued patients. May be the maintenance of a normal activity pattern contributes to fatigue problems.

Improved physical fitness and muscle strength, and increased attention for fatigue probably all play different roles in decreasing fatigue and improving quality of life in patients with GBS or CIDP. Also the motivational aspect of increased social contacts with fellow-patients, besides promoting exercise adherence, possibly has lead to better psychological performances.

Fatigue and endurance intolerance are still not widely recognized by neurologists and rehabilitation physicians and remain part of the most important reasons for decrement of quality of life and physical functioning[2]. Our results are encouraging. However, further training intervention studies should be performed, preferable in more patients, and in a controlled and randomized fashion.

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CHAPTER 3.3

Follow-up of fatigue, fitness, and quality of life in Guillain-Barré syndrome and CIDP, 2 years after training intervention

Garssen M.P.J.[1], Bussmann J.B.J.[2], Welter T.G.[2], Schmitz P.I.M.[3], Stam H.J.[2], and van Doorn P.A.[1]

From the Departments of Neurology[1] (Garssen, van Doorn), Rehabilitation Medicine[2] (Bussmann, Welter, Stam), and Statistics[3] (Schmitz); Erasmus Medical Center, Rotterdam, The Netherlands

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ASTRACT

Objective A previous study showed that a 12-week medically supervised physical training program significantly reduced severe fatigue and improved physical fitness and quality of life in neurologically recovered Guillain-Barré syndrome and stable CIDP patients. The aim of the present study was to determine whether training effects were still present, on average 2.2 years after this training intervention.

Methods All previously trained patients were asked to participate in the current follow-up study, completed the same questionnaires and underwent the same physical measurements as before. Ongoing physical exercise training was additionally evaluated.

Results Self-reported fatigue scores as measured by the Fatigue Severity Scale were still significantly decreased (23%, p=0.001), and comparable with post-training values. Also other outcome measures (maximum physical power, muscle strength, impact of fatigue, anxiety scores, and quality of life) remained improved.

Conclusions Training intervention induces long-term positive effects on fatigue, fitness and quality of life in neurologically recovered GBS patients and stable CIDP patients suffering from residual fatigue.

INTRODUCTION

Weakness in Guillain-Barré syndrome (GBS) and Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) can improve after immune-intervention. However, the majority of GBS and CIDP patients remain severely fatigued, different from the transient and mild fatigue healthy persons may experience.[1] Recently we studied the initial effect of a structured and medically supervised 12- week bicycle exercise training in 20 severely fatigued but otherwise 'neurologically relatively well-recovered' patients with GBS or with stable CIDP.[2] This study showed that aerobic training was feasible, resulted in reduced self-reported fatigue, and in improved physical fitness, functional outcome, and quality of life. The aim of the present study was to determine whether training effects were still present, more than 2 years after the training intervention.

METHODS

Patients

Sixteen 'neurologically relatively well recovered' GBS-patients and 4 neurologically stable CIDP-patients (14 female and 6 male), recruited from the GBS/CIDP databank at the Erasmus Medical Center Rotterdam and the Dutch GBS patients association, participated in a bicycle exercise training more than 2 years ago.[2] Patients were eligible when they were severely fatigued (defined as mean fatigue severity score (FSS) of at least 5.0 out of 7.0), neurologically stable, and without other reasons for fatigue. Other in- and exclusion criteria are described in detail elsewhere.[2] All trained patients were asked to participate in the current follow-up study. Patients who agreed to participate, completed the same questionnaires, and underwent the same physical measurements as two years earlier (see outcome measures).[2] All patients gave informed consent. The Ethics Committee of Erasmus MC approved the study.

Initial training program

The initial training program consisted of a 12-week medically supervised bicycle exercise training, with 3 sessions every week. Each session consisted of 5 minutes warm-up (65% of maximum heart rate as measured before training), 30 minutes of cycling, and 5-10 minutes cool-down cycling. The first weeks, training intensity increased from 70% to a maximum of 90% of maximal heart rate. After the third week the load of the home trainer was increased weekly, depending on patients' physical ability. After this intervention, no further training program was offered.

Outcome measures

Outcome measures were the same as in the previous study. Primary outcome measure was self-reported fatigue.[3] Secondary outcome measures were physical fitness measures; maximal power output (POmax) and isokinetic muscle strength; and scores derived from the Fatigue Impact Scale,[4] GBS disability score, Hospital Anxiety and Depression Scale,[5] Rotterdam Handicap Scale[6]; and two quality of life scores (EuroQol[7] and Short Form-36 Health Questionnaire [SF-36]).

Ongoing physical exercise

Ongoing physical exercise was evaluated by asking the patients whether they continued to participate in sports or aerobic exercise after finishing the training intervention more or less frequently. We additionally asked the frequency and duration of each sports session.

Statistical analysis

Outcome measures more than 2 years after training intervention were compared with pre- and post-training values. Primary outcome was analyzed using the paired t-test. Secondary outcomes were analyzed using the paired t-test, sign-test, Wilcoxon signed-rank test, and ANOVA with repeated measures, using Stata version 8.0 and SPSS version 10.1.

RESULTS

Patient characteristics

One female GBS patient did not want to participate again, without explaining her reason. Two female patients (1 GBS, 1 CIDP) completed the questionnaires, but were not motivated to adhere the physical fitness measurements again. Two other female patients were excluded from analysis because they did not finish the initial training program (due to reasons not related to the training intervention), resulting in 15 participants included in the analysis. The physical fitness and questionnaire values of patients dropped from analysis were within the range of values of the other patients.

Mean age was 55 years (37-68), onset of disease 5.4 years (3-12) ago, MRC sumscore 59 (52-60), and GBS disability score 1 (n=12) or 2 (n=3; 1 GBS and 2 CIDP). Mean duration since finishing the training program until follow-up measurements was 2.2 years (1.7-2.5). None of the patients changed in MRC sumscore or GBS disability score.

Primary outcome

FSS. Mean reduction of self-reported fatigue compared to pre-training values was 23% (p=0.001), which was not different from the fatigue reduction directly after the training intervention (20%, p=0.56) (table 1).

Table 1. Severity of fatigue, impact of fatigue, anxiety, depression, handicap and quality of life scores

		Baseline	12 weeks	2.2 years
		Before training	After training	Follow-up[4]
		(n=18)	(n=18)	(n=15)
Variable				
FSS		6.1 (0.65)	4.8 (1.53)[1]	4.7 (0.99)[1]
FIS	Cognitive (n=10)	1.37 (0.98)	0.81 (0.96)[1]	1.03 (0.92)[1]
	Physical (n=10)	2.18 (0.81)	1.13 (0.89)[1]	1.19 (0.89)[1]
	Social (n=20)	1.35 (0.75)	0.81 (0.81)[1]	0.77 (0.77)[1]
HAD	Anxiety	1.89 (0.48)	1.59 (0.30)[2]	1.72 (0.35)[2]
	Depression	1.71 (0.37)	1.39 (0.28)[1]	1.54 (0.35)[3]
RHS*		3.56	3.89[1]	3.89
EuroQol**		70	80[1]	78[1]
SF-36	PCS**	44.0	50.1[2]	45.6
	MCS**	51.6	55.9	54.5

Legend to Table 1. [1] Significant change from baseline, $p<0.01$. [2] Significant change from baseline, $p<0.05$, [3] $p=0.05$. All data are mean values (SD). [4] No significant differences were found with post-training data. FSS = Fatigue Severity Scale; FIS = Fatigue Impact Scale; HAD = Hospital Anxiety and Depression Scale; RHS = Rotterdam Handicap Scale; EuroQol = The EuroQol Health Status; SF-36 = Short Form-36 Health Questionnaire, PCS = Physical Component Summary, MCS = Mental Component Summary. * RHS data are centiles and were available in 14 patients, ** EuroQol and SF-36 PCS and MCS data are centiles.

Secondary outcomes

Impact of fatigue, anxiety, depression, handicap and quality of life scores are listed in table 1. Results of physical fitness (maximal power output and muscle strength) measurements are listed in table 2. Generally, significant differences were still found compared to the pre-training situation, and no significant differences were found compared to the values obtained directly after the training period.

Ongoing physical exercise

Ten patients (67%) still participated in sports or aerobic exercise on a regular basis, on average 1,2 times (range 1-3 times) a week during 30-120 minutes. Five patients did not participate in sports after finishing the training program. From the 10 patients still participating in sports, six patients participated in sports (fitness, swimming, tennis, cycling or running) with the same intensity compared to pre-training status, three patients with increased, and one patient with decreased intensity.

Table 2. Cardio-respiratory cycle ergometer test and maximum isokinetic muscle strength variables

	Baseline		12 weeks	2.2 years
	Before training		After training	Follow-up[4]
	(n=18)		(n=18)	(n=15)
Variable				
Aerobic capacity				
POmax (Watt)	133	(38)	172 (53)[1]	171 (51)[1]
HRmax (bpm)	164	(17)	172 (12)[1]	167 (16)
*Isokinetic muscle strength**				
Elbow flexion (Watt)	27.7	(13.2)	31.4 (14.9)[1]	31.7 (12.8)
Elbow extension (Watt)	27.6	(14.0)	32.7 (16.7)[1]	35.7 (17.6)[1]
Knee flexion (Watt)	39.3	(17.6)	43.2 (19.7)	50.0 (20.1)[1]
Knee extension (Watt)	74.4	(30.4)	84.8 (33.8)[1]	92.8 (34.9)[1]
Σ Strength elbow	27.6	(13.3)	32 (15.6)[1]	33.7 (15.0)[1]
Σ Strength knee	56.8	(23.4)	64 (25.4)[1]	71.4 (26.5)[1]

Legend to Table 2. [1] Significant change from baseline, $p<0.01$. All data are mean values (SD). [4] No significant differences were found with post-training data. VO2max = peak oxygen uptake; POmax = maximal power output; HRmax = maximal heart rate; bpm = beats per minute; Σ Strength = sum of all tested muscle groups. * Isokinetic muscle strength values were available in 14 patients.

DISCUSSION

In a previous study is was found that training intervention was feasible, and resulted in 20% reduction of self-reported fatigue (as measured by the FSS), 29% increase of maximal power output (POmax, measure of aerobic capacity), and improvement of functional outcome and quality of life.[2] These results were encouraging and an important reason to explore the long-term effect.

We found a significant 23% reduction of self-reported fatigue, which was comparable with values obtained directly after the training period (20% reduction). Maximal 'power output' and muscle strength (except elbow flexion), remained significantly improved compared to pre-training values. Also functional outcomes, anxiety scores, and quality of life scores remained improved, with no significant differences compared to the situation immediately after the training program.

Although the cause of fatigue and the exact physiological and psychological contribution of the 12-week during aerobic training intervention in treatment of severe fatigue remain to be elucidated, there appears to be an objectively and subjectively evaluated long-term positive effect. In an earlier study it was found that severe fatigue after GBS is present independent of the duration after GBS.[1] Therefore, the long-term positive effect of training intervention on

fatigue is unlikely to be caused by a natural reduction of fatigue after GBS. Since all patients participated less frequently and less intensively in sports than during the training intervention period, and the MRC sumscores and GBS disability scores at follow-up remained unchanged, it is also unlikely that the persistent benefits of reduced fatigue could be explained by ongoing reconditioning activities only. It seems that patients became more convinced of their physical capabilities, and were less afraid and more capable to perform rather high level (short-lasting) maximal physical effort, as measured by the increased POmax and muscle strength measurements. Presumably, training has taught our patients that increased physical activity can be performed without getting new neurological complaints or 'relapse' feelings, and thus helped them to take the barrier.

Although this study needs to be repeated with a group of patients not receiving the training program these results favor a long-term effect of training. We now seem to be able to give some advises to severely fatigued GBS and CIDP patients, and discuss the possibility of participation in medically supervised training programs. It has to be studied whether such an intensive training program is needed, and which components of training are most important. Studies elucidating the pathophysiological mechanisms of fatigue and physical training, and studies evaluating new treatment strategies remain needed.

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CHAPTER 4

Studies on occurrence and possible causes of residual fatigue

CHAPTER 4.1

Residual fatigue is independent of antecedent events and disease severity in Guillain-Barré syndrome

Garssen M.P.J., van Koningsveld R., and van Doorn P.A.

From the Department of Neurology; Erasmus Medical Center, Rotterdam, The Netherlands

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ABSTRACT

The occurrence of severe fatigue after Guillain-Barré syndrome (GBS), and its relation with disease course, clinical characteristics, and antecedent infections was studied in 100 GBS patients. Severe fatigue, expressed as a mean Fatigue Severity Scale (FSS) score of 5.0 or more, was present in 60% of all patients. It was more frequently present in females and in patients over 50 years ($p<0.01$). There was no significant relationship between fatigue severity and the level of functional disability at nadir, antecedent events or infections, clinical variables, and time to follow-up after GBS.

INTRODUCTION

Despite apparently 'good' neurological recovery after Guillain-Barré syndrome (GBS) in approximately three-quarters of all patients[4], it was noticed that the majority of patients remained restricted in daily and social activities due to fatigue.[7] Fatigue seriously affects quality of life, and most patients report fatigue among their three most disabling symptoms.[7] It was recently shown that an exercise-training program could significantly reduce fatigue.[3] However, it is presently unknown whether complaints of fatigue are related to the maximal level of severity of disease, whether it is related to antecedent events and infections, and when fatigue after GBS is first noticed.

A prospective nationwide survey in the Netherlands was conducted, aiming to increase knowledge on the spectrum of the GBS syndrome and to increase insight in the occurrence and pathophysiology of residual fatigue. Distinctive characteristics were found for mildly and severely affected GBS patients.[8] We now report the additional evaluation of self-experienced fatigue, and the relation between fatigue and different clinical characteristics, antecedent events, and infections, in mild and severely affected patients. Increasing knowledge of fatigue may be of importance in understanding the underlying pathophysiological mechanisms, and might lead to more specific therapies.

PATIENTS AND METHODS

Patients

A 2-year nationwide prospective survey was conducted in all but three hospitals in the Netherlands.[8] After obtaining informed consent, the neurologists filled in a questionnaire for every new patient fulfilling the NINCDS criteria of GBS, and sent it, together with a serum sample, to the investigators. After the 2-year study period, a questionnaire was sent to all patients.[8] All patients gave informed consent prior to their inclusion in the study. The study was approved by the Ethics Committee of Erasmus Medical Center and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Antecedent infections

Clinical features of preceding infections with influenza- or influenza like illness, gastro-enteritis or diarrhea, respiratory tract and 'other infections' were scored prospectively. Preceding infections were considered positive when patients reported symptoms meeting the CDC definitions for nosocomial infections, *and* when they occurred within 3 weeks before the start of the first symptoms of GBS. The presence of *Campylobacter jejuni*, CMV, EBV and *Mycoplasma pneumoniae* was additionally studied, using serological tests as previously described .[8]

Characteristics of patients and neurological signs and symptoms

Data obtained from the questionnaires completed by the neurologists were; age, sex, muscle strength (MRC sumscore), sensory and cranial nerve involvement, therapy, and the worst GBS-disability score (f-score), and were collected prospectively. Patients were considered mildly affected when the f-score was < 3 (able to walk unaided at nadir) and severely affected when the maximal f-score was ≥ 3 (unable to walk unaided at nadir).[5] Data obtained from the questionnaires sent to the patients were; presenting symptoms, presence of sensory symptoms, days until nadir, and self-reported fatigue.

Fatigue assessment

All patients were asked to complete the Fatigue Severity Scale (FSS), a simple 9-item self-reported fatigue questionnaire, with mean scores ranging from 1 ("no signs of fatigue") to 7 ("most disabling fatigue").[6] Severe fatigue was defined as a mean FSS-score of 5.0 or more.[7] The FSS demonstrates a good internal consistency, test-retest reliability, and validity in immune-mediated polyneuropathies.[7]

Statistics

Differences in characteristics, preceding infections, symptoms and signs, and self-reported fatigue (FSS) were calculated with a chi-square test without continuity correction, the Fisher's exact test, or the Wilcoxon-Mann-Witney U test when appropriate. All calculations were performed using STATA 8.0. A p value < 0.05 was considered significant.

RESULTS

Baseline characteristics

In the 2-year period, 139 GBS patients and 14 MFS patients entered the prospective study. Fifty-three males and 47 females returned the questionnaires (total 100), i.e. 65% of the total group, and 72% of the group of GBS patients. There were no differences in age and sex distribution between the responders and the non-responders. However, the non-responders group consisted of significantly more mildly affected patients compared to the responder group. In the responder group 89 of these patients were diagnosed as GBS and 11 had Miller Fisher syndrome (table 1). Mean age was 44.9 (SD 18.9). Mean time after onset of disease until completing the questionnaire was 16 months (SD 6.8 months, range 1-33 months). At time of completing the questionnaire, the majority of patients (79%) still were within 6 to 24 months after disease onset. In 69% a clinical infection preceded the symptoms of GBS, which was confirmed by positive serology in 31%.[8]

Table 1. Characteristics of patients at follow-up, mean 16 months after nadir

Characteristic (number, percentage)	Severe fatigue (FSS ≥ 5.0) N=59	Non-severe fatigue (FSS < 5.0) N=41	Total N=100
Fatigue score (mean, SD)	6.3 (0.6)	3.0 (1.2)	4.9 (1.8)
Age ≥ 50	33 (70%)[1]	14 (30%)	47 (47%)
Male	24 (45%)	29 (55%)	53 (53%)
Female	35 (74%)[1]	12 (26%)	47 (47%)
Time to follow-up in months (mean, SD)	15.6 (7.3)	15.8 (6.2)	16 (6.8)
GBS disability score at nadir (mean, SD)	3.7 (1.0)	3.4 (1.3)	3.5 (1.1)
Clinical pure motor variant *	10 (19%)	12 (34%)	22 (25%)
Clinical infection present	40 (68%)	29 (71%)	69 (69%)
Positive infection serology (n=75) **	14 (30%)	9 (31%)	23 (31%)

Legend to Table 1. All values are given in numbers and corresponding percentages or if indicated in mean values with a standard deviation (SD) or range; for subgroups of patients with (FSS ≥ 5.0) and without severe fatigue (FSS<5.0) and for the total group of patients. **[1]** Significant difference between patients with and without severe fatigue (p<0.03). * Data were available in 87 patients. ****** Infection serology was available in 75 patients, and tested for *Campylobacter jejuni*, CMV, EBV and *Mycoplasma pneumoniae*.

Fatigue

Severe fatigue was found in 60% of patients. Severe fatigue was significantly more frequent present in female patients (74% in females vs 45% in males, p=0.003), and more frequently in patients of 50 years and older (70% vs 49%, p=0.03). Three out of 11 Miller Fisher syndrome patients (27%) reported severe fatigue. This was significantly less compared to the GBS group (p= 0.02). No significant correlations were found between the level of the fatigue scores and the pure motor or motor-sensory subtype of GBS. No significant correlations were found between the FSS scores, and the MRC sumscores and f-scores at nadir, and between the FSS scores and time to follow-up. No relation was found between the level of fatigue, clinically antecedent infections, and infection serology. The numbers of positive infection serology were to small to allow meaningful conclusions on whether fatigue might be associated with any specific infection. No difference was found in the occurrence of severe fatigue in GBS patients with and without serologically confirmed antecedent infections**.**

DISCUSSION

In this cross-sectional study we investigated the presence of fatigue in a nationwide study. None of the patients participated in earlier studies on the assessment of fatigue. In previous studies it was reported that severe fatigue (FSS>5.0) is present in about 80% of patients with immune-mediated polyneuropathies, and that FSS-scores of healthy controls range from 2.2 to 2.9.[3,7] In the current study 78% of all GBS patients had a mean FSS-score above 3.0, and 60%

suffered from severe fatigue. Only 27% of the Miller Fisher syndrome patients reported severe fatigue.

Our study confirmed previous published data about severe fatigue; it occurs significantly more frequent in female patients, and is not significantly related to the duration of fatigue complaints after GBS.[7] In the present study, we additionally found that impaired muscle strength (as evaluated by the MRC sumscore), GBS-disability score, and sensory deficits in the initial phase of GBS, were not significantly related to fatigue. We also found that severe fatigue is significantly associated with age over 50 years, and that complaints of fatigue are already present much earlier after the initial phase of disease than described before.[7] Finally, fatigue seems not related to antecedent events or infections.

In this study the percentage of severe fatigue was lower than reported before (60 vs 80%). This might be due to differences in study population; we found that severe fatigue occurs more frequently in older patients, and the patient population we studied was considerable younger compared to the previous study (44.9 vs 56.1 years). Additionally, the duration of symptoms after GBS in our patient group was shorter (1.3 vs 5.2 years). This could be of importance, since patients who are still in the recovery phase of GBS might not be fully aware of other residual complaints like fatigue, because they are not able to perform the same physical activities like neurologically 'recovered' patients may do. A selection bias could have influenced our results since 65% of the patients returned the questionnaire and the non-responder group consisted of more mildly affected patients than the responder group. One could speculate whether mildly affected patients were less fatigued and thereby less motivated to complete the questionnaire. However, this is not very likely while the questionnaires focussed mainly on disease-related items and fatigue was only a small topic. However, also other reasons why patients did not participate in our survey can be suggested, and could have biased our data analysis in either direction. Our results should be interpreted with some caution, because we did not systemically exclude possible confounders of fatigue, like baseline co-morbidities and depression. However, it has been investigated before that severe fatigue is very frequently present in non-depressed GBS patients.[3]

The cause of fatigue is presently not known. It might be explained as a post-traumatic stress disorder after a potentially life threatening disease. On the other hand, recent long-term follow-up studies showed that residual neuropathy is present in approximately half of all patients, even when these patients showed apparently 'good' neurological recovery, which might suggest possible involvement of 'peripheral' disturbances in the pathophysiology of fatigue.[1,3] Additionally, MFS patients suffered less frequently from severe fatigue, suggesting the involvement of (subclinical) motor nerve dysfunction in the pathophysiology of fatigue. However, no association was found between fatigue and the severity of disease. Additionally decreased physical condition might play a role in the pathogenesis of fatigue.[1] Since older age at onset of disease is related to a less favorable functional outcome, this might contribute to the higher incidence of severe fatigue in elderly patients.[9]

This study confirms the high incidence and the long duration of severe fatigue after GBS. Fatigue was more frequently present in older patients and in females, however, we did not find a relation with functional disability at nadir, clinical variables, and antecedent events or infections. New studies should be directed towards possible underlying pathophysiological mechanisms and treatment of this long-lasting complaint that seriously interferes with quality of life, even years after functional recovery.

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CHAPTER 4.2

Nerve conduction studies in relation to residual fatigue in Guillain-Barré syndrome

Garssen M.P.J.[1], van Doorn P.A.[1], and Visser G.H.[2]

From the Departments of Neurology[1] (Garssen, van Doorn) and Clinical Neurophysiology[2] (Visser); Erasmus Medical Center, Rotterdam, The Netherlands

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ABSTRACT

Many Guillain-Barré syndrome (GBS) and Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) patients recover well, but suffer from excessive fatigue, which may persist for years and reduce quality of life considerably. In order to determine whether residual subclinical peripheral nerve dysfunction is a possible underlying mechanism of fatigue, we performed standardized nerve conduction (NC) studies in 16 fatigued patients, mean 6.5 years after diagnosis. Thirteen were relatively well recovered from GBS and 3 had stable CIDP. In contrast to CIDP, most NC values in GBS patients were remarkably restored and within normal values. No correlations were found between the electrophysiological findings and the fatigue scores, muscle strength, or functional scores. This study demonstrates that fatigue in GBS is not explained by residual nerve dysfunction, using conventional NC measurements.

INTRODUCTION

Guillain-Barré syndrome (GBS), an immune-mediated polyradiculoneuropathy with a broad clinical spectrum, is characterized by different patterns of nerve conduction (NC) failure, resulting in symmetric progressive muscle weakness with loss of myotatic reflexes [3, 9, 22]. Although most patients show relatively good neurological recovery after GBS, severe residual fatigue and endurance intolerance are serious and disabling long-term effects in the majority of patients [17]. These complaints of fatigue, different from the transient and mild fatigue healthy persons can experience, seem independent of muscle strength, sensory deficits, duration of symptoms, and actual disability score, and are significantly associated with a reduced quality of life [17]. The underlying pathophysiological mechanisms of fatigue in these well-recovered GBS patients are still unknown, and electrophysiological studies in these patients are lacking.

It is known from various electrophysiological studies in the (sub) acute phase of disease, that different GBS subtypes can be distinguished, ranging from a pure motor form to the classical demyelinating type of the disease [1]. The acute inflammatory demyelinating polyneuropathy (AIDP) variety is the most common subtype of GBS in western countries [23]. Little is known about long-term electrophysiological outcome, especially after good neurological recovery. Only in a recent long-term follow-up study, mean 7.0 years after the onset of GBS, it was shown that axonal loss was associated with permanent weakness of the anterior tibial muscle, caused by insufficient reinnervation [5].

We hypothesized that residual subclinical peripheral nerve dysfunction, i.e. demyelination, could contribute to fatigue in the otherwise well-recovered AIDP patients with good muscle strength values. We performed standardized NC measurements in a group of fatigued GBS patients, mean 6.5 years after onset of disease.

PATIENTS AND METHODS

Patient population

Sixteen fatigued patients, 13 neurologically 'relatively well-recovered' GBS-patients and 3 neurologically stable patients with chronic inflammatory demyelinating polyneuropathies (CIDP), fulfilling the diagnostic criteria, participated in this observational study, mean 6.5 years (range 3.0-18.3) after onset of disease. All GBS patients initially suffered clinically from AIDP, a diagnosis based on the combination of motor and sensory system involvement. In 6 of these patients NC studies were available, supporting the clinical diagnosis of AIDP. One CIDP patient still needed intermittent intravenous immunoglobulins, the other CIDP patients were in remission. Patients were recruited from the GBS/CIDP databank at the Erasmus Medical Center Rotterdam and the Dutch GBS patients association. All patients initially participated in a training intervention study on treatment of severe fatigue, more than 2 years ago [8].

Patients were eligible for the training intervention when they were severely fatigued (defined as mean fatigue severity score (FSS) of at least 5.0 out of 7.0) [13], and neurologically stable [12]. All patients had been screened to exclude concomitant conditions (i.e. depression) or use of medication that might cause or influence fatigue [8]. All trained patients were asked to participate in this electrophysiological study. Needle examination was not performed because most of these neurological well-recovered AIDP patients already took part in previous studies. We did not want to influence patients' voluntary participation, and to repeat inconvenient needle examinations. The Ethics Committee of Erasmus MC approved this study.

Nerve conduction studies

All measurements were performed with a Viking IV Select (Nicolet Biomedical; Madison, WI).

Using standard electrophysiological techniques, motor NC studies (NCS) and compound muscle action potentials (CMAP) were studied in the right-sided lower and upper extremity, using AgCl surface electrodes. Motor NCS of the peroneal nerve was performed with stimulation of the nerve at the ankle and knee, including NC velocity across the fibular head, and recording of the CMAP from the extensor digitorum brevis muscle. The median nerve was stimulated at the wrist and forearm, and the ulnar nerve at the wrist, forearm, and across the elbow. The CMAP amplitudes were subsequently recorded from the abductor pollicis brevis and abductor digiti minimi muscles. F-waves of the peroneal nerve were studied when a CMAP was obtained. For all motor NCS the distal stimulation point was 8cm proximal of the active electrode. Sensory NCS were performed, using antidromic stimulation techniques of the sural, median, and ulnar nerve in the ipsilateral extremities. The sensory nerve action potential (SNAP) of the sural nerve was recorded using AgCl surface electrodes positioned behind the lateral malleolus, and the nerve was stimulated 14 cm proximal of the active electrode. For the median and ulnar nerve, ring electrodes were positioned around the digits 3 and 5, respectively. The median nerve was stimulated in the palm, wrist and elbow and the ulnar nerve at the wrist and below and above the elbow. All NCS were performed according to Buschbacher [4]. The measured parameters were distal motor latencies (DML), motor NCV, CMAP amplitude (top-baseline), F-response latency, sensory NCV, SNAP amplitude [top-baseline], and CMAP and SNAP areas under the curve. A value was defined as abnormal when it fell outside the reference values (adjusted for age, length, body mass index) [4].

Special attention was focused on motor nerve conduction block (CB) or focal motor or sensory NCV slowing, to exclude possible confounding effects of common compression neuropathies. A definite motor CB was defined as a CMAP amplitude or area reduction after proximal versus distal stimulation of >50%, a possible motor CB as a CMAP amplitude or area reduction >30% in the upper extremities and >40% in the lower extremities [6]. The formula for calculating amplitude or area reduction was: (distal – proximal amplitude or area) / (distal amplitude or area) x 100%. Values were only regarded valid and calculated when the distal CMAP amplitude was >1.0 mV. Ulnar (compression) neuropathy at the elbow was defined as a

focal motor and/or sensory NCV slowing of >10m/s over the elbow compared to the forearm, peroneal (compression) neuropathy was defined as >6m/s motor NCV slowing over the fibula head compared to the lower leg, and >0.5ms latency difference between the wrist-palm, and the palm-digit 3 traject for the median nerve [4]. A carpal tunnel syndrome was ruled out based on the international guidelines in electrophysiological studies published by the AAEM [11]. The studied arm and leg of all patients were warmed during at least 20 minutes, using warm water blankets connected to a heating device (Cincinatti Sub-Zero Norm-o-Temp Hyper-Hypothermia unit with PlastiPad reusable blankets; water temperature set at 41°C). Skin temperatures during measurements were at least 31 °C measured at the ankle and 32 °C at the wrist.

Other Assessments

Parallel with the NCS, patients were evaluated using several validated assessment scales. Earlier assessments of the Fatigue Severity Scale (FSS) in 10 sex- and age-matched healthy individuals were used as fatigue reference values for our patients [8].

The GBS Disability Score (or f-score) is a disability scale with 7 options, ranging from 0 ("healthy") to 6 ("dead"). The scores for patients included in this study ranges from 1 ("minor symptoms or signs, capable of running") to 2 ("able to walk at least 10 meters across an open space without assistance, walking frame, or stick, but unable to run") [12].

The Medical Research Council (MRC)-sumscore is a summation of the MRC grades, given in full numbers of the following muscle pairs: upper arm abductors, elbow flexors, wrist extensors, hip flexors, knee extensors, and dorsal foot flexors. The MRC-sumscore ranges from 0 (paralysis) to 60 (normal strength) [12, 18]

The Fatigue Severity Scale (FSS), a 9-item questionnaire with answers ranging from 1 ("strongly disagree") to 7 ("strongly agree") for each inquiry in relation to fatigue. The FSS is calculated as the mean score of these 9 items, with answers ranging from 1 ("no signs of fatigue") to 7 ("most disabling fatigue") [13, 17]

The EuroQol Health Status, is a simple self assessed visual scale, with answers ranging from 0 (resembles the worst imaginable health status) to 100 (the best health status) corresponding for that moment [7].

Statistics

Relations between muscle strength, GBS disability score, and quality of life, and NC data were studied, using scatter plots. Because these analyses did not show any differences between the various assessments, additional analyses were not performed. Due to the primary aim of this study and the absence of a control group, only the FSS appeared to be relevant for further statistical analyses. We used the one-way ANOVA test to study electrophysiological differences (DML, motor / sensory NCV, CMAP / CSNAP amplitude and area, peroneal nerve F-response, motor blocks / compression, and sensory compression) between the groups of patients with

and without severe fatigue (respectively defined as FSS ≥5 and FSS<5). A p-value <0.05 was considered statistical significant. SPSS version 10.1 was used.

Table 1. Baseline characteristics GBS and CIDP patients

Characteristics	GBS (n=13)	CIDP (n=3)
Sex Male	6	0
Female	7	3
Years since diagnosis (range)	5.7 (3.1-12.1)	9.9 (3.0-18.3)
Age (range)	52.1 (26-66)	53.3 (37-68)
AIDP (n)	13	--
GBS disability score		
nadir (range)	3.8 (2-5)	3.3 (2-4)
F=2 (n)	1	1
F=3 (n)	2	
F=4 (n)	8	2
F=5 (n)	2	
follow-up (range)	1.1 (1-2)	1.7 (1-2)
F=1 (n)	12	1
F=2 (n)	1	2
MRC-sumscore		
60 (n)	12	
58 (n)	1	1
56 (n)		1
52 (n)		1
FSS (range)	4.8 (2.4-6.3)	4.9 (4.4-5.2)
EuroQol (range)	78.7 (65-95)	68.3 (60-80)

Legend to Table 1. All data are given in mean values and its range. GBS = Guillain-Barré syndrome; CIDP = Chronic Inflammatory Demyelinating Polyneuropathy; AIDP = Acute Inflammatory Demyelinating Polyneuropathy; GBS disability score: F = 0 (healthy, no symptoms or signs), F = 1 (minor symptoms or signs, capable of running), F = 2 (able to walk at least 10 meters across an open space without assistance, walking frame, or stick, but unable to run), F = 3 (able to walk 10 meters with walking frame, sticks or support), F = 4 (bed or chair bound, unable to walk), F = 5 (assisted ventilation required for at least part of the day or night); MRC = Medical Research Council, sumscore ranges from 0 (paralysis) to 60 (normal strength); FSS = Fatigue Severity Scale, scores ranging from FSS = 1 (no signs of fatigue), to FSS = 7 (most disabling fatigue); EuroQol ranges from 0 (worst imaginable health status) to 100 (the best health status) corresponding for that moment.

RESULTS

Patient characteristics

Patient characteristics are listed in table 1. All GBS patients initially at least clinically suffered from AIDP. The GBS disability scores were assessed at nadir for the GBS patients, and for the CIDP patients the worst scores at any time during the illness were taken (table 1). CIDP patients had lower MRC-sumscores and lower EuroQol scores. Fatigue scores as measured with the FSS, were comparable in GBS (4.8, range 2.4-6.3) and CIDP (4.9, range 4.4-5.2) patients, but were significantly worse than scores obtained in healthy individuals (2.2, range 1.6-2.8) [8].

Nerve conduction findings

NC values are listed in table 2. All data of both GBS and CIDP patients were pooled and calculated as mean values (range was included). No carpal tunnel syndrome was found. The number of patients with abnormal values and the unexcitable nerves are listed separately. All CIDP patients had moderate to severe abnormal nerve conduction values in the majority of the measured nerves, while in the GBS patient group values were mostly normal or only slightly abnormal. Moreover, 9 out of the 32 abnormal values could be attributed to 1 single GBS patient (table 2). Motor NCV and sensory areas under the curve of the median nerve fell outside the normal range in 6 out of 13 GBS patients, however, these values were 'borderline' abnormal (motor NCV range: 40.6-50.0, mean 45.4; sensory area range: 4.0-14.0, mean 8.3). Conduction blocks were only found in 1 GBS patient (peroneal nerve, between distal knee and ankle) and in two CIDP patients (1 ulnar nerve in both patients, and median nerve in 1 patient).

No relation was found between electrophysiological measurements (DML, motor / sensory NCV, CMAP / CSNAP amplitude and area, peroneal nerve F-response, motor blocks / compression, and sensory compression) and muscle strength, GBS disability score, and quality of life. No significant differences in NC variables were found between the group of patients with and without severe fatigue (table 3). In addition, the GBS patient with the worst FSS score (FSS=6.3) did not show any NC abnormalities. This patient had a maximal MRC-sumscore (60), and a GBS disability score of 1. In contrast, the GBS patient with the best FSS score (FSS=2.4) had abnormal values in 9 out of 22 measured variables (table 2). This latter patient also had a maximal MRC-sumscore and a GBS disability score of 1. Additional analyses on the retrospectively collected NC data in 6 GBS patients did not reveal clear features that might have predicted the occurrence of severe fatigue.

Table 2. Nerve conduction values in GBS and CIDP patients

		GBS		CIDP	
		All patients (n=13)	Patients with abnormal values (n)	All patients (n=3)	Patients with abnormal values (n)
Motor					
DML	Per	4.3 (3.1-7.2)	1*	6.1 (3.9-8.4)	2 (1xNR)
	Med	5.2 (4.3-7.4)	2	5.5 (4.3-8.0)	1
	Uln	2.6 (2.1-3.8)	1	4.0 (2.8-6.0)	1
NCV	Per	43.9 (27.4-51.6)	1*	30.9 (18.4-43.3)	2 (1xNR)
	Med	49.9 (40.6-59.3)	6*	29.8 (22.2-43.3)	3
	Uln	60.5 (49.0-70.0)	0	34.8 (19.7-51.1)	3
CMAP	Per	7.3 (0.1-14.3)	1*	0.5 (0.4-0.5)	3 (1xNR)
	Med	6.0 (2.4-8.6)	1	4.1 (1.5-5.4)	1
	Uln	10.5 (7.6-12.7)	0	6.1 (2.4-10.1)	2
AREA	Per	20.3 (0.2-42.6)	1*	1.9 (1.6-2.1)	3 (1xNR)
	Med	21.2 (10.3-34.5)	1	14.3 (4.7-21.2)	1
	Uln	31.9 (22.5-50.2)	0	18.8 (6.2-28.0)	2
F-resp	Per	45.9 (36.9-59.7)	1* (NR)	61.5 (61.5-NR)	3 (2xNR)
Sensory					
NCV	Sur	45.3 (33.3-53.5)	2 *	--	(3xNR)
	Med	49.3 (34.0-61.4)	2	35.9 (23.0-49.0)	2 (1xNR)
	Uln	63.8 (54.7-77.7)	0	61.1 (61.1-NR)	2 (2xNR)
SNAP	Sur	10.9 (3.7-23.1)		--	(3xNR)
	Med	21.1 (10.5-41.1)	1	9.3 (7.4-11.1)	2 (1xNR)
	Uln	17.1 (5.8-36.0)	0	7.8 (3.0-13.0)	2 (1xNR)
AREA	Sur	10.4 (1.0-34.0)		--	(3xNR)
	Med	10.4 (4.0-17.0)	6*	12.5 (6.0-19.0)	2 (1xNR)
	Uln	8.2 (3.0-21.0)	5*	10.0 (7.0-13.0)	1

Legend to Table 2. Per = peroneal nerve; Med = medial nerve; Uln = ulnar nerve. Motor / sensory NC studies: DML = distal motor latency (in ms); NCV = nerve conduction velocity (in m/s); AMP = amplitude top-baseline (in mV); AREA = area under the curve; F-resp = F-response (in ms). All data are given in mean values and its range. The number of patients with abnormal values is listed separately for both GBS and CIDP patients. NR = not recordable. * = one single patient had abnormal values in all these indicated measurements.

Table 3. Nerve conduction values in severely and non-severely fatigued GBS patients

		GBS patients (n=13)	
		Non-severely fatigued (n=6) (FSS < 5.0)	Severely fatigued (n=7) (FSS ≥ 5.0)
FSS		3.9 (2.4-4.8)	5.6 (5.0-6.3)
Motor			
DML	Per	4.5 (3.2-7.2)	4.2 (3.1-5.2)
	Med	4.8 (4.3-5.1)	5.5 (4.4-7.4)
	Uln	2.6 (2.4-2.9)	2.7 (2.1-3.8)
NCV	Per	43.8 (27.4-51.6)	44.0 (36.5-49.1)
	Med	52.1 (46.2-59.3)	48.1 (40.6-55.8)
	Uln	62.3 (53.1-70.0)	59.1 (49.0-67.7)
CMAP	Per	7.6 (0.1-13.9)	7.0 (1.7-14.3)
	Med	6.0 (4.4-7.9)	6.0 (2.4-8.6)
	Uln	9.8 (8.5-12.2)	11.0 (7.6-12.7)
AREA	Per	20.7 (0.2-42.6)	20.0 (5.2-36.7)
	Med	19.9 (12.4-29.8)	22.4 (10.3-34.5)
	Uln	29.1 (22.5-34.7)	34.4 (25.9-50.2)
F-resp	Per	44.1 (39.2-49.8) (1x NR)	47.2 (36.9-59.7)
Sensory			
NCV	Sur	46.2 (41.1-53.5)*	44.6 (33.3-51.0)
	Med	52.2 (45.0-61.0)	50.6 (34.0-60.0)
	Uln	66.2 (54.7-77.7)	62.0 (56.9-68.4)
SNAP	Sur	10.2 (3.7-16.3)*	11.4 (4.8-23.1)
	Med	19.6 (11.2-36.9)	22.3 (10.5-41.1)
	Uln	15.0 (6.0-30.0)	19.0 (9.0-36.0)
AREA	Sur	13.8 (1.0-34.0)*	8.0 (3.0-16.0)
	Med	9.0 (4.0-16.0)	11.6 (7.0-17.0)
	Uln	7.5 (3.0-11.0)	8.9 (3.0-21.0)

Legend to Table 3. No significant differences were found between the severe and non-severely fatigued group of GBS patients in any of the studied variables. Per = peroneal nerve; Med = medial nerve; Uln = ulnar nerve. Motor / sensory NC studies: DML = distal motor latency (in ms); NCV = nerve conduction velocity (in m/s); AMP = amplitude top-baseline (in mV); AREA = area under the curve; F-resp = F-response (in ms). All data are given in mean values and its range. NR = not recordable. * = only available in 5 GBS patients.

DISCUSSION

This study is one of the sparse electrophysiological long-term follow-up studies in GBS, and the first study aiming to elucidate possible underlying pathophysiological mechanisms of fatigue in 'neurologically well-recovered' GBS patients, using conventional electrophysiological NC techniques. In our homogeneous group of AIDP patients, a few, most borderline, abnormal values were found. Most patients showed remarkably good recovery in motor and sensory NC, which was at least in accordance with previous findings [5, 10, 19].

No relation was found between NC measurements, muscle strength, functional scores, and quality of life. The single GBS patient with the most NC abnormalities further illustrated the lack of a relation between NC abnormalities and fatigue. This patient had the lowest level of fatigue as measured with the FSS (mean FSS 2.4) (table 2). Moreover, the most severely fatigued patient (mean FSS 6.3) had completely normal NC studies. The techniques we used to detect abnormal nerve function seemed appropriate, as can also be concluded from the obvious abnormal values found in the group of CIDP patients.

Some limitations of our study have to be mentioned. Clinically, all GBS patients initially both had motor and sensory symptoms, compatible with AIDP, although confirmation of the initial clinical diagnosis by earlier conducted electrophysiological studies was only available in 6 patients. In addition, besides NC studies, no needle studies were performed in the present study. However, these clinically well-recovered AIDP patients appeared to have relatively normal CMAPs, and the sural SNAPs were generally normal, suggesting that major axonal degeneration is unlikely.

Based on follow-up studies, in which persisting signs of demyelination were not associated with poor recovery, we considered NC studies potentially relevant [2, 5, 10, 16, 19]. Persisting signs of demyelination in our neurologically relatively well-recovered AIDP patients could have lead to complaints of fatigue, and the aim of this study was to elucidate its possible underlying mechanisms. It was recently shown that impaired muscle strength of ankle dorsiflexion in GBS during long-term follow-up correlates with axonal damage, and that insufficient functional compensatory reinnervation is found more frequently than persisting signs of demyelination [5]. The relation between residual muscle weakness or axonal damage and complaints of fatigue, however, were not studied before. From the retrospectively collected NC data obtained during the acute phase of disease in only 6 GBS patients, no features were identified that predict severe fatigue. However the limitation of these data makes it impossible to draw firm conclusions about a possible relationship between NC abnormalities in the acute phase of disease and long lasting fatigue.

We only found minor abnormalities with conventional NC techniques. Because NC studies measure large nerve fiber function, dysfunction of small nerve fibers or other 'minor' defects in peripheral nerves cannot be excluded. Maybe more sensitive techniques or other non-conventional functional studies of the nerves, like conduction velocity distribution (CVD) [20],

in which smaller and slower conducting myelinated fibers can be evaluated, or motor-unit number estimation (MUNE) [14, 15], can contribute to elucidate pathophysiological mechanisms of fatigue in GBS. In addition, it can be hypothesized that fatigue is caused by ineffective muscle activation, as a result of a decreased number but larger size of remaining motor units [15]. Recovery after GBS could be accompanied with reinnervation of most muscle fibers, reflected by normal peak muscle strength and normal NC values, but impaired sustained muscle performances. Finally, it may be that fatigue is caused more by psychological than physical (or peripheral) disturbances [8]. In that case further non-conventional electrophysiological studies aiming to discriminate between 'peripheral' and 'central' origin of fatigue could be useful in elucidating at least some underlying pathophysiological mechanisms [21].

In conclusion, long-term NC studies in AIDP revealed a remarkably good recovery of electrophysiological nerve function. Underlying pathophysiological mechanisms of fatigue in GBS could not be explained by conventional NC studies. Further studies, including studies aiming to elucidate possible predicting factors of fatigue are warranted.

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CHAPTER 4.3

Conduction velocity distribution in neurologically well-recovered but fatigued Guillain-Barré syndrome patients

Garssen M.P.J.[1], Blok J.H[2], van Doorn P.A.[1], and Visser G.H.[2]

From the Departments of Neurology[1] (Garssen, van Doorn) and Clinical Neurophysiology[2] (Blok, Visser); Erasmus Medical Center, Rotterdam, The Netherlands

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ABSTRACT

Many patients with Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP) suffer from excessive fatigue. To assess whether this fatigue might be related to changes in slow-conducting nerve fibers, we determined the conduction velocity distribution (CVD) in the median nerve. Thirteen fatigued but neurologically well-recovered GBS patients, 2 fatigued and stable CIDP patients, and 19 healthy controls participated in this study. Conventional maximal nerve conduction velocities (NCV) did not show differences between GBS patients and healthy controls. However, in both GBS and CIDP patients the CVD was altered, showing significant narrowing of the velocity distribution with loss of the fastest- and slowest-conducting fibers. These changes were most pronounced in the subgroup of patients with the lowest fatigue scores. We therefore conclude that the observed CVD changes in patients are not likely to contribute to persisting complaints of fatigue after GBS.

INTRODUCTION

Guillain-Barré syndrome (GBS) is characterized by nerve conduction (NC) failure, and can be subdivided according to clinical and electrophysiological characteristics.[5,13,24] In western countries, the most common subtype is acute inflammatory demyelinating polyneuropathy (AIDP), clinically characterized by combined motor and sensory nervous system involvement.[24] Despite good neurological recovery in the majority of GBS patients, many remain severely fatigued.[21] Fatigue is experienced as one of the most disabling residual symptoms, but its cause is unknown.

Long-term electrophysiological studies have shown that muscle weakness and poor neurological recovery tend to be associated with persistent axonal loss, but not with persisting signs of demyelination.[8] Conversely, the lack of muscle weakness in many clinically recovered AIDP patients suggests that residual fatigue problems results from persisting demyelination or suboptimal remyelination rather than axonal loss.[8,14,20] We hypothesized that the largest fibers show near-complete recovery, yielding normal values in standard NC studies, whereas smaller fibers recover only partially from demyelination. It is conceivable that fatigue complaints originate at least partly in this kind of disturbances of smaller-sized myelinated fibers, which normally innervate fine motor-control muscles.[10] Because these muscles generally have the lowest axonal innervation ratios, they could be most sensitive for changes in myelination pattern, leading to increased fatigue perception. Other contributing factors might be that the orderly recruitment according to motor unit sizes or the synchronization of motor units is disturbed after remyelination or immobilization.[22]

The smaller- and slower-conducting myelinated fibers can be evaluated by studying the conduction velocity distribution (CVD). It is known both from experimental nerve resection studies and from studies in diabetic patients that altered CVD may be found alongside normal conventional (maximal) nerve conduction velocities (NCVs).[4,7,25] Hence, the CVD seems more sensitive than conventional NC studies in detecting signs of conduction failure, and an appropriate tool to elucidate possible contributions of these slower-conducting myelinated fibers to residual symptoms like fatigue, in neurologically well-recovered GBS patients. Additionally, two fatigued CIDP patients were measured in order to evaluate whether the CVD method seems also applicable and sensitive enough to detect abnormalities in these patients.

MATERIALS AND METHODS

Patient population

Thirteen GBS patients and 2 patients with stable chronic inflammatory demyelinating polyneuropathy (CIDP) initially participated in a training intervention study on treatment of severe fatigue, more than 2 years ago.[11] All patients fulfilled the clinical diagnostic criteria for

GBS or CIDP,[1,3] and were neurologically well-recovered. All GBS patients suffered clinically from AIDP. Patients were eligible for the training when they were severely fatigued [fatigue severity scale score (FSS) at least 5.0 out of 7.0],[18] neurologically stable (no changes in GBS disability score),[17] with onset of GBS/CIDP > 6 months and <6 years ago, age of at least 18 years, and a GBS disability score of ≤3 (able to walk 10 meters). All patients had been screened to exclude concomitant conditions (i.e., malignancy, chronic infections, hypothyroidism, anemia, renal and liver disease, chronic pulmonary and cardiovascular disease, chronic fatigue syndrome, diabetes) or use of medication that might cause or influence fatigue (e.g., benzodiazepines, antidepressants and immunotherapy) within 4 weeks before onset of the study.[11] Additional exclusion criteria were depression, hypertension, and use of β-blocking drugs.

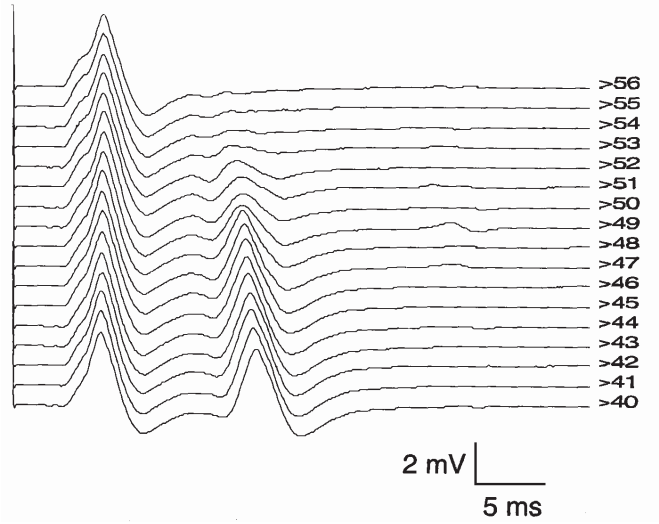
In the present observational CVD study, patients were additionally evaluated using the GBS disability score,[17] Medical Research Council (MRC) sumscore,[17] and Fatigue Severity Scale.[18] Controls were 19 healthy volunteers and family members of the examined patients. The controls filled in various questionnaires and declared to the best of their knowledge that they were not familiar with any kind of disease that could influence electrophysiological measurements. The experiments were performed in conformity with the principles embodied in the Declaration of Helsinki. All patients gave informed consent.

Measurement protocol

All measurements were performed on a Viking Select (Nicolet Biomedical, Madison, WI), using Ag-AgCl cup electrodes. Conventional motor NC studies of the peroneal, median and ulnar nerve were recently performed in the fatigued GBS patients.[12] A value was defined as abnormal when it fell outside the reference values (adjusted for age, length, and body mass index).[6] These conventional NC studies revealed the greatest tendency to abnormal motor NC values in the median nerve (borderline values in 6 of 13 patients; NC range 40.6-50.0 m/s, mean 45.4 m/s). We therefore measured the CVD of this nerve by using Hopf's collision technique.[15,16]

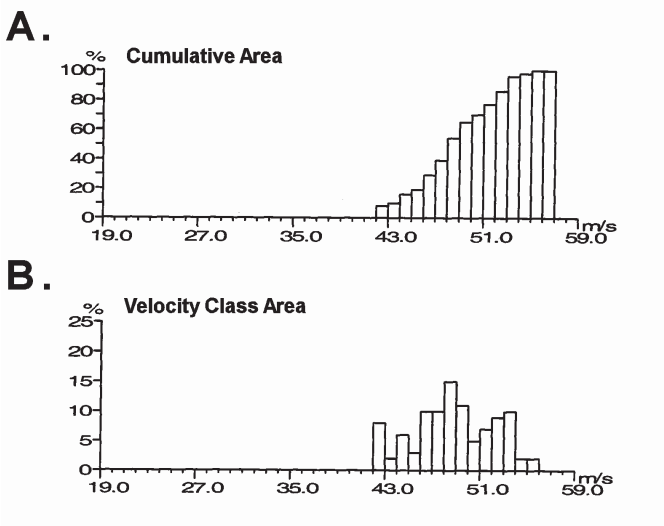
Patients were pre-warmed for at least 20 minutes, using warm water blankets connected to a heating device (Norm-o-Temp Hyper-Hypothermia unit with PlastiPad reusable blankets; water temperature set to 41°C; Cincinnati Sub-Zero Products, Cincinnati, OH), resulting in skin temperatures during measurements of at least 33°C at the wrist. A clinical or subclinical carpal tunnel syndrome, according to published criteria, was excluded in all patients.[2] All measurements were performed on the right arm, unless a carpal tunnel syndrome was found. Compound muscle action potentials (CMAPs) were recorded from the abductor pollicis brevis muscle (high- and low-pass filters at 2 Hz and 10 kHz for the conventional NC studies, and 2 Hz and 5 kHz for CVD determination). After stabilizing and relaxing the arm (60° elbow flexion, pronated position), the maximal median motor NCV (NCVmax) was determined. Subsequently, up to 32 proximal (P) and distal (D) supramaximal stimuli were given (150%, 1 Hz, 0.2 ms duration), with stepwise increasing interstimulus interval (ISI). When both stimuli are simultaneous, only the distally elicited action potential (AP) generates a CMAP because of collision of the antidromic

Figure 1. Conduction velocity distribution of a single GBS patient



Legend to Figure 1. CVD of a GBS patient. The first, always-present maximal CMAP results from the distally elicited orthodromic AP. With increasing ISI, the number of axons blocked by the collision of distally elicited antidromic and proximally elicited orthodromic APs decreases. The slowest velocity is derived from the lowest ISI that results in a maximal second CMAP (lowest trace).

Figure 2. Conduction velocity distribution histogram



Legend to Figure 2. CVD histograms of a GBS patient. (A) Size of the CMAP area (y-axis) as percentage of the maximum CMAP, generated by all fibers with NCV up to a specific NCV value (x-axis). Each NCV value corresponds to a particular ISI (not shown; see text). (B) The stepwise increase in CMAP area is equated with the number of fibers with a particular NCV (as percentage of the total population). In this patient, maximal NCV is 54.8 m/s, CVD10 = 43.0 m/s, CVD50 = 47.7 m/s, and CVD90 = 52.4 m/s.

AP generated at D and the orthodromic AP elicited at P between the two stimulus sites. If the ISI (P later than D) is sufficiently long, the antidromic APs of the fastest-conducting fibers no longer collide but are conducted proximally. Provided that the refractory period of these nerve fibers has elapsed, the stimulus given at P can then elicit a small, second CMAP (Fig. 1). The stepwise increase in the second CMAP that results from the stepwise increase in ISI is taken to be proportional to the number of fibers conducting with the NCV corresponding to that particular ISI (Fig. 2). The slowest velocity is derived from the ISI at which this second CMAP reaches its maximum size. The overall results were visualized in a conduction velocity histogram (Fig. 2).

Statistics

Each patient underwent two measurements, performed in immediate succession, which resulted in mean estimates of the 90th (CVD90), 50th (CVD50), and 10th (CVD10) percentiles of the CVD. The width of the distribution was calculated as CVD90-CVD10. Relations between assessment scales and CVD characteristics, and differences between patients with (FSS ≥5) and without (FSS<5) severe fatigue were analyzed using the one-way ANOVA in SPSS version 10.1 (SPSS, Chicago, Il), unless indicated otherwise.

RESULTS

Six male and 7 female GBS patients [age 52.1±9.7 years (range 26-66)], 2 female CIDP patients [age 61.5±9.2 years (55 and 68)], and 8 male and 11 female healthy controls [age 42.2±15.1 years (range 22-63)] participated in this study. Time since diagnosis was 5.7 years (range 3.1-12.1) for the GBS patients and 10.6 years (3.0 and 18.3) for the CIDP patients.

Patient disability scores are listed in Table 1, and electrophysiological findings in Table 2. No carpal tunnel syndrome was found in either the patient or control group. There was no significant difference in the conventional maximal NCV between GBS patients and healthy controls (Table 2). CIDP patients had significantly reduced maximal NCV and CVD values (all $p<0.01$). GBS patients showed statistically significant narrowing of the velocity distribution (mean 7.2 m/s vs. 11.7 m/s in controls; $p=0.014$, Mann-Whitney test), with loss of extreme values (Table 2 and Fig. 3). Because these results might be biased by the somewhat older age of our GBS patient population, the same analyses were performed in an age-matched control subgroup (n=13; age 50.7 ± 9.6, range 28-63 years). GBS patients still showed significant narrowing of the CVD width (mean 7.2 m/s vs. 10.2 m/s; $p=0.03$, Mann-Whitney test), whereas maximal NCV did not differ significantly, excluding an age effect causing the difference in width of CVD values. Both CIDP patients also showed significant narrowing of the CVD width (mean 4.2 m/s). The CVD percentiles themselves (CVD90, CVD 50, and CVD10) showed no significant differences between GBS patients and the group of controls. Although there were no statistically significant differences between severely and non-severely fatigued GBS patients, CVD changes tended to

be most pronounced in the non-severely fatigued group of GBS patients (Fig. 4). No significant relations were found between CVD parameters and muscle strength or GBS disability scores at the time of evaluation.

Table 1: Overview of disability scores

Disability scores in means (range)		GBS (n=13)	CIDP (n=2)
GBS disability score *	at nadir	3.8 (2-5)	4.0 (4)
	F=2	1	--
	F=3	2	--
	F=4	8	2
	F=5	2	--
	at study time	1.1 (1-2)	1.5 (1-2)
	F= 1	12	1
	F= 2	1	1
MRC sumscore †	at study time		
	60	12	
	58	1	1
	56		1
FSS ‡		4.8 (2.4-6.3)	4.8 (4.4-5.2)

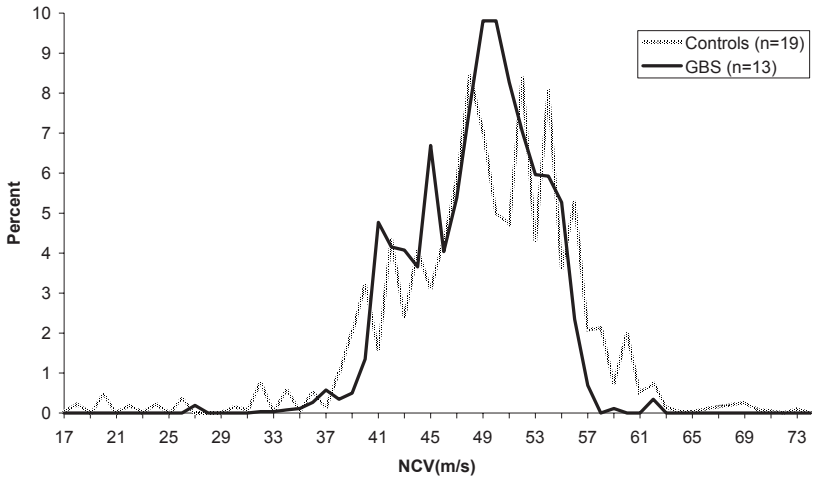
Legend to Table 1. * GBS disability score ranges from 0 (healthy, no symptoms or signs) to 5 (assisted ventilation required for at least part of the day or night); † MRC sumscore ranges from 0 (paralysis) to 60 (normal strength); and ‡ FSS ranges from 1 (no signs of fatigue) to 7 (most disabling fatigue).

Table 2: Overview of conduction velocity distribution (CVD) and maximal NCV values

NC variablemeans (range)	GBS (n=13)	CIDP (n=2)	Controls (n=19)
CVD 10	43.9 (37.6-49.8)	26.5 (17.3-35.8)*	41.7 (21.0-50.2)
CVD 50	48.5 (41.5-53.8)	29.4 (18.4-40.3)*	49.4 (37.2-58.7)
CVD 90	51.1 (42.7-56.5)	30.7 (19.7-41.7)*	53.4 (42.3-68.0)
CVD width	7.2 (2.3-13.4)*	4.2 (2.3-6.0)*	11.7 (6.1-33.7)
Maximal NCV	52.5 (43.3-57.6)	31.0 (20.1-41.8)*	55.8 (45.0-71.1)

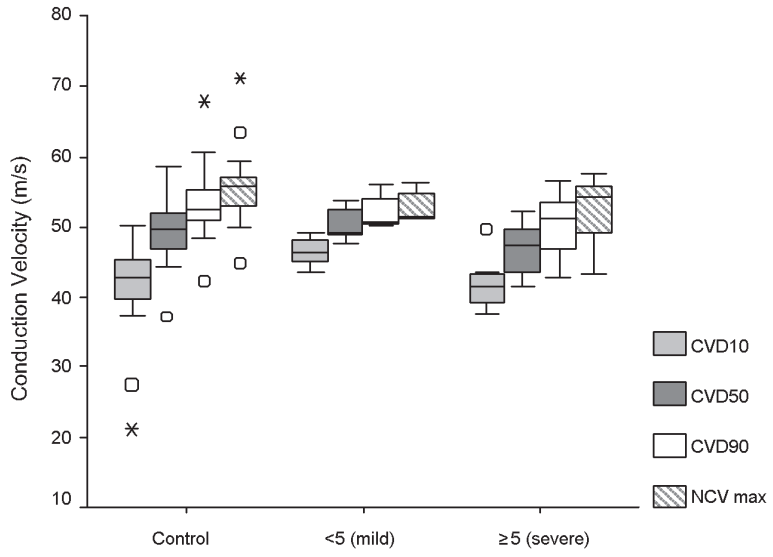
Legend to Table 2. Data given represent motor NCV values in m/s in the right median nerve, and are expressed as group means (range included). Asterisk indicates a statistically significant difference between patients and healthy controls ($p<0.05$).

Figure 3. Conduction velocity distribution for GBS patients and controls



Legend to Figure 3. NCV histogram, representing group means of CVD's of both GBS patients and healthy controls, showing narrowing with loss of extreme values (not significant for individual NCV values). Ordinate values represent the percentage of the number of fibers (averaged over all subjects) with a particular NCV.

Figure 4. Conduction velocity percentiles in controls and in non-severely and severely fatigued patients



Legend to Figure 4. Boxplots of CVD percentiles and maximum NCV in healthy subjects (N=19), severely (FSS ≥5; N=7) and non-severely (FSS < 5; N=6) fatigued GBS patients. The plots show median values (horizontal bar), the 25th – 75th interquartile range, maximum values (⊤), and minimum values (⊥). Asterisks indicate extreme values, and circles indicate outliers. CVD narrowing is most pronounced in the non-severely fatigued group (FSS<5).

DISCUSSION

In this study we performed CVD measurements in fatigued but neurologically well-recovered GBS patients and in two stable CIDP patients. The CVD method appeared feasible in these groups of patients. No significant differences were found in any of the determined CVD percentiles CVD90, CVD50, and CVD10 between GBS patients and healthy controls. However, the width of the CVD is significantly smaller in GBS patients. Measurements of the two fatigued CIDP patients, studied in order to evaluate the applicability of the CVD method in these patients, confirmed the observations of narrowing of CVD width in GBS patients. The difference in width of 4.5 m/s (11.7 - 7.2 m/s) between healthy controls and GBS patients is the result of the combination of a somewhat larger CVD10 (2.2 m/s between group averages; Table 2) and a somewhat smaller CVD90 (2.3 m/s) in GBS patients. There are changes in CVD, although the results for either end of the distribution independently are too small to reach statistical significance. Furthermore, the symmetry of these changes shows that the highest and lowest conduction velocity are affected similarly. The trend to a loss of faster-conducting fibers is in line with recently published long-term follow-up measurements in GBS.[9] That study showed that approximately half of all GBS patients could be diagnosed as having a residual neuropathy. The long-term loss of small-sized as well as large-sized myelinated fibers, as observed in our study, seems a potentially important additional finding. It might indicate the inability of the peripheral nervous system to remyelinate in an accurate way, leading to a differentiated nerve fiber distribution compared to the situation before the onset of GBS.

We do not expect that the known limitations of Hopf's technique significantly influenced this outcome. These limitations include implicit assumptions regarding the nerve refractory periods (which are deducted from the latency of the muscle responses before the NCV values are calculated), and the fact that possible changes in the NCV of axons in a different state of excitability are not accounted for. Additionally, the CVD method equates percentages of CMAP area with percentages of nerve fibers.[16,23] In doing so, the CVD method ignores phase cancellation effects, and assumes that all nerve fibers contribute equally to the CMAP. Because it is known that faster-conducting nerve fibers tend to belong to larger motor units, the observed CVD percentiles will be higher than the true values (the 10% smallest fibers will contribute less than 10% of the maximum CMAP area). However, the resulting biases may be expected to have similar consequences for findings in both patients and controls. This is confirmed by our observations in the CIDP patients, who showed the largest reduction in each of the assessed CVD percentiles as anticipated.

Although Figure 4 shows that the narrowing of the CVD tends to be most pronounced in the non-severe group, no significant differences were found between severely and non-severely fatigued GBS patients. This suggests that the observed CVD changes in the GBS patients are probably not related to fatigue. However, the preliminary results of our pilot study should be confirmed in a larger study, which also includes a group of neurologically well-recovered but

non-fatigued GBS patients. Such a group might provide additional and conclusive information regarding the relation between complaints of fatigue and changes in CVD. The cause of fatigue in GBS patients remains unknown; therefore we can only speculate that other electrophysiological mechanisms might be involved. For example, a decreased number of motor units, or even psychological factors may play a role.[8,11,19]

Despite the shortcomings of the CVD method, its simplicity, rapidity of execution, higher sensitivity for changes in NCV than conventional techniques, and good tolerability make this method a rather accurate and additional tool to evaluate long-term changes in conduction velocity. The persistence of changes in CVD in neurologically well-recovered but fatigued GBS patients and the absence of abnormalities on conventional NC studies in these patients warrants further attention.

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CHAPTER 4.4

Contribution of central and peripheral factors to residual fatigue in Guillain-Barré syndrome

***Garssen M.P.J.[1], *Schillings M.L.[2], van Doorn P.A.[1], van Engelen B.G.M.[3], and Zwarts M.J.[2]**

From the Department of Neurology[1] (Garssen, van Doorn), Erasmus Medical Center, Rotterdam, and the Departments of Clinical Neurophysiology[2] (Schillings, Zwarts) and Neurology[3] (van Engelen), Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

*Both authors contributed equally to this manuscript

Muscle and Nerve, resubmitted

ABSTRACT

To dissect fatigue, we determined the relative contribution of peripheral and central factors during a 2-minute fatiguing sustained maximal voluntary contraction (MVC), in 10 fatigued but neurologically relatively 'well-recovered' Guillain-Barré syndrome (GBS) patients, and 12 age and sex matched healthy controls. Physiological fatigue was defined as the decline of voluntary force during the MVC of the biceps brachii. Relative amounts of peripheral fatigue and central activation failure (CAF) were determined combining voluntary force and force responses to electrical stimulation. Surface EMG was used to determine muscle fiber conduction velocity (MFCV). During the first minute of sustained MVC, peripheral fatigue developed slower in patients. Central fatigue only occurred in patients. The MFCV was higher in patients. The initial MVC, decrease of MVC, the initial force response and initial CAF did not significantly differ between both groups. Although these results suggest that peripheral changes are involved in the pathogenesis of fatigue after GBS, also central mechanisms seem to play a role.

INTRODUCTION

Guillain-Barré syndrome (GBS), a monophasic immune-mediated disease of the peripheral nervous system, is characterized by acute symmetrical limb weakness and reduction or loss of myotatic reflexes as a consequence of nerve conduction (NC) failure.[5,14,33] Various clinical and electrophysiological subtypes can be distinguished, ranging from a pure motor form to the classical demyelinating type of the disease.[5,14,33] Despite relatively good neurological recovery, the majority of GBS patients remain severely fatigued.[22] In order to elucidate possible 'peripheral' pathophysiological mechanisms of these fatigue complaints in GBS patients, conventional NC and conduction velocity distribution (CVD) studies have been performed (Garssen et al. Conduction velocity distribution in neurologically well-recovered but fatigued Guillain-Barré syndrome patients, Muscle and Nerve 2005). CVD values showed narrowing of the spectrum of different NC velocities, with loss of the extreme values, but a correlation between NC alterations and severe fatigue could not be found. Although fatigue is one of the most disabling residual symptoms and seriously affects quality of life in GBS patients, its pathophysiological mechanisms remain unknown.

Presently no exact definition of fatigue exists, and especially in GBS a definition of fatigue is lacking. Possible definitions may range from difficulty in initiation of or sustaining voluntary activities[8] to a reduction of the maximal force generating capacity of a muscle induced by exercise.[12] Since different physical and psychological factors might contribute to fatigue in GBS,[13,22] we hypothesize that residual fatigue in GBS has a peripheral neuromuscular origin, possibly combined with additional central components. The hypothesis of central nervous system involvement may be related to central white matter lesions, which can be found in some patients in the acute phase of GBS,[15,19,23,25,31] or to the decreased concentrations of hypocretin in the liquor of some GBS patients, the pathophysiological hallmark of narcolepsia-cataplexia.[3,24] Complaints of fatigue after GBS might also be of psychological origin, a consequence of a potentially life threatening disease like GBS.

To date it is possible to dissect the relative contributions of peripheral and central factors to physiological fatigue during a sustained contraction;[28] force loss due to disturbances in the neuromuscular junction and muscle tissue are regarded as peripheral, and any disturbances in the nervous system as central.[4,12,30] We used this technique to study the different aspects of fatigue after GBS and discuss its possible underlying pathophysiological mechanisms.

MATERIALS AND METHODS

Patient Population

Eleven 'neurologically relatively well-recovered' GBS patients (defined as patients with GBS-disability score of 1 or 2)[16] participated in this observational study. All GBS patients initially

suffered clinically from acute inflammatory demyelinating polyneuropathy (AIDP). In 7 patients an electromyogram (EMG) was available, supporting this initial clinical diagnosis of AIDP. The patients initially participated in a training intervention study on treatment of severe fatigue.[13] Patients were eligible for this training study when they were severely fatigued (mean fatigue severity scale (FSS) score at least 5.0 out of 7.0),[17] and neurologically stable (no apparent change in GBS-disability score for at least 3 months).[16] All patients had been screened to exclude concomitant conditions (i.e. depression) or use of medication that might cause or influence fatigue. This training program improved self-reported fatigue scores, but self-experienced fatigue remained significantly increased in patients compared to controls.[13] Twelve age and sex-matched healthy controls were included. Controls were healthy volunteers or acquaintances of the examined patients. All participants gave written informed consent. The local ethics committee of the Radboud University Nijmegen Medical Center approved the protocol and experiments were performed in accordance with the Declaration of Helsinki.

Assessment Scales of Experienced Fatigue

Before the participants underwent the measurements, they were additionally evaluated using two assessment scales; the FSS and Abbreviated Fatigue Questionnaire (AFQ).

The *Fatigue severity scale (FSS)* is a 9-item questionnaire with answers ranging from 1 ("strongly disagree") to 7 ("strongly agree") for each inquiry in relation to fatigue. The mean score of the 9 inquiries ranges from 1 ("no signs of fatigue") to 7 ("most disabling fatigue"). The FSS is a brief and simple self-assessed questionnaire, evaluating fatigue in the past week. The FSS was recently validated and examined in terms of its reproducibility (internal consistency, reliability and validity, test-retest) in patients with immune-mediated polyneuropathies and translated into Dutch before its use.[17,22] The FSS was completed before the start of the experiment.

The *Abbreviated Fatigue Questionnaire (AFQ)* is a 4-item questionnaire. As in the FSS, each item is answered on a 7-point scale. Scores range from 4 to 28; a higher score indicates a higher level of self-perceived fatigue. The Dutch version of the AFQ was used. It was filled out just before the start and just after the end of the physiological measurement, referring to the level of experienced fatigue at the current moment.[1,2]

Physiological Factors of Fatigue

Experimental set-up and protocol

The experimental setup has been published before.[26,27](Schillings et al. Experienced and physiological fatigue in neuromuscular disorders, 2005) The protocol was based on the twitch interpolation technique.[12] Subjects sat in a chair with their left arm fixed in a dynamometer in a horizontal position with the shoulder in abduction, the elbow in a right angle and the forearm supinated. Trunk and elbow were stabilized using common made pads.

Initially, subjects made three short MVCs, each separated by a 1-minute rest. Then, after a 10-minute rest period, subjects were instructed to make a 2-minute sustained MVC of their biceps brachii muscle. Before and directly after contraction, a stimulus event (described below) was applied to the relaxed muscle. During MVC, stimulus events were applied every 15s, starting directly after the start of contraction.

Electrical stimulation

Electrical stimulation was applied over the motor points. To determine stimulus intensity and to get subjects used to stimulation, before the start of the protocol stimuli were applied repetitively to the relaxed muscle. Meanwhile, the current was increased until the force did not rise anymore. This intensity was used in all stimulus events.

A stimulus event consisted of five times a 5-pulse 100-Hz train (duration 40ms). Pulse duration was 100µs. The average of the five force responses to the five short trains is referred to as 'the force response' and is used for analysis. During voluntary contraction the inter-train interval was 325ms, during rest the inter-train interval was 1000ms. Pilot experiments showed that these inter-train intervals were appropriate to avoid fusion of the single force responses. Potentiation does not occur with this type of stimulus event. Therefore, it was not necessary to precede the initial stimulus event by a voluntary contraction.

Force analysis

The force of elbow flexion was measured at the wrist. Force was sampled at a rate of 2 kHz and low pass filtered (1 kHz). The maximal resolution of force measurement was 0.1 N bit^{-1}. The initial MVC was determined as the maximum value of the three short MVCs. During sustained MVC, voluntary force values reported are the averages of 1s of data directly before electrical stimulation. Force responses upon stimulation during sustained MVC were corrected for variations of voluntary force via linear interpolation between the moment of stimulation and 325 ms after.

Central activation failure (CAF^t) and peripheral fatigue (PF^t) at time t during sustained MVC were determined from the force data as described extensively elsewhere.[28] Thus, when $F_{sx}{}^t$ is the superimposed force response to stimulation at time t, F^t is the actual MVC at time t (mean over 1s of data) and β is the ratio of stimulated force over force capacity of the muscle, CAF^t is determined as

$$CAF^t = \frac{F_s^t}{\beta \cdot F^t + F_s^t}$$

The ratio β is determined using force values generated at the start and at the end of sustained MVC. The β used is the mean value calculated from these two moments. $F_s{}^b$ represents the force response to stimulation during rest before sustained MVC, $F_s{}^e$ after the end of sustained MVC.

The suffixes *0* and *T* refer to the start and the end of sustained contraction, respectively. Thus:

$$\beta = mean(\beta^0, \beta^T)$$

in which

$$\beta^T = \frac{F_s^e - F_x^T}{F^T} \quad \text{and} \quad \beta^0 = \frac{F_s^b - F_x^0}{F^0}$$

As described before,[28] peripheral fatigue at time *t* during sustained MVC is determined from the voluntary and stimulated force data as

$$P^t = 1 - \frac{\beta \cdot F^t}{(1 - CAF^t) \cdot F_s^b}$$

The total amount of peripheral fatigue after the 2-minute sustained MVC is also expressed as the relative change of force responses after electrical stimulation in rest after and before sustained MVC.[26] Force analyses were performed in Mat lab 6.5 (The Math Works) and Microsoft Excel 2000.

SEMG analysis

Surface EMG (sEMG) was measured using a multi-electrode array of five gold-coated electrodes that were placed in line (electrode diameter 2 mm; inter electrode distance 3 mm) parallel to the fibre direction of the biceps brachii muscle, distal to the motor points. A reference electrode was placed at the elbow joint. During placement of the electrode array, both monopolar and bipolar EMG was monitored visually and values of impedances and cross correlations between the adjacent electrode positions were checked. If electrode placement was not satisfactory, the device was replaced.

Monopolar signals were amplified, band pass filtered (3.2-800 Hz) and A/D-converted (16 bits with a resolution of 0.5 μV bit^{-1} at a rate of 4 kHz/channel). A common-made time code generator synchronized force- and sEMG-data. SEMG analysis was done on 1 s of data just before stimulation. MFCV was determined from four out of five electrodes.[26] The upper limit of MFCV was set at 8 m s^{-1}, based on physiological limits. SEMG analyses were performed in Mat lab 6.5.

Statistical analyses

For each subject, linear regression analysis using the least squares method determined the slopes of CAF, PF, MFCV and MVC during the first minute, during the second minute and during the total 2-minute sustained contraction. One-sample T-tests were used to test if slopes deviated from 0. Between-group differences were analyzed with independent-samples T-tests. Pearson's correlations were performed to study the relationship between experienced fatigue

and physiological fatigue variables. Significance level was set at $p \leq 0.05$ (two-tailed). Statistical analyses were performed in SPSS version 12.0.1.

RESULTS

Baseline characteristics

Baseline characteristics are listed in Table 1. The measurement of 1 GBS patient failed due to technical problems, resulting in participation of 10 GBS patients and 12 age and sex matched healthy controls.

Table 1

Characteristics in means (range)		GBS (n=10)	Controls (n=12)
Sex	Male	5	6
	Female	5	6
Years since diagnosis		6.9 (4.1-13.1)	--
Age		55.6 (48-67)	53.8 (31-69)
GBS-disability score at nadir		3.8 (2-5)	--
	F=2	1	--
	F=3	2	--
	F=4	5	--
	F=5	2	--
GBS-disability score at follow-up		1.1 (1-2)	--
	F= 1	9	--
	F= 2	1	--
FSS-score at follow-up		4.9 (2.9-6.9)	--
	≥5.0	4	--
	<5.0	6	--
MRC-sumscore at follow-up		59.8 (58-60)	60 (60)
	60	9	12
	58	1	--

Legend to Table 1. Baseline characteristics. All values are given in means, and range included. GBS-disability score ranges: F = 0 (healthy, no symptoms or signs), F = 1 (minor symptoms or signs, capable of running), F = 2 (able to walk at least 10 meters across an open space without assistance, walking frame, or stick, but unable to run), F = 3 (able to walk 10 meters with walking frame, sticks or support), F = 4 (bed or chair bound, unable to walk), F = 5 (assisted ventilation required for at least part of the day or night); FSS score ranges from 1 (no signs of fatigue) to 7 (most disabling fatigue); MRC-sumscore ranges from 0 (paralysis) to 60 (normal strength).

Experienced fatigue

FSS. The mean self-reported fatigue scores as measured with the FSS were high (mean 4.9 ± 1.3, range 2.9 – 6.9, Table 1), similar to previous findings in GBS, and worse than scores previously obtained in healthy individuals (range 2.2 - 2.9, p< 0.01).[13,22] Four patients were still severely fatigued (mean FSS score at least 5.0). Controls only completed the AFQ.

AFQ. Answering the AFQ, patients reported a mean AFQ score of 11.7 ± 4.6 (range 6 - 19), which was significantly higher than scores obtained in the healthy controls (7.8 ± 3.0, range 4 – 12; $p = 0.032$). AFQ values obtained directly after exercise showed a trend to have increased in patients (mean difference 3.10 ± 4.58; $p = 0.061$), but not in controls (mean difference 0.40 ± 5.05; $p = 0.808$).

Physiological fatigue

The initial MVC, that is the short MVC obtained before the start of sustained contraction, was 177.6 ± 73.8 N in patients, which was not significantly lower than 204.0 ± 58.5 N in controls ($p = 0.361$). F^0, that is the mean force produced over 1 s directly at the start of sustained MVC, neither differed significantly between patients and controls (patients: 139.9 ± 63.3 N; controls: 165.2 ± 53.0 N; $p = 0.318$; Fig. 1A). MVC decreased similarly ($p = 0.242$) during sustained MVC with 40.0 ± 20.0 % in patients and 49.2 ± 15.9 % in controls. The slopes of relative MVC decrease were similar in patients and controls (Table 2).

Table 2

	First minute			Second minute		
slope	controls	GBS	p	controls	GBS	p
MVC (% s^{-1})	-.528 (.262)	-.351 (.301)	.156	-.238 (.137)	-.344 (.236)	.230
MFCV (.10^{-1} ms^{-2})	-.216 (.128)	-.178 (.125)	.531	-.022 (.102)	-.039 (.099)	.711
PF (.10^{-2} s^{-1})	.607 (.291)	.226 (.264)	.005	.199 (.140)	.277 (.286)	.412
CAF (.10^{-2} s^{-1})	-.040 (.165)	.153 (.193)	.020	.077 (.127)	.071 (.190)	.925

Legends to Table 2. Slopes of maximal voluntary force (MVC), muscle fiber conduction velocity (MFCV), peripheral fatigue (PF) and central activation failure (CAF) during the first and second minute of sustained maximal voluntary contraction. During the first minute PF increases slower and CAF increases faster in patients than in controls.

Peripheral fatigue

The amplitude of the initial force response during rest did not significantly differ between patients and controls (patients: 11.3 ± 4.1 N, controls: 15.3 ± 6.8 N; $p = 0.124$). Directly after sustained MVC, this amplitude was declined by 33.5 ± 21.0 % in patients and by 45.9 ± 11.5 % in controls ($p = 0.120$). Fig. 1C shows the increase of peripheral fatigue in the course of sustained MVC. During the first minute of sustained MVC, peripheral fatigue increased slower in patients than in controls (Table 2). In contrast, during the second minute patient and control slopes were similar (Table 2). MFCV at the start of contraction was higher in patients than in controls (Fig. 1B;

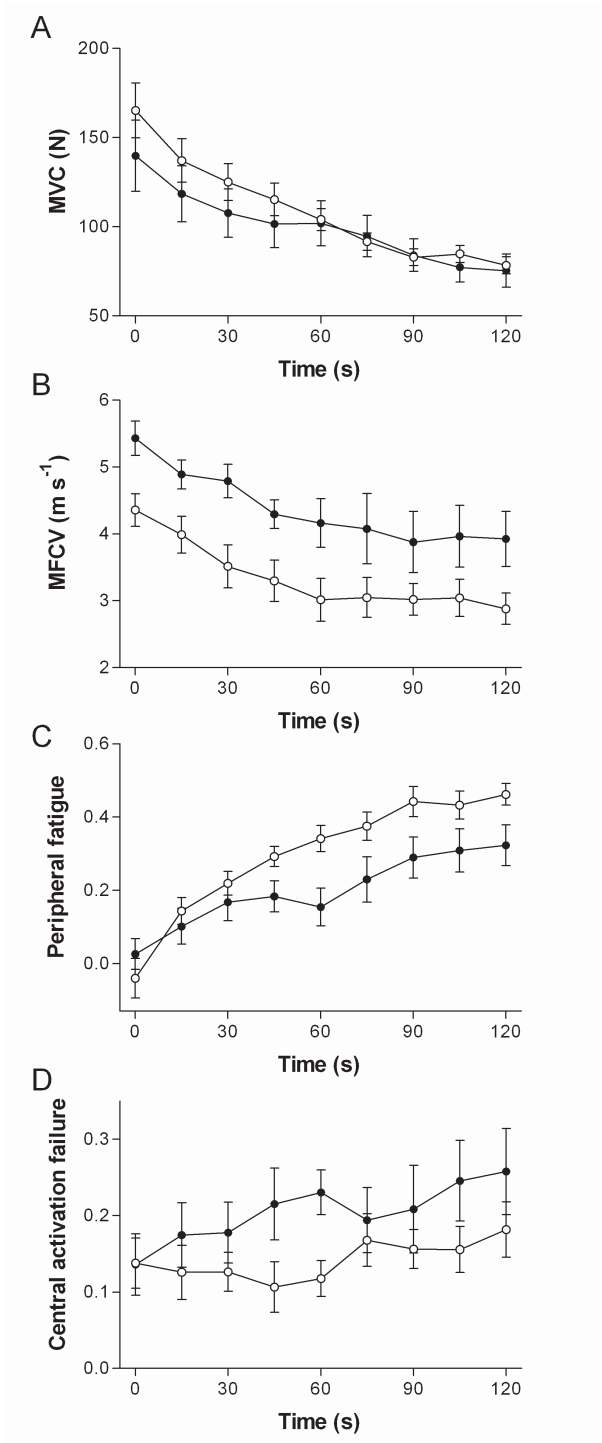

Figure 1.
Legend to Figure 1. Maximal voluntary contraction (A), muscle fibre conduction velocity (B), peripheral fatigue (C), and central activation failure (D) for GBS patients and healthy controls during 2-minute sustsained MVC. Healthy subjects are represented by a '○', GBS patients by a '•'.

patients: 5.4 ± 0.7 m s^{-1}; controls: 4.4 ± 0.8 m s^{-1}; $p = 0.008$). Its relative decline during sustained MVC was similar in the groups, in the first as well as in the second minute of sustained MVC.

Central activation failure and fatigue

Fig. 1D shows that CAF did not differ between patients and controls directly at the start of sustained contraction (patients: 0.14 ± 0.13; controls: 0.14 ± 0.11; $p = 0.971$). In patients, CAF increased significantly during the first minute of sustained MVC ($p = 0.033$), whereas it did not deviate from zero in controls ($p = 0.425$). In the second minute, slopes of CAF were similar in patients and controls (Table 2). The total amount of central fatigue, determined as $CAF^{120} - CAF^{0}$, did not significantly differ between both groups (patients: 0.12 ± 0.18; controls: 0.04 ± 0.11; $p = 0.24$), although it seemed to deviate from zero in patients ($p = 0.065$), but not in controls ($p = 0.205$).

Correlations

We have tested correlations between FSS, AFQ or AFQ change scores and the physiological measures (CAF^{0}, $CAF^{0\text{-}30}$, slopes of CAF, central fatigue, peripheral fatigue, and slopes of peripheral fatigue, initial MVC, MVC at the start of sustained contraction, maximum possible force, and slopes of MFCV) for patients and controls separately. Significant correlations were only found between AFQ and the slope of CAF in the second minute in control subjects ($R = 0.729$, $p = 0.011$), and between AFQ and the slope of peripheral fatigue in the first minute in patients ($R = 0.666$, $p = 0.035$).

DISCUSSION

The relative contributions of peripheral and central aspects of residual fatigue in neurologically 'well-recovered' GBS patients were determined during a 2-minute sustained MVC. The main findings of this pilot study were slower development of peripheral fatigue during the first minute of this sustained contraction, a significantly faster occurrence of central fatigue, and a higher initial MFCV in GBS patients compared to control subjects. The total amount of physiological fatigue and the course of MFCV did not significantly differ between both groups. These findings might be a consequence of persistent axonal loss or persistent changes in myelination pattern of motor neurons after GBS. Different possible underlying mechanisms of fatigue are discussed.

Many patients recovered from GBS indicate their complaints of fatigue as endurance intolerance. This was supported by the experienced fatigue, determined with the AFQ. Fatigue values obtained directly before and after sustained MVC, showed a trend to increase by exercise in patients but not in controls.

In contrast to results in patients with a current diagnosis of a neuromuscular disorder or chronic fatigue syndrome, the initial CAF values in healthy subjects and GBS patients were similar.[27](Schillings et al. Experienced and physiological fatigue in neuromuscular disorders, 2005) These previous studies suggest that central functioning might be related to the level of experienced fatigue. In GBS patients, no relation was found between the self-experienced fatigue and peripheral or central fatigue. In the GBS patients we examined, central fatigue occurred during the first minute of sustained MVC, whereas it could not be detected in healthy controls. In the latter part of the exercise, the levels of central fatigue in patients and controls were similar. Additional and different from GBS patients, patients with chronic fatigue syndrome suffer from severe fatigue all day long, and fatigue seems to be less specifically triggered by physical exercise.[34] This observation is supported by the CAF values; in patients with chronic fatigue syndrome these values are already increased at the start of a sustained MVC, while in GBS patients these values initially are normal, and only increase during the first minute of sustained MVC, supporting patients' opinion that fatigue after GBS seems more an endurance problem and exercise related.

The observation that peripheral fatigability in fatigued but neurologically 'well-recovered' GBS-patients was lower than in healthy controls is similar to previous observations in patients with (slowly) progressive neuromuscular disorders.(Schillings et al. Experienced and physiological fatigue in neuromuscular disorders, 2005) Better muscular endurance in patients recovered from GBS compared to control subjects has also been reported in a recently published long-term follow-up study.[10] Reduced peripheral fatigue might be a consequence of less occlusion of blood flow in the studied muscle; with smaller force production, and thus lower intramuscular pressure, occlusion of blood flow is reduced, and consequently, peripheral fatigue will also be reduced. GBS patients tended to have a lower MVC than healthy controls. This observation is in line with observations about long-term muscle strength values after GBS as described before.[10,13,35] Many patients in these studies seemed neurologically well recovered, reflected by normal functional scores and maximal MRC sumscores, but isokinetic muscle strength values were lower than in healthy controls. These decreased maximal muscle strength values may also be involved in the pathophysiology of fatigue. It was described previously that increased fatigability inevitably occurs in patients with muscle weakness, regardless of the different underlying peripheral or central or neurological disorders.[21] We, however, did not detect a correlation between MVC and experienced fatigue. Finally, reduced peripheral fatigue might also be caused by a changed muscle fiber type composition after recovery from GBS. We hypothesize that recovery after GBS is accompanied by reinnervation of muscle fibers, but that part of the fibers may be lost. To restore muscle strength, the reinnervated muscle fibers become hypertrophic, as supported by the significantly higher MFCV in patients. It can be hypothesized that the occurrence of central fatigue is related to the decreased number of remaining motor units.[20] Changed muscle organization may require different demands on the central nervous system. The normal interplay between numbers of recruited MUs in relation to

the firing frequency is disturbed. It could well be that the smaller number of motor axons in GBS gives rise to the relatively fast increase in CAF during the first minute since the dropout of only a few MUs could already give rise to a relatively large central activation failure.

Some methodological issues of the current study should be addressed. The experimental setup of the 2-minute sustained contraction, in which patients are actively encouraged, was used to discriminate between peripheral and central aspects of fatigue. This experimental situation is different from normal daily life, in which a sustained MVC is used much less than for example repetitive or cyclic muscle contractions. A test that had avoided blood occlusion in all subjects, like cyclic muscle contractions, additionally could have led to different results regarding peripheral fatigue. The recent finding of reinnervation in many neurologically well-recovered GBS patients,[10,11] in combination with the to be expected changes in muscle anatomy, might suggest that other electrophysiological techniques like estimation of motor-unit numbers (MUNE) can be of additional value. Only a few studies are performed using MUNE techniques in GBS,[18,20] but its relationship with fatigue was never studied. Another point to discuss is the activity-dependent hyperpolarization. It is known that voluntary contraction leads to membrane hyperpolarization of active motor axons.[32] This might result in activity-dependent conduction blocks when the impulse transmission is (critically) lowered after apparent recovery from demyelination.[6,7] Although our patients generally showed normal maximal nerve conduction velocities (Garssen et al. Nerve conduction studies in relation to residual fatigue in Guillain-Barré syndrome, J Neurol 2005), the CVD was altered (Garssen et al. Conduction velocity distribution in neurologically well-recovered but fatigued Guillain-Barré syndrome patients, Muscle and Nerve 2005) This implicitly suggests a contribution of persisting changes in myelination pattern to the pathogenesis of fatigue, in particular activity-dependent membrane hyperpolarization.[6] In future studies, it would be of additional value to study the possible involvement of these exercise induced nerve conduction blocks.

Additionally, many FSS items are based on physical consequences of fatigue. Because many patients indicate their fatigue as a result of impaired endurance intolerance, this might indirectly lead to an overestimation of these complaints of fatigue. However, our patients were neurologically seen 'well recovered' and it is known from other studies that the FSS is an adequate tool to evaluate fatigue.[9,13,22,29] Finally, we only found a few significant correlations between physiological measures of fatigue and experienced fatigue severity. This might be partly due to the relatively small number of subjects in this study.

To conclude, this pilot study was feasible for neurologically 'well-recovered' GBS patients. The study revealed valuable data concerning possible underlying pathophysiological mechanisms of their self-experienced fatigue, and paves the way for more definitive and larger studies. Physiological parameters showed faster occurrence of central fatigue and slower development of peripheral fatigue in the first minute of sustained MVC in GBS patients. Although we only found a few significant correlations, these results, together with the increased MFCVs, suggest that peripheral changes after GBS may contribute to the experienced fatigue. However, also

central mechanisms cannot be ignored; the interplay between these mechanisms and the overall causes of fatigue are still not clear.

A larger, prospective and controlled study, including electrophysiological measurements like CAF and MUNE and aiming to elucidate the mechanisms of fatigue after GBS, is warranted in fatigued compared to non-fatigued GBS patients.

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CHAPTER 4.5

Understanding the favourable effects of physical exercise: relationships between physical fitness, fatigue and functioning in Guillain-Barré syndrome and CIDP

Bussmann J.B.J.[1], Garssen M.P.J.[2], van Doorn P.A.[2], and Stam H.J.[1]

Departments of Rehabilitation Medicine (Bussmann and Stam)[1] and Neurology (Garssen and van Doorn)[2], Erasmus Medical Center, Rotterdam, The Netherlands

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ABSTRACT

Objective To elucidate the effects of physical exercise in severely fatigued Guillain-Barré syndrome (GBS) and Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) patients, and to clarify the mutual relationships between five domains studied in these patients: physical fitness, fatigue, objectively measured actual mobility, perceived physical functioning, and perceived mental functioning.

Patients and Methods Twenty patients and 10 healthy comparison subjects were included in this study. Only patients participated in a 12-week physical exercise program. Main outcome measure was the percentage of significant relationships between each pair of domains and was determined and converted to a relationship score (RS), which could range from 0 (no relationship between two domains) to 4 (very strong relationship).

Results A small percentage significant relationships was found between the domain physical fitness and the other four domains (mean RS score 0.33). A higher percentage significant relationships was found between the domains fatigue and perceived physical functioning, and between perceived mental functioning and actual mobility (both mean RS score of 2.0).

Conclusions Changes in fatigue, actual mobility and perceived functioning seem not to be influenced by changes in physical fitness. This study stresses the presence and importance of additional effects of a physical training program, not directly related to increasing fitness.

INTRODUCTION

Guillain-Barré syndrome (GBS) is an immune-mediated polyradiculoneuropathy affecting one to two per 100,000 of the population.[1] Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) may be considered a chronic variety of GBS. Although the greater part of the GBS-patients experience rather good neurological recovery, severe fatigue is an important residual and disabling complaint, seriously affecting quality of life.[2]

Aerobic training is generally focused on increasing physical fitness, and it is generally accepted that in this way other beneficial effects are also obtained. For example, aerobic training has shown to improve physical fitness, to decreases fatigue, and to improve quality of life in patients with multiple sclerosis.[3] In other patient groups also positive effects on mood, depression or mental functioning are reported.[4,5] It was hypothesized that a 12-week physical exercise program also might have different positive effects in severely fatigued GBS and CIDP patients. Therefore, a non-controlled training study was conducted in 20 severely fatigued patients. A group of 10 healthy subjects underwent the same baseline measurements, but did not participate in the training intervention.[6] Outcome measures represented the different parts of the International Classification of Functioning, Disability and Health (ICF).[7] Statistically significant and clinically relevant differences were found between measurements post- and pre-training, and between patients and comparison subjects. However, no changes and differences were found in actual mobility as measured with an activity monitor.[6]

However, the aim of the study was twofold; besides assessing the effect of training on physical fitness and other parameters,[6] another aim was to obtain insight into the mechanisms behind the training effects. The categories of the ICF were not considered fully adequate for that second purpose. Therefore, we assumed that another classification distinguishing 5 domains would be more appropriate: physical fitness, fatigue, actual mobility, perceived physical functioning, and perceived mental functioning. Generally can be stated that data analysis focusing on the effect of training does not provide insight in the effect mechanisms and mutual relationships between outcome domains.

The aim of the present study, therefore, was to clarify the mutual relationships between these 5 domains, and to obtain insight in the mechanisms of the effects of physical exercise. Relationships were studied in a) the difference data (differences between baseline and post training) in the group of patients, supported by b) cross-sectional analysis of the baseline data of patients and by c) cross-sectional analysis of the data of the group of healthy comparisons.

METHODS

Patient selection, in- and exclusion criteria, training intervention, measurement protocol, instruments and outcome measures are described in more detail elsewhere, as are the results of the intervention part of the study.[6] These results are summarized in Table 1.

Table 1. Mean values of the variables used in the analysis of this paper, at baseline (patients and controls) and post-training (patients only)

Domains & outcome measures	Patients Baseline	Patients post-training*	Controls baseline†
Physical fitness			
Peak oxygen uptake (ml/kg/min)	25	30†	33‡
Peak power output (W)	133	172†	190‡
Muscular fitness (W)	57	64†	69
Fatigue			
FSS	6.1	4.8†	2.2#
Actual mobility			
Percentage active (%)	10.7	11.2	12.2
Percentage active & standing (%)	26.2	25.0	28.5
Body motility (g)	0.0112	0.0119	0.0120
Perceived physical functioning			
SF36-physical	44.0	50.1*	58.4#
FIS-physical	2.18	1.13†	0.23#
Rotterdam Handicap Scale	3.56	3.78†	4.00#
Perceived mental functioning			
HAD	3.60	2.98†	2.70#
SF36-mental	51.6	55.9	55.7
FIS cognition	1.37	0.81†	0.25#

*: post-training patient data compared to patient baseline data, $p < 0.05$

†: post-training patient data compared to patient baseline data, $p < 0.01$

‡: control baseline data compared to patient baseline data, $p < 0.05$

#: control baseline data compared to patient baseline data, $p < 0.01$

Subjects

Sixteen neurologically 'relatively well–recovered' GBS-patients and 4 neurologically stable CIDP patients participated in the training study (14 female, 6 male, median age 49 yr).[6] All patients were severely fatigued (defined as Fatigue Severity Scale Score ≥ 5), neurologically stable (defined as no apparent changes in GBS-disability score for at least 3 months), and all patients were screened to exclude other possible explanations for their fatigue complaints.[6] Ten sex and age (maximum 5 years difference) matched healthy and non-fatigued subjects (6 female, 4 male, median age 51 year), not known with any disease or use of medication, were recruited from patients' own environment. They did not participate in the training program. The Ethics Committee of Erasmus Medical Center approved the study.

Intervention

The training program for the patient group consisted of 3 supervised cycle training sessions per week, for a 12-week period.[6] Each session, during which heart rate (HR) was monitored, consisted of a 5-minute warming up (at 65% of HRmax), 30 minutes training with a stepwise increase of cardiac load during the program, starting with 70% of HRmax to a maximum of 85-90% of HRmax. Every training session was finished with a 5 to 10 minutes cooling down.

Instruments and outcome measures

Patients underwent all measurements two times, at baseline and after the training program. In the healthy control group only baseline measurements were performed. Outcome measures were categorized into five different domains: physical fitness, self-reported fatigue, actual mobility (i.e. objectively measured functioning, defined by body postures and motions), perceived physical functioning (i.e. perceived problems with physical functioning) and perceived mental functioning (i.e. perceived problems with psychological / mental functioning). Not all measured and calculated outcome measures were included in the analyses of the present study. Criteria used for selecting or rejecting a single outcome measure were: the degree in which an outcome measure was assessed to fit or represent a specific domain, a preference for summary scores compared to sub scores, and finally, as far as possible a balance in number of outcome measures for each of the five different domains.

Physical fitness

Peak oxygen uptake (ml/kg/min) and *peak power output* (W) were determined using an incremental, adaptive cycle ergometer test (Jaeger, Breda, the Netherlands), during which heart rate and gas exchange, including oxygen uptake was registered continuously with the K4b^2 exercise testing system (Cosmed Srl., Rome, Italy). The highest physical load level (peak power output, POpeak) and the mean oxygen uptake (VO_2peak) during the last 30 s of the highest load level were included as outcome measures. To assess *muscular fitness*, knee extensors and flexors were measured bilaterally with a computerized muscle force measurement device (Biodex,

Biometrics Europe, Almere, the Netherlands). Subjects performed with each leg 10 flexion and 10 extension movements with maximal contractions at two angular speeds (60°/s and 180°/s). Muscular fitness was expressed by the mean power per movement (expressed in W).

Fatigue

Fatigue was measured with the *Fatigue Severity Scale* (FSS), a 9-item self-reported questionnaire with answers ranging from 1 ("strongly disagree") to 7 ("strongly agree") for each inquiry. The FSS score is calculated as the mean score of the 9 inquiries, ranging from 1 ("no signs of fatigue") to 7 ("most disabling fatigue").[2,8]

Actual mobility

Actual mobility (e.g. duration and distribution of standing, sitting, walking, cycling and transitions from one position to another) during normal daily life was objectively measured using an Activity Monitor (AM).[9,10] The AM, based on body-fixed accelerometers and a portable recorder (Vitaport technology), has been extensively validated and used before. After a measurement, mobility-related activities are automatically detected from the measured acceleration signals by custom-made software. To obtain comparable data in our patients, a period of 24 hours consecutive recording time (3 am till 3 am next day) was extracted for statistical analysis. Three AM outcome measures were included in the present analysis: the *percentage of time a patient was active* (e.g., walking, cycling, climbing stairs, and general movement), the *percentage of time a patient was active or standing*, and the *body motility value*, which can be regarded as being related to the overall level of physical activity during the measurement.[9]

Perceived physical functioning

Perceived physical functioning was calculated by using the *36-item Short Form Health Survey* (SF-36).This generic health status questionnaire, consisting of 36 items, assigns 8 different domains. From these items, a physical and mental summary score can be calculated.[11,12,13] In this domain, the physical summary score was used. The *Fatigue Impact Scale* (FIS) is a 40-item questionnaire with answers ranging from 0 ("no problem") to 4 ("extreme problem"), evaluating the impact of fatigue on the levels of cognitive [10 items], physical [10 items], and social functioning [20 items]. For this domain, the physical subscale was used.[14,15] Additionally, the *Rotterdam Handicap Scale* (RHS) was used. The RHS is a 9-item health status questionnaire, mainly focusing on physical aspects, with answers on each inquiry ranging from 1 ("unable to fulfill tasks/activities") to 4 ("complete fulfillment of tasks/activities").[15]

Perceived mental functioning

Perceived mental functioning was calculated by using the *Hospital Anxiety and Depression scale* (HAD). The HAD is a 14-item screening tool, used to assess anxiety and depression.[17,18] A second outcome measure within this domain was the mental summary score of the *36-item Short Form*

Health Survey (SF-36).[11,12,13] The cognitive subscale of the *Fatigue Impact Scale* (FIS) was selected as a third and final outcome measure of mental functioning.[14,15]

Data analysis

Each domain was represented by three outcome measures, except for the fatigue domain (FSS score only, see also Table 1). Pearson correlation coefficients were calculated between all outcome measures of different domains. For example, between two domains, including three outcome measures each, nine correlation coefficients were calculated. If a p-value of a correlation coefficient was < 0.1 – this was considered most appropriate for the purpose of this study, because of the relatively small number of patients - a relationship was considered significant. In this way the number and percentage of significant relationships between domains could be calculated. The percentage was assumed to reflect the strength of the relationship between two domains. To facilitate data presentation and interpretation, the percentage of significant relationships between domains was converted to values (relationship score, RS), ranging from 0 to 4: <20% of the relationships significant (RS = 0, no relationship between two domains), >= 20% and < 40% (RS = 1, weak relationship), >=40% and < 60% (RS = 2, moderate relationship), >=60% and <80% (RS = 3, strong relationship), and >=80% of the relationships being significant (RS = 4, very strong relationship). This way of analysis was applied to three different data sets: the difference (between post-training and baseline) data in the patient group, the cross-sectional data of the patient group, and the cross-sectional data of the comparison group.

RESULTS

The correlation coefficients between all outcome measures are shown in Table 2a and 2b. The degree in which the five domains were related to each other for the three different data sets were derived from these data (Table 3). Although some differences between these data sets were found, the trends and patterns were generally similar. A low percentage significant relationships was found between the central topic of the training program – physical fitness – and other domains, as expressed by low relationship scores in the upper part of Table 3 (mean RS = 0.33) A higher percentage of significant relationships was found between fatigue and perceived physical functioning (mean RS = 2.0), between perceived physical and perceived mental functioning (mean RS = 1.0), and between perceived mental functioning and objectively measured actual mobility (mean RS = 2.0).

	Physical fitness			Fatigue	Actual mobility			Perceived physical functioning			Perceived mental functioning		
	VO2peak	POpeak	Pmusc	FSS	%act	%act+stand	motility	SF36phys	FISphys	RHS	HAD	SF36ment	FIS cog
VO2peak	×	.55**	-.15	-.40	-.07	-.19	-.30	-.02	-.19	.16	.26	.06	.11
POpeak	.68***	×	-.02	-.30	-.05	-.17	-.18	.31	-.13	-.04	.04	-.09	.10
Pmusc	.26	.48	×	-.31	.04	.06	-.05	-.10	-.08	.09	-.00	.18	-.00
FSS	-.29	-.11	-.01	×	-.11	.10	.14	-.46*	.11	.14	-.09	.25	.17
%act	.33	.45*	.50	-.11	×	.77***	.63**	.31	.51**	-.42*	.62**	-.49*	.03
%act+stand	.20	.04	.25	.10	.73**	×	.49*	.16	.40	-.48*	.59**	-.60**	-.00
Motility	-.10	-.29	-.11	-.08	.44*	.68**	×	.12	.02	-.34	.21	-.19	-.11
SF36phys	.20	.46*	.16	-.48**	.24	-.04	.19	×	.00	-.18	-.03	-.39	-.11
FISphys	-.22	-.15	.18	.68***	-.18	.17	-.05	-.51**	×	-.37	.61***	-.60**	.64**
RHS	.48**	.54**	.46	-.38	.08	-.14	.30	.26	-.18	×	-.40	.37	.03
HAD	.10	.04	-.14	.29	.33	.57**	.52**	-.22	.24	-.31	×	-.65***	.59**
SF36ment	-.10	-.18	.21	.03	-.37	-.42*	-.25	-.40*	.16	.33	-.70***	×	-.61**
FIScogn	.13	.15	-.27	.36	.39	-.08	-.20	-.29	.51**	.06	.36	-.11	×

Legend to Table 2a. Correlation coefficients between all outcome measures, categorised according to the 5 domains. The coefficients of the difference data of the patients are shown in the upper-right part of the table, the cross-sectional patient data in the lower-left part. Significant relationships between outcome measures of different domains are stressed by grey cells.

*: 0.05<p<=0.1; **: 0.01>p<=0.05; ***: p<0.01

	Physical fitness			Fatigue	Actual mobility			Perceived physical functioning			Perceived mental functioning		
	VO2peak	POpeak	Pmusc	FSS	%act	%act+stand	motility	SF36phys	FISphys	RHS	HAD	SF36ment	FIS cog
VO2peak	×												
POpeak	.72*	×											
Pmusc	.14	-.23	×										
FSS	-.46	-.59*	-.05	×									
%act	-.44	-.46	.33	.51	×								
%act+stand	-.49	-.45	.58	.25	.88***	×							
Motility	-.10	-.24	.08	.03	.71**	.60*	×						
SF36phys	.55*	.20	-.02	-.55	-.14	-.11	.34	×					
FISphys	-.32	-.67**	-.53	.72**	.62*	.52	.26	-.30	×				
RHS										×			
HAD	-.54	-.68**	-.40	.82***	.73**	.59*	.30	-.50	.76**		×		
SF36ment	.38	.71**	.33	-.44	-.71**	-.67**	-.59*	-.18	-.54		-.72**	×	
FIScogn	-.43	-.65**	-.87*	.39	.59*	.68*	.33	-.22	.80**		.73**	-.66**	×

Legend to Table 2b. Correlation coefficients between all outcome measures, categorised according to the 5 domains. The coefficients of the cross-sectional data of the healthy control group are shown. Significant relationships between outcome measures of different domains are stressed by grey cells.

*: 0.05<p<=0.1; **: 0.01>p<=0.05; ***: p<0.01

Table 3. The degree in which five domains are pair-wise related to each other, for each of the three data sets. The strength of the relationship is expressed by relationship scores, which can range from 0 (no relationship between two domains) to 4 (very strong relationship between two domains)

			Relationship scores		
Domains			post-training – baseline patients	baseline patients	baseline controls
physical fitness					
	vs.	fatigue	0	0	1
		actual mobility	0	0	0
		perc. physical functioning	0	1	1
		perc. mental functioning	0	0	2
fatigue					
	vs.	actual mobility	0	0	0
		perc. physical functioning	1	3	2
		perc. mental functioning	0	0	1
actual mobility					
	vs.	perc. physical functioning	1	0	0
		perc. mental functioning	2	1	3
perceived physical functioning					
	vs.	perc. mental functioning	1	1	1

DISCUSSION

The aim of this study was to clarify the mutual relationships between different outcome domains, and to obtain insight how a training program effects fatigue and different types of actual and perceived functioning. The training study showed significant improvements in physical fitness and in most other outcome measures when comparing baseline and post-training values.[6] The aim of the training program was mainly focused on changing physical fitness. It was assumed that other effects would be mainly affected by this improvement in physical fitness. However, detailed data analyses as performed in the present study only found a limited number of significant relationships between physical fitness and other domains, strongly suggesting that physical fitness is not the main contributor to functional improvement in these patients. Training resulted in improved fitness, but improvements in perceived fatigue and functioning do not seem to be significantly influenced by improved fitness. A possible

explanation for this phenomenon is that the effects in the domains fatigue and functioning are mainly caused by additional or secondary effects of the training program. Although the design of the current study does not allow statements on causal relationships, the most plausible explanation is the important role of psychological factors: attention of researchers and physical therapists provided to the patients, increased self-confidence, and the social aspect of the training program (training was simultaneously given to 3 or 4 patients) might be all important factors. If so, a physical training program has a dual effect: not only improving fitness, but also changing mental functioning and, by this way, other domains of functioning. This explanation seemed supported by the subjective impression of the researchers and physical therapists involved in this study. The observation that physical training has a positive effect on mood and mental functioning has been described before. For example, in a review article of Lett et al.[4], positive effects of exercise on mood were described in patients with Coronary Heart Disease. In another review article it was reported that exercise therapy results in a slightly favorable effect on depression in Chronic Fatigue Syndrome patients compared to control subjects.[5]

There were some remarkable findings. There were relatively many significant relationships between perceived mental functioning and objectively measured actual mobility. In literature, the positive relationship between these domains is frequently reported.[19,20] However, in the present study generally inverse relationships were found between actual mobility and mental functioning, e.g. a higher level (or a larger change) of mental functioning was associated with a lower level (or a smaller or negative change) of actual mobility. An inverse relationship between mental functioning and physical activity is described before, as a result of excessive exercise and overtraining.[19] In our study, it might be a consequence of patients trying to maintain their normal activity level, while their capability is lowered by (subclinical) neurological deficits. This might even result in more complaints of fatigue, and subsequently in decreased physical and mental functioning. This hypothetical phenomenon is worth to pay further attention to in the nearby future. Secondly, significant relationships were frequently found between perceived fatigue and perceived physical functioning. This can be attributed to their actual mutual relationship, but partly also by instrument characteristics: the Fatigue Severity Scale evaluates the perceived severity of fatigue, but a detailed look at the items reveals that most items measure mainly the impact of fatigue on physical functioning.

The study is not without limitations. Firstly, the training study was not controlled and therefore factors not related to the focus of the training program, i.e. improving fitness, may have contributed to the different effects. Secondly, the methodology used in this paper can be discussed; although outcome measures were not selected depending on their relationships with other measures, they were selected from a larger set of outcome measures within a domain, and summarized in a table and figure in a clearly defined but still arbitrary way. However, additional ways of data exploration using other data analysis strategies – e.g. taking other outcome measures or summarizing data in other ways, not presented in this paper - showed that the main conclusions do not change when using other methods. Another point concerns validity;

the degree in which outcome measures represent a specific domain. E.g., is the percentage of 24 hr that a patient is active a valid measure of actual mobility and does the FSS score really represent fatigue? However, we have been careful in this process, and choices of instruments and domains have been based on literature (e.g. validity studies) and thorough examination of the measurement instruments, and the different items and outcome measures. Finally, the data of the present study are not completely independent: outcome measures within a domain can and will be related (see also Table 2), and the difference data of the patients will not be independent from the baseline data. Although data analysis showed that dependencies exist, they are not that strong that the data can not be regarded sufficiently valid.

The main conclusion of this study is that a poor relationship exists between (changes in) physical fitness and other functional measures. Physical training in GBS and CIDP patients, aiming to increase physical fitness, has positive effects on physical fitness, fatigue and most functional outcome measures, but changes in fatigue, actual mobility and perceived functioning seem not to be influenced by changes in physical fitness. This was confirmed by cross-sectional analyses in patients and comparisons. Therefore, this study stresses the presence and importance of additional effects of a physical training program, not directly related to increasing fitness.

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CHAPTER 5

General discussion and future perspectives

5. GENERAL DISCUSSION AND FUTURE PERSPECTIVES

In this thesis studies concerning incidence, treatment, and possible causes of residual fatigue in immune-mediated polyneuropathies, in particular in Guillain-Barré syndrome (GBS) are described. Also an overview of treatment regimens and a study on a new combination of drug therapy in the acute phase of GBS are included.

The main part of this thesis is about fatigue, which remains frequently present for a prolonged period of time after the acute phase of GBS. The incidence of fatigue was evaluated cross-sectional within a nationwide prospective study. Studies on treatment of fatigue include a pharmacological intervention study, a physical exercise training intervention and a follow-up study on the long-term effect of this training intervention. Studies about possible underlying pathophysiological mechanisms of residual fatigue include various electrophysiological studies, a study aiming to elucidate the contribution of peripheral and central components of fatigue, and finally a study aiming to describe the direct relationships between physical exercise training on fatigue, physical and mental functioning and quality of life.

In this chapter the main findings of these different studies will be discussed and suggestions for future studies will be made. The first part of this discussion focuses on fatigue and its assessment in general and the assessment and incidence of fatigue after GBS in particular (paragraph 5.1 and 5.2). Subsequently, possible underlying pathophysiological mechanisms related to fatigue are discussed and suggestions for future research about fatigue are made (paragraph 5.3). The final part of this chapter focuses on treatment of GBS in the acute phase and also includes proposals for future studies (paragraph 5.4).

5.1 FATIGUE

Many definitions of fatigue are known. Fatigue might be defined as *'extreme and persistent tiredness, weakness or exhaustion – mental, physical or both*[1], or as *'a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities'*[2] Fatigue could be pleasurable if the activity is linked to a reward, like winning a competition. For clinical use in neurological disorders, fatigue might be best defined as '*difficulty in initiation of or sustaining voluntary activities*'.[3]

Perception of fatigue is often a non-specific and highly subjective experience, and may be based on both physical and / or mental changes. Self-perception of fatigue in patients may be complicated to a great extend by confounding factors like pain, muscle weakness, sleep disturbances or psychiatric disorders like depression or post-traumatic stress. Additionally, physicians may have various definitions in their own minds, not matching with patients' own definition of fatigue. Fatigue can have major impact on psychological well being, on physical functioning and normal activities in daily life, on employment, quality of life, and on patients'

direct environment. Fatigue might be part of a (neurological) disease, a result of psychiatric disturbances, a side effect of medication, or a result of a perpetuating circle of deconditioning;[3] in that case, the patient may experience a worsening of neurological complaints after any kind of activities, which may lead to avoidance of these activities in order to prevent worsening of complaints. This may lead to a decreased physical fitness and on its turn to lower levels of activity and higher levels of fatigue.[4]

5.1.1 What is known about fatigue after GBS

Complaints of residual fatigue and endurance intolerance after GBS was paid little attention to in the past, and never studied systematically before 1999 **(see also introduction, paragraph 1.6).**[4-8] It was initially described that patients who were clinically recovered from GBS may exhibit deficits during strenuous exercises requiring maximal effort and muscular endurance,[7] suggesting that fatigue might be a consequence of muscle weakness and endurance intolerance. It was additionally found in more than half of 122 GBS patients that loss of power and poor condition may persist for 3-6 years after the initial phase of disease, also suggesting fatigue being a result of residual deficits of the peripheral nervous system and being a consequence of physical dysfunction.[8] Remarkably, physically recovered patients showed these changes as well, rising questions about the physical origin of fatigue.[8] Others mentioned that physical fatigue often and mainly occurred in the first year after onset of GBS without clearly disabling patients.[5] In 1999, Merkies et al. performed a cross-sectional study to compare the presence and severity of fatigue in 113 patients with immune-mediated diseases and 113 healthy individuals.[9] It was found that severe fatigue was present in 80% of patients. Fatigue was a long-term complaint, significantly related to gender, and associated with a reduced quality of life. The majority of patients rated their complaints about fatigue among one of their three most disabling symptoms. Additionally, fatigue appeared to be independent of age and clinical features at the time of investigation, like muscle strength, sensory deficits, functional ability, and surprisingly, also the duration of symptoms since the onset of GBS. This might suggest the additional involvement of psychological factors in the underlying pathophysiology of fatigue.[9] Although this was the first systematical study about fatigue after GBS, some important methodological issues had to be addressed; a stable clinical condition was based on the subjective report of patients themselves, and possible confounding factors of fatigue like sleep disturbances, depression, and level of physical (in)activity were not systemically investigated.

5.1.2 What can be hypothesized about fatigue after GBS

Different hypotheses may rise from the above-mentioned data in paragraph 5.1.1. Maybe fatigue has to be considered a result of a disturbed interaction between various physiological and psychological control systems; a disturbed interplay between structural and / or functional integrity of sensory, motor and cognitive systems. Maybe fatigue is best understood as a disturbed sense of normal or physiological fatigue, induced by changes in one or more variables

regulating physical work output, or by a dissociation between the level of internal input (central factors) and perceived exertion from applied effort (peripheral factors).[3] For example, when there is a normal function of the sensory and motor pathways for physical activities, but a loss of interest and motivation due to a depression, then the subjective sense of fatigue is mainly a result of reduced internal input.

Thus before the start of the studies described in this thesis, it was already known that fatigue is highly frequent and an important and disabling residual symptom. Although different underlying mechanisms ranging from physically towards more psychologically oriented mechanisms have been postulated, this was never studied systematically. Possible therapies aiming to reduce these complaints of fatigue were largely unknown. These were important reasons to conduct the studies described in this thesis. Because GBS is a disease of the peripheral nervous system, with great bearing on psychosocial status it was hypothesized that fatigue might be a consequence of both physical (especially peripheral) and psychological factors.

5.2 ASSESSMENT OF FATIGUE

Given the range of mechanisms probably underlying fatigue, the different manifestations and confounding effects of disease symptoms and/or treatment, it is important to have reliable and valid methods to assess fatigue. A useful assessment method needs to reflect the problems reported by the patients, not only in order to increase insight in its causes, but also to improve its management and to verify the effects of different treatment regimens.[1] For research concerning a complex and highly subjective complaint of fatigue, it is unlikely that any one scale or quantification method is appropriate for measuring all aspects of fatigue. Therefore, many self-reported scales concerning fatigue assessment and different methods attempting to quantify fatigue and study fatigue more objectively have been developed.[1] It is known that different assessment scales might measure fundamentally different aspects of fatigue. Different aspects of fatigue assessment scales make them more or less valuable in evaluating this problem in a particular group of patients.

Measurement techniques can be divided into two categories; [2;10] subjective fatigue scales that measure patients' perceived level of fatigue, and objective fatigue measurements, aiming to quantify the patients' level of fatigue through various assessments methods. These methods range from multidimensional fatigue scales evaluating different physical and cognitive domains, to changes in muscle force generation and changes in physical conditioning. We used both subjective as well as objective fatigue measurement methods to evaluate possible contributing factors and possible treatment regimens of 'post-GBS-fatigue'.[7;9;11-13]

5.2.1 Subjective measurement of fatigue

A useful scale should fulfill the following requirements; simple / understandable, none-time consuming, applicable with little or no special training, valid, reliable, responsive to changes over time in the underlying condition, yet relatively insensitive to symptoms or signs fluctuations, and it should provide results that easily can be interpreted by others. [14] Assessment scales are particular useful when they are able to increase insight in possible pathophysiological mechanisms, and can be used in follow-up and periodical assessment of fatigue. Subjective fatigue scales can be divided into two categories, in either one-dimensional scales, attempting to measure fatigue as a single construct, like the fatigue severity scale (FSS), or multi-dimensional scales, attempting to measure fatigue as several constructs or differentiate among various forms of fatigue (e.g., physical, cognitive, and psychosocial), like the multidimensional fatigue impact scale (FIS).[2;10]

Subjective assessment of fatigue in this thesis was mainly based on the FSS, and as an addition to this scale, the FIS. Besides measuring the intensity of fatigue related symptoms, the FSS also measures the impact of fatigue on specific types of functioning.[1] The FSS is brief and easy to administer and score, and therefore useful as outcome measure and screening instrument. The FSS has a high internal consistency, good test-retest reliability, and is sensitive to change with time and after treatment.[1;9;15] The FSS was additionally chosen not only because it is one of the best known and frequently used fatigue scales[1], but also because this scale is able to derive a clear single score (capturing heterogeneous and subjective symptoms and behaviors). The FSS is the only fatigue assessment scale that has shown good psychometric properties in patients with immune-mediated polyneuropathies. The FIS was added because it additionally evaluates fatigue on three different areas of functioning: cognitive, physical, and psychosocial, rather than fatigue severity or phenomenology.[16] Its internal consistency, validity and reproducibility has been established in patients with MS, hypertension, and primary biliary cirrhosis, suggesting that the scale could be used in intervention trials.[17] We translated the FIS into Dutch (and re-translated the FIS into an English version again). The FIS, not validated for immune-mediated polyneuropathies, was used for making a more specific inventory of fatigue related problems besides the evaluation of different fatigue treatments and comparison of fatigue complaints between patients and healthy individuals. The FIS was also used to increase further insight in the areas of functioning involved in fatigued immune-mediated polyneuropathy patients.

Some authors criticized the FSS for assessing a combination of very general and very specific aspects of the patients' experience of fatigue and for its limited utility in examining the ways in which fatigue affects patients' lives.[18] However, assessment of fatigue using the FSS and the FIS essentially showed the same results and trends in the studies described in this thesis **(chapter 3)**. Both severity as well as impact of fatigue on cognitive, physical, and social functioning showed corresponding changes during the two treatment trials described in this thesis **(chapter 3.1 and 3.2)**. Both assessment scales showed good discrimination between

fatigued patients and healthy controls, and seemed appropriate to make an inventory of the fatigue problem in GBS.

5.2.2 Objective measurement of fatigue

Objective, performance based measures attempt to quantify the patients' level of fatigue, including physical, but also mental and social aspects of fatigue.[2;10] Objective fatigue measures have been used rather limited in research, and clinical applications are not widespread in contrast to subjective assessment methods (e.g. fatigue assessment scales). Evaluation the physical component of fatigue may include registration of changes in aerobic capacity during a physical exercise test, evaluation of changes in muscle force after physical exercise, or electrophysiological performances during a sustained (voluntary) muscle contraction.

The objective measurements used in this thesis to evaluate fatigue were the above mentioned physical exercise test, isokinetic muscle force measurements, electrophysiological measurements during a sustained 2-minute voluntary muscle contraction, and the measurement of actual mobility during normal daily life **(chapter 3 and 4)**. These techniques added different kinds of information, and were useful in evaluating the effect of physical exercise training and to increase insight in the possible pathophysiological mechanisms of fatigue, as described below.

5.2.3 Limitations of studies performed for evaluating treatments and causes of fatigue

Drawbacks of the training intervention study and its long-term follow-up evaluation **(chapter 3.2 and 3.3)** are mainly the lack of a control group of non-fatigued GBS patients, the relatively small group of participating patients, and the drop-out of some patients in the follow-up study. The lack of a non-fatigued GBS control group and the small group of patients were also drawbacks of the study evaluating the favorable effects of physical exercise in relation to physical fitness, fatigue and functioning, as described in **chapter 4.5.** In this study, aiming to obtain insight into the mechanisms behind the training effects, outcome measures were composites from a larger set of outcome measures, since the International Classification of Functioning, Disability and Health (ICF) was considered not fully adequate for that purpose. Therefore, a hypothetical model consisting of 5 predefined but arbitrary chosen domains were formulated: physical fitness, fatigue, objectively measured actual mobility, perceived physical functioning, and perceived mental functioning. This way of looking to the data certainly has limitations, since changing predefined and validated assessment scales in new and arbitrarily divided domains may lead to different results. Another point of discussion concerns validity: in which degree does an outcome measure represent a specific domain (e.g., is the percentage of a patient being active a valid measure of actual mobility, does the FSS score really represent the level of fatigue)? However, the construction of these arbitrary domains was a result of a careful examination of known and previously validated assessment instruments, items and outcome measures.

Also some limitations concerning the electrophysiological studies **(chapter 4.2 – 4.4)** have to be mentioned. An electrophysiological confirmation (eg. AIDP or AMAN) of the clinical diagnosis AIDP in the acute phase of disease was not available in all patients. Additionally, due to ethical reasons, we did not perform needle examinations. Although these clinically well-recovered patients appeared to have relatively normal compound muscle action potentials (CMAPs) and the sural sensory nerve action potentials (SNAPs) were generally normal, this suggests that major axonal degeneration was unlikely. A control group with healthy individuals was also studied, however, a control group with non-fatigued GBS patients was not examined yet. Although we only found minor abnormalities in NC velocities in the fatigued GBS patients, we don't know whether the 'normal' results might still be slightly reduced compared with non-fatigued patients. We performed a dichotomisation in severely and non-severely fatigued patients, however, it is debatable whether this dichotomisation was sufficient to compensate this shortcoming. The definition of severe fatigue we used was obtained from a cross-sectional validation study.[9] Severe fatigue was defined as a FSS score of the 95th percentile in healthy controls, meaning a FSS score of 5.0 or higher. However, in studies about fatigue in multiple sclerosis (MS), a FSS score of 4.0 or higher already was considered as cut-off point for severe fatigue. We found a trend that changes in CVD was higher in non-severely fatigued patients, suggesting that alterations in CVD were not an important contributor to severe residual fatigue. However, in case of comparing (severely) fatigued patients with non-fatigued patients (e.g. without dichotomisation of severe and non-severe fatigue), this might have lead to a more prominent role of changes in CVD in the pathogenesis of fatigue then presently suggested (see paragraph 5.3.4b). Finally, there are some limitations of the cross-sectional study about the occurrence of fatigue **(chapter 4.1)**, these are described separately in the next paragraph 5.3.1.

5.3 FATIGUE AND GBS

In this paragraph the occurrence of fatigue after GBS is described first. Hereafter the different studies about treatment and possible causes of fatigue described in this thesis will be discussed in relation to central and peripheral aspects of fatigue after GBS.

5.3.1 Presence of fatigue after GBS

As mentioned in the introduction **(chapter 1)** and in paragraph 5.1.1, fatigue has been briefly addressed as a complaint in the past.[4-8] The first study that systematically evaluated fatigue after GBS was published in 1999, and showed that severe self-reported fatigue was present in 80% of patients with immune-mediated polyneuropathies, and persisted for years even after apparent recovery.[9] In a recently published prospective study in Sweden it was shown that fatigue was present in 38% after 1 year of follow-up, and 40% after 2 years follow-up.[19] Although fatigue in

this study was assessed in a very simple way, using a one-dimensional visual analogue scale, it stresses the importance of the problems with fatigue after GBS.

To re-evaluate the presence of fatigue, we conducted a cross-sectional study, within a prospective nationwide study. In this study, the presence of fatigue after GBS and its relation with disease course, clinical characteristics, and antecedent infections was evaluated **(chapter 4.1)**. We found that severe fatigue was present in 60% of all patients and found that is was significantly more frequent in female patients, which confirmed previous data.[9] Severe fatigue was also significantly more present in patients over 50 years of age. Fatigue was considered a highly disabling entity, irrespective of various clinical variables such as impaired muscle strength, GBS-disability score, and sensory deficits. The percentage of patients suffering from severe fatigue was lower than reported before (60 vs. 80%).[9] This might be due to differences in study population. It was found that severe fatigue occurs more frequently in older patients, and the patient population we now studied was considerable younger compared to the previous study (44.9 vs. 56.1 years). Also the time lag from onset of GBS was shorter in this study (1.3 vs. 5.2 years). This could be of importance since patients who are still in the recovery phase of GBS might not be fully aware of other residual complaints like fatigue, because they are not able to perform the same physical activities like neurologically 'recovered' patients may do. This might also contribute to the different percentage of fatigued patients found in the Swedish study.[19]

Like values of fatigue in the earlier conducted cross-sectional study about fatigue,[9] the results of the study discussed in this thesis also have to be interpreted with some caution; possible confounders of fatigue, like baseline co-morbidities or depression, were not systemically excluded as we did in the other studies presented in this thesis. In the amantadine trial **(chapter 3.1)** and in the physical training study **(chapter 3.2)**, in which 80 and 16 severely fatigued GBS patients were included, all patients were carefully screened to exclude known confounding factors like depression and anaemia. Although confounding factors or methodological drawbacks possibly influence the results of all studies aiming to study the incidence of fatigue, our study at least indicate that fatigue is a severe and frequently present problem after GBS. The opinions of many physicians involved in treatment and follow-up of GBS patients support these observations.

5.3.2 Peripheral and central aspects of fatigue after GBS

As was hypothesized in paragraph 5.1.2, fatigue might be a result of a disturbed interaction between various physiological (organic) and psychological (non-organic) control systems; a disturbed interplay between structural and / or functional integrity of sensory, motor and cognitive systems. In this paragraph an artificial dissection is made between physiological and psychological components of fatigue that could attribute to fatigue in GBS. Fatigue is arbitrarily divided in peripheral and central aspects (see figure 1).

Peripheral fatigue (see paragraph 5.3.3) is defined as fatigability or endurance intolerance due to disturbances in functions of anterior horn cells, nerve roots and peripheral nerves, the neuromuscular junction and / or skeletal muscles (figure 1 and 2). *Central fatigue* (see paragraph 5.3.4) is defined as a result of either structural or psychological changes within the central nervous system (figure 1).

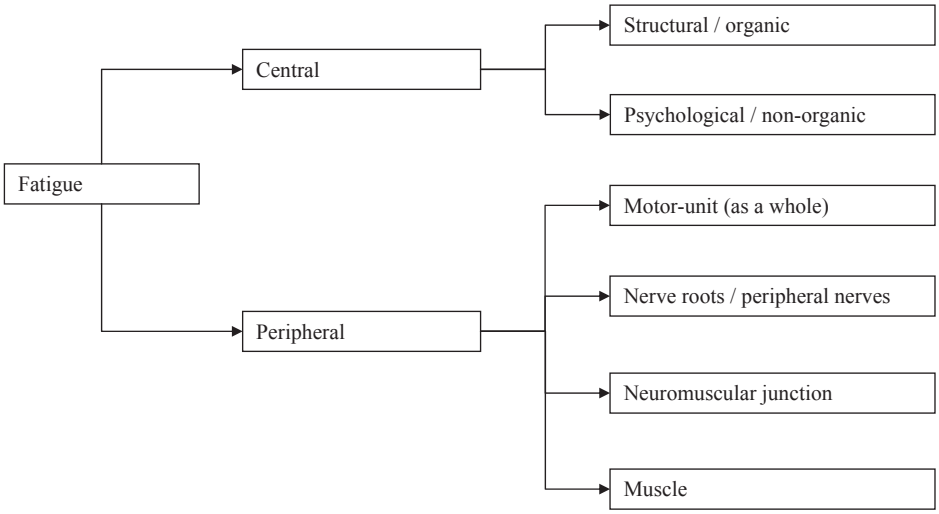

Figure 1. Artificial dissection between central (structural and psychological) and peripheral (motor-unit, roots / nerve, neuromuscular junction or muscle) components that could attribute to fatigue in GBS.

Because we aimed to increase insight in possible underlying mechanisms, we excluded known confounding factors of fatigue as much as possible. In all studies on fatigue described in this thesis (except the study on the occurence of fatigue **[see chapter 4.1]**) patients were screened to exclude concomitant conditions (i.e., malignancy, chronic infections, hypothyroidism, anaemia, renal and liver disease, chronic pulmonary and cardiovascular disease, chronic fatigue syndrome, diabetes) or use of medication that might cause or influence fatigue (e.g., benzodiazepines, antidepressants and immunotherapy) <4 weeks before onset of the study. Additional exclusion criteria were hypertension, use of β-blocking drugs, and depression (defined as a Hospital Anxiety and Depression Scale / depression subscale score of 10 or less[20]). Furthermore, none of the patients included in our studies had experienced this kind of fatigue before the onset of GBS.

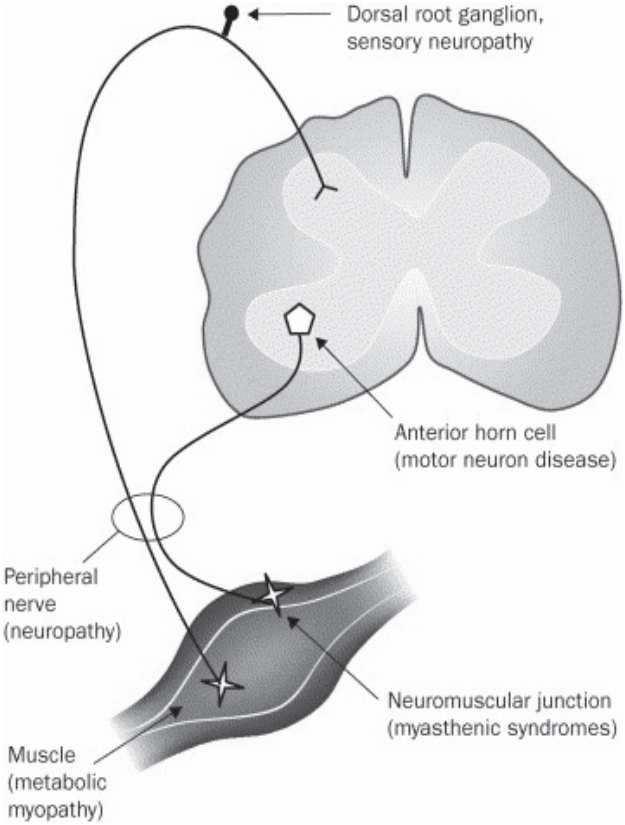

Figure 2. General sites of pathology in muscle fatigability and neuromuscular fatigue (peripheral fatigue).
From Chaudhuri and Behan, Fatigue in neurological disorders, Lancet 2004.

5.3.3a Central aspects of fatigue - structural aspects:

Although GBS is a disease of the peripheral nervous system, possible structural central aspects contributing to fatigue cannot be ruled out completely. The hypothesis of central nervous system involvement in GBS is partly put forward because of the observation of central white matter lesions, which have been found in some patients in the acute phase of GBS.[21-24]Additionally, in some patients with GBS a decreased concentration of hypocretin in the cerebrospinal fluid (CSF) has been found.[25-27] Decreased titers of hypocretin in the CSF, the pathophysiological hallmark of narcolepsia-cataplexia, might indicate a possible central contribution to residual fatigue.[28;29] However, narcolepsy is a sleep disorder characterized by excessive daytime sleepiness and cataplexia, not comparable with complaints of fatigue in GBS patients. The mechanism for low hypocretin in some GBS patients is unclear but may point to immune-mediated hypothalamic dysfunction.[28] Excessive daytime sleepiness has been reported in GBS patients, even after recovery from major neurological symptoms.[28] Although the complex role of hypocretin in

neuroendocrine and autonomic homeostasis remains to be elucidated, this substance might provide a biological link between symptoms of excessive sleepiness and fatigue and GBS.[28] These findings (e.g. low hypocretin levels in CSF) in some GBS patients probably do not play a major role in the pathophysiology and occurrence of fatigue after GBS in general. However, it might be interesting in future studies about fatigue in GBS patients, to evaluate the presence of white matter lesions and to determine the concentrations of hypocretin in the CSF.

5.3.3b Central aspects of fatigue - psychological aspects:

In the study evaluating amantadine as treatment of severe fatigue after GBS **(chapter 3.1)**, it was shown that amantadine was not effective. Most reduction of fatigue was observed during the pre-treatment period. However, reduction of fatigue was also achieved during the consecutive visits, during placebo as well as during amantadine treatment, suggesting that increased attention for fatigue provided by this study has an ameliorating influence on fatigue. Krupp et al. and the Canadian MS Research Group observed a similar phenomenon in the fatigue treatment studies in MS patients.[30;31]

Patients who participated in the 12-week during bicycle exercise training **(chapter 3.2)** reported that increased physical activity in the past often resulted in increased neurological complaints, resembling the initial phase of GBS or CIDP, which resulted in threatening and anxious feelings of getting a relapse. Due to the medical supervised training patients became confident in their own physical capabilities and a negative circle seemed to be broken.

In the long-term follow-up study after the training intervention **(chapter 3.3)**, a sustained fatigue reduction was found, which seemed unlikely to be caused by a natural or spontaneously reduction of fatigue after GBS because an earlier study showed that fatigue is long-lasting.[9] It was also unlikely that persistent benefits of reduced levels of fatigue could be explained by ongoing reconditioning activities only, since all patients participated less frequently and less intensively in sports than during the training intervention period, and functional neurological scores remained unchanged to post-training values. It seemed that patients became more convinced of their physical capabilities, and were less afraid and more capable to perform rather high level (short-lasting) maximal physical effort, as measured by the increased maximal power output and muscle strength measurements.

We suspected an important role for physical reconditioning in decreasing fatigue, however, we generally found no or only few relations between improved physical fitness and fatigue perception. Training resulted in improved fitness, which was attributed to the training program, but changes in perceived fatigue and functioning did not seem to be significantly influenced by improved fitness **(chapter 4.5)**, supporting an additional role for (positive) psychological effects.

Another contributor to a possible psychological origin of fatigue might be that GBS is a potentially life threatening disease, an important reason to develop a post-traumatic stress disorder with complaints of fatigue. Although we excluded patients with depression, we did not

perform a systematic neuropsychological screening of the fatigued GBS patients, implicating that there is no guarantee that post-traumatic stress is not involved in the pathogenesis of fatigue.

5.3.4a Peripheral aspects of fatigue - number of motor-units:

Motor-unit number estimation (MUNE) techniques provide objective and meaningful estimates of axonal loss in diseases affecting the motor system. MUNE can be an additional tool in GBS patients in following and quantification the extend of recovery after axonal damage.[32;33] Sparse electrophysiological follow-up studies after GBS suggested changes in motor-unit number estimation, with gradual recovery of the number of motor-units after nadir. The MUNE technique could also be of additional value in patients who suffered from a pure demyelinating form of GBS. Low-amplitude distal CMAPs are presumably due to axonal degeneration, but conduction blocks in very distal nerve segments are not excluded. Serial MUNE might be helpful to determine mechanisms for recovery. An increase in MUNE values indicates axonal regeneration, whereas an increase in CMAP amplitude without significant changes in MUNE might suggest remyelination.[32] Studying these mechanisms in fatigued and in non-fatigued GBS patients could give additional information in the pathogenesis of fatigue.

It can be hypothesized that different components of fatigue are caused by ineffective muscle activation, a result of a decreased number but larger size of remaining motor units.[33] Theoretically, recovery after GBS can be accompanied with reinnervation of muscle fibers with hypertrophy of reinnervated muscles, reflected by normal peak muscle strength and normal nerve conduction values, but resulting in impaired sustained muscle performances. The suggestion that hypertrophic reinnervated muscles may play a role in the pathogenesis of fatigue or endurance intolerance was partly supported by our finding that muscle fiber conduction velocity was significantly higher in fatigued GBS patients than in healthy controls **(chapter 4.4)**. Additionally, it can be hypothesized that a decreased number of remaining motor units after GBS results in a changed organization within the muscle, which may require different demands on the central nervous system. In that situation the normal interplay between numbers of recruited motor-units in relation to the firing frequency might be disturbed. It could well be that the drop-out of motor-units in GBS gives rise to a relatively fast increase of central activation failure as we found in our fatigued patients, and subsequently results in an increased fatigue perception and complaints of endurance intolerance.

It is still debatable which MUNE technique is most appropriate is assessing axonal loss, partly because different statistical methods have been used to estimate the number of motor-units, all with their own advantages and disadvantages.[34;35] We performed MUNE in our fatigued GBS patients, however, we did not include data about this MUNE study in this thesis. The main reason is that currently effort is undertaken to evaluate new methods for analysing MUNE most adequately.

5.3.4b Peripheral aspects of fatigue - nerve conduction studies:

We performed different nerve conduction (NC) studies in our fatigued patients **(chapter 4.2)**. Although it is known from various electrophysiological studies that different GBS subtypes can be distinguished, ranging from a pure motor axonal form (AMAN) to the classical demyelinating type of the disease (AIDP),[36] all GBS patients participating in these studies, clinically had motor and sensory involvement compatible with AIDP. One long-term follow-up study showed that axonal loss is associated with permanent weakness, caused by insufficient reinnervation.[37] We hypothesized that residual subclinical peripheral nerve dysfunction, i.e. demyelination, could contribute to long-lasting fatigue in our otherwise well-recovered AIDP patients with good muscle strength values (suggesting little or no substantial axonal loss). Although some methodological remarks can be made (see paragraph 5.2.3), most routine motor and sensory NC velocities we measured in the fatigued patients were remarkably within normal values, and no correlations were found between the electrophysiological findings and the fatigue scores, muscle strength, and functional scores. Because this observation suggested that fatigue in GBS is not explained by residual nerve dysfunction, it was hypothesized that the conventional NC measurement technique used, was not sufficient to detect abnormalities in nerve conduction in these patients. Additionally, dysfunction of small nerve fibers or other 'minor' defects in peripheral nerves could not be excluded, mainly because NC studies only measure large nerve fiber function. Therefore we conducted a conduction velocity distribution (CVD) study, which is a sensitive and non-conventional electrophysiological method evaluating peripheral nerve dysfunction, including smaller and slower conducting myelinated fibers **(chapter 4.3)**. An important finding was the existence of nerve conduction failure alongside normal conventional NC values, suggesting that the peripheral nervous system is unable to remyelinate in a fully accurate way, leading to a less differentiated or less sophisticated nerve fiber distribution compared to the situation before onset of GBS. We noticed narrowing of the velocity distribution with loss of the fastest and slowest conducting fibers. Surprisingly, these changes were most pronounced in the subgroup of patients with the lowest fatigue scores, suggesting that the CVD changes we have measured in GBS patients are unlikely to contribute to persisting complaints of severe fatigue after GBS.

5.3.4c Peripheral aspects of fatigue - muscle:

Although follow-up data about muscle anatomy after a GBS episode are lacking, there are indications that GBS might lead to changes in muscle anatomy. In one study, GBS patients showed slightly better muscular endurance tolerance than control subjects.[38] A selective loss of axons innervating type IIb motor fibers, with a subsequent switch of muscle fibers during reinnervation to more fatigue resistant type I or type IIa fibers was suggested. This parallels findings made in diabetic patients; diabetic patients may have increased endurance but reduced strength and work performance.[39] It is also known from animal models that denervation-induced atrophy is usually more severe in type IIb versus type IIa or I muscle fibers.[40-42] Additionally, patients with

chronic heart failure who engage in regular physical exercise show enhanced oxidative enzyme activity in the skeletal muscle and a concomitant re-shift from type II to fatigue resistant type I fibers.[43]

It was also found that an aerobic training program in these chronic heart failure patients resulted in increased physical peak power and muscle strength, however, training surprisingly did not result in a more active lifestyle as measured with the Rotterdam activity monitor (RAM).[44;45] We also expected an improved activity pattern and increased muscular endurance in our patients after the physical exercise-training program as described in **chapter 3.2.** However, also in our trained GBS patients, no increase in everyday physical activity or endurance related activities was found when using the RAM. It was surprising to notice that even baseline RAM values did not reveal significant differences between severely fatigued GBS patients and healthy controls. It was hypothesized that the RAM was not sensitive enough to detect changes in this group of patients. On the other hand, it might be hypothesized that changing the level of daily physical activity possibly is not an important adaptation strategy in these fatigued patients. It might be suggested that the maintenance of a normal activity pattern contributes to the long-lasting fatigue problems.

In our study evaluating central and peripheral components of fatigue during a 2-min sustained maximal voluntary contraction (MVC) **(chapter 4.4)**, we found that peripheral fatigue developed slower in patients, and muscle fiber conduction velocity was higher in patients, suggesting changes in muscle anatomy. It was suggested that peripheral changes contributed to the pathogenesis of fatigue. However, this experimental situation is different from normal daily life, in which a sustained MVC is used much less frequently than for example repetitive or cyclic muscle contractions. A test that had avoided blood occlusion in all subjects, like cyclic muscle contractions, additionally could have led to different results regarding muscle fiber conduction velocity or peripheral fatigue, and possibly would be more helpful to understand the involvement of muscle changes in normal daily life.

5.3.5 Conclusion about fatigue and GBS

Fatigue in apparently 'well-recovered' GBS patients has serious effects on cognitive, physical, and social functioning, and seriously affects quality of life. Although an important restriction of our research was the relatively small number of patients, and the absence of a non-fatigued recovered GBS control group, we were still able to study many different aspects involved in the pathogenesis of fatigue. Presently there are enough indications that 'several systems' are involved in post GBS fatigue. To illustrate the complexity of the pathogenesis of fatigue, we summarised some possible involved mechanisms / systems in fatigue in figure 3.

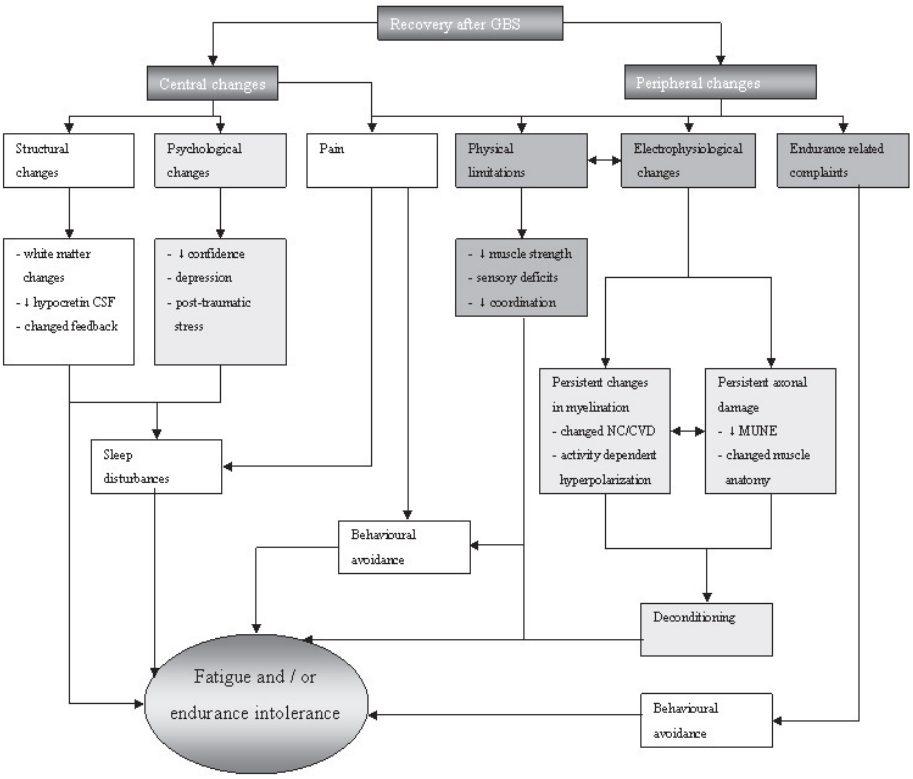

Figure 3. Possible contributors to residual fatigue after GBS.

= **not** yet seriously studied
= **partly** or indirectly studied
= **most** directly studied

Both changes in physical and psychological interactions play a role. Physical training is feasible and improves (long-term) physical fitness. However, changes in perceived fatigue and functioning seem to be more a result of increased confidence, rather then a result of improved fitness. Due to this positive effects obtained in the training intervention, but also due to the limited positive effects obtained in the amantadine trial, it can be concluded that fatigue can be reduced by different medical interventions. Attention for fatigue and increased self-confidence both have an important and ameliorating effect on fatigue.

Although fatigue has been regarded by some in the past as a medically unexplained symptom due to somatisation, we are now able to describe residual fatigue not only as a serious and multifactorial complaint, but also as a complaint that includes more than psychological aspects only, needing serious attention. Although additional studies aiming to elucidate

pathophysiological mechanisms and to develop new treatment strategies remain needed, we currently advise all stable but fatigued GBS patients to participate in a medically supervised physical training program.

5.3.6 Future perspectives about fatigue and GBS

Many factors contributing to residual fatigue after GBS are still unknown. Many new questions rised after the studies described in this thesis. A potentially life threatening disease like GBS might lead to different psychological disturbances. Whether and how these psychological changes are related to fatigue is presently unknown. Psychological testing and cognitive behavior therapy possibly could be of additional value. Although it is not suspected that many patients suffer from central lesions in the acute phase, it might still be interesting to evaluate the presence of white matter lesions in GBS patients, with special attention to the hypothalamic region. In addition, systematically evaluating CSF hypocretin titers might also be of some additional value, especially when comparing fatigued with non-fatigued patients. Presently, no data exist about changes in MUNE in fatigued and in non-fatigued GBS patients. It could be of additional value to further investigate this. Also the presence of CVD abnormalities alongside normal conventional NC studies in (non) severely fatigued patients suggests that further studies in (non) severely fatigued and non-fatigued GBS patients could be of additional value to elucidate whether changes in CVD contribute to residual fatigue.

We also found a high percentage of severe fatigue in mildly affected GBS patients, confirming an earlier conducted study,[9] but we did not perform electrophysiological studies in these patients. It might be useful to study activity-dependent hyperpolarization, since it is known that voluntary contraction produces activity-dependent membrane hyperpolarization of active motor axons.[46] This hyperpolarization can result in activity-dependent conduction blocks when the impulse transmission is (critically) lowered after apparently recovery from demyelination.[47;48] It would be interesting to study the possibility of these exercise induced nerve conduction blocks. This might play a role in fatigue and endurance intolerance, also in neurologically well-recovered GBS patients.

Additionally, not all aspects of possibly involved components of the peripheral nervous system are studied in this thesis. For example, no attention was paid at the neuromuscular junction. To date some (mainly non-clinical) observations indicate a possible role of the neuromuscular junction in the pathogenesis of GBS.[49;50] Whether disturbances of the neuromuscular junction may result in residual fatigue is unknown. Finally, there are some indications that residual changes in muscle anatomy may occur. This at least might raise the question whether needle muscle biopsies could be of additional value in future studies to elucidate the underlying mechanisms of fatigue.

Regarding treatment strategies, we performed a training study with a rather high intensity. Most positive effects of this training intervention were reached already after 6 weeks. This implicates the usefulness of a new training study, aiming to evaluate which training regimen

is most convenient for the patients. Since we only trained neurologically stable patients able to walk independently, it is unknown whether patients still recovering or patients in a worse neurological condition might benefit from any kind of (limited) training intervention. It now needs to be studied which intensity, frequency and duration of training offers the best strategy to relieve residual fatigue in a wide range of GBS patients.

5.4 TREATMENT OF GBS

5.4.1 Treatment in the acute phase of GBS

As described in the introduction **(chapter 1)**, it has been shown that GBS-patients unable to walk independently, may improve after plasma exchange (PE) and intravenous immune-globulins (IVIg). [51,52,53] IVIg is nowadays the preferred treatment.[54] The combination of IVIg with methylprednisolone (MP) does not result in significant better improvement, if not corrected for important prognostic factors. [54,55,56] Despite the availability of these treatments, (long-lasting) morbidity and mortality are still considerable. We concluded that new treatments should focus on suppressing disease activity as quickly as possible. This could lead to reduction in disease severity and to a more rapid recovery, presumably by preventing demyelination and (secondary) axonal damage. Therefore we conducted an open label pilot study as described in **chapter 2.2** on the additional effect of mycophenolate mofetil (MM, Cellcept®), when added to the combination of IVIg and MP. MM, a purine antagonist inhibiting B and T cell activity, was chosen because it is a fast acting immune-suppressive agent, possibly effective in CIDP and some other immune-mediated disorders, and without major side effects when combined with other immune-modulating drugs.[57] However, the combination with MM did not show significant improvement after 4 weeks and 6 months when compared to historical controls treated with the combination of IVIg-MP.

It is certainly not excluded that there are minor differences favouring this combined treatment since data obtained in a small group of non-randomised patients (n=26) were compared with historical data from a large group of patients (n=112). This comparison is mainly useful in detecting major differences and not in minor differences between groups. Additionally, although the dosage of MM is a standard dosage, a late start of MM or an inadequate duration of therapy might contribute to the lack of efficacy. In different studies aiming to treat patients with immune mediated diseases, MM was administered for at least 5 months up to 3 years.[22-24,30-32] However, we studied the acute and monophasic disease course in GBS, suggesting that the chosen duration of MM administration seems accurate. Nevertheless, in an acute disease with rapid onset like GBS, it might still be better to start treatment as early as practically possible.

Another explanation for a lack of major effect of MM might be that MM does not interfere with the crucial immunopathological pathways in GBS. To date there is increasing evidence that early changes in nerve fibers are accompanied by the presence of antiganglioside antibodies,

macrophage recruitment, and complement deposits, suggestive for a more selective antibody-mediated attack of the nerve rather than T cell mediated disease.[19,33-35] It has recently been shown in mouse models that inhibition of auto-reactive antibodies seems important in preventing activation of complement and macrophages.[19] It is known that treatment with IVIg or PE interferes with these auto-reactive antibodies and complement activation.[36] Although MM strongly inhibits T cell proliferation, still a possible contributor to the pathogenesis of GBS, it is likely that it does not play a major role in the inhibition of these auto-reactive antibodies and possibly does not interfere with complement activation.[20] Even if a T cell mediated immune response is important in different stages of GBS, it is reasonable to assume that important nerve damage already took place even before MM was administered and lymphocyte proliferation was inhibited.

The easy way of administration of MM, the rather good side-effect profile, even when combined with other immune-modulatory medication, seemed attractive as an additional treatment in the acute phase of GBS. Unfortunately, the results of this study were not encouraging to conduct a large randomized controlled trial studying the exact additional value of MM in combination with IVIg and MP.

5.4.2 Conclusions and future perspectives about treatments in GBS

MM seems not of additional value when combined with IVIg and MP in treatment of GBS patients unable to walk independently. In most of the conducted GBS trials, treatment was only started when patients were unable to walk independently (severe patients). A consequence might be that treatment starts to late at least in some patients. It is likely that in these patients, a serious immune-attack on the peripheral nerves has already been effectuated. It has never been studied whether immune-modulating medication (e.g. IVIg), administered as quickly as possible, results in better outcome. It can be hypothesized that prevention of nerve damage results in a faster and better neurological outcome than waiting for (partial) nerve recovery after nerve damage already has been established. Presently, it is also unknown whether repeated treatment sessions with IVIg would be better than one treatment session of 2 or 5 consecutive days alone. It might also be hypothesized that extended treatment leads to better outcome. This seems to be supported by results of a study favouring 6 compared to 3 days of 0.4g/kg/day IVIg (in patients with contra-indications for PE),[58] and in patients suffering from treatment related fluctuations, who might improve after a second administration of IVIg.[59] Another important question for future research is which GBS patients should be treated. Only one study evaluated the effect of PE in mild patients. It was shown that early treatment in these patients might be helpful. Since patients with mild disease might also suffer from long-lasting morbidity, including residual fatigue, new treatment studies should also focus on IVIg treatment of these patients.[60] Finally, although IVIg and PE are effective, at least in hastening recovery, it is still a matter of debate whether these treatments are the best treatment options for GBS. One should not be surprised when, based on new insights in the pathophysiology of GBS, medication inhibiting

or preventing complement activation or medication directly interfering with anti-ganglioside autoantibodies will conquer new and prominent places in the treatment of GBS in the nearby future.[49] Although some methodological and logistical problems have to be resolved before a treatment trial with these kind of drugs can be initiated, direct intervention with predefined immunopathological hallmarks may be an important future perspective in the treatment of GBS.

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CHAPTER 6

Summary / samenvatting

6.1 SUMMARY

Chapter 1 is the general introduction of this thesis, in which different aspects of the Guillain-Barré syndrome (GBS) are described. GBS is an acute post-infectious polyneuropathy, in which the immune system plays an important role. Insight in pathogenesis, clinical and electrophysiological features, functional outcome, and residual complaints is increasing. To date, fatigue is considered one of the most disabling residual symptoms, seriously affecting quality of life. The considerable percentages of (long-lasting) morbidity and mortality, as well as the residual complaints of severe fatigue, were the most important reasons to initiate this study, entitled; 'treatment of GBS and causes and treatment of residual fatigue'. Items discussed in the introduction range from diagnosis to pathogenesis and treatment of GBS. Attention is partially focused towards prognosis and outcome, in particular towards residual fatigue.

Chapter 2.1 is a review about the peripheral neuropathies GBS, chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN), all potentially treatable immune-mediated disorders. It was postulated that the use of appropriate assessment scales to evaluate the effects of treatment is essential. Recent clinical trials and Cochrane reviews on the effect of various treatments in patients with GBS, CIDP and MMN are discussed. It is concluded that intravenous immunoglobulin (IVIg) remains the cornerstone of treatment for GBS, but that combinations of treatment may be even more effective. Also studies on prognostic factors related to improvement are discussed. Whether patients with Miller Fisher syndrome or those with mild GBS should also be treated remains a matter of debate. IVIg is the best studied therapy for CIDP patients. IVIg is effective and is one of the most important treatments in these patients. Whether steroids are able to eradicate the disease besides suppressing disease activity in CIDP remains to be established. Some GBS patients have secondary deterioration or finally turn out to have CIDP; additional information in this group of patients may lead to more appropriate disease management. Most patients with CIDP and those with MMN need long-term treatment. New treatment strategies should also focus on the effect and the costs of treatment during long-term follow up.

In **chapter 2.2** a multi-center open label study on the additional effect of Mycophenolate Mofetil (MM) when added to the combination of IVIg and intravenous methylprednisolone (MP) is described. An important reason for this study was that, despite different treatments, GBS remains associated with considerable co-morbidity, mortality, and long-lasting residual deficits. The aims of this pilot study were to investigate the safety of this treatment combination and to study the potential additional effect of MM on the outcome in patients with GBS. Patients were treated for 6 consecutive weeks with MM in a dosage of 2g daily, and for 5 days with 0.4 g/kg of body weight IVIg and 500 mg MP daily. Because the IVIg-MP treatment group of the Dutch IVIg-MP trial was used as control group, identical outcome measures were used. The primary endpoint was the percentage of patients showing improvement with at least one grade on the GBS-disability scale, 4 weeks after inclusion. Twenty-six patients were included in analysis. Sixty-

two percent reached the primary endpoint in the group of patients treated with IVIg-MP-MM, as compared with 68% in the group treated with IVIg-MP (OR 1.3, 95% CI 0.6-3.2, p=0.54). None of the secondary endpoints showed any significant differences either. Complications and adverse events were comparable in both groups. It was concluded that although side effects were generally mild, there appears to be no significant improved outcome in the group of patients additionally treated with MM. It was concluded that new treatment studies are warranted.

In **chapter 3.1** a double-blind, placebo controlled, cross-over study is described, aiming to reduce fatigue with amantadine treatment, in 80 severely fatigued GBS patients. Fatigue was assessed using the Fatigue Severity Scale (FSS) and Fatigue Impact Scale (FIS). Patients could participate when they were severely fatigued (defined as FSS ≥ 5.0), and other possible confounding factors causing fatigue were excluded. Amantadine was not superior to placebo. However, some reduction of fatigue was observed both during the pre-treatment period and during the consecutive visits, both in the placebo and amantadine treated group, suggesting that increased attention for fatigue provided by this study already had an ameliorating influence on fatigue. Also secondary outcome measures including impact of fatigue, anxiety and depression, handicap, and quality of life did not reveal any significant difference. Fatigue scores obtained from the FSS (fatigue severity) as well as from the FIS (impact of fatigue on cognitive, physical, and social functioning) showed the same trends and changes during the consecutive follow-up visits.

In **chapter 3.2** the favourable results are discussed of a 12-week during bicycle exercise training in 20 severely fatigued patients. Sixteen patients were relatively good recovered from GBS and 4 had stable chronic inflammatory demyelinating polyneuropathy (CIDP). Self-reported fatigue scores as measured with the FSS, as well as aerobic capacity and isokinetic muscle strength improved significantly compared to baseline measurements. Daily physical activity, as measured with the Rotterdam activity monitor (RAM) showed that endurance related physical activities (e.g., duration of standing, walking, cycling and transitions from positions), did not show any significant improvement. It was suggested that changing the level of daily physical activity is not an important adaptation strategy in these fatigued patients. Maybe the maintenance of normal activity patterns contributes to fatigue.

Both GBS and CIDP patients showed comparable significant improvements on the FSS and FIS. Patients reported that increased physical activity in the past often resulted in increased neurological complaints, resembling the initial phase of GBS or CIDP, and resulting in threatening and anxious feelings of getting a relapse. This medical supervised training showed the opposite, patients became confident, and a negative circle seemed to be broken. It was suggested that the motivational aspect of increased social contacts with fellow-patients, besides promoting exercise adherence, has also lead to better psychological performances. Quality of life improved, mainly on the physically focused domains of the SF-36, suggesting being a result of improved physical fitness and muscle strength. Most patients (80%) were motivated to continue with regular training activities.

In **chapter 3.3** the long-term follow-up of fatigue, quality of life, physical fitness and muscle strength in GBS and CIDP patients is described, evaluated 2 years after training intervention. Mean reduction of self-reported fatigue compared to pre-training values was not different from the fatigue reduction observed directly after the training intervention. Also maximal 'power output' and muscle strength (except elbow flexion), remained significantly improved compared to pre-training values. It seemed that lower fatigue scores and improved functional scores were not a result of natural reduction of fatigue after GBS nor could be explained by ongoing reconditioning activities. Patients became more convinced of their physical capabilities, and were less afraid and more capable to perform rather high level (short-lasting) maximal physical effort, as measured by the increased maximal power output and muscle strength measurements. Presumably, training has taught the patients that increased physical activity can be performed without getting new neurological complaints or 'relapse' feelings, and thus helped them to take the barrier. Although some methodological remarks had to be made, these results favoured a long-term effect of a physical training intervention.

The results of a cross-sectional study within a prospective nationwide study in the Netherlands, in which the presence of fatigue after GBS was investigated, is described in **chapter 4.1**. The occurrence of severe fatigue, and its relation with disease course, clinical characteristics, and antecedent infections was studied in 100 GBS patients. Severe fatigue, again expressed as a mean FSS-score of at least 5.0, was present in 60% of all patients; it was more frequently present in females and in patients over 50 years ($p<0.01$). It was noticed that complaints of fatigue are already present rather early after the initial phase of disease. There was no significant relationship between fatigue severity and the level of functional disability at nadir (impaired muscle strength, GBS-disability score, and sensory deficits), antecedent events or infections in the initial phase of GBS, and time to follow-up after GBS. The percentage of severe fatigue was lower than reported before (60 vs 80%), which might be due to differences in methodology and in study population; the lower mean age of patients in this study, and the shorter duration of symptoms after GBS. It was suggested that patients who are still in the recovery phase of GBS might not be fully aware of other residual complaints like fatigue, mainly because they are not able to perform the same physical activities like neurologically 'recovered' patients may do.

In **chapter 4.2** we describe standardized motor and sensory nerve conduction (NC) studies in 13 well-recovered but fatigued GBS patients and 3 stable CIDP patients, mean 6.5 years after diagnosis. The aim was to determine whether residual subclinical peripheral nerve dysfunction is a possible underlying mechanism of fatigue. Motor NC measurements were performed in the peroneal, median, and ulnar nerve, and sensory NC measurements in the sural, median, and ulnar nerve. In contrast to CIDP, most NC values in GBS patients were remarkably within normal ranges. No correlations were found between the electrophysiological findings and the fatigue scores, muscle strength, functional scores, and quality of life. The single GBS patient with the lowest fatigue scores had the most NC abnormalities, which further illustrated the lack of a

relation between NC abnormalities and fatigue. This study demonstrated that severe fatigue in GBS is not explained by residual nerve dysfunction, using conventional NC measurements.

In **chapter 4.3** a study concerning conduction velocity distribution (CVD) in the median nerve in 13 fatigued but neurologically well-recovered GBS patients, 2 fatigued and stable CIDP patients, and 19 healthy controls is described. Although conventional NC studies showed no gross abnormalities in motor NC, it was shown that both GBS and CIDP patients had significant narrowing of the conduction velocity distribution, with loss of the fastest and slowest conducting fibers. These changes were most pronounced in the subgroup of patients with the lowest fatigue scores. We concluded that it was unlikely that the CVD changes contribute to persisting complaints of severe fatigue after GBS. However, CVD values of the (non)-severely fatigued GBS patients were only compared with healthy individuals, and not with non-fatigued GBS patients.

In **chapter 4.4** the relative contribution of peripheral and central factors during a fatiguing sustained maximal voluntary contraction (MVC), in ten (self-reported) fatigued but neurologically relatively 'well-recovered' GBS patients, and 12 age and sex matched healthy controls is described. Self-reported fatigue was evaluated using the FSS and Abbreviated Fatigue Questionnaire (AFQ). Physiological fatigue was defined as the decline of voluntary force during a 2-minute sustained MVC of the biceps brachii. The relative amounts of peripheral fatigue and central activation failure (CAF) were determined combining voluntary force and force responses to electrical stimulation. Additionally, surface EMG was used to determine muscle fiber conduction velocity (MFCV) during the contraction. During the first minute of sustained MVC, peripheral fatigue developed slower in patients, and central fatigue occurred in patients but not in controls. The MFCV was higher in patients. Because the initial MVC, the decrease of MVC, initial force response and the initial CAF did not significantly differ between both groups, it was suggested that mainly peripheral changes seem to be involved in the pathogenesis of fatigue after GBS. However, also central mechanisms cannot be ruled out.

In **chapter 4.5** a study is described aiming to obtain more insight into the mechanisms behind the favourable effects of physical exercise in a group of fatigued GBS and CIDP patients, and aiming to clarify the mutual relationships between the domains fatigue, physical fitness, objectively measured actual mobility, and perceived physical and mental functioning. Generally, no or only few relationships were found between physical fitness and the other four domains, which strongly suggested that physical fitness is not the main contributor to functional improvement during the treatment of these patients. More significant relationships were found between fatigue and perceived physical functioning, between perceived physical and mental functioning, and between perceived mental functioning and actual mobility. It was postulated that training results in improved fitness, which has to be attributed to the training program, but changes in perceived fatigue and functioning do not seem to be significantly influenced by improved fitness. This study stressed the presence and importance of additional effects of a physical training program, not directly related to its focus of increasing fitness. A

possible explanation could be that additional or secondary effects of the training program like - attention provided to the patients and the social aspect of training with fellow-patients and increased self-confidence - mainly caused these effects. The methodology and validity of data analysis in this non-controlled study was discussed, however, additional data exploration using other data analysis strategies showed that the main conclusions did not change when using other methods.

Chapter 5 is the general discussion describing the most important findings of the studies in this thesis related to what is known from literature. It starts with the discussion about several aspects of fatigue assessment. An arbitrarily dissection in central and peripheral fatigue is made. The relations between the occurrence, treatment and possible pathophysiological mechanisms of residual fatigue are discussed. Finally, the treatment options during the acute phase of GBS and future perspectives about GBS treatment are discussed.

6.2 SAMENVATTING

Hoofdstuk 1 is de algemene inleiding van dit proefschrift. Hierin worden verschillende aspecten van het Guillain-Barré syndroom (GBS) beschreven. GBS is een postinfectieuze polyneuropathie, waarbij het immuunsysteem (=afweersysteem) een belangrijke rol speelt. Er is voortschrijdend inzicht in de pathogenese (=onderliggende oorzaken) van deze ziekte. Daarnaast is inmiddels veel bekend over de verschillende klinische verschijningsvormen, over bevindingen bij klinisch neurofysiologisch onderzoek (=elektrisch spierzenuw onderzoek), over het uiteindelijke herstel en over het bestaan van de diverse neurologische restverschijnselen. Een van de belangrijkste restverschijnselen is vermoeidheid. De vermoeidheid is vaak dusdanig ernstig dat het bij menig GBS patiënt de kwaliteit van leven duidelijk vermindert. Het feit dat een aanzienlijk aantal GBS patiënten neurologische restverschijnselen houdt, in combinatie met het feit dat een groot percentage GBS patiënten vaak jarenlang last heeft van ernstige vermoeidheidsklachten, waren belangrijke redenen te starten met de diverse onderzoeken zoals beschreven in dit proefschrift; "behandeling van GBS en oorzaken en behandeling van het restverschijnsel vermoeidheid". De diverse onderwerpen die worden besproken in de introductie variëren van het stellen van de diagnose tot aan de pathogenese en behandeling van GBS. De prognose en restverschijnselen komen uitvoerig aan bod, met bijzondere aandacht voor het restverschijnsel vermoeidheid, omdat dit een van de meest invaliderende restverschijnselen is.

Hoofdstuk 2 gaat over de behandeling van immuungemedieerde polyneuropathieën in het algemeen, en van GBS in het bijzonder. **Hoofdstuk 2.1** betreft een overzichtsartikel over de polyneuropathieën GBS, chronische inflammatoire demyeliniserende polyneuropathie (CIDP), een chronische variant van GBS, en multifocale motore neuropathie (MMN). Het afweersysteem is betrokken bij deze 3 potentieel behandelbare polyneuropathieën. Het is van belang om goede onderzoeksschalen te gebruiken bij het evalueren van het effect van therapie. Onderzoeken bij grote aantallen GBS patiënten hebben aangetoond dat intraveneus toegediende immuunglobulinen (IVIg = behandeling met afweerstoffen via een infuus) de hoeksteen van de behandeling is. Daarnaast worden in het artikel diverse studies besproken waarin de rol van prognostische factoren (=factoren die de prognose van de ziekte kunnen voorspellen) op het herstel werden onderzocht. Het blijft een discussiepunt of patiënten met het Miller Fisher syndroom, een GBS variant waarbij oogbolmotoriek- en coördinatiestoornissen de belangrijkste kenmerken van de ziekte zijn, en of patiënten met een milde GBS variant al dan niet met IVIg behandeld moeten worden. Tenslotte werd beschreven dat IVIg op dit moment de best bestudeerde en werkzame therapie is voor de behandeling van CIDP. Met betrekking tot de behandeling van CIDP is het nog niet goed uitgezocht of corticosteroïden (=prednison-achtige medicijnen) naast het remmen en het onderdrukken van de ziekteactiviteit, de ziekte ook daadwerkelijk kunnen genezen. Er worden ook patiënten beschreven bij wie aanvankelijk de diagnose GBS werd gesteld, maar bij wie het uiteindelijk bleek te gaan om het (acute) begin van de chronische variant CIDP. Er bestaat duidelijk behoefte aan extra onderzoek bij deze groep

patiënten, mede omdat dit dan een adequatere behandeling tot gevolg zou kunnen hebben. In tegenstelling tot GBS moeten de meeste patiënten met CIDP en MMN zeer langdurig behandeld worden. Nieuwe behandelingsstrategieën zouden zich naast nieuwe behandelingsopties ook moeten richten op de hoge kosten die de verschillende langdurige behandelingen mee zich mee brengen.

In **hoofdstuk 2.2** wordt een zogeheten 'open-label' studie beschreven (een studie waarbij de zowel de onderzoekers als mede de patiënten weten welk medicijn wordt onderzocht) naar het additionele effect van Mycophenolaat Mofetil (MM), toegediend naast een combinatiebehandeling van IVIg en methylprednisolon (MP). Het betreft een studie waaraan verschillende grotere ziekenhuizen in Nederland en België hebben deelgenomen. MM is een zogeheten purine antagonist. Dit medicijn zorgt er voor dat B en T cellen van het immuunsysteem niet meer worden aangemaakt, in de veronderstelling dat de immuungemedieerde schade aan het perifere zenuwstelsel hierdoor beperkt blijft. Een belangrijke reden voor deze studie was, ondanks de reeds bestaande reeks behandelingsopties bij GBS, de ziekte nog steeds gepaard gaat met een aanzienlijk percentage aan co-morbiditeit, mortaliteit en langdurige restverschijnselen. Het doel van de studie was om te onderzoeken of de behandelingscombinatie met de drie eerder genoemde medicijnen een veilige combinatie lijkt, en om te kijken of deze combinatiebehandeling effectiever lijkt dan behandeling met IVIg en MP alleen (zonder MM). Patiënten werden gedurende 6 weken behandeld met MM, in een dosering van 2 gr per dag, in combinatie met 0.4 mg/kg lichaamsgewicht IVIg en 500 mg MP per dag, gedurende de eerste 5 dagen. Omdat de controle groep een historische controlegroep was uit een eerder uitgevoerde Nederlandse IVIg-MP trial, werden de uitkomstmaten precies hetzelfde gehouden. Het primaire eindpunt was het percentage patiënten dat ten minste 1 punt verbeterde op de 'GBS-disability' schaal, 4 weken na inclusie in de studie. Er werden in totaal 26 patiënten geïncludeerd in de analyse. Tweeënzestig procent van de patiënten behandeld met de combinatie MM-IVIg-MP behaalde het primaire eindpunt tegenover 68% in de historische controle groep, hetgeen niet significant verschillend was. Ook de secundaire uitkomstmaten lieten geen significante verschillen zien. Complicaties of ernstige bijwerkingen waren vergelijkbaar in beide groepen patiënten. Geconcludeerd werd dat, ondanks het vergelijkbare percentage aan bijwerkingen in beide groepen, er geen significant betere uitkomst was bij patiënten die additioneel werden behandeld met MM. Nieuwe studies naar de behandeling van GBS in de acute fase werden aanbevolen.

In **hoofdstuk 3** worden studies met betrekking tot de behandeling van vermoeidheid besproken. In **hoofdstuk 3.1** wordt een zogeheten dubbel blinde, placebo (=nepmedicijn) gecontroleerde, 'cross-over' studie beschreven naar het effect van amantadine op vermoeidheid. In totaal deden 80 ernstige vermoeide GBS patiënten mee aan deze studie. Vermoeidheid werd gemeten door gebruik te maken van de Fatigue Severity Scale (FSS = vermoeidheidsschaal met betrekking tot de ernst van de vermoeidheidsklachten) en de Fatigue Impact Scale (FIS = vermoeidheidsschaal met betrekking tot de gevolgen van vermoeidheid op lichamelijk,

cognitief en sociaal functioneren). Patiënten kwamen in aanmerking voor deelname aan de studie indien ze ernstig vermoeid waren (gedefinieerd als FSS score van 5 of meer), en andere mogelijke verklaringen voor vermoeidheid waren uitgesloten. Amantadine bleek niet beter dan placebo. Echter, er werd wel afname van de vermoeidheidsklachten geconstateerd gedurende de periode van 2 weken voorafgaand aan de daadwerkelijke behandeling met amantadine of placebo, en gedurende de opeenvolgende behandelingsperiodes met zowel amantadine als placebo. Er werd gesuggereerd dat de aandacht voor de vermoeidheidsklachten tijdens deze studie op zichzelf al een gunstig effect heeft op de ernst van de vermoeidheidsklachten. Ook de diverse secundaire uitkomstmaten zoals de gemeten gevolgen van vermoeidheid (FIS), angst en depressie, handicap, en kwaliteit van leven lieten geen significante verbetering zien. De vermoeidheidsscores zoals gemeten met de FSS en de FIS lieten dezelfde trends en veranderingen zien gedurende de opeenvolgende 'follow-up' bezoeken.

In **hoofdstuk 3.2** worden de gunstige resultaten van een 12 weken durende fietstraining bij 20 ernstig vermoeide patiënten beschreven. Zestien patiënten waren neurologisch redelijk goed hersteld van GBS en 4 patiënten bevonden zich in een stabiele fase van CIDP. Door de training werd de vermoeidheid (o.a. gemeten met de FSS) significant minder, en lieten een maximale lichamelijke conditietest en spierkrachtmetingen significante verbeteringen zien ten opzichte van metingen voorafgaand aan de training. Alleen de dagelijkse lichamelijke activiteit, gemeten met de Rotterdamse activiteiten monitor (RAM) liet geen significante verbetering zien in fysieke activiteiten (zoals staan, zitten, lopen, fietsen of positieveranderingen van bijvoorbeeld zitten naar staan) en in activiteiten waarin uithoudingsvermogen cq duurvermogen (bijvoorbeeld langer achtereen staan) een rol lijkt te spelen. Gesuggereerd werd dat veranderingen in het dagelijks patroon van lichamelijke activiteiten niet een belangrijk adaptatie mechanisme lijkt te zijn voor vermoeide GBS patiënten. Als mogelijke verklaring voor vermoeidheid werd zelfs het handhaven van een normaal dagelijks activiteiten patroon genoemd. De positieve effecten van de trainingsstudie in de GBS en CIDP patiënten waren vergelijkbaar. Patiënten gaven aan dat een toename van lichamelijke activiteit in het verleden vaak resulteerde in een toename van neurologische klachten. Deze klachten zouden weer lijken op de initiële klachten van GBS of CIDP, waardoor er het bedreigende en angstige gevoel ontstond om voor de tweede keer de ziekte te krijgen. Deze training liet echter het tegenovergestelde zien. Patiënten kregen meer zelfvertrouwen en een negatieve cirkel leek doorbroken. Gesuggereerd werd dat het motiverende aspect van toegenomen sociale contacten met lotgenoten, naast de stimulans van het bijwonen van alle trainingen, ook heeft bijgedragen aan de verbeterde psychologische prestaties. Tevens verbeterde de kwaliteit van leven significant, hetgeen met name was terug te voeren op een verbetering van de lichamelijk georiënteerde domeinen van de kwaliteit van leven vragenlijst. Hieruit werd geconcludeerd dat de verbeterde kwaliteit van leven tevens het gevolg zou kunnen zijn van een verbeterde lichamelijke conditie en spierkracht. Een ander belangrijk winstpunt van deze trainingsstudie was dat de meeste patiënten erg

gemotiveerd waren om door te gaan met reguliere trainingsactiviteiten na afloop van deze trainingsinterventie.

In **hoofdstuk 3.3** worden de lange-termijn bevindingen met betrekking tot vermoeidheid, kwaliteit van leven, en lichamelijke conditie en spierkracht beschreven, ruim 2 jaar na afloop van de trainingsstudie zoals beschreven in het voorgaande hoofdstuk 3.2. De gemiddelde daling van vermoeidheid, vergeleken met de vermoeidheidsscores voorafgaand aan de trainingsstudie was vergelijkbaar met de daling van vermoeidheid direct na afloop van de trainingsstudie. Ook maximale 'lichamelijke arbeid' en spierkracht (behalve buigkracht elleboog) bleven significant beter vergeleken met waarden voorafgaand aan de training. Het werd onwaarschijnlijk geacht dat de verbeterde vermoeidheidsscores en verbeterde scores op het gebied van lichamelijk en geestelijk functioneren het gevolg zijn van een natuurlijke reductie van vermoeidheidsklachten of het gevolg zijn van toegenomen lichamelijke activiteit leidend tot een betere conditie. Patiënten kregen meer zelfvertrouwen in hun lichamelijke mogelijkheden. Daarbij waren patiënten minder bang en zelfs beter in staat tot het leveren van (kortdurende) maximale lichamelijke inspanning, zoals gemeten met de maximale conditietest en spierkrachtonderzoek. Het zou kunnen zijn dat de training patiënten heeft overtuigd dat lichamelijke inspanning kan worden geleverd zonder dat er nieuwe neurologische klachten of klachten gelijkend op de initiële klachten van GBS of CIDP ontstaan. Hiermee leek een psychologische grens en negatieve cirkel van een afnemende lichamelijke conditie doorbroken. Ondanks enkele methodologische haken en ogen, kon worden geconcludeerd dat een lichamelijke trainingsstudie bij vermoeide GBS en CIDP patiënten een gunstig lange-termijn effect heeft.

In **hoofdstuk 4** worden de diverse studies besproken naar het voorkomen van vermoeidheid en naar de mogelijke onderliggende oorzaken van vermoeidheid. Allereerst worden de resultaten van een zogeheten cross-sectionele studie in een prospectieve studie in geheel Nederland beschreven in **hoofdstuk 4.1**. Het voorkomen van ernstige vermoeidheid, de relatie van vermoeidheid met het ziekte beloop, klinische karakteristieken en voorafgaande infecties werd bestudeerd bij 100 GBS patiënten. Ernstige vermoeidheid, wederom uitgedrukt als een FSS score van 5 of meer, was aanwezig bij 60% van alle patiënten. Daarbij was bij vrouwen en bij een patiënten ouder dan 50 jaar significant ($p<0.01$) vaker sprake van ernstige vermoeidheid. Klachten van ernstige vermoeidheid konden al vrij snel na de initiële fase van de ziekte optreden. Er werd geen significante relatie gevonden tussen de gemeten vermoeidheidsscores en de ernst van neurologische uitval tijdens het dieptepunt van de ziekte (spierkracht, 'GBS-disability score', en gevoelsstoornissen). Er werk ook geen relatie gevonden met aan GBS gerelateerde voorafgaande infecties en de duur van follow-up na de acute fase. Het percentage vermoeidheid was lager dan in een eerdere studie werd beschreven (60 vs 80%). Dit zou het gevolg kunnen zijn van methodologische verschillen en verschillen in studiepopulatie; de gemiddelde leeftijd in deze studie was lager en de follow-up duur na de initiële fase van de ziekte was significant korter. Gesuggereerd werd dat patiënten die zich nog steeds in een neurologische herstelfase bevinden zich misschien niet zozeer bewust zijn van of gehinderd

worden door vermoeidheidsklachten. Misschien is dit met name het gevolg van het feit dat deze patiënten nog niet in staat zijn dezelfde lichamelijke activiteiten te ontplooien als neurologisch herstelde patiënten.

In **hoofdstuk 4.2** wordt een elektrofysiologische studie beschreven. Het betreft een gestandaardiseerd motoor en sensoor zenuwgeleidingsonderzoek bij 13 goed herstelde maar vermoeide GBS patiënten en in 3 stabiele CIDP patiënten, gemiddeld 6,5 jaar na de diagnose. Het doel van deze studie was om te onderzoeken of resterende 'subklinische' disfunctie van het perifere zenuwstelsel een mogelijke onderliggende oorzaak van vermoeidheid zou kunnen zijn. Er werd motoor zenuwgeleidingsonderzoek verricht van de nervus peroneus (=een beenzenuw), de nervus medianus en ulnaris (=onderarmzenuwen). Het sensoor zenuwgeleidingsonderzoek werd verricht aan de nervus suralis (=een beenzenuw), en de nervus medianus en ulnaris. In tegenstelling tot de bevindingen bij de deelnemende CIDP patiënten vielen de meeste zenuwgeleidingsresultaten bij GBS patiënten opvallend vaak binnen de normaalwaarden. Er werd geen relatie gevonden tussen de bevindingen bij het zenuwgeleidingsonderzoek en de vermoeidheidsscores, spierkracht, lichamelijk functioneren, en kwaliteit van leven. De GBS patiënt met de laagste vermoeidheidsscores en de meeste afwijkingen bij het zenuwgeleidingsonderzoek was een goede illustratie voor het ontbreken van een relatie tussen afwijkingen bij het zenuwgeleidingsonderzoek en het restverschijnsel vermoeidheid. Uit deze studie kwam naar voren dat vermoeidheid na GBS niet verklaard lijkt te worden door resterende zenuwdisfunctie, gemeten op basis van conventioneel zenuwgele idingsonderzoek.

In **hoofdstuk 4.3** wordt een studie beschreven naar de verdeling van zenuwgeleidingssnelheden (CVD) in de nervus medianus, gemeten bij 13 vermoeide maar neurologisch herstelde GBS patiënten, 2 vermoeide en stabiele CIDP patiënten en 19 gezonde controles. Ondanks de eerdere bevindingen dat conventioneel zenuwgeleidingsonderzoek geen duidelijke afwijkingen liet zien bij vermoeide GBS patiënten (zie hoofdstuk 4.2), werd bij zowel de GBS als bij de CIDP patiënten een versmalling geconstateerd van de CVD, met verlies van zowel de snelst alsmede de langzaamst geleidende zenuwvezels. Deze bevindingen waren het meest uitgesproken in de subgroep van patiënten met de laagste vermoeidheidsscores. Geconcludeerd werd dat het onwaarschijnlijk lijkt dat persisterende klachten van vermoeidheid het gevolg zijn van een veranderde CVD, waarbij wel opgemerkt dient te worden dat deze groep vermoeide GBS patiënten alleen werd vergeleken met gezonde controles en niet met niet vermoeide GBS patiënten.

In **hoofdstuk 4.4** wordt de relatieve bijdrage van perifere en centrale factoren tijdens een 2-minuten durende maximale spiercontractie (MVC) beschreven bij 10 vermoeide maar neurologisch relatief goed herstelde GBS patiënten en 12 leeftijd en geslacht 'gematchte' gezonde controles. De door de patiënten gerapporteerde vermoeidheid werd geëvalueerd middels de FSS en de 'Abbreviated Fatigue Questionnaire' (AFQ = verkorte vermoeidheidsvrag enlijst). Fysiologische vermoeidheid werd gedefinieerd als de afname van vrijwillige maximale

kracht gedurende 2 minuten aanspannen van de musculus biceps brachii (bovenarmspier). De relatieve percentages van perifere vermoeidheid en van centrale activatie stoornis (CAF) werden afgeleid uit de combinatie van geleverde vrijwillige kracht en de respons op elektrische stimulatie. Aanvullend werd nog een oppervlakte EMG gebruikt om de spiervezelgeleidin gssnelheid te meten tijdens de maximale aanspanning. Gedurende de eerste minuut van de aanspanning was de ontwikkeling van perifere vermoeidheid lager bij patiënten dan bij controles, en trad centrale vermoeidheid alleen op bij patiënten. Daarnaast was de spierveze lgeleidingssnelheid hoger in patiënten. Aangezien de initiële MVC, de daling van de MVC, de initiële krachtrespons en de initiële CAF niet significant verschilden tussen beide groepen, werd gesuggereerd dat met name perifere veranderingen betrokken lijken te zijn bij de pathogenese van vermoeidheid na GBS. Echter, ook centrale vermoeidheid lijkt voor een deel betrokken te zijn in de pathogenese van vermoeidheid na GBS.

In **hoofdstuk 4.5** wordt een studie beschreven die als doel heeft meer inzicht te verkrijgen in de mechanismen die ten grondslag liggen aan de gunstige effecten van een 12 weken durend fiets trainingsprogramma bij een groep vermoeide GBS en CIDP patiënten **(zie hoofdstuk 3.2).** Wederzijdse relaties tussen 5 verschillende domeinen, te weten vermoeidheid, lichamelijke conditie, objectief gemeten dagelijkse mobiliteit, en ervaren fysiek en mentaal functioneren, werden nader geanalyseerd. Er werden hooguit enkele relaties gevonden tussen lichamelijke conditie en de andere 4 domeinen, waardoor gesuggereerd werd dat een verbeterde lichamelijke conditie niet de belangrijkste bijdragende factor is aan de functionele verbetering na afloop van de training. Meer significante relaties werden gevonden tussen vermoeidheid en het ervaren fysiek functioneren, en tussen het ervaren fysiek en mentaal functioneren, en tussen het ervaren mentaal functioneren en dagelijkse mobiliteit. Verondersteld werd dat training resulteert in een verbeterde lichamelijke conditie, hetgeen een direct gevolg is van de trainingsstudie, echter dat de veranderingen in ervaren vermoeidheid en het functioneren niet significant worden beïnvloed door een verbeterde lichamelijke conditie. Deze studie benadrukte de aanwezigheid en niet te onderschatten effecten van additionele effecten van een fysiek trainingsprogramma, niet direct gerelateerd aan het doel van de studie; een verbeterde lichamelijke conditie. Een mogelijke verklaring zou kunnen zijn dat met name additionele of secundaire effecten van de training zorgen voor de gunstige resultaten. Gedacht kan worden aan een aandachtseffect, toegenomen zelfvertrouwen, en de aan sociale aspecten van trainen met lotgenoten. De methodologie en validiteit van de data analyse in deze ongecontroleerde studie zou kunnen worden bediscussieerd, echter, ook additionele data exploratie leidde tot dezelfde conclusies.

Hoofdstuk 5 is de algemene discussie van het proefschrift. Relaties tussen de bevindingen rond het voorkomen van vermoeidheid, de behandeling en mogelijke onderliggende mechanismen van vermoeidheid, en nieuwe behandelingen van GBS in de acute fase worden beschreven en gerelateerd aan wat bekend is vanuit eerder gepubliceerd medisch wetenschappelijk onderzoek. Hieraan voorafgaand worden enkele aspecten beschreven

rondom het meten van vermoeidheid, en wordt een opsplitsing van vermoeidheid in centrale en perifere componenten nader uiteengezet. Naar aanleiding van de diverse studies beschreven in dit proefschrift kan worden geconcludeerd dat vermoeidheid het gevolg is van een combinatie van zowel geestelijke als lichamelijke factoren. Daarnaast bestaat er nu de mogelijkheid om deze vermoeidheidsklachten te behandelen.

LIST OF ABBREVIATIONS

AFQ = abbreviated fatigue questionnaire
AIDP = acute inflammatory demyelinating polyneuropathy
AMAN = acute motor axonal neuropathy
AMSAN = acute motor sensory axonal neuropathy
AP = action potential
CAF = central activation failure
CB = conduction block
CI = confidence interval
CIDP = chronic inflammatory demyelinating polyneuropathy
CSF = cerebrospinal fluid
CMAP = compound muscle action potential
CMV = cytomegalovirus
CVD = conduction velocity distribution
D = distal stimulation
DML = distal motor latency
EAN = experimental autoimmune neuritis
EBV = Epstein Barr virus
EMG = electromyography
F = force
FIS = fatigue impact scale
FSS = fatigue severity scale
GBS = Guillain-Barré syndrome
HAD = hospital anxiety and depression scale
HR = heart rate
ISI = interstimulus interval
IVIg = intravenous immunoglobulin
LLN = lower limit of normal
MCS = mental component summary
MFCV = muscle fiber conduction velocity
MFS = Miller Fisher syndrome
MGUS = monoclonal gammopathy of undetermined significance
MM = mycophenolate mofetil
MMN = multifocal motor neuropathy
MP = methylprednisolone
MRC = Medical Research Council
MU = motor unit
MUNE = motor unit number estimation

MVC = maximal voluntary contraction
NC = nerve conduction
NINCDS = National Institute of Neurological and Communicative Disorders and Stroke
OR = odds ratio
P = proximal stimulation
PCS = physical component summary
PE = plasma exchange
PF = peripheral fatigue
PO = power output
RAM = Rotterdam activity monitor
RHS = Rotterdam handicap scale
SEMG = surface electromyography
SF-36 = short form-36
SNP = single nucleotide polymorphism
ULN = upper limit of normal

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CURRICULUM VITAE

The author was born in Zutphen in the Netherlands on the 19th of April 1970. From 1982 to 1986 he attended the 'Gymnasium, Stedelijk Lyceum' in Zutphen, followed by the 'Atheneum, Stedelijk Lyceum' in Zutphen from 1986 to 1989. He studied medicine at the Erasmus University in Rotterdam, and finished his study in 1997. Hereafter he started his residency in Neurology at the Erasmus Medical Center Rotterdam. From 1998 he combined his residency with clinical research underlying this thesis at the Erasmus University Rotterdam. In December 2005 he will finish his residency, and from January 2006 he will be neurologist in the Jeroen Bosch Hospital in 's-Hertogenbosch.