The Guillain-Barré Syndrome

Clinical subgroups, prognosis and treatment

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Het Syndroom van Guillain-Barré:
Klinische subgroepen, prognose en behandeling
(met een samenvatting in het Nederlands)

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Toen Hij nu Kafarnaum binnenging,
kwam een hoofdman tot Hem met een bede, en zeide:
Here, mijn knecht ligt thuis, verlamd, met hevige pijn.
Jezus zeide tot hem: Zal ik komen en hem genezen?
(Matheus 8, vers 5-7.)

As Jesus went into Capernaum,
a centurion came up to Him, begging Him and saying,
Lord, my servant boy is lying at the house paralyzed
and distressed with intense pains. Jesus said to him,
shall I come and restore him?
(Matthew 8, 5-7.)

voor Maja, Eva, Eline en Mathijn
mijn ouders, schoonouders

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Contents

Outline of the thesis

The Guillain-Barré syndrome (GBS) is a heterogeneous disease. The literature dealing with the clinical pattern, prognosis and therapy of GBS is reviewed in the first Chapter. New studies may define subgroups within the clinically defined syndrome on the basis of clinical, epidemiological, electrophysiological, pathological, microbiological or immunological criteria. The data obtained during the Dutch GBS study evaluating the effect of intravenous immune globulins (IVIg) in comparison with plasma exchange (PE) gave the opportunity to further investigate the clinical symptoms and the laboratory features of 147 GBS patients; a general summary of these features is given in Chapter 2.

The first aim of this thesis was to evaluate whether clinical subgroups of GBS are present, to describe the clinical features in relation to the antecedent infections, electrodiagnostic and immunologic parameters and to evaluate treatment effect (PE or IVIg) in these subgroups. In Chapter 3 the clinical pattern of acute motor neuropathy and its relation with *Campylobacter jejuni* (*C. jejuni*) infection is described, while in Chapter 4 cytomegalovirus related GBS features are presented. In Chapter 5 the clinical and immunological differences between *C. jejuni* induced acute motor-sensory neuropathy and *C. jejuni* induced acute motor neuropathy are described and discussed.

Not only the clinical pattern is variable, but also the clinical course and outcome. The second objective was to identify prognostic factors related with outcome of GBS and to assess whether there are differences in prognostic factors between IVIg and PE treatment. The selection of patients with a poor prognosis may be helpful for future therapeutic studies (Chapter 6).

One of these new therapies may be the combination of IVIg together with intravenous methylprednisolone (MP). Therefore, the third aim was to evaluate whether this combined treatment was more effective than IVIg alone (Chapter 7).

Finally, 8 to 10% of the GBS patients experience a secondary deterioration after IVIg, MP-IVIg or PE treatment. Since it is important to know who are at risk for such fluctuations we assessed the risk factors for these treatment related fluctuations in GBS patients (Chapter 8).

A general discussion of the findings with recommendations for further research is given in Chapter 9.

Chapter 1

The Guillain-Barré Syndrome

an introduction to the history, diagnostic criteria, prognosis and treatment

'The Guillain-Barré syndrome is easy to diagnose but impossible to define'

(Munsat and Barnes)

Contents Chapter 1

1.1 Historical review

The Guillain-Barré syndrome is characterized by a subacute onset of muscle weakness, usually symmetrical, with loss of reflexes and variable sensory loss. Octave Landry was in 1859 the first who gave a detailed description of a syndrome now known as the Guillain-Barré syndrome. He described 10 patients and summed up the progression of the illness as follows: 'the paralysis may be preceded by a feeling of fatigue, tingling, and at times transitory cramps; the paralysis is ascending and spreads from the lower limbs to the upper with the weakness starting in the distal parts; the respiratory muscles may be involved leading to death; the sensory symptoms are usually minimal but the sensory and motor system may be equally involved'. Westphal was the first to use the term 'Landry's ascending paralysis'.

In 1916, during the first world war, the famous report of Guillain, Barré and Strohl appeared. Two French soldiers with a clinical picture similar to earlier descriptions of the illness were mentioned but with additional information on the cerebrospinal fluid. They found an excess of protein without an increase in cells in the cerebrospinal fluid (Guillain et al. 1916). This is now well known as the 'dissociation albuminocytologique'. In a publication in 1936 Guillain listed what he regarded as the main features of the disorder:

1. an onset characterized either by paralytic phenomena or paresthesias and/or pain, or all three, with or without premonitory symptoms such as a sore throat, malaise, digestive disturbances, and stiffness of muscles
2. motor disturbances leading to flaccid paralysis of the muscles of the lower limbs and later the trunk and upper limbs, the paralysis affecting chiefly the distal muscles of the limbs
3. fibrillary twitching, occasionally
4. slight atrophy of the distal muscles, occasionally
5. ataxia in a moderate number
6. abolition of tendon reflexes in the domain of the paralyzed muscles
7. subjective sensory disturbances such as pain, cramps, formication and numbness
8. rather minor, infrequent, and transitory objective changes in sensibility, both cutaneous and deep, especially at the periphery of the limbs
9. astereognosia, occasionally

10. difficulty and slowness in micturation and loss of perception of the passage of urine in a few cases, and sphincter disturbances in even fewer
11. transient palsy of cranial nerves, notably the VII th, and occasionally the extraocular nerves, the Vth, IXth, the Xth and the XIIth, sometimes leading to fleeting disturbances of phonation, swallowing, respiration, and cardiac rhythm.

Guillain insisted that the disorder was not fatal, thereby separating 'his' disorder from the disease pattern described by Landry. The patients with the ascending paralysis of Landry usually did not have facial weakness in contrast to the patients described by Guillain, Barré and Strohl and later others also used the presence of sensory loss to differentiate Landry's paralysis from the Guillain-Barré syndrome. Landry's paralysis was considered to be a strictly motor disorder and the Guillain-Barré syndrome (GBS) characterized by pain or other outspoken sensory disturbances (Haymaker, Kernohan, 1949).
In 1949 Webb Haymaker and James Kernohan reported 50 fatal cases under the title 'Landry-Guillain-Barré syndrome' and gave an overview of the literature of GBS. They pointed out that Landry in fact described more clinical forms than just the motor disorder. They emphasized that the clinical pattern of an acute neuropathy is very broad and that GBS is a disorder in which motor involvement is striking with a variable degree of sensory involvement. Moreover, they stated that GBS constitutes a certain narrow group within a broad spectrum due to the restrictions made by Guillain, Barré and Strohl on the amount of protein and the number of cells in the spinal fluid.
In their own series of 50 fatal GBS cases Haymaker and Kernohan observed that though some cases had been diagnosed as suffering from the Guillain-Barré syndrome and others from Landry's paralysis, all had a common pathology. They, therefore, proposed the use of the term Landry-Guillain-Barré syndrome. Their article reopened the discussion of the exact criteria of GBS.

1.2 Diagnostic criteria

In 1960 Osler and Sidell emphasized the importance of the criteria laid down by Guillain, Barré and Strohl. They presented clinical examples of patients who were unfortunately wrongly diagnosed as GBS and they made a plea to reject the cases with severe sensory loss, involvement of bladder and bowel and raised cells counts in the cerebrospinal fluid.

At the end of the seventies new diagnostic criteria for GBS were established (Asbury et al. 1978; Asbury, 1981). The criteria set up by a committee of the National Institute of Neurological and Communitive Disorders and Stroke with Dr Asbury as chairman and revised in 1990 are based on clinical, laboratory and electrodiagnostic criteria and are the following (Asbury, Cornblath, 1990):

I. Features required for diagnosis

a. progressive motor weakness of more than one limb. The degree ranges from minimal ataxia, to total paralysis of the legs, with or without mild ataxia, to total paralysis of the muscles of all four extremities and the trunk, bulbar and facial paralysis and external opthalmoplegia.

b. areflexia. Universal areflexia is the rule, though distal areflexia with definite hyporeflexia of the biceps and knee jerks will suffice if other features are consistent.

II. Features strongly supportive of the diagnosis

A. clinical features

1. Progression. Symptoms and signs of motor weakness develop rapidly but cease to progress by four weeks into the illness. Approximately 50 % will reach the nadir by two weeks, 80% by three weeks and 90% by four weeks.
2. Relative symmetry.
3. Mild sensory symptoms and signs.
4. Cranial nerve involvement. Facial weakness occurs in approximately 50% and is frequently bilateral. Other cranial nerves may be involved, particularly those innervating the tongue and muscles of deglutition, and sometimes the extraocular motor nerves. On occasion (less than 5%) the neuropathy may begin in the nerves to the extraocular muscles or other cranial nerves.
5. Recovery. It usually begins two to four weeks after progression stops. Recovery may be delayed for months.
6. Autonomic dysfunction. Exclude other causes for these symptoms, such as pulmonary embolism.
7. Absence of fever at onset of neuritic symptoms.

Variants

1. Fever at onset of neuritic symptoms.
2. Severe sensory loss with pain.
3. Progression beyond four weeks.

4. Cessation of progression without recovery or with major permanent residual deficit remaining.
5. Sphincter dysfunction. Transient bladder paralysis may occur during the evolution of symptoms.
6. Central nervous system involvement. Need not exclude the diagnosis if other features are typical.

The additional laboratory and electrodiagnostic criteria are:

B. Cerebrospinal fluid (CSF) features strongly supportive of the diagnosis

1. CSF protein. After the first week of symptoms, CSF protein is elevated or has been shown to rise on serial lumbar punctures.
2. CSF cells. Counts of 10 or fewer mononuclear leukocytes/mm3 in CSF.

Variants

1. No CSF protein rise in the period of one to ten weeks after the onset of symptoms (rare).
2. Counts of 11 to 50 (≤ 150/3 cells) mononuclear leukocytes/mm3 in CSF.

C Electrodiagnostic features strongly supportive of the diagnosis

Approximately 80% will have evidence of nerve conduction slowing or block at some point during the illness. Conduction velocity is usually less than 60% of normal, but the process is patchy and not all nerves are effected. Distal latencies may be increased to as much as three times normal. Use of F-wave responses often gives good indication of slowing over proximal portions of nerve trunks and roots. Up to 20 % of patients will have normal conduction studies. Conduction studies may not become abnormal until several weeks into the illness.

III Features casting doubt on the diagnosis

1. Marked persistent asymmetry of weakness.
2. Persistent bladder or bowel dysfunction.
3. Bladder or bowel dysfunction at onset.
4. More than 50 mononuclear leukocytes/mm3 in CSF.
5. Presence of polymorphonuclear leukocytes in CSF.
6. Sharp sensory level.

IV Features that rule out the diagnosis

1. A current history of hexocarbon abuse. This includes huffing of paint lacquer vapors or addictive glue sniffing.
2. Abnormal porphyrin metabolism indicating a diagnosis of acute intermittent porphyria.
3. A history or finding of recent diphteric infection, either faucial or wound, with or without myocarditis.
4. Features clinically consistent with lead neuropathy (upper limb weakness with prominent wrist drop; may be asymmetrical) and evidence of lead intoxication.
5. The occurrence of a purely sensory syndrome.
6. A definite diagnosis of a condition such as poliomyelitis, botulism, hysterical paralysis, or toxic neuropathy (e.g. from nitrofurantoin, dapson, or organophosphorus compounds) which occasionally may be confused with GBS.

1.3 Clinical implications for the diagnosis of the Guillain-Barré syndrome in the daily neurological setting

Since immunomodulating therapies have become available, early recognition of GBS is of utmost importance. It is likely that early treatment may improve outcome (see Chapter 6: the prognosis of GBS). Since there is no pathognomonic test diagnostic criteria for GBS were developed. The first point is to differentiate GBS from other causes of acute or subacute motor weakness. The (sub)acute occurrence of motor weakness in the arms and/or legs may have several causes and the classification of these causes is based on the localization of the lesion (table 1).

level	examples
• brainstem/spinal cord	myelitis transversa
	infarct of the pons
• lower motor neuron	poliomyelitis
• peripheral nerve	Guillain-Barré syndrome
	toxins
• neuromuscular transmission	myasthenia gravis
	botulism
	Lambert-Eaton
• muscle	polymyositis
	rhabdomyolysis

Table 1. Causes of acute motor weakness

Acute weakness caused by poliomyelitis or by muscle diseases are quite rare in developed countries. The most common cause of an acutely evolving quadriparesis is GBS. The classical presentation of ascending motor weakness accompanied by areflexia, sensory disturbances with mild objective sensory findings, and preservation of bowel and bladder function provides a firm basis for the diagnosis. For those with an atypical presentation the clinician should wonder whether the patient has GBS since this has therapeutical implications.

History	Exclude other causes
• 1. nausea, vomiting	thallium intoxication
	organophosphate intoxication
	acute intermittent porphyria
	lead poisoning
• 2. weakness occurring within a few hours without sensory loss/deficit	hypokaliemia
	hypermagnesemia
	hypophosphatemia
	myasthenia gravis
	botulism
• 3. Bladder/bowel dysfunction	spinal cord lesion
Neurological examination	
• 4. prominent asymmetric weakness	poliomyelitis
	vasculitic neuropathies
	mononeuritis multiplex
• 5. Fever	poliomyelitis
	vasculitis
	hyperthyroidism
• 6. Sharp level of sensory loss; Dispropriate weakness of legs in comparison to the arms;	spinal cord lesion -lumbar, thoracal
Severe weakness of arms and legs without cranial nerve involvement	-cervical
• 7. recent loss of hair	thallium intoxication
• 8. skin, kidney and/or lung lesions	vasculitis

Table 2. Differential diagnosis of acute muscle weakness with low or absent reflexes according to presenting signs or symptoms.

Moreover, the above mentioned criteria may be insufficient and if applied too stringently may exclude patients who will benefit from immunomodulating treatment.
By history and neurological investigation other causes of acute muscle weakness can be excluded. A number of red flags are shown in table 2.

The standard teaching that GBS produces an acellular spinal fluid with increased protein is a common source of confusion. Most patients develop this 'albuminocytologic dissociation' during the course of their illness, but the protein concentration is only elevated in half of the patients when the lumbar puncture is performed in the first week after onset of symptoms, and the cell count is occasionally increased. The major indication for a lumbar puncture at the time of diagnosis is to exclude other causes of acute motor weakness. A cerebrospinal fluid pleiocytosis provokes suspicion of other causes such as poliomyelitis, myelitis transversa, vasculitis or GBS related to human immunodeficiency virus or *Borrelia burgdorferi* infection. If the history or physical examination is suggestive of a spinal cord lesion a lumbar puncture should not be performed until a magnetic resonance imaging of the spinal cord has ruled out a lesion compressing the spinal cord.
Nerve conduction studies are a useful adjunct in the diagnosis of the Guillain-Barré syndrome, but have its limitations. In our opinion the electrodiagnostic criteria of Asbury and Cornblath (1990) have put too much emphasis on conduction block and conduction slowing. In the first week of the illness nerve conduction may be normal. In a longitudinal follow-up in 135 GBS patients Meulstee et al (1994) showed that in the first week the distal motor latencies and compound muscle action potentials after distal stimulation were abnormal in more than 80% of the patients. Slowed motor and sensory conduction velocities were present in over 50% of the patients.
A conduction block, considered to be specific for demyelination, was however only found in 31% for the ulnar nerve, 37% for the median and 15% for the peroneal nerve following the rigid criteria proposed by Asbury and Cornblath (1990). Meulstee and colleagues concluded that the optimal time for final electrodiagnostic testing is at nadir, which corresponds usually with 2 weeks after onset of muscle weakness. Since the effect of treatment is predominantly seen if treatment starts within the first two weeks after onset of weakness the EMG at 2 weeks is predominantly confirmatory with respect to the diagnosis. Possibly MRI of the cauda equina may contribute to the diagnosis of GBS in early cases and in those where electrophysiologic abnormalities are equivocal.

Gorson et al. (1996) recently reported that 18 of 19 patients with 'typical' GBS had nerve root enhancement of the cauda equina on gadolinium-enhanced lumbosacral MRI. In two of these 18 patients the EMGs were normal except for slightly prolonged F-responses and decreased recruitment pattern. Moreover, nerve root enhancement correlated with presence of pain, disability grade and duration of recovery. Unfortunately, this method is not sensitive for the diagnosis of patients presenting with some variants of GBS.

1.4 Clinical pattern

The incidence of GBS varies from 1 to 2 per 100.000 persons per year. In the paragraph on the history it has already been mentioned that it has been attempted to narrow the clinical picture as much as possible, but GBS remains a heterogeneous disease. The extent of disability ranges from some difficulty in walking and/or climbing stairs to an almost explosive onset leading to tetraplegia within 24 to 48 hours. Sensory symptoms often start before onset of muscle weakness but in general loss of sensation is mild, but may occasionally be severe. Pain is a common symptom occurring in up to 72% of cases. The types of pain can vary from dysaesthesia, axial and radicular pain, meningism, myalgia, joint pain to visceral discomfort (Ropper, Shanini 1984; Pentland, Donald, 1994).

In the majority of the patients weakness begins in the legs. It often starts distally, but it may begin in the proximal muscles or have a global distribution (van der Meché et al. 1991; Ropper et al. 1991; Gibbels, Giebisch, 1992). The muscle weakness remains mild in 25% of the GBS patients, whereas severe involvement leading to respiratory insufficiency occurs in 25-35% of the patients. During the course of the disease the sensory system may be involved or completely spared.

Autonomic dysfunction is often present (de Jager, Sluiter, 1991; Zochodne, 1994). The most common presentations of autonomic dysfunction are hypertension and tachycardia. Other signs, such as cardiac arrhythmias, blood pressure fluctuations, gastrointestinal dysfunction, sweating dysfunction and urinary retention may also occur. They are usually mild but may occasionally be life-threatening. Patients with severe motor weakness are at risk for such events (de Jager, Sluiter, 1991; Zochodne, 1994). A recent study showed, however, that vagal overreactivity assessed by eyeball pressure testing could be demonstrated in 30% of GBS patients and did not only occur in severely affected patients (Flachenecker et al. 1996).

1.5 Variants and subgroups within the clinically defined syndrome

Several clinical variants have been recognized: the Miller Fisher syndrome, characterized by ophthalmoplegia, ataxia, and areflexia; a lower bulbar variant with weakness starting in the facial and bulbar muscles; and syndromes with restricted disturbances such as pure ophthalmoplegia and pure pandysautonomia (Ropper et al. 1991; Ropper, 1994). Furthermore, syndromes are recognized with a similar time course that may possibly be included as variants: pure sensory loss, pure ataxia and paraparesis (Ropper et al. 1991; Ropper, 1994).

Some of these variants are associated with specific antibodies against gangliosides. Gangliosides or glycolipids are present in human peripheral nerves and are implicated as antigens in immune-mediated neuropathies (Dalakas, Quarles, 1996). Anti-GQ1b IgG antibodies are specifically seen in GBS patients with ophthalmoplegia, either in the context of the Miller Fisher syndrome, in patients with pure ophthalmoplegia or in classical GBS patients with severe oculomotor involvement (Chiba et al. 1993; Willison et al. 1993; Yuki et al. 1993a; Jacobs et al. 1995). Anti-GM1 antibodies and anti-GD1a antibodies have been associated with acute or chronic motor neuropathy (Yuki et al. 1990; van den Berg et al. 1992; Yuki et al. 1993c; Irie et al. 1994; Kornberg et al. 1994; Carpo et al. 1996). Further, a patient has been described with a pharyngeal-cervical-brachial variant of GBS who had anti-GT1a and anti-GD1a IgG antibodies in the serum (Mizoguchi et al. 1994). Acute oropharyngeal palsy has been associated with antibodies to GQ1b and GT1a gangliosides (O'Leary et al. 1996). Finally, an acute ataxic neuropathy has been linked with cross-reactive antibodies to GD1b and GD3 gangliosides (Willison et al. 1994).

1.6 Antecedent events

Upper respiratory tract and gastrointestinal symptoms precede the onset of weakness in about two-third of the patients (Winer et al. 1988b; Ropper, 1992; Parry, 1993; Hartung et al. 1995b). The interval between these symptoms and onset of weakness is usually one to three weeks.

Many organisms have been related with the occurrence of GBS; especially herpes simplex, cytomegalovirus (CMV), varicella zoster, Epstein-Barr virus, *Mycoplasma pneumoniae* and *Campylobacter jejuni* infection (Winer et al. 1988b; Ropper et al. 1991; Parry, 1993).

1.7 Prognosis

In 25% of the patients the disease is mild and these patients will remain ambulant during the course of the disease. In the other patients the disease progresses and finally, artificial ventilation is necessary in 20-30% of the patients (McKhann et al. 1988; van der Meché et al. 1992; Ropper, 1992; Hund et al. 1993). After a period of progression a plateau phase follows, which may take several weeks. Subsequently recovery starts. For those who are no longer able to walk independently anymore the median time towards being able to do so again takes about 85 days without therapy (McKhann et al. 1988). Recent data have shown that the percentage of patients who fully recover is lower than previously thought, about 60-65% in stead of 85% (de Jager, Minderhoud 1991; Kleyweg 1990, thesis). Twenty-five to 30% of the patients have mild disability and 5% are left with severe residual deficits: they remain bed or wheelchair bound. De Jager and Minderhoud (1991) reported on the residual signs in a group of 57 patients admitted to their hospital during a 28-year period. All these patients were severely afflicted and needed artificial respiration. After a follow-up period varying from two to 24 years 35% of the patients had recovered completely, 35% had minimal residual deficits and 30% had a moderate or severe residual paresis. Weakness was most profound in distal muscles and in the muscles innervated by nerves running along an entrapment site. Sensory signs were still present in 49% of the patients. More than half of the patients considered themselves to be cured, although physical examination showed that only 35% had completely recovered. Fifteen percent of the adult patients did not return to work.

Can one predict those who will have a poor outcome? Recent studies have shown that older age, need for ventilatory support, a severe, rapidly progressive course of weakness and low compound muscle action potentials after distal nerve stimulation (EMG) are predictors of poor outcome (Ropper, 1986; Gruener et al. 1987; McKhann et al. 1988; Winer et al. 1988a; Miller et al. 1988; Smith, Hughes, 1992; Palace, Hughes, 1994; Rees et al. 1995b).

1.8 Treatment

1.8.1 General medical care

Supportive treatment is of utmost importance for the optimum management of GBS patients. The patients must be monitored carefully and patients with declining pulmonary function or autonomic instability must be admitted to

an intensive care unit. The clinical condition can deteriorate rapidly, therefore vital capacity should be measured every 4 to 6 hours. If vital capacity declines to 15 ml/kg elective intubation is performed. Severe bilateral facial palsy can intervene with the proper assessment of the vital capacity. When bulbar weakness is present one may intubate the patient earlier to prevent aspiration or obstructive apnea.
General supportive care with reference to feeding, prevention of infections, thrombosis, decubitus and protection against pressure palsies is of primary importance.
Pulmonary embolism occurs in up to 5% of the immobilized GBS patients (Hund et al. 1993; Ropper, 1994). To prevent venous thrombosis and pulmonary embolism in bedridden GBS patients treatment with subcutaneous heparin 5000 U twice daily is advised, when the patient will be immobilized for a long time coumarin derivates are usually necessary.
Sinus tachycardia is common and generally does not require treatment. Bradycardias may sometimes occur following tracheal suction, indicating the need for continuous cardiac monitoring. A complete heartblock or sinus arrest, although rare, may require a temporary endocardial pacemaker.
Treatment of pain is usually disappointing. If the pain is mainly musculoskeletal non-steroidal anti-inflammatory drugs are useful. Neuropathic pain responds poorly to these drugs and is often resistant to carbamazepine and amitriptyline. Airfilled mattresses have been found to be a highly important measure in reducing pain. Physiotherapy is needed to prevent contractures. Finally, it is important to give psychological support to the patient and the family; the GBS patient organization may be of help in this respect.

1.8.2 Immunomodulatory treatment

Therapy should be focussed on the prevention of long-term disability. Therapy should stop the progressive course as soon as possible. More adverse events occur in those who are severely affected. A less severe course of the disease may therefore result in earlier recovery and less complications.

1.8.2.1 Corticosteroids

Corticosteroids have been beneficial in the treatment of chronic inflammatory demyelinating disease with features similar to those of GBS and have been applied for over 40 years in GBS. They have been the mainstay of treatment for acute GBS. Two randomized, controlled trials, one using oral

corticosteroids for two weeks and the other, using a short course of high-dose intravenous methylprednisolone intravenously showed that these drugs given early in GBS are not effective (Hughes et al. 1978; Guillain-Barré Syndrome Steroid Trial Group, 1993). In the GBS steroid study (1993) 242 adult patients were randomized to receive either 500 mg intravenous methylprednisolone (MP) per day or a placebo for 5 days. Patients were diagnosed by standard clinical criteria and entered the trial within 15 days of onset of neurological symptoms. No significant difference in any outcome variable between patients treated with MP and those given placebo was found. The most important finding was the difference between the groups in disability grade at 4 weeks after randomization, which was only a 0.06 grade (95% confidence interval (c.i.) - 0.23 to 0.36) greater improvement in the MP than the placebo group. The 39 patients in the MP group who required ventilation did so for a median time of 18 days, 9 days shorter than the 44 patients who had a placebo and required ventilation (95% c.i. -9.6 to 27.6). The median time to walk unaided was 38 days in the MP patients and 50 days in the placebo patients (difference 12 days, (95% c.i. - 21.3 to 45.3). Thus the use of corticosteroids alone in GBS currently lacks justification (Ropper, 1992;

Guillain-Barré Syndrome Steroid Trial Group, 1993). Shortly after this conclusion the results of our pilot-study evaluating the additional effect of intravenous methylprednisolone in the treatment of GBS with intravenous immune
globulins became available (The Dutch Guillain-Barré Study Group, 1994).

1.8.2.2 Plasmapheresis

Plasmapheresis (PE) is a technique that permits the selective removal of plasma constituents from the circulation. Separation is achieved by either a centrifugal cell separator or filtration across a semipermeable membrane. Adequate amounts of replacement fluids are needed to provide hemodynamic stability. In general dilute solutions of albumin or fractioned albumin are used. PE is thought to remove or dilute circulating factors implicated in the pathogenesis of GBS.

Two large clinical studies demonstrated beneficial effects of PE in patients with severe GBS, in terms of shortening the time to recovery (The Guillain-Barré study group in North America, 1985; French Cooperative Group on plasma exchange in Guillain-Barré Syndrome, 1987). The North American trial included 245 patients and the French trial 220 patients. The time on the

respirator was significantly shorter in the plasma exchanged groups in comparison to the placebo treated group and the median time until independent locomotion was decreased from 85 to 53 days in the North American study and from 110 days to 70 days in the French trial.
PE was particularly effective in patients who received this treatment within 7 days of onset and for patients who required mechanical ventilation after entry into the study.
Long-term benefit from PE was observed in the French study, as demonstrated by full recovery of muscular strength at one year in 71% in the PE treated group versus 52% in the control group ($p = 0.007$; adjusted for prognostic factors). However, PE did not affect the incidence of residual severe motor disability (11% in both groups) (French Cooperative Group on plasma exchange in Guillain-Barré Syndrome, 1992).
Contraindications for PE are cardiovascular dysautonomia, recent myocardial infarction and sepsis. Bouguet et al (1993) reported the complications of PE in the French GBS trial. The study was based on 220 patients allocated either to PE ($n = 109$) or placebo ($n = 111$). A total of 105 patients underwent 390 plasma exchanges. Fifty-five patients received albumin (208 sessions) as replacement fluid, and 50 patients received fresh frozen plasma (182 sessions). A total of 253 adverse incidents were recorded. At least one adverse incident occurred in 39% of PE sessions among 80 (76%) patients. In 15 patients, plasma exchange treatment had to be discontinued because of severe intolerance (six patients, including three patients with severe bradycardias), intercurrent complications, mainly infections (four patients), and technical difficulties. One patient with pneumococcal septicaemia and pneumonia died during the second plasma exchange session. Fresh frozen plasma was associated with more adverse incidents than albumin (135 vs. 118, $p = 0.008$). The occurrence of adverse events was also related to the hemoglobin level assessed before the PE session ($p = 0.04$). Otherwise, the frequency of adverse effects did not depend on technical modalities (type of equipment, anticoagulation). Age, sex, previous history, severity of muscle weakness, and the need for mechanical ventilation, as assessed on inclusion in the study, did not modify the risk of adverse effects. They concluded that fresh frozen plasma should be abandoned as replacement fluid in plasma exchanges of GBS patients. They also underlined the need for close monitoring of patients during sessions and, especially, for attention to contraindications. Some adverse incidents could be attributed to the underlying disease rather than to the plasma exchange session (Bouget et al. 1993).

In general, it is estimated that there are three deaths per 10.000 procedures (Hund et al. 1993). Therefore it is reasonable to reserve PE for patients who are unable to walk or who are rapidly worsening, although recent data of an interim analysis of a study of PE in mildly affected GBS patients suggest that a short course of PE results in earlier recovery than without treatment (Raphael et al. 1996).

1.8.2.3 Intravenous immune globulins (IVIg)

IVIg has shown to be effective in a variety of immune-mediated diseases (Thornton, Griggs, 1994; van der Meché, Van Doorn, 1995). Based on positive results in chronic inflammatory demyelinating polyneuropathies and an uncontrolled pilot study in GBS (Kleyweg et al. 1988) a multicentre study comparing IVIg with PE was conducted in the Netherlands. After 150 patients had been treated, function had improved by one grade or more in 34% of the patients treated with PE, as compared with 53% of those treated with IVIg (difference, 19%; 95% c.i. - 3 to 34%; $p = 0.024$). The median time to improvement by one grade was 41 days with PE and 27 days with IVIg ($p = 0.05$). Also other secondary criteria favored IVIg: the proportion of patients with multiple complications ($p < 0.01$) and the proportion of patients needing artificial respiration in the second week after start of treatment ($p < 0.05$). Based on the main outcome criterion it was concluded that in acute GBS, treatment with IVIg is at least as effective as PE. Other small studies report similar conclusions, also in children (Urtasun et al. 1992; Vallee et al. 1993; Notarangelo et al. 1993; Kamei et al. 1993; Jackson et al. 1993; Ishikawa et al. 1993; Andersen, 1993; Vajsar et al. 1994; al-Qudah, 1994; Bril et al. 1996). However, some other studies mentioned worsening during or after IVIg treatment (Irani et al. 1993; Castro, Ropper, 1993), which even prompted an editorial suggesting not to use IVIg in GBS (Bleck, 1993). Recently, a large multicentre study co-ordinated by Prof. Dr R.A.C. Hughes (UK) comparing IVIg with plasma exchange and plasma exchange followed by IVIg has confirmed the efficacy of IVIg (Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group 1997).

1.8.2.4 Treatment related fluctuations

Treatment related fluctuations after PE (Osterman et al. 1986; Ropper et al. 1988; Osterman et al. 1988) or IVIg (Kleyweg, van der Meché, 1991; Irani et al. 1993) have been reported to occur in about 8-10% of the patients. These fluctuations are considered to be additional evidence for the beneficial effect of PE and IVIg. In the 147 patients who took part in the Dutch GBS trial comparing IVIg with PE five of 72 patients in the PE group and nine of 74 in the IVIg group showed such fluctuations.

Chapter 2

The clinical and laboratory features of 172 patients with Guillain-Barré syndrome

(unpublished data)

'Spectrum bias is the tendency for the effectiveness of a test (or treatment) to vary as a function of clinical, pathologic, or comorbid variables including disease severity'

(Ransohoff and Fernstein)

Contents Chapter 2

2.1. Introduction

Guillain (1936) stated that the Guillain-Barré syndrome (GBS) is easy to recognize, but since then there has been much debate about the clinical findings defining GBS. In 1990 Asbury and Cornblath defined the new and presently used diagnostic criteria of GBS. Since GBS encompasses a heterogeneous group, subgroups may be defined on the basis of electrophysiological, pathological, immunological or microbiological factors. In this thesis the clinical variability in relation to antecedent infections will be emphasized. Therefore, in this chapter the clinical and laboratory features of 172 patients, who were followed prospectively for at least 6 months, are presented.

2.2 Epidemiology

2.2.1 Age and sex

The age at onset of GBS varied in our study from 5 to 81 years (figure 1). The mean age was 50 years. It has to be noted that children are underrepresented, which is caused by the inclusion criteria.
There were 85 (49%) males and 87 (51%) females.

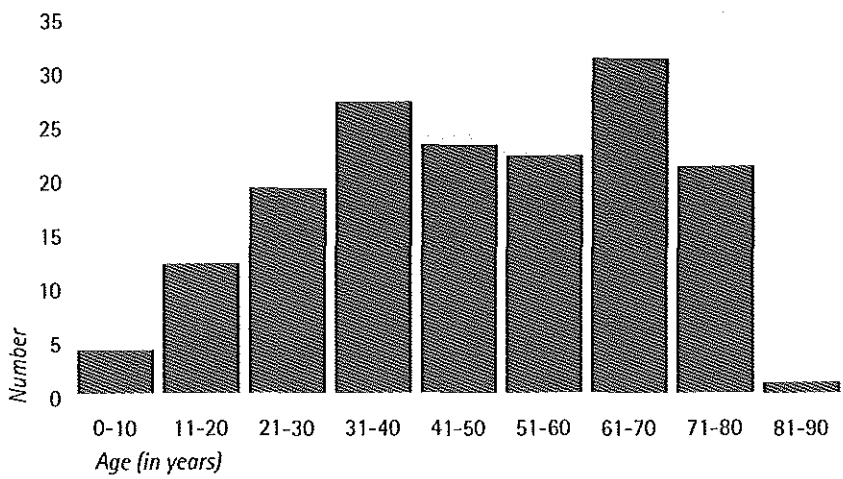


Figure 1. The age distribution of 172 GBS patients.

2.2.2 Seasonal distribution

An onset of GBS tended to occur more frequently in winter and autumn, however this tendency was not significant. The cases per month are shown in figure 2.

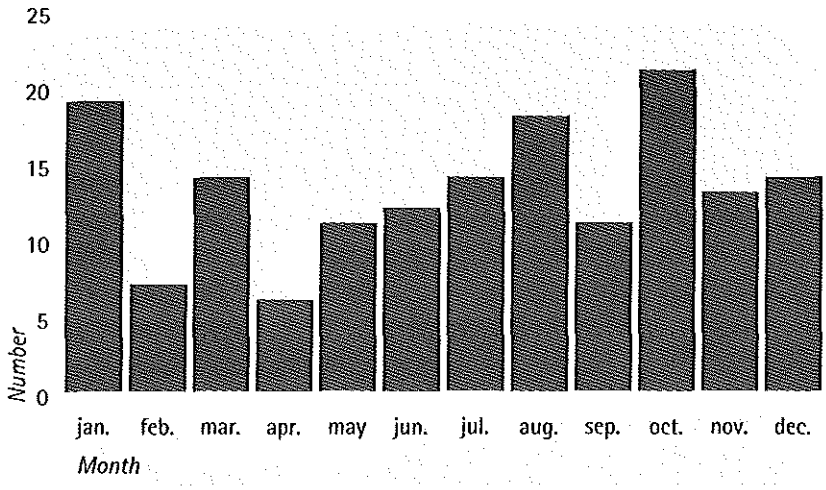


Figure 2. Seasonal distribution of onset of GBS

2.2.3 Preceding events

A preceding event was defined as any reported event within 4 weeks before onset of the illness. Twenty-nine (17%) of the 172 patients had an episode of diarrhea before onset of weakness and 66 (40%) had a preceding upper respiratory tract infection.

Nineteen (76%) of the 25 GBS patients with diarrhea had positive C. *jejuni* serology in comparison to 30 (23%) of the 129 other tested GBS patients (chi-square test: $p < 0.001$). The duration of the diarrhea varied from two to 14 days, the mean duration was 6.2 days. The diarrhea was usually watery and accompanied with fever. The time from onset of diarrhea until onset of muscle weakness varied from zero to 26 days, on average it was 6.7 days. Onset of muscle weakness until time of treatment and the severity of muscle weakness did not differ significantly between the group with and the group without a preceding gastrointestinal illness.

Four patients reported an operation as an antecedent event.

Stricker et al. (1994) performed a case-control study parallel to the Dutch

GBS trial to evaluate drugs and other determinants as potential causes of GBS. More cases than controls suffered from infections of the respiratory, gastrointestinal or urinary tract prior to the onset of neurological symptoms. The GBS patients used significantly more frequently antipropulsives (loperamide), penicillins and vaccines; this has been related to the antecedent infections. The use of oral contraceptives was significantly lower in female cases than in female controls.

2.3 Clinical symptoms

2.3.1 Distribution of muscle weakness

Predominant distal weakness was present in 59 (35%) of the 167 patients (no accurate data available for 5 patients), predominant proximal weakness in 43 (26%) patients, global weakness in 55 (33%) patients and a mixed pattern in 10 (6%) patients.

2.3.2 Severity of muscle weakness

At the time of randomization 34 (20%) GBS patients were not able to walk 10 meters independently, 110 (64%) GBS patients were bedbound and 28 (16%) needed artificial respiration. The time duration until the stage of an inability to walk (inclusion criterion for the studies) varied from zero until 14 days. The mean time was 5.6 days. Thirty-five patients had a rapid onset and were randomized within 48 hours; at that time most of them were bedbound and five needed artificial ventilation.

Twenty-eight patients were on the ventilator at the time of randomization. The mean time from onset of weakness to this point was 5.7 days (95% confidence interval (c.i.) 4.2 - 7.3 days) for this group. For the whole group the mean time until nadir was 9.1 days (95% c.i. 8.4 - 9.9 days).

At the time of nadir the severity of weakness expressed by the MRC-sumscore varied from zero to 56, mean 29 (95% c.i. 26 - 31). Thirty-four (20%) of the 170 patients had a MRC-sumscore of ≤ 12. For two patients the MRC-sumscore could not be assessed adequately. At nadir 13 (8%) remained unable to walk with aid, 88 (51%) were bedbound and 70 (41%) patients needed artificial respiration. One patient died early in the course of the disease.

This study did not include the characteristics of the GBS patients with a mild course. An inclusion criterion for the study was the inability to walk 10 meters independently. This selection can be one explanation for the higher

incidence of artificial respiration during the course of the disease in our study population, which was 41%, whereas in other studies this percentage varied between 20 to 30% (Winer et al. 1988a; Ropper, 1992; Gibbels, Giebisch, 1992). The referral pattern may be an other explanation; many of the centers involved are also secondary referral centers.

2.3.3 Pain, paresthesias and initial sensory loss

108 (63%) of the 172 GBS patients experienced pain at the time they were seen by their neurologist. 136 (79%) patients complained of paresthesias. At the time of entry to the study 42 (29%) GBS patients did not have sensory loss, 84 (58%) had mild sensory loss and 18 (13%) had severe sensory loss.

2.3.4 Sensory loss during follow-up

Sensory loss during follow-up was not evaluated in the MP-IVIg trial. Data concerning this sensory loss were only available for 147 GBS patients who participated in the PE-IVIg trial. During follow-up 27 patients did not develop sensory deficits, these were the patients with acute (pure) motor neuropathy. Their clinical characteristics, electrodiagnostic and laboratory features will be described in Chapter 3. Two weeks after onset of therapy 95 patients had mild sensory loss and 25 severe sensory loss. Data at 4 weeks were available for 136 patients; 48 patients (35%) did not have sensory loss (anymore), 68 (50%) had mild sensory loss and 20 (15%) severe sensory loss.

2.3.5 Cranial nerve involvement

At the start of treatment and 4 weeks later the following cranial nerve deficits were found in the 147 GBS patients who participated in the PE-IVIg trial; see table 1.

The VIII nerve was not affected clinically, but formal testing was not included in the study. At start of treatment involvement of more than two cranial nerves occurred in nine patients, 4 weeks later this involvement was present in nine patients.

cranial nerve weakness	number (%)	
	at entry	at week 4
• II	1	1
• III,IV,VI	12 (8%)	17 (12%)
• V	3?*	3?*
• VII	50 (34%)	44 (30%)
unilateral	15	10
bilateral	35	34
in association with other cranial nerves	18	11
• IX	9 (6%)	6 (4%)
• X-XII	4 (3%)	10 (7%)

* *data not reliable*

Table 1. Cranial nerve involvement in 147 GBS patients

2.3.6 Clinical improvement

The median time to improve at least one functional grade on a six point scale was 41 days for the PE group, 27 days for the IVIg group and 20 days for the MP-IVIg group (logrank test: p=0.004). The median time to reach the stage of independent locomotion was 69 days for the PE group, 55 days for the IVIg group and 27 days for the MP-IVIg group (logrank test: p=0.02).

2.4 Laboratory findings

2.4.1 Cerebrospinal fluid (CSF)

Nineteen (14%) of 137 tested GBS patients had more than 10/3 (but less than 150/3) cells in the CSF. This increased cell amount was not related with a concomitant cytomegalovirus (CMV) or *C. jejuni* infection.

2.4.2 Antecedent infections

CMV serology was performed in 163 patients and the IgM titre was elevated in 22 (14%) GBS patients. Forty-nine (32%) out of 154 patients had positive *C. jejuni* serology. *Mycoplasma pneumoniae* serology was positive in 3 of the 138 tested patients. Elevated titres of Epstein-Barr virus was found in only 2 of the 138 tested patients.
The presence of a *C.jejuni* or a CMV infection is similar as in other studies, but the occurrence of EBV is lower as reported before (Dowling, Cook, 1981; Winer et al. 1988b; Ropper et al. 1991; Rees et al 1995b).

2.4.3 ESR

At start of treatment and two weeks later the ESR was tested in the patients who participated in the PE-IVIg trial. An ESR of more than 12 before start of treatment was found in 85 (65%) out of 130 patients. Ten of these 85 patients had an ESR of ≥ 60. Two weeks later 93 (75%) out of 124 GBS patients had an ESR >12. Of these patients 33 (26%) had an ESR of ≥ 60. ESR was not related with a preceding infection, severity of motor weakness or sensory loss, or outcome, but showed a significant association with treatment.

Only seven (11%) of the 61 patients treated with PE had an ESR of ≥ 60, whereas this occurred in 26 (38%) of the 68 patients treated with IVIg (chi-square test: p=0.001). Eleven (9%) of 129 patients had an ESR of ≥ 100, one in the PE group and 10 in the IVIg group, again a significant difference (chi-square test: p=0.008). The ESR rise decreased during follow-up and was not related with the severity of the disease.
So, an elevated ESR after IVIg treatment needs not to be examined further, unless other signs suspect for vasculitis are present.

2.4.4 Liver functions

During the PE-IVIg trial liver functions were also tested. Oomes et al (1996) investigated the liver functions in relation with a preceding infection and applied therapy. In this overview their findings will be summarized. In 100 consecutive patients with GBS liver function on admission and at fixed intervals after either IVIg or PE treatment was tested. On admission, 38% showed a plasma alanine aminotransferase elevation, gamma glutamyl transferase elevation, or both of more than 1.5 times the upper limit of normal. Ten of these patients had serologic evidence of recent CMV infection!

The remaining 28 patients were negative for other known causes of liver damage, including infection with EBV or hepatitis A, B, and C, alcohol abuse, hepatotoxic drugs, recent surgery, and concurrent liver disease. In the IVIg-treated group, the percentage of patients with elevated liver function tests increased from 35% before to 69% shortly after treatment at 2 weeks post admission ($p < 0.005$). In the PE treated group, this percentage decreased somewhat from 41% to 36% (not significant). There was also a significant rise in median plasma activity of the various liver enzymes in the IVIg group. At 1 month, however, the significant difference had disappeared. The conclusion of the study was that many patients with GBS had mild liver function disturbances without obvious cause. In addition, IVIg treatment was associated with mild transient liver function disturbances through an unknown mechanism.

Chapter 3

Guillain-Barré Syndrome without sensory loss (acute motor neuropathy)

a subgroup with specific clinical, electrodiagnostic and laboratory features

Brain 1995; 118: 814-847

Contents Chapter 3

3.1 Introduction

The Guillain-Barré syndrome (GBS) is an acute demyelinating polyneuropathy with relatively symmetrical paresis and a wide range of severity. GBS is a heterogeneous disorder which encompasses clinical subtypes (Asbury, Cornblath, 1990). Onset of weakness of the bulbar muscles instead of weakness starting in the legs is the most remarkable indication that the syndrome encompasses different entities. However, within the 'classical forms' of the disease, clinical variations are also evident. Muscle weakness of the limbs may be distributed diffusely or there may be a predominance of proximal or distal muscle weakness. The sensory system may be severely involved or completely spared. Variability in the clinical spectrum may be the result of different pathogenic mechanisms and this may also indicate a variability in response to treatment.

One of the subgroups in GBS may be the patients with an acute motor neuropathy. There have been a few reports of adult patients with this neuropathy occurring after a *Campylobacter jejuni (C. jejuni)* infection (Yuki et al. 1990, 1991) and which is sometimes related to the presence of anti-GM1 antibodies (Yuki et al. 1990, 1991, 1992; Gregson et al. 1991; van den Berg et al. 1992; Kornberg et al. 1994; Yuki 1994). After analyzing the results of a multicenter trial comparing the effect of IVIg and PE in patients with GBS (van der Meché et al. 1992), we studied a subgroup of patients without sensory loss (motor GBS patients). In this study the clinical features of these patients are described together with the laboratory parameters, electrophysiological findings and the response to IVIg or PE treatment.

3.2 Patients and Methods

3.2.1 Inclusion criteria and follow-up

A group of 147 patients enrolled in the Dutch GBS trial were followed for 6 months. The details of eligibility and follow-up have been described elsewhere (van der Meché et al. 1992). At each visit the patients were questioned about paresthesias and sensory deficits; neurological examination included evaluation of the cranial nerves, assessment of the functional score (F-score) (van der Meché et al. 1992), a sum-score consisting of the Medical Research Council (MRC) scores for six bilateral muscle groups (MRC-sumscore) (Kleyweg et al. 1991), and evaluation of the sensory system (two-point discrimination, position sense and tactile function in the hands and feet). Inability

to discriminate two points at a distance of 5 mm or more on the index finger was considered abnormal. Patients were considered to have motor GBS, when no sensory deficits were found at initial examination or during follow-up.
A more strict subgroup, called 'pure' motor GBS patients, consisted of patients who did not have paresthesias at onset of the illness and who did have available electrophysiological data indicating normal sensory nerve conduction velocities and sensory nerve action potentials (SNAP), following the criteria of Ropper et al (1991).
To assess the distribution of weakness on entry to the study, the strength of a number of proximal and distal muscles was assessed according to the MRC score. For the arms we used abduction of the arm and flexion of the forearm to assess proximal weakness and extension of the fingers and abduction of the thumb as indicators of distal weakness. For the proximal muscles of the legs flexion and extension of the hips was used while dorsiflexion of the feet and extension of the greater toes indicated the strength of the distal muscles.
A patient was considered to have predominantly proximal weakness when the sum of the MRC scores of the proximal muscles of the arms or the legs was at least 3 points less than the sum of the MRC scores of the distal muscles.

For distal weakness the sum-score of the proximal muscles had to be at least 3 points more than the sum of the distal muscles. Global weakness was defined as a difference in the sum of the MRC-scores between proximal and distal muscle weakness of the limbs between +2 and -2. Mixed weakness indicated more proximal weakness in the arms and more distal weakness in the legs, or visa versa.

3.2.2 Laboratory investigations

Pre-treatment serum samples were tested using an enzyme-linked immunosorbent assay (ELISA) for the presence of IgA, IgM and IgG antibodies to *C. jejuni* using an acid-glycine extract from *C. jejuni* as antigen (Herbrink et al. 1988). An ELISA was also used to detect IgM and IgG antibodies to ganglioside GM1 (Jacobs et al. 1995). The initial serum samples were examined for evidence of a recent infection with cytomegalovirus (CMV), Epstein Barr virus (EBV), hepatitis A and B, *mycoplasma pneumoniae*, influenza, parainfluenza, adenovirus, mumps, measles, herpes simplex and varicella zoster. IgM antibodies to CMV, EBV and hepatitis A and B were analyzed by ELISA. The other tests were complement fixation assays.

3.2.3 Electrodiagnostic studies

Electrodiagnostic testing was performed using standardized conventional techniques at entry, one week and 4 weeks after randomization. The details of testing have been reported earlier (van der Meché et al. 1991). Recruitment pattern on maximal voluntary effort was also tested and estimated as follows: interference pattern (IP) = normal i.e. full pattern; mixed pattern (MP) = reduced pattern; single pattern (SP) = single motor units recognisable; 0 = no motor units. To assess the presence of demyelination in the motor group we used the electrophysiological criteria of Cornblath (1990). However, no distinction was made between conduction block or dispersion since both are due to demyelination and difficult to differentiate, which was somewhat differently to Cornblath's approach. We introduced a threshold value below a distal compound muscle action potential (CMAP) of 5 mV: the difference between the proximal and distal elicited amplitude had to be at least 1 mV, because with low distal CMAPs the use of ratio's and percentages may become rather meaningless (van der Meché et al. 1985). The criteria for demyelination: CMAP reduction, prolonged distal motor latencies (DMLs) and reduction in conduction velocity in motor nerves (m-NCV) were scored for each patient; one point for each positive item with a maximum of six points for two investigated nerves and nine points for three nerves.

3.2.4 Statistical analysis

Several clinical and laboratory characteristics of the motor and the 'pure' motor GBS patients were compared with the other GBS patients using the chi-square test and the Wilcoxon-Mann-Whitney two-sample test. For the motor group and the group of the other GBS patients the time taken to reach improvement in the functional score by at least one grade and the time to achieve independent walking was analyzed by the method of Kaplan and Meier and the logrank test.

3.3 Results

3.3.1 Epidemiology and antecedent infections

Twenty-seven out of 147 patients (18%) fulfilled the criteria of motor GBS (table 1). Nine patients complained initially of paraesthesias but similar to the other 18 patients with motor GBS no sensory disturbances were found during clinical examination on entry or at follow-up. In seven patients the

paraesthesias were only located in the extremities, in two patients they were also present in the face. Most cases occurred in July/August (seven patients) and in December/January (seven patients). They were incidental with no geographical predilection.
Twenty-three (85%) of the 27 patients had been ill during the four weeks prior to the onset of GBS symptoms; diarrhea as a preceding event was significantly more common in this group than in the other 120 patients (table 1).

3.3.2 Clinical features

The patients with motor GBS had a significantly more rapid onset, the nadir was reached earlier and their cranial nerves were less frequently involved in comparison to the other 120 patients and they also had a distal predominant weakness which was less frequently seen in the other 120 patients (table 1). Four patients of the motor group had cranial nerve involvement initially. During follow-up, only seven of the 27 patients (26%) developed cranial nerve deficits and nine of the 27 patients (33%) required artificial respiration. In the other 120 patients this last percentage was slightly higher (45%) (p=0.30). In those patients of the motor group with distal-dominant weakness no involvement of the cranial nerves was found while in those with predominant proximal weakness cranial nerve involvement occurred in two of the three motor GBS patients (67%), in the group with global weakness in one of the four patients (25%) and in the mixed pattern group in both patients (overall p-value = 0.02). Only three of the 18 patients (17%) with predominant distal weakness needed artificial respiration in comparison with all three patients (100%) with predominant proximal weakness and 50% of the patients with global or mixed weakness (overall p-value =0.03).

Features	motor GBS (n=27)	other GBS (n=120)	P-value[b]
Age (mean±SD)	43.1±20.7	48.5±18.8	ns[c]
Sex			
• men	17 (63%)	59 (49%)	ns
• women	10 (37%)	60 (51%)	
Clinical characteristics			
• Time until F ≥ 3 (in days, mean)[a]	3.9 (2.6-5.1)	6.1 (5.4-6.8)	0.002[c]
• Time until nadir (in days, mean)	6.3 (4.9-7.7)	9.1 (8.5-9.9)	<0.001[c]
• Cranial nerve involvement	7 (26%)	81 (68%)	<0.001
• Predominant weakness			
Distal	18 (67%)	32 (27%)	<0.001
Proximal	3 (11%)	30 (25%)	ns
Global	4 (15%)	48 (40%)	0.01
Mixed	2 (7%)	10 (8%)	ns
• MRC-sumscore at entry,mean	32 (25-38)	37 (35-39)	ns[c]
• MRC-sumscore at nadir,mean	25 (18-32)	28 (25-31)	ns[c]
Antecedent infections			
• gastrointestinal tract	11 (41%)	16 (13%)	0.001
Laboratory findings			
• positive *C. jejuni* serology	16/24[d] (67%)	30/109[d] (28%)	<0.001
• positive CMV serology	0/26[d] (0%)	20/112[d] (18%)	0.02
• IgG anti-GM1 antibodies	10/24[d] (42%)	5/109[d] (5%)	<0.001

Table 1. Factors distinguishing motor GBS patients from other GBS patients.

Between brackets percentages or 95% confidence interval
a: F-score: 0 denotes healthy; 1, having minor symptoms and signs but fully capable of manual work; 2, able to walk ≥ 10 m without assistance; 3, able to walk ≥ 10 m with a walker or support; 4, bedridden or chairbound; 5,requiring assisted ventilation for at least part of the day; and 6, dead.
b: p-values were derived from the chi-square test,two tailed unless indicated otherwise. c: Wilcoxon-Mann-Whitney test,two tailed. d: number tested
Motor GBS= patients with the Guillain-Barré syndrome, who did not have sensory loss on clinical examination during a follow-up period of 6 months. ns= not significant; MRC=medical research council score; CMV = cytomegalovirus;
C.jejuni = Campylobacter jejuni

3.3.3 Cardiovascular disturbances

Two (6 %) of the 27 patients had signs of cardiovascular disturbances during follow-up and this was not significantly different compared with the other 120 patients (12%) (p= 0.46). One patient had a transient tachycardia and one a transient episode of low blood pressure.

3.3.4 Effect of treatment

Recovery of the 27 patients with motor GBS was compared with that of the other 120 patients. Only two (13%) of the 16 motor GBS patients treated with IVIg did not achieve independent walking (F=2) within 6 months, while more than half (55%) of the 11 motor GBS patients after PE treatment did not reach F=2 (p=0.02) (fig. 1 and fig. 2). Also the median time to reach independent walking was reduced for the motor GBS group treated with IVIg as compared to the motor patients treated with PE, although not significant (logrank test: p=0.07).

In the motor GBS patients with a positive *C. jejuni* serology a significant difference was found in the response to treatment: none of six patients treated with PE improved towards the stage of independent walking, while the mean time to reach independent locomotion for those treated with IVIg (10 motor GBS patients) was 55 days (figure 3): logrank test:p=0.002.

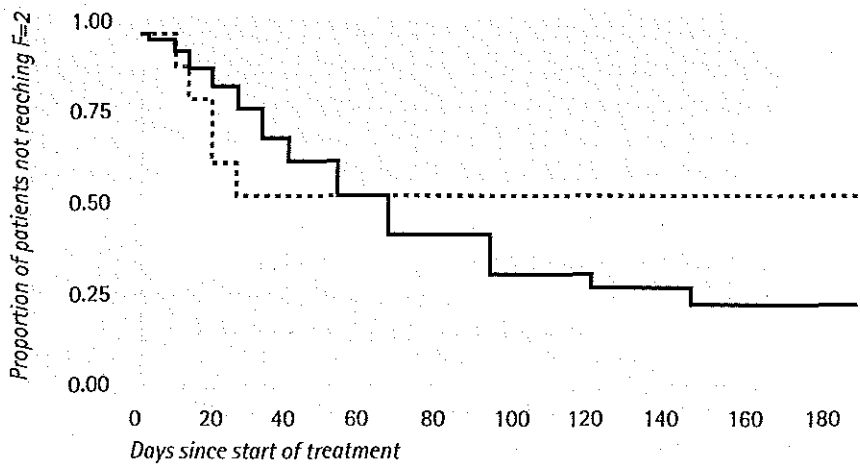


Figure 1.Kaplan-Meier curves indicating the number of patients not managing to walk independently during the follow-up period of 181 days after treatment with PE (logrank test: not significant).

motor GBS patients treated with PE

other GBS patients treated with PE

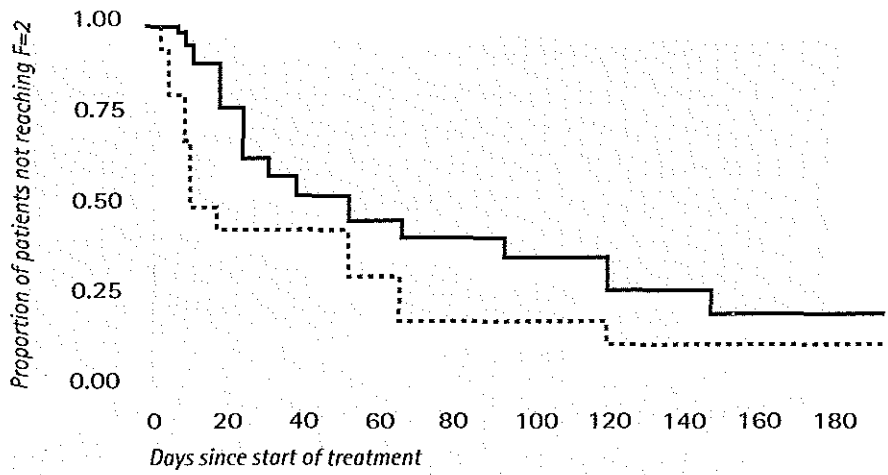


Figure 2. Kaplan-Meier curves indicating the number of patients not managing to walk independently during the follow-up period of 181 days after treatment with IVIg (logrank test: p=0.07).

motor GBS patients treated with IVIg

other GBS patients treated with IVIg

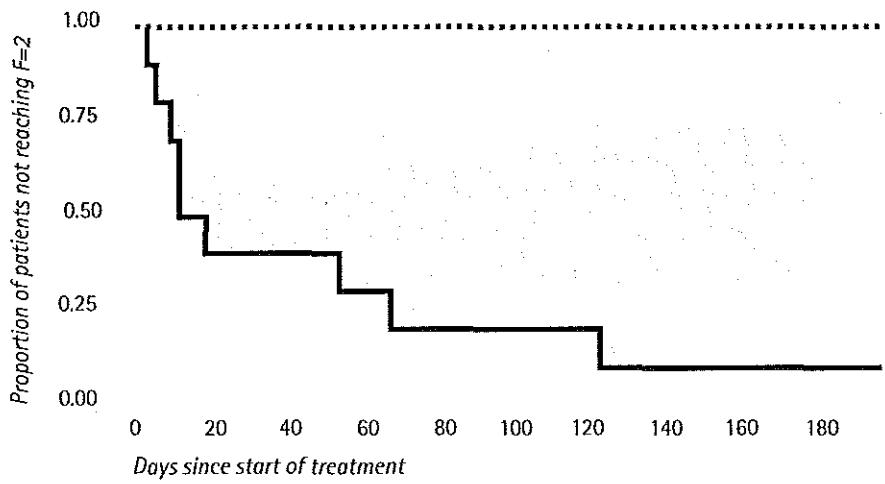


Figure 3. Kaplan-Meier curves indicating the proportion of patients with an acute motor neuropathy after a C. jejuni infection, who did not recover to independent locomotion during 181 days of follow-up, according to treatment group (logrank test: p=0.002).

PE= plasma exchange IVIg= intravenous immune globulin treatment

motor GBS patients with a C. jejuni infection treated with PE

motor GBS patients with a C. jejuni infection treated with IVIg

3.3.5 Laboratory findings

The anti-GM1 antibodies were present more often in the motor group ($p<0.001$, table 1). Sixty percent of the 17 patients with a distal-dominant limb weakness at onset had anti-GM1 antibodies. Evidence for a recent *C. jejuni* infection was often found in the motor group (table 1). The mean value of protein in the cerebrospinal fluid did not differ significantly. It was 1.15 g/l in the motor GBS group and 1.50 g/l in the other 120 GBS patients. Serological evidence of a recent CMV infection or other viral infections were not found in the motor group.

3.3.6 Electrophysiology

Electrophysiological data were available for 24 of the 27 motor GBS patients. Data from the second EMG concerning ulnar and median motor nerve studies of the motor and other GBS patients are presented in table 2. DMLs were shorter in motor GBS patients, amplitudes lower and the recruitment pattern more reduced, although not always significantly different. In the first ulnar study 78% of the motor group had a low recruitment pattern (0/SP) in comparison with 45% in the other group ($p=0.01$). For the median nerve these values were 59% for the motor group and 37% for the others ($p=0.09$). The mean value of the DMLs in the third EMG for both median and ulnar nerve of the two groups showed strongly significant differences: for the motor group the mean ulnar DML was 2.9 and the median DML 4.0, while this was 4.9 for the ulnar DML ($p = 0.002$) and 7.1 for the median DML ($p<0.001$) in the other group.

Using the scoring system for demyelination as described in Patients and methods, we found no item fulfilling the criteria of demyelination in 12 motor GBS patients, one item in eight patients and two items in the remaining four patients. Needle myography was performed in 21 patients, usually in three muscles in all three scheduled EMGs. Abundant denervation potentials in two or more muscles were seen in at least one of the three EMGs (score=3) in three patients and in one muscle in seven additional patients; the other 11 patients had no or only sporadic denervation potentials. Fairly severe axonal damage was, therefore, observed in 10 out of 21 patients.

Sensory conduction evaluation was available for 23 of the 27 patients and normal conduction velocity and amplitude were found in 18 patients. In two of the other five patients, median and ulnar sensory potentials were absent; the other three patients had amplitudes below 10 μV, but normal nerve conduction velocity. Three of these five patients had paresthesias at onset of their illness.

	motor GBS		other GBS		P-value[a]
	MEAN	CI	MEAN	CI	
Median nerve					
• Number	20	-	98	-	
• Distal latency (msec)	4.7	3.2-6.1	6.3	5.6-7.0	0.01
• CV (m/sec)	53	49-58	50	48-53	0.70
• Amplitude (mV)					
Wrist	3.6	1.7-5.6	5.1	4.3-6.1	0.09
Elbow	2.9	0.9-1.1	4.6	3.8-5.5	0.03
• Recruitment pattern					
0 or SP (no/no tested)	10/19 (53%)	-	35/88 (40%)	-	0.30[b]
MP or IP(no/no tested)	9 /19 (47%)	-	53/88 (60%)	-	
Ulnar nerve					
• Number	20	-	98	-	
• Distal latency (msec)	3.2	2.9-3.5	4.1	3.7-4.5	0.12
• CV (m/sec)	56	50-63	54	52-57	0.71
• Amplitude (mV)					
Wrist	3.9	1.5-6.2	5.9	5.0-6.8	0.02
Elbow	3.0	0.7-5.4	5.2	4.3-6.0	0.004
• Recruitment pattern					
0 or SP (no/no. tested)	12/20 (60%)	-	33/86 (38%)	-	0.08[b]
MP or IP(no/no tested)	8/20 (40%)	-	53/86 (62%)	-	

Table 2. Motor nerve conduction studies in motor GBS patients and the other GBS group: mean and 95% Confidence Interval (CI)

CV = conduction velocity; IP = normal i.e full pattern; MP = mixed pattern; SP = single pattern; 0 = no motor units; no = number of patients; no tested= number of patients tested a: p-values were derived from the Wilcoxon-Mann-Whitney test, two-tailed unless indicated otherwise;
b chi-square test, two tailed

3.3.7 'Pure' motor GBS patients

A more strictly defined subgroup of 'pure' motor GBS patients was formed by excluding nine patients with paresthesias, two patients with a reduction of the sensory nerve potentials and another two patients without available EMG data. Fourteen patients (9.5%) were left in this subgroup. Comparison of this 'pure' motor group with the other 133 GBS patients showed the same significant clinical differences as described above for the 27 clinically defined motor GBS patients.

3.4 Discussion

Twenty-seven out of 147 patients (18%) had motor GBS. A slightly lower incidence was found by Gibbels and Giebisch (1992): 13% of 266 patients. At least fourteen patients of our 147 GBS patients (9.5%) had a 'pure' motor variant according to the stricter criteria of Ropper et al (1991).

Although nine patients reported paresthesias, this seems to reflect a non-specific symptom in at least five of them, since no clinical or electrophysiological changes were found in the sensory system. Sensory demyelination cannot be totally excluded, however, since demyelination may be present outside the segment of the nerve under study. On the other hand certain changes in the sensory potentials may also be a non-specific effect since sensory amplitudes are very vulnerable to minimal dispersion (van der Meché et al. 1988). Even when we exclude the patients with paresthesias and those with a reduction of the sensory potentials the same significant clinical and laboratory differences are found when compared with the other GBS patients. Therefore our clinical criteria may be sufficient to define motor GBS.

In this Dutch population motor GBS patients can be distinguished from other GBS patients since they have a more rapid onset of weakness; they reach nadir earlier; they have a distal-dominant weakness; they lack cranial nerve involvement; their symptoms are preceded by a gastro-intestinal illness caused by a recent *C. jejuni* infection; and high titres of anti-GM1 antibodies are present in their serum.

Distal-dominant muscle weakness in acute motor neuropathy has been reported occasionally (Yuki et al. 1990, 1991) and is frequently present in our motor group, while the overall distribution of weakness in our 147 GBS patients correspond with the findings of other studies of large groups of GBS patients (Winer et al. 1988a; Ropper et al. 1991; Gibbels, Giebisch, 1992).

Involvement of cranial nerves is usually related to the severity of muscle weakness (Winer et al. 1988a; Ropper et al. 1991), but our motor patients do not have a mild disease; the mean MRC-sumscore at nadir was lowest in this group. Lack of cranial nerve involvement, distal onset of weakness and a possibly lower incidence of respiratory insufficiency suggest a selective involvement of the long nerve fibres. The distal predilection may be associated with a random distribution of demyelination or be the result of a dying back mechanism after primary or secondary axonal involvement (van der Meché, Meulstee, 1988; van der Meché et al. 1988, 1991).

More insight into the pathogenesis of acute motor neuropathy is given by the high incidence of diarrhea (41%) and the presence of a recent *C. jejuni* infection (67%). In the overall GBS population a preceding gastro-intestinal illness occurs in 10-20% of the patients (Winer et al. 1988a; Ropper et al. 1991). It is likely that the gastro-intestinal episodes, often due to *C. jejuni*, have an important role in the initiation of the disease. It has been shown that cross-reaction of anti-GM1 antibodies with lipopolysaccharides from certain strains of *C. jejuni* may occur (Yuki et al. 1992) and that *C. jejuni* contain GM1-like structures (Yuki et al. 1993b). These anti-GM1 antibodies, which in our GBS population are highly associated with motor GBS patients, may react with the peripheral nervous system and give the above mentioned clinical picture.

Our motor GBS patients resemble the acute motor axonal neuropathy (AMAN) in Chinese children including the association with *C. jejuni* infection (McKhann et al. 1993). Onset is also acute with a symmetrical, flaccid weakness. However, unlike our motor group, AMAN occurs seasonally in rural areas and affects mainly children and young adults.

Also the electrophysiological findings are similar to those found in AMAN (McKhann et al. 1993) and in Japanese patients with acute motor neuropathy (Yuki et al. 1990, 1991) showing low CMAPs, normal or slightly prolonged DMLs and normal m-NCVs, with denervation potentials in limb muscles, suggesting axonal dysfunction. Whether this is a primary or a secondary process following demyelination at the terminal segments remains a matter of controversy at this moment (Yuki, 1994; Feasby, 1994; Cros, Triggs, 1994).

The motor GBS patients seem to respond well to IVIg and this may have important therapeutic consequences. This is the first study, although with a small number of patients and with retrospective subgroup analysis, indicating a difference in effect between PE and IVIg in a specific subgroup of GBS

patients. The reason for this difference is not clear, but intriguing since a favorable effect of IVIg and a poor response after PE has also been reported in the chronic multifocal motor neuropathies (Pestronk et al. 1990; Chaudhry et al. 1993; Nobile-Orazio et al. 1993; Azulay et al. 1994). Further studies are necessary to confirm these preliminary findings.
In conclusion, motor GBS patients represent a separate entity. Creating subgroups such as patients with an acute motor neuropathy may be important for further clarification of the pathogenesis of GBS and might have implications for the choice of therapy.

Chapter 4

Cytomegalovirus infection and Guillain-Barré Syndrome

the clinical, electrophysiologic and prognostic features

Neurology 1996; 47: 668 - 673

Contents Chapter 4

4.1 Introduction

Guillain-Barré syndrome (GBS) is an inflammatory, usually demyelinating polyneuropathy clinically characterized by an acute onset of symmetrical progressive muscle weakness with loss of myotatic reflexes (Asbury, Cornblath, 1990). GBS represents patients with a wide clinical spectrum (van der Meché et al. 1988; Asbury, Cornblath, 1990; Thomas, 1992; van der Meché, van Doorn, 1995). There are variations in the clinical pattern and differences in immunologic (Hartung et al. 1995a; van der Meché, Van Doorn, 1995), electrophysiologic (van der Meché et al. 1988; Yuki, 1994; Feasby, 1994) and pathologic findings (Honavar et al. 1991). These differences may indicate the involvement of distinct pathogenic mechanisms in GBS. In about one-half to two-thirds of GBS patients there is a history of a preceding infectious illness (Winer et al. 1988b; Hartung et al. 1995b). Much interest has centered around *Campylobacter jejuni (C. jejuni)*, the most common antecedent infection in GBS (van der Meché et al. 1992; Hartung et al. 1995b). We recently described a subgroup of GBS patients with an acute motor neuropathy who have specific clinical, electrophysiologic, and laboratory findings, including an association with a *C. jejuni* infection (Visser et al. 1995, Chapter 3). Furthermore, *C. jejuni* infection is associated with the presence of anti-GM1 antibodies and is related to a more severe outcome (van der Meché et al. 1992; Rees et al. 1995b). Cytomegalovirus infection (CMV) is the second most common antecedent infection in GBS, occurring in 11-15 % of the patients (Dowling et al. 1980; Winer et al. 1988b). Besides younger age, female preponderance and occurrence of liver function disturbances, there has not been specific characteristics linked with a preceding CMV infection in GBS patients (Dowling et al. 1980; Oomes et al. 1996). We studied the clinical pattern and electrophysiologic data of 20 GBS patients with a recent CMV infection out of a group of 134 GBS patients, who participated in the Dutch GBS trial (van der Meché et al. 1992) and from whom pre-treatment sera were available. We compared these characteristics with the earlier described findings of the *C. jejuni* -related GBS group and the remaining group of patients in whom these infections were not present.

4.2 Patients and Methods

The study population included all 134 GBS patients with clinically defined GBS who were followed prospectively in the Dutch GBS trial (van der Meché et al. 1992) and who had available pretreatment sera. To be included, patients had to be within two weeks of onset of the neuropathy and not be able to walk 10 meters independently. The exclusion criteria have been mentioned elsewhere (van der Meché et al. 1992). At entry into the study, patients were questioned about presence of paresthesias, prodromal symptoms, and onset of weakness. Neurologic examinations were performed at study entry and 16 times during 6 months of follow-up- three times a week during weeks 1 and 2, once a week through week 6 and in weeks 8, 10, 14, 18, 22, and 26. The examination of the motor system consisted of assessment of the functional score (F-score) and the Medical Research Council scores for six bilateral muscle groups, yielding a summary score (MRC-sumscore) ranging from 60 (normal) to zero (quadriplegic) (Kleyweg et al. 1988). At entry, distribution of muscle weakness (e.g., global, predominant proximal or distal, or mixed weakness) was determined as described before (Visser et al. 1995). At each visit all cranial nerves was tested and recorded as being positive or negative (no involvement).

The examination of the sensory system at entry and 4 weeks later included: two-point discrimination at digit II of both hands, proprioception and tactile function in the hands and feet. During the other visits (twice a week during weeks 1 and 2, weeks 4, 5, 6, 8, 10, 14, 18, 22 and 26), sensory loss was determined by assessing two-point discrimination at digit II of both hands, tactile function of the arms and legs, and proprioception of the toes. Inability to discriminate two points at a distance of 5 mm or more was considered abnormal. Tactile function was tested using cotton wool and position sense by passive movement of the distal phalanx of the index finger and of the big toe. For each abnormal finding in the assessment of the sensory system 1 point was given, so severity of sensory loss could range from 0 (no sensory loss) up to 10 at entry and week 4 (abnormal two-point discrimination in both hands, proprioception and disturbed tactile function at both arms and legs) and up to 8 at the other visits (abnormal two-point discrimination in both hands, disturbed tactile function of arms and legs and proprioception of the toes). This report includes analysis of the sensory system at three points-at study entry, during the first 2 weeks and at week four. The severity of sensory loss was classified as none, mild or severe. Sensory loss at entry and at week

four was classified as severe when the score was ≥ 8 of 10. Sensory loss during the first two weeks was defined as severe when the score on at least two visits was ≥ 6 of eight.

4.2.1 Laboratory investigations

Pretreatment serum samples were tested using an enzyme linked immunosorbent assay (ELISA) for the presence of IgA, IgM and IgG antibodies to *C. jejuni* using an acid-glycine extract from *C. jejuni* as antigen (IgG: indirect ELISA (Herbrink et al. 1988), IgM and IgA: class-capture ELISA (Herbrink et al. 1987)). IgM antibodies against CMV were determined by ELISA (Vidas, bioMésieux, Mercy-l'Etoile, France). ELISA and thin layer chromatography overlay was used to detect IgA, IgG and IgM antibodies to ganglioside GM1 (Jacobs et al. 1995).

4.2.2 Electrodiagnostic studies

Electrodiagnostic testing was performed using standardized conventional techniques at entry and 1 and 4 weeks after randomization. The details of testing have been reported earlier (Meulstee et al. 1995a). Briefly, motor nerve conduction studies were performed on ulnar and median nerves in the forearm. Sensory nerve conduction velocities of ulnar and median nerves were measured antidromically. Amplitudes and duration of the evoked motor and sensory responses were measured with surface electrodes. With concentric needle electrodes, small hand muscles and anterior tibial muscles were tested for the presence of denervation potentials. Recruitment pattern on maximal voluntary effort was also tested and estimated as follows: interference pattern (IP) = normal i.e., full pattern; mixed pattern (MP) = reduced pattern; single pattern (SP) = single motor units recognizable; 0 = no motor units. An abnormal compound muscle action potential (CMAP) amplitude reduction was present if the observed decrease in CMAP amplitude exceeded the upper limit of normal; in cases where the CMAP amplitude after distal stimulation was < 5 mV, CMAP amplitude reduction was defined as abnormal if the difference between distal and proximal stimulation was at least 1mV (van der Meché et al. 1985).

4.2.3 Statistical analysis

Several clinical and electrophysiologic characteristics of the different groups were analyzed using the chi-2 test for comparison of proportions, or the

Kruskal-Wallis test for comparison of means of ordinal variables between more than two groups. The time to reach the stage of independent locomotion between the different groups was analyzed by the method of Kaplan and Meier and the logrank test.

4.3 Results

4.3.1 General

Serological testing of the pretreatment serum could be performed in 134 (91%) of the 147 patients. The clinical pattern of the patients without available pretreatment sera did not differ from the pattern of the other 134 patients. Virus-specific IgM antibodies against CMV were found in 20 (15%) of the 134 patients and 46 (34%) of the 134 patients had serological evidence for a recent *C. jejuni* infection. Three patients had both positive *C. jejuni* and CMV serology. For the analysis we had to decide whether these patients belonged to the group of *C. jejuni* or to the CMV group. In two of these three patients IgA and IgM antibodies against *C. jejuni* were normal and IgG just above the upper limit of normal, while both had high IgM antibody titers against CMV. The other patient had elevated IgA titers and normal levels of IgM and IgG antibody titers against *C. jejuni*, whereas the IgM antibody titre against CMV was high. Therefore it was decided to include these three patients in the CMV group, although the third patient could have both a recent CMV as well as a *C. jejuni* infection. Analysis of the data without these three patients did not change the results.

The mean age for the patients with a CMV infection was significantly younger (36 years) in comparison with the mean age for the *C. jejuni* group (51 years) and for the group of other GBS patients (48 years). Although CMV-related GBS occurred more frequently in women, this was not significant (table 1). In the CMV-associated GBS group, only one patient had anti-GM1 IgM antibodies, and IgA or IgG antibodies were not found at all.

4.3.2 Epidemiology and antecedent episodes

The population of 134 GBS patients provided the demographic data for the seasonal distribution of GBS in relation to CMV and *C. jejuni* infections. Both CMV- and *C. jejuni*-associated GBS occurred more often during the second part of the year, although no clear seasonal preponderance could be found. Forty-six (34%) of the 134 patients had an upper respiratory tract

infection and 25 (19%) a prodromal gastrointestinal illness. A history of respiratory symptoms in a period of one month before the onset of muscle weakness was given by nine of the 20 CMV-GBS patients, one of whom also had diarrhea. Seven of the 20 patients had myalgia, headache, or fever and only four patients did not have preceding symptoms. The history of the respiratory symptoms did not differ between the CMV group and the others-GBS group (see table 1). As expected, diarrhea occurred significantly more frequent in the *C. jejuni* group than in the CMV or other GBS group.

4.3.3 Clinical characteristics

4.3.3.1 Sensory symptoms

The three groups showed significant differences in the presentation and severity of sensory loss. Sensory symptoms were most often found in the CMV group, whereas in the *C. jejuni* group the patients usually had no or only mild sensory loss. Paresthesias were very common in the CMV group (90%) and in the other GBS patients (86%) and occurred only in 26 (60%) of the 43 patients with *C. jejuni* infection (p= 0.002) (table 1). For only two of the 134 GBS patients (in the group without CMV or *C. jejuni* infection) accurate assessment of the severity of sensory loss was not possible due to lack of sufficient data. At randomization 12 (60%) of the 20 patients with a CMV infection had mild sensory loss and five (25%) severe, whereas in the group of the 43 *C. jejuni*-associated GBS patients, 19 (44%) had mild and two (5%) severe sensory loss; in the other 69 patients mild sensory loss occurred in 45 (65%) and severe in 11 (16%) patients (overall p-value = 0.001, p-value between the CMV and *C. jejuni* group <0.001). In figure 1 the severity of sensory loss during the first two weeks and at week 4 for the three subgroups is shown.

During the first 2 weeks of follow-up, reliable assessment of the sensory system (as mentioned in the Methods) could be made in 126 patients. Thirteen of the 19 patients with CMV (68%) had severe sensory loss, whereas this occurred in only 11 (28%) of the 39 patients with *C. jejuni* infection and in 28 of the 68 (41%) other patients (p=0.001).

Four weeks after randomization full assessment of the sensory system was performed in 123 patients. At this time, seven (35%) of the 20 patients with CMV still had severe sensory loss in comparison to three (8%) of the 37 patients with *C. jejuni* and five (8%) of the other 66 patients.

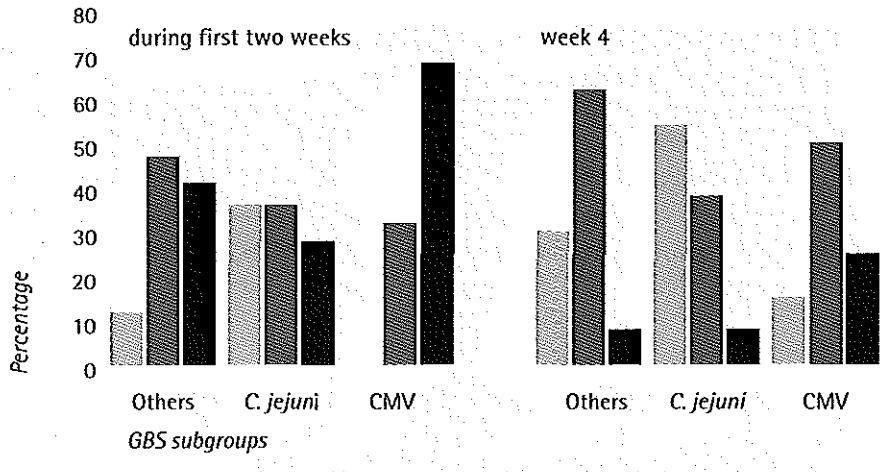


Figure 1. Severity of sensory loss during the first two weeks (p=0.001) and at week 4 after onset of therapy (p=0.002), according to the antecedent infection.

none
mild
severe sensory loss

Only three patients of the CMV group (15%) did not have sensory symptoms anymore in comparison with 20 (54%) of the *C. jejuni* group and 20 (30%) of the other GBS patients (p=0.002) (see figure 1).

4.3.3.2 Cranial nerve involvement and pattern of weakness

At the time of randomization no differences between the percentages of presence of cranial nerve deficits were found among the three different groups (see table 1). During follow-up, however, cranial nerve deficits occurred in 16 (80%) of the 20 patients with CMV, in 21 (48%) of the 43 patients with *C. jejuni* and in 46 (65%) of the 71 other patients (p=0.05). These cranial nerve deficits were usually bilateral facial palsies.
Eight (40%) of the 20 CMV-GBS patients had global, five (25%) predominant proximal and six (30%) predominant distal weakness. In the *C. jejuni* group predominantly distal weakness was often present- in 20 (46%) of the 43 patients. Eight (19%) of these 43 patients had global weakness and 12 (28%) proximal weakness. Of the 71 other GBS patients, 26 (38%) had global, 16 (24%) predominant proximal weakness and 21 (31%) predominant distal weakness.

Characteristics	CMV-GBS	C. jejuni-GBS	other GBS patients	P-Value[a]
• Number of patients	20	43	71	
• Sex M/F	7/13	24/19	40/31	ns
• Age (mean ± SD)	36 ± 16	51 ± 20	48 ± 19	0.01[b]
Antecedent episodes				
• gastrointestinal illness	1 (5%)	18 (42%)	6 (8%)	<0.001
• UTI	8 (40%)	9 (21%)	29 (41%)	
• others/none	11 (55%)	16 (37%)	36 (50%)	
Clinical characteristics				
• Paresthesias	18 (90%)	26 (60%)	61 (86%)	0.002
• Cranial nerve deficits				
at entry	9 (45%)	17 (40%)	37 (52%)	ns
during follow-up	16 (80%)	21 (49%)	46 (65%)	0.05
• MRC-sumscore				
at entry	41 (7-52)[c]	36 (0-52)[c]	40 (11-56)[c]	ns[b]
during follow-up	21 (0-52)[c]	28 (0-50)[c]	37 (0-56)[c]	0.01[b]
• Artificial respiration	13 (65%)	19 (44%)	26 (37%)	0.08
• Time until nadir (in days)	10 (6-18)[c]	7 (2-21)[c]	8 (3-21)[c]	0.06[b]
Treatment				
• F=2 after 8 weeks				
Overall	7 (35%)	17 (40%)	44 (62%)	0.02
After PE	1/9 (11%)	6/23 (26%)	23/36 (64%)	0.002
After IVIg	6/11 (55%)	11/20 (55%)	21/35 (60%)	ns
• F=2 after 6 months				
Overall	15 (75%)	24 (56%)	63 (87%)	<0.001
After PE	7/9 (78%)	9/23 (39%)	32/36 (89%)	<0.001
After IVIg	8/11 (73%)	15/20 (75%)	31/35 (89%)	ns

Table 1. Comparison of clinical characteristics between the CMV-GBS group, C. jejuni-GBS group and the other GBS patients.

Between brackets percentages; [a] p-values were derived from the chi-square test,two tailed unless indicated otherwise. [b] Kruskal-Wallis test. [c] median and between brackets the 95% interpercentile range; ns= not significant; MRC=medical research council score; CMV = cytomegalovirus; *C. jejuni* = *Campylobacter jejuni*; UTI=upper respiratory tract infection; F=2: able to walk independently; PE=plasma exchange; IVIg=intravenous immune globulins

4.3.3.3 Severity of weakness during follow-up, effect of treatment and prognosis

The average MRC-sumscore at the start of treatment did not differ significantly between the three groups; however, progression of the disease in the CMV and *C. jejuni* group was more severe than in the other GBS patients. At nadir, the MRC-sumscores were significantly lower in these two groups in comparison to the other 71 GBS patients and artificial respiration was most often necessary in the CMV group, in 13 of the 20 patients (65%) (see table 1).

Figure 2 shows the proportion of patients being able to walk independently in relation to time since the start of treatment for the three different groups.

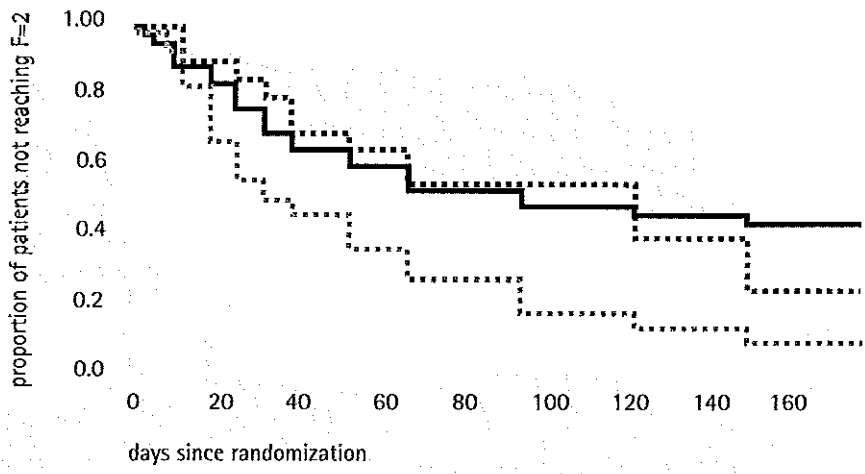


Figure 2. Kaplan-Meier curves indicating the proportion of patients, who did not recover to the stage of independent locomotion (F=2) during 182 days of follow-up, according to the preceding infection (P< 0.001).

——— *C. jejuni*

– – – *CMV*

▪▪▪ *Others*

The median time to be able to walk independently was the longest for the CMV group at 125 days, was 97 days for the *C. jejuni* group and 41 days for the other GBS patients (logrank test: p<0.001). The outcome after 6 months tended to be better for the CMV group compared with the *C. jejuni* group, but both were worse compared with the group without these two infections. When the three different groups were compared according to the treatment received (plasma exchange (PE) or intravenous immune globulins (IVIg)), we found significant differences in response to treatment with PE, whereas after treatment with IVIg, no significant differences were found. The median times to the recovery of independent locomotion were 55 days for the 11 CMV patients treated with IVIg, 34 days for the 20 *C. jejuni*-IVIg treated group and 27 days for the other 35 patients treated with IVIg (logrank test: p=0.41). For the PE treated patients, these median times were 153 days for the 9 CMV patients, > 181 days for the 23 C. *jejuni* patients and 41 days for the 36 other GBS patients (logrank test: p < 0.001). In table 1 the percentages of patients able to walk independently two and six months after start of PE or IVIg are shown for each subgroup. Only one of the nine CMV-GBS patients treated with PE was able to walk independently after 2 months in comparison to six of the 11 CMV-GBS patients treated with IVIg (p=0.04).

4.3.4 Electrophysiology

Data from all EMGs concerning motor and sensory ulnar and median nerve studies of the three groups are presented in table 2. CMAPs were lower in the CMV and *C. jejuni* groups, especially one and four weeks after onset of therapy. Low sensory nerve action potentials (SNAPs) ≤ 10 μV occurred more often in the CMV and the other GBS groups than in the *C. jejuni* group. All GBS patients with a CMV infection on whom an EMG was done at week 4 had SNAPs less than 10 μV after stimulation of the ulnar nerve. Of the five patients on whom an third EMG was not carried out, the second EMG showed SNAPs below 10 μV in four of them. Distal motor latencies were longer in the CMV and other GBS patients, but not significantly different compared to the values of the *C. jejuni* patients (data not shown). Recruitment pattern was lowest in the *C. jejuni* group (see table 2). Motor and sensory conduction velocities, percentage of conduction blocks and denervation activity did not differ significantly among the three groups.

Characteristics	CMV-GBS	C. jejuni-GBS	other GBS patients	P-Value
CMAP ≤ 3 mV				
• ulnar nerve				
entry	9/20[a] (45%)	15/36[a] (42%)	16/59[a] (27%)	0.20
week 1	8/20 (40%)	21/37 (57%)	12/60 (20%)	0.001
week 4	6/16 (38%)	19/35 (54%)	8/53 (15%)	<0.001
• median nerve				
entry	12/19 (63%)	15/37 (40%)	21/58 (36%)	0.12
week 1	11/19 (58%)	20/37 (54%)	22/61 (36%)	0.11
week 4	8/16 (50%)	16/36 (44%)	17/55 (30%)	0.25
SNAP ≤ 10μV				
• ulnar nerve				
entry	13/19 (68%)	16/34 (47%)	44/58 (76%)	0.02
week 1	15/19 (79%)	19/34 (56%)	43/56 (77%)	0.07
week 4	14/14 (100%)	17/34 (50%)	38/53 (72%)	0.002
• median nerve				
entry	16/19 (84%)	16/37 (43%)	39/58 (67%)	0.006
week 1	15/18 (83%)	21/35 (60%)	44/59 (75%)	0.15
week 4	15/16 (94%)	19/34 (56%)	34/53 (64%)	0.03
• Recruitment pattern				
entry 0/SP	5/14 (36%)	20/28 (71%)	21/51 (41%)	0.02
week 1 0/SP	5/14 (36%)	15/29 (52%)	22/55 (40%)	ns
week 4 0/SP	4/13 (64%)	13/31 (42%)	14/45(31%)	0.08
• Conduction block				
entry	5/20 (25%)	11/36 (31%)	23/59 (39%)	ns
week 1	7/20 (35%)	10/37 (27%)	19/60 (32%)	ns
week 4	3/16 (19%)	14/35 (40%)	21/39 (40%)	ns

Table 2. Comparison of electrophysiologic characteristics between the CMV-GBS group, C-jejuni-GBS group and the other GBS patients.

Between brackets percentages

a: number tested; ns= not significant; CMV = cytomegalovirus; *C. jejuni* = *Campylobacter jejuni*; CMAP= compound muscle action potential; SNAP= sensory nerve action potential; SP= single pattern; 0 = no motor units recognizable

4.4 Discussion

This analysis of the clinical pattern of 134 Dutch GBS patients focuses on the preceding CMV infection and gives further evidence for the heterogeneity of this clinically defined disease. The contrast with the earlier described clinical pattern of *C. jejuni* related GBS is striking (Visser et al. 1995, Chapter 3). Several clinical features further characterize CMV-associated GBS patients. They were younger and often developed severe sensory loss (clinically and electrophysiologically) with cranial nerve involvement and respiratory insufficiency. Some of these factors need further comment.

There was a strong relation between CMV infection and development of severe sensory loss in GBS patients. Although GBS is predominantly a disease of the motor system, there may be persisting sensory symptoms in GBS patients (Sobue et al. 1983). Severe sensory loss can occur and has a strong impact on the capability to walk and on the quality of life of these patients. Therefore, scales assessing the outcome in GBS patients should include sensory function.

Another important new finding in our series of CMV associated patients was the initially severe course of the disease resulting in respiratory insufficiency in 65% of the patients and a poor outcome at an early stage. Since the patients could be included in the study only when they were not able to walk 10 meters independently, this group of GBS patients over-represent those with severe weakness and this may explain the high percentage of artificial respiration during follow-up for the whole group. Those treated with PE, particularly, did not show improvement to the stage of independent locomotion during the first 2 months after start of therapy. The high frequency of respiratory insufficiency and the involvement of the proximal muscles and facial nerves in the CMV associated GBS group may indicate predominant dysfunction of the short nerves. Since age is an important prognostic factor, (van der Meché et al. 1992; van der Meché, Van Doorn, 1995) the younger age of CMV-GBS patients may explain the ability to recover at an even later stage during the disease (see figure 2). An alternative explanation may be that CMV-associated GBS patients have a more severe demyelination in comparison with the other patients or have a more strategic localization of the demyelinating lesions, e.g., in the nerves involved in respiration. Both have a high potential for recovery compared to wide spread axonal degeneration, the cause of late and incomplete recovery that might be involved in the *C. jejuni* group, which do not show early recovery (van der Meché et al. 1991; Rees et al. 1995; Visser et al. 1995).

Treatment for CMV-associated GBS should be optimized with the aim to prevent the initially severe course. The response to IVIg seemed better than to PE, but both groups were small. However, for the different groups treated with IVIg, the median time to the stage of independent locomotion was longest for the CMV group (55 days) in comparison to the *C. jejuni* and the other GBS group. The results of the ongoing double-blind, multicentre trial assessing the possible synergistic effect of intravenous methylprednisolone in combination with IVIg may indicate whether this treatment lead to an improved early outcome for the CMV-GBS group (The Dutch Guillain-Barré Study Group, 1994).

This study supports the presumption that the heterogeneity of GBS is due to different pathophysiologic mechanisms. Not only the features of the CMV- and *C. jejuni*-GBS group clearly differ, but the third GBS group, the remainder of the patients, could also be distinguished from the patients in the first two groups. Further research is needed to disclose the pathophysiologic mechanisms involved in the CMV-associated GBS subgroup.

In conclusion, this study showed that the clinical pattern of GBS, especially the severity of sensory loss, depended upon the antecedent infection. Determining the causal viral or bacterial infection may have important implications for predicting outcome. Investigation of the clinical subgroups may result in a better understanding of the different pathophysiologic mechanisms involved in GBS.

Chapter 5

C. jejuni induced acute motor-sensory neuropathy and acute motor neuropathy

two distinct entities?

(submitted for publication)

Contents Chapter 5

5.1 Introduction

Guillain-Barré syndrome (GBS) is a heterogeneous disease (Asbury, Cornblath, 1990; van der Meché, van Doorn, 1995). Recent studies show that preceding infections have an important role in determining the clinical presentation in GBS (Ho et al. 1995; Visser et al. 1995, 1996 (Chapter 3,4); Jacobs et al. 1996). *Campylobacter jejuni* (*C. jejuni*) is the most common infection associated with GBS. In the Western world *C. jejuni* infections have been related with acute motor GBS (Visser et al. 1995, Chapter 3). In a collaborative study by Chinese and American scientists also an association was found with a pure motor axonal form, which has been called acute motor axonal neuropathy or AMAN (McKhann et al. 1993; Ho et al. 1995). Recent immunohistochemical studies in AMAN showed that an antibody- and complement-mediated attack on the axolemma of motor fibers is likely to play a role in these patients (Hafer-Macko et al. 1996). In China, a limited number of patients with both motor and sensory involvement has been identified; this has been called acute motor and sensory axonal neuropathy or AMSAN. The diagnosis of AMSAN was based on the pathology showing ongoing wallerian-like degeneration of fibers in the ventral and dorsal roots and in the peripheral nerves only minimal demyelination (Griffin et al. 1996). Two of the four discussed patients had serological evidence of a recent *C. jejuni* infection. Based on immunopathology Griffin et al. (1996) suggested that AMAN and AMSAN are caused by a similar immunopathogenetic mechanism with a specific immune attack directed toward certain epitopes on the axon. It is suggested that AMSAN in fact represents a more severe form of AMAN. The clinical, laboratory and electrodiagnostic features of a group of Dutch patients with acute motor GBS strongly resemble the features of AMAN (Visser et al. 1995). Both are associated with *C. jejuni* infection and anti-GM1 antibodies. In a group of 147 GBS patients, we found that 14 GBS patients developed a severe motor-sensory neuropathy after a *C. jejuni* infection. To investigate whether *C. jejuni* associated acute severe motor-sensory GBS (AMSN) in the Western world represents indeed a more severe form of acute motor GBS (AMN) we analyzed the features of these two groups.

5.2 Patients and Methods

All patients were entered into the Dutch GBS trial, a multicentre clinical trial comparing the effect of intravenous immune globulins (IVIg) with plasma exchange (PE). The background, design and results of this study have been published elsewhere (van der Meché et al. 1992). Before the start of treatment the following features were determined: age, sex, antecedent episodes in the four weeks before onset of weakness (a gastrointestinal or upper respiratory tract infection), time from onset of weakness until start of treatment, distribution of muscle weakness (predominantly distal, proximal, global or mixed according to the method described elsewhere (Visser et al. 1995)), Functional (F)-score (van der Meché et al. 1992), MRC-sumscore (Kleyweg et al. 1991), presence of sensory loss and cranial nerve deficits.

The method of assessment of severity of motor weakness and sensory loss (none, mild or severe) during follow-up has been described elsewhere (Visser et al. 1996).

Pretreatment serum samples were tested using an enzyme linked immunosorbent assay (ELISA) for the presence of IgA, IgM and IgG antibodies to *C. jejuni* using an acid-glycine extract from *C. jejuni* as antigen (IgG: indirect ELISA (Herbrink et al. 1988), IgM and IgA: class-capture ELISA (Herbrink et al. 1987)). Antibody assays were performed with a panel of gangliosides comprising GM1, GM2, GM3, GD1a, GD1b, GT1b, GQ1b, LM1 in an ELISA and thin layer chromatography overlay technique according to the method described by Jacobs et al. (1996).

The patients with positive *C. jejuni* serology and without sensory loss during follow-up were the patients with acute motor GBS (AMN) and those with severe sensory loss during follow-up formed the acute severe motor-sensory group (AMSN).

Electrodiagnostic testing was performed using standardized conventional techniques at entry and 1 and 4 weeks after randomization. The details of testing have been reported earlier (Meulstee et al. 1995a). To assess the presence of demyelination we used the slightly modified electrophysiological criteria of Cornblath (1990). The criteria for demyelination: CMAP reduction, prolonged distal motor latencies (DMLs) and reduction in conduction velocity in motor nerves (m-NCV) were scored for each patient; one point for each positive item with a maximum of three points for one nerve and six points

for the investigated median and ulnar nerves (Visser et al. 1995, Chapter 3). Several clinical and laboratory characteristics of the two groups were analyzed using the chi-2 test for comparison of proportions and the Wilcoxon-Mann-Whitney test for comparison of means of ordinal variables between the two groups.

5.3 Results

5.3.1 Clinical characteristics

C. jejuni infection was present in 46 (34%) of the 133 tested patients; 14 patients had an AMN and 14 patients had the clinical presentation of AMSN. Three AMSN patients had a concomitant cytomegalovirus infection. Analysis of the data without these three patients did not change the results. The results are shown in table 1. The patients with AMN significantly more often had a gastrointestinal illness before onset of muscle weakness and a predominant distal weakness in comparison to the AMSN group. The AMSN patients significantly more frequently experienced paresthesias before onset of muscle weakness, had during follow-up more frequently cranial nerve involvement and needed more often artificial ventilation, although the severity of muscle weakness as expressed by the MRC-sumscore did not differ between the two groups. Recovery was the same in both groups, although the AMN patients treated with PE did significantly worse in comparison to the AMSN patients treated with PE, while they did slightly, but not significantly, better after IVIg treatment.

Features	AMN (N=14)	AMSN (N=14)	P-value[b]
Age (mean ± SD)	45 ± 23	46 ± 21	ns[c]
Sex			
men	10 (63%)	6 (49%)	ns
women	4 (37%)	8 (51%)	
Clinical characteristics			
• Time until F ≥ 3 (in days, mean)[a]	2.9 (1.8 - 4.0)	5 (2.4 - 7.6)	ns[c]
• Time until nadir (in days, mean)	6.6 (4.2 - 9.0)	9.6 (6.6 - 12.5)	0.05[c]
• Cranial nerve involvement	4 (29%)	12 (86%)	0.002
• Predominant weakness			
Distal	11 (79%)	5 (36%)	0.02
Proximal	1 (7%)	2 (14%)	ns
Global	1 (7%)	6 (43%)	0.03
Mixed	1 (7%)	1 (7%)	ns
• F-score at nadir[a]			
F=3	1 (7%)	0 (0%)	0.03
F=4	9 (64%)	3 (21%)	
F=5	4 (29%)	11 (79%)	
• MRC-sumscore at entry,mean	30 (21 - 39)	36 (27 - 45)	ns[c]
• MRC-sumscore at nadir,mean	20 (10 - 30)	21 (10 - 31)	ns[c]
• F ≤ 2 after 6 months[a]			
Overall	8 (57%)	9 (64%)	ns
After IVIg treatment	8/9 (89%)	3/6 (50%)	0.1
After PE treatment	0/5 (0%)	6/8 (75%)	0.008
Antecedent infections			
• gastrointestinal tract	8 (57%)	2 (14%)	0.02

Table 1. Clinical factors associated with AMN and AMSN patients.
Between brackets percentages or 95% confidence interval
a: F-score: 0 denotes healthy; 1, having minor symptoms and signs but fully capable of manual work;2, able to walk ≥ 10 m without assistance; 3, able to walk ≥ 10 m with a walker or support; 4, bedridden or chairbound; 5,requiring assisted ventilation for at least part of the day; and 6, dead.b: p-values were derived from the chi-square test, two tailed unless indicated otherwise. c: Wilcoxon-Mann-Whitney test,two tailed.ns= not significant; MRC=medical research council score

5.3.2 Immunology

In the AMN group, 11 (79%) of the 14 patients had raised anti-ganglioside antibody titers as compared with 4 (29%) of the 14 AMSN patients (p=0.008). Eleven (79%) of the 14 AMN patients had anti-GM1 antibodies in comparison to 3 (21%) of the 14 AMSN patients (p=0.002). In the AMN group, one (7%) patient had anti-GM2, six (43%) had anti-GD1b and two (14%) had anti-LM1 antibodies, while in the AMSN group two (14%) had anti-GD1b and one had anti-GQ1b antibodies (differences not significant). None of the patients had raised antibody titers against GM3, GD1a or GT1b.

5.3.3 Electrophysiology

Electrophysiological data were available for 12 of the 14 AMN patients and 13 of the 14 AMSN patients. Data from the second EMG obtained at the time of nadir concerning ulnar and median motor nerve studies of the AMN and AMSN patients are presented in table 2. In one AMN patient both nerves were inexitable and in one patient the median nerve was inexitable with low CMAPs after distal stimulation of the ulnar nerve. Three AMSN patients had inexitable median and ulnar nerves (see table 2). DMLs were slightly shorter in AMN patients. The mean value of the DMLs in the third EMG, obtained three weeks after the second one, showed significant differences between the two groups: for the AMN group the mean ulnar DML was 2.8 (95% c.i. 2.3 - 3.4) and the median DML 3.9 (95% c.i. 2.4 - 5.4), while this was 4.7 (95% c.i. 3.8 - 6.4) for the ulnar DML (p = 0.03) and 6.7 (95% c.i. 4.7 - 8.6) for the median DML (p=0.03) in the AMSN group. Nerve conduction velocities and amplitudes after distal nerve stimulation of the median and ulnar nerves did not differ significantly between the two groups.

Sensory conduction evaluation was available for 11 of the 14 AMN patients and 12 of the 14 AMSN patients at the second EMG. In one of the AMN patients median and ulnar sensory potentials were absent; three AMN patients had amplitudes below 10μV of the ulnar and median sensory potentials; one patient of only the ulnar sensory potential and one of only the median sensory potential, but nerve conduction velocities were normal in all these patients. In five of the AMSN patients median and ulnar sensory potentials were absent; three patients had either absent ulnar or median sensory potentials. Only one AMSN patient had a sensory potential of both ulnar and median nerve above 10μV with normal conduction velocities.

Using the scoring system for demyelination as described in the methods, we found no item fulfilling the criteria of demyelination in five AMN and two AMSN patients. The items for demyelination were slightly more often positive in the AMSN group (table 2).

	AMN		AMSN		P-value[a]
	MEAN	CI	MEAN	CI	
Median nerve					
• Number	11	-	13	-	
• Distal latency (msec)	5.0	2.5-7.4	7.2	5.1-9.3	0.05
• CV (m/sec)	51	45-58	46	34-58	0.70
• Amplitude(mV)					
Wrist	3.1	0.5-5.6	5.1	1.4-6.3	0.60
Elbow	2.3	0.2-4.5	3.7	1.4-6.1	0.50
Ulnar nerve					
• Number	12	-	12	-	
• Distal latency (msec)	3.2	2.9-3.6	4.5	3.0-6.0	0.19
• CV (m/sec)	59	45-72	50	39-61	0.32
• Amplitude(mV)					
Wrist	2.2	0.4-4.1	3.4	0.7-6.1	0.68
Elbow	0.7	0.2-1.3	2.8	0.6-5.0	0.17
Demyelination					
• no data	2		1		
• nerves inexitable	1		3		
• 0/6 (0/3[b]) items positive	5		1 (1[b])		
• 1/6 (1/3[b])items positive	2 (2[b])		-		
• 2/6 items positive	2		6		
• 3/6 items positive	-		1		
• 4/6 items positive	-		1		

Table 2. Motor nerve conduction studies in AMN and AMSN patients: mean and 95% Confidence Interval (CI)

CV = conduction velocity;

a: p-values were derived from the Wilcoxon-Mann-Whitney test, two-tailed.

b only one nerve investigated. Positive items for demyelination: CMAP reduction, prolonged distal motor latencies (DMLs) and reduction in conduction velocity in motor nerves (m-NCV) were scored for each patient; one point for each positive item with a maximum of three points for one and six points for the two investigated nerves.

5.4 Discussion

This study shows that the clinical, immunological and electrophysiological features of *C. jejuni* associated AMN and AMSN are different. AMN is characterized by a preceding gastrointestinal illness, rapid onset of weakness, an early nadir, an initially predominant distal weakness and sparing of the cranial nerves. The AMSN patients on the other hand often have paresthesias before onset of muscle weakness, global weakness, high incidence of respiratory insufficiency and often cranial nerve involvement. The rare occurrence of diarrhea in the *C. jejuni* associated AMSN patients is an interesting finding that can not be easily explained. Although both forms show some difference in distribution of muscle weakness, the severity of weakness and outcome is similar.

AMN is associated with presence of anti-GM1 antibodies, but for the AMSN patients we were unable to detect a specific antiganglioside antibody phenotype.

The electrophysiological data show that DMLs are shorter in AMN patients compared to the DMLs in AMSN patients and sensory potentials are as expected more often present in the AMN group. Motor nerve conduction velocities and amplitudes after distal nerve stimulation of the median and ulnar nerves did not differ significantly between the two groups.

These differences in clinical, immunological and electrophysiological findings make it unlikely that both forms are caused by a similar immunopathogenetic process. Therefore, in our study AMSN seems not to be just a more severe manifestation of AMN.

The possible mechanism in acute motor (axonal) GBS or AMN related to *C. jejuni* is that enteric infection of certain strains of *C. jejuni* induces an antibody response to GM1 (Oomes et al. 1995; Yuki et al. 1995); these antibodies may recognize GM1 or other glycoconjugates at the nodes of Ranvier and bind with or without complement activation to that location (Takigawa et al. 1995) leading to impairment of conduction, possibly by interfering with sodium channels, resulting in paresis. The binding of these antibodies may further activate the immune system and attract macrophages which strip the myelin from the axon (Hafer-Macko et al. 1996). After a few weeks axonal degeneration may occur.

Our data show that both groups have minor signs for demyelination using the stringent criteria proposed by Cornblath and Asbury (1990), although more items were positive in the AMSN than in the AMN group. These data

suggest a primary axonal neuropathy similar to that of AMAN and AMSAN as described by the group of Griffin et al.(1996). For our patients, however, we prefer to use AMN / AMSN in stead of AMAN / AMSAN, since by EMG methods it is difficult to determine whether the acute polyneuropathies are primary demyelinating or axonal (van der Meché et al. 1991; Meulstee et al 1995a). Moreover, the terms AMAN and AMSAN are based on very carefully executed pathological studies; autopsies are, however, rare in the Western world.

Based upon clinical and immunological findings we conclude that in the Western world AMSN is not simply a more severe manifestation of AMN. It is likely that a different immune pathogenetic process occurs in AMSN; future research is needed to identify this mechanism.

Chapter 6

Prognosis of the Guillain-Barré syndrome after treatment with high-dose intravenous immune globulins or plasma exchange

the pivotal role of a preceding gastrointestinal illness on the effect of treatment

(submitted for publication)

Contents Chapter 6

6.1 Introduction

Guillain-Barré syndrome (GBS) is an acute immune-mediated disease of the peripheral nervous system with a wide range of clinical symptoms and a great variability in outcome. Artificial respiration is required in 10-35% of the patients and 5-10% may have permanent disabling weakness, imbalance or sensory loss (de Jager, Minderhoud, 1991; Ropper, 1992; van der Meché, van Doorn, 1995).

Plasma exchange (PE) improves the early outcome and we have shown that high-dose intravenous immune globulins (IVIg) are at least as effective as PE (van der Meché et al. 1992). Although IVIg is potentially a safer and more convenient treatment, morbidity is still considerable. For those with a poor prognosis, additional treatment needs to be developed. Therefore identification of easily obtainable prognostic factors has therapeutic implications. Furthermore, prediction of the clinical course may help to improve information to and support of the individual patient.

Until now severely reduced amplitude of muscle action potentials on myography (Gruener et al. 1987; Miller et al. 1988; Winer et al. 1988a; Cornblath et al. 1988; McKhann et al. 1988), older age (Gruener et al. 1987; Winer et al. 1988a; McKhann et al. 1988; Smith, Hughes, 1992; Rees et al. 1995b), need for ventilatory support (Miller et al. 1988; Winer et al. 1988a; McKhann et al. 1988; Rees et al. 1995b) and a severe, rapidly progressive course of the disease (Ropper, 1986; Miller et al. 1988; Winer et al. 1988a; McKhann et al. 1988; Palace, Hughes, 1994; Rees et al. 1995b) have been associated with a poor outcome in the studies of GBS patients dealing with multivariate analysis. In the article about the efficacy of IVIg, we briefly commented on these known prognostic factors, primarily with the aim of adjusting for imbalances of these prognostic factors between the two treatment groups (van der Meché et al. 1992). At randomization and during follow-up we also assessed a number of other clinical and laboratory features. Antecedent infections and anti-GM1 antibodies were determined and electrodiagnostic studies were performed longitudinally. We and others have already commented on the prognostic role of a recent *Campylobacter* infection (van der Meché et al. 1992; Rees et al. 1995b; Jacobs et al. 1996). In this study multivariate analysis (logistic regression) was performed, firstly using clinical factors and then with the addition of ancillary investigations.

The study was performed (1) to confirm previous factors related to a poor outcome and to assess new prognostic factors, (2) to identify prognostic

factors of GBS patients after IVIg treatment and to determine differences in prognostic factors between IVIg and PE and (3) to construct practical models to predict short-term outcome (at 8 weeks) and outcome at 6 months.

6.2 Methods

6.2.1 Outline of the study

All patients were entered into the Dutch GBS trial, a multicenter clinical trial comparing the effect of IVIg and PE, the background, design and results of which have been published elsewhere (van der Meché et al. 1992). In brief, 147 consecutive patients in 15 centers, fulfilling the criteria for GBS, who were unable to walk 10 meters independently and were within two weeks of the onset of weakness were included in the study. The criteria for exclusion were age under 4 years, a previous episode of GBS, previous allergic reactions to properly matched blood products, known selective IgA deficiency, pregnancy, severe concurrent medical disease or unavailability for follow-up during the next six months. To assess the motor function at randomization and during follow-up, a seven-point functional scale and the Medical Research Council sumscore (MRC-sumscore) for six bilateral muscle groups (abduction of the arm, flexion of the forearm, extension of the wrist, flexion of the leg, extension of the knee and dorsal flexion of the foot) were used. The MRC-sumscore ranged from 60 (normal) to 0 (quadriplegic) (Kleyweg et al. 1991). The functional scale (F-score) was defined as follows: 0 = healthy; 1 = minor symptoms and signs but fully capable of manual work; 2 = able to walk more than 10 m without assistance; 3 = able to walk 10 m with a walker or support; 4 = bedridden or chairbound (unable to walk 10 m with a walker or support); 5 = requiring assisted ventilation for at least part of the day; and 6 = dead.

6.2.2 Clinical assessment at the start of treatment

Before the start of treatment the following features were determined: age, sex, antecedent episodes in the four weeks before onset of weakness (a gastrointestinal or upper respiratory tract infection), time from onset of weakness until start of treatment, distribution of muscle weakness (predominantly distal, proximal, global or mixed according to the method described elsewhere (Visser et al. 1995)), F-score, MRC-sumscore, presence of sensory loss and cranial nerve deficits.

6.2.3 Clinical assessment during follow-up

During follow-up: the F-score, MRC-sumscore and presence of cranial nerve palsies were determined 3 times a week during week 1 and 2, once a week up to week 6, and in week 8, 10, 14, 18, 22 and 26. The method of assessment of severity of sensory loss (none, mild or severe) during the first two weeks of follow-up has been described elsewhere (Visser et al. 1996). The 147 GBS patients were followed up in a prospective study and the highest functional score, lowest MRC-sumscore, severity of sensory loss at nadir, and time until the lowest MRC-sumscore (time until nadir) could be determined from the data. These factors were known within the first two weeks of follow-up.

6.2.4 Electrodiagnostic studies at start of treatment and during follow-up

Electrodiagnostic testing (EMG) was performed using standardized conventional techniques at entry, one week and 4 weeks after randomization. The details of testing have already been reported (Meulstee et al. 1995a). Since other studies emphasized the importance of the prognostic value of electrophysiologic parameters (Winer et al. 1988a; Cornblath et al. 1988; McKhann et al. 1988), these variables were tested extensively. We used the amplitude of the compound muscle action potential (CMAP) of the abductor pollicis brevis muscle (APB) after distal stimulation of the median nerve, the CMAP of the abductor digiti quinti muscle (ADQ) after distal stimulation of the ulnar nerve and the sum of these CMAPs. The EMG data obtained at randomization and one week later were used. Improvement of the distal compound muscle action potentials after stimulation of the ulnar and median nerves was also taken into account. Improvement of the CMAP after one week was established when the increase in the CMAP of the individual nerves at the second investigation was >1mV in comparison to the first EMG and the summated compound action potential improved by more than 2mV. As our study is the first with a prospective follow-up of electrophysiological data in a large group of GBS patients, these measurements were included in the univariate and multivariate analysis. The peroneal nerve was tested in only 52 patients. Recruitment pattern on maximal voluntary effort, an important prognostic factor in univariate analysis (Meulstee et al. 1995b), was available for only 101 patients. These data were therefore excluded from the analyses.

6.2.5 Laboratory studies before onset of treatment

Our report of the results of the Dutch GBS trial included data of *Campylobacter jejuni (C. jejuni)* serology, tested by counterimmunoelectrophoresis (van der Meché et al.1992). As better techniques have become available, all pretreatment samples were retested using an enzyme-linked immunosorbent assay (ELISA) for the presence of IgA, IgM and IgG antibodies to *C. jejuni* using an acid-glycine extract from *C. jejuni* as antigen (IgG: indirect ELISA, (Herbrink et al. 1988) IgM and IgA: class-capture ELISA (Herbrink et al. 1987)). The ELISA test to detect IgA, IgM and IgG antibodies to ganglioside GM1 was also optimized and thin layer chromatography was used for confirmation (Jacobs et al. 1996). IgM antibodies against cytomegalovirus (CMV) in the initial serum samples were determined by ELISA (Vidas, bioMésieux, Mercy-l'Etoile, France).

6.2.6 Statistical Methods

Endpoints were the ability to walk independently at 8 weeks and after 6 months. Eight weeks was chosen as one endpoint because half of the 147 patients were able to walk independently at this point. The final clinical assessment was performed at 6 months. Patients who are not able to walk independently at this stage are likely to be the ones who are left with considerable clinical deficits.

The identification of prognostic factors for each combination of binary outcome (ability to walk independently at 8 weeks and after 6 months) and set of potential prognostic factors was performed using the following strategy. (1) Each factor was recoded to a binary variable if necessary. Cut-off points were based on literature or median values. Factors with three categories were recoded to two dummy variables. (2) Univariate associations for each factor separately were assessed with the chi-square test without correction for continuity. (3) Forward and backward stepwise logistic regressions were applied with two different sets of entry and drop criteria: p-enter=0.25, p-remove=0.35 and p-enter=0.15, p-remove=0.20. Only factors with significant ($p<0.05$, Wald test) coefficients were finally maintained. (4) For the selected factors the interaction with treatment was incorporated into the model when significant ($p<0.05$). (5) The overall fit of the model was studied using the Hosmer-Lemeshow test. (6) For each combination of outcomes of the selected prognostic factors (that is a covariate pattern), the prediction and 95% confidence limits of the prediction were calculated. A graph of this

prediction (and confidence limits) versus the index values (linear combination of the prognostic factors from the logistic model for each covariate pattern) is presented for the two treatments separately.
Firstly, the clinical features were analyzed in rank-order, followed by the electrodiagnostic and laboratory findings.

6.3 Results

6.3.1 Univariate Analysis of factors influencing outcome

Outcome at 8 weeks and 6 months

Table 1 summarizes the results of the univariate analyses of the baseline characteristics. Of all potential prognostic clinical factors evaluated, age ≥ 50 years, MRC-sumscore below 40, a preceding gastrointestinal illness, being bedbound or on the ventilator were associated with a significantly increased risk of not being able to walk independently 8 weeks or 6 months after the start of therapy. An upper respiratory tract infection (URTI) was related to an improved outcome 8 weeks after the start of treatment, but did not remain significant at the endpoint of 6 months. Rapid onset of weakness (≤ 4 days) before the start of treatment only resulted in a poor outcome at 6 months, and was not of significance at eight weeks.

Table 1 also summarizes the univariate analysis of prognostic factors obtained through ancillary investigations obtained at randomization. A CMAP of the ADQ ≤ 3 mV was associated with a poorer outcome at both 8 weeks and 6 months, while a CMAP of the APB ≤ 3 mV was not a prognostic factor and the sum of the CMAPs ≤ 6 mV was only a relevant prognostic factor at 8 weeks. Presence of anti-GM1 antibodies reached statistical significance at 6 months and a recent *C. jejuni* infection was strongly associated with a poor outcome at that stage.
Table 2 gives details of the univariate analysis of the clinical and electrophysiological data obtained during the first two weeks of follow-up (at nadir). MRC-sumscore ≤ 30 and the fact that ventilation was required during follow-up were associated with a decreased recovery. The low compound muscle action potential after distal stimulation of the ulnar nerve, median nerve and the sum of these potentials obtained 1 week after randomization were all strongly related to a poorer recovery. Improvement of the amplitude of more than 1 mV between the first and second EMG indicated an improved outcome (table 2).

Endpoints			8 weeks		6 months	
Factors		number (N)	not able to walk independently (%)	P-Value	not able to walk independently (%)	P-Value
Clinical factors						
• age	<50 years	73	28 (38%)	0.004	11 (15%)	0.01
	≥ 50 years	74	45 (62%)		24 (33%)	
• MRC sum	< 40	73	46 (63%)	0.001	27 (37%)	<0.001
score at entry	≥ 40	74	27 (37%)		8 (11%)	
• diarrhea	yes	27	20 (74%)	0.005	14 (52%)	<0.001
	no	120	53 (44%)		21 (18%)	
• URTI	yes	52	18 (35%)	0.007	8 (15%)	0.08
	no	95	55 (58%)		27 (28%)	
• onset of	≤ 4 days	76	40 (53%)	ns	25 (33%)	0.007
weakness	>4 days	71	33 (46%)		10 (14%)	
• F-score at	3	29	6 (21%)	0.002	3 (10%)	0.075
entry	4	93	53 (67%)		23 (25%)	
	5	25	14 (56%)		9 (36%)	
Laboratory findings						
• CMAP ADQ	≤3 mV	43	28 (65%)	0.039	17 (40%)	0.006
	> 3 mV	82	37 (45%)		14 (17%)	
• SUM of the	≤ 6 mV	43	29 (67%)	0.007	14 (33%)	ns
CMAPs	>6 mV	78	34 (44%)		16 (21%)	
• anti-GM1	yes	23	13 (57%)	ns	9 (39%)	0.05
antibodies	no	110	52 (47%)		22 (20%)	
• *C. jejuni*	yes	46	28 (61%)	0.04	20 (44%)	<0.001
infection	no	87	37 (43%)		11 (13%)	
• CMV infection	yes	20	13 (65%)	0.1	5 (25%)	ns
	no	118	60 (47%)		28 (24%)	

Table 1. Univariate analysis of clinical, electrodiagnostic and laboratory factors associated with a difference in the ability to walk independently at 8 weeks and 6 months after start of treatment

URTI=upper respiratory tract infection; CMAP=compound muscle action potential; ADQ= abductor digiti quinti; *C. jejuni=Campylobacter jejuni*; CMV= cytomegalovirus

Endpoint			6 months	
Factors		number (No.)	No. not able to walk independently (%)	P-Value
Clinical factors				
• time until nadir	≤ 8 days	75	22 (29%)	0.10
	> 8 days	72	13 (18%)	
• MRC-sumscore at nadir	≤ 30	69	29 (42%)	< 0.001
	> 30	78	7 (8%)	
• cranial nerve deficits	yes	88	16 (18%)	0.07
	no	59	19 (32%)	
• F-score at nadir	3	9	1 (11%)	< 0.001
	4	74	11 (15%)	
	5	64	23 (35%)	
• Severity of sensory loss	none	27	8 (30%)	< 0.001
	mild	95	14 (15%)	
	severe	25	13 (52%)	
Electromyography at nadir				
• CMAP ADQ	≤ 3 mV	44	21 (48%)	<0.001
	>3 mV	82	10 (12%)	
• CMAP APB	≤ 3 mV	60	22 (37%)	0.002
	>3 mV	67	9 (13%)	
• SUM of the CMAPs	≤ 6 mV	43	21 (49%)	<0.001
	>6 mV	81	10 (12%)	
difference second CMAP - first CMAP ADQ	>1mV	31	2 (6%)	0.006
	≤ 1 mV	89	28 (31%)	
difference second CMAP -first CMAP APB	>1mV	33	2 (6%)	0.003
	≤ 1 mV	87	28 (32%)	
difference second - sum of CMAPs	>1mV	33	3 (9%)	0.01
sum of first CMAPs	≤ 1 mV	83	26 (31%)	

Table 2. Univariate analysis of clinical and electrodiagnostic factors known at nadir and associated with a difference in the ability to walk independently 6 months after start of treatment

CMAP=compound muscle action potential, ADQ= M. abductor digiti quinti; APB= M. abductor pollicis brevis

	8 weeks		6 months	
Variables	Odds ratio	P-value	Odds ratio	P-value
Clinical factors at start of treatment				
• age ≥ 50 years	0.35	0.005	0.25	0.009
• MRC-sumscore < 40	0.39	0.011	0.24	0.004
• Diarhea *	0.09	0.003	0.05	<0.001
• Time of onset of weakness ≤ 4days	ns	ns	0.26	0.006
Clinical factors and laboratory features at start of treatment				
• age ≥ 50 years	0.26	0.001	0.25	0.009
• MRC-sumscore < 40	0.38	0.011	0.24	0.004
• Diarhea*	0.06	0.001	0.05	<0.001
• Time of onset of weakness ≤ 4days	ns	ns	0.26	0.006
• CMV infection	0.21	0.008	ns	ns

** for the PE group only; ns=not significant*

Table 3. Clinical, and laboratory factors known at start of treatment related to inability to walk independently 8 weeks and 6 months after onset of therapy

6.3.2 Multivariate Analysis

6.3.2.1 Outcome at week 8

Both the MRC-sumscore and the F-score are measurements of the severity of muscle weakness. We found that the MRC-sumscore was a more powerful predictor of outcome. Therefore, the MRC-sumscore was chosen for the multivariate analyses. Using all clinical factors known at the time that treatment started, multivariate analysis revealed that age ≥ 50 years, a preceding gastrointestinal illness, MRC-sumscore of < 40 and absence of cranial nerve involvement remained independent factors indicating a poor prognosis at 8 weeks, while a preceding upper respiratory tract infection was related to an improved outcome. These five factors were put in a final model and three of them remained independently significant: age ≥ 50 years, a preceding gastrointestinal illness and MRC-sumscore of < 40. Thereafter these factors were evaluated for treatment interactions and it was found that diarrhea was only of significance in the PE treated group. In table 3 the odds ratios for the

different prognostic factors are shown. The data from multivariate analysis allow the development of tables of probabilities of reaching the stage of independent locomotion. Table 4 shows the formulas, the predicted probabilities for the most discriminating clinical factors for the two treatment groups at the 8-week endpoint.
After inclusion of the laboratory data, one additional independent prognostic factor could be found; a recent CMV infection indicated a poor outcome at 8 weeks (table 3). The electrodiagnostic data did not give rise to additional independent risk factors.
On the basis of these four factors known at randomisation, the predicted probabilities of being able to walk independently after 8 weeks and the prognostic index for the individual patient can be calculated (table 4). In figure 1 the prognostic index in relation to the predicted probabilities with the 95% confidence intervals are shown. For example if a patient is younger than 50 years, had diarrhea before onset of weakness with at start of treatment a MRC-sumscore of less than 40 without serological evidence of a CMV infection the chance of being able to walk independently after 2 months is 7% after PE treatment and 61% after IVIg treatment (see table 4). From the table one can read the prognostic index in addition: -2.62 for PE and 0.43 if the patient was treated with IVIg. In figure 1 it is shown that a prognostic index of -2.62 after PE treatment correlates with a predicted probability of 7% with a 95% confidence interval of 0-20%. If the patient is treated with IVIg the predicted probability is 61% with a 95% confidence interval of 50-75%
(see figure 1). The predictive value for the PE treated group ranges from 0 % (95% c.i. 0 - 9%) when all unfavourable factors are present to 91% (95% c.i. 73 - 97%) when the patient has all the favourable factors. These values range from 18% (95% c.i. 5 - 51%) to 75% (95% c.i. 55 - 88%) for the IVIg group (figure 1).

		Clinical factors at randomisation		Clinical and laboratory factors at randomisation			
		PE	IVIg	PE	IVIg	PE	IVIg
Patient status				**CMV positive**		**CMV negative**	
Age < 50 years							
• No diarrhea							
MRC-sumscore	≥ 40	0.79	0.75	0.56 (0.24)	0.51 (0.04)	0.91 (2.30)	0.75 (1.09)
	< 40	0.59	0.55	0.26 (-1.05)	0.35 (-0.61)	0.73 (1.01)	0.61 (0.43)
• Diarrhea							
MRC-sumscore	≥ 40	0.23	0.75	0.05 (-2.64)	0.51 (0.04)	0.21 (-1.32)	0.75 (1.09)
	< 40	0.10	0.55	0.00 (-4.67)	0.35 (-0.61)	0.07 (-2.62)	0.61 (0.43)
Age ≥ 50 years							
• No diarrhea							
MRC-sumscore	≥ 40	0.56	0.52	0.18 (-1.52)	0.23 (-1.23)	0.63 (0.53)	0.55 (0.19)
	< 40	0.33	0.31	0.06 (-2.81)	0.18 (-1.51)	0.32 (-0.76)	0.39 (-0.47)
• Diarrhea							
MRC-sumscore	≥ 40	0.08	0.52	0.03 (-3.98)	0.23 (-1.23)	0.60 (0.33)	0.55 (0.19)
	< 40	0.04	0.31	0.05 (-3.00)	0.18 (0.51)	0.01 (-4.38)	0.39 (-0.47)

Table 4. Predicted probabilities of being able to walk independently 8 weeks after start of treatment using the most discriminating prognostic factors

CMV=cytomegalovirus

Between brackets indices: the prognostic index for an individual patient at week 8 with the clinical and laboratory data has been calculated as follows: for the PE treated group index= 0.69-1.34 x age (age < 50 years=0, age ≥ 50=1)+0.98 x MRC-sumscore at start of treatment (MRC-sumscore < 40=0, MRC-sum score ≥ 40=1) -2.75 x diarrhea (no diarrhea=0, diarrhea=1) -1.56 x CMV (no CMV infection=0, CMV infection=1) and for the IVIg group index = 0.69-1.34 x age+0.98 x MRC-sumscore -1.56 x CMV. This index may be transferred to figure 1 to estimate the confidence limits.

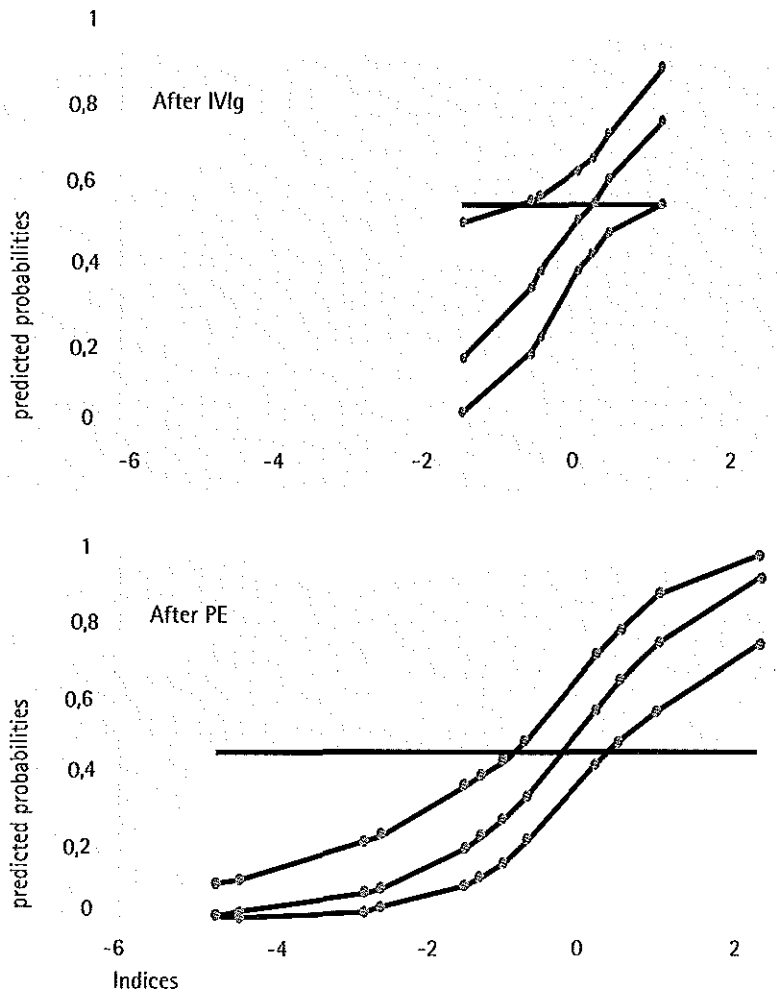


Figure 1: graph of the prediction (and confidence limits) versus the index values (linear combination of the prognostic factors from the logistic model for each covariate pattern) of the most discriminating clinical and laboratory prognostic factors 8 weeks after start of treatment for the two treatments.
The horizontal line indicates the average chance of reaching independent locomotion.

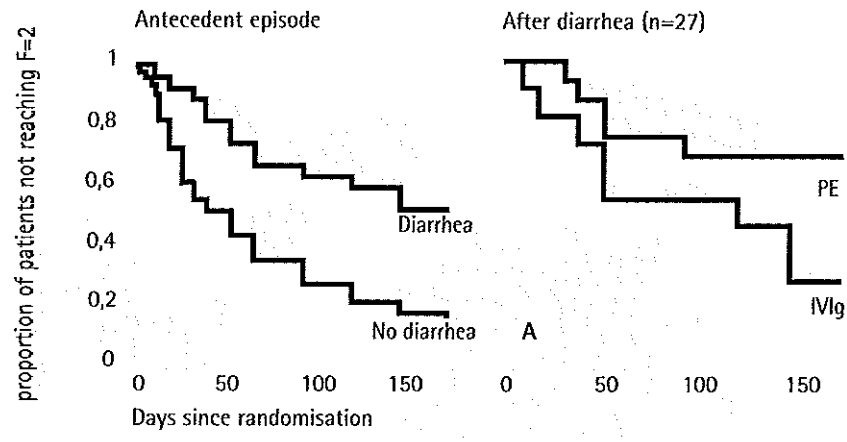
6.3.2.2 Outcome at 6 months

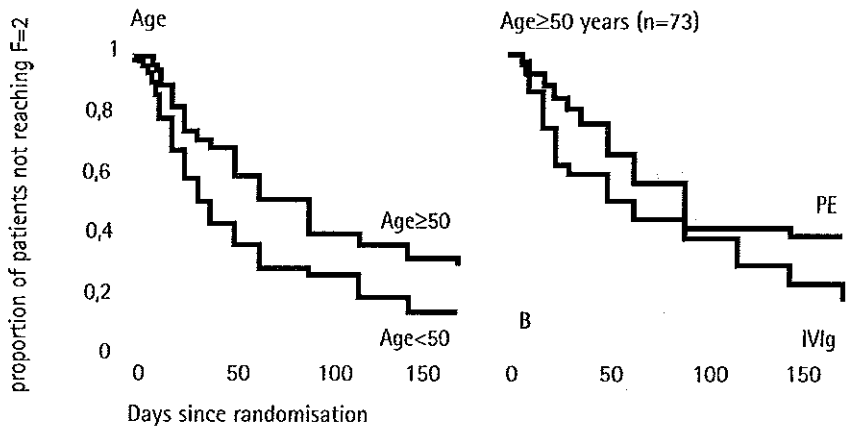
The clinical factors which were still of prognostic importance at the endpoint at 6 months were the following: older age (≥ 50 years), diarrhea, rapid onset of weakness until start of treatment (≤ 4 days) and a low MRC-sumscore (< 40) (table 3). These factors in relation to the proportion of patients who did not reach independent locomotion and according to the treatment effect are shown in the Kaplan-Meier curves (figure 2). There was a significant difference in treatment effect for those with a rapid progression of weakness and for those who had preceding diarrhea before onset of muscle weakness. Thereafter these four factors with the treatment interactions were again analyzed in a multivariate model as described in the methods. Again, diarrhea was only of significance in the PE treated group.

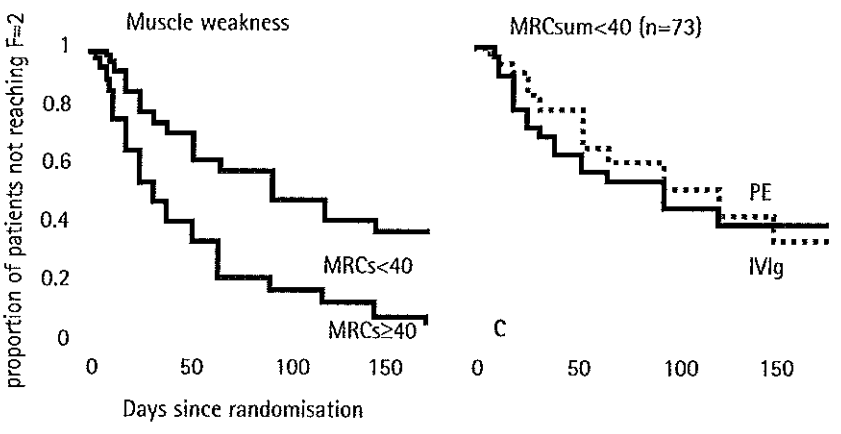
Addition of the ancillary laboratory or electrodiagnostic factors revealed only one new independent prognostic factor: serological evidence of a recent *C. jejuni* infection. However in the final model only older age, diarrhea, rapid onset of weakness until the start of treatment and a low MRC-sumscore remained significant. The prognostic indices and the predicted probabilities of reaching independent locomotion 6 months after therapy are shown in table 5 and figure 3.

Patient status		Time of onset of weakness			
		> 4 days		≤ 4 days	
		PE	IVIg	PE	IVIg
Age < 50 years					
• No diarrhea					
MRC-sumscore	≥ 40	0.99 (4.79)	0.96 (3.23)	0.96 (3.14)	0.90 (2.19)
	< 40	0.95 (3.02)	0.89 (2.11)	0.80 (1.37)	0.75 (1.08)
• Diarrhea					
MRC-sumscore	≥ 40	0.77 (1.23)	0.96 (3.23)	0.40 (-0.42)	0.90 (2.19)
	< 40	0.37 (-0.54)	0.89 (2.11)	0.10 (-2.19)	0.75 (1.08)
Age ≥ 50 years					
• No diarrhea					
MRC-sumscore	≥ 40	0.96 (3.11)	0.90 (2.17)	0.81 (1.46)	0.76 (1.13)
	< 40	0.79 (1.34)	0.74 (1.05)	0.42 (-0.31)	0.50 (0.02)
• Diarrhea					
MRC-sumscore	≥ 40	0.45 (0.28)	0.90 (2.17)	0.14 (-1.63)	0.76 (1.13)
	< 40	0.10 (-2.22)	0.74 (1.05)	0.02 (-3.87)	0.50 (0.02)

Table 5. Predicted probabilities of being able to walk 6 months after start of treatment using the most discriminating prognostic factors
In brackets: indices. The prognostic index for an individual patient can be calculated as follows: for the PE treated group index= 1.22-1.38 x age(age <50 years=0, age ≥ 50=1)+1.45 x MRC-sum score at start of treatment (MRC-sum score < 40=0, MRC-sumscore ≥ 40=1)-2.92 x diarrhea (no diarrhea=0, diarrhea=1) +1.35 x onset of weakness before start of treatment (≤ 4 days=0, > 4 days=1) and for the IVIg treated group index=1.22-1.38 x age+1.45 x MRC-sum score +1.35 x onset of weakness before start of treatment.


Antecedent episode
After diarrhea (n=27)
proportion of patients not reaching F=2
1
0,8
0,6
0,4
0,2
0
Diarrhea
No diarrhea
PE
IVIg
A
0
50
100
150
Days since randomisation


Age
Age≥50 years (n=73)
proportion of patients not reaching F=2
1
0,8
0,6
0,4
0,2
0
Age≥50
Age<50
PE
IVIg
B
0
50
100
150
Days since randomisation


Muscle weakness
MRCsum<40 (n=73)
proportion of patients not reaching F=2
1
0.8
0.6
0.4
0.2
0
MRCs<40
MRCs≥40
PE
IVIg
C
0
50
100
150
Days since randomisation

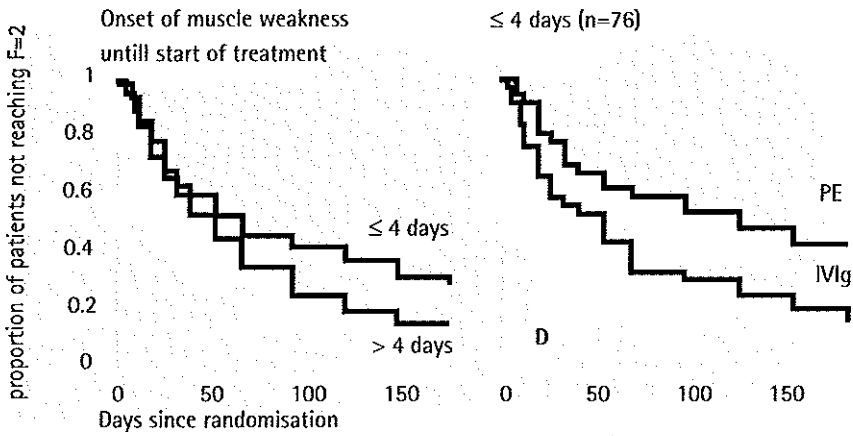


Figure 2. Kaplan-Meier curves indicating the proportion of patients who did not recover to independent locomotion (F=2) during 182 days of follow-up, according to the independent prognostic factor and according to treatment.

A: according to the presence of diarrhea (p(logrank) <0.001), and the prognostic factor diarrhea (n=27) according to the effect of PE (n=16) or IVIg (n=11), p(logrank)=0.04

B: according to age (p(logrank) = 0.005), and the prognostic factor age ≥ 50 (n=73) according to the effect of PE (n=40) or IVIg (n=33), p(logrank)= ns

C: according to the severity of muscle weakness (p(logrank) <0.001), and the prognostic factor MRC-sumscore < 40 (n=73) according to the effect of PE (n=39) or IVIg (n=34), p(logrank)=ns

D: according to the progression of muscle weakness (p(logrank) =ns), and the prognostic factor rapid progression of weakness (n=76) according to the effect of PE (n=37) or IVIg (n=39), p(logrank)=0.02

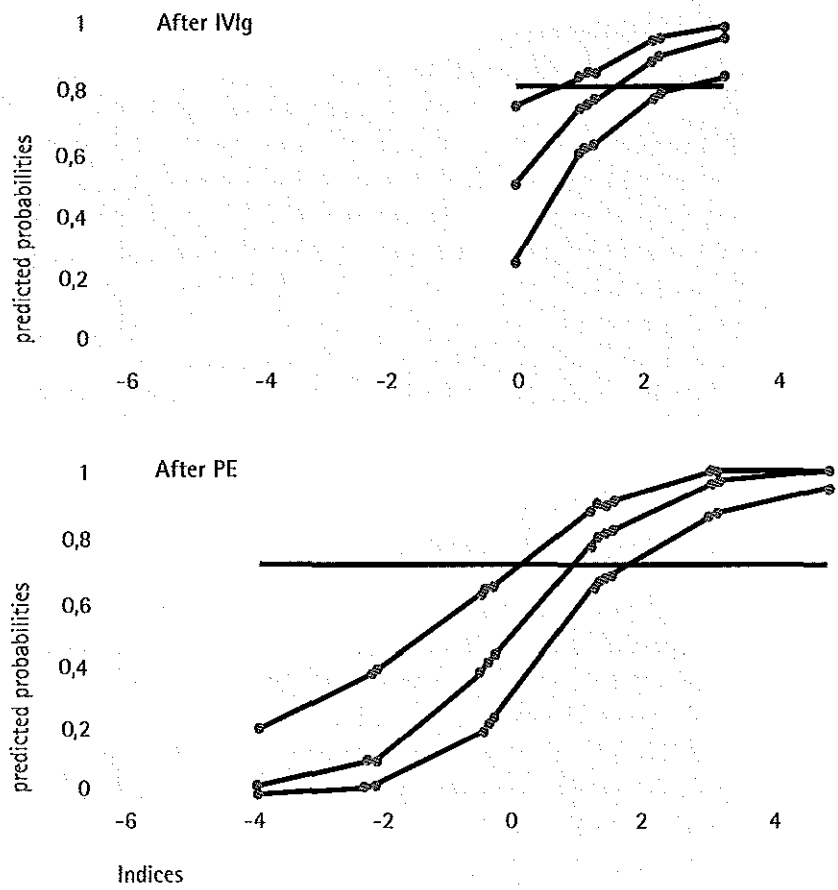


Figure 3: graph of the prediction (and confidence limits) versus the index values (linear combination of the prognostic factors from the logistic model for each covariate pattern) of the most discriminating clinical prognostic factors 6 months after start of treatment for the two treatments. The horizontal line indicates the average chance of reaching independent locomotion.

6.4 Discussion

This multivariate analysis of the clinical, electrodiagnostic and laboratory data of 147 GBS patients participating in the Dutch GBS trial produced several new findings of importance for the prediction of outcome for the individual GBS patient. The study is unique in the sense that the patients were followed up in a prospective study and closely monitored according to a predefined protocol, the laboratory results were obtained from pretreatment serum samples and electrodiagnostic testing was performed serially, at randomization and one week later (van der Meché et al. 1992; Meulstee et al. 1995). The available parameters were then tested in rank-order according to the sequence in which they became available in the clinical setting. This different method of obtaining and analyzing the data may explain certain differences in predictors of outcome in comparison to other studies dealing with the prognosis of GBS patients.

The analysis dealing with early outcome (8 weeks) revealed the following independent predictors of poor outcome (inability to walk independently): a preceding gastrointestinal illness, older age (≥ 50 years), a low MRC-sumscore (< 40) and a recent CMV infection. The same clinical factors were found at the endpoint at 6 months, with the additional factor of a rapid onset of weakness (≤ 4 days until F= 3 or more). Most importantly, we found a difference between PE and IVIg, as diarrhea was only a poor prognostic predictor in the PE group. With the use of these easily obtainable factors, the chance of being able to walk independently 8 weeks and 6 months after the start of treatment with IVIg or PE can be predicted accurately within the confidence limits.

Of the treatment studies dealing with prognosis in GBS, only the North American study (McKhann et al. 1988) has looked at prognosis at 8-12 weeks. The researchers also found that severity of muscle weakness, indicated by respiratory insufficiency and older age were related to a poor outcome. In their analysis they did not consider the other factors of prognostic importance that we determined: a history of a gastrointestinal illness and laboratory support of a recent CMV infection.

The prognostic value of positive IgM CMV serology in predicting early outcome has not been reported before, as other studies looked at outcome at 6 or 12 months (Winer et al. 1988a) or did not add this factor into multivariate analysis (Gruener et al. 1987; Miller et al. 1988; McKhann et al. 1988; Smith, Hughes, 1992). Recently we emphasized the clinical and prognostic

importance of the assessment of a recent CMV infection in GBS (Visser et al. 1996, Chapter 4). Although in general the CMV-related GBS patients initially had a fulminant course, most of the patients recovered at a later stage. This may be due to the younger age of these patients (Visser et al. 1996, Chapter 4).

The most powerful predictor of outcome for early and intermediate recovery was an antecedent episode of diarrhea. Only two recent studies with a relatively small number of patients indicated that a history of diarrhea is associated with poor outcome (Smith, Hughes, 1992; Palace, Hughes, 1994). The studies with a large number of GBS patients and dealing with prognosis did not take this factor into account (Winer et al. 1988a; McKhann et al. 1988). Although diarrhea and *C. jejuni* infection were analyzed as independent factors, they are in fact strongly related to each other. Seventy-five percent of the patients with diarrhea had positive *C.jejuni* serology, yet only half of the patients with positive serology had preceding diarrhea. Furthermore, *C.jejuni* has been found to be strongly associated with motor GBS and anti-GM1 antibodies (Yuki et al. 1990; Rees et al. 1995a; Rees et al. 1995b; Visser et al. 1995; Jacobs et al. 1996). Because of the close relation in the multivariate analysis only diarrhea remained statistically significant in the final models.

The analysis of treatment interactions revealed that diarrhea is only of prognostic value in the PE group. This is consistent with earlier findings that showed that patients with *C. jejuni* infection, anti-GM1 antibodies and motor GBS improved less after PE compared to IVIg (Visser et al. 1995, Chapter 3; Jacobs et al. 1996). All patients with diarrhea and with poor outcome received the full regimen of PE. Another difference between PE and IVIg was a rapid onset of weakness. This difference can possibly be explained by the fact that on average IVIg was started one day earlier than PE.

An important prognostic factor was the severity of muscle weakness determined by the MRC-sumscore. Severity of muscle weakness, usually indicated by need of artificial respiration, as a prognostic factor has also been emphasized in several other studies (Raphael et al. 1986; Miller et al. 1988; Winer et al. 1988a; McKhann et al. 1988; Rees et al. 1995b). This has important implications for the decision at which stage of the disease to start treatment. Both the French and North American study concluded that plasma exchange in GBS is mainly effective when it is carried out early in the course of the disease (The Guillain-Barré study group, 1985; French Cooperative Group on plasma exchange in Guillain-Barré Syndrome, 1987). The aim should be to stop the progression of the disease as soon as possible and this has to be

balanced against the costs. It should be realized that the severity of weakness is the only factor that can be influenced, as age and antecedent infections are unchangeable prognostic factors. Outcome could possibly be improved if treatment is given when the patient does not have severe weakness or when treatment is started early in those with a rapid progression. Seventy-three of the 147 patients had a MRC-sumscore of less than 40 at start of treatment and the median time from onset of muscle weakness until start of treatment was 5.5 (4.6 - 6.2) days in this group. This finding indicates that treatment in these patients could have been started earlier. So, early recognition may be of importance for the long-term prognosis. Thirteen of these 73 (17%) patients, who had a MRC-sumscore < 40 were bedbound within 48 hours after onset of muscle weakness. For this group therapy should especially be focused on new or additional treatment.

As IVIg is readily available and easily applicable with far fewer side effects than PE (van der Meché et al. 1992; Bouget et al. 1993) there will certainly be a tendency to treat GBS patients at an early stage of the disease. It is suggested to treat patients with predictors of poor outcome, e.g. a rapid progressive course, older age and/or diarrhea, as early as possible.

Rafael et al (1996) are studying the effect of PE in 'mildly' affected GBS patients. Interim analysis of this study suggest that two sessions of PE results in earlier recovery in comparison to no treatment. Therefore, similar studies should be performed to evaluate the optimum dose of IVIg, especially in relation to the severity of muscle weakness in GBS.

In contrast to other studies (Gruener et al. 1987; Miller et al. 1988; Cornblath et al. 1988; McKhann et al. 1988) the neurophysiological data did not give a reliable guide to the assessment of the prognosis. Although technical differences may explain some of the results, it is more likely that other factors such as severity of muscle weakness and diarrhea overshadow the importance of the electrodiagnostic findings, especially if the muscle weakness assessment is performed at the same time as the electrodiagnostic studies.

In conclusion, we confirm the importance of older age, a rapid onset and severe weakness as being important prognostic factors for outcome after 6 months. We emphasize the importance of diarrhea as a prognostic factor for the PE treated group only. Furthermore, we have shown that CMV is an important factor predicting delayed early recovery. With easily obtainable clinical data and one serological factor one is able to accurately predict the chance of reaching the stage of independent locomotion at 8 weeks and 6 months after the start of treatment.

Chapter 7

Treatment of the Guillain-Barré syndrome with high-dose immune globulins combined with methylprednisolone

a pilot study

Ann Neurol 1994; 35: 749-752.

Ann Neurol 1995; 37: 683-684 (reply)

Contents Chapter 7

7.1 Introduction

The Guillain-Barré syndrome (GBS) is a severe, subacute, immune-mediated polyneuropathy. In the previous decade it was demonstrated that plasma exchange (PE) reduced morbidity and improved outcome (The Guillain-Barré study group, 1985; French Cooperative Group on plasma exchange in Guillain-Barré Syndrome, 1987). We recently showed that high-dose immune globulins given intravenously (IVIg) are at least or even more effective than PE (van der Meché et al. 1992). Although IVIg is potentially a safer and more convenient treatment, morbidity is still considerable (van der Meché et al. 1992).

Therefore, it is necessary to search for additional treatment. We decided to evaluate the effect of treatment with the combination of IVIg and methylprednisolone (MP-IVIg) in 25 patients with GBS. The aims of this pilot study were to see whether there is a tendency for an improved outcome with MP-IVIg and whether this treatment is safe in GBS patients, before deciding to perform a large-scale randomized trial.

7.2 Patients and methods

Twenty-five consecutive patients in eight centres, fulfilling the criteria for acute GBS (Asbury, Cornblath, 1990), unable to walk 10 meters independently and within two weeks of the onset of weakness, were included in the study. The criteria for exclusion were age less than 16 years, a previous episode of GBS, previous allergic reactions to properly matched bloodproducts, known selective IgA deficiency, use of steroids, pregnancy, severe concurrent medical disease and unavailability for follow-up during the next six months. Only patients who gave informed consent took part. The protocol was approved by the ethics committee of each institution. IVIg (Central Laboratory of the Dutch Red Cross Bloodtransfusion Service (CLB), Amsterdam, the Netherlands) was given in a dose of 0.4 g per kilogram bodyweight per day for 5 consecutive days. MP was administered intravenously at a dosage of 0.5 g per day also during 5 consecutive days.

The degree of motor function was expressed on a seven-point functional scale as described earlier (van der Meché et al. 1992).

Assessments were made at study entry, once a week through week 4, in weeks 8, 10, 14, 18, 22, and 26. For each patient these follow-up assessments were done by the same clinician.

Electromyography was performed at study entry and four weeks later. This report includes only data obtained at entry concerning the amplitude of the compound muscle action potential of the abductor pollicis brevis muscle after distal stimulation of the median nerve.
Additional laboratory studies included routine testing of blood, urine, and cerebrospinal fluid, IgA, IgG, and IgM measurements; tests for antibodies against the ganglioside GM1; and serological studies for *Campylobacter jejuni.*
The F scores at entry and follow-up for the 25 patients treated with MP-IVIg were compared with the F scores in the group of 74 patients treated with IVIg in the previously performed Dutch GBS study (van der Meché et al. 1992), using the same outcome criteria as in that study. The main outcome criterion was improvement by at least one functional grade 4 weeks after entry into the study.
The secondary outcome measures were the time required to improve by at least one functional grade and the time required to improve to independent walking.
Percentages in independent groups were compared by the chi-square test. The personal-computer program STATA (version 2.05) was used. The time to reach an end point, as stated above, was analyzed by the method of Kaplan and Meier and the logrank test.

7.3 Results

Base line characteristics, especially those suggested to be of prognostic value (Winer et al. 1988a; McKhann et al. 1988; van der Meché et al. 1992) did not differ between the 74 patients treated with IVIg and the 25 patients treated with MP-IVIg (table).

7.3.1 Main outcome

In the MP-IVIg group, 19 (76%) of the 25 patients improved by one or more functional grades after four weeks, as compared with 39 (53%) of the 74 patients treated with IVIg alone (p=0.04). In a multivariate analysis (logistic regression) including the variables that may be of prognostic value (see table) the main outcome result remained significantly different in favor of the MP-IVIg treatment group.

Base line characteristics

	MP-IVIg	IVIg
• No. of patients	25	74
• Age (mean)	47.2	46.2
• Duration of disease ≤ 7 days at entry (%)	84	76
• Functional score at entry (%)		
3 ambulant with support	20	18
4 bedridden	68	66
5 artificial respiration	12	16
• Amplitude of compound muscle action potential ≤ 3mV (number tested/ %)	15/27	63/27
• Anti-GM1 antibodies (%)	40	30
• Positive *Campylobacter jejuni* serology (number tested/%)	25/24	63/25

* comparison with the chi-square test; age was tested with the unpaired ranksum test of Wilcoxon.

Table. Distribution of factors shown to have prognostic importance in previous studies, according to treatment group

7.3.2 Secondary outcome measures

At each time of data collection after entry, the proportion of patients who did not improve on the functional scale is shown in a Kaplan-Meier curve (fig. 1). The median time until improvement by one functional grade was 27 days for the IVIg group and 20 days for the MP-IVIg group (log rank test: p=0.04). The median time to recover to independent locomotion was 55 days for the IVIg treatment group and 27 days for the MP-IVIg treatment group (p=0.10) (fig. 2).

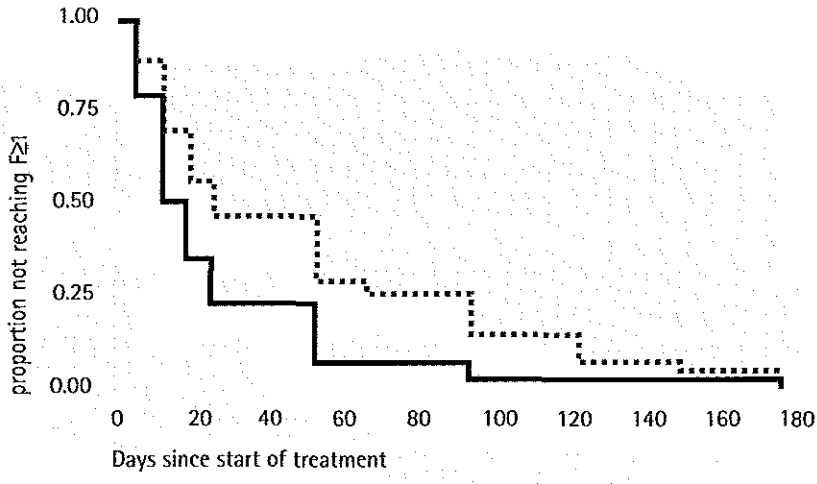


Figure 1. Kaplan-Meier Curves indicating the proportion of patients who did not have improvement by one or more functional grades during 182 days of follow-up, according to treatment group.

IVIg
MP-IVIg

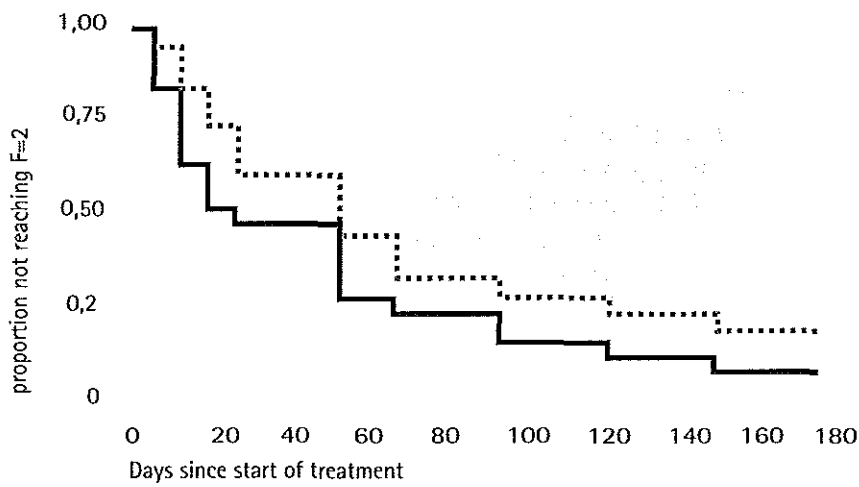


Figure 2. Kaplan-Meier Curves indicating the proportion of patients who did not recover to independent locomotion (Functional grade 2) during 182 days of follow-up, according to treatment group.

IVIg
MP-IVIg

7.3.3 Other outcome measures

The percentage of patients requiring artificial respiration was 24% in the MP-IVIg treatment group and 35% in the IVIg treatment group. The mean duration of intubation was 6 days for the MP-IVIg group and 15 days for the IVIg group. When calculated only for patients who received mechanical ventilation, these values were 26 and 43 days.

7.3.4 Safety of treatment and complications during follow-up

In 6 patients, treatment-related side effects were reported. One patient developed a *Candida albicans* infection in the mouth, one patient had fluid retention, in two patients a transient hyperglycaemia occurred, one patient developed a cystitis in the second week after treatment and one patient had an exacerbation of acne vulgaris.

All patients received the full dose of IVIg and MP. Combined treatment may therefore be safely applied, although one should be aware that the usual corticosteroid side effects may occur.

The following complications were seen: one patient with signs of severe autonomic dysfunction (especially a fluctuating bloodpressure) developed a pneumonia while on the respirator, a transient bradycardia occurred in one patient and a delirium was seen in one patient in the third week after treatment.

Treatment-related fluctuations after treatment with PE or IVIg occur in about 10 percent of the patients. With MP-IVIg the incidence of treatment-related fluctuations was not increased; it occurred in 2(8%) of the 25 patients. One patient improved after repeated MP-IVIg treatment. During this treatment the patient developed a transient, possibly allergic, skinreaction. The other patient was bedbound, while progression of muscle weakness occurred.

No clinical improvement was observed during the first 4 weeks after the second treatment.

7.4 Discussion

We decided to treat 25 GBS patients with the combination of IVIg and MP for a number of reasons. Firstly, steroids decrease disease activity in the rat experimental allergic neuritis model (Watts et al. 1989). Secondly, two open studies suggested a beneficial effect of high-dose intravenous MP in GBS patients (Haaß et al. 1988; Dowling et al. 1980). Thirdly, steroids are effective in chronic idiopathic demyelinating polyradiculoneuropathy (CIDP), which partly resembles GBS (Dyck et al. 1982). Lastly, although

there is no experience with the synergistic effect of combined treatment of IVIg and MP in GBS, limited experience has been obtained in chronic refractory thrombocytopenic purpura (ITP). One patient with ITP who inadequately reacted to either IVIg or corticosteroids responded dramatically during combined treatment (Duncombe et al. 1986).

The results of this pilot study suggest that the combined MP-IVIg treatment is more effective than IVIg treatment alone. The 25 patients were recruited from the same geographic region as the control patients, and the methodology (van der Meché et al. 1992) in the studies was similar; however, the present study was non-randomized, which means that the results need to be interpreted carefully. Furthermore, another IVIg preparation was used in this study compared to the previous study. Over the years, however, we have been using both Gammagard (Hyland, Baxter), which was used in the previous GBS study, and the Dutch (CLB) immune globulin product alternately in individual patients with CIDP, without observing any clinical difference in efficacy between the two products.

In an attempt to substantiate our findings further, we also compared the outcome of the 25 MP-IVIg patients with the results from other treatment studies. In this study the median time to walk unaided was 27 days, while with PE this end point was reached after 53 days in the North American trial (The Guillain-Barré study group, 1985) and after 70 days in the French trial (French Cooperative Group on plasma exchange in Guillain-Barré Syndrome, 1987). The percentage of patients unable to walk independently after 6 months was 8% in the MP-IVIg group; 18% in the North American PE group and 19% in the Dutch IVIg group. Therefore, the MP-IVIg group seems to have the most favorable outcome so far, using similar follow-up methodology. Recently, while this pilot study was being carried out, the results of a double-blind trial concerning the treatment with intravenous MP in GBS patients were published (Guillain-Barré Syndrome Steroid Trial Group, 1993). The main conclusion of that study was that a short course of high-dose intravenous MP given early in the course of GBS is ineffective. Use of PE in the placebo group, however, could have obscured a possible beneficial effect of MP. Sixty-six patients (53%) in the MP treated group and 77 (65%) in the placebo group received PE, a difference that is almost significant ($p=0.08$). PE could have even been started some days after randomization and in the 'PE possibly intended' group, PE finally was significantly more often applied in the placebo group compared to the MP group ($p=0.01$).

These findings raise the possibility that this MP trial is not conclusive. On the other hand it may be that MP alone or in combination with PE has little effect, but that MP in combination with another immune modulator such as IVIg has a synergistic effect. This is in fact suggested by the results of our pilot study. From the results of this pilot study and from the results of our group of 74 historical control subjects, we conclude that the response to MP-IVIg treatment in severely affected GBS patients was better compared to the effect of IVIg treatment alone. Since the effect of treatment was evaluated in an open study and with a relatively small number of patients, a double-blind randomized study is needed before applying this treatment more generally. A multicentre study comparing 2 groups of 100 patients each, one group receiving MP-IVIg and the other placebo-IVIg, is in preparation.

Chapter 8

Risk factors for treatment related clinical fluctuations in Guillain-Barré syndrome

(submitted for publication)

Contents Chapter 8

8.1 Introduction

The effect of plasma exchange (PE) and intravenous immune globulins (IVIg) has been established in the treatment of Guillain-Barré syndrome (GBS) (The Guillain-Barré study group, 1985; van der Meché et al. 1992; French Cooperative Group on plasma exchange in Guillain-Barré Syndrome, 1987,1992). One of the most important prognostic factors for the outcome of GBS patients is severity of muscle weakness (Miller et al. 1988; Winer et al. 1988a; McKhann et al. 1988; Rees et al. 1995b). In an attempt to improve this outcome neurologists may be tempted to apply PE or IVIg at an earlier stage of the disease, namely when the patients are still able to walk independently (Raphael et al. 1996). However, early relapses, treatment related fluctuations, occur in eight to ten percent of the treated patients (Osterman et al. 1986; Ropper et al. 1988; Osterman et al. 1988; Kleyweg, van der Meché, 1991). Especially GBS patients who are treated early in the course of their disease may be at risk for these relapses (Ropper et al. 1988). The aim of this study involving 172 GBS patients was to confirm or challenge this finding and to identify risk factors for the occurrence of these treatment related fluctuations.

8.2 Patients and methods

All patients participated in either the Dutch GBS trial, a multicenter clinical trial comparing the effect of IVIg and PE (van der Meché et al. 1992), or in the Dutch IVIg - methylprednisolone (MP) pilot study (The Dutch Guillain-Barré Study Group, 1994, Chapter 7). The background, design and results of these two studies have been published elsewhere (van der Meché et al. 1992; The Dutch Guillain-Barré Study Group, 1994). Briefly, 172 consecutive patients, fulfilling the criteria for GBS, unable to walk 10 meters independently and within two weeks of the onset of weakness were included in these studies.

The motor function at randomization and during follow-up was assessed using a seven-point functional scale (van der Meché et al. 1992) and Medical Research Council sumscore (MRC-sumscore) for six bilateral muscle groups. The MRC-sumscore ranged from 60 (normal) to zero (quadriplegic) (Kleyweg et al. 1991).

At the time of randomization the following features were determined: age, sex, antecedent episodes in the four weeks before onset of weakness: a gastrointestinal - or upper respiratory tract infection (URTI), time from onset

of weakness until randomization, distribution of muscle weakness, F-score, MRC-sumscore, presence of sensory loss and cranial nerve deficits.
At study entry and 16 times during six months of follow-up: three times a week during weeks 1 and 2, once a week through week 6 and in weeks 8, 10, 14, 18, 22, and 26 neurological examinations were performed.
To assess the distribution of muscle weakness on entry to the study, the strength of a number of proximal and distal muscles was assessed according to the MRC score as described earlier (Visser et al. 1995, Chapter 3).
Severity of sensory loss at the time of randomization and during follow-up was classified according to the method described elsewhere (Visser et al. 1996, Chapter 4). For the 25 patients who participated in the IVIg-MP pilot study no follow-up data of the sensory system were available since this was not tested prospectively.
A treatment related fluctuation was defined as (Kleyweg, van der Meché, 1991):
1. improvement in functional score of at least one grade or improvement in MRC-sumscore of more than five points within four weeks, followed by a decrease in the MRC-sumscore of more than five points or a worsening in functional score of at least one grade; or:
2. stabilization of the clinical course for more than one week followed by a worsening of more than five points on the MRC-sumscore or at least one grade of the functional score. In the last situation, an arrest of progression of muscle weakness for more than one week, is considered to be caused by treatment and not to be in accordance with the natural course. Improvement, stabilization and deterioration had to be documented in at least two subsequent examinations by the same investigator.

Pre-treatment serum samples were tested using an enzyme linked immunosorbent assay (ELISA) for the presence of IgA, IgM and IgG antibodies to *Campylobacter jejuni* (*C. jejuni*) using an acid-glycine extract from *C. jejuni* as antigen (IgG: indirect ELISA, (Herbrink et al. 1988) IgM and IgA: class-capture ELISA (Herbrink et al. 1987)). ELISA test was also used to detect IgA, IgM and IgG antibodies to ganglioside GM1 with thin layer chromatography for confirmation (Jacobs et al. 1996). IgM antibodies against CMV were determined by ELISA (Vidas, bioMésieux, Mercy-l'Etoile, France).
Electrodiagnostic testing (EMG) was performed using standardized conventional techniques at entry, one week and 4 weeks after randomization.
The details of testing have been reported earlier (Meulstee et al. 1995a).

8.3 Results

Treatment related clinical fluctuations were found in 16 (9%) of the 172 patients. Five patients were treated with PE, nine with IVIg and two with MP-IVIg. The treating neurologists regarded the worsening in three patients as 'mild' (although the worsening fulfilled the criteria) and these patients were therefore not retreated. Thirteen (seven percent) of the 172 received a second treatment; four (five percent) in the PE group, seven (nine percent) in the IVIg group and two (eight percent) in the IVIg-MP treated group. These differences between the treatment groups were not significant.

The clinical, laboratory and electrodiagnostic characteristics of the patients with treatment related fluctuations were compared with the group of GBS patients without fluctuations; the results are summarized in table 1 and 2. Age, sex, time of onset of muscle weakness until start of treatment and presence of cranial nerve deficits at the time of start of treatment were not related with an increased incidence of treatment related fluctuations. At start of treatment and during follow-up there were no significant differences between the two groups in severity of muscle weakness, as assessed by the F-score and MRC-sumscore. The time until nadir tended to be longer for the patients with fluctuations in comparison with the other patients (table 1).

Features	GBS patients without fluctuations (n=156)	GBS patients with fluctuations (n=16)	P-value[a]
Age (mean ± SD)	47.5 ± 19.4	46.4 ± 19.4	ns
Sex			
• men	77 (48%)	9 (56%)	ns
• women	82 (52%)	7 (44%)	
Clinical characteristics			
• Time until F≥ 3 (in days, mean)	5.6 (5.0 - 6.2)	5.4 (3.6 - 7.3)	ns[b]
• Time until nadir (in days, mean)	9.0 (8.2 - 9.7)	11 (8.4 - 13.6)	0.08[b]
• Cranial nerve involvement			
at start of treatment	67 (43%)	6 (38%)	ns
during follow-up	90 (58%)	9 (56%)	ns

Table 1. The clinical and laboratory data of GBS patients with and without treatment related fluctuations.

Features	GBS patients without fluctuations (n=156)	GBS patients with fluctuations (n=16)	P-value[a]
Clinical characteristics			
• Predominant weakness			
Distal	59 (37%)	0 (0%)	0.003
Proximal	36 (23%)	7 (44%)	0.06
Global	47 (30%)	8 (50%)	0.09
Mixed	9 (6%)	1 (6%)	ns
• MRC-sumscore at entry, mean	36 (34-38)	40 (34-45)	ns[b]
• MRC-sumscore at nadir , mean	28 (26 -31)	31 (22-40)	ns[b]
• Motor GBS group	27/147 (17%)	0 (0%)	0.06
Antecedent infections			
• URTI	61/155 (39%)	7/14 (50%)	ns
• gastrointestinal tract	29 (19%)	0 (0%)	0.06
Laboratory findings			
• positive *C. jejuni* serology	45/140[c] (32%)	4/14[c] (29%)	ns
• positive CMV serology	18/148[c] (12%)	4/15[c] (27%)	0.1
• anti-GM1 antibodies	31/140[c] (22%)	0/14[c] (0%)	0.05

Table 1 (continued). The clinical and laboratory data of GBS patients with and without treatment related fluctuations.

Between parentheses percentages or 95% confidence interval a: p-values were derived from the chi-square test, two tailed unless indicated otherwise. b: Wilcoxon-Mann-Whitney test, two tailed. c: number tested Motor GBS = patients with the Guillain-Barré syndrome, who did not have sensory loss on clinical examination during a follow-up period of 6 months. ns = not significant; MRC= medical research council score; CMV = cytomegalovirus; *C.jejuni = Campylobacter jejuni*

Interestingly, none of the patients with treatment fluctuations had predominant distal weakness, which was in fact the most important factor for not getting fluctuations (table 1). Furthermore, treatment related fluctuations did not occur in the patients without sensory signs (the acute motor neuropathy group). This clinical observation was confirmed by the EMG data which showed significant lower SNAPs amplitudes in the treatment related fluctuation group (table 2).

Characteristics	GBS patients without fluctuations (n=96)	GBS patients with fluctuations (n=14)	P-value
• SNAP ulnar nerve			
entry	12 (9-14)	8 (1-14)	ns
week 1	14 (8-13)	4 (0-12)	0.06
week 4	11 (8-14)	6 (0-16)	0.006
• SNAP median nerve			
entry	13 (10-16)	7 (0-16)	0.06
week 1	12 (8-15)	4 (0-10)	0.02
week 4	12 (8-15)	3 (0-9)	0.004
• Recruitment pattern			
M. Abductor digiti quinti			
entry O/SP	49/92[a] (53%)	3/11[a] (27%)	0.10
week 1 O/SP	42/95[a] (44%)	3/11[a] (27%)	ns
week 4 O/SP	28/88[a] (32%)	2/10[a] (20%)	ns
• Recruitment pattern			
M. Abductor pollicis brevis			
entry O/SP	40/96[a] (42%)	3/10[a] (30%)	ns
week 1 O/SP	41/96[a] (43%)	4/11[a] (36%)	ns
week 4 O/SP	29/91[a] (32%)	3/10[a] (30%)	ns

Table 2. Electrodiagnostic characteristics of GBS patients with and without treatment related fluctuations.

Between brackets percentages or 95% confidence intervals

ns= not significant; CMAP= compound muscle action potential; SNAP= sensory nerve action potential SP= single pattern; 0 = no motor units recognizable

[a] number of patients tested

Considering antecedent infections, none of the patients with fluctuations had preceding diarrhea; this was, however, not related with a *C. jejuni* infection since this infection occurred in similar proportions in both groups. On the other hand more patients with fluctuations tended to have a CMV infection compared with the patients without fluctuations.
In addition to the excess of sensory involvement, the EMGs showed a somewhat better recruitment pattern in the fluctuating group (table 2); this may in part reflect the more global and proximal distribution of weakness in this group compared to the non-fluctuating group. The EMG data did not show significant differences in mean compound muscle action potentials after distal stimulation of the ulnar or median nerve, ulnar and median motor and sensory conduction velocities, percentage of conduction blocks and distal motor latencies between the groups.

8.4 Discussion

We studied the risk factors for treatment related fluctuations in a group of 172 GBS patients treated with either PE, IVIg or MP-IVIg with the assumption that the nature of these fluctuations is the same for the applied immunomodulating therapies. Sixteen of 172 patients, five in the PE group, nine in the IVIg group and two in the MP-IVIg group showed fluctuations. This study gives more insight into the factors causing susceptibility to treatment related fluctuations. Those with preceding diarrhea, distal onset of muscle weakness, a clinical pattern of acute motor neuropathy or presence of anti-GM1 antibodies are not at risk.
In our study treatment related fluctuations occurred only in the GBS patients with sensory loss. The clinical and laboratory characteristics of GBS patients with acute motor neuropathy characterized by a rapid onset of weakness, an early reaching of nadir, a distal-dominant weakness, lack of cranial nerve involvement, a preceding gastrointestinal illness caused by a recent *C. jejuni* infection and a presence of high titres of anti-GM1 antibodies have been described before (Visser et al. 1995, Chapter 3). Our present results give more substantial evidence that different pathophysiological mechanisms are involved in the GBS subgroups we defined and that they are of therapeutic importance (The Dutch Guillain-Barré Study Group, 1994; Visser et al. 1995).

Insight into risk factors for fluctuations may lead to a better understanding of the underlying mechanisms involved. Theoretically, treatment related fluctuations may occur under two circumstances. First, relapses after therapy may take place when treatment is applied early in the disease course. At that time the 'disease process' is still very active and treatment arrests the progression only temporarily. Worsening of weakness occur shortly after cessation of therapy and theoretically treatment related fluctuations could have been prevented by applying therapy for a longer period. Second, relapses after treatment may occur when there is an ongoing immune (re)activation resulting in a more protracted clinical course. Factors which triggered the immune mediated demyelination more chronically activate or after a latent phase, induced by therapy, reactivate the immune system. Under these circumstances there may be a relatively long interval between the cessation of treatment and the occurrence of a relapse.

In our study, rapid onset or a relative short period of progression seems not to be a risk factor for the occurrence of fluctuations, which argues against the first hypothesis and is in disagreement with the suggestion made by Ropper et al (1988) that early treatment may result in an increased risk of relapses.

The fluctuations occurred more often in those who after start of treatment showed a more protracted disease process; the time until nadir tended to be longer in the patients with fluctuations. Also the time of onset of worsening was usually more than 10 days after start of therapy (Kleyweg, van der Meché, 1991). These findings argue in favor of the second theory. Moreover, Osterman et al studying relapses after PE reported a similar finding (Osterman et al. 1988).

Our findings are of importance for the patients with an acute motor neuropathy, since these patients may show a rapid progression after onset of muscle weakness (Chapter 3) and early treatment may improve outcome in these patients.

Further studies are needed to resolve the underlying mechanisms involved in the GBS patients with fluctuations.

Chapter 9

General discussion and summary;
future directions

Contents Chapter 9

9.1 Summary of the studies

The Guillain-Barré syndrome (GBS) is a (sub-)acute immune-mediated polyneuropathy, clinically characterized by a rapid progressive muscle weakness which can lead to respiratory insufficiency. The diagnosis of GBS is based on a number of clinical and electrodiagnostic criteria. These criteria are discussed in Chapter 1. In this chapter also the differential diagnosis, the heterogeneity of the clinical pattern, the prognosis and treatment of GBS is discussed. Although in the past it has been attempted to define the homogeneity of GBS this thesis shows that there are different clinical subgroups, probably related to different pathogenetic mechanisms.

In Chapter 2 the clinical spectrum of 172 GBS patients is summarized. The results are based upon patients who had to fulfill the inclusion criteria of the trials. Therefore, GBS patients with a mild course of the disease -those who remained able to walk independently- were excluded.

In Chapter 3 the characteristics of the GBS patients with an acute motor neuropathy are presented. We studied 27 patients out of a group of 147 patients who did not have sensory loss during a follow-up period of 6 months (AMN). These patients had a distinct clinical pattern compared to the other 120 GBS patients. The clinical course was marked by a more rapid onset of weakness (3.9 vs. 6.1 days, $p=0.002$), an earlier nadir (6.3 vs. 9.1 days, $p<0.001$), an initially predominant distal weakness (67% vs. 27%, $p<0.001$), sparing of the cranial nerves (26% vs. 68%,$p<0.001$) and the disease was more often preceded by a gastrointestinal illness (41% vs. 13%,$p=0.001$) often caused by a *C. jejuni* infection (67% vs. 28% in the other GBS patients, $p<0.001$). High titres of anti-GM1 antibodies were also significantly more common in AMN patients (42% vs. 5%, $p<0.001$). Electromyographic data of the AMN patients at nadir revealed little or no evidence for demyelination. Abundant denervation activity was present in half of the patients. The response to immune globulin (IVIg) treatment was better compared to plasma exchange (PE). With the latter treatment significantly fewer AMN patients reached the stage of independent locomotion after a follow-up period of 6 months especially if the acute motor neuropathy occurred after a *C. jejuni* infection.

The distinctive clinical, electrophysiological and laboratory features of AMN patients show that the acute motor neuropathy presents a specific subgroup within the Guillain-Barré syndrome. Based on our data IVIg is the treatment of choice for these patients.

In about two-third of the patients GBS is preceded by infections, in particular *C. jejuni* and Cytomegalovirus (CMV) infection. We found that none of the patients with an acute motor neuropathy had a preceding CMV infection. Therefore, we studied the clinical and electrophysiological features of 20 CMV associated GBS patients and compared the findings with earlier established data of *C. jejuni* related GBS patients (n=43) and of GBS patients without these proven infections (n=71). The results of this study are presented in Chapter 4. We demonstrate that CMV related GBS patients have a different clinical pattern in comparison to the other two GBS groups. They are significantly younger, have a severe initial course, indicated by a high frequency of respiratory insufficiency, and during follow-up often develop cranial nerve involvement and severe sensory loss. This is in contrast to *C. jejuni* infection which is related with motor GBS. Both infections are related with delayed recovery in comparison to the GBS patients without these infections. This study extends the heterogeneity of GBS in relation to the antecedent infections. The relation of *C. jejuni* with AMN is, however, not strict and in Chapter 5 the clinical, immunological and electrophysiological features of 14 patients with an acute severe motor sensory neuropathy (AMSN) following a *C. jejuni* infection are described and compared with the features of 14 *C. jejuni* associated AMN patients. In contrast to the AMN patients the AMSN patients usually experience paresthesias before onset of muscle weakness, do not have preceding diarrhea, present often with global weakness and frequently develop cranial nerve involvement. The severity of muscle weakness is the same in both groups, although the AMSN patients have a higher incidence of respiratory insufficiency. Moreover, AMSN has no association with the presence of anti-GM1 antibodies. The AMSN patients also show little evidence for demyelination by EMG methods.

The data indicate that, although *C. jejuni* can induce both AMN and AMSN, in the Western world AMSN is not simply a more severe manifestation of AMN, but may even represent a distinct clinical entity.

GBS is an acute polyneuropathy with a great variability in outcome. Both IVIg and PE treatment result in earlier recovery, but morbidity is still considerable. Identification of prognostic factors may lead to better information for the patients and furthermore may lead to a better selection of those patients with a poor prognosis in whom more aggressive treatment may be evaluated in future clinical trials.

In Chapter 6, our results of the prognosis and the factors related with outcome are presented. We studied 147 patients with GBS who participated in the Dutch multicentre study to determine the influence of clinical, laboratory and electrodiagnostic factors on the prognosis of this syndrome. These data were analyzed in rank-order according to the sequence in which they became available in the clinical setting. It was decided to measure the outcome at two endpoints: at 8 weeks as half of the patients had recovered to independent locomotion by then and at 6 months, the endpoint of the study. For the selected factors obtained after logistic regression, interaction with treatment was incorporated and the prediction with the 95% confidence intervals was calculated for each combination of outcomes of the selected prognostic factors.

Multivariate analysis revealed three clinical factors and one laboratory factor predicting outcome (inability to walk independently) at 8 weeks: a preceding gastrointestinal illness (yes, no), age (≥ 50, < 50 years), MRC-sumscore (< 40, ≥ 40) at the start of treatment and a recent CMV infection (yes, no). The same prognostic factors, but not CMV infection, were found at the endpoint at 6 months. In addition, rapid progression of weakness (≤ 4 or >4 days from the onset of weakness until loss of independent locomotion or becoming bedridden) proved also a factor of prognostic significance. Analysis of treatment interactions revealed an important difference between PE and IVIg: diarrhea was only a significant prognostic factor of poor outcome in the PE treated group. This indicates that patients with preceding diarrhea do better after IVIg compared to PE treatment. At this point it should be stressed that the patient groups with preceding diarrhea, *C. jejuni* infection, high titres of anti-GM1 antibodies and AMN heavily overlap; in fact subgroup analysis for all these parameters showed better results for IVIg.

This analysis showed that the main predictors of outcome in GBS are clinical factors. Patients with preceding diarrhea show better progress after IVIg treatment. With these easily obtainable clinical factors, the prediction of outcome can be calculated accurately and ranges from 0% (95% c.i. 0 - 9%) - 91% (95% c.i. 73 - 97%) at 8 weeks and 2% (95% c.i. 0 - 20%) - 99% (95% c.i. 94 - 100%) at 6 months for the PE treated group to 18% (95% c.i. 5 - 51%) - 75% (95% c.i. 55 - 88%) at 8 weeks and 50% (95% c.i. 25 - 75%) - 96% (95% c.i. 84 - 99%) at 6 months for the IVIg treated group.

Although IVIg is an effective treatment, morbidity of GBS is still considerable. Eighteen percent of the GBS patients treated with IVIg were not able to walk independently 6 months after start of treatment. Therefore search for new or additional treatment is necessary. In Chapter 7 the results of our pilot study assessing the effect of combined treatment of IVIg with MP are shown. In an open study 25 patients with GBS were treated with IVIg 0.4 g per kg bodyweight per day for 5 days and intravenous MP 500 mg per day for 5 days. The results of this combined treatment, MP-IVIg, were compared with the results of 74 historical control patients who were treated with IVIg in the Dutch GBS trial. In the MP-IVIg group significantly more patients: 19 of the 25 patients (76 percent) improved by one or more functional grades after four weeks, as compared with 39 of the 74 patients (53 percent) treated with IVIg alone ($p=0.04$). Also the median time required to improve until independent walking was reduced in the MP-IVIg group. This pilot study suggests that combined treatment with MP-IVIg in patients with GBS is more effective than treatment with immune globulins alone; a randomized clinical trial should confirm this. Such a study coordinated at the University Hospital Rotterdam is in progress.

After an initial stabilization or improvement eighth to ten percent of GBS patients treated with IVIg, PE or IVIg-MP show a secondary deterioration. In Chapter 8 the risk factors for treatment related clinical fluctuations were evaluated in a group of 172 patients with GBS. Clinical, laboratory and electrodiagnostic features of all 16 GBS patients with treatment related fluctuations, of whom 13 were retreated, were compared with those who did not have fluctuations. No significant differences were found between PE treated GBS patients and patients treated with IVIg either alone or in combination with MP.

None of the GBS patients with preceding gastrointestinal illness, initial predominant distal weakness, acute motor neuropathy or anti-GM1 antibodies showed treatment related fluctuations. On the other hand patients with fluctuations showed a trend to have the fluctuations after a protracted disease course. It is therefore suggested that treatment related clinical fluctuations are due to a more prolonged immune attack. There is no indication that the fluctuations are treatment modality related.

9.2 Future directions

9.2.1 Pathogenesis

The results of our studies show that subgroups of GBS patients are present and the clinical variables are associated with microbiological, electrodiagnostic and immunological factors. These associations are, however, not absolute. For example, an acute motor neuropathy is not always related with a *C. jejuni* infection or anti-GM1 antibodies. Moreover, a *C. jejuni* infection can also give a Miller Fisher syndrome or an acute severe motor-sensory neuropathy. It has long been puzzling whether GBS is heterogeneous only with respect to severity whereby one pathophysiological mechanism is involved or whether the heterogeneity is caused by differences in pathophysiological mechanisms. The data shown in this thesis support the last hypothesis.
Our results therefore have implications for further research of the pathophysiological mechanisms involved in GBS.

9.2.1.1 Acute motor neuropathy (AMN) - C. jejuni

There exists a strong association between *C. jejuni* infection, AMN and anti-GM1 antibodies as discussed in Chapter 3. GM1 reactive epitopes are present in the lipopolysaccharide capsule of some *C. jejuni* strains (Yuki et al. 1994a; Yuki et al. 1995) and in especially the large motor nerves of the peripheral nervous system (Dalakas, Quarles, 1996). Oomes et al (1995) showed that *C.jejuni* bacteria are able to absorb anti-GM1 antibodies of the IgG class. This suggests that molecular mimicry might play a role in the pathogenesis. As mentioned in Chapter 3 the acute motor neuropathy in the Dutch population strongly resembles AMAN in Northern China. Also AMAN often follows an infection with *C. jejuni* and is often associated with anti-GM1 antibodies (Ho et al. 1995, Chapter 5).
Why IVIg may be more effective in our AMN group is not clear; anti-idiotypic interaction (Yuki, Miyagi 1996) may play a role but it could also be due to binding and neutralizing *C.jejuni* antigens (Gold et al. 1996) or inhibition of the binding of anti-GM1 to its target antigen by IVIg (Malik et al. 1996). Future studies have to confirm the superior efficacy of IVIg in AMN in comparison to PE.

9.2.1.2 Acute severe motor-sensory neuropathy (AMSN) - C. jejuni

Fourteen GBS patients developed a severe motor sensory neuropathy after a *C. jejuni* infection (see Chapter 5). The clinical patten is distinct from that of

AMN as shown in Chapter 5. The involved pathogenetic immune process is not known as yet and further studies are needed to detect any specific peripheral nerve epitope that may be involved in this group.

9.2.1.3 CMV associated GBS

The pathophysiological mechanisms are unknown for CMV associated GBS. It is likely that the unraveling of the pathophysiological mechanisms in GBS will be extended to CMV infection. Molecular mimicry between certain peptide sequences of CMV and homologous sequences of the peripheral nerve glycoprotein P0 has been described (Jahnke et al. 1985) and could be one of the possible mechanisms to link a preceding CMV infection with a subsequent immune-mediated nerve damage. Other myelin components of the peripheral nervous system that may be of importance in the pathogenesis of CMV induced GBS are sulfated glycosphingolipids. In patients with CMV infection antibodies against sulfated glycosphingolipids have been detected (Neyts et al. 1992; Ogawa-Goto et al. 1994) and anti-sulfatide antibodies have been found in patients with predominantly sensory neuropathies and in one GBS patient with extensive sensory loss (van den Berg et al. 1993). However, the presence of these antibodies in GBS patients with a CMV infection has not been reported yet.

It is possible that anti-GM2 antibodies are important in CMV associated GBS. Recently, a case-report of GBS associated with anti-GM2 antibody caused by a CMV infection was described (Niwa et al. 1995). Although the anti-GM2 antibody was decreased transiently by PE, the clinical symptoms progressed. The symptoms advanced very rapidly during IVIg therapy associated with re-elevation of the anti-GM2 antibody. Following ganciclovir administration, however, the symptoms diminished within 7 days and the anti-GM2 antibody fell dramatically. The authors speculated that the reason for the observed effectiveness of ganciclovir was direct suppression of activation of CMV, followed by the inhibition of the production of demyelinating antibodies including the anti-GM2 antibody (Niwa et al. 1995).
Irie et al (1996) found high titers of serum IgM and IgG anti-GM2 antibodies in three GBS patients with an acute CMV infection. Moreover, the titers of anti-GM2 antibodies decreased on absorption with CMV-infected cells.
We are completing a search for anti-peripheral nerve antibodies in this second largest group of antecedent infections involved in GBS and recently confirmed the association of anti-GM2 antibodies with CMV related GBS (Jacobs et al, in press).

9.2.1.4 other infections related with GBS and its variants

It seems worthwhile to study other antecedent infections in relation with GBS and the variants of GBS. Other infections may play a role in the acute motor neuropathy group and in the patients with mild and/or severe motor-sensory deficits. *Mycoplasma pneumoniae* may induce autoimmune neuropathies by anti-Gal-C antibodies (Kusunoki et al. 1995) and recently a case report linked a rare variant of GBS: pure dysautonomia with an EBV infection (Bennett et al. 1996).

9.2.2 Improvement of therapy

9.2.2.1 Selection of patients with poor prognosis

More attention should be focused on those patients with a poor short-term and long-term outcome; those with a preceding CMV infection, a preceding *C. jejuni* infection or with preceding diarrhea, older age and severe and rapid progression of muscle weakness. Outcome could possibly be improved if treatment is given when the patient does not yet have severe weakness and certainly when treatment is started early in those with rapid progression. Twenty-eight of the 172 patients were on the ventilator at start of treatment. In this group the mean time from onset of muscle weakness until start of treatment was 5.7 (95% c.i. 4.2 - 7.3) days (see Chapter 2). These findings indicate that treatment in these patients could have been started earlier. So, early recognition and prompt treatment may be of importance for the long-term prognosis.

Furthermore, one should consider new or additional treatments especially for the group with a worse prognosis. One of these treatment strategies might be the combination of MP-IVIg as is now under study, but more aggressive forms of immune therapy may be considered in clinical trials in patients with a bad prognosis.

9.2.2.2 More individualized treatment

Our studies suggest that IVIg may be more effective in patients with preceding *C. jejuni* and CMV infection in comparison to PE treatment. We did not find a factor which indicated superior efficacy of PE. We have, therefore, chosen IVIg as the primary treatment for all GBS patients. In centers where PE is still used it is advisable to use IVIg for at least the patients with

C.jejuni or CMV infection, despite the fact that our observations have not been confirmed yet.
In CMV related GBS patients further therapeutic considerations are possible. CMV may persist in the body (especially in the bladder) over a longer period and may go on to act as a source of antigen. This may lead to the choice of an IVIg product with a high content of anti-CMV IgG. This product is now used in the double-blind trial evaluating the effect of IVIg in combination with MP. Also, the use of antiviral medication, such as ganciclovir, alone or in combination with IVIg may be a therapeutic possibility. Two patients with CMV associated GBS improved after ganciclovir treatment (Lindsten et al. 1994; Niwa et al. 1995); these anecdotal reports do, however, not give any circumstantial evidence of the effect of ganciclovir since the course of GBS is variable. Studies are needed to evaluate whether an active viral replication is ongoing at the time of onset of the CMV associated polyneuropathy. Presence of such an active viral replication may give a theoretical basis for the use of ganciclovir.

9.2.2.3 Dose of IVIg

Until now we have used IVIg at a dosage of 0.4 g/kg for 5 days. In Kawasaki's disease IVIg in a dose of 1g/kg for 2 days is more effective than 0.4 g/kg for 5 days (Barron et al. 1990). In GBS there have been no dose-efficacy studies of IVIg. It might be that also in GBS a higher dose given in a shorter period is more effective; it is however possible that with this regimen patients experience more side-effects. Especially in patients with autonomic instability the high protein content and volume load of IVIg may lead to side effects.
If we are going to treat patients at an earlier stage, one may wonder whether in patients with favourable prognostic factors a lower dose of IVIg is also effective. The preliminary report of Rafael's study (1996) on the effect of PE applied in 'mildly' affected GBS patients suggest that two sessions of PE results in earlier recovery than no treatment. Therefore, similar studies may be performed to evaluate to optimum dose of IVIg, especially in relation to the severity of muscle weakness in GBS.

Samenvatting

Het syndroom van Guillain-Barré is een (sub)acute meestal immuungemedieerde polyneuropathie, klinisch gekenmerkt door een progressieve verlamming van de armen en benen, hetgeen zelfs kan leiden tot een insufficiënte ademhaling. De diagnose berust op een aantal criteria die in ***Hoofdstuk 1***, de inleiding, besproken worden. Tevens wordt in dit hoofdstuk ingegaan op de differentiaal diagnose, het heterogene klinische beeld, de prognose en de behandeling van het syndroom. Hoewel in het verleden getracht is het Guillain-Barré syndroom (GBS) zo homogeen mogelijk te maken, wordt in dit proefschrift aangetoond dat er verschillende klinische beelden zijn, waaraan waarschijnlijk verschillende pathofysiologische mechanismen ten grondslag liggen.

Allereerst wordt in ***Hoofdstuk 2*** de diversiteit van het klinisch beeld van 172 GBS patiënten beschreven, waarbij opgemerkt dient te worden, dat patiënten met een mild beloop niet in de analyse betrokken waren, aangezien deze patiënten niet aan de inclusiecriteria van de trials voldeden.

In ***Hoofdstuk 3*** wordt ingegaan op de kenmerken van de patiënten met een acute motore neuropathie (AMN). Deze patiënten hebben een specifiek klinisch, immunologisch en electrofysiologisch beeld. Deze patiënten vertonen tijdens het beloop van de ziekte geen gevoelstoornissen, hoewel zij voorafgaande aan de ziekte soms wel tijdelijk tintelingen kunnen hebben bemerkt. Zij presenteren zich meestal met een distale zwakte met voorafgaand aan de zwakte een periode met diarree. Bij het merendeel van de patiënten ontstaat er ernstige zwakte, echter slechts bij 25% treedt er hersenzenuwuitval op. Het laboratorium onderzoek toont vaak positieve *Campylobacter jejuni* serologie en de aanwezigheid van anti-GM1 antilichamen. Het electrodiagnostisch onderzoek laat lage distale amplitudes zien zonder geleidingsblokkades. Bij deze groep patiënten lijkt het effect na behandeling met intraveneuze immuunglobulinen IVIg) beter dan na behandeling met plasmaferese (PE).

In ***Hoofdstuk 4*** worden de klinische en electrofysiologische verschijnselen van het GBS na een recente cytomegalovirus (CMV) infectie beschreven. De meeste GBS patiënten met een recente CMV infectie, vastgesteld middels

sterk verhoogde IgM titer bij ELISA, vermelden voor het optreden van de zwakte een bovenste luchtweginfectie, echter algemene malaise, koorts en hoofdpijn komt ook vaak voor. In vergelijking tot de andere GBS patiënten zijn de CMV geassocieerde GBS patiënten significant jonger. Het beloop van de ziekte is aanvankelijk ernstig; bij 65% van de patiënten treedt er respiratoire insufficientie op. De patiënten ontwikkelen vrijwel altijd hersenzenuwuitval, meestal een dubbelzijdige n. facialis uitval, en ernstige gevoelsstoornissen. Zowel de *C. jejuni*- als de CMV infecties zijn geassocieerd met een ernstiger beloop in vergelijking tot het herstel van de patiënten zonder deze infecties.

In ***Hoofdstuk 5*** wordt aangetoond, dat een *C. jejuni* infectie niet alleen een AMN maar ook een ernstige motore sensibele neuropathie (AMSN) kan veroorzaken. De klinische, immunologische en electrofysiologische verschillen tussen *C. jejuni* geassocieerde AMSN en AMN worden in dit hoofdstuk besproken. Bij de AMSN patiënten komt de aanwezigheid van paresthesieën, globale zwakte, hersenzenuwuitval en ademhalingsinsufficiëntie vaker voor. De ernst van de zwakte en het beloop is voor beide groepen hetzelfde. Het electrodiagnostisch onderzoek laat ook bij de AMSN patiënten weinig aanwijzingen voor een demyeliniserende polyneuropathie zien. AMSN heeft geen relatie met de aanwezigheid van anti-GM1 antistoffen. Deze bevindingen wijzen erop dat AMSN niet een eindstadium van AMN is, doch een apart ziektebeeld met waarschijnlijk -een nog te bepalen- specifiek immunologisch proces.

In ***Hoofdstuk 6*** worden de prognostische factoren, die bij GBS van belang zijn besproken. Dit is de eerste studie waarbij de prognostische factoren na behandeling met intraveneuze immuunglobulinen geanalyseerd werden. Het vaststellen van de prognose is van belang voor het bepalen van het beloop en de uitkomst voor de individuele patiënt. Tevens kunnen op grond hiervan patiënten met een slechte prognose voor nieuwe therapeutische trials geselecteerd worden. Wij onderzochten 147 GBS-patiënten, die hadden deelgenomen aan de Nederlandse multicenter studie waarbij het effect van IVIg vergeleken werd met PE. De klinische, laboratorium en electrodiagnostische gegevens werden geanalyseerd in de volgorde waarin zij beschikbaar kwamen in de klinische situatie. Besloten werd de uitkomst, tenminste 10 meter zelfstandig lopen, op twee tijdstippen te evalueren, namelijk op 8 weken, waarbij de helft

van de patiënten dit einddoel hadden bereikt en bij 6 maanden, het eindpunt van de studie. Voor de onafhankelijke factoren werd de interactie met behandeling geïncorporeerd en de voorspellende waarde met de 95% betrouwbaarheidsintervallen voor iedere combinatie van deze geselecteerde factoren berekend.
Multivariate analyse toonde drie belangrijke klinische factoren en een laboratoriumfactor, die voorspelling van de uitkomst na 8 weken mogelijk maken: een aan de ziekte voorafgaande periode van diarree (ja, neen), leeftijd (ouder of jonger dan 50 jaar), MRC-som-score bij aanvang van de behandeling (meer of minder dan 40 uit 60) en een recente CMV infectie (ja, neen). Dezelfde prognostische factoren, behalve een recente CMV infectie, werden gevonden bij het eindpunt op 6 maanden, waarbij een snelle progressie van de spierzwakte (meer of minder dan 4 dagen tussen het begin van de zwakte en niet meer zelfstandig kunnen lopen) een additionele prognostische factor bleek te zijn. Analyse van de interacties met behandeling leerde dat er een belangrijk verschil bestond tussen PE en IVIg therapie. Diarree was alleen in de met PE behandelde groep een significante prognostische factor.
Deze analyse toont ons dat de belangrijkste factoren voor het voorspellen van

de uitkomst klinische factoren zijn: antecedente periode met diarree, leeftijd, ernst van de zwakte en snel progressief beloop van de ziekte. De patiënten met voorafgaande diarree hebben een betere prognose na behandeling met IVIg. Met deze eenvoudig te verkrijgen klinische factoren kan de kans op herstel berekend worden. Deze ligt tussen de 0% (95% betrouwbaarheidsinterval (c.i) 0 - 9%)- 91% (95% c.i. 73 - 97%) na 8 weken en 2%(95% c.i. 0 - 20%) - 99% (95% c.i. 94 - 100%) na 6 maanden in de met plasmaferese behandelde groep en 18% (95% c.i. 5 - 51%) - 75% (95% c.i. 55 - 88%) na 8 weken en 50% (95% c.i. 25 - 75%) - 96% (95% c.i. 84 - 99%) in de met IVIg behandelde groep.

Uit de Nederlandse GBS-trial is gebleken dat IVIg een effectieve behandeling is, die gezien het aantal bijwerkingen en de eenvoud van toedienen de voorkeur geniet boven plasmaferese. Ondanks deze behandeling is 18% van de patiënten 6 maanden na het begin van de behandeling niet in staat zelfstandig te lopen. Daarom is de mogelijkheid van andere therapieën onderzocht. In een open studie werden 25 GBS-patiënten gedurende 5 dagen behandeld met IVIg in een dosering van 0.4 g/kg per dag gecombineerd met 500 mg methylprednisolon (MP), intraveneus toegediend. De resultaten van dit

onderzoek staan beschreven in ***Hoofdstuk 7***. Het effect van deze behandeling werd vergeleken met een groep van 74 GBS-patiënten, die in de eerste Nederlandse GBS-trial werden behandeld met alleen IVIg. De inclusie en exclusie criteria, de follow-up en primaire uitkomstmaat waren voor beide studies hetzelfde. Vier weken na start van de behandeling met de combinatietherapie trad bij 19 van de 25 (76%) GBS patiënten verbetering met een of meer functionele graden op in vergelijking met 39 van de 74 (53%) GBS patiënten, die alleen met IVIg behandeld waren. Dit verschil in de primaire uitkomstmaat was significant verschillend (p=0.04). Tevens was de mediane tijd tot zelfstandig lopen bij deze groep korter. De resultaten van het onderzoek gaven aanleiding om een dubbelblind, multicenter onderzoek op te zetten ter evaluatie van het additionele effect van MP bij IVIg. Dit onderzoek is gaande en wordt gecoördineerd vanuit het Academisch Ziekenhuis Rotterdam.

Na behandeling met PE of IVIg treedt bij 8-10% van de behandelde patiënten een secundaire verslechtering (een behandeling gerelateerde fluctuatie) op. Het is belangrijk te weten welke patiënten vooral kans hebben om deze fluctuaties te krijgen. In ***Hoofdstuk 8*** wordt de analyse naar de risicofactoren voor deze fluctuaties beschreven. De klinische, laboratorium en electrodiagnostische gegevens van 16 GBS patiënten met fluctuaties (waarbij 13 patiënten opnieuw behandeld werden) werden vergeleken met de patiënten, die geen fluctuaties vertoonden. Het optreden van behandeling gerelateerde fluctuaties was niet significant verschillend tussen de PE, IVIg en de IVIg-MP behandelde groepen. Geen enkele patiënt met voorafgaande diarree, met initieel distale zwakte, een acute motore neuropathie of met anti-GM1 antistoffen vertoonde een secundaire achteruitgang. De conclusie van dit onderzoek is, dat de fluctuaties niet afhankelijk zijn van de behandeling. De fluctuaties berusten waarschijnlijk op een specifiek onderliggend pathogenetisch mechanisme, waarbij de langere duur van het immunologisch proces een mogelijke factor is.

In ***Hoofdstuk 9*** wordt in de discussie verder ingegaan op de pathogenetische mechanismen bij de verschillende subgroepen. Verder wordt besproken hoe de therapie voor de individuele patiënt verbeterd kan worden en waar verder onderzoek zich op zou kunnen richten.

Chapter 10

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List of abbreviations

ADQ	Abductor digiti quinti
AMAN	Acute motor axonal neuropathy
AMN	Acute motor neuropathy
APB	Abductor pollicis brevis
AMSAN	Acute motor-sensory axonal neuropathy
AMSN	Acute motor-sensory neuropathy
C. jejuni	*Campylobacter jejuni*
C.I.	Confidence interval
CMAP	Compound muscle action potential
CMV	Cytomegalovirus
CSF	Cerebrospinal fluid
CV	Conduction velocity
DML	Distal motor latency
ELISA	Enzyme linked immunosorbent assay
F-score	Functional score
GBS	Guillain-Barré syndrome
IP	Normal i.e. full pattern
IVIg	Intravenous immune globulins
MP	Methylprednisolone
MP-IVIg	Intravenous methylprednisolone combined with intravenous immune globulins
MRC	Medical Research council score
NO	Number of patients
NCV	Nerve conduction velocity
PE	Plasma exchange/plasmapheresis
SNAP	Sensory nerve action potential
SP	Single pattern
U(R)TI	Upper (respiratory) tract infection

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Curriculum Vitae

De schrijver van dit proefschrift werd op 15 juni 1960 geboren te 's-Gravendeel. In 1978 behaalde hij het eindexamen atheneum B aan het Chr. Lyceum te Dordrecht, waarna de N-propedeuse aan de Landbouw Hogeschool te Wageningen gevolgd werd.
Vanaf 1979 studeerde hij geneeskunde aan de Erasmus Universiteit Rotterdam en behaalde in december 1985 het artsexamen (cum laude).
Van januari 1986 tot augustus 1989 was hij als algemeen arts werkzaam in het Tshilidzini ziekenhuis in het ontwikkelingsgebied Venda (destijds een van de thuislanden van Zuid-Afrika). In 1988 werd aan de Witswaterrand Universiteit te Johannesburg het diploma 'Tropical Medicine and Hygiene' (cum laude) behaald.
In augustus 1989 keerde hij met zijn vrouw en kinderen (Eva, Eline, met Mathijn op komst) terug naar Nederland om vervolgens van 1 januari 1990 tot 1 januari 1996 de opleiding neurologie met de aantekening klinische neurofysiologie te volgen (opleiders neurologie: aanvankelijk Prof. Dr A. Staal, later zijn promotor Prof. Dr F.G.A. van der Meché; opleider klinische neurofysiologie: Dr J. Meulstee).
Als staflid neurologie verbonden aan het Academisch Ziekenhuis Rotterdam werd de functie als coördinator van de Nederlandse Guillain-Barré studie voortgezet en neuroimmunologisch onderzoek verricht bij multipele sclerose.
Sinds 1 september 1996 is de auteur als neuroloog werkzaam in het St. Elisabeth Ziekenhuis te Tilburg.
In december 1995 werd het artikel 'Guillain-Barré syndrome without sensory loss (acute motor neuropathy). A subgroup with specific clinical, electrodiagnostic and laboratory features. Brain 1995; 118: 841-847.' bekroond met de C.U. Ariëns Kappers prijs.

List of publications

The Chapters 3-8 are adapted from the following articles:

Guillain-Barré syndrome without sensory loss (acute motor neuropathy). A subgroup with specific clinical, electrodiagnostic and laboratory features. Brain 1995; 118: 841-847.
Visser LH, van der Meché FGA, van Doorn PA, Meulstee J, Jacobs BC, Oomes PG, Kleyweg RP, and the Dutch Guillain-Barré Study Group. (Chapter 3)

Cytomegalovirus infection and Guillain-Barré syndrome; the clinical, electrophysiologic and prognostic features. Neurology 1996; 47: 668-673.
Visser LH, van der Meché FGA, Meulstee J, Rothbarth PhH, Jacobs BC, Schmitz PIM, van Doorn PA, and the Dutch Guillain-Barré Study Group. (Chapter 4)

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