Epidemiological and clinical aspects of the Guillain-Barré syndrome

R. van Koningsveld

Lay out and Cover design: studio EigenWijs, Ellen Verbeek, info@studio-eigenwijs.nl

Picture page 136 Aad van der Kooij, www.chon.nl

Printed by Print Partners Ipskamp, Enschede

ISBN 90-9015341-1

Epidemiological and clinical aspects of the

Guillain-Barré syndrome

Epidemiologische en klinische aspecten van het Guillain-Barré syndroom

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
Rector Magnificus

Prof.dr.ir. J.H. van Bemmel

en volgens het besluit van het College van Promoties.
De openbare verdediging zal plaatsvinden op
woensdag 19 december 2001 om 9.45 uur

door

Rinske van Koningsveld

Geboren te Bemmel

Promotiecommissie:

Promotor:	Prof. dr. F.G.A. van der Meché
Co-promotoren:	Dr. P.A. van Doorn
	Dr. P.I.M. Schmitz
Overige leden:	Prof. dr. W.F.M. Arts
	Prof. dr. A. Hofman
	Prof. dr. J.H.J. Wokke

The studies described in this thesis were performed at the department of Neurology, Erasmus University Medical Center Rotterdam, the Netherlands and at the department of Neurology, Sint Elisabeth Hospital, Curaçao, the Netherlands Antilles

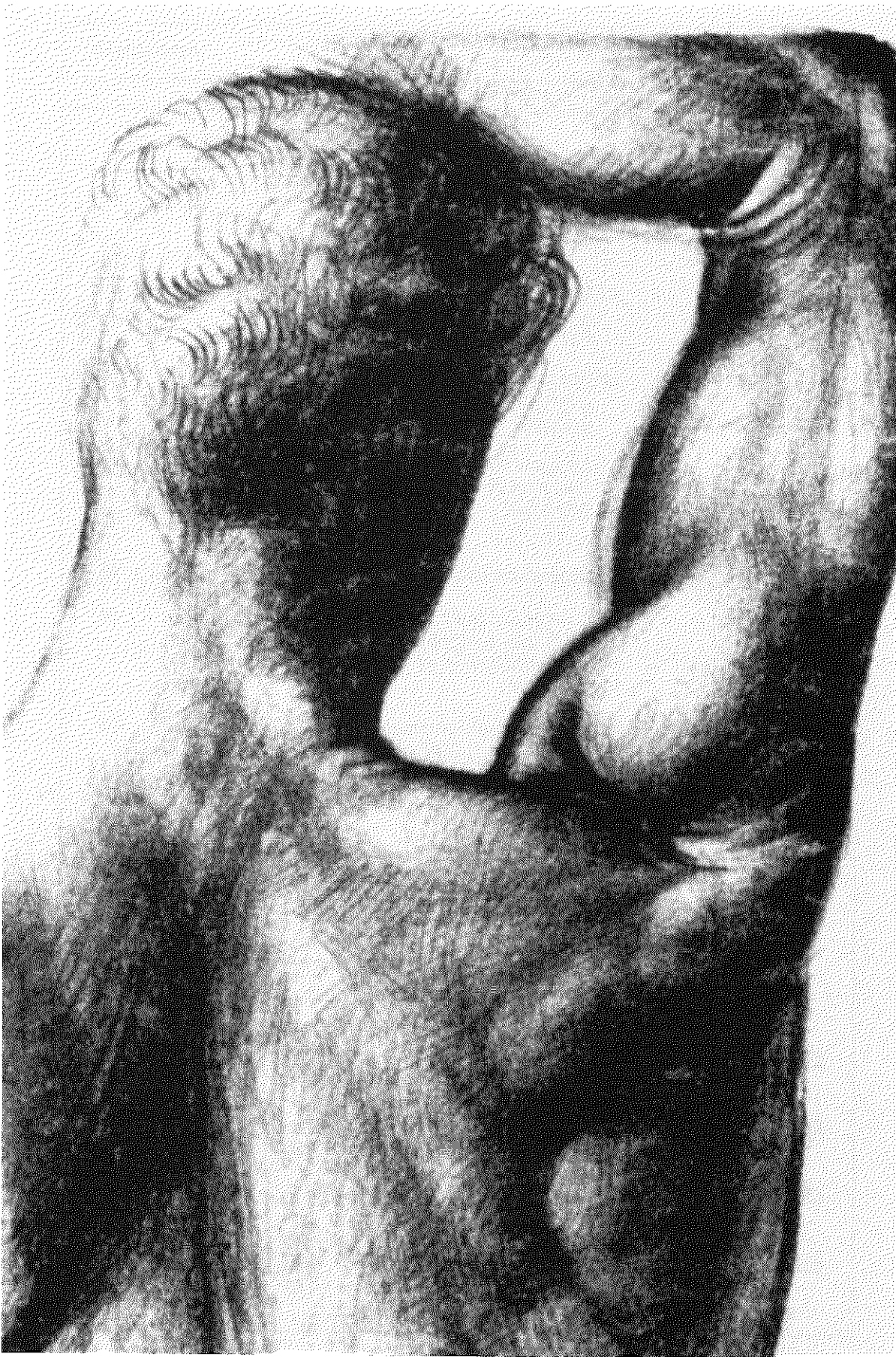
The publication of this thesis was financially supported by the BioScience Division of Baxter.

ter nagedachtenis aan mijn vader

Epidemiological and clinical aspects of the

Guillain-Barré syndrome

Contents



chapter 01

The Guillain-Barré Syndrome; an introduction

Based on the Chapter "The Guillain-Barré syndrome"; F.G.A. van der Meché, MD, PhD, R. van Koningsveld, MD in "Investigating neurological disease" by Hofman A and Mayeux R.

1.1 Introduction

The Guillain-Barré syndrome (GBS) is an acute immune-mediated disorder of the peripheral nerves. The essential features are a rapidly progressive, more or less symmetrical weakness of the limbs and decreased or absent tendon reflexes. The weakness reaches its nadir (maximum severity) by definition within four weeks, but it is usually seen within two weeks. In 20-30% of the patients, weakness is so severe that artificial ventilation is needed. People of all age, gender or race can be affected by this polyneuropathy. The first symptoms of GBS are often preceded by an infection. Seventy percent of the patients report influenza-like symptoms, a respiratory infection or a gastro-enteritis within the three weeks prior to the onset of the disease.
The first description of what is now called the Guillain-Barré syndrome, was given by J.B.O. Landry in 1859 [1]. The summation of clinical characteristics was extended by typical findings in the cerebrospinal fluid as described by G. Guillain, J.A. Barré and A. Strohl in 1916 [2]. As research progressed, many studies reported on the clinical diversity of GBS. As a consequence, the concept of GBS shifted from a single clinical entity to a disease with heterogeneity in presentation, course and outcome.
Nowadays GBS is considered to be a post-infectious immune-mediated acute polyneuropathy with a heterogeneous symptomatology.

1.2 Diagnosis

"Guillain-Barré syndrome is a recognisable entity for which the basis for diagnosis is descriptive in our present state of knowledge. The features, which allow a diagnosis, include clinical, laboratory, and electrodiagnostic criteria. The problem is not with recognition of a typical case, but with knowing the boundaries by which the core disorder is delimited. The following criteria are established, in light of current knowledge and opinion, to define those limits". This is how the first diagnostic criteria for GBS were introduced in 1978 by an ad hoc National Institute of Neurological Disorders and Stroke (NINCDS) committee [3]. Motivation for the set up of these criteria was the increasing incidence of GBS in association with the swine-flu vaccine campaign in 1976. As research progressed and knowledge was expanded, the criteria were revised in 1990 (table 1) [4]. Originally, these criteria were set up to facilitate epidemiological research. In practice it seems appropriate to define GBS clinically, according to the simple diagnostic criteria and subsequently add further characteristics. This may result in subgroups within the broad clinical definition. Depending on the time-course, the pattern of weakness and

the presence of sensory symptoms, different diagnoses have to be considered.

Table 1 Diagnostic criteria

Guillain-Barré syndrome

Features Required for the Diagnosis

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

Features Strongly Supportive of the Diagnosis

- Progression over days to a maximum of four weeks.
- Relative symmetry.
- Mild sensory signs or symptoms.
- Cranial nerve involvement.
- Onset of recovery 2-4 weeks after progression stops.
- Autonomic dysfunction.
- Initial absence of fever.
- Elevated CSF protein after the first week of symptoms.
- CSF cell counts of 10 or fewer mononuclear leukocytes/mm^3.
- Abnormal electrodiagnostics with conduction slowing or block.
- No other identifiable cause.

Features That Rule out the Diagnosis

- A current history of hexacarbon use.
- Abnormal porphyrin metabolism.
- A history or finding of recent diphtheric infection.
- Lead intoxication.
- The occurrence of a purely sensory syndrome.
- Diagnosis of poliomyelitis, botulism, hysterical paralysis or toxic neuropathy.

Adapted from the revised version of the diagnostic criteria for GBS, set up by the National Institute of Neurological Disorders and Stroke [4]

1.3 Pathogenesis

The clinical picture of polyneuropathy in GBS is the result of damage to the myelin sheet and/or axon. This damage appears to be the result of an aberrant immune response to an infectious agent. The role of the immune system in the development of GBS originates, among others, from the fact that 70% of the GBS patients reports a preceding infection prior to the onset of symptoms. Furthermore, the course of the disease can be influenced by immune-modulating therapies as plasmapheresis (PE) and intravenous immunoglobulins (IVIg). Finally, with the finding of antibodies directed against structures in the peripheral nerve, the role of the immune system seems indisputable.

In most cases the nerve damage is primarily caused by demyelination. Pathophysiological studies show lymphocytic infiltrates in spinal roots and peripheral nerves, followed by macrophage-mediated segmental stripping of the myelin [5]. As a consequence electrical nerve impulses are disrupted leading to slowing of nerve conduction and in some cases to conduction block [6]. In some cases, mostly severely affected patients, the inflammatory demyelination is accompanied by destruction and loss of axons [7-9]. It is difficult to distinguish these cases from the primary axonal forms in which the primary immune attack is directed against the nerve axons [10-12]. In these cases macrophages penetrate the basal lamina of the Schwann cell resulting in destruction of the axons. This process is without significant demyelination and lymfocytic infiltrates are scarcely present [10]. The clinical phenotype of the primary axonal form and primary demyelinating form followed by secondary axonal degeneration is similar. Since pathological material from GBS patients is scarce and electrophysiological techniques are not able to discriminate between primary or secondary axonal degeneration, the discrimination between these two groups is generally not possible in daily practise.

It is not exactly known when and how nerve tissue becomes involved in the immune response and this has been a major subject of GBS research over the last years. At present the theory of "molecular mimicry" draws the attention and up to now it appears to be the most attractive hypothesis in the development of GBS. As reaction to the presence of a microbial agent, antibodies and/or T cells are produced to act directly against the microbial antigens. Due to the structural resemblance of the antigens and host tissue, the antibodies and/or T cells not only destruct the pathogen but also cause damage to the host tissue [13]. In GBS, the most extensively described relation between a pathogen, host tissue and antibodies is the relation between a preceding infection with *Campylobacter jejuni (C.jejuni)* and the presence of serum anti-ganglioside antibodies cross-reacting with lipopolysaccharides from *C.jejuni* [13-16]. Gangliosides are a subgroup of membrane glycolipids present in the nervous system. Different types of gangliosides are described. The composition of

gangliosides in axons or myelin, but also in motor and sensory nerves and in ventral and dorsal nerve roots, varies [13]. As will be described below, the difference in presence and type of ganglioside are related to the presence of certain clinical subgroups in GBS.
Not all infections with *C.jejuni* or other pathogens result in the development of GBS. Furthermore, anti-ganglioside antibodies are not exclusively found in patients with GBS. From this, it follows that other components are necessary to induce the development of GBS. Most likely hostfactors play a role resulting in a susceptibility to develop GBS. The latter may be genetically determined or dependent on the immune status of an individual. The fact that there is no straightforward genetic component responsible for the development of GBS in general is supported by the lack of familial clustering and the lack of convincing associations with any of the HLA classes [17-21]. A promising start is made to investigate the role of polymorphisms in certain immune response genes in the development of GBS [20;22;23].

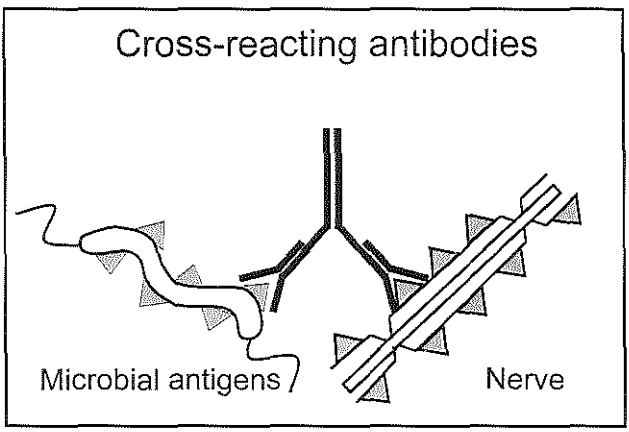


Figure 1
Molecular Mimicry in GBS

1.4 Subgroups

As mentioned, GBS is considered to be a heterogeneous disorder. Because the pathophysiological mechanism has not been fully elucidated it is not known what the exact contribution is of preceding infections and the presence of anti-ganglioside antibodies. Recent studies reporting on the relation with certain immune-response gene polymorphisms have revitalised the thought that hostfactors are likely to play a role [24]. It is not known if subgroups are completely based on similar underlying pathophysiologic mechanisms and consequently, the diversity of the clinical picture of GBS is fully determined by the preceding infection, presence of anti-ganglioside antibodies and/or hostfactors. Another possibility is that different mechanisms play a role, which result in a similar clinical picture.
Classification of the subgroups is possible on different levels of the disease and characte-

ristics on several levels of the disease can be found in one subgroup (table 2 and figure 2). The most common subgroup in the western world is the sensory-motor variant. It is the classical descending paralysis with both involvement of the motor and sensory fibres. This probably most resembles the Guillain-Barré syndrome as described by G. Guillain, J.A. Barré and A. Strohl in 1916 [2]. On the level of electrophysiology and pathophysiology, the sensory-motor variant can be termed as acute inflammatory demyelinating polyneuropathy (AIDP). As mentioned earlier, this subgroup is characterised by primary demyelination, sometimes accompanied by axonal loss. With respect to the preceding infections and related anti-ganglioside antibodies, this variant has been associated with the Cytomegalovirus (CMV) and the presence of anti-GM2 antibodies [25-29]. Patients with a preceding CMV infection are characterised by a younger age, a relatively severe course with a high frequency of respiratory insufficiency, often cranial nerve involvement and severe sensory loss [25].

The pure motor form accounts for 10-20% of the cases. It is, beside the absence of sensory deficits, characterised by a rapid onset of weakness, initially predominant distal weakness, an earlier nadir and sparing of the cranial nerves [30]. In the pure motor type, a preceding infection with *C.jejuni* is frequently described together with the presence of anti-GM1, anti-GM1b and anti-GalNAc-GD1a antibodies [30-33]. This pure motor form is also described in Japan and China and, based on electrophysiological and pathophysiological findings, called "AMAN" (acute motor axonal neuropathy) [34-36]. Here again, a preceding infection with *C.jejuni* is frequently described together with the presence of anti-GM1 [36;37]. Besides the AMAN variant also patients with severe sensory-motor symptoms were described in China, termed "AMSAN" (acute motor-sensory axonal neuropathy). Based on pathological findings, the authors suggested that "AMSAN" could be a more severe form of "AMAN" [35]. Because pathology is scarce and electrophysiological techniques are not able to discriminate between primary or secondary axonal degeneration, the terms "AMAN" and "AMSAN" are not frequently used [7;38-41].

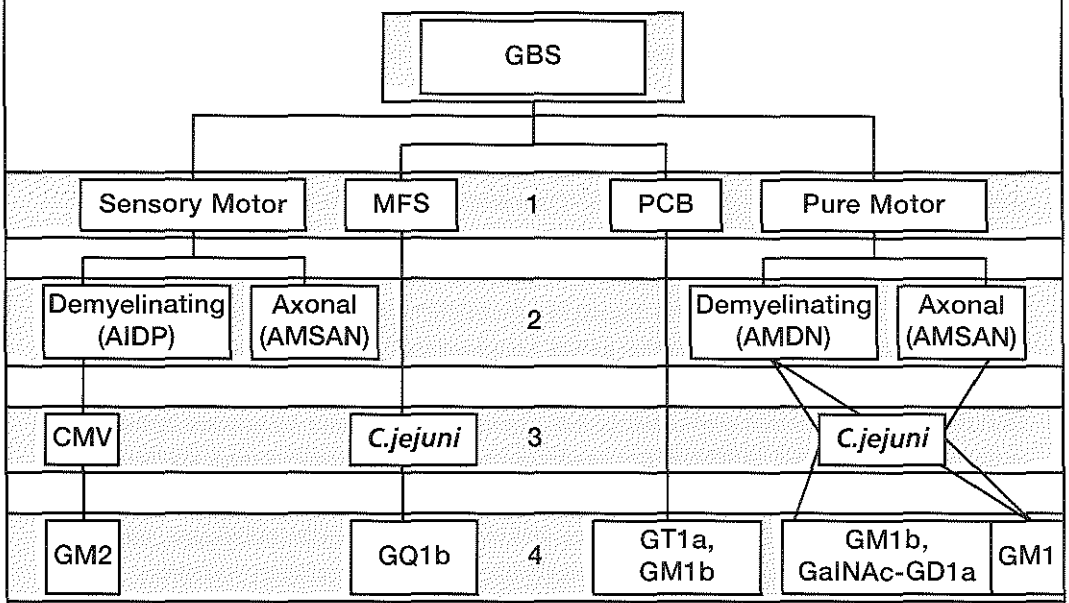
In other variants of GBS cranial nerve dysfunction is the most prominent feature. The most frequently reported subtype is the Miller Fisher syndrome (MFS). This syndrome, characterised by ophtalmoplegia, ataxia and absence of the tendon reflexes, occurs in 5% of all GBS cases [42]. In MFS, the respiratory muscles are seldom affected and the disease appears to run a relatively mild course. A preceding infection with *C.jejuni* is also frequently reported in MFS and anti-GQ1b antibodies are almost always present [43;44].

In case of the pharyngo-cervico-brachial (PCB) variant, difficulty in speech and swallowing is most prominent. In PCB, the facial nerve is often affected and there is progressive weakness in the oropharyngeal muscles, the neck, shoulders and proximal arm muscles [45-48]. Mild weakness of the limbs and reduced tendon reflexes do not exclude the diagnosis

of PCB. Associations have been described between PCB and antibodies against GT1a and GM1b [48-51].

In a study concerning these cranial variants, significant overlap was found between the variants and the classical GBS. In 59% of the cases, where symptoms started in the oculomotor region, difficulty in swallowing followed, indicating involvement of the lower cranial nerves. In 33% of the cases, where symptoms started in the lower cranial nerve region, the oculomotor nerves became involved. In both variants, about half of the patients developed a descending weakness in the extremities [52].

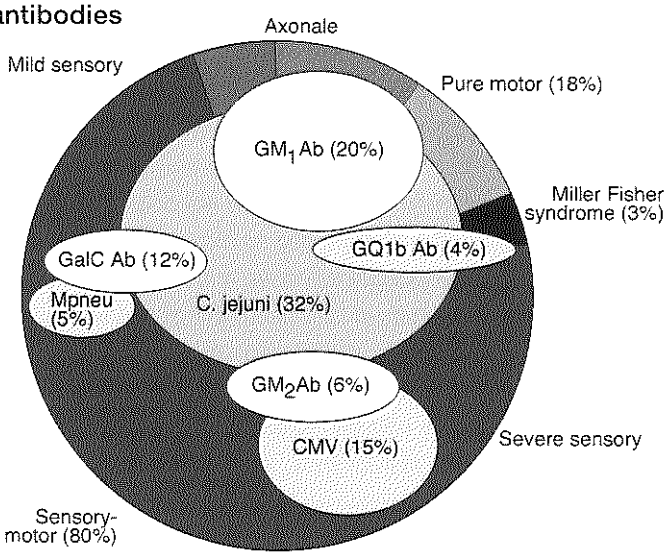
Table 2 Guillain-Barré syndrome, patterns within the clinical concept.



MFS	Miller Fisher syndrome
PCB	Pharyngo-Cervico-Brachial variant
AIDP	Acute Inflammatory Demyelinating Polyneuropathy
AMSAN	Acute Motor-Sensory Axonal Neuropathy
AMDN	Acute Motor Demyelinating Neuropathy
AMAN	Acute Motor Axonal Neuropathy
CMV	Cytomegalovirus
C.jejuni	*Campylobacter Jejuni*

1 Clinical subgroups
2 Electrophysiological/ Pathophysiological
3 Infections
4 Anti-ganglioside antibodies

Figure 2 Association between clinical subgroups, infections and anti-ganglioside antibodies



1.5 Treatment

Supportive treatment

Although at present specific treatment is available, general care is still of utmost importance for the GBS patient. Because of the risk of autonomous dysfunction and the unpredictable course of the disease, the patient should be carefully monitored from the beginning. In doing so, one should especially be aware of the possibility of respiratory distress, aspiration and autonomic dysfunction. The latter expresses itself as wide fluctuations of pulse or blood pressure, cardiac arrest or ileus. Pain often is a great burden to the patient. Although special mattresses and frequent repositioning may be helpful, even the use of epidural morphine application has been advocated [53].

Specific treatment

Table 3 gives an overview of all randomised controlled clinical trials (RCT) and two pilot studies performed in GBS patients. In most of these studies, only patients were included who were within 2 weeks after onset of symptoms and unable to walk independently. Outcome measurements were mostly based on the Hughes' disability scale. Table 4 shows this scale which assesses a disability score (f-score) of patients mainly based on mobility [54]. The first RCT was performed in 1978 [54]. Unfortunately, it could not show the benefit of low dose prednisone as sole treatment. In 1993, a RCT was conducted to investigate the efficacy of high dose prednisone on improvement in GBS patients [55]. Again no positive effect was found at 4 weeks.

The efficacy of PE was the first to be demonstrated in two large clinical trials [56;57]. In both studies, improvement started earlier and artificial respiration was significantly less frequently indicated in patients treated with PE compared to patients who received only supportive treatment. In the above described RCTs, only severely affected patients were included, i.e. patients unable to walk independently. In 1997, a paper was published on the beneficial effect of PE, also in patients who were only mildly affected [58].
The positive results of PE treatment reflected not only considerable decrease of morbidity, but also a considerable degree of economic savings. However, drawbacks of PE treatment were its contraindications, the invasive character and treatment failures during administration.
Based on the positive results of IVIg treatment of patients with chronic inflammatory demyelinating polyneuropathy (CIDP) and other autoimmune mediated diseases, a RCT was conducted aiming for equal efficacy of IVIg and PE in GBS patients [59]. If IVIg and PE would prove to be equally efficient, IVIg would be preferable since it is widely available and easy to administer. In the Netherlands, 150 GBS patients were included. This study showed that IVIg was at least as effective as PE in terms of improvement in mobility at 4 weeks. Subsequently, an international study has been published including 383 patients [60].
Besides confirmation of the positive effect of IVIg, this RCT investigated the effect of treatment with PE followed by treatment with IVIg. The equal effect of IVIg and PE could be confirmed. However, no significant additional effect was found of the combined treatment. Based upon the above described results, IVIg can now be regarded as an effective treatment for patients with GBS and is generally preferable.
Although IVIg improves outcome, morbidity is still considerable. Therefore, the need remains to investigate alternative or additional therapy for GBS patients. This has led to the conduction of a pilot study on the additional effect of methylprednisolone (MP) on standard IVIg treatment [61]. The positive results of this study were the base for the RCT on the additional effect of MP described in this thesis.

Table 4 The Hughes' disability scale

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

Table 3 Treatment trials in GBS

Year	Investigators	n	Therapy under investigation	Primary endpoint	Result
1978	Hughes et al. [54]	40	Low dose prednisone vs placebo	Improvement of 1 grade on the Hughes'disablity scale at 1, 3 and 6 months after randomisation	No difference
1984	Hughes et al.[76]	30	PE vs supportive care	Improvement of 1 grade on the Hughes'disablity scale at 1 month after randomisation	No difference
1985	The GBS study group [56]	245	PE vs supportive care	Improvement of 1 grade on the Hughes'disablity scale at 1 month after randomisation	Significant difference
1987	French Cooperative Group on PE in GBS [57]	220	PE (albumin or fresh frozen plasma) vs supportive care	The time to recover walking with assistance	Significant difference
1992	The Dutch GBS study group [59]	150	IVIg vs PE	Equal improvement on the Hughes'disablity scale at 1 month after randomisation	No difference
1993	GBS steroid trial group [55]	242	High dose prednisone vs placebo	Improvement of 0.5 grade on the Hughes'disablity scale at 1 month after randomisation	No difference
1994	The Dutch GBS study group [61]	25	MP/IVIg vs IVIg (pilot study)	Improvement of 1 grade on the Hughes'disablity scale at 1 month after randomisation	Significant difference
1997	French Cooperative Group on PE in GBS [58]	556	0 vs 2 PE in mild patients, 2 vs 4 PE in moderate patients, 4 vs 6 in severe patients	The time to onset of motor recovery in mild group, the time to reach Hughes' grade 3 in moderate and severe group	Significant difference in mild and moderate group, no difference in severe group
1997	PE/Sandoglobulin GBS trial group [60]	379	PE vs IVIg vs PE/IVIg	The difference in mean improvement in disability grade after 1 month, < 0.5 on Hughes'disability grade for equivalence.	No difference between IVIg, PE and IVIg/PE
2001	French Cooperative Group [77]	39	3 days IVIg vs 6 days IVIg (pilot study)	The time needed to reach Hughes' grade 3	No difference
2001	The Dutch GBS study group	225	MP/IVIg vs IVIg	Improvement of 1 grade on the Hughes'disablity scale at 1 month after randomisation	Paragraph 4.1

1.6 Prognosis

The retrospective epidemiological survey described in this thesis shows that in about 28% of the patients, the disease runs a relatively mild course and these patients remain ambulant during the course of the disease [62]. In the other patients the disease progresses and finally, artificial ventilation is necessary in 20 to 30% of these patients [42;59;63]. After a period of progression a plateau phase follows which may take several weeks or months. Subsequently recovery starts. Without specific therapy, the median time towards independent walking takes about 85 days for patients not able to walk independently [63]. Randomised trials on the effect of PE and IVIg showed a median time towards walking between 49 and 70 days [56;57;59;60].The reported mortality rates range from 2 to 12% [56-60;64-66]. The lower rates are mainly derived from treatment trials where patients with serious co-morbidity are excluded.
De Jager and Minderhoud studied long term outcome in 57 patients. With a follow-up time varying between 2 and 24 years, they found that 35% of the patients was fully recovered, in 35% of the patients a mild handicap was left and 30% of the patients suffered from a severe handicap [67]. Fletcher et al. studied long-term outcome in 60 GBS patients requiring mechanical ventilation. The mortality appeared to be 20%. However, 79% of the survivors eventually regained independent ambulation [68].
Outcome may be predicted in an early stage of disease using prognostic indicators, identified in a variety of studies. Most studies show that older age, need for ventilatory support, a rapidly progressive course and low compound muscle action potentials after distal nerve stimulation (EMG) are predictors of poor outcome [63;64;68-73]. In the Dutch IVIg GBS trial, a multivariate analysis on the collected data of 147 GBS patients was performed in order to study prognostic factors [74]. The importance of older age, a rapid onset and severity of weakness were confirmed. The most powerful predictor in this study was, however, an antecedent episode of diarrhoea. Rees et al. also found that a preceding infection with *C.jejuni*, the commonest recognised cause of diarrhoea, was an important prognostic factor [75]. The Italian Guillain-Barré study group again reported an antecedent gastro-enteritis as a predictor of worse outcome even as the Plasma Exchange/-Sandoglobulin GBS Trial Group [66;73]. Interestingly, in the Dutch trial, diarrhoea was only an important prognostic factor in the patients treated with PE and not in patients treated with IVIg [31;74].
In conclusion the prognosis of GBS varies from complete recovery to death depending on prognostic factors and applied therapy. Frequently described predictors of poor outcome are older age and severe neurological damage at nadir (expressed by the need of artificial ventilation). Factors associated with a mild course of GBS are not known and are being studied as part of this thesis.

1.7 Outline of this thesis

This thesis focuses on the heterogeneity of GBS. Because the pathophysiological mechanism has not been fully elucidated, it is only partially known what causes this heterogeneity and determines the differentiation into specific subgroups.
Besides a contribution to the unravelling of the pathophysiological mechanism, description and recognition of the subgroups is important because the prognosis and response to therapy may differ.
The first part of this thesis describes the epidemiology of GBS **(Chapter 2)**. Epidemiology can provide clues on the etiology by studying the disease at different time periods, at different places and among different types of people. Paragraph 2.1 describes a review on the literature regarding the worldwide epidemiology of GBS. Paragraph 2.2 describes an epidemiological survey in the Southwest Netherlands. This survey comprises 476 patients and provides an overall incidence rate (IR) for GBS in the Netherlands together with IR for age, gender and seasons. Paragraph 2.3 describes the results of a study on the increasing number of GBS cases observed on the Dutch Antilles island Curaçao. IR and clinical characteristics of the patients are assessed and compared with the results of the Dutch survey on GBS.
The second part of this thesis describes studies on clinical aspects of GBS **(Chapter 3)**. In the first two paragraphs the clinical subgroup of mild patients is described. Paragraph 3.1 describes a retrospective study and provides data on clinical characteristics and preceding infections in mildly affected patients. Paragraph 3.2 describes a prospective study on mild patients. Here, the focus is on the differences in the time course of the disease compared to the severely affected patients. It includes an analysis of serological proven preceding infections and the presence of anti-ganglioside antibodies. Furthermore, the outcome in mild patients is described and the need to treat this group of patients is discussed. Paragraph 3.3 describes the course of the disease and outcome of a clinical subgroup of GBS, the Miller Fisher syndrome patients. In **Chapter 4** firstly, the results of a double blind placebo controlled randomised trial on the additional effect of methylprednisolone on standard treatment with IVIg is described. In paragraph 4.2 the effect of publication of the positive effect of intravenous immunoglobulin therapy in GBS patients on the referral pattern is described. In **Chapter 5**, the general discussion, the main results are discussed and conclusions together with suggestions for future studies are given.
Chapter 6 is a summary in English and in Dutch.

1.8 Bibliography

01. Landry J. Note sur la paralysie ascendante aigue. Gaz Hebd Med Chir 1859;6:472-488.
02. Guillain G, Barré JA, Strohl A. Sur un syndrome de radiculonevrite avec hyperalbuminose du liquide cephalo-rachidien sans reaction cellulaire. Bull Mem Soc Med Hop Paris 1916;40:1462-1470.
03. Asbury AK, Arnason BG, Karp HR, McFarlin DE. Criteria for diagnosis of Guillain-Barré syndrome. Ann Neurol 1978;3:565-566.
04. Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain-Barré syndrome. Ann Neurol 1990;27:Suppl:S21-4.
05. Asbury AK, Arnason BG, Adams RD. The inflammatory lesion in idiopathic polyneuritis. Its role in pathogenesis. Medicine (Baltimore) 1969;48:173-215.
06. Hughes RA, Hadden RD, Gregson NA, Smith KJ. Pathogenesis of Guillain-Barré syndrome. J Neuroimmunol 1999;100:74-97.
07. Berciano J, Coria F, Monton F, Calleja J, Figols J, LaFarga M. Axonal form of Guillain-Barré syndrome: evidence for macrophage-associated demyelination. Muscle Nerve 1993;16:744-751.
08. Fuller GN, Jacobs JM, Lewis PD, Lane RJ. Pseudoaxonal Guillain-barré syndrome: severe demyelination mimicking axonopathy. A case with pupillary involvement. J Neurol Neurosurg Psychiatry 1992;55:1079-1083.
09. Hall SM, Hughes RA, Atkinson PF, McColl I, Gale A. Motor nerve biopsy in severe Guillain-Barré syndrome. Ann Neurol 1992;31:441-444.
10. Feasby TE, Gilbert JJ, Brown WF, et al. An acute axonal form of Guillain-Barré polyneuropathy. Brain 1986;109:1115-1126.
11. Griffin JW, Li CY, Macko C, et al. Early nodal changes in the acute motor axonal neuropathy pattern of the Guillain-Barré syndrome. J Neurocytol 1996;25:33-51.
12. Hafer-Macko C, Hsieh ST, Li CY, et al. Acute motor axonal neuropathy: an antibody-mediated attack on axolemma. Ann Neurol 1996;40:635-644.
13. Ang, C. W. Molecular mimicry in the Guillain-Barré syndrome.Thesis 2001
14. Gregson NA, Rees JH, Hughes RA. Reactivity of serum IgG anti-GM1 ganglioside antibodies with the lipopolysaccharide fractions of Campylobacter jejuni isolates from patients with Guillain-Barré syndrome. J Neuroimmunol 1997;73:28-36.
15. Jacobs BC, Hazenberg MP, van DP, Endtz HP, van der Meche FG. Cross-reactive antibodies against gangliosides and Campylobacter jejuni lipopolysaccharides in patients with Guillain-Barré or Miller Fisher syndrome. J Infect Dis 1997;175:729-733.
16. Yuki N, Taki T, Takahashi M, et al. Molecular mimicry between GQ1b ganglioside and lipopolysaccharides of Campylobacter jejuni isolated from patients with Fisher's syndrome. Ann Neurol 1994;36:791-793.
17. Chiba A, Kusunoki S, Kuwata S, Juji T, Shibata Y, Kanazawa I. HLA and anti-GQ1b IgG antibody in Miller Fisher syndrome and Guillain-Barré syndrome. J Neuroimmunol 1995;61:85-88.

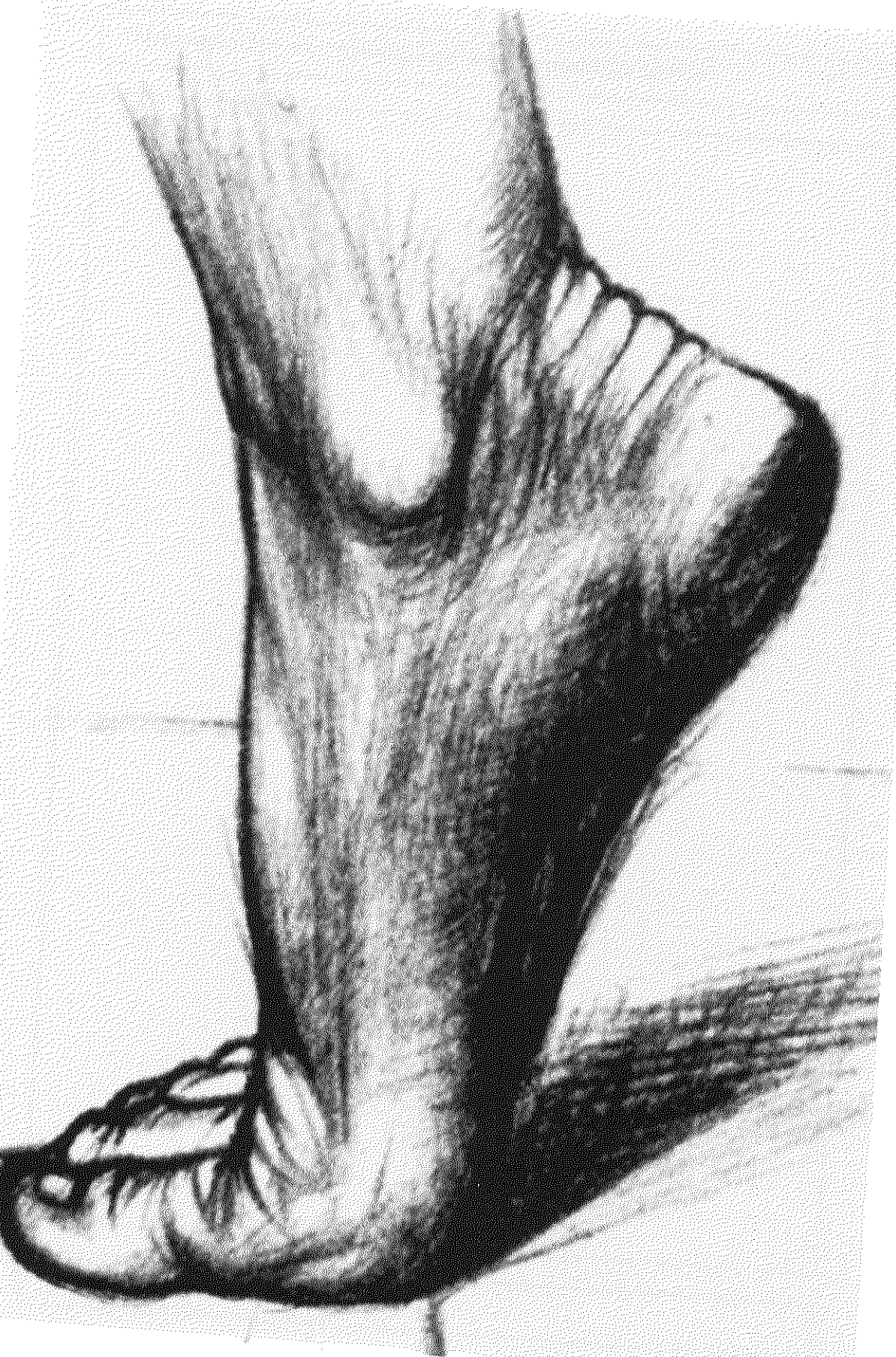
18. Hillert J, Osterman PO, Olerup O. No association with HLA-DR, -DQ or -DP alleles in Guillain-Barré syndrome. J Neuroimmunol 1991;31:67-72.
19. Kaslow RA, Sullivan-Bolyai JZ, Hafkin B, et al. HLA antigens in Guillain-Barré syndrome. Neurology 1984;34:240-242.
20. Ma JJ, Nishimura M, Mine H, et al. HLA and T-cell receptor gene polymorphisms in Guillain-Barré syndrome. Neurology 1998;51:379-384.
21. Winer JB, Briggs D, Welsh K, Hughes RA. HLA antigens in the Guillain-Barré syndrome. J Neuroimmunol 1988;18:13-16.
22. van der Pol WL, van Den Berg LH, Scheepers RH, et al. IgG receptor IIa alleles determine susceptibility and severity of Guillain-Barré syndrome. Neurology 2000;54:1661-1665.
23. Vedeler CA, Raknes G, Myhr KM, Nyland H. IgG Fc-receptor polymorphisms in Guillain-Barré syndrome. Neurology 2000;55:705-707.
24. van der Pol WL, van Den Berg LH, Scheepers RH, et al. IgG receptor IIa alleles determine susceptibility and severity of Guillain-Barré syndrome. Neurology 2000;54:1661-1665.
25. Visser LH, van der Meché FGA, Meulstee J, et al. Cytomegalovirus infection and Guillain-Barré syndrome; the clinical, electrophysiologic and prognostic features. Neurology 1996;47:668-673.
26. Irie S, Saito T, Nakamura K, et al. Association of anti-GM2 antibodies in Guillain-Barré syndrome with acute cytomegalovirus infection. J Neuroimmunol 1996;68:19-26.
27. Jacobs BC, van DP, Groeneveld JH, Tio-Gillen AP, van der Meché FG. Cytomegalovirus infections and anti-GM2 antibodies in Guillain-Barré syndrome. J Neurol Neurosurg Psychiatry 1997;62:641-643.
28. Yuki N, Tagawa Y. Acute cytomegalovirus infection and IgM anti-GM2 antibody. J Neurol Sci 1998;154:14-17.
29. Khalili-Shirazi A, Gregson N, Gray I, Rees J, Winer J, Hughes R. Antiganglioside antibodies in Guillain-Barré syndrome after a recent cytomegalovirus infection. J Neurol Neurosurg Psychiatry 1999;66:376-3791.
30. Visser LH, van der Meché FGA, Van Doorn PA, et al. Guillain-Barré syndrome without sensory loss (acute motor neuropathy). A subgroup with specific clinical, electrodiagnostic and laboratory features. Dutch Guillain-Barré Study Group. Brain 1995;118:841-847.
31. Jacobs BC, Van Doorn PA, Schmitz PIM, et al. Campylobacter jejuni infections and anti-GM1 antibodies in Guillain-Barré syndrome. Ann Neurol 1996;40:181-187.
32. Ang CW, Yuki N, Jacobs BC, et al. Rapidly progressive, predominantly motor Guillain-Barré syndrome with anti-GalNAc-GD1a antibodies. Neurology 1999;53:2122-2127.
33. Yuki N, Ang CW, Koga M, et al. Clinical features and response to treatment in Guillain-Barré syndrome associated with antibodies to GM1b ganglioside. Ann Neurol 2000;47:314-321.
34. McKhann GM, Cornblath DR, Griffin JW, et al. Acute motor axonal neuropathy: a frequent cause of acute flaccid paralysis in China. Ann Neurol 1993;33:333-342.
35. Griffin JW, Li CY, Ho TW, et al. Guillain-Barré syndrome in northern China. The spectrum of

neuropathological changes in clinically defined cases. Brain 1995;118:577-595.
36. Yuki N, Yoshino H, Sato S, Miyatake T. Acute axonal polyneuropathy associated with anti-GM1 antibodies following Campylobacter enteritis. Neurology 1990;40:1900-1902.
37. Ho TW, Mishu B, Li CY, et al. Guillain-Barré syndrome in northern China. Relationship to Campylobacter jejuni infection and anti-glycolipid antibodies. Brain 1995;118:597-605.
38. Cros D, Triggs WJ. There are no neurophysiologic features characteristic of "axonal" Guillain-Barré syndrome. Muscle Nerve 1994;17:675-677.
39. van der Meché FGA, Meulstee J, Kleyweg RP. Axonal damage in Guillain-Barré syndrome. Muscle Nerve 1991;14:997-1002.
40. Fuller GN, Jacobs JM, Lewis PD, Lane RJ. Pseudoaxonal Guillain-Barré syndrome: severe demyelination mimicking axonopathy. A case with pupillary involvement. J Neurol Neurosurg Psychiatry 1992;55:1079-1083.
41. Brown WF, Feasby TE, Hahn AF. Electrophysiological changes in the acute "axonal" form of Guillain-Barré syndrome. Muscle Nerve 1993;16:200-205.
42. Ropper AH. The Guillain-Barré syndrome. N Engl J Med 1992;326:1130-1136.
43. Yuki N, Sato S, Tsuji S, Ohsawa T, Miyatake T. Frequent presence of anti-GQ1b antibody in Fisher's syndrome. Neurology 1993;43:414-417.
44. Jacobs BC, Endtz HPh, van der Meché FGA, Hazenberg MP, Achtereekte HAM, Van Doorn PA. Serum anti-GQ1b IgG antibodies recognize surface epitopes on Campylobacter jejuni from patients with Miller Fisher syndrome. Ann Neurol 1995;37:260-264.
45. Ropper AH. Unusual clinical variants and signs in Guillain-Barré syndrome. Arch Neurol 1986;43:1150-1152.
46. Emilia-Romagna Study Group on Clinical and Epidemiological Problems in Neurology. Guillain-Barré syndrome variants in Emilia-Romagna, Italy, 1992-3: incidence, clinical features, and prognosis. J Neurol Neurosurg Psychiatry 1998;65:218-224.
47. Ropper AH, Wijdicks EFM, Truax BT. Guillain-Barré Syndrome. Philadelphia: FA Davis Company, 1991.
48. Koga M, Yuki N. Pharyngeal-cervical-brachial Guillain-Barré syndrome. Advances in Clinical Neurosciences 2000;10:173-185.
49. Mizoguchi K, Hase A, Obi T, et al. Two species of antiganglioside antibodies in a patient with a pharyngeal-cervical-brachial variant of Guillain-Barré syndrome. J Neurol Neurosurg Psychiatry 1994;57:1121-1123.
50. Koga M, Yuki N, Ariga T, Morimatsu M, Hirata K. Is IgG anti-GT1a antibody associated with pharyngeal-cervical-brachial weakness or oropharyngeal palsy in Guillain-Barré syndrome? J Neuroimmunol 1998;86:74-79.
51. Koga M, Yuki N, Hirata K. Antiganglioside antibody in patients with Guillain-Barré syndrome who show bulbar palsy as an initial symptom. J Neurol Neurosurg Psychiatry 1999;66:513-516.
52. Ter Bruggen JP, van der Meché FGA, de Jager AEJ, Polman CH. Ophthalmoplegic and lower

cranial nerve variants merge into each other and into classical Guillain-Barré syndrome. Muscle Nerve 1998;21:239-242.

53. Genis D, Busquets C, Manubens E, Davalos A, Baro J, Oterino A. Epidural morphine analgesia in Guillain-Barré syndrome. J Neurol Neurosurg Psychiatry 1989;52:999-1001.
54. Hughes RAC, Newsom-Davis J, Perkin GD, Pierce JM. Controlled trial of prednisolone in acute polyneuropathy. Lancet 1978;2:750-753.
55. Guillain-Barré Syndrome Steroid Trial Group. Double-blind trial of intravenous methylprednisolone in Guillain-Barré syndrome. Lancet 1993;341:586-590.
56. The Guillain-Barré study group. Plasmapheresis and acute Guillain-Barré syndrome. Neurology 1985;35:1096-1104.
57. French Cooperative Group on plasma exchange in Guillain-Barré Syndrome. Efficiency of plasma exchange in Guillain-Barré syndrome: role of replacement fluids. Ann Neurol 1987;22:753-761.
58. The French Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome. Appropriate number of plasma exchanges in Guillain-Barré syndrome. Ann Neurol 1997;41:298-306.
59. van der Meché FGA, Schmitz PIM, Dutch Guillain-Barré Study Group. A randomized trial comparing intravenous immune globulin and plasma exchange in Guillain-Barré syndrome. N Engl J Med 1992;326:1123-1129.
60. Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group. Randomised trial of plasma exchange, intravenous immunoglobulin, and combined treatments in Guillain-Barré syndrome. Lancet 1997;349:225-230.
61. The Dutch Guillain-Barré Study Group. Treatment of Guillain-Barré syndrome with high-dose immune globulins combined with methylprednisolone: a pilot study. Ann Neurol 1994;35:749-752.
62. van Koningsveld R, Van Doorn PA, Schmitz PIM, Ang CW, van der Meché FGA. Mild forms of Guillain-Barré syndrome in an epidemiologic survey the Netherlands. Neurology 2000;54:620-625.
63. McKhann GM, Griffin JW, Cornblath DR, Mellits ED, Fisher RS, Quaskey SA. Plasmapheresis and Guillain-Barré syndrome: analysis of prognostic factors and the effect of plasmapheresis. Ann Neurol 1988;23:347-353.
64. Winer JB, Hughes RAC, Osmond C. A prospective study of acute idiopathic neuropathy. I. Clinical features and their prognostic value. J Neurol Neurosurg Psychiatry 1988;51:605-612.
65. Ng KK, Howard RS, Fish DR, et al. Management and outcome of severe Guillain-Barré syndrome. Q J Med 1995;88:243-250.
66. The Italian Guillain-Barré Study Group. The prognosis and main prognostic indicators of Guillain-Barré syndrome. A multicentre prospective study of 297 patients. Brain 1996;119:2053-2061.
67. de Jager AEJ, Minderhoud JM. Residual signs in severe Guillain-Barré syndrome: analysis of 57 patients. J Neurol Sci 1991;104:151-156.
68. Fletcher DD, Lawn ND, Wolter TD, Wijdicks EF. Long-term outcome in patients with Guillain-Barré syndrome requiring mechanical ventilation. Neurology 2000;54:2311-2315.
69. Ropper AH. Severe acute Guillain-Barré syndrome. Neurology 1986;36:429-432.

70. Gruener G, Bosch EP, Strauss RG, Klugman M, Kimura J. Prediction of early beneficial response to plasma exchange in Guillain-Barré syndrome. Arch Neurol 1987;44:295-298.
71. Miller RG, Peterson GW, Daube JR, Albers JW. Prognostic value of electrodiagnosis in Guillain-Barré syndrome. Muscle Nerve 1988;11:769-774.
72. Smith GD, Hughes RAC. Plasma exchange treatment and prognosis of Guillain-Barré syndrome. Q J Med 1992;85:751-760.
73. Hadden RD, Karch H, Hartung HP, et al. Preceding infections, immune factors, and outcome in Guillain-Barré syndrome. Neurology 2001;56:758-765.
74. Visser LH, Schmitz PIM, Meulstee J, Van Doorn PA, van der Meché FGA. Prognostic factors of Guillain-Barré syndrome after intravenous immunoglobulin or plasma exchange. Neurology 1999;53:598-604.
75. Rees JH, Soudain SE, Gregson NA, Hughes RAC. Campylobacter jejuni infection and Guillain-Barré syndrome. N Engl J Med 1995;333:1374-1379.
76. Greenwood RJ, Newsom-Davis J, Hughes RAC, et al. Controlled trial of plasma exchange in acute inflammatory polyradiculoneuropathy. Lancet 1984;1:877-879.
77. Raphael JC, Chevret S, Harboun M, Jars-Guincestre MC. Intravenous immune globulins in patients with Guillain-Barré syndrome and contraindications to plasma exchange: 3 days versus 6 days. J Neurol Neurosurg Psychiatry 2001;71:235-238.



chapter 02

Epidemiology of the Guillain-Barré syndrome

2.1 Epidemiology of the Guillain-Barré syndrome: a review

Incidence rates

GBS can affect all people and is not restricted to specific areas nor related to factors as gender, age, race, standard of living or climate. Over the years 29 studies were assessed on the epidemiology of GBS (table 1). The reported crude incidence rates (IR) vary from 0.16 to 2.2 cases per 100.000 persons per year. When evaluating epidemiological data based on population surveys it is important to consider 1) the method of case ascertainment, 2) the time period under investigation and 3) the size of the population. The most commonly used method of case ascertainment is the use of the NINCDS criteria for GBS [1]. When restricting to the studies that used these criteria, to a time period ≥7 years (median number of years under investigation) and to studies including ≥54 patients (median number of patients under investigation), the IR varies from 0.83-1.49/100.000. The studies were performed between 1935 and 1997 and there appears to be no change in IR over the years. Although GBS affects people from all ages, a clear increase in incidence with age has been reported in most studies [2-6]. Besides the increase in IR with age, some studies show a peak around 20-30 years (a bimodal age distribution) [7-10].

In general, men are more frequently affected than women. In only four studies this difference reached statistical significance [2;5;6;11].

Two third of the GBS patients notice an infection approximately one to three weeks before the onset of weakness. Although some of these infections tend to show a seasonal preponderance, there is hardly ever a significant difference between seasons reported in the occurrence of GBS. From the studies reporting on the seasonal occurrence of GBS, there appears to be a slight lean towards autumn and early winter [2;4;6;12-14].

Antecedent factors

Many factors preceding GBS have been described with the suggestion that they play a role in the aetiology of the disease. Convincing are the associations with certain viruses and bacteria [15;16]. Also extensively described is the relationship with specific vaccines or drugs but most observations are, however, anecdotal [17-22]. Little doubt is left about the relationship of GBS with the swine-flu vaccination in 1976 and the use of the antidepressive drug, Zimeldine [18;19]. Finally, cases have been outlined where GBS followed pregnancy, surgery and malignancies [23-25]. Here again, no cause-and-effect relationship has been established so far. In conclusion, the relation between certain bacteria and viruses and the occurrence of GBS is generally accepted. The relation with factors as drugs, vaccines, pregnancy and malignancy however, are anecdotal and subject of discussion.
Campylobacter jejuni (C.jejuni), cytomegalovirus (CMV), Epstein-Barr virus (EBV) and *Mycoplasma pneumonia* are micro-organisms most frequently reported as preceding agent [26-29]. Recently, most attention has been drawn by *C.jejuni*. In 1984, Kaldor and Speed reported a preceding infection with this Gram-negative flagellated rod in 38% of their GBS patients [26]. This relationship has been confirmed extensively and much effort has been made to further investigate this association [15;27;30-34]. This has led to the definition of a *C.jejuni*-related subgroup which is associated with a pure motor form, a more severe clinical course and anti-GM1 antibodies [15;35;36]. Similarly, an association has been demonstrated between a preceding CMV infection, a more severe course of the disease and anti-GM2 antibodies [28;37].
If preceding factors would be the only etiologic factor in GBS, one should expect outbreaks of GBS on a regular base. Although not regular, some outbreaks have been described. The most extensively studied outbreak is the one associated with the swine-flu vaccine in 1976 and will be discussed in more detail below. Also in 1976, a 300 times the expected IR was found in Jordan [38]. A few weeks after a community-wide waterborne outbreak of acute diarrhoea, 16 cases of GBS were found within one month. In the light of the current knowledge of *C.jejuni* as frequent preceding infection, it is well possible that this agent was responsible for this outbreak. In 1968 in Colombia, 17 cases were identified within two months but no clear common factor could be found [39].

The swine-flu vaccine

In the fall of 1976, over 35 million inhabitants of the United States received a vaccine containing the A/New Jersey swine influenza virus. Two months later a marked increase of GBS was reported among receivers of the vaccine and the vaccination program was suspended. A nation wide surveillance was set up by the Centers for Disease Control

and Prevention (CDC). They established an attributable risk of vaccine-related GBS in the adult population of just under one case per 100.000 vaccinations [19]. The validity of this study was heavily criticised because it was performed in a crisis atmosphere and lacked diagnostic guidelines [40]. A commission was ordered to re-evaluate the cases and it was finally concluded that there was a relative risk of 4-8 times for GBS in the first six weeks after vaccination [41]. What really caused this increase has never been fully understood. Some findings make it even more disputable whether there has really been an increase in incidence. First, earlier vaccination programs, some including vaccination against the swine-flu, were never associated with an increase in incidence. Second, nation wide surveys in the years after 1976 did not show a relation between the influenza vaccine and GBS [42-44]. Third, US Army personnel was yearly vaccinated with a swine-flu vaccine and no increase in the number of GBS cases was found [45]. If there indeed was an increase in GBS cases due to the vaccine, it seems to be uniquely related to that particular type of swine-flu vaccine.

The Chinese paralytic syndrome

A unique epidemiological phenomenum concerning GBS is the so-called "Chinese paralytic syndrome". This variant of GBS has been recognised for at least 20 years in Northern China. McKhann et al. described a group of 3200 patients with remarkable epidemiological features. This group mainly consists of children in rural areas who are predominantly affected during late summer. Most of these patients suffered from the subtype 'acute motor axonal neuropathy' (AMAN) which is electrophysiologically and pathologically characterised by motor axonal degeneration with minimal cellular inflammation [46;47]. A prospective study showed a significantly higher percentage of serologically proven *C.jejuni* infections in the AMAN patients compared to healthy controls [48].

In conclusion, GBS can affect people worldwide, regardless of age, gender or race. In the literature, IR are reported between 0.83 to 1.49/100.000. Men and older patients are more frequently affected. Two third of the GBS patients experience an infection in the weeks prior to the first symptoms. A preceding infection with *C.jejuni* is most frequently reported.

Table 1 Reported Incidence rates of Guillain-Barré Syndrome

Study Population	Period of Study	Number of Pat.	Incid.crude	Incid.age-adj.	NINCDS criteria
Carlisle, England [49]	1955-1961	3	0.6	-	No
Guam [50]	1960-1966	5	1.9	-	No
Iceland [51]	1954-1963	13	0.7	-	No
Olmsted County,USA [52]	1935-1976	40	1.7	-	No
Israel [53]	1969-1972	89	0.75	0.8	No
San Joaquin County, USA [54]	1972-1976	18	1.2	1.4	No
Campania, Italy [55]	1971-1980	46	0.16	-	No
Olmsted County, USA [5]	1935-1980	48	1.7	1.9	Yes
Hordaland, Norway [2]	1957-1982	109	1.1	1.2	Yes
Larimer County, USA [56]	1975-1983	29	2.2	-	No
Ringkobin County, Denmark [7]	1965-1982	51	1.1	1.1	No
Benghazi, Libya [12]	1983-1985	27	1.7	1.7	Yes
Perth, Australia [8]	1980-1985	109	1.4	1.4	Yes
Copenhagen County, Denmark [9]	1977-1984	34	2.0	-	Yes
Nairobi, Kenya [57]	1974-1981	54	-	-	No
Sardinia, Italy [58]	1961-1980	120	0.4	-	No
Uusimaa County, Southern Finland [59]	1981-1985	62	1.1	-	Yes
Oxfordshire, England [4]	1974-1986	72	1.1	1.2	Yes
Ferrera, Italy [13]	1981-1987	16	1.3	1.1	Yes
Vermont, USA [60]	1980-1985	51	1.6	-	Yes
Ontario and Quebec, Canada [61] Ontario	1983-1989	1302	2.07	2.02	No
Quebec	1983-1989	1031	2.25	2.30	No
Alcoi, Spain [62]	1987-1991	5	0.9	-	Yes
Tanzania [63]	1984-1992	59	0.83	-	Yes
South-west Stockholm County, Sweden [14]	1973-1991	84	1.49	1.56	Yes
Cantabria, Spain [10]	1975-1988	69	0.95	0.86	Yes
Emilia-Romagna region, Italy [3]	1992-1993	94	1.20	-	Yes
South-east England [64]	1993-1994	79	1.20	-	Yes
South-west Netherlands [11]	1987-1996	476	1.18	1.14	Yes
Spain [6]	1985-1997	337	0.85	0.86	Yes

Bibliography

01. Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain-Barré syndrome. Ann Neurol 1990;27:Suppl:S21-4.
02. Larsen JP, Kvale G, Nyland H. Epidemiology of the Guillain-Barré syndrome in the county of Hordaland, western Norway. Acta Neurol Scand 1985;71:43-47.
03. Emilia-Romagna Study Group on Clinical and Epidemiological Problems in Neurology. A prospective study on the incidence and prognosis of Guillain-Barré syndrome in Emilia-Romagna region, Italy (1992-1993). Neurology 1997;48:214-221.
04. Winner SJ, Evans JG. Age-specific incidence of Guillain-Barré syndrome in Oxfordshire. Q J Med 1990;77:1297-1304.
05. Beghi E, Kurland LT, Mulder DW, Wiederholt WC. Guillain-Barré syndrome. Clinicoepidemiologic features and effect of influenza vaccine. Arch Neurol 1985;42:1053-1057.
06. Cuadrado JI, de Pedro-Cuesta J, Ara JR, et al. Guillain-Barré syndrome in Spain, 1985-1997: epidemiological and public health views. Eur Neurol 2001;46:83-91.
07. Bak P. Guillain-Barré syndrome in a Danish county. Neurology 1985;35:207-211.
08. Hankey GJ. Guillain-Barré syndrome in western Australia, 1980-1985. Med J Aust 1987;146:130-133.
09. Halls J, Bredkjaer C, Friis ML. Guillain-Barré syndrome: diagnostic criteria, epidemiology, clinical course and prognosis. Acta Neurol Scand 1988;78:118-122.
10. Sedano MJ, Calleja J, Canga E, Berciano J. Guillain-Barré syndrome in Cantabria, Spain. an epidemiological and clinical study. Acta Neurol Scand 1994;89:287-292.
11. van Koningsveld R, Van Doorn PA, Schmitz PIM, Ang CW, van der Meché FGA. Mild forms of Guillain-Barré syndrome in an epidemiologic survey the Netherlands. Neurology 2000;54:620-625.
12. Radhakrishnan K, el-Mangoush MA, Gerryo SE. Descriptive epidemiology of selected neuromuscular disorders in Benghazi, Libya. Acta Neurol Scand 1987;75:95-100.
13. Paolino E, Govoni V, Tola MR, Casetta I, Granieri E. Incidence of the Guillain-Barré syndrome in Ferrara, northern Italy, 1981-1987. Neuroepidemiology 1991;10:105-111.
14. Jiang GX, de Pedro-Cuesta J, Fredrikson S. Guillain-Barré syndrome in South-west Stockholm, 1973-1991, 1. Quality of registered hospital diagnoses and incidence. Acta Neurol Scand 1995;91:109-117.
15. Winer JB, Hughes RAC, Anderson MJ, Dones JM, Kangro H, Watkins RPF. A prospective study of acute idiopathic neuropathy. II. Antecedent events. J Neurol Neurosurg Psychiatry 1988;51:613-618.
16. Arnason BGW. Acute inflammatory demyelinating polyradiculoneuropathies. In: Dyck PJ, Thomas PK, Lambert EH, Bunge R, eds. Peripheral neuropathy. Philadelphia: W.B. Saunders, 1984:2050-2100.
17. Kinnunen E, Farkkila M, Hovi T, Juntunen J, Weckstrom P. Incidence of Guillain-Barré syndrome during a nationwide oral poliovirus vaccine campaign. Neurology 1989;39:1034-1036.
18. Fagius J, Osterman PO, Siden A, Wiholm BE. Guillain-Barré syndrome following zimeldine treatment. J Neurol Neurosurg Psychiatry 1985;48:65-69.

19. Schonberger LB, Bregman DJ, Sullivan JZ, et al. Guillain-Barré syndrome following vaccination in the national influenza immunization programm, United States, 1976-1977. Am J Epidemiol 1979;110:105-123.
20. Raschetti R, Maggini M, Popoli P, et al. Gangliosides and Guillain-Barré syndrome. J Clin Epidemiol 1995;48:1399-1405.
21. Cabrera J, Griffin DE, Johnson RT. Unusual features of the Guillain-Barré syndrome after rabies vaccine prepared in suckling mouse brain. J Neurol Sci 1987;81:239-245.
22. Pollard JD, Selby G. Relapsing neuropathy due to tetanus toxoid. Report of a case. J Neurol Sci 1978;37:113-125.
23. Jiang GX, de Pedro-Cuesta J, Strigard K, Olsson T, Link H. Pregnancy and Guillain-Barré syndrome : a nationwide register cohort study. Neuroepidemiology 1996;15:192-200.
24. Arnason BG, Asbury AK. Idiopathic polyneuritis after surgery. Arch Neurol 1968;18:500-507.
25. Klingon GH. Guillain-Barré syndrome associated with cancer. Cancer 1965;18:157-163.
26. Kaldor J, Speed BR. Guillain-Barré syndrome and Campylobacter jejuni: a serological study. Br Med J 1984;288:1867-1870.
27. Jacobs BC, Rothbarth PH, van der Meché FG, et al. The spectrum of antecedent infections in Guillain-Barré syndrome: a case-control study. Neurology 1998;51:1110-1115.
28. Visser LH, van der Meché FGA, Meulstee J, et al. Cytomegalovirus infection and Guillain-Barré syndrome; the clinical, electrophysiologic and prognostic features. Neurology 1996;47:668-673.
29. Steele JC, Thanasophon S, Gladstone RM, Fleming PC. Mycoplasma pneumoniae as a determinant of the Guillain-Barré syndrome. Lancet 1969;4:710-714.
30. Ropper AH. Campylobacter diarrhea and Guillain-Barré syndrome. Arch Neur 1988;45:655-656.
31. Speed BR, Kaldor J, Watson J, et al. Campylobacter jejuni/campylobacter coli-associated Guillain-Barré syndrome. Immunoblot confirmation of the serological response. Med J Aust 1987;147:13-16.
32. Vriesendorp FJ, Mishu B, Blaser MJ, Koski CL. Serum antibodies to GM1, GD1b, peripheral nerve myelin, and Campylobacter jejuni in patients with Guillain-Barré syndrome and controls: correlation and prognosis. Ann Neurol 1993;34:130-135.
33. Mishu B, Ilyas AA, Koski CL, et al. Serologic evidence of previous Campylobacter jejuni infection in patients with the Guillain-Barré syndrome. Ann Intern Med 1993;118:947-953.
34. Rees JH, Soudain SE, Gregson NA, Hughes RAC. Campylobacter jejuni infection and Guillain-Barré syndrome. N Engl J Med 1995;333:1374-1379.
35. Visser LH, van der Meché FGA, Van Doorn PA, et al. Guillain-Barré syndrome without sensory loss (acute motor neuropathy). A subgroup with specific clinical, electrodiagnostic and laboratory features. Dutch Guillain-Barré Study Group. Brain 1995;118:841-847.
36. Jacobs BC, Van Doorn PA, Schmitz PIM, et al. Campylobacter jejuni infections and anti-GM1 antibodies in Guillain-Barré syndrome. Ann Neurol 1996;40:181-187.

37. Ang CW, Jacobs BC, Brandenburg AH, et al. Cross-reactive antibodies against GM2 and CMV-infected fibroblasts in Guillain-Barré syndrome. Neurology 2000;54:1453-1458.
38. Khoury SA. Guillain-Barré syndrome: epidemiology of an outbreak. Am J Epidemiol 1978;107:433-438.
39. Lopez F, Lopez JH, Holguin J, Flewett TH. An acute outbreak of acute polyradiculoneuropathy in Colombia in 1968. Am J Epidemiol 1973;98:226-230.
40. Kurland LT, Wiederholt WC, Kirkpatrick JW, Potter HG, Armstrong P. Swine influenza vaccine and Guillain-Barré syndrome. Epidemic or artifact? Arch Neurol 1985;42:1089-1090.
41. Langmuir AD, Bregman DJ, Kurland LT, Nathanson N, Victor M. An epidemiologic and clinical evaluation of Guillain-Barré syndrome reported in association with the administration of swine influenza vaccines. Am J Epidemiol 1984;119:841-879.
42. Hurwitz ES, Holman RC, Nelson DB, Schonberger LB. National surveillance for Guillain-Barré syndrome: January 1978-March 1979. Neurology 1983;33:150-157.
43. Kaplan JE, Katona P, Hurwitz ES, Schonberger LB. Guillain-Barré syndrome in the United States, 1979-1980 and 1980-1981. Lack of an association with influenza vaccination. JAMA 1982;248:698-700.
44. Hurwitz ES, Schonberger LB, Nelson DB, Holman RC. Guillain-Barré syndrome and the 1978-1979 influenza vaccine. N Engl J Med 1981;304:1557-1561.
45. Johnson DE. Guillain-Barré syndrome in the US Army. Arch Neurol 1982;39:21-24.
46. McKhann GM, Cornblath DR, Griffin JW, et al. Acute motor axonal neuropathy: a frequent cause of acute flaccid paralysis in China. Ann Neurol 1993;33:333-342.
47. Griffin JW, Li CY, Ho TW, et al. Guillain-Barré syndrome in northern China. The spectrum of neuropathological changes in clinically defined cases. Brain 1995;118:577-595.
48. Ho TW, Mishu B, Li CY, et al. Guillain-Barré syndrome in northern China. Relationship to Campylobacter jejuni infection and anti-glycolipid antibodies. Brain 1995;118:597-605.
49. Brewis M, Poskanzer DC, Rolland C, Miller H. Neurological disease in an English city. Acta Neurol Scand 1966;42:1-89.
50. Chen KM, Brody JA, Kurland LT. Patterns of neurologic diseases on Guam. Arch Neurol 1968;19:573-578.
51. Gudmundsson KR. Prevalence and occurrence of some rare neurological diseases in Iceland. Acta Neurol Scand 1969;45:114-118.
52. Kennedy RH, Danielson MA, Mulder DW, Kurland LT. Guillain-Barré syndrome: a 42-year epidemiologic and clinical study. Mayo Clin Proc 1978;53:93-99.
53. Soffer D, Feldman S, Alter M. Epidemiology of Guillain-Barré syndrome. Neurology 1978;28:686-690.
54. Hogg JE, Kobrin DE, Schoenberg BS. The Guillain-Barré syndrome epidemiologic and clinical features. J Chronic Dis 1979;32:227-231.
55. D'Ambrosio G, De AG, Vizioli R. Epidemiology of Guillain-Barré syndrome in Campania (south Italy). Preliminary results. Acta Neurol 1983;5:245-252.

56. Kaplan JE, Poduska PJ, McIntosh GC, Hopkins RS, Ferguson SW, Schonberger LB. Guillain-Barré syndrome in Larimer county, Colorado: a high- incidence area. Neurology 1985;35:581-584.
57. Bahemuka M. Guillain-Barré syndrome in Kenya: a clinical review of 54 patients. J Neurol 1988;235:418-421.
58. Congia S, Melis M, Carboni MA. Epidemiologic and clinical features of the Guillain-Barré syndrome in Sardinia in the 1961-1980 period. Acta Neurol (Napoli) 1989;11:15-20.
59. Farkkila M, Kinnunen E, Weckstrom P. Survey of Guillain-Barré syndrome in southern Finland. Neuroepidemiology. 1991;10:236-241.
60. Koobatian TJ, Birkhead GS, Schramm MM, Vogt RL. The use of hospital data for public Health surveillance of Guillain-Barré syndrome. Ann Neurol 1991;30:618-621.
61. McLean M, Duclos P, Jacob P, Humphreys P. Incidence of Guillain-Barré syndrome in Ontario and Quebec, 1983- 1989, using hospital service databases. Epidemiology 1994;5:443-448.
62. Matias-Guiu J, Martin R, Blanquer J, et al. Incidence of Guillain-Barré syndrome and ganglioside intake in Alcoi, Spain. Neuroepidemiology 1993;12:58-60.
63. Howlett WP, Vedeler CA, Nyland H, Aarli JA. Guillain-Barré syndrome in northern Tanzania: a comparison of epidemiological and clinical findings with western Norway. Acta Neurol Scand 1996;93:44-49.
64. Rees JH, Thompson RD, Smeeton NC, Hughes RA. Epidemiological study of Guillain-Barré syndrome in south east England. J Neurol Neurosurg Psychiatry 1998;64:74-77.

2.2 Epidemiology of the Guillain-Barré syndrome in the Southwest Netherlands

Based on the article "Mild forms of Guillain-Barré syndrome in an epidemiological survey in the Netherlands". van Koningsveld R., MD, Van Doorn P.A., MD, PhD, Schmitz P.I.M., PhD, Ang C.W., MD, PhD, Van der Meché F.G.A., MD, PhD. Neurology 2000;54: 620-625

Abstract

Objective: Assessment of incidence rates of the Guillain-Barré syndrome (GBS) in the Netherlands over a ten-year period. Investigation of a relationship between possible seasonability in GBS and the occurrence of preceding infections.

Methods: Records of GBS patients admitted between 1987 and 1996 from all 45 hospitals in the Southwest of the Netherlands were evaluated covering a population of 4.2 million inhabitants.

Results: 476 patients met the NINCDS-criteria for GBS. This resulted in a crude incidence rate (IR) of 1.18/100.000 inhabitants. This IR increased linearly with age ($p<0.01$). Men were more frequently affected than women ($p<0.01$). No seasonal preponderance for GBS was found, nor for any of the preceding infections.

Conclusion: Overall IR in the Netherlands are similar to those found in other studies. The incidence increases linearly with age and men are more frequently affected than women. There appears to be no relationship between the seasonal occurrence of preceding infections and the incidence of GBS within the year.

Introduction

Epidemiological knowledge of the Guillain-Barré syndrome (GBS) is limited with respect to recent findings regarding preceding infections, prognostic factors and treatment options. Overall, 15 studies on GBS using the National Institute of Neurological Disorders and Stroke criteria (NINCDS) have shown incidence rates (IR) between 0.8 and 2.0 per 100.000 inhabitants [1-15]. Some of the more recent studies have also reported on the epidemiology of preceding infections [4,6,12].

Here, we report an epidemiological study, retrospectively performed over a period of ten years in the Southwest of the Netherlands. We assessed the IR of GBS in the Netherlands and its fluctuations over a period of 10 years. Furthermore, we hypothesised a relationship between seasonal distribution of GBS and preceding infections. It has been suggested that the failure to find a seasonal preponderance of GBS is due to the fact that there is an opposite seasonal occurrence between the most frequent antecedent events [16].

Material and Methods

The area and time-period

The survey was carried out in the Southwest of the Netherlands; an area comprising 4.2 million inhabitants which is about 25% of the population of the Netherlands. It consists of

eight well-defined health regions and is considered to be representative for the Netherlands. We investigated all GBS cases admitted to the hospitals between January 1, 1987 and December 31, 1996.

Case-collection

After obtaining permission from the neurologists in all 45 hospitals, medical records were collected of patients discharged under the international classification of disease code for GBS (ICD-9, 357.0). This code covers the following diagnosis: acute infectious polyneuritis, postinfectious polyneuritis, GBS and Miller Fisher syndrome. To exclude false-positive cases, each case was re-evaluated by a senior-neurologist using the NINCDS-criteria for GBS [17]. To screen for false-negative cases, records were reviewed of patients discharged under ICD-codes 357.8 (other specified inflammatory and toxic neuropathies) and 357.9 (not-specified inflammatory and toxic neuropathies) in three randomly selected hospitals. These codes are considered to be the most reasonable alternatives when GBS-patients are erroneously discharged.

For each patient data were obtained concerning age, sex, duration of admission, symptoms and signs, days to nadir, complications and functional grading score (f-score) at fixed points (nadir, two weeks, eight weeks and six months). The f-score is a disability scale often used in clinical trials concerning GBS [18]. The following preceding infections were scored from stool- and serological studies: *C.jejuni*, Cytomegalovirus, Epstein-Barr virus and Mycoplasma pneumoniae.

Statistics

We used the Poisson distribution for calculating 95% confidence intervals for the IR. Differences in IR regarding gender, age group or year of admission were calculated with a chi-square test without continuity correction. All calculations were performed using STATA 5.0 for Windows 95 (Stata Statistical Software, Release 5.0, College Station, TX). A p value < 0.05 was considered to be significant.

Results

During the period under investigation the number of inhabitants increased from 3.8 million in 1987 to 4.2 million in 1996 (source; Statistics Netherlands). According to the ICD-code 615 patients were discharged with the diagnosis GBS. After re-evaluation, 494 patients met the NINCDS-criteria and 116 patients did not. Among the latter group were patients with chronic inflammatory demyelinating polyneuropathy (n=24) and patients reporting a typical GBS-like pattern with symptoms and signs too weak to meet the NINCDS-criteria (n=18); 13 patient-files were not available. Eighteen of the 494 patients had to be excluded

because their domicile was outside the borders of the predefined area. Under the code 357.8 and 357.9 no patients were identified meeting the criteria for GBS. Table 1 shows the characteristics of 476 patients analysed in this study.

Table 1.
Characteristics of the patients (n= 476)

Characteristic	% of cases
age > 50	46 (476)
men	59 (476)
sensory signs or symptoms	67 (442)
cranial nerve involvement	40 (472)
artificial respiration needed	17 (472)
rapid onset of disease (<4 days until being bedbound)	32 (434)
severe maximum weakness (MRC<40)	36 (394)
mortality	3.4 (476)
median hospital stay (interquartile range)	29 days (15-53)

* number in parentheses is number of patients on which information was available

The overall crude IR was 1.18 per 100.000 inhabitants (95% CI 1.08-1.29). The age-adjusted IR, using the European population as a standard 19, was 1.14/100.000 (95% CI 1.04-1.24). The crude IR for men was 1.42 (95% CI 1.26-1.59) and for women 0.94 (95% CI 0.82-1.09) (p=0.0001). The IR per age group shows a linear increase with age (p<0.01) (figure 1). The IR from 1987 to 1996 shows only a slight (non-significant) decline over the years. Figure 2 shows the seasonal distribution of the IR. No clear fluctuation was found although there was a slight increase in incidence in June and during most winter months. No clear (opposite) peaks of occurrence for any of the four infections were found throughout the year.

Discussion

In this study we investigated the IR and seasonal fluctuations of GBS in the Netherlands. When evaluating epidemiological data based on population surveys it is important to consider the method of case ascertainment, the size of the population and the time period under investigation. We used accepted diagnostic criteria (NINCDS) with the reasonable assumption that all GBS patients are seen by a general practitioner and referred to a neurologist. We studied 476 cases recruited in a ten-year period resulting in one of the largest epidemiological studies on GBS worldwide.

The crude IR of 1.18/100.000 inhabitants and age-adjusted IR of 1.14/100.000 inhabitants found in this survey, are in agreement with other studies using NINCDS criteria. The gender difference in IR reaching a significant level has only been reported earlier in two studies where NINCDS criteria were used [3,10].

In our study we found a linear increase in incidence with age ($p<0.01$) without an additional peak around 20-30 years as has been described in other studies [1,4,5,9,13,20-22]. Of those studies describing a linear increase with age [2,3,6,8,10,] only one reached a significant level [2].

In most studies, including ours, the reported IR over the years suggest that there is no change in incidence over time [1,15,20,21]. Although there is hardly ever a significant difference between seasons reported, there appears to be a slight lean towards studies reporting the occurrence of GBS more often in the autumn and early winter [1,3,8,11,23]. Data in our study are also suggestive for the preference for the winter months. We were unable to confirm the suggestion that a clear lack of seasonal preponderance is due to the occurrence of specific infections since the most frequent antecedent infections we have studied did not show opposite seasonality [16].

Figure 1. Incidence rates per age group

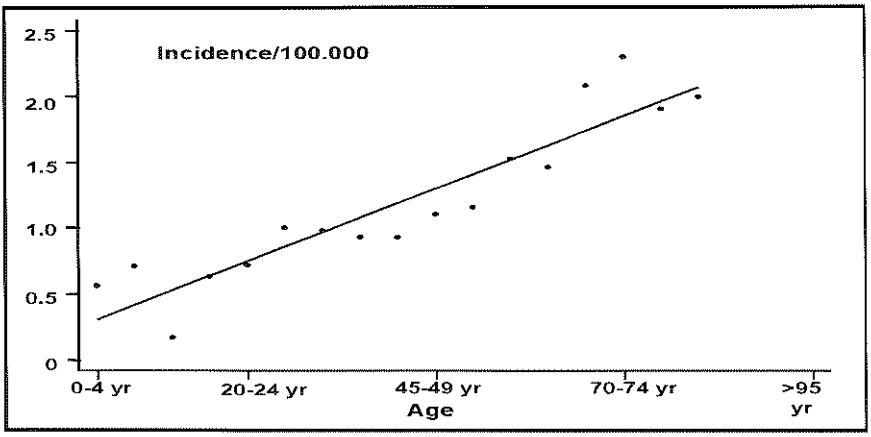
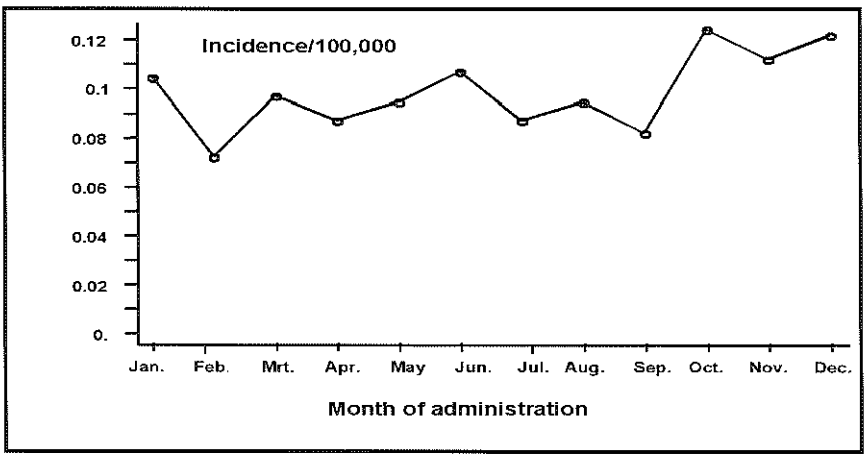


Figure 2. Incidence rates per month



Bibliography

01. Jiang GX, de Pedro-Cuesta J, Fredrikson S. Guillain-Barré syndrome in South-west Stockholm, 1973-1991, 1. Quality of registered hospital diagnoses and incidence. Acta Neurol Scand 1995; 91(2):109-117.
02. Koobatian TJ, Birkhead GS, Schramm MM, Vogt RL. The use of hospital data for public Health surveillance of Guillain-Barré syndrome. Ann Neurol 1991; 30:618-621.
03. Larsen JP, Kvale G, Nyland H. Epidemiology of the Guillain-Barré syndrome in the county of Hordaland, western Norway. Acta Neurol Scand 1985; 71(1):43-47.
04. Sedano MJ, Calleja J, Canga E, Berciano J. Guillain-Barré syndrome in Cantabria, Spain. an epidemiological and clinical study. Acta Neurol Scand 1994; 89(4):287-292.
05. Rees JH, Thompson RD, Smeeton NC, Hughes RA. Epidemiological study of Guillain-Barré syndrome in south east England. J Neurol Neurosurg Psychiatry 1998; 64(1):74-77.
06. Emilia-Romagna Study Group on Clinical and Epidemiological Problems in Neurology. A prospective study on the incidence and prognosis of Guillain-Barré syndrome in Emilia-Romagna region, Italy (1992-1993). Neurology 1997; 48(1):214-221.
07. Farkkila M, Kinnunen E, Weckstrom P. Survey of Guillain-Barré syndrome in southern Finland. Neuroepidemiology 1991; 10(5-6):236-241.
08. Winner SJ, Evans JG. Age-specific incidence of Guillain-Barré syndrome in Oxfordshire. Q J Med 1990; 77(284):1297-1304.
09. Hankey GJ. Guillain-Barré syndrome in western Australia, 1980-1985. Med J Aust 1987; 146(3):130-133.
10. Beghi E, Kurland LT, Mulder DW, Wiederholt WC. Guillain-Barré syndrome. Clinicoepidemiologic features and effect of influenza vaccine. Arch Neurol 1985; 42(11):1053-1057.
11. Radhakrishnan K, el-Mangoush MA, Gerryo SE. Descriptive epidemiology of selected neuromuscular disorders in Benghazi, Libya. Acta Neurol Scand 1987; 75(2):95-100.
12. Howlett WP, Vedeler CA, Nyland H, Aarli JA. Guillain-Barré syndrome in northern Tanzania: a comparison of epidemiological and clinical findings with western Norway. Acta Neurol Scand 1996; 93:44-49.
13. Halls J, Bredkjaer C, Friis ML. Guillain-Barré syndrome: diagnostic criteria, epidemiology, clinical course and prognosis. Acta Neurol Scand 1988; 78(2):118-122.
14. Matias-Guiu J, Martin R, Blanquer J, Gonzalez MJ, Falip R, Oltra A et al. Incidence of Guillain-Barré syndrome and ganglioside intake in Alcoi, Spain. Neuroepidemiology 1993; 12(1):58-60.
15. Paolino E, Govoni V, Tola MR, Casetta I, Granieri E. Incidence of the Guillain-Barré syndrome in Ferrara, northern Italy, 1981-1987. Neuroepidemiology 1991; 10(3):105-111.
16. Hughes RA, Rees JH. Clinical and epidemiologic features of Guillain-Barré syndrome. J Infect Dis 1997; 176:S92-S98.
17 Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain-Barré syndrome

Ann Neurol 1990; 27:Suppl:S21-4.

18. Hughes RAC, Newsom-Davis J, Perkin GD, Pierce JM. Controlled trial of prednisolone in acute polyneuropathy. Lancet 1978; 2:750-753.
19. Cancer incidence in five continents. Volume V. IARC Sci Publ 1987;(88):1-970.
20. Bak P. Guillain-Barré syndrome in a Danish county. Neurology 1985; 35(2):207-211.
21. McLean M, Duclos P, Jacob P, Humphreys P. Incidence of Guillain-Barré syndrome in Ontario and Quebec, 1983- 1989, using hospital service databases. Epidemiology 1994; 5(4):443-448.
22. Jiang GX, Cheng Q, Link H, de Pedro-Cuesta J. Epidemiological features of Guillain-Barré syndrome in Sweden, 1978-93. J Neurol Neurosurg Psychiatry 1997; 62(5):447-453.
23. Congia S, Melis M, Carboni MA. Epidemiologic and clinical features of the Guillain-Barré syndrome in Sardinia in the 1961-1980 period. Acta Neurol (Napoli) 1989; 11(1):15-20.

2.3 Gastro-enteritis-associated Guillain-Barré syndrome on the Caribbean Island of Curaçao

Based on the article "Gastro-enteritis-associated Guillain-Barré syndrome on the Caribbean Island of Curaçao". R. van Koningsveld,MD; R. Rico,MD; I. Gerstenbluth,MD; P.I.M. Schmitz,PhD; C.W. Ang,PhD; I.S.J. Merkies, PhD; B.C. Jacobs,PhD; Y. Halabi,MD; H.Ph. Endtz,PhD; F.G.A. van der Meché,PhD; P.A. van Doorn,PhD. Neurology 2001;56:1467-1472

Abstract

Background: Over the years, an increase in the number of Guillain-Barré syndrome (GBS) patients has been observed in Curaçao, the Netherlands Antilles.

Methods: Clinical and serological data were obtained from records of patients, admitted between 1987 and 1999 and fulfilling the NINCDS criteria for GBS. When possible, serum and stool samples were collected. The results were compared with a large Dutch epidemiological study.

Results: Forty-nine patients were identified resulting in an overall crude incidence rate (IR) in Curaçao of 2.53/100.000 inhabitants (95% CI 1.87-3.35) (Dutch study 1.18, rate ratio (RR) of 2.14, $p<0.001$). The IR in Curaçao increased from 1.62 in period 1987-1991 to 3.10 in the period 1992-1999, RR 5.22 (95% CI 2.48-10.2, $p=0.02$). The IR showed a curved linear shape within a year. In comparison with the Dutch group, patients from Curaçao were characterised by a more severe course of the disease with a mortality rate of 23% (3.4% in the Dutch group, $p<0.001$), a higher percentage of preceding gastro-enteritis ($p<0.001$) and less involvement of the sensory system ($p<0.001$). In eight of ten serum samples evidence was found for a recent infection with *Campylobacter jejuni*.

Conclusion: This study reports a steady increase in incidence of GBS over the years in association with a more pronounced seasonal preponderance and a more severe course. The clinical characteristics suggest a role for *C.jejuni*. An isolated island population is an excellent base to study a multifactorial disease of unknown pathogenesis.

Introduction

Over the years the Guillain-Barré syndrome has shifted from a single entity of an acute flaccid paralysis with absent tendon reflexes to a spectrum of subgroups within the broad clinical definition. Studying these subgroups, based on clinical, pathological, electrophysiological or epidemiological findings, may help to unravel the etiology of GBS. Epidemiological phenomena are important since they can contribute to a better understanding of pathophysiological mechanisms.

Here, we describe a study on the occurrence of GBS on the island Curaçao, one of the Netherlands Antilles. In recent years there appears to be an increase in the number of GBS patients in Curaçao and the individual cases seem to be characterised by a more severe course. We compared epidemiological, clinical and serological features of the GBS cases from Curaçao with a control group of GBS patients from the Netherlands. Studying an increase in incidence of a rare, multi-causal disease in an isolated population could lead to more insight in its pathophysiological mechanisms and detection of possible unknown co-factors.

Methods

The area and time-period

The study was carried out in Curaçao, one of the five islands of the Netherlands Antilles. Curaçao is an autonomous part of the Dutch Kingdom and more than 95% of the population has the Dutch nationality. This island is located near the cost of Venezuela and has a population of approximately 150.000. We studied all GBS cases admitted in the only neurological department on the island from January 1, 1987 to April 31,1999.
As a control, we used data from a large population survey in the Netherlands. That study included all cases that were admitted between January 1, 1987 and December 31, 1996 in all 45 hospitals in the Southwest part of the Netherlands (4.2 million inhabitants) [1].

Collection of cases and controls

Medical records were collected of all patients discharged under the international classification of disease code for GBS (ICD-9, 357.0). This code covers the following diagnoses: acute infectious polyneuritis, postinfectious polyneuritis, GBS and Miller Fisher syndrome. To exclude false-positive cases, each case was re-evaluated by a senior-neurologist using the NINCDS-criteria for GBS [2]. To screen for false-negative cases in Curaçao, all records were reviewed of patients discharged under ICD-codes 357.8 (other specified inflammatory and toxic neuropathies) and 357.9 (not-specified inflammatory and toxic neuropathies). These two codes are considered to be the most likely alternatives when patients are erroneously discharged. In the Southwest Netherlands this was done in three randomly selected hospitals. Data were obtained regarding age, sex, antecedent events, neurological signs and symptoms, treatment, days to nadir, complications, duration of admission and functional grading score (f-score) at fixed points [3]. We used the following parameters to indicate the severity of the disease: artificial ventilation, rapid onset of the disease (being bedbound within four days after the start of weakness), severe maximum weakness (Medical Research council (MRC) sumscore < 40/60) and mortality. When possible, serum and stool samples were collected to screen for antecedent infections.
We scored the preceding infections that are most frequently associated with GBS namely influenza- or influenza like illness, respiratory tract infection, gastro-enteritis or diarrhoea and other infections [4]. The CDC criteria for nosocomial infections [5] were used to define the antecedent infections that occurred within three weeks before start of first symptoms of GBS. The following infections were scored from stool- and serological studies: Campylobacter jejuni (stool and serology), *Salmonella, Shigella, Yersinia, Cytomegalovirus (CMV), Epstein-Bar virus (EBV) and Mycoplasma pneumoniae.*
Data on *C.jejuni* infections among the general population were derived from the only laboratory on the island where stool cultures are carried out. We collected 121 serum samples

from healthy inhabitants of Curaçao for controls. Twenty-nine were collected in March 1999, 40 in June 1999 and 52 in November 1999.

Statistics

We used the Poisson distribution for calculating the 95% confidence intervals for the IR. Differences in IR per gender or age group were calculated with a chi-square test without continuity correction. For graphical representation of the increase in incidence over the years in Curaçao, we used the method of restricted cubic splines [6]. To analyse trends in the IR, multivariate Poisson regression was used with year-of-admission and month-of-admission as variables.

Differences in characteristics between cases from Curaçao and the Southwest Netherlands were, depending on the data, univariately tested using the chi-square test without continuity correction, Fisher's exact test or- the Wilcoxon-Mann-Witney U test.

All calculations were performed using STATA 5.0 for Windows 95 (Stata Statistical Software, Release 5.0, College Station, TX). A p value < 0.05 was considered to be significant.

Results

Population and patients figures

In Curaçao the number of inhabitants increased from 152,314 in 1987 to 152,694 in 1997 (source; Statistics Netherlands). Since at the time of analysis the number of inhabitants in 1998 and 1999 was not available, we used the number of 1997 as an approximation.

From January 1987 to May 1999, 65 patients were discharged with the ICD-code for GBS. Fifty-six patients met the NINCDS criteria for GBS, seven had another diagnosis such as chronic inflammatory demyelinating polyneuropathy or radiculitis and two patients were too mildly affected to meet the criteria for GBS. Another seven patients had to be excluded because they were not inhabitants of Curaçao. No cases were identified with code 357.8 and 357.9 that met the criteria for GBS. In the Southwest Netherlands 476 patients met the criteria for GBS in the period 1987-1996, within a population of approximately 4.2 million inhabitants.

Incidence rates

We found an overall crude incidence rate (IR) of 2.53/100.000 inhabitants (95% CI 1.87-3.35) in Curaçao. The IR in the Southwest Netherlands was 1.18/100.000, resulting in a rate ratio (RR) of 2.14 (95% CI 1.56-2.88, $p<0.001$). In Curaçao, the IR for men was 3.28/100.000 (95% CI 2.21-4.69), for women 1.86/100.000 (95% CI 1.12-2.90), RR 1.77 ($p= 0.03$). Comparison with the IR per gender in the Dutch study showed no differences. The IR in Curaçao increased with age ($p=0.02$). This linear increase in incidence with age

was also found in the Dutch study.
Figure 1 shows the incidence rates from 1987 to 1999 for Curaçao and the Southwest Netherlands. A model, using multivariate Poisson regression, showed a trend in increasing IR from 1987 to 1999 in Curaçao (p=0.09). Figure 2 shows the IR per month. In contrast to the situation in the Netherlands, GBS is more prevalent in the months January, February and December in Curaçao with a decline towards zero in the months April, May and June.

Figure 1
Incidence rate of GBS in Curaçao and the Southwest Netherlands, 1987-1999

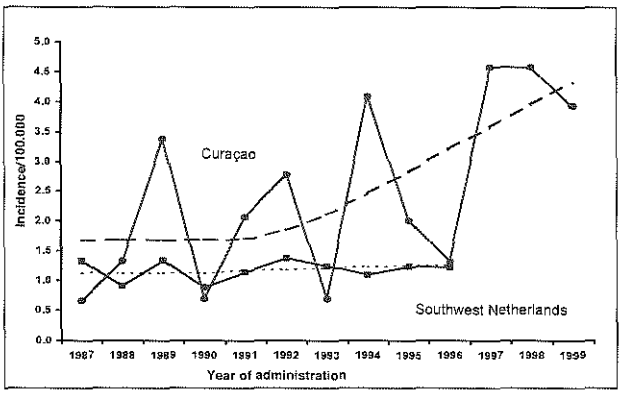
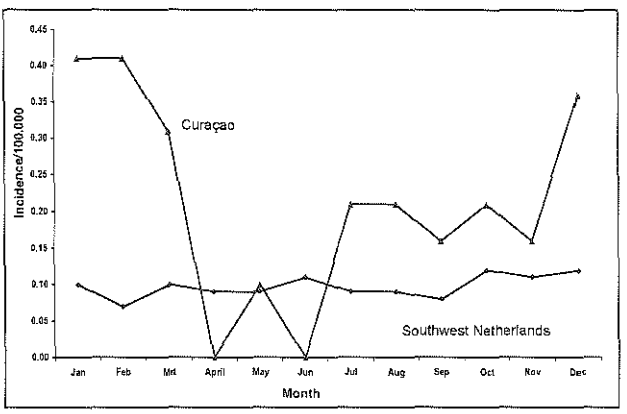


Figure 2
Incidence rate per month in Curaçao and the Southwest Netherlands



Characteristics

Table 1 shows the characteristics of the patients in Curaçao and the Southwest Netherlands. The frequency of characteristics representing the severity of the disease (artificial ventilation, rapid onset of disease, maximum weakness, and mortality) are all significantly increased in the Curaçao group. Ten patients died in the Curaçao group, 18 to 120 days after start of weakness. The age varied from 36 to 86 years, they had no severe concomitant diseases and were all treated with IVIg. All ten patients were admitted to the intensive care unit and monitored. In five patients autonomic dysfunction was reported. Six patients were transferred to the neurological ward because they showed sufficient recovery. After 1-7 days they were found death in bed or died after unsuccessful reanimation.

Table 1.
Characteristics of GBS patients from Curaçao and the Southwest Netherlands

Characteristic	Curaçao	SW Netherlands	p value
	% (n)*	% (n)*	
age > 50 years	37 (49)	46 (476)	0.24
men	39 (49)	59 (476)	0.77
sensory signs or symptoms	17 (46)	67 (442)	**< 0.01**
cranial nerve involvement	35 (49)	40 (472)	0.47
artificial ventilation needed**	31 (49)	17 (472)	**0.01**
rapid onset of disease **	83 (36)	32 (434)	**< 0.01**
severe maximum weakness**	60 (43)	36 (394)	**< 0.01**
mortality**	23 (43)	3.4 (476)	**< 0.01**

*Number of patients from which information was available

**Characteristics representing the severity of the disease (described under 'methods')

Preceding infections

Table 2 shows the reported preceding infections in the patient group from Curaçao and the Netherlands. Fifty-five percent of the patients in Curaçao reported a gastro-enteritis as preceding infection. In eight of ten patients, serological evidence was found for a recent infection with *C.jejuni*. One of the two negative patients had a borderline antibody titer. From the faeces of that patient, *C.jejuni* was cultured.

Table 2. Preceding infections in GBS patients from Curaçao and the Southwest Netherlands

	Curaçao	SW Netherlands	
	% (n)*	% (n)*	p value
Infections clinical			
Influenza- or Influenza-like	25 (44)	25 (387)	0.98
Respiratory tract	5 (44)	22 (387)	**0.01**
Gastro-enteritis/ diarrhoea	55 (44)	20 (388)	**< 0.01**
Other	7 (44)	12 (389)	0.30
Infections serological			
Campylobacter jejuni	80 (10)	32 (134)	**< 0.01**
Cytomegalovirus	0 (4)	19 (239)	1
Epstein-Barr virus	N.P.	7 (212)	
Mycoplasma pneumoniae	N.P.	9 (197)	

* Number of patients from which information was available
N.P. = not performed

Additional analysis of Curaçao cases

From these results, three observations stand out. Firstly, it appears that the IR runs a more or less stable course from 1987 to 1991, while from 1992 the IR starts to increase (figure 1). Secondly, analysis of the preceding infection resulted in a high percentage of gastro-enteritis in the Curaçao group. Finally, in contrast to most other studies, we observed a seasonal fluctuation (figure 2). We investigated these three findings in more detail.

We compared the group of patients diagnosed in the stable years (n= 12,1987-1991) with the group admitted during the years in which the IR increased (n=37, 1992-1999). The overall IR from 1987-1991 was 1.62 (95% CI 0.36-2.83), the overall IR from 1992 to1999 was 3.10 (95% CI 2.18-4.27), RR 5.23 (p=0.02). Table 3 shows the clinical characteristics of the two periods. Regarding the preceding infections, a difference was found in the percentage of gastro-enteritis (36% in 1987-1991, 61% in 1992 to 1999, p=0.19).

Table 3. Characteristics of patient group 1987-1991 and patient group 1992-1999

Characteristic	Curaçao	Curaçao	
	1987-1991	1992-1999	
	% (n=12)	% (n=37)	p value
age > 50 years	25	40	0.49
men	67	60	0.74
sensory signs or symptoms	25	15	0.41
cranial nerve involvement	25	38	0.50
artificial respiration needed	17	35	0.29
rapid onset of disease	75	86	0.60
severe maximum weakness	42	68	0.17
mortality	0	27	**0.04**
gastro-enteritis	36	61	0.19

We compared the characteristics of both periods with the group of patients from the Dutch study. For the period 1987-1991, there were only differences found for the percentage of sensory involvement (25% in Curaçao 1987-1991 versus 67% in the Southwest Netherlands, p=0.004) and rapid onset of weakness (75% in Curaçao 1987-1991 versus 32% in the SW Netherlands, p=0.02). For the period 1992-1999, besides a difference in the percentage of sensory involvement (15% in Curaçao 1992-1999 versus 67% in the Netherlands, p<0.001), significant differences were found for all four characteristics representing the severity of the disease. Finally, a higher percentage of gastro-enteritis was reported in the 1992-1999 group (61% versus 20% in the Southwest Netherlands, p<0.001).

To explore the increase in reported gastro-enteritis among GBS patients, we collected data on positive *C.jejuni* stool cultures among the general population in Curaçao. Data available from 1988 to August 2000, showed an increase in the number of positive cultures in 1999 and 2000 (n=1064, mean number 81). To explore the high percentage of serologically proven *C.jejuni* infections in the GBS patients, we analysed 121 serum samples from healthy controls from Curaçao. Twenty-three of the 121 samples (19%) were positive for *C.jejuni* while in the GBS group, eight of the ten were positive (80%, p<0.001).
In figure 2 the pattern of seasonality shows a curved linear shape with a peak in the months January, February and December and a decline towards zero in the months April, May and June. We used Poisson regression with restricted cubic splines to fit the IR per month and year in a model. Figure 3 shows higher IR over the recent years and a more pronounced seasonal preponderance. Inserting seasons instead of months into the model resulted in a low IR in spring (p=0.001) and summer (p=0.06) and no difference in autumn (p=0.19) compared to the IR in winter. To explore this seasonal preponderance, we analysed data on *C.jejuni* cultured from stools taken from the general population per month from 1993-1999. Figure 4 shows the seasonal fluctuation of the number of cultured *C.jejuni* among the general population as well as the seasonal fluctuation of the GBS cases.

Figure 3
Incidence rate per year and month in Curaçao

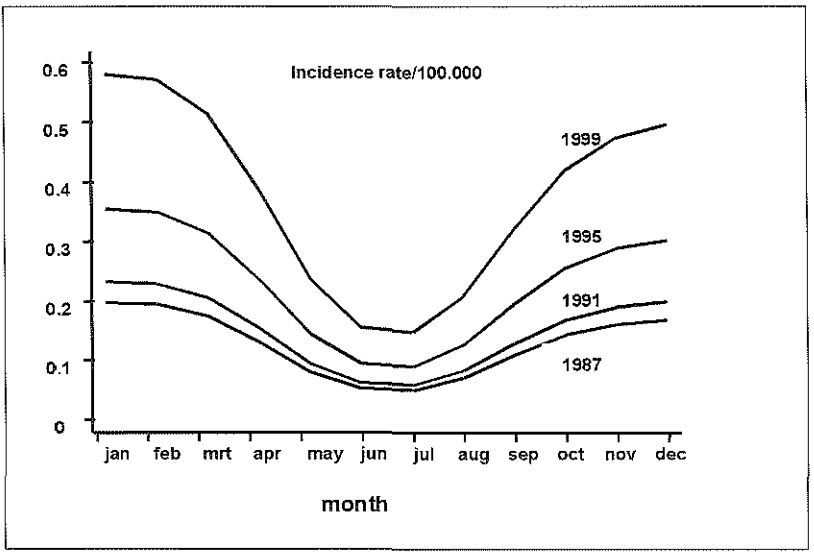
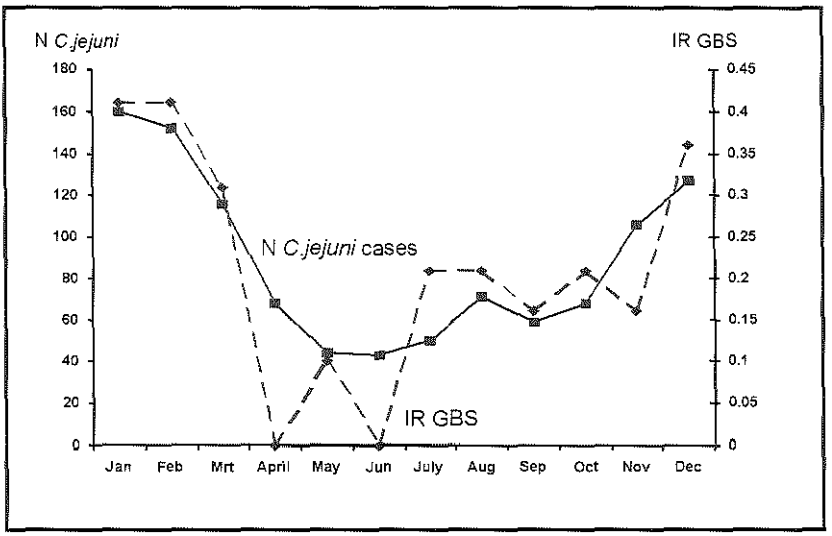


Figure 4
Number of cultured C.jejuni per month among general population in Curaçao (1988-August 2000) and IR GBS per month (1987-1999)



Discussion

This is the first study reporting an increase in incidence rate of GBS over a longer period associated with an increasing mortality rate, an increasing seasonal fluctuation and an increasing percentage of preceding gastro-enteritis.

The first question however, is whether the increasing number of patients truly reflects an increase in IR of GBS. This study was performed retrospectively and for the complete study period, hospital discharge data and the NINCDS criteria were used. Screening hospital discharge data is an accepted method for studying the epidemiology of a disease, provided that accepted diagnostic criteria are used and that the disease is likely to result in hospitalisation [7]. This study was based on and identical in methodology to a survey performed in the Southwest Netherlands. In that study, 476 cases were analysed resulting in one of the largest epidemiological studies on GBS worldwide. Data of that study were in agreement with the literature on the epidemiology of GBS. In conclusion, we consider the study as performed in Curaçao to be consistent, making it reasonable to assume that the increase in number of GBS patients truly reflects a rise in IR.

Three other studies have reported an increase in IR of GBS over the years. In contrast to our study, in two studies no differences were found with regard to age, clinical characteristics, preceding infections or severity of the disease. It was concluded that the most plausible

explanation was chance occurrence [8,9]. The study from Ferrara, Italy, reported that the increase in incidence predominantly affected people over 50 years of age in urban centres [10]. In Curaçao, we found an overall IR of 2.53 per 100.000 inhabitants. This is higher than most other studies including that in the Southwest Netherlands. The high IR in Curaçao is mainly due to the increase starting from about 1992. An incidence rate as high as 3.10 over a six-year period (1992-1999) has never been described. We found that men were more frequently affected than women (p=0.03). In three other studies using NINCDS criteria, this difference also reached a significant level [1,11,12]. The linear increase with age found in this study is in agreement with other studies [1,7,8,11-13] although some studies describe a bimodal pattern [14-16]. Studies on seasonal fluctuations often report a preference for the colder months but seldom reach a significant difference [8,11,14]. In China, a variant of GBS has been described which occurs mainly in summer [17]. This "Chinese paralytic syndrome" has been recognised for at least 20 years and affects predominantly children and young adults in rural areas. The study in Curaçao is the first in which the seasonal preponderance is based on incidence rates with significant differences between the seasons.

Despite the relatively low number of cases one could speculate about the cause of the incidence increase in Curaçao. An increase in the occurrence of an infectious agent can result in an increase of the number of GBS patients. More frequent exposure to the pathogen or the introduction of a particular strain, which more often triggers GBS, can also be possible causes.

C.jejuni is the most frequently reported antecedent infection in association with GBS [18-20]. We suggest that *C.jejuni* plays a crucial role in the increase of GBS cases in recent years in Curaçao. Firstly, we found a higher percentage of gastro-enteritis associated GBS in recent years. Since evidence for a recent infection with *C.jejuni* was found in eight out of the ten recently collected serum samples, it is likely that this pathogen is the predominant cause of gastro-enteritis. There was no increase in the number of *C.jejuni* cultured between 1988 and 1998 among the general population. This suggests that the increase in GBS cases is more likely to be induced by a more pathogenic strain than due to an increase in the occurrence of *C.jejuni* on the whole. The increase in the number of *C.jejuni* cultured among the general population in 1999 and 2000 could be due to the introduction of a new, more advanced culturing technique. Recently, a start was made to type the bacteria cultures in order to gain more insight in the spectrum of strains.

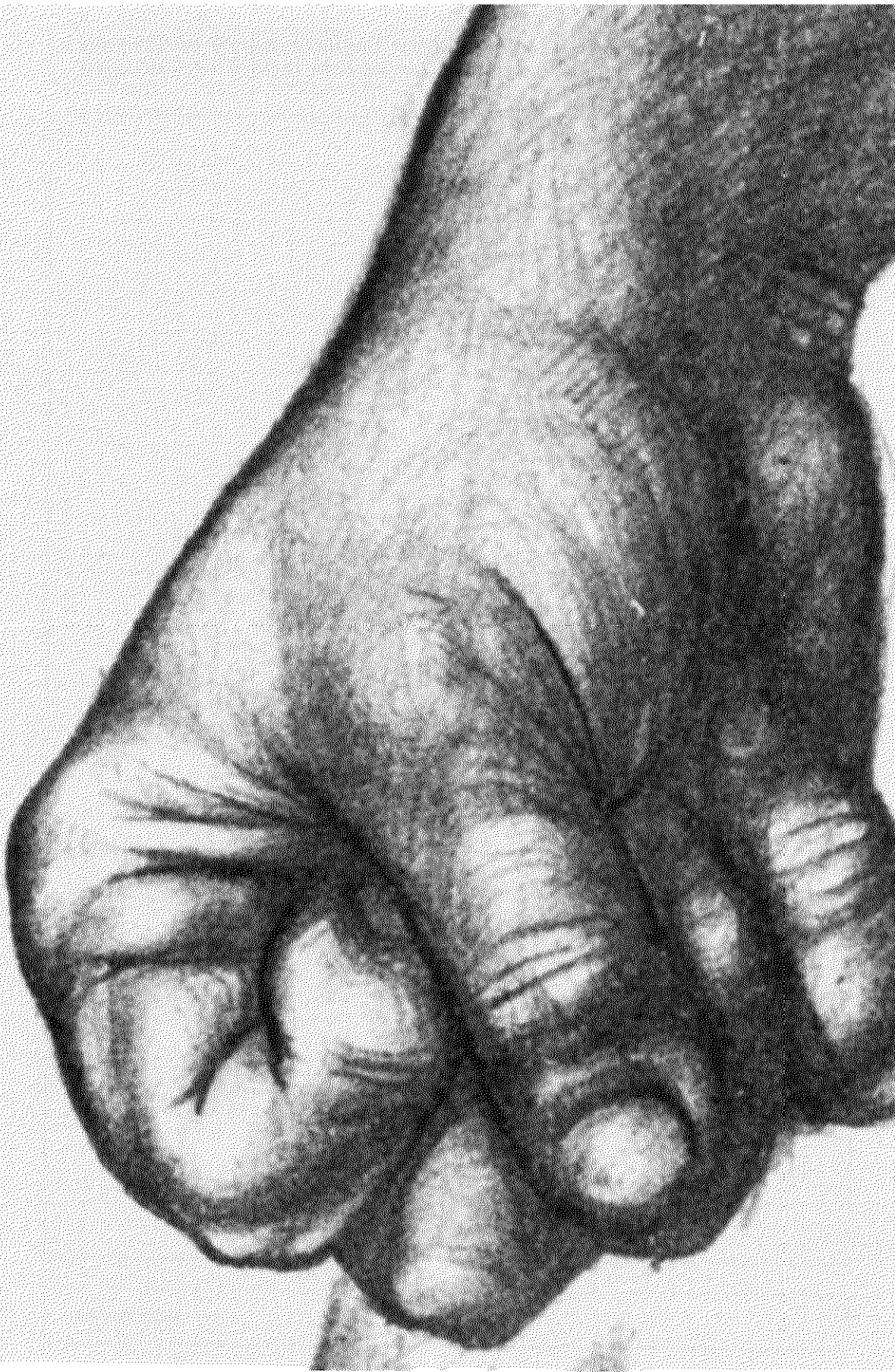
The observation that GBS runs a more severe course with a higher mortality rate also points to *C.jejuni* since different studies report on the association between a preceding *C.jejuni* infections and a more severe course of GBS [18,21-23]. In most studies, the pure motor variant of GBS accounts for 10-20% of all cases [20]. Because this subtype is also associated with a preceding *C.jejuni* infection, the 83% of pure motor cases we found is

again suggestive for the relationship with *C.jejuni* [20,24]. In "the Chinese paralytic syndrome" the pure motor variant was also more frequently found. A prospective study showed a significantly higher percentage of serological proven *C.jejuni* infections in those cases compared to healthy controls [25]. A final indication of *C.jejuni* as a key player is the seasonal fluctuation. Although the curve linear shape of the occurrence of *C.jejuni* very much resembles the pattern of the IR of GBS, this requires further investigation since it is based on numbers and not on incidence rates. Because not every *C.jejuni* infection results in the development of GBS, *C.jejuni* alone can not entirely account for the increase in IR of GBS. Therefore, a role for host factors and/or environmental factors must be considered. Prospective research in this isolated island population can be of great value in determining factors involved in the pathofysiological mechanism of the Guillain-Barré syndrome.

Bibliography

01. van Koningsveld R, Van Doorn PA, Schmitz PIM, Ang CW, van der Meché FGA. Mild forms of Guillain-Barré syndrome in an epidemiologic survey the Netherlands. Neurology 2000; 54:620-625.
02. Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain-Barré syndrome. Ann Neurol 1990; 27:Suppl:S21-4.
03. Hughes RAC, Newsom-Davis J, Perkin GD, Pierce JM. Controlled trial of prednisolone in acute polyneuropathy. Lancet 1978; 2:750-753.
04. Jacobs BC, Rothbarth PH, van der Meche FG, Herbrink P, Schmitz PI, de KM et al. The spectrum of antecedent infections in Guillain-Barré syndrome: a case-control study. Neurology 1998; 51(4):1110-1115.
05. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. Am J Infect Control 1988; 16(3):128-140.
06. Heuer C. Modeling of time trends and interactions in vital rates using restricted regression splines. Biometrics 1997; 53:161-177.
07. Koobatian TJ, Birkhead GS, Schramm MM, Vogt RL. The use of hospital data for public Health surveillance of Guillain-Barré syndrome. Ann Neurol 1991; 30:618-621.
08. Winner SJ, Evans JG. Age-specific incidence of Guillain-Barré syndrome in Oxfordshire. Q J Med 1990; 77(284):1297-1304.
09. Kaplan JE, Poduska PJ, McIntosh GC, Hopkins RS, Ferguson SW, Schonberger LB. Guillain-Barré syndrome in Larimer county, Colorado: a high- incidence area. Neurology 1985; 35(4):581-584.
10. Govoni V, Granieri E, Casetta I, Rosaria Tola M, Paolino E, Fainardi E et al. The incidence of Guillain-Barré syndrome in Ferrara, Italy: Is the disease really increasing? J Neurol Sci 1996; 137:62-68.
11. Larsen JP, Kvale G, Nyland H. Epidemiology of the Guillain-Barré syndrome in the county of Hordaland, western Norway. Acta Neurol Scand 1985; 71(1):43-47.
12. Beghi E, Kurland LT, Mulder DW, Wiederholt WC. Guillain-Barré syndrome. Clinicoepidemiologic features and effect of influenza vaccine. Arch Neurol 1985; 42(11):1053-1057.
13. Emilia-Romagna Study Group on Clinical and Epidemiological Problems in Neurology. A prospective study on the incidence and prognosis of Guillain-Barré syndrome in Emilia-Romagna region, Italy (1992-1993). Neurology 1997; 48(1):214-221.
14. Jiang GX, de Pedro-Cuesta J, Fredrikson S. Guillain-Barré syndrome in South-west Stockholm, 1973-1991, 1. Quality of registered hospital diagnoses and incidence. Acta Neurol Scand 1995; 91(2):109-117.
15. Rees JH, Thompson RD, Smeeton NC, Hughes RA. Epidemiological study of Guillain-Barré syndrome in south east England. J Neurol Neurosurg Psychiatry 1998; 64(1):74-77.
16. Halls J, Bredkjaer C, Friis ML. Guillain-Barré syndrome: diagnostic criteria, epidemiology, clinical course and prognosis. Acta Neurol Scand 1988; 78(2):118-122.

17. McKhann GM, Cornblath DR, Griffin JW, Ho TW, Li CY, Jiang Z et al. Acute motor axonal neuropathy: a frequent cause of acute flaccid paralysis in China. Ann Neurol 1993; 33(4):333-342.
18. Kaldor J, Speed BR. Guillain-Barré syndrome and Campylobacter jejuni: a serological study. Br Med J 1984; 288:1867-1870.
19. Rees JH, Soudain SE, Gregson NA, Hughes RAC. Campylobacter jejuni infection and Guillain-Barré syndrome. N Engl J Med 1995; 333(21):1374-1379.
20. Jacobs BC, Van Doorn PA, Schmitz PIM, Tio-Gillen AP, Herbrink P, Visser LH et al. Campylobacter jejuni infections and anti-GM1 antibodies in Guillain-Barré syndrome. Ann Neurol 1996; 40:181-187.
21. van der Meché FGA, Schmitz PIM, Dutch Guillain-Barré Study Group. A randomized trial comparing intravenous immune globulin and plasma exchange in Guillain-Barré syndrome. N Engl J Med 1992; 326(17):1123-1129.
22. Vriesendorp FJ, Mayer RF, Koski CL. Kinetics of anti-peripheral nerve myelin antibody in patients with Guillain-Barré syndrome treated and not treated with plasmapheresis. Arch Neurol 1991; 48(8):858-861.
23. Winer JB, Hughes RAC, Anderson MJ, Dones JM, Kangro H, Watkins RPF. A prospective study of acute idiopathic neuropathy. II. Antecedent events. J Neurol Neurosurg Psychiatry 1988; 51:613-618.
24. Visser LH, van der Meché FGA, Van Doorn PA, Meulstee J, Jacobs BC, Oomes PG et al. Guillain-Barré syndrome without sensory loss (acute motor neuropathy). A subgroup with specific clinical, electrodiagnostic and laboratory features. Dutch Guillain-Barré Study Group. Brain 1995; 118(Pt 4):841-847.
25. Ho TW, Mishu B, Li CY, Gao CY, Cornblath DR, Griffin JW et al. Guillain-Barré syndrome in northern China. Relationship to Campylobacter jejuni infection and anti-glycolipid antibodies. Brain 1995; 118:597-605.



chapter 03

Clinical aspects of the Guillain-Barré syndrome

3.1 Mild forms of the Guillain-Barré syndrome; a retrospective study

Based on the article "Mild forms of Guillain-Barré syndrome in an epidemiological survey in the Netherlands". van Koningsveld R., MD, Van Doorn P.A., MD, PhD, Schmitz P.I.M., PhD, Ang C.W., PhD, Van der Meché F.G.A., MD, PhD. Neurology 2000;54: 620-625

Abstract

Objective: Determination of distinctive characteristics in GBS patients who are only mildly affected (able to walk unaided at nadir).

Methods: Records of GBS patients admitted between 1987 and 1996 from all 45 hospitals in the Southwest of the Netherlands were evaluated covering a population of 4.2 million inhabitants.

Results: Four hundred seventy-six patients met the NINCDS-criteria for GBS. Patients under 50 years of age ($p<0.01$) and men ($p=0.01$) were more frequently found in the mildly affected group. In both groups a preceding infection was reported in 70% of the cases. In the severely affected group serological evidence for infections with *C.jejuni*, CMV, EBV and Mycoplasma pneumoniae was found more frequently than in the mildly affected group (41% vs.16%, $p=0.001$).

Conclusion: Distinctive characteristics for mildly and severely affected patients were found regarding age, gender and preceding infections. This suggests that other infectious agents or host factors may be involved in mild forms of GBS.

Introduction

Information on subgroups, clinical course, treatment and the pathogenesis of GBS mostly derives from clinical trials including our own studies [1,2]. These treatment studies have been restricted to the more severely affected patients, i.e. patients unable to walk unaided at nadir (point in time of maximum severity of the disease). Therefore knowledge on GBS is mainly based on this subgroup of patients.

Here, we report an epidemiological study, retrospectively performed over a period of ten years in the Southwest of the Netherlands. We assessed the clinical characteristics of the complete spectrum of patients from severely to mildly affected. Knowledge of factors limiting the disease may be of importance in unravelling its pathogenesis and the development of new treatments.

Material and Methods

Paragraph 2.2 gives detailed description of the methods used in this study. In addition the following information was used to study the differences between mildly and severely affected patients.

Patients were considered to be mildly affected when the f-score was < 3 (able to walk unaided at nadir) and severely affected when the maximal f-score was ≥ 3 (unable to walk

unaided at nadir). The f-score is a disability scale often used in clinical trials concerning GBS [3]. In the analyses of differences between mildly and severely affected patients, those with an f-score of 6 (dead) were left out (n=16). Inclusion of grade 6 patients in the severe group could lead to distorted results regarding the duration of hospitalisation, days to nadir and other factors related to the progression of symptoms. The scores 1 to 5 indicate a functional state which patients may reach due to GBS. Attainment of an f-score of 6 is not automatically due to progression and can also occur as a complication of the disease. Inclusion of grade 6 patients would not have influenced the results regarding the differences in serological proven infections between mildly and severely affected patients (see results section).

Definition of events

We scored the events most frequently associated with GBS namely cancer, surgery, vaccination and pregnancy [4-7] as positive when they occurred within three weeks before the start of the first symptoms of GBS.

Data on preceding influenza- or influenza like illness, respiratory tract infection, gastro-enteritis or diarrhoea and other infections were obtained from chart reviews and were considered positive when patients reported symptoms meeting the criteria for these infections according to the CDC definitions for nosocomial infections [8] and when they occurred within 3 weeks before the start of the first symptoms of GBS. The following infections were scored from stool- and serological studies: *C.jejuni* (stool and serology), *Salmonella, Shigella, Yersinia,* CMV, EBV and *Mycoplasma pneumoniae*.

Statistics

Depending on the data, differences between mildly and severely affected patients were univariately tested using the chi-square test without continuity correction, Fisher's exact test or the Wilcoxon-Mann-Witney U test and multivariately using logistic regression. Outcome was adjusted for age and gender simultaneously using logistic regression. All calculations were performed using STATA 5.0 for Windows 95 (Stata Statistical Software, Release 5.0, College Station, TX). A p value < 0.05 was considered to be significant.

Results

Table 1 shows the characteristics of the 476 patients. For the total group, outcome at 8 weeks and 6 months was worse for the group age $\geq$ 50 years (both $p<0.01$). Women were less frequently able to walk independently after 8 weeks than men ($p=0.06$); this difference was not found at 6 months. In a multivariate analysis testing age and gender, only age had an effect on the ability to walk independently at 8 weeks ($p<0.01$) and at 6 months ($p<0.01$).

Table 1. Characteristics of the patients

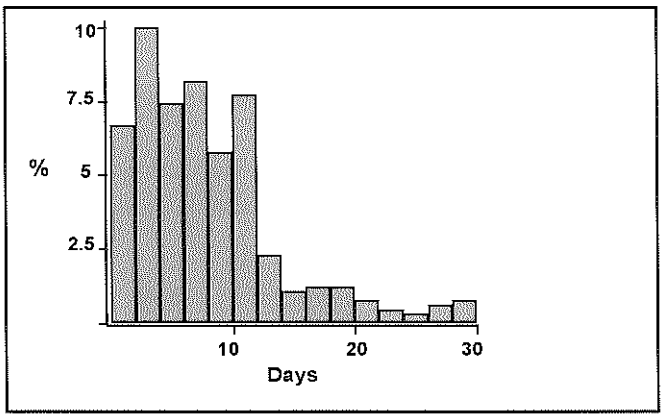
Characteristics	Total group (n=476)	Mildly affected (n=121) % cases	Severely affected (n=315) % cases	p value
age > 50	46 (476)	31 (121)*	51 (315)	< 0.01
men	59 (476)	69 (121)	55 (315)	0.01
sensory signs or symptoms	67 (442)	60 (118)	69 (294)	0.10
cranial nerve involvement	40 (472)	41 (121)	40 (315)	0.83
complications	15 (436)	2 (121)	21 (315)	< 0.01
median hospital stay (interquartile range)	29 days (15-53)	13 days (8-20)	39 days (22-67)	< 0.01
median days to nadir (interquartile range)	8 days (5-12)	7 days (3-11)	9 days (5-13)	< 0.01

* number in parentheses is number of patients on which information was available

F-score at nadir

Figure 1 shows the distribution of days until nadir for the total group with a median of eight days (range 1-30 days). The median for the mildly affected group was 7 days and for the severe group 9 days (p<0.01).

Figure 1. Days to nadir



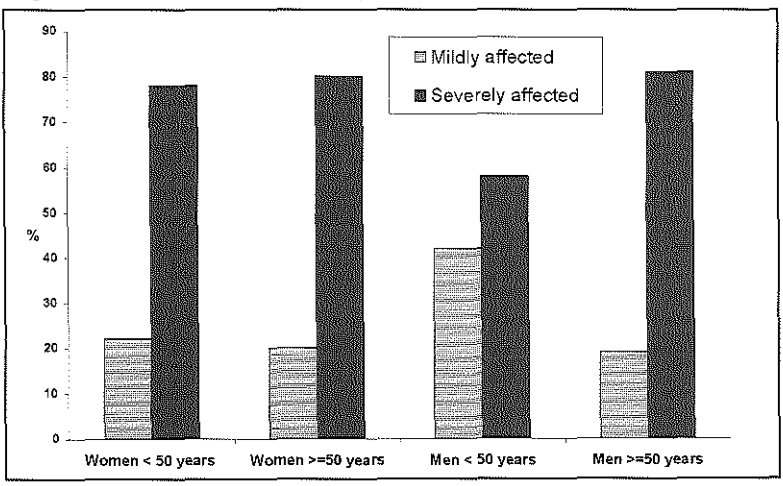
We were able to obtain the f-score at nadir for 436 patients. One hundred twenty-one patients (28%) were mildly affected and 315 patients (72%) were severely affected (table 1). Significantly more mildly affected patients were men (p=0.01) and below 50 years of age (p<0.01)(figure 2). In a logistic regression, age and gender both maintained their influence on being "mildly or severely affected at nadir" (age p<0.01, gender p=0.02).

Table 2. Antecedent events and infections

Event	% cases
Cancer	1.5 (468)*
Surgery	2 (445)
Vaccination	3 (440)
Pregnancy	2 (190)
Infections clinically	**% cases**
Influenza- or Influenza-like	25 387)
Respiratory tract	22 (387)
Gastro-enteritis/ Diarrhea	20 (388)
Other	12 (389)
Total	**72 (391)**
Infections stool or serology	**% cases**
C.jejuni stool	9 (138)
Shigella stool	0 (121)
Salmonella stool	0 (121)
Yersinia stool	1 (105)
C.jejuni serology	32 (134)
CMV serology	18 (239)
EBV serology	7 (212)
Mycoplasma pneumonia serology	9 (197)
Total	**33 (352)**

* number in parentheses is number of patients on which information was available

Figure 2. Mildly and severely affected patients per age group and gender



Antecedent events and infections

Table 2 shows the events and infections preceding GBS in the total group. Seventy-two percent of the cases reported that an infection preceded the initial symptoms of GBS whereas in 33% a stool culture or serology was positive for one or more agents. Among the 47 other clinically reported infections the following were reported more than once: pneumonia (7), cystitis (5), sinusitis (3) and otitis media (2), herpes zoster (2), varicella zoster (2).

Table 3. Serological screening of infections in mildly and severely affected patients

Infections	Mildly affected % positive	Severely affected % positive	p value
C.jejuni	21 (14)*	33 (114)	0.37
CMV	10 (40)	20 (184)	0.13
EBV	3 (36)	8 (167)	0.24
Mycoplasma pneumonia	3 (34)	10 (153)	0.20
Total	16 (55)	41 (220)	<0.01

* number in parentheses is number of patients of which serum sample was available

There was no significant difference in reported infections for the mildly and severely affected patients (73% and 71% respectively). This is in contrast with the serological results where in the severe group 90 out of 220 (41%) and in the mild group 9 out of 55 (16%) were positive ($p<0.01$, table 3). The results regarding *C.jejuni* stool cultures differed from these findings; in the mild group 7 of 29 (24%) cultured stools were positive whereas 6 of 100 (6%) in the severe group ($p<0.01$).

Multivariate analysis on the outcome of being mildly or severely affected now showed that age $\geq$ 50 years ($p=0.06$), men ($p=0.07$), presence of diarrhoea ($p=0.09$) and positive serology for *C.jejuni*, CMV, EBV or *mycoplasma pneumonia* ($p=0.02$) are more frequently associated with the more severe clinical course.

Complications and recurrence

Complications were found in 67 cases including 20 times autonomic dysfunction and 29 complications reported during intensive care admission (pneumonia, atelectasis, deep venous thrombosis, sepsis). Sixteen patients died (3.4%). In 11 patients GBS reoccurred (2.5%) with a mean period of 16 months between the two episodes (2-47 months). One patient had three episodes of GBS (once in 1987, twice in 1991). There was no difference between the mildly and severely affected patients in recurrence rate. There appeared to be no relation between the severity of the first period and the chance of being mildly or

severely affected during the subsequent episode.

Discussion

In this study we described characteristics of mildly affected GBS patients versus severely affected patients. We found 28% of the patients to be mildly and 72% to be severely affected. In three other studies the percentages of mildly affected patients were respectively 19, 23 and 24 [9-11]. In our study, age and gender were related to the maximum severity of the disease and therefore the chance of being mildly or severely affected. No previous studies report on women being more frequently severely affected than men. There are however studies on CMV related GBS, that report a more severe course and a higher incidence in young women [12]. We tested this in a multivariate analysis and showed that there was no relationship between the predominance of women in our severe group and the presence of CMV infections. As in this study, older age is often described as a prognostic factor for worse outcome [9,13-15]. This is the first study however reporting age as a predictor for a more severe course of the disease. Another finding which has not been earlier described is that women had a worse outcome at 8 weeks compared to men. In a multivariate analysis only age had influence on the ability to walk independently both at 8 weeks ($p<0.01$) and 6 months ($p<0.01$).

That more than 70% of the patients reported a preceding infection confirms the established consensus concerning the triggering role of infections in GBS [16-18]. Although *C.jejuni* infections are generally associated with a more severe clinical course [1,19,20], we also found positive serology and positive stool cultures in the mildly affected group. Surprisingly, the percentage of positive stool cultures for *C.jejuni* was higher in the mild group. Additional information showed that in the mild group, stools were cultured on indication (most patients had a clinical gastro-enteritis) whereas culturing in the severe group was more often part of a standard procedure. Future prognostic studies are needed to show whether different strains of *C.jejuni* are responsible for the severity of GBS, and whether host factors further determine the course of the disease. Serological screening of the four most frequently reported antecedent infections resulted in significantly more positive patients in the severe group compared to the mild group (41% vs.16%). Considering the similar incidence of clinically reported infections, one may conclude that the common known infections preceding GBS are of less importance in mildly affected patients.

Bibliography

01. van der Meché FGA, Schmitz PIM, Dutch Guillain-Barré Study Group. A randomized trial comparing intravenous immune globulin and plasma exchange in Guillain-Barré syndrome. N Engl J Med 1992; 326(17):1123-1129.
02. The Dutch Guillain-Barré Study Group. Treatment of Guillain-Barré syndrome with high-dose immune globulins combined with methylprednisolone: a pilot study. Ann Neurol 1994; 35(6):749-752.
03. Hughes RAC, Newsom-Davis J, Perkin GD, Pierce JM. Controlled trial of prednisolone in acute polyneuropathy. Lancet 1978; 2:750-753.
04. Kinnunen E, Farkkila M, Hovi T, Juntunen J, Weckstrom P. Incidence of Guillain-Barré syndrome during a nationwide oral poliovirus vaccine campaign. Neurology 1989; 39(8):1034-1036.
05. Schonberger LB, Bregman DJ, Sullivan JZ, Keenlyside RA, Ziegler DW, Retailliau HF et al. Guillain-Barré syndrome following vaccination in the national influenza immunization programm, United States, 1976-1977. Am J Epidemiol 1979; 110:105-123.
06. Jiang GX, de Pedro-Cuesta J, Strigard K, Olsson T, Link H. Pregnancy and Guillain-Barré syndrome : a nationwide register cohort study. Neuroepidemiology 1996; 15:192-200.
07. Klingon GH. Guillain-Barré syndrome associated with cancer. Cancer 1965; 18:157-163.
08. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. Am J Infect Control 1988; 16(3):128-140.
09. Emilia-Romagna Study Group on Clinical and Epidemiological Problems in Neurology. A prospective study on the incidence and prognosis of Guillain-Barré syndrome in Emilia-Romagna region, Italy (1992-1993). Neurology 1997; 48(1):214-221.
10. Winer JB, Hughes RAC, Osmond C. A prospective study of acute idiopathic neuropathy. I. Clinical features and their prognostic value. J Neurol Neurosurg Psychiatry 1988; 51(5):605-612.
11. The Italian Guillain-Barré Study Group. The prognosis and main prognostic indicators of Guillain-Barré syndrome. A multicentre prospective study of 297 patients. Brain 1996; 119(Pt 6):2053-2061.
12. Visser LH, van der Meché FGA, Meulstee J, Rothbarth P, Jacobs BC, Schmitz PIM et al. Cytomegalovirus infection and Guillain-Barré syndrome; the clinical, electrophysiologic and prognostic features. Neurology 1996; 47:668-673.
13. Sedano MJ, Calleja J, Canga E, Berciano J. Guillain-Barré syndrome in Cantabria, Spain. an epidemiological and clinical study. Acta Neurol Scand 1994; 89(4):287-292.
14. Rees JH, Thompson RD, Smeeton NC, Hughes RA. Epidemiological study of Guillain-Barré syndrome in south east England. J Neurol Neurosurg Psychiatry 1998; 64(1):74-77.
15. Bak P. Guillain-Barré syndrome in a Danish county. Neurology 1985; 35(2):207-211.
16. van der Meché FGA, Van Doorn PA. Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy; immune mechanisms and update on current therapies. Ann Neurol 1995; 37:S14-S31.

17. Jacobs BC, Rothbarth PH, van der Meche FG, Herbrink P, Schmitz PI, de KM et al. The spectrum of antecedent infections in Guillain-Barré syndrome: a case-control study. Neurology 1998; 51(4):1110-1115.
18. Hahn AF. Guillain-Barré syndrome. Lancet 1998; 352(9128):635-641.
19. Kaldor J, Speed BR. Guillain-Barré syndrome and Campylobacter jejuni: a serological study. Br Med J (Clin Res Ed) 1984; 288(6434):1867-1870.
20. Winer JB, Hughes RAC, Anderson MJ, Dones JM, Kangro H, Watkins RPF. A prospective study of acute idiopathic neuropathy. II. Antecedent events. J Neurol Neurosurg Psychiatry 1988; 51:613-618.

3.2 Infections and course of the disease in mild forms of Guillain-Barré syndrome

Based on the article "Infections and course of the disease in mild forms of Guillain-Barré syndrome". Van Koningsveld R., MD, Schmitz P.I.M., PhD, C.W. Ang, MD, PhD, Van der Meché F.G.A., MD, PhD, Van Doorn P.A., MD, PhD. Accepted for publication by Neurology

Abstract

Objective: Twenty-eight percent of the patients with the Guillain-Barré syndrome (GBS) remain able to walk unaided. Studying patients with the mild form of GBS can further contribute to knowledge of the spectrum of the syndrome and explore whether this subgroup may need treatment with IVIg.

Methods: Patients fulfilling the NINCDS-criteria for GBS were included in a nation wide survey over a two-year period. Clinical characteristics and serum samples were collected prospectively. In addition, a questionnaire was filled in concerning the course and outcome of the disease.

Results: We included a total number of 139 patients. Nineteen (14%) of the included patients were mildly affected, 120 (86%) were severely affected. Infections with Epstein-Barr virus were found more frequently in mildly affected patients ($p=0.02$). The degree of severity of the disease between mildly and severely affected patients was different on the day of admission ($p<0.01$). Thereafter, the groups showed a remarkable similar rate of progression. The pure motor form of GBS occurred more frequently in the mild group ($p=0.02$). Thirty-eight percent of the mildly affected patients reported problems in the hand function and an inability to run at 3 and 6 months (all female, $p=0.02$).

Conclusion: The difference in severity of GBS seems to be determined in an early phase of the disease. Preceding infections may influence the initial immune attack determining the severity of the disease. The presence of residual signs in patients with mild disease may advocate the use of early treatment in mildly affected patients.

Introduction

The Guillain-Barré syndrome (GBS) is a heterogeneous disease. Much effort has been made to describe subgroups of patients, primarily based on cohorts of severely affected GBS patients. Because the pathophysiological mechanism is not fully elucidated, it is not known which factors determine maximal severity, course of the disease and residual symptoms.

Another subgroup, the mildly affected patients, comprise 5 to 28% of all GBS cases, and it is surprising how little information is available about this substantial group [1-5]. We previously performed a retrospective study on the group of patients who remain mildly affected, i.e. able to walk independently at nadir (maximum severity). However, due to the retrospective design, we were unable to study whether there were differences between the mildly and severely affected patients with respect to progression, the course of the neurological symptoms

and residual disability. In addition to a better insight in the pathophysiological mechanisms, further inventarisation might also give information whether mildly affected patients should be treated with intravenous immunoglobulins (IVIg). This is important since IVIg treatment is currently not given routinely to mild patients in most centers.
We performed a 2-year nation-wide prospective study in which we gathered information on preceding infections, patients' characteristics including detailed information on the time course of neurological symptoms and signs, and the presence of anti-ganglioside antibodies.

Material and Methods

Patients

From February 1998 to February 2000, all but three hospitals in the Netherlands participated in this study. After obtaining a written informed consent, the neurologists filled in a questionnaire for every new GBS patient and sent it, together with a serum sample to the investigators. Only patients fulfilling the National Institute of Neurological Disorders and Stroke criteria (NINCDS) [7] for GBS were included. For reasons of comparability, patients with the Miller Fisher variant (MFS) were excluded. At the end of the two-year study period, a questionnaire was sent to all patients.

Preceding infections and anti-ganglioside antibodies

The following preceding infections, judged clinically, were scored prospectively: influenza- or influenza-like illness, respiratory tract infection, gastro-enteritis or diarrhoea and "other infections". They were considered positive when patients reported symptoms meeting the criteria for these infections according to the Center of Disease Control (CDC) definitions for nosocomial infections [8] and when they occurred within three weeks before onset of the first symptoms of GBS. Based on earlier studies, we tested the presence of infection with *C.jejuni*, cytomegalovirus (CMV) and *Mycoplasma pneumoniae* serologically as described before [9]. Screening for Epstein-Barr virus (EBV) infection was done using a commercially available IgM capture enzyme-linked immunosorbent assay (Biotest AG, Dreieich, Germany). The assay was performed according to the instructions of the manufacturer. We screened for IgG and IgM antibody reactivity against GM1, GM2, GD1a and GQ1b using ELISA as described previously [10].

Characteristics of the patients and neurological signs and symptoms

The following characteristics and neurological signs were obtained from the questionnaire sent by the neurologist: age, sex, sensory involvement, cranial nerve involvement, therapy and the worst score (f-score) on the Hughes' scale. We defined patients as "severely affected" when their worst f-score was ≥ 3 (unable to walk unaided at nadir). Patients were

considered to be "mildly affected" when their worst f-score was ≤ 2 (able to walk unaided at nadir).

The course of the disease

The following data concerning the course of the disease were obtained from the patient's questionnaire: presenting symptoms, time of onset of sensory symptoms (before, during or after start of muscle weakness), days until nadir, symptoms with which recovery started (less weakness of limbs, less sensory deficits, better speech, less ventilation problems). As most studies on GBS concern the severely affected patients (unable to walk at nadir), the course of the disease is mainly monitored with the Hughes' disability scale (f-score) [6]. This scale focuses on mobility and therefore may not be sufficient to study the course of the disease in mild patients. We designed a questionnaire in which patients could score the course of the disease using four items: sensory symptoms, cranial nerve dysfunction, arm-hand disability and mobility. The Hughes' disability scale was used to represent the mobility [6]. Because this scale is used often and is validated, it was used to design the other three scales. Day 1 was defined as the day of the first symptom. Patients could rank their symptoms on a 0 (no symptoms) to 5 scale. With respect to the sensory symptoms, a score of 5 represented complete hypesthesiae on arms and/or legs. With respect to the arm/hand function and mobility, a score of 5 represented complete paralysis of the upper limbs and lower limbs respectively. With respect to cranial nerve dysfunction, patients could score on a 0 to 2 scale. A score of 0 represented no cranial nerve dysfunction, 1 represented some double vision with or without facial nerve involvement, 2 represented complete ophthalmoplegia and/or facial nerve involvement. Before the questionnaire was sent, it was validated on a small group of patients.

Outcome variables

Sensory symptoms, cranial nerve deficits, hand-arm function and mobility were assessed at 1,2,3 and 6 months after the onset of the first symptoms.

Statistics

Differences in preceding infections, anti-ganglioside antibodies, characteristics, symptoms and signs and outcome between mildly and severely affected patients were tested using the chi-square test without continuity correction, Fisher's exact test or the Wilcoxon-Mann-Witney U test where appropriate. The course of the disease was assessed with a questionnaire that was not fully validated. We used graphics to report these results and performed a generalised-estimating-equations-regression model to test differences between mildly and severely affected patients while accounting for the correlated outcomes

due to the longitudinal design. In this model a first-order autoregressive structure for the correlation between the time-points appeared to be appropriate. All calculations were performed using STATA 6.0 for Windows 97(Stata Statistical Software, Release 6.0, College Station, TX). A p value < 0.05 was considered to be significant.

Results

The patient group

In the two-year period 158 patients entered the study. Three patients were excluded because they were misdiagnosed (chronic idiopathic demyelinating polyneuropathy, cervical stenosis and Lyme disease). Two patients were excluded because they died shortly after inclusion and no further information could be obtained. Fourteen patients were excluded because they had MFS. One hundred and twenty of the remaining 139 patients (86%) were severely affected and 19 patients were mildly affected (14%). The mean period between start of weakness and the time the patient-questionnaire was filled in, was 16 months (range 1-33 months). This time window did not differ significantly between the mildly and severely affected patients.

Preceding infections and anti-ganglioside antibodies

Table 1 shows the preceding clinical infections, results from the serological infection studies and the presence of anti-ganglioside antibodies. There was no difference in the percentage of reported preceding clinical infections between the two groups except for the reported "other infections". These consisted of 1 patient reporting fever and 1 patient reporting pneumonia in the mildly affected group. In the severely affected group, 1 patient had an infection with Helicobacter pylori and 1 patient reported a paronychium. The results of the serological screening showed a difference in the percentage of preceding EBV infections (50% in the mild group and 23% in the severe group, p=0.02). Anti-ganglioside antibodies were found less frequently in the mildly affected group ($p = 0.03$).

Characteristics and neurological signs

Table 2 shows the characteristics and neurological signs for the total group and for the mildly and severely affected patients. More females (p=0.05) and patients under 50 years of age (p=0.01) were found in the mildly affected group. Furthermore, the pure motor variant was more frequently found in the mildly affected group (p=0.02).

Table 1 Preceding infections and anti-ganglioside antibodies

	Total n=139 n (%)	Mild n=19 n (%)	Severe n=120 n (%)	p value
Clinical preceding infections				
Influenza-like infection	38 (28)	4 (22)	34 (29)	0.55
Respiratory infection	40 (29)	3 (18)	37 (31)	0.16
Gastro-enteritis	29 (22)	4 (21)	25 (22)	0.95
Other infections	4 (3)	2 (11)	2 (2)	0.03
Total	93 (67)	11 (58)	82 (68)	0.37
Serological positive infections	n = 107	n = 18	n= 89	
C.jejuni	21 (20)	3 (17)	18 (20)	0.73
CMV	15 (14)	5 (28)	10 (11)	0.07
EBV	29 (27)	9(50)	20 (22)	0.02
Mycoplasma pneumoniae	2 (2)	0(0)	2 (2)	0.52
Anti-ganglioside antibodies	n = 97	n = 17	n= 80	
GM1	19 (20)	0	19 (24)	0.02
GM2	10 (10)	1 (6)	9 (11)	0.51
GD1a	12 (12)	1 (6)	14 (14)	0.37
GQ1b	10 (10)	0	10 (13)	0.12
Total	34 (35)	2 (12)	32 (40)	0.03

Table 2 Characteristics and neurological signs

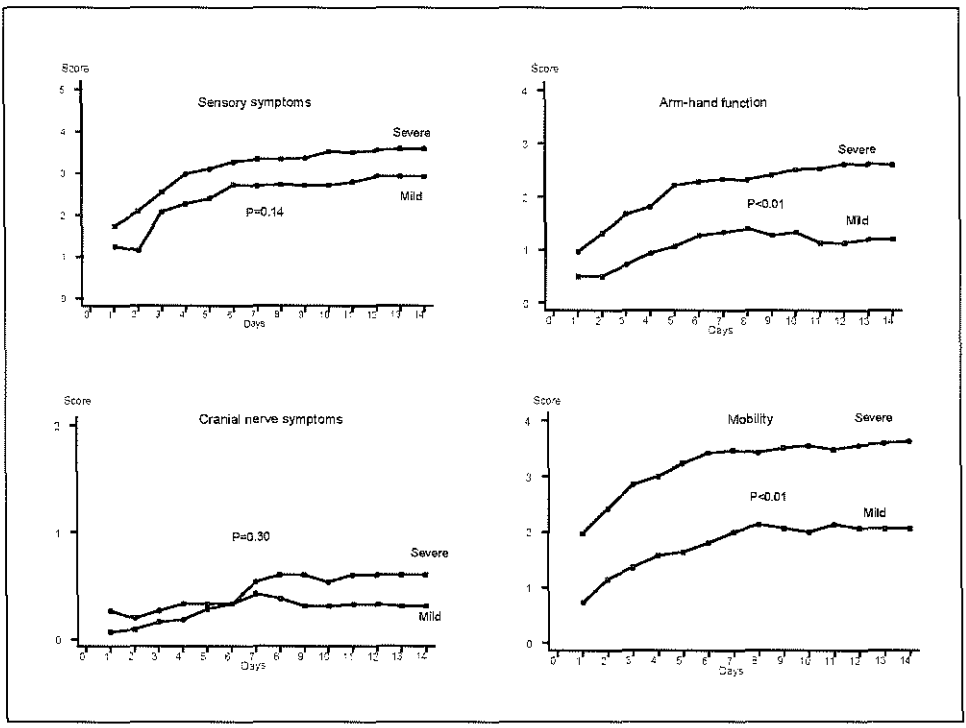
* =n (%)	Total n=139	Mild n=19	Severe n=120	p value
Age >50 years	71 (52)	3 (16)	68 (57)	0.01
Male	80 (58)	7 (37)	73 (61)	0.05
Pure motor variant	24 (18)	7 (37)	17 (15)	0.02
Cranial nerve deficits	72 (52)	13 (68)	59 (49)	0.12
Therapy	117 (87)	4 (22)	113 (97)	< 0.01

The course of the disease

Figure 1 shows the course of the disease for the mildly and severely affected patients, expressed by the course of the sensory symptoms, cranial nerve deficits, arm-hand function and mobility. In all four items, a difference is already seen on day one, while the rate of progression between day 2 to day 14 is strikingly similar for both groups.

There was no difference in presenting symptoms between the mildly and severely affected patients. Furthermore, there was no difference in time of onset of sensory symptoms between the two groups (47% before, 27% during and 18% after onset of weakness, 8% unknown). Both groups reported a median time of 10 days (range 2-30) to reach nadir. No difference was found in symptoms with which the recovery started.

Figure 1
Course of GBS during first 14 days for mildly and severely affected patients

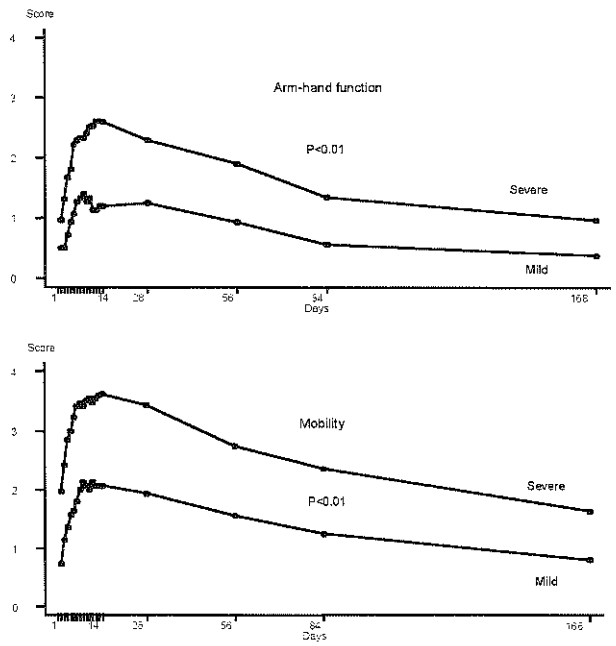


Outcome variables

There was no significant difference in sensory symptoms and cranial nerve dysfunction at 1,2,3 and 6 months after onset of the disease between both groups. Figure 2 shows the

arm-hand function and mobility during the first 14 days and 1,2,3 and 6 months after onset of the disease. Even after six months, a considerable proportion of mild patients still had residual disability.

Figure 2
Arm-hand function and mobility (f-score) during six months in mild and severely affected patients.



Discussion

This study reports on preceding infections, anti-ganglioside antibodies, clinical characteristics, course and outcome in patients with a mild form of GBS, compared with severely affected patients. Before interpreting our findings, it is important to discuss whether the study population is representative.

Based on the incidence rate of GBS in the Netherlands (1.18/100.000), the 158 patients that entered the study in two years cover about 50% of the total number of expected patients. Although almost all hospitals agreed to participate in this study, a number of large centres did not report any patients to the investigators. This suggests a selection

bias at hospital level more than a selection at patient level. The percentages of preceding infections, characteristics and neurological signs for the total group (table 1 and 2) are similar to the figures reported in earlier studies except for the high percentage of positive EBV serology [5,9,11]. We found 14% of the patients to be mildly affected in contrast to the 28% reported in our previous (incidence-based) study [5]. The fact that we excluded the MFS patients additionally contributes to the lower percentage on which we report here. Taken together, we consider this study population representative although the percentage of mildly affected patient might be underestimated.

We confirmed the similar distribution of clinical infections between the mild and severe patient as reported in the Dutch epidemiological study [5]. Not only in the mild group (50%), but also overall (27%) we found a higher percentage of preceding EBV infections. Because in the present study, a different assay to detect EBV infections was used, we validated the assay with a group of control sera (n=86). This control group showed a low percentage of positive EBV serology (3.5%) and the difference with the overall percentage in the GBS group was highly significant. Although it needs to be confirmed, this study suggests that an infection with EBV more frequently results in a mild form of GBS.

Except in MFS patients, there are no studies available on the presence of anti-ganglioside antibodies in GBS patients with only mild weakness. We found a striking absence of anti-ganglioside antibodies in mild patients. Earlier studies, mostly based on severely affected patients, describe an association between the antecedent *C.jejuni* infections, anti-GM1 antibodies and the pure motor form of GBS [12-14]. In the mildly affected group we found no patients with anti-GM1 antibodies, but a high percentage of patients had the pure motor variant. Furthermore, the distribution of preceding *C.jejuni* infections did not differ between the groups. It appears that the pure motor variant in the mildly affected patients in this study does not result from a preceding *C.jejuni* infection and the generation of anti-GM1 antibodies.

As described in earlier studies, we found an association between the presence of anti-GQ1b antibodies and ophthalmoplegia in the total group [15,16]. Despite the presence of ophthalmoplegia in the mild group these patients did not have any anti-GQ1b antibodies.

Because the Hughes' disability scale measures mobility problems in GBS patients and we were particularly interested in mildly affected patients, we suggested that it was probably more accurate to measure the course of the disease using four items. Do the results as shown in figure 1, inform us about the course and possible pathophysiology of mild versus severe patients? When interpreting the results it is important to realise that most mildly affected patients were not treated while most severely affected patients did receive treatment. This may have influenced the course. However, there is a consistent repetitive difference between mildly and severely affected patients in all four graphs. This could suggest a difference in initial immune attack. However, based on the current data it is not possible to

distinguish whether this is due to a difference in preceding agents, the presence anti-ganglioside antibodies or to yet unidentified hostfactors. The difference in distribution of preceding infections with EBV and anti-ganglioside antibodies in the mild and severe group suggest that these factors may play a role. While the graph on mobility problems (Hughes' disability scale) highly resembles the other figures, it may be concluded that the other three items provide little additional information.

In contrast to our expectations, mildly affected patients reported considerable mobility problems. One randomised clinical trial showed the effectiveness of plasmapheresis in mild patients [17]. Considering the reported residual signs in mildly affected patients and the effectiveness of IVIg [18], it seems appropriate to investigate this treatment in this group of patients.

We can conclude that mildly and severely affected patients show differences in preceding infections and anti-neural immune response. The course of the disease showed remarkable and consistent differences between the two groups, suggesting that the severity of the disease is determined in a very early phase. Finally, the residual complaints in patients who are only mildly affected warrant studies on treatment with IVIg in mildly affected GBS patients.

Bibliography

01. Green DM, Ropper AH. Mild Guillain-Barré syndrome. Arch Neurol 2001; 58:1098-1101.
02. Winer JB, Hughes RAC, Osmond C. A prospective study of acute idiopathic neuropathy. I. Clinical features and their prognostic value. J Neurol Neurosurg Psychiatry 1988; 51(5):605-612.
03. The Italian Guillain-Barré Study Group. The prognosis and main prognostic indicators of Guillain-Barré syndrome. A multicentre prospective study of 297 patients. Brain 1996; 119:2053-2061.
04. Emilia-Romagna Study Group on Clinical and Epidemiological Problems in Neurology. A prospective study on the incidence and prognosis of Guillain-Barré syndrome in Emilia-Romagna region, Italy (1992-1993). Neurology 1997; 48(1):214-221.
05. van Koningsveld R, Van Doorn PA, Schmitz PIM, Ang CW, van der Meché FGA. Mild forms of Guillain-Barré syndrome in an epidemiologic survey the Netherlands. Neurology 2000; 54:620-625.
06. Hughes RAC, Newsom-Davis J, Perkin GD, Pierce JM. Controlled trial of prednisolone in acute polyneuropathy. Lancet 1978; 2:750-753.
07. Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain-Barré syndrome. Ann Neurol 1990; 27:Suppl:S21-4.
08. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. Am J Infect Control 1988; 16(3):128-140.
09. Jacobs BC, Rothbarth PH, van der Meché FG, Herbrink P, Schmitz PI et al. The spectrum of antecedent infections in Guillain-Barré syndrome: a case-control study. Neurology 1998; 51(4):1110-1115.
10. Ang CW, Jacobs BC, Brandenburg AH, Laman JD, van der Meché FG, Osterhaus AD et al. Cross-reactive antibodies against GM2 and CMV-infected fibroblasts in Guillain-Barré syndrome. Neurology 2000; 54(7):1453-1458.
11. Hahn AF. Guillain-Barré syndrome. Lancet 1998; 352:635-641.
12. Jacobs BC, Van Doorn PA, Schmitz PIM, Tio-Gillen AP, Herbrink P, Visser LH et al. Campylobacter jejuni infections and anti-GM1 antibodies in Guillain-Barré syndrome. Ann Neurol 1996; 40:181-187.
13. Visser LH, van der Meché FGA, Van Doorn PA, Meulstee J, Jacobs BC, Oomes PG et al. Guillain-Barré syndrome without sensory loss (acute motor neuropathy). A subgroup with specific clinical, electrodiagnostic and laboratory features. Dutch Guillain-Barré Study Group. Brain 1995; 118:841-847.
14. Yuki N, Handa S, Taki T, Kasama T, Takahashi M, Saito K. Cross-reactive antigen between nervous tissue and a bacterium elicits Guillain-Barré syndrome: molecular mimicry between ganglioside GM1 and lipopolysaccharide from Penner's serotype 19 of Campylobacter jejuni. Biomed Res 1992; 13:451-453.
15. Chiba A, Kusunoki S, Obata H, Machinami R, Kanazawa I. Serum anti-GQ1b IgG antibody is associated with opthalmoplegia in Miller Fisher syndrome and Guillain-Barré syndrome: clinical and immunohistochemical studies. Neurology 1993; 43:1911-1917.

16. Kusunoki S, Chiba A, Kanazawa I. Anti-GQ1b IgG antibody is associated with ataxia as well as ophthalmoplegia. Muscle Nerve 1999; 22:1071-1074.
17. The French Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome. Appropriate number of plasma exchanges in Guillain-Barré syndrome. Ann Neurol 1997; 41(3):298-306.
18. van der Meché FGA, Schmitz PIM, Dutch Guillain-Barré Study Group. A randomized trial comparing intravenous immune globulin and plasma exchange in Guillain-Barré syndrome. N Engl J Med 1992; 326(17):1123-1129.

3.3 Course of the disease and treatment evaluation in the Miller Fisher syndrome

Based on the short communication "Course of the disease and treatment evaluation in the Miller Fisher syndrome". Van Koningsveld R., MD, Schmitz P.I.M., PhD, Van der Meché F.G.A., MD, PhD, Van Doorn P.A., MD, PhD. Submitted

Abstract

Objective: The Miller Fisher syndrome (MFS) is considered to be a benign variant of the Guillain-Barré syndrome (GBS). However, no studies are available focussing on the course of the disease and outcome in MFS. Because MFS has a low incidence rate, information on treatment of MFS is anecdotal and mainly derives from case-reports. We describe the course and outcome in a prospectively collected group of MFS patients. Together with a review of the literature, we aim to provide a better basis for treatment evaluation in MFS patients.

Methods: Patients fulfilling the NINCDS-criteria for GBS and MFS patients were included in a nation-wide survey in the Netherlands over a two-year period. From all patients, clinical characteristics and serum samples were collected prospectively. In addition, a questionnaire was filled in by the patients concerning the course of the disease and outcome.

Results: Twelve MFS patients were included. Although less severe, the progression rate and the course of the disease were similar to that in GBS patients. At three and six months, 20% of the MFS patients reported problems with mobility. The review of the literature indicated favourable results of treatment in most MFS patients.

Conclusion: The course of the disease in MFS clearly resembles that of GBS patients. Because of the low incidence rate of MFS, a randomised trial does not seem feasible, while IVIg and PE treatment are proven to be beneficial in GBS patients. It seems plausible to consider treatment in at least the severely affected MFS patients, despite the lack of solid evidence in this subgroup of patients with an immune-mediated polyneuropathy.

Introduction

In 1956, Miller Fisher described three patients with a clinical picture of external ophthalmoplegia, severe ataxia and areflexia [1]. It was not until a rise in the cerebrospinal fluid protein level in the third patient was found, that he suspected a close relation with the Guillain-Barré syndrome (GBS). Since then, the triad of external ophthalmoplegia, severe ataxia and areflexia was named after Miller Fisher and was considered a benign variant of GBS. Describing MFS as benign appears to be based more upon clinical experience and case reports rather than on the results of large clinical studies. The course of the disease and the outcome has never been the main focus of studies reporting on MFS. It is therefore unknown whether there is a ground for standard therapy with plasmapheresis (PE) or intravenous immunoglobulin (IVIg) in these patients. Because MFS is a rare disease, conducting a randomised trial would be difficult to manage within a reasonable number

of years or centres.
Here, we report a prospective study on the course and outcome in MFS together with a review of the literature on the effect of treatment in patients with MFS.

Material and Methods

This study is part of a large nation-wide prospective study on GBS in the Netherlands. Detailed information is described in paragraph 3.2. From February 1998 to February 2000, patients fulfilling the National Institute of Neurological Disorders and Stroke criteria (NINCDS) [2] for GBS and patients with MFS were included. Based on the triad of external ophthalmoplegia, severe ataxia and areflexia, the MFS patients were selected and GBS patients were used as control group. We prospectively collected serum samples and information concerning preceding infections, neurological signs, age and sex of the patients. At the end of the study a questionnaire was sent to all patients. Hereby information was collected concerning the course of the disease including presenting neurological symptoms and outcome. Patients were asked to score the course of the disease during the first 14 days after onset of the disease using four different items (sensory symptoms, cranial nerve deficits, arm-hand disability and mobility). Patients could rank their symptoms on a 0 (no symptoms) to 5 scale. With respect to the sensory symptoms, a score of 5 represented complete hypesthesiae on arms and/or legs. With respect to the arm/hand function and mobility, a score of 5 represented complete paralysis of the upper limbs and lower limbs respectively. With respect to cranial nerve dysfunction, patients could score on a 0 to 2 scale. A score of 0 represented no cranial nerve dysfunction, 1 represented some double vision with or without facial nerve involvement, 2 represented complete ophthalmoplegia and/or facial nerve involvement.
Depending on the data, differences between MFS and GBS patients were univariately tested using the chi-square test without continuity correction, Fisher's exact test or the Wilcoxon-Mann-Witney *U* test. All calculations were performed using STATA 6.0 for Windows 97 (Stata Statistical Software, Release 6.0, College Station, TX). A p value < 0.05 was considered to be significant.

Results

In the two-year period 12 patients fulfilled the criteria for MFS and 140 fulfilled the criteria for GBS. Table 1 shows the characteristics of the ten MFS patients on which sufficient information was available. No difference was found in the percentage of reported preceding clinical and serological positive infections between the MFS and GBS patients. Significantly more anti-GQ1b antibodies were found in the MFS patient group.

Table 1 Characteristics and neurological signs in MFS patients

Patient	Sex	Age	Preceding infection	Serology	Anti-ganglioside antibodies	F-score at nadir	Therapy	Outcome at 3 months
01	M	22	Respiratory	-	GQ1b, GD1a	2	IVIg	Recovered
02	M	25	Gastro-enteritis	NA	NA	1	IVIg	Recovered
03	M	27	Influenza-like	-	GQ1b,GM1	4	IVIg	Recovered
04	F	35	Gastro-enteritis	-	GQ1b,GM1	4	IVIg	Recovered
05	M	39	Gastro-enteritis and sinusitis	NA	NA	3	IVIg	Recovered
06	F	41	Gastro-enteritis	*C.jejuni*	GQ1b	4	IVIg	Unable to run
07	M	43	None	-	GQ1b	2	IVIg	Recovered
08	M	49	Gastro-enteritis	-	-	2	IVIg	Recovered
09	F	50	Influenza-like	-	-	1	None	Recovered
10	M	68	Influenza-like	EBV	NA	4	None	Bedbound

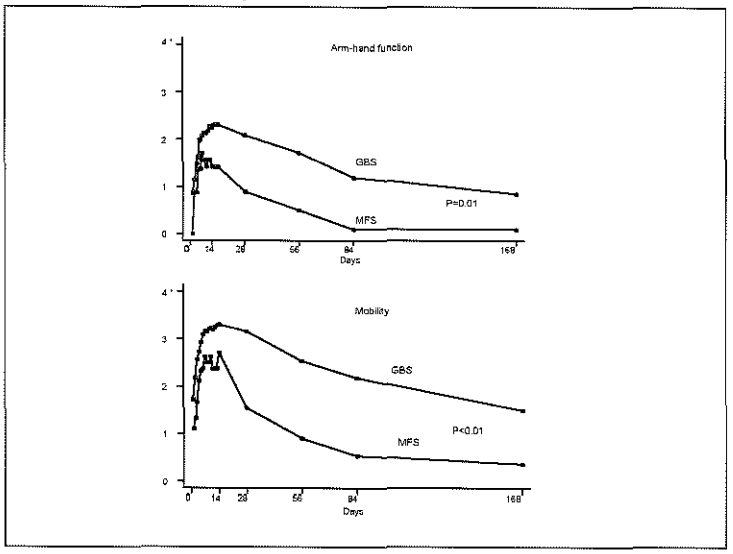
NB: NA= no serum sample available

- = negative

The MFS patients included seven men and three women aged 22 to 68 years (mean 41 ± 16). In the MFS group 80% of the patients reported double vision and/or other cranial nerve problems as presenting symptoms, in the GBS group this was eight percent (p=0.09). The MFS patients reported a median time of 7.5 days to reach nadir, whereas a median time of ten days was reported by the GBS group (p=0.71).

With respect to the course of the disease in the first 14 days, there was a significant difference in the severity of cranial nerve deficits between the MFS and GBS patients. With respect to the sensory symptoms, arm-hand function and mobility, GBS patients reported more deficits at the first day. On the following days the progression at the three levels was remarkable similar between the GBS and the MFS patients. At week four and eight, more GBS patients reported sensory symptoms than MFS patients ($p<0.01$). At month three and six, this difference was not statistically significant. Four weeks after onset of the disease, 90% of the MFS patients reported to be severely fatigued. Six months after onset this was 50%, compared to 70% in the GBS patients (p=0.2). At six months more MFS patients reported cranial nerve deficits than GBS patients ($p<0.01$). Figure 1 shows the arm-hand function and mobility for MFS and GBS patients at the first 14 days, 1, 2 ,3 and 6 months after onset of the disease. One patient reported to be unable to run at three months and one patient reported to be bedbound at three months due to severe ataxia (20%). The latter patient reported to be only able to walk with help at six months (10%).

Figure 1 Arm-hand function and mobility (f-score) during six months in MFS and GBS patients.



* 0-5 scale to indicate the level of paralysis in arms or legs

In this study eight of the ten patients were treated with IVIg, the remaining two patients were untreated. The treated patients were younger than the untreated (p=0.01). No difference in sex and f-score at nadir was found between the treated and untreated patients. Table 2 gives an overview of the available studies reporting on treatment results in MFS patients.

Table 2 Reported studies on treatment of MFS

Year	Investigators	n	Therapy	Result
1980 [7]	Blau et al.	2	Methylprednisolone	No recovery
1981 [9]	Irvine et al.	1	Plasmapheresis	Recovery
1981 [10]	Littlewood	1	Plasmapheresis	Recovery
1981 [11]	Maisey	2	Plasmapheresis	No recovery
1993 [12]	Arakawa et al.	1	IVIg	Recovery
1994 [13]	Zifko et al.	1	IVIg	Recovery
1998 [14]	Chida et al.	2	Plasmapheresis	Recovery*
1997 [15]	Mahalati et al.	3	Plasmapheresis	Recovery
1999 [16]	Yeh et al.	2	Plasmapheresis	Recovery
2000 [17]	Turner et al.	1	IVIg	Recovery**

* the two patients recovered but developed bilateral facial palsy

** the patient recovered but developed occipital infarction

Discussion

In this study we described the course of the disease and outcome of 12 prospectively included MFS patients. The reported preceding infections were diverse and thereby mimicking the distribution of infections in GBS. Berlit et al. reviewed clinical characteristics, preceding infections and long-term outcome in a number of small studies with a total of 223 cases [3]. There, a respiratory tract infection was by far the most common site of a preceding infection in MFS. As reported previously [4;5], we found a high percentage of anti-GQ1b antibodies although these were not specifically associated with a preceding *C.jejuni* infection.

The high percentage of male and the relative young age of onset are comparable with other studies [3]. With respect to the course of the disease, it is not surprising that MFS patients report significantly more often cranial nerve deficits as GBS patients do. The similar pattern of progression in MFS and GBS patients is remarkable. This may suggest an underlying similar pathophysiological mechanism. With respect to outcome, a considerable percentage of MFS patients reports problems at three and six months, among which the problem of fatigue. Realising that these patients were almost all treated, these residual signs could have been worse without treatment. The reported residual signs can thus be an argument in favour of treatment of MFS patients. Besides, other findings must be considered in the evaluation of treatment in MFS patients. The similarity in the course of progression confirms the opinion that MFS is a (relatively mild) clinical variant of GBS and the benefit of IVIg or PE treatment in GBS patients is widely accepted. The French Cooperative Group on Plasma Exchange in GBS, even showed benefit of treatment in mild patients [6]. Another argument in favour of treatment is the fact that in one third to 50% of the patients, in whom the disease initially started as MFS, progresses to prominent muscle weakness and in some cases the need for artificial ventilation [7;8]. Finally, almost all studies described in table 2, report favourable results of treatment. However, these results must be interpreted with caution because no control group was involved and it was not always described in what way the treatment effect was assessed. Additionally, it is not known how many MFS cases are treated without publication of the negative effect. In the evaluation one should be aware of this publication bias.

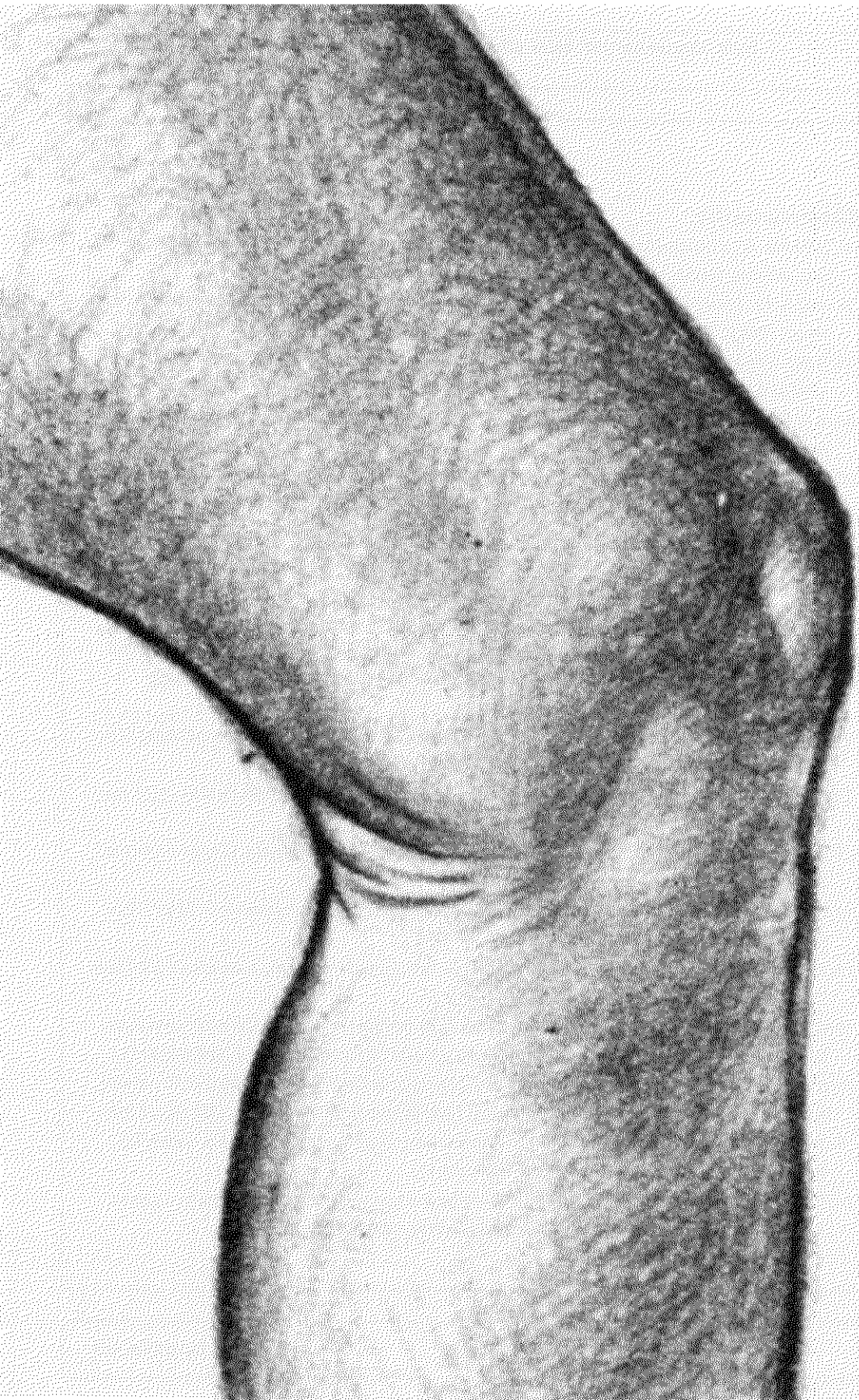
The randomised controlled trial (RCT) is widely accepted as the optimal way to study treatment effect. Unfortunately MFS is a rare disease, which makes it difficult to conduct a randomised trial within a reasonable number of years and reasonable number of participating centres.

The purpose of this study was to describe the course and outcome of MFS patients and draw attention to the issue whether these patients should be treated. Because treatment has never been evaluated by a RCT, reliable evidence is lacking. However, because of the

arguments stated above, of which the similarity in course of the disease with GBS is an important one, it seems attractive to treat MFS patients, especially those who are severely affected.

Bibliography

01. Fisher M. An unusual variant of acute idiopathic polyneuritis (syndrome of ophthalmoplegia, ataxia and areflexia). N Engl J Med 1956;255:57-65.
02. Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain-Barré syndrome. Ann Neurol 1990;27:Suppl:S21-4.
03. Berlit P, Rakicky J. The Miller Fisher syndrome. Review of the literature. J Clin Neuroophthalmol 1992;12:57-63.
04. Yuki N, Sato S, Tsuji S, Ohsawa T, Miyatake T. Frequent presence of anti-GQ1b antibody in Fisher's syndrome. Neurology 1993;43:414-417.
05. Willison HJ, Veitch J, Paterson G, Kennedy PG. Miller Fisher syndrome is associated with serum antibodies to GQ1b ganglioside. J Neurol Neurosurg Psychiatry 1993;56:204-206.
06. The French Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome. Appropriate number of plasma exchanges in Guillain-Barré syndrome. Ann Neurol 1997;41:298-306.
07. Blau I, Casson I, Lieberman A, Weiss E. The not-so-benign Miller Fisher syndrome: a variant of the Guilain-Barré syndrome. Arch Neurol 1980;37:384-385.
08. Ter Bruggen JP, van der Meché FGA, de Jager AEJ, Polman CH. Ophthalmoplegic and lower cranial nerve variants merge into each other and into classical Guillain-Barré syndrome. Muscle Nerve 1998;21:239-242.
09. Irvine AT, Tibbles J. Treatment of Fisher's variant of Guillain Barré syndrome by exchange transfusion. Can J Neurol Sci 1981;8:49-50.
10. Littlewood R, Bajada S. Successful plasmapheresis in the Miller-Fisher syndrome. Br Med J (Clin Res Ed) 1981;282:778
11. Maisey DN, Olczak SA. Successful plasmapheresis in the Miller-Fisher syndrome. Br Med J (Clin Res Ed) 1981;282:1159
12. Arakawa Y, Yoshimura M, Kobayashi S, et al. The use of intravenous immunoglobulin in Miller Fisher syndrome. Brain Dev 1993;15:231-233.
13. Zifko U, Drlicek M, Senautka G, Grisold W. High dose immunoglobulin therapy is effective in the Miller Fisher syndrome. J Neurol 1994;241:178-179.
14. Chida K, Takase S, Itoyama Y. Development of facial palsy during immunoadsorption plasmapheresis in Miller Fisher syndrome: a clinical report of two cases. J Neurol Neurosurg Psychiatry 1998;64:399-401.
15. Mahalati K, Dawson RB, Collins JO, Lietman S, Pearlman S, Gulden D. Characteristics of 73 patients, 1984-1993, treated by plasma exchange for Guillain-Barré syndrome. J Clin Apheresis 1997;12:116-121.
16. Yeh JH, Chen WH, Chen JR, Chiu HC. Miller Fisher syndrome with central involvement: successful treatment with plasmapheresis. Ther Apher 1999;3:69-71.
17. Turner B, Wills AJ. Cerebral infarction complicating intravenous immunoglobulin therapy in a patient with Miller Fisher syndrome. J Neurol Neurosurg Psychiatry 2000;68:790-791.



chapter 04

Randomised Controlled Trials in the Guillain-Barré syndrome

4.1 Randomised trial on the additional effect of methylprednisolon on standard treatment with intravenous immunoglobulin in Guillain-Barré syndrome

*Based on the article "Randomised trial on the additional effect of methylprednisolone on standard treatment with intravenous immunoglobulin in Guillain-Barré syndrome". Van Koningsveld R., MD, Schmitz P.I.M., PhD, Visser L.H., MD, PhD, Van der Meché F.G.A., MD, PhD ,Van Doorn P.A., MD, PhD and the Dutch Guillain-Barré syndrome study group**

Abstract

Background: Intravenous immunoglobulin (IVIg) is an effective treatment in patients with the Guillain-Barré syndrome (GBS). Despite IVIg treatment morbidity is still considerable and mortality is 3-5%. Based on the positive results of a pilot study, we conducted an international, multicenter, double blind, placebo-controlled study on the additional effect of methylprednisolon (MP) on standard treatment with IVIg.

Methods: All patients were treated with IVIg (0.4 g/kg of bodyweight) and randomised to receive intravenous MP (500 mg) or placebo for five consecutive days. Patients were only included when they were unable to walk unaided for ten meters and were still within their first 14 days from the onset of weakness. Because age is a recognised prognostic factor, patients were stratified for age < or ≥ 50 years. Primary outcome was defined as improvement of one or more grades on the Hughes' disability scale, four weeks after randomisation, compared with the score at entry.

Results: We analysed 225 patients on an intention-to-treat base and adjusted for the two age groups. The percentage of patients that reached the primary endpoint in the MP/IVIg group was 68% and in the placebo/IVIg group 56%, p=0.05. Including all prognostic factors (age, number of days before randomisation, MRC score at entry and CMV infection) in a logistic regression model, this p-value was 0.015. Although not significant, most of the secondary outcome measurements were in favour of the MP/IVIg treatment group. No considerable differences in side effects were found between the two treatment groups.

Conclusion: GBS patients, unable to walk independently and treated within 14 days after onset of weakness, show faster improvement when receiving additional treatment with MP on standard treatment with IVIg. Furthermore, no considerable side effects were reported. Altogether, we advice to add MP to standard therapy of IVIg in patients with GBS.

Introduction

The Guillain-Barré syndrome (GBS) is acute immune-mediated polyneuropathy. With an incidence rate of 1-1.5 per 100.000 inhabitants, GBS is the most common cause of acute flaccid paralysis in the developed countries [1;2]. Although spontaneous recovery generally starts 2 weeks after the maximum weakness is reached, a large number of patients have residual deficits ranging from fatigue to complete paralysis of the lower limbs [3-5].
Based on the suspected immune-mediated character of GBS the effects of several treatments have been investigated. The efficacy of plasmapheresis (PE) was demonstrated in two large randomised controlled trials (RCT) [6;7]. In both studies, improvement started earlier

and artificial respiration was less often required in the patients treated with PE. In 1992, the results of a Dutch RCT showed equal efficacy of treatment with PE and IVIg [8]. In 1997, this result was confirmed by the PE/Sandoglobulin GBS trial group [9]. This trial also showed that the effect of combined PE and IVIg treatment is not superior to PE or IVIg alone [9]. Because treatment with IVIg is safer and more convenient than PE treatment, IVIg can now be regarded as a preferred treatment for patients with GBS [10;11].
Despite this, GBS is still a severe disease with serious morbidity after 6-12 months [5;12]. Furthermore, many patients report to be severe fatigue [3]. Therefore, the need for other therapeutic options is evident. Based on the positive results of a pilot study [13], we conducted a double blind RCT on the additional effect of high-dose intravenous methylprednisolon (MP) on standard treatment with IVIg. We hypothesised that in the MP/IVIg group, relatively more patients would improve at least 1 grade on the Hughes'disability scale, four weeks after randomisation than in the IVIg group (primary endpoint). The Hughes' disability scale is a disability scale most often used in RCT concerning GBS [14].

Patients and methods

Patients

All patients admitted in the 36 participating centers and fulfilling the NINCDS criteria for GBS were evaluated for randomisation [15]. A patient was eligible when the onset of weakness was within two weeks, when he/she was unable to walk independently for ten meters (f-score at least 3) and had signed the informed consent form. Exclusion criteria were: age below six years, suffering from GBS before, a previous severe allergic reaction to properly matched blood products, a known selective IgA deficiency, pregnancy, steroid treatment, contraindications for steroid treatment, suffering from severe concurrent disease or an inability to follow-up. The protocol was approved by the ethics committee of every participating centre.

Treatment

All patients received treatment with IVIg (Gammagard SD, Baxter Healthcare, Hyland Division) which was started as soon as possible after randomisation. Patients received 0.4g IVIg per kilogram bodyweight per day for five consecutive days. Treatment with MP or placebo had to start within 48 hours after start of treatment with IVIg. Patients randomised to receive intravenous MP, received a masked bag with 500 mg MP per day for five consecutive days. Children received 8 mg MP per kilogram bodyweight per day for five consecutive days (maximum 500mg/day). Patients randomised to receive only IVIg, received a masked bag with 100ml normal saline (placebo) for five days.

Outcome measures

The primary endpoint was defined as the percentage of patients that improved one or more grades on the Hughes' disability scale four weeks after randomisation, compared with the score at time of entry. Secondary endpoints were the percentage of patients able to walk independently after eight weeks, time required to improve at least one grade on the Hughes' disability scale, time required to improve until independent walking, difference in grade on the Hughes' disability scale at six months and one year and difference in need and duration of artificial respiration.

Based on the results of the first RCT on IVIg and the pilot study on the additional effect of MP [8;13], we estimated the chance to improve one or more grades on the Hughes' disability scale four weeks after randomisation 50% for the IVIg group and 70% for the IVIg/MP group. The two-sided alpha was set at 0.05 and the beta error at 0.2. Two interim analyses were planned. With these parameters it was calculated that 114 patients would be needed in each treatment arm.

Assessments

Cranial nerve dysfunction, the Hughes' disability score and the Medical Research Council (MRC) sumscore were measured every week during the first eight weeks after entry, every two weeks during week 9-14, every four weeks during week 15-26 and once at week 52 ór until the patient reached the functional score of one or zero. The Hughes' disability scale is a seven point functional scale were 0 represents healthy, 1; minor symptoms and capable of running, 2; able to walk 10 meters or more without assistance but unable to run,3; able to walk 10 meters across an open space with help,
4; bedridden or chairbound, 5; requiring assisted ventilation for at least part of the day, 6; dead [14]. The MRC sumscore was assessed in six bilateral muscles of arms and legs, yielding a sumscore ranging from 60 (normal) to 0 (quadriplegic) [17].

Sensory symptoms were scored at entry, at 4, 8, 14, 26 and 52 weeks after randomisation. Additional studies included routine testing of blood, urine and cerebrospinal fluid; electrophysiology; serological screening for preceding infections with *C.jejuni*, CMV, EBV and *Mycoplasma pneumoniae,* the presence of anti-ganglioside antibodies, and stool cultures for a preceding infection with *C.jejuni*.

Adverse events

The adverse events were monitored daily and evaluated each next visit. These adverse events included: respiratory tract infection, urinary tract infection, intravenous catheter sepsis, gastrointestinal bleeding, deep venous embolism, pulmonary embolism, serum glucose level >10 mmol/l, renal failure and delirium. Every major adverse event was reported as

soon as possible to the coordination centre.

Randomisation procedure

Based on the prognostic influence of age, randomisation was stratified according to age < or ≥ 50 years [8;9;18]. Furthermore, block randomisation was used with random block sizes of 4,6 or 8. A 24h-telephone service provided randomisation numbers according to the randomisation list. The local hospital pharmacist prepared the trial medication corresponding with the trial number.

Statistical analysis

Percentages in independent groups were compared by the chi-square test (without correction for continuity) with and without adjustment for age. Mean values in independent groups were compared by the Mann-Whitney U test. The time to reach an endpoint was analysed by the method of Kaplan and Meier and the log-rank test. For multivariate analyses of the dichotomous endpoint, we used logistic regression. All analyses were performed on an intention-to-treat basis followed by a per protocol analysis with the personal-computer program STATA (version 6).

Results

Randomisation

Between July 1994 and July 2000, 285 GBS patients were assigned for randomisation (figure 1). Twenty-three patients could not be included because they did not meet the inclusion criteria. Twenty-nine patients could not be randomised because they met one or more exclusion criteria. The most frequently reported exclusion criterion was treatment with immuno-supressiva within one month before randomisation. Two hundred thirty-three patients were randomised of which eight had to be excluded from the analysis because no measurement at four weeks, the time of the primary end-point, was available. Table 1 shows the base-line characteristics for the two treatment groups.

Table 1 Baseline characteristics of treatment groups

Characteristics	IVIg/Placebo group (n=113)	IVIg/MP group (n=112)
Men	57 (50)*	73 (65)
Median age in years	52	58
Age ≥ 50 years	65 (58)	68 (61)
F-score at randomization		
3	32 (28)	26 (23)
4	80 (71)	77 (69)
5	1 (1)	9 (8)
Median number of days of muscle weakness before randomization	6	4
Diarrhea	30 (26)	30 (27)

* number (percentage of total)

Primary endpoint (table 2)

In an overall ITT analysis, 56% of the placebo group showed improvement of one or more grades on the Hughes' disability scale while this was 68% in the MP-treated group (p=0.06). After adjustment for the two age groups this p-value was 0.05 (odds-ratio 1.73, 95% CI 1-3). For the per protocol analysis 20 patients were excluded, mostly because of minor treatment violations. Again 56% of the placebo group showed improvement of one or more grades on the Hughes' disability scale, in the MP-treated group this was 70%, p=0.03. After adjustment for the two age groups this p-value was 0.02 (odds-ratio 1.96, 95% CI 1-3.5).

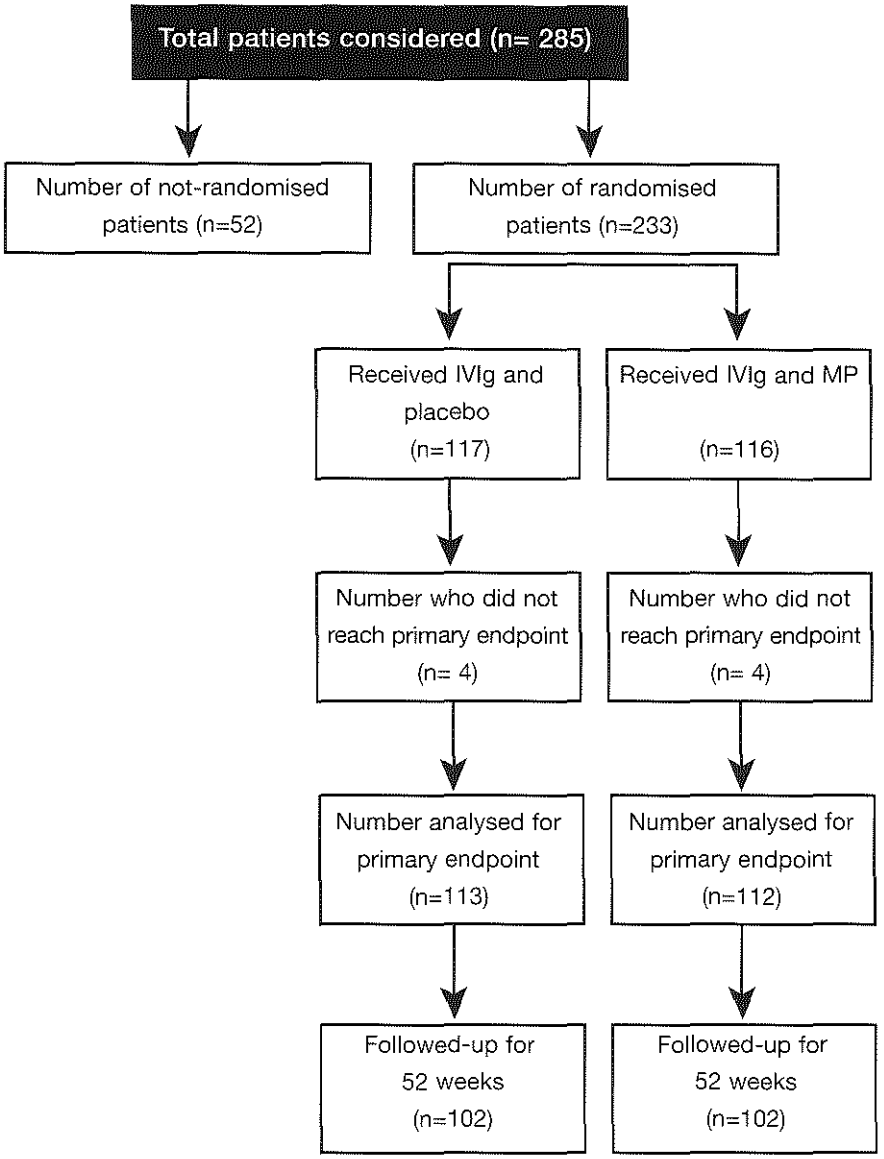
Table 2 Primary endpoint: percentage of patients that improve one or more grades on the Hughes' disability scale four weeks after randomization

Primary Endpoint	IVIg/Placebo group n=113)	IVIg/MP group (n=112)	Improvement Odds ratio (95% CI)	P value	Age adjusted Odds ratio (95% CI)	p-value
ITT*	56%	68%	1.68 (0.97-2.88)	0.06	1.73 (1-3)	0.05
PP*	56%	70%	1.88 (1.05-3.33)	0.03	1.96 (1.1-3.5)	0.02

*ITT: intention to treat analyses (n=225)

PP: per protocol analyses (n=205)

Figure 1 Trial Profile



Secondary endpoints (table 3)

Table 3 shows the results of the secondary outcome measurements. None of the six variables showed a significant difference between the two groups. Figure 2 shows the Kaplan Meier curves of the proportion of patients that were unable to walk independent (f-score>2) until 52 weeks (p=0.37). Figure 3 shows the proportion of patients that improved one or more functional grades during the 52 weeks of follow-up (p=0.15).

Table 3 Secondary endpoints

Secondary endpoints	IVIg/Placebo group (n=113)	IVIg/MP group (n=112)	p-value
Percentage of patients able to walk independently after eight weeks	60%	70%	0.14
Number of days required to improve at least one grade on the Hughes' disability scale (median)	21 days	21 days	0.15
Number of days required to improve until independent walking, f=2 (median)	56 days	28 days	0.37
Difference in grade on the Hughes' disability scale at six months (median)	3 grades	3 grades	0.41
Difference in grade on the Hughes' disability scale at one year (median)	3 grades	3 grades	0.37
Need of artificial respiration	23%	21%	0.77
Duration of artificial respiration (median)	31 days	42 days	0.51

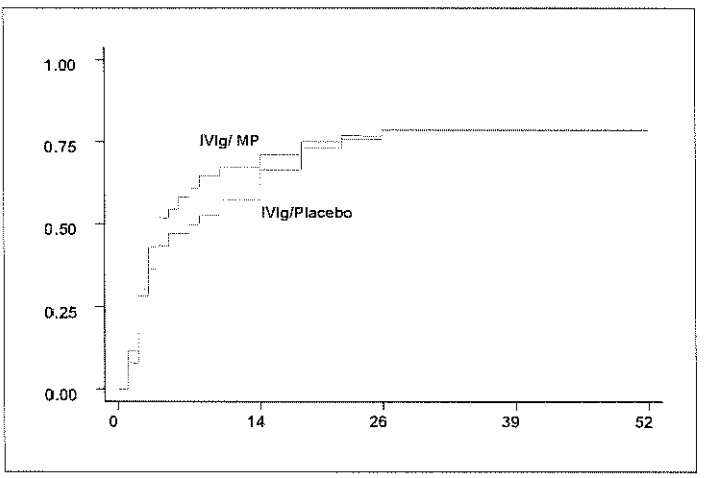


Figure 2
Kaplan-Meier curves indicating the proportion of patients who recovered to independent locomotion (f=2) during 52 weeks of follow-up

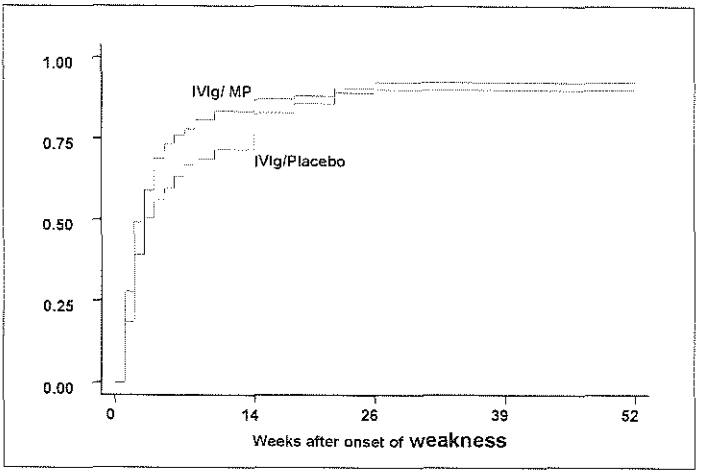


Figure 3
Kaplan-Meier curves indicating the proportion of patients that improved one or more grades on the Hughes' disability scale during 52 weeks of follow-up

Prognostic factors

We performed univariate logistic regression on the following variables: treatment, sex, age < or ≥ 50 years, number of days between onset of weakness and randomisation, number of days from onset of weakness until f=4 was reached (only for f>3), sensory involvement, MRC-score at entry, preceding upper respiratory tract infection, diarrhoea, infection with EBV, CMV, Mycoplasma pneumoniae or Campylobacter jejuni. The following variables showed a significant negative effect on the outcome: age ≥ 50 years, less than 4 days between onset of weakness and randomisation, MRC-score < 40/60 at entry and a preceding infection with CMV. We included these variables, together with treatment in a multivariate logistic regression model. All variables showed a p-value < 0.01, including treatment (p=0.015).

Major Complications

In the placebo group four patients died. One patient died on the second day after randomisation due to a subarachnoid hemorrhage. The second patient died 22 weeks after randomisation, due to an intracerebral bleeding. The third patient suffered from severe autonomic dysfunction resulting in hypoxic ischeamic encephalopathy and multi-organ failure. After discussion with the family it was decided to stop artificial respiration at four weeks after randomisation. The fourth patient died five months after randomisation due to a cerebro vascular accident after operation on a damaged aortavalve due to endocarditis.
In the MP-treated group six patients died. The first patient died from a cardiac arrest on the second day after randomisation. The second patient died four weeks after randomisation due to a gastro-intestinal bleeding. The third patient was found dead nine weeks after randomisation while he was recovering from GBS, probably due to a cardiac arrest. The

fourth patient died three months after randomisation probably due to a cardiac arrest. The fifth patient died, five months after randomisation from sepsis. The sixth patient died seven months after randomisation due to a cardiac arrest.

Minor complications

A urinary tract infection was reported in 30% of the cases in the placebo group and 18% in the MP-group (p=0.02). A serum glucose level >10mmol/l was more frequently found in the MP-group (21% versus 7% in the placebo group), p<0.01. With respect to autonomic dysfunction, hypertension was more frequently reported in the placebo group (13% versus 2% in the MP-group, p<0.01).

Discussion

In this trial we investigated the additional effect of methylprednisolon on standard treatment with IVIg in patients with Guillain-Barré syndrome. Patients were included when they were unable to walk independently and were within the first two weeks of the disease. The primary endpoint was defined as the percentage of patients that improved one or more grades on the Hughes' disability scale four weeks after randomisation, compared with the score at time of entry.

Despite randomisation, some differences were found in the baseline characteristics between the two treatment groups that need to be taken into account while interpreting the results. The difference in sex distribution between the two groups probably did not influence the outcome since there is no indication in the literature that there is a difference in treatment response between men and women. What most likely influences outcome is the distribution of f-scores at time of randomisation. In the IVIg/MP group eight percent of the patients had an f-score of five while this was only one percent in the IVIg/placebo group. The fact that more severely affected patients were included in the MP group negatively affects the outcome and therefore the assessed treatment effect in the MP group could be underestimated. The Sandoglobulin GBS trial group reported that a shorter duration from onset of weakness to randomisation had a negative effect on the outcome at four weeks [9]. In this study the median number of days between onset of disease and randomisation was six days for the placebo group and four days for the MP group, which again could result in an underestimation of the treatment effect in the MP group.

In the previous trial comparing the effect of IVIg and plasma exchange [8], the percentage that improved in the IVIg group was 53%. The outcome of 56% in the IVIg/placebo group in this study can therefore be regarded as a confirmation of the assessed effect in the former trial. The ITT analysis showed that 69% of the patients reached the primary endpoint in the IVIg/MP group, and 56% of the patients treated in the IVIg/Placebo group (p=0.06). After

adjustment for age the p-value was 0.05. The PP analysis also showed improvement in 56 % of the IVIg/Placebo patients, but 70% improvement in the IVIg/MP group, p=0.03 (after adjustment for age p=0.02). The multivariate analysis, including all relevant prognostic factors, favoured the combination of IVIg/MP treatment even more (p=0.015). Taking further into account the effect of the distribution of baseline characteristics, the positive effect of the addition of MP on standard IVIg treatment seems convincing. However, the secondary outcome measurements indicate that this effect mainly has a short-term character. The Kaplan-Meier curves in figure 1 and figure 2 show that the additional effect of MP is predominantly in the first 14 weeks. Furthermore, the percentage of patients that improved to an f-score of two at week eight was still higher in the MP-group while this difference was not found at six months and one year after randomisation.

We investigated the prognostic factors that proved to be of influence in earlier trials on GBS [8;9;16]. The effect of age ≥ 50 years, a low MRC score at entry and a preceding infection with CMV on a worse outcome were confirmed. As reported by the Sandoglobulin GBS trial group, we found that a shorter duration from onset of weakness to randomisation had a negative effect on the outcome at four weeks [9]. Their suggestion that patients randomised in a later stadium, were closer to the onset of spontaneous recovery is likely to hold true in this study. We did not find a prognostic influence of gastro-enteritis or a preceding infection with *C.jejuni*. This confirms an earlier study in which the negative effect of a preceding infection with *C.jejuni* on outcome was only found in patients treated with PE and not in patients treated with IVIg [19].

With respect to the adverse effects, more death occurred in the MP-group. Since four of the six patients died more than eight weeks after randomisation it is unlikely that this is related to the drug under investigation. Of the minor complications, a serum glucose >10mmol/l was more frequently reported in the MP-group. Additional analysis showed that this effect was present in the first eight weeks and after that no significant difference was found in the two groups. The rise in serum glucose due to MP-use can therefore be regarded as transient.

We conclude that methylprednisolone added to the standard treatment of IVIg improves outcome in patients with GBS because it hastens recovery, especially in the first months after onset of the disease. Although this study offers new treatment possibilities for patients with GBS, the long term morbidity and mortality are still considerable. Therefore, the search for drugs that generate long-term effects has to continue.

Acknowledgements

The trial was supported by Baxter Healthcare, Hyland Division. We would like to thank Prof. Martin Lee for his critical remarks and valuable suggestions.

Appendix

The following investigators participated in the study:

• J.A. van Leusden and M.M. Veering, Medisch Centrum Alkmaar, Alkmaar • R. Bijlsma and A. Hovestadt, Eemland Ziekenhuis, Amersfoort • C.H. Polman, J.J. Heimans and R.P.M. Strijers, Academisch Ziekenhuis Vrije Universiteit, Amsterdam • I.N. van Schaik, Academisch Medisch Centrum, Amsterdam • W.H.J.P. Linssen, Sint Lucas Andreas Ziekenhuis, Amsterdam • L. Harms, Medizinische Fakultat Charité, Berlijn • M. Van Zandijcke and V. Schotte, Academisch Ziekenhuis Sint Jan, Brugge • P.Y.K. Van den Bergh and C.J.M. Sindic, Clinique Universitaire St. Luc, Brussel • R.A.J.A.M. Bernsen, Bosch Medicentrum, Den Bosch • J.T.J. Tans and A.W. de Weerd, Medisch Centrum Haaglanden, Den Haag • D.L.J. Tavy, Ziekenhuis Leyenburg, Den Haag • W.J. Feikema, Deventer Ziekenhuizen, Deventer • R.P. Kleijweg, Albert Schweitzer Ziekenhuis, Dordrecht • A. Vermeij, Diaconessenhuis, Eindhoven • J. de Jonge and K. Keizer, Catharina Ziekenhuis, Eindhoven • J.A.G. Geelen and G. Wilts, Medisch Spectrum Twente, Enschede • Th.J.M.Breuer, Sint Annaziekenhuis, Geldrop • F. Visscher and A.M. Boon, Stichting Oosterschelde-ziekenhuizen, Goes • A.E.J. de Jager and T.W. van Weerden, Academisch Ziekenhuis Groningen, Groningen • P.J.J. Koehler and J.W. Vredeveld, Atrium Medisch Centrum, Heerlen • W. Hacke and E. Hund, Ruprecht - Karls Universitat, Heidelberg • J.C. Koetsveld-Baart, St. Streekziekenhuis Midden Twente, Hengelo • J.J.G.M. Verschuuren and A.R. Wintzen, Leids Universitair Medisch Centrum, Leiden • E. de Vries-Leenders, IJsselmeer Ziekenhuizen, Lelystad • M. de Baets and H. Kerkhoff, Academisch Ziekenhuis Maastricht, Maastricht • B.G.M. van Engelen, G.W. Padberg and H.M. Vingerhoets, Universitair Medisch Centrum St. Radboud, Nijmegen • J. Meulstee, M.J.J. Prick, W.I.M. Verhagen and C.W.G.M. Frenken, Nijmeegs Interkonfessioneel Ziekenhuis Canisius-Wilhelmina, Nijmegen • H.A.W. Sinnege, Medisch Centrum Rijnmond-Zuid, Rotterdam • H.W.M. Anten, Maasland Ziekenhuis, Sittard • R.L.A.A. Schellens, Sint Elisabeth Ziekenhuis, Tilburg • L.H. van den Berg and H. Franssen, Universitair Medisch Centrum Utrecht, Utrecht • B.J. van Kasteren and J.A.P. Hiel, Sint Joseph Ziekenhuis, Veldhoven

Bibliography

01. Rees JH, Thompson RD, Smeeton NC, Hughes RA. Epidemiological study of Guillain-Barré syndrome in south east England. J Neurol Neurosurg Psychiatry 1998;64:74-77.
02. van Koningsveld R, Van Doorn PA, Schmitz PIM, Ang CW, van der Meché FGA. Mild forms of Guillain-Barré syndrome in an epidemiologic survey the Netherlands. Neurology 2000;54:620-625.
03. Merkies IS, Schmitz PI, Samijn JP, van der Meché FG, van DP. Fatigue in immune-mediated polyneuropathies. European Inflammatory Neuropathy Cause and Treatment (INCAT) Group. Neurology 1999;53:1648-1654.
04. de Jager AEJ, Minderhoud JM. Residual signs in severe Guillain-Barré syndrome: analysis of 57 patients. J Neurol Sci 1991;104:151-156.
05. Fletcher DD, Lawn ND, Wolter TD, Wijdicks EF. Long-term outcome in patients with Guillain-barré syndrome requiring mechanical ventilation. Neurology 2000;54:2311-2315.
06. The Guillain-Barré study group. Plasmapheresis and acute Guillain-Barré syndrome. Neurology 1985;35:1096-1104.
07. French Cooperative Group on plasma exchange in Guillain-Barré Syndrome. Efficiency of plasma exchange in Guillain-Barré syndrome: role of replacement fluids. Ann Neurol 1987;22:753-761.
08. van der Meché FGA, Schmitz PIM, Dutch Guillain-Barré Study Group. A randomized trial comparing intravenous immune globulin and plasma exchange in Guillain-Barré syndrome. N Engl J Med 1992;326:1123-1129.
09. Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group. Randomised trial of plasma exchange, intravenous immunoglobulin, and combined treatments in Guillain-Barré syndrome. Lancet 1997;349:225-230.
10. Hahn AF. Guillain-Barré syndrome. Lancet 1998;352:635-641.
11. Hughes, R. A., Raphael, J. C., Swan, A. V., and van, Doorn PA. Intravenous immunoglobulin for Guillain-Barré syndrome (Cochrane Review). Cochrane Database Syst Rev 2001;2.
12. Hadden RD, Karch H, Hartung HP, et al. Preceding infections, immune factors, and outcome in Guillain-Barré syndrome. Neurology 2001;56:758-765.
13. The Dutch Guillain-Barré Study Group. Treatment of Guillain-Barré syndrome with high-dose immune globulins combined with methylprednisolone: a pilot study. Ann Neurol 1994;35:749-752.
14. Hughes RAC, Newsom-Davis J, Perkin GD, Pierce JM. Controlled trial of prednisolone in acute polyneuropathy. Lancet 1978;2:750-753.
15. Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain-Barré syndrome. Ann Neurol 1990;27:Suppl:S21-4.
16. Visser LH, Schmitz PI, Meulstee J, Van Doorn PA, van der Meché FGA. Prognostic factors of Guillain-Barré syndrome after intravenous immunoglobulin or plasma exchange. Dutch Guillain-Barré studygroup. Neurology 1999;53:598-604
17. Medical Research Council. Aids to the investigation of the peripheral nervous system. London:

Her Majesty's Stationary Office, 1976.

18. McKhann GM, Griffin JW, Cornblath DR, Mellits ED, Fisher RS, Quaskey SA. Plasmapheresis and Guillain-Barré syndrome: analysis of prognostic factors and the effect of plasmapheresis. Ann Neurol 1988;23:347-353.
19. Jacobs BC, Schmitz PI, van der Meché FG. Campylobactery jejuni Infection and treatment for Guillain-Barré Syndrome. N Engl J Med 1996;335:208-209.

4.2 Changes in referral pattern and its effect on outcome in patients with Guillain-Barré Syndrome

Based on the short communication "Changes in referral pattern and its effect on outcome in patients with Guillain-Barré Syndrome". Van Koningsveld R., MD, Van Doorn P.A., MD, PhD, Schmitz P.I.M., PhD, Van der Meché F.G.A., MD, PhD. Neurology 2001;56:564-566

Abstract

Objective: A multicentre trial in the Netherlands showed equal efficacy of treatment with plasma-exchange (PE) and intravenous immune-globulin (IVIg) in patients with the Guillain-Barré syndrome (GBS). Since IVIg is also available in smaller centers it is no longer necessary to transfer patients for treatment purposes. In this study we investigated the change in referral pattern of GBS patients after publication of this study. Additionally, we compared outcome parameters of patients admitted in small centers with patients admitted in large centers to investigate whether the referral pattern has been appropriately adapted after the general availability of a new treatment (IVIg).

Methods: Hospital records of GBS patients admitted to all 45 hospitals in the Southwest Netherlands (4.2 million inhabitants) in the period 1987-1990 and 1994-1996 (n=266) were reviewed.

Results: In the second period, after the publication of the PE/IVIg trial, more patients in small centers were treated with IVIg ($p<0.001$). Before publication 40% of the patients was transferred to larger centers compared with 23% thereafter ($p=0.05$). High-risk patients were still transferred to large centers. There was no increase of complications in small centers after 1992 despite the decrease of referral to large centers. More complications were reported in large centers. This is explained by the higher percentage of severely affected patients admitted to large centers.

Conclusion: The introduction of IVIg resulted in less patients being transferred from small to large centers while high-risk patients are still being transferred appropriately. This change in referral pattern of GBS patients has led to a more optimal use of different levels of care facilities.

Introduction

The Guillain-Barré syndrome (GBS) is an acute immune-mediated polyneuropathy characterized by a flaccid weakness, reduced or absent tendon reflexes and, to a variable degree, involvement of the cranial nerves and the sensory system. The incidence rate varies from 1-2 per 100.000 inhabitants per year and increases with age [1;2].

Two large randomized trials established the role of plasma exchange (PE) as a treatment option for GBS [3;4]. In 1992, a Dutch randomized trial showed equal efficacy of treatment with PE and intravenous immune globulin (IVIg) in patients with GBS [5]. This outcome was confirmed by a large trial studying the effect of treatment with PE, IVIg and combined treatment of PE and IVIg [6]. Because treatment with IVIg is straightforward, widely available,

well tolerated and less prone to complications than PE, it has since 1992 become the treatment of choice in the Netherlands.
After 1992, we noted a decrease in the number of GBS patients referred to our hospital and other large centers. Since IVIg can be administered in small centers it was hypothesized that it was no longer necessary to transfer patients to larger centers for treatment purposes. In this study we investigated the change in treatment strategy and in referral pattern after the introduction of IVIg. Because GBS runs a rapidly progressive course and complications such as hypoventilation and autonomic dysfunction can occur, it is questionable whether it is a positive development not to transfer patients to large centers. To answer this, we also studied outcome parameters in the period before and after 1992, in patients admitted to small centers as well as large centers.

Patients and methods

This study was part of an epidemiological survey on GBS in the Southwest Netherlands [2]. In this survey patients were selected when they were discharged with the international classification of disease code for GBS (ICD-9, 357.0) in all 45 hospitals from 1987 to 1996. Patients fulfilling the National Institute for Neurological Disorders and Stroke (NINCDS) criteria for GBS were included in the analysis (n=476) [7].
To investigate the change in referral pattern we defined two periods in the analysis. In both periods a clinical trial was conducted making them comparable in that respect. Period 1 is the period in which the PE/IVIg trial was performed (January 1987 to January 1990). Period 2 was the period in which a subsequent study was performed with combined IVIg and high dose methylprednisolone therapy (IVIg/MP trial) (July 1994 to December 1996). In both periods we studied the differences in outcome between small and large centers (n=25, n=20 respectively). Because the median number of beds in the hospitals was 380, we defined hospitals with less than 380 beds as small centers.
We used the following parameters to study outcome: walking independently after two weeks, eight weeks and six months, mortality and complications. As confounding factors we included age, sex, f-score at nadir [8] and therapy.
Differences in treatment choice, referral pattern, outcome parameters and confounding factors were calculated with a chi-square test without continuity correction, or when necessary a Fisher's exact test or the Wilcoxon-Mann-Witney *U* test. All calculations were performed using STATA 5.0 for Windows 95 (Stata Statistical Software, Release 5.0, College Station, TX). A p value < 0.05 was considered to be significant.

Results

In the two periods under study, 266 patients fulfilled the NINCDS criteria for GBS. Table 1

shows the characteristics of the patient group.
Figure 1 shows the choice of treatment in small centers in the two periods. In period 1, 11% of the patients was treated with IVIg, in period 2 this increased to 53% (p<0.001). In period 1, 40% of the patients was transferred from small to large centers whereas in period 2 only 23% was transferred (p=0.05).

Table 1. Characteristics of GBS patients

Characteristic	% (n)
Age > 50	47 (266)*
Men	62 (266)
Sensory signs or symptoms	68 (249)
Cranial nerve involvement	35 (264)
Artificial respiration needed	14 (265)
Rapid onset of disease (<4 days until being bedbound)	30 (246)
Mortality	2 (251)

* Number of patients on which information was available

Figure 1.
Treatment choice for all GBS patients admitted in small centers

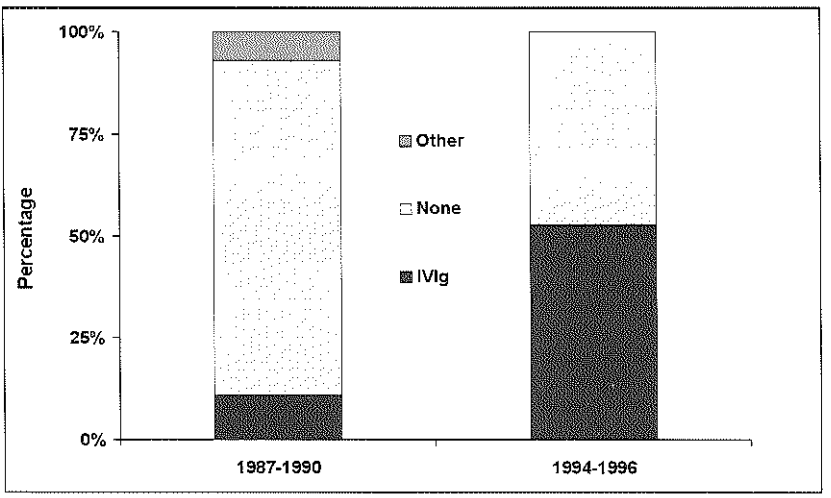


Table 2 shows the outcome parameters in small and large centers for both periods. Analysis of the confounding factors in period 1 showed no differences in the distribution of sex and age between the small and large centers. There were fewer patients receiving therapy in small centers compared to large centers (p<0.001), but there were also less

patients severely affected in small centers (f-score ≥3) ($p<0.001$). In period 2, no significant difference was found for the four confounding factors. Table 3 represents the distribution of maximum f-scores per period for small versus large centers.

To study the effect of the change in referral pattern on outcome in more detail, we analysed the group of patients who are believed to be at highest risk when not appropriately referred to larger centers when necessary. These are the patients unable to walk independently or bedbound and are therefore especially at risk for the need of artificial respiration and the development of complications. In this high-risk group we also found that less patients were referred in period 2 and thus more patients stayed in small centers. Analysis showed no more complications or mortality in period 2 in the small centers, only one patient received artificial ventilation in a small center in period 2.

Table 2. Outcome parameters for small and large centers per period

Outcome	Period 1 Jan.1987- Jan.1990 n=142			Period 2 July 1994-Dec.1996 n=124		
	small (%)	large (%)	p value	small (%)	large (%)	p value
Mortality	0	3	0.56	0	2	1.0
Able to walk at 2 weeks	50	24	**0.008**	47	38	0.40
Able to walk at 8 weeks	76	57	0.06	88	74	0.20
Able to walk at 6 months	93	80	0.15	97	87	0.17
Complications	5	28	**0.005**	3	19	**0.02**

Table 3. Maximum f-score small versus large centers per period

F-score at nadir	Period 1		Period 2	
	small % (n)*	large % (n)*	small % (n)*	large % (n)*
1	0 (0)	3 (3)	0 (0)	3 (3)
2	31 (9)	15 (15)	45 (14)	27 (24)
3	17 (5)	7 (7)	13 (4)	17 (15)
4	52 (15)	47 (48)	39 (12)	42 (37)
5	0 (0)	25 (26)	3 (1)	9 (8)
6	0 (0)	3 (3)	0 (0)	2 (2)
Total	100 (29)	100 (102)	100 (31)	100 (89)
p-value small versus large centers	p=0.003		p=0.50	

* Number of patients on which information was available

Discussion

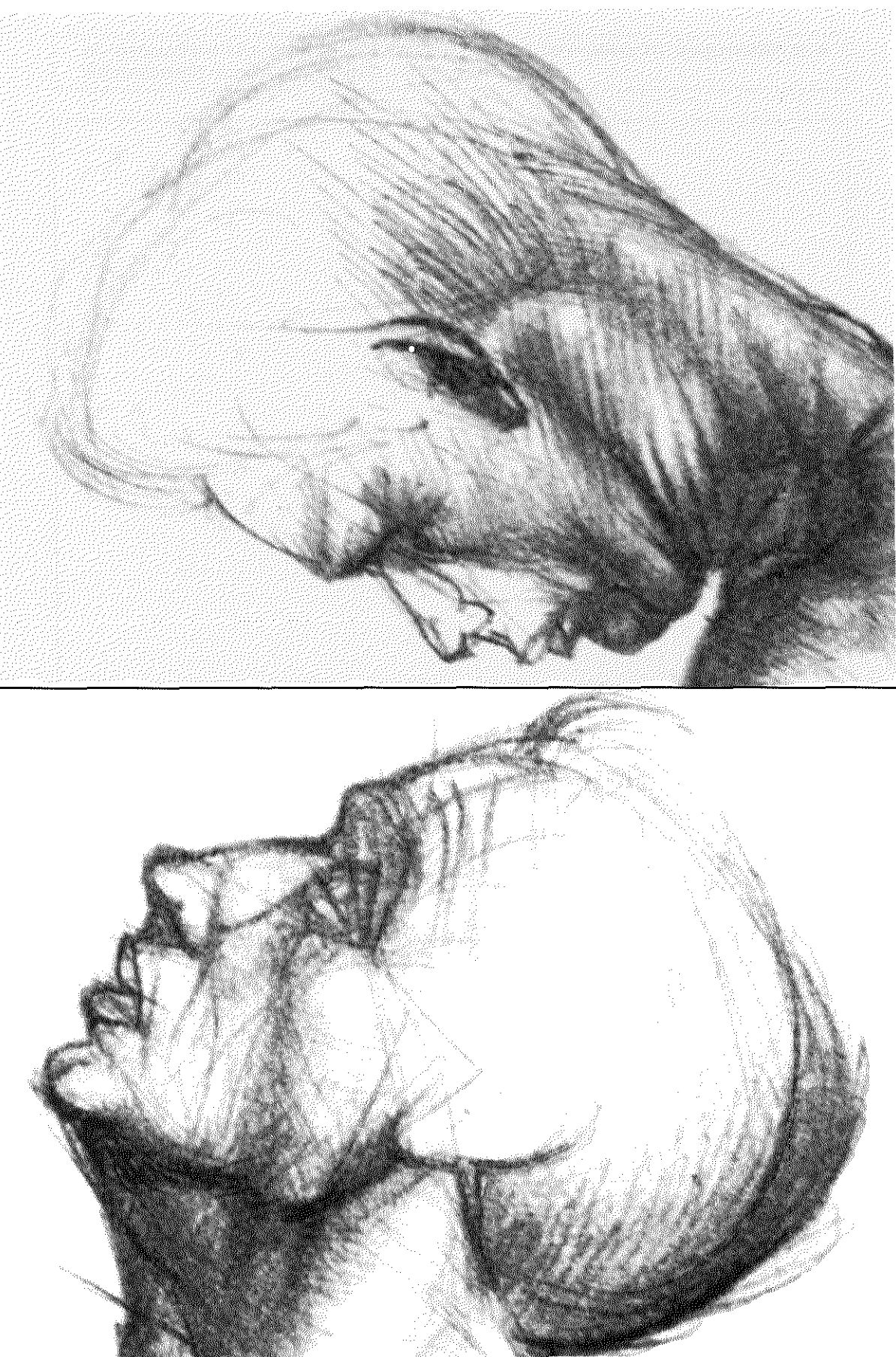
This study is part of a large population based survey performed in Southwest Netherlands [2]. In this survey we studied 476 cases recruited in a ten-year period resulting in one of the largest epidemiological studies on GBS world-wide. The figures from this survey are in agreement with data reported in literature. Therefore we assume that the data reported in this study are reliable and can serve as a basis to study the effect of publication of the PE/IVIg trial on the referral pattern and the outcome in GBS patients.

In this study we found that less patients were referred from small to large centers during the second period. Because there were significantly more patients treated with IVIg in small centers, it seems reasonable to assume that the introduction of IVIg is an important cause for the change in the referral pattern. GBS is a rare disease and therefore not all neurologists in every hospital have the opportunity to become experienced with the unexpected course of the disease and the risk of hypoventilation and autonomic dysfunction. In general, it has been advised to refer GBS patients to large centers with experienced personnel working in the intensive care facilities [1;9]. There is no study available reporting on the referral pattern in GBS and it is not known whether patients admitted in small centers do worse than those in large centers. This study showed that there are no important differences in the outcome parameters between small and large centers. In period 1, there were more patients able to walk independently after two weeks in the small centers and there were fewer complications. This can be entirely explained by a less severely affected group remaining in those these centers compared to the group admitted to large centers. In period 2, there were no differences in outcome between small and large centers except a higher percentage of complications found in large centers in period 2. This is compatible with the relatively high presence of severely affected patients admitted to large centers. We found no more complications and no increase in mortality in period 2 in the small centers. This indicates that high-risk patients are still being transferred appropriately. The fact that only one patient received mechanical ventilation in a small center in period 2 suggests that, although facilities for ventilation are available in small centers, it is a policy to transfer those patients to large centers.

In conclusion, the publication of the PE/IVIg study has had important consequences in the management of GBS patients in the Netherlands. It resulted in a more selective referral of severely affected GBS patients to large centers. When the results of a treatment trial are likely to cause a change in the treatment of a large percentage of a patient group, one should realize that this could have consequences for the referral pattern. When this is appropriately adapted it can lead to a more optimal use of different levels of care facilities.

Bibliography

1. Hahn AF. Guillain-Barré syndrome. Lancet 1998;352:635-641.
2. van Koningsveld R, Van Doorn PA, Schmitz PIM, Ang CW, van der Meché FG. Mild forms of Guillain-Barré syndrome in an epidemiologic survey the Netherlands. Neurology 2000;54:620-625
3. The Guillain-Barré study group. Plasmapheresis and acute Guillain-Barré syndrome. Neurology 1985;35:1096-1104.
4. French Cooperative Group on plasma exchange in Guillain-Barré Syndrome. Efficiency of plasma exchange in Guillain-Barré syndrome: role of replacement fluids. Ann Neurol 1987;22:753-761.
5. van der Meché FGA, Schmitz PIM, Dutch Guillain-Barré Study Group. A randomized trial comparing intravenous immune globulin and plasma exchange in Guillain-Barré syndrome. N Engl J Med 1992;326:1123-1129.
6. Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group. Randomised trial of plasma exchange, intravenous immunoglobulin, and combined treatments in Guillain-Barré syndrome. Lancet 1997;349:225-230.
7. Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain-Barré syndrome. Ann Neurol 1990;27:Suppl:S21-4.
8. Hughes RAC, Newsom-Davis J, Perkin GD, Pierce JM. Controlled trial of prednisolone in acute polyneuropathy. Lancet 1978;2:750-753.
9. Ropper AH. The Guillain-Barré syndrome. N Engl J Med 1992;326:1130-1136.



chapter 05

General Discussion

General Discussion

The studies described in this thesis concern epidemiological and clinical aspects of the Guillain-Barré syndrome. It also includes the results of a randomised placebo controlled trial on the additional effect of methylprednisolone on standard treatment with intravenous immunoglobulin. By studying epidemiological and more clinically related phenomena, we aimed to get more insight in the mechanisms that cause the differentiation of GBS into subgroups. Describing and recognising the GBS subgroups, especially the mild variant is furthermore important because the response to therapy and the long-term prognosis may differ.

In this chapter the main findings of the studies will be discussed and suggestions for future studies will be made. First, some methodological aspects will be considered.

Methodological aspects

The studies described in this thesis are based on patients that fulfilled the NINSCDS criteria for GBS [1]. These criteria were originally set up to investigate and control the large number of reported cases of GBS in association with the swine-flu vaccination. To prevent the inclusion of false-positive cases, rather strict criteria were defined.

Although the use of these criteria in this thesis was necessary to make the results comparable with other studies in this field, there certainly are drawbacks to the application of these strict criteria. In the study on the incidence rate of GBS in the Southwest Netherlands for example, 18 patients had to be left out of the analysis because symptoms and signs were too weak to meet the criteria. These patients probably suffered from a very mild form of GBS. Therefore the reported incidence rate of 1.18/100.000 inhabitants might be an underestimation of the true number of GBS cases in the Southwest Netherlands. In both the retrospective and the prospective study on mild forms of GBS, again only patients were included that fulfilled the NINCDS criteria. It is very likely that thereby a number of very mild patients were not included. Studying these very mildly affected patients might have further contributed to the assessment of characteristics that influence the course of the disease. Therefore, future studies should also consider inclusion of these very mildly affected patients.

With respect to the study on Curaçao some remarks must be made concerning the control groups. We used the data from the survey from the Southwest Netherlands to compare the distribution of characteristics of the Curaçao patients, thus GBS cases from the Netherlands were used as control group. These Dutch patients did not derive from the same source population as the patients from Curaçao, which would have been the optimal control group. However, the use of a control group of available patients from Curaçao (e.g. the group of 12 patients diagnosed in 1987 to 1991) would not be feasible because the low number would generate too little power. The epidemiological characteristics of GBS are very similar in different studies from all over the world (chapter 1). Therefore it seems justified to use the Dutch patients as the control group. To interpret the high percentage of positive *C.jejuni* serology in the GBS patients on Curaçao, a control group was needed. The finding of a high percentage of positive *C.jejuni* infections was only available some months after the onset of disease. The need to obtain serum samples from the general population was not an issue until then. We took samples of around 40 sera in March, June and November 1999, while the ten samples from the cases were obtained randomly during 1998 and early 1999. Certainly because the incidence of *C.jejuni* infections shows a seasonal fluctuation (paragraph 2.3), the difference between the two groups could be the result of the above described difference in sampling-time rather than a true difference in the percentage of preceding *C.jejuni* infections. Currently, studies are undertaken to

investigate the relation between the incidence of *C.jejuni* and GBS prospectively.
In this thesis two studies concern the mild forms of GBS. With the interpretation and comparison of the results of these studies, it is important to be aware of the different character of both studies. The first study was part of an epidemiological survey. The main purpose was to assess incidence rates on GBS in the Netherlands. The information was retrospectively collected from patient records and the assessment of the differences between mild and severe patients was done without defining the determinants beforehand. An important point here is that the numbers and percentages resulting from this study are based on a survey that covered all neurological departments in all hospitals in the Southwest Netherlands resulting in a large number of GBS patients. This makes the obtained numbers and percentages from this study representative which is not the case in the prospective study (paragraph 3.2). Here, the aim was to collect clinical and serological data and not to assess incidence rates. The cases were presented by participating neurologists implying that the composition of the study group depended on these neurologists. Therefore selection bias cannot be ignored in this study. In contrast with the retrospective study, the serum samples of all patients were prospectively and systematically collected and tested all together at once in the same laboratory setting. Overall, while interpreting the results and the discussion on the mild form of GBS, when it concerns the characteristics of the patients (age and gender etc.) one might consider valuing the findings from the retrospective study as more appropriate. When it comes to the preceding infections, the data from the prospective study seem to be more valid.
The last remark concerns the use of the terms "retrospective study" and "prospective study" in the following discussion. The term "retrospective study" will be used to address to the study on mild forms as described in paragraph 3.1. The term "prospective study" will be used to address to the study on mild forms as described in paragraph 3.2.

Epidemiology

Epidemiology studies the distribution of a disease and assesses factors that influence this distribution. Information obtained from epidemiological studies can be utilised in several ways [2]. First, it can help to elucidate the etiology of a disease by combining epidemiological data with information from other disciplines. Second, it can be utilised to evaluate the consistency of epidemiological data with etiological hypotheses developed either clinically or experimentally. Third, it can provide a basis for development and evaluation of preventive procedures and public health practices.
Essential in the epidemiology is the matter of causation and causal inference. With our present knowledge and insights it has become clear that almost all diseases are multifactorially induced. Different attempts have been made to organise this complex process in order to

gain a better understanding of the occurrence of diseases. A rather simple but convenient concept is the host-agent-environment theory in which the occurrence of a disease is the result of the presence of an agent which causes the disease in a susceptible person, given certain environmental circumstances. A probably more realistic but more complex view of disease aetiology is the web of causation. In this concept all predisposing factors to a disease and their complex relations with each other and with the disease are considered. The last theory discussed here, proposed by Rothman [3] is the concept of sufficient cause and component causes. A sufficient cause is defined as a set of minimal conditions and events (component causes) that inevitably produces disease. A given disease is considered to have a fixed number of sufficient causes. If a component cause is a member of all sufficient causes it becomes a necessary cause. While at present too little information is available about different causes in most diseases, it might be too early for practical use of this concept.

It appears that the use of the theories described above depends on the quantity of information that is available on a disease. In GBS, the pathophysiological mechanism is largely unknown but information is available on several factors involved in the occurrence. It seems therefore appropriate to use the host-agent-environment model to describe the mechanisms involved in the occurrence of GBS from an epidemiological point of view. We will regard the patient as the host and the preceding infections as the agent.

Age

As in many other studies [4-7], we found a significant increase in incidence with age in the study on the IR of GBS in the Southwest Netherlands (paragraph 2.2). This finding could suggest an increase in host susceptibility with age, provided that a certain agent is present in a given environment. Unfortunately the incidence rate of (preceding) infections alters with age as well as the environmental factors. As in many other illnesses, age cannot be of assistance in formulating a hypothesis of causation in GBS. However, in the assessment of other causal relationships an adjustment must be made for age because the relation with the occurrence of the disease is often very strong.

With respect to the subgroups considered here, an association is described between younger age and the mild group (paragraph 3.1, 3.2), the MFS patients (paragraph 3.3 and [8]), the CMV group [9] and the Chinese paralytic syndrome [10]. The relation with the mild forms will be discussed separately. In most patients with MFS, anti-GQ1b antibodies are present [11;12]. It would be interesting to study the relation between the presence and/or quantity of anti-GQ1b antibodies and age. If the level of anti-GQ1b antibodies decreases with age this can possibly explain the presence of MFS in younger patients and contribute to the evidence that anti-GQ1b antibodies indeed play a role in the pathofysiological mechanism of MFS.

Because in MFS patients the disease tends to run a mild course, age could be a confounding factor in the relation between MFS and the mild group.
The fact that younger age is associated with CMV-related GBS might be explained by the fact that the incidence of CMV infection is higher at younger age. As in the MFS group, it would be interesting to investigate the relation between age and the presence of anti-GM2 antibodies since the presence of these anti-ganglioside antibodies is associated with CMV-related GBS [13;14].
The Chinese paralytic syndrome almost only affects children and young adults in rural areas in the summer [10]. Until now, no clear explanation is found for this typical pattern. Because of the typical clinical pattern and age distribution, one could suggest that these patients in fact suffer from poliomyelitis. However, the hallmarks of poliomyelitis - inflammatory cells in the CSF and motor neurone loss in the spinal cord- are absent [10].

Gender
In general, men are more frequently affected by GBS than women (paragraph 2.1, 2.2, 2.3). Because the numerous differences between men and women are not only biological but also from environmental origin, it is difficult to speculate about the origin of this gender difference and what it may learn about the cause and determinants of GBS. Because of the many differences between men and women, it is surprising that there is hardly any variation in this difference among the subgroups. One study in the United Kingdom [15] reported more men in the *C.jejuni* associated subgroup (not statistically significant). This could be explained by the higher incidence rate of *C.jejuni* infections among men [16].

Geography
The geographical distribution of a disease represents not only climatically characteristics but also differences in race, religion and social economic status. Here again, it is difficult to determine what is host-related, environmental-related or agent-related. For example certain religions come together with a specific diet, which can be regarded as an environmental factor. Also religion is highly associated with race, which is a factor that influences the host susceptibility. Finally, the occurrence of infectious pathogens, in case of GBS regarded as the agent, is very much determined by climatically conditions. Except for the described high incidence areas in China and Curaçao, there is a striking similarity in the distribution of epidemiological characteristics as incidence rate, age and gender in studies from all over the world (paragraph 2.1). From this, it is clear that following the host-agent-environment theory, these three factors must be present everywhere. Unfortunately, it may well be possible that for every zone or place, a different combination of host-agent and environmental factors is needed to generate GBS.

Seasonal variation

The interest in the seasonal pattern of the occurrence of GBS is probably induced by the high incidence of GBS cases in the summer in case of the Chinese paralytic syndrome and by the frequent presence of a preceding infection before onset of GBS. Infections are highly related to seasons, for example infections with *C.jejuni*, which show a peak in summer and early fall [16]. Fluctuations in incidence of a disease being related to difference in seasons can be explained not only by climatic differences but also by sociologic changes following the seasons. The simplest example is eating habits; barbecue-parties during the summer months. Except for a few reported trends in favour of the colder months of the year, no seasonal distribution is reported except in the Chinese paralytic syndrome and the patient group in Curaçao (paragraph 2.1, 2.2, 2.3). In Curaçao it is likely that the seasonal fluctuation of GBS is induced by the fluctuation of infections with *C.jejuni* within the year (paragraph 2.3). This finding is highly suggestive for a role for *C.jejuni* as (one of the) agent in the occurrence of GBS and a unique example of an epidemiological finding that confirms and thereby strengthens a relationship which is previously described in other scientific settings. Earlier reports on the relation between *C.jejuni* infections and the occurrence of GBS were namely derived from laboratory studies [17-19].

Conclusion and direction for future research

With the use of models of causality, an attempt is made to understand the etiology and differentiation into subgroups of GBS from an epidemiological perspective. The increase in incidence with age does not provide any clues because it is likely that not only the host susceptibility alters with age but also environmental factors and the incidence of preceding infections. With respect to the subgroups, the mild patient group, the MFS patients, the CMV related group and the Chinese paralytic syndrome are more frequently found at a younger age. In the MFS and in the CMV-related group, an association is described with respectively anti-GQ1b antibodies and anti-GM2 antibodies. If future studies can show an association between age and the presence of anti-ganglioside antibodies, this not only explains the preference to occur at younger age for the two subgroups but also gives support to the suggested role of anti-ganglioside antibodies in the etiology of GBS. Because of the numerous differences between men and women it is difficult to explain the higher incidence of GBS in men.

Overall, there is a striking similarity in the distribution of epidemiological characteristics as described in studies from all over the world. This suggests that the factors involved in the etiology of GBS must be present all over the world. Yet, it is also a fact that much knowledge including hypotheses on the mechanisms involved in the etiology of is GBS derived from exceptional and small clusters of patients showing distinctive epidemiological features.

All together, it is therefore recommended to apply the theory of sufficient cause and component causes on the present knowledge of GBS. Future studies should aim to construct a sufficient cause for every epidemiological phenomenon concerning GBS. Hereby, it is well possible that this leads to the identification of one, or more, necessary causes. Identification of necessary causes could be a valuable tool to clarify the pathogenesis of GBS.

Clinical Aspects

Studying characteristics of patients that developed a mild form of GBS, may generate clues about the mechanisms that induce this differentiation and thereby determine the course of the disease. In this thesis, two studies are described concerning mild patients. The first study was retrospectively conducted and part of a large epidemiological survey (paragraph 2.2). In this study we aimed to describe the group of mild patients and explore whether other differences than the level of severity existed, compared to the severely affected patient group. The results of that study encouraged us to perform the prospective study, which is described in paragraph 3.2. Some remarks must be made before evaluating and comparing the two studies on mild GBS patients. Table 1 shows that in both studies age less than 50 years was associated with a mild form of GBS. With respect to gender, the results were opposite and because of the numerous, and difficult to assess differences between men and women, this characteristic will not be considered here. From the retrospective as well as from the prospective study a preceding infection with *C.jejuni* or *Mycoplasma pneumoniae* does not seem to be an important factor in the differentiation into mild or severe GBS. In case of a preceding CMV infection, the outcome in the retrospective study differed from the outcome in the prospective study. In the latter study, serum samples were prospectively collected and tested. Therefore, we regard the data from this prospective study more representative and conclude that although not significant, an infection with CMV more frequently precedes GBS in the mildly affected group than in the severely affected group. The EBV results are more complicated. In the retrospective study, no difference was found between the two groups and the percentage with positive serology in the total group (mildly and severely patients) is comparable with earlier reports [20]. In the prospective study, significantly more EBV infections preceded a mild course. However, the percentage with positive serology in the total group (mildly and severely patients) was much higher than in earlier reports [20]. One explanation for this finding could be the use of a new technique for testing the antibody response to EBV in the serum of the GBS patients. Therefore we tested a control group of non-GBS patients, which was already tested with the former technique. Because the percentage of positive serology was comparable in both tests, we conclude that the finding of a high percentage of preceded EBV infections among mild patients truly reflects the distribution of EBV infections in this group.

Only in the prospective study, we were able to assess the distribution of anti-ganglioside antibodies and found an absence of anti-GM1 and anti-GQ1b antibodies in the mildly affected patients. Because of the low numbers, these findings must be interpreted with caution. It seems more appropriate to consider the difference in the total number of anti-ganglioside antibodies (12% in the mild group versus 45% in the severe group, p=0.01), rather than speculate about the absence or presence of a particular anti-ganglioside antibody.

Table 1 Distribution of characteristics of mildly affected GBS patients in the retrospective and prospective study.

	Retrospective study (n=121)	Prospective study (n=19)
Age > 50 years	31% (121*)	16% (19)
Men	69% (121)	37% (19)
C.jejuni	21% (14)	17% (18)
CMV	10% (40)	28% (18)
EBV	3% (36)	50% (18)
Mycoplasma pneumoniae	3% (34)	0% (18)
Anti-GM1 ab	NA**	0% (17)
Anti-GM2 ab	NA	6% (17)
Anti-GD1a ab	NA	6% (17)
Anti-GQ1b ab	NA	0% (17)

* number of patients available

** NA = not available

All together it seems rational to centre the discussion around the major, and most convincing findings; the relation of mild forms with young age and the low percentage of anti-ganglioside antibodies in general.

Although age is frequently reported as prognostic factor for worse outcome [5;21-23], the studies described in this thesis are the first to show that age also influences the course and progression of the disease. Unfortunately, as mentioned earlier, age can not simply be regarded as a hostfactor. The influence of young age on the course of the disease can be a result of a high incidence rate at younger age of an agent that causes a mild course of the disease. From the results of the prospective study, it is attractive to mention EBV as responsible agent for determining a mild course. Unfortunately, no figures are available on the incidence rate of EBV in the Netherlands, so it is not known whether EBV infections occur more frequently at young age. The assessment of IR of EBV at young age, together with assessment of EBV serology in GBS patients in future studies might give support to the relation between a preceding EBV infection and the induction of a mild course of the disease.

C.jejuni infections in developed countries show a peak in incidence at age <1 year and at the age between 15 and 30 years [16]. If a preceding infection would be the only, or an important factor in the differentiation into mild or severe form, one would, based on the relation between young age and a mild course, also expect a relation between preceding *C.jejuni* infection and a mild course. However, infections with *C.jejuni* can result in both mild and in severe forms of GBS. That *C.jejuni* can precede a severe course of GBS is shown in patients from Curaçao, as described in paragraph 2.3, and is reported by others [19;24;25]. It is remarkable that most of these studies, including the Curaçao study, report on the frequent presence of anti-GM1 antibodies in the severe cases that were preceded with *C.jejuni* [19;25]. We found no anti-GM1 antibodies in patients with the mild form of GBS. This makes it attractive to attribute an important role to the presence of anti-GM1 antibodies, but also to anti-ganglioside antibodies in general, in the differentiation into a mild or severe form of GBS. Here again, the question rises whether there is a relation between age and anti-ganglioside antibody response, since this relation would further support an important role for anti-ganglioside antibody response in the course of the disease. One explanation could be that, with the progression of age the triggering of an anti-ganglioside antibody response increases, resulting in more damage to the nerves, causing a severe form of GBS. Although less likely, it can also be that the expression of gangliosides in the nervous system membrane changes during life and thereby increases the potential site of binding resulting in more damage.

With the above-described relations, an attempt is made to explain the differentiation in the course of the disease between mild and severe forms of GBS. This was done with the results available from our studies. However, it is very likely that much more factors, probably not with equal strength, play a role in the differentiation into subgroups. This is probably a very complex process where the interplay of different preceding agents, in persons with different hostfactors, in different environments, results in the development of subgroups of GBS.

Conclusion and direction for future research

The studies on mild forms of GBS showed several differences in characteristics between patients with a mild course of GBS compared to patients with a severe course of the disease. Both the retrospective and the prospective study showed a relation between age and the differentiation into mild or severe GBS. Several differences were suggested explaining this relation with age, for example the increasing IR of the associated preceding infections with age. Interesting is the low percentage of patients with anti-ganglioside antibodies in the mild group.

In order to further elucidate the complex mechanism by which the course of the disease

differentiates into a mild or a severe form, it is advisable to conduct further epidemiological research. First, the results of the epidemiological studies may generate clues that give direction to the work in other fields of research. For example, the studies described here show the importance of assessing the relation between age and anti-ganglioside antibody response. Before that, it seems appropriate to confirm the finding of the low anti-ganglioside antibody response in mild patients. Also confirmation of the distribution of preceding infections in the mild group is needed before definite relations can be considered.
Second, the epidemiological theories of causation, for example the earlier mentioned theory of sufficient and component causes, can be used to structure and integrate information generated in different fields of research in GBS.

Treatment

In the introduction it was already stated that despite the availability of specific treatment like IVIg, morbidity and mortality is still considerable in GBS. Paragraph 4.2 describes a study in which the morbidity and mortality is compared between GBS patients admitted in small versus large centres. With the availability of IVIg treatment in small centres, the need to transfer patients to larger centres in order to receive treatment became obsolete. The results of this study showed that mortality and morbidity in GBS patients was independent of the type of healthcare facility. The exploration of other or additional therapeutic options is therefore needed. Furthermore, with the ongoing broadening of the spectrum of GBS, it seems appropriate to explore the need of therapy in subgroups. In this thesis we focussed on the mild form of GBS and on patients with MFS. By studying the course of the disease and the outcome, we explored the need for treatment studies in these two groups. We found that mildly affected patients report affected mobility at three and six months. Additionally, many patients reported severe fatigue and endurance intolerance. Because IVIg is the treatment of choice in the Netherlands, this seems the therapy of choice to study in mild forms of GBS. With respect to the prognosis, patients with mild forms of GBS must be made aware of the chance of incomplete recovery and the problem of fatigue.
Although MFS is generally considered to be a benign variant of GBS, we showed in paragraph 3.3 that this GBS subgroup certainly not always recovers without residual signs. Furthermore in this group, again severe fatigue was reported as a major problem at three and six months after onset of the disease. Due to the low incidence of MFS, we concluded in paragraph 3.3 that conduction of an RCT in MFS does not seem feasible. Based on several arguments, the most important being the resemblance of the course of the disease with GBS, it was argued that treatment could be considered in especially the severely affected MFS patients, despite the lack of evidence provided by an RCT. Here again, one should be aware of the chance of incomplete recovery and fatigue when informing a

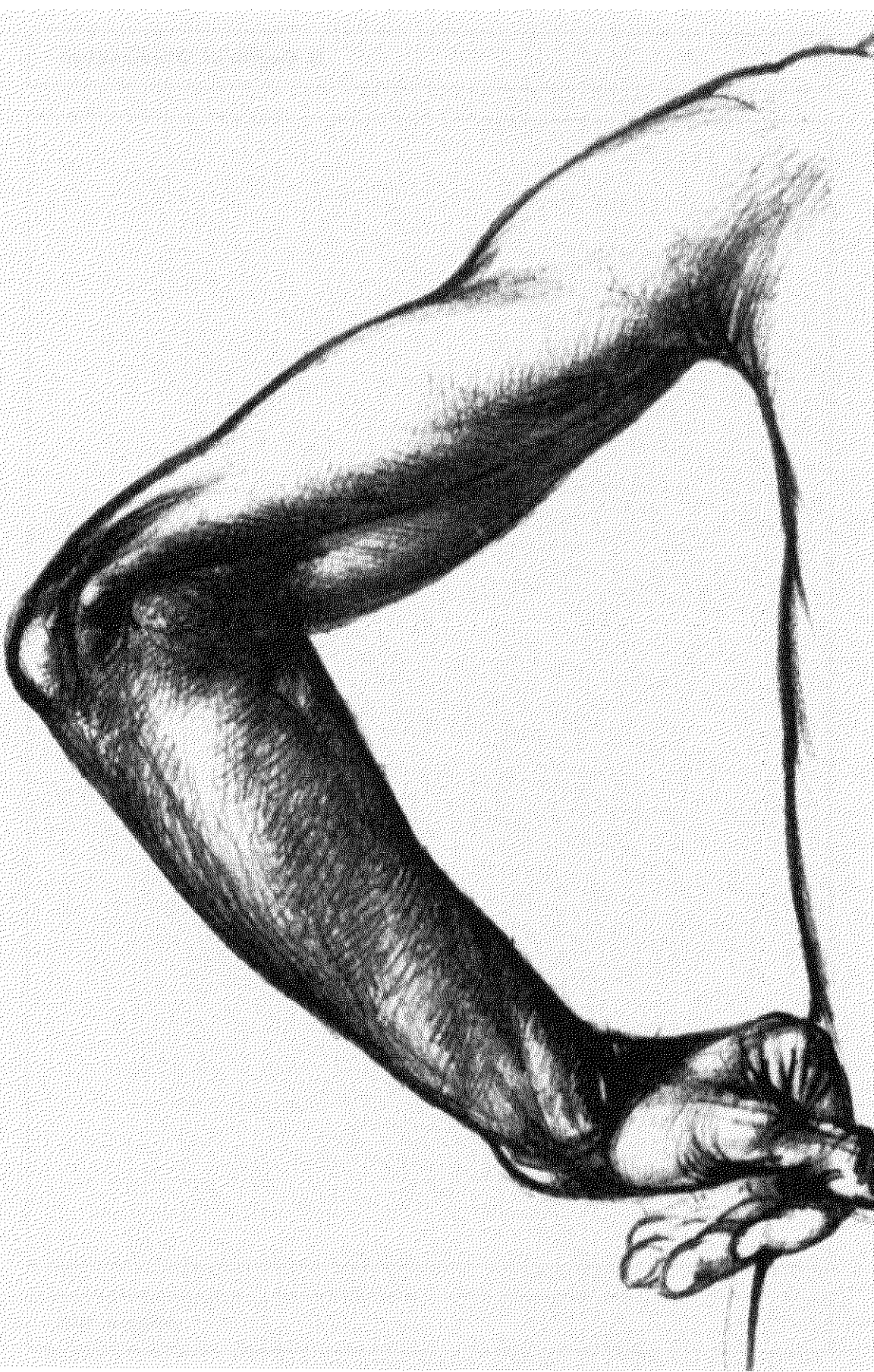
MFS about the prognosis of the disease.
Paragraph 4.1 describes the results of a RCT on the additional effect of methylprednisolone on standard treatment with IVIg in patients with GBS. From 1994 to 2000, 225 patients were randomised to receive either IVIg and MP or IVIg and placebo. Based on the reported prognostic influence of age, patients were stratified >50 years and ≥50 years of age. The primary endpoint was defined as the percentage of patients that improve one or more grades on the Hughes'disability scale. The ITT analysis showed that 56% of the patients in the placebo group reached the primary endpoint compared to 68% in the MP group (p=0.06, after adjustment for age p=0.05). Including the relevant prognostic factors in a regression analysis the effect of MP treatment was convincing with a p-value 0.0015. The secondary endpoints almost all represented long-term conditions and did not show a difference between the two groups, emphasising that the additional effect of MP in GBS mostly acts in the first months. The results of this RCT now offer an additional treatment option in patients with GBS.

Conclusions and direction to future research
Mildly affected GBS patients may still have considerable problems in mobility at three and six months after onset of the disease. The positive effect of PE in mildly affected patients has been described [26]. Since treatment with IVIg is preferable to PE, investigation of the effect of IVIg in patients with a mild form of GBS is indicated. This could be evaluated in a setting where only mild patients are included, or these patients could be included in a RCT, where IVIg will at least be administered in a control group.
Also in MFS not all patients recover without residual signs. Because of the low incidence rate of this subgroup and the resemblance with GBS, one might consider treating patients who are severely affected with IVIg. Both patients with the mild form of GBS and MFS reported fatigue as a major problem after physical recovery was completed. At this moment, different studies are conducted to investigate the benefit of therapy in fatigued patients who initially suffered from a severe form of GBS. If the results indicate that these treatments are effective, a study can be undertaken to study the effect in patients who suffered from a mild form of GBS or MFS.
Our study describes the positive effect of the combination of IVIg and MP. It was shown that this effect was mainly achieved during the first three months after onset. Long term morbidity in GBS is still considerable. New treatment studies should therefore preferably focus on the reduction of long-term nerve damage due to GBS.

Bibliography

01. Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain-Barré syndrome. Ann Neurol 1990;27:Suppl:S21-4.
02. Lilienfeld AM, Lilienfeld DE. Laying the foundations; the epidemiologic approach to disease. In: Foundations of epidemiology. 1990:3-22.
03. Rothman KJ, Greenland S. Causation and causal inference. In: Modern epidemiology. 1998:7-28.
04. Larsen JP, Kvale G, Nyland H. Epidemiology of the Guillain-Barré syndrome in the county of Hordaland, western Norway. Acta Neurol Scand 1985;71:43-47.
05. Emilia-Romagna Study Group on Clinical and Epidemiological Problems in Neurology. A prospective study on the incidence and prognosis of Guillain-Barré syndrome in Emilia-Romagna region, Italy (1992-1993). Neurology 1997;48:214-221.
06. Winner SJ, Evans JG. Age-specific incidence of Guillain-Barré syndrome in Oxfordshire. Q J Med 1990;77:1297-1304.
07. Beghi E, Kurland LT, Mulder DW, Wiederholt WC. Guillain-Barré syndrome. Clinicoepidemiologic features and effect of influenza vaccine. Arch Neurol 1985;42:1053-1057.
08. Berlit P, Rakicky J. The Miller Fisher syndrome. Review of the literature. J Clin Neuroophthalmol 1992;12:57-63.
09. Visser LH, van der Meché FGA, Meulstee J, et al. Cytomegalovirus infection and Guillain-Barré syndrome; the clinical, electrophysiologic and prognostic features. Neurology 1996;47:668-673.
10. McKhann GM, Cornblath DR, Griffin JW, et al. Acute motor axonal neuropathy: a frequent cause of acute flaccid paralysis in China. Ann Neurol 1993;33:333-342.
11. Jacobs BC, Endtz HPh, van der Meché FGA, Hazenberg MP, Achtereekte HAM, Van Doorn PA. Serum anti-GQ1b IgG antibodies recognize surface epitopes on Campylobacter jejuni from patients with Miller Fisher syndrome. Ann Neurol 1995;37:260-264.
12. Yuki N, Sato S, Tsuji S, Ohsawa T, Miyatake T. Frequent presence of anti-GQ1b antibody in Fisher's syndrome. Neurology 1993;43:414-417.
13. Jacobs BC, van DP, Groeneveld JH, Tio-Gillen AP, van der Meché FG. Cytomegalovirus infections and anti-GM2 antibodies in Guillain-Barré syndrome. J Neurol Neurosurg Psychiatry 1997;62:641-643.
14. Irie S, Saito T, Nakamura K, et al. Association of anti-GM2 antibodies in Guillain-Barré syndrome with acute cytomegalovirus infection. J Neuroimmunol 1996;68:19-26.
15. Rees JH, Soudain SE, Gregson NA, Hughes RAC. Campylobacter jejuni infection and Guillain-Barré syndrome. N. Engl J Med 1995;333:1374-1379.
16. Blaser MJ. Epidemiologic and clinical features of Campylobacter jejuni infections. J Infect Dis 1997;Suppl 2:103-105.
17. Speed BR, Kaldor J, Watson J, et al. Campylobacter jejuni/campylobacter coli-associated Guillain-Barré syndrome. Immunoblot confirmation of the serological response. Med J Aust 1987;147:13-16.

18. Mishu B, Ilyas AA, Koski CL, et al. Serologic evidence of previous Campylobacter jejuni infection in patients with the Guillain-Barré syndrome. Ann Intern Med 1993;118:947-953.
19. Jacobs BC, Van Doorn PA, Schmitz PIM, et al. Campylobacter jejuni infections and anti-GM1 antibodies in Guillain-Barré syndrome. Ann Neurol 1996;40:181-187.
20. Jacobs BC, Rothbarth PH, van der Meché FG, et al. The spectrum of antecedent infections in Guillain-Barré syndrome: a case-control study. Neurology 1998;51:1110-1115.
21. Sedano MJ, Calleja J, Canga E, Berciano J. Guillain-Barré syndrome in Cantabria, Spain. an epidemiological and clinical study. Acta Neurol Scand 1994;89:287-292.
22. Bak P. Guillain-Barré syndrome in a Danish county. Neurology 1985;35:207-211.
23. Rees JH, Thompson RD, Smeeton NC, Hughes RA. Epidemiological study of Guillain-Barré syndrome in south east England. J Neurol Neurosurg Psychiatry 1998;64:74-77.
24. Kaldor J, Speed BR. Guillain-Barré syndrome and Campylobacter jejuni: a serological study. Br Med J 1984;288:1867-1870.
25. Yuki N, Yoshino H, Sato S, Miyatake T. Acute axonal polyneuropathy associated with anti-GM1 antibodies following Campylobacter enteritis. Neurology 1990;40:1900-1902.
26. The French Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome. Appropriate number of plasma exchanges in Guillain-Barré syndrome. Ann Neurol 1997;41:298-306.



chapter 06

Summary
Samenvatting

6.1 Summary

In this thesis studies are described concerning epidemiological and clinical aspects of the Guillain-Barré syndrome. GBS is an immune-mediated disease affecting the peripheral nerves resulting in a flaccid paralyis with or without involvement of the sensory system and cranial nerves.
We studied the heterogeneity of GBS and thereby aimed to gain more insight in the pathophysiological mechanism and clinical characterisation of the subgroups.

Chapter 2 describes the epidemiological studies in this thesis. First, in **paragraph 2.1** an overview is given of the main epidemiological features on GBS described in the literature. Two unique epidemiological phenomena, the "swine-flu vaccin incident" and the "Chinese paralytic syndrome" are described in more detail.
Paragraph 2.2. describes the epidemiological survey on GBS in the South-west Netherlands. With 476 patients included in this study, it is one of the largest studies in this field. All patients fulfilling the NINCDS-criteria for GBS were included from all hospitals in the South-west Netherlands from 1987 to 1996. This resulted in a crude incidence rate of 1.18/100.000 inhabitants. The IR increased linearly with age and men were significantly more frequently affected than women. No seasonal preponderance was found, despite the fact that the occurrence of the most frequently associated preceding infections, shows a seasonal fluctuation.
Paragraph 2.3 describes the study on the increasing number of GBS patients on the Carribean island Curaçao. Here again, patients were included fulfilling the NINCDS-criteria for GBS. This resulted in an IR of 1.62 in the period 1987-1991 and an IR of 3.10 in the period 1992-1999, RR 5.22 (95%CI 2.5-10.2, p=0.02). The IR within the year showed a clear seasonal distribution. The patient group was characterised by a severe course with high mortality and a high percentage of pure motor forms. These findings, together with the high percentage of preceding gastro-enteritis reported and the high percentage of positive *C.jejuni* infections in the serum or stools of the patients, suggest a major role of *C.jejuni* in this increase in incidence of GBS in Curaçao.

In **Chapter 3** studies are described on various clinical aspects of GBS. **Paragraph 3.1 and 3.2** concern studies on patients in which GBS runs a mild course, i.e. they remain able to walk unaided at maximum progression of the disease. Until now, most studies on GBS report on severely affected patients. Theories on the pathophysiological mechanism and results of treatment trials are therefore mainly based on severe patients while the retrospective study, described in paragraph 3.1 showed that 28% of the GBS patients is only mildly affected. Patients in this study derived from the survey as described in paragraph 2.2. Because the distribution of the preceding clinical infections did not differ between the mild and severe patients in contrast to the preceded serological proven infections, we suggested that other pathogens could be responsible for the mild forms of GBS. To explore this, we performed a prospective study, which is described in paragraph 3.2. Here, almost all hospitals in the Netherlands reported their GBS patients in a two-year period. This resulted in 139 patients of which 14% was mildly affected. In the collected serum samples, significantly more preceding infections with EBV were found in the mild patients. Furthermore, significantly less anti-ganglioside antibodies were found in the mild group and we concluded that this could be a factor involved in the determination of the course

of the severity of GBS.
In **paragraph 3.3** the treatment of the Miller Fisher patients was evaluated by studying the course of the disease and outcome in 12 patients included in the prospective study as described in paragraph 3.2. Because the course of the disease very much mimics that of GBS and a treatment trial would not be feasible because of the low incidence, we suggest that severely affected MFS patients can be treated with IVIg.

Chapter 4 deals with randomised treatment trials in GBS. First, in **paragraph 4.1** the results are described of a RCT on the effect of additional treatment with methylprednisolon (MP) on standard IVIg treatment. Two hundred twenty-five severely affected patients were included and it was shown that 56% of the placebo group and 68% of the MP-treated group reached the primary endpoint, p=0.06, p=0.05 after adjustment for age. After inclusion of the prognostic factors (age, number of days between onset of weakness and randomisation, MRC-score at entry and preceding CMV infection), the difference between the MP-treated and placebo group reached a p-value of 0.015.
Paragraph 4.2 describes a study on the effect of publication of the former RCT on IVIg treatment in GBS in the Netherlands on the referral pattern of patients in the Netherlands. We hypothesised that the result of the positive treatment effect of IVIg in GBS patients, could be that more patients were treated in small centres because IVIg is available there. This could result in worse outcome for patients admitted in those small centers because GBS can give autonomic dysfunction and a need for mechanical ventilation, i.e. complications and events with which small centers have less experience. Our study showed indeed that fewer patients were referred from small to large centres after the introduction of IVIg. It also showed that this did not result in higher mortality or morbidity in small centers. We therefore concluded that high-risk patients were still transferred properly and thereby the introduction of IVIg has led to a more optimal use of specialised health-care facilities.

Chapter 5 is the general discussion. In this chapter an attempt is made to translate the findings in this thesis to epidemiological concepts on etiology. Before that, some methodological aspects are discussed. Finally, besides general conclusions, guidelines and suggestions for future research are given.

6.2 Samenvatting

Dit proefschrift beschrijft epidemiologische en klinische aspecten van het Guillain-Barré syndroom (GBS). GBS is een immuun-gemedieerde ziekte van de perifere zenuwen. Klinisch resulteert dit in een slappe verlamming van de ledematen, al dan niet gepaard gaande met gevoelstoornissen en uitval van de hersenzenuwen.
De nadruk in dit onderzoek ligt op de heterogeniteit van GBS. Hiermee werd beoogd meer inzicht te krijgen in het pathofysiologische mechanisme van deze ziekte. Tevens werd beoogd te komen tot een verdieping en uitbreiding van de karakterisatie van de diverse klinische subgroepen.

Hoofdstuk 2 beschrijft de epidemiologische studies van dit proefschrift. Allereerst wordt in **paragraaf 2.1** een overzicht gegeven van epidemiologische kenmerken van GBS zoals beschreven wordt in de literatuur. Twee unieke epidemiologische fenomenen worden nader belicht, te weten het incident rond het "swine-flu vaccine" en het zogenaamde "Chinese paralytic syndrome".
Paragraaf 2.2. beschrijft een onderzoek naar het voorkomen van GBS in Zuidwest Nederland. Met het aantal van 476 patiënten, is dit één van de grootste studies geworden op het gebied van de epidemiologie van GBS. Alle patiënten die tussen 1987 en 1996 in ziekenhuizen in Zuidwest Nederland waren opgenomen en die voldeden aan de NINCDS-criteria voor GBS, werden geïncludeerd in de studie. Dit resulteerde in een incidentie van 1.18/100.000 inwoners. De incidentie steeg lineair met de leeftijd en mannen waren significant vaker aangedaan dan vrouwen. Er werd geen seizoensafhankelijkheid gevonden, ondanks het feit dat de bekende voorafgaande infecties bij GBS wel een seizoensvoorkeur kunnen hebben.
Paragraaf 2.3 beschrijft de studie naar het toenemende aantal GBS patiënten op Curaçao. In deze studie werden wederom patiënten geincludeerd die voldeden aan de NINCDS-criteria voor GBS. Voor de periode 1987-1991 werd een incidentie van 1.62/100.000 gevonden, voor de periode 1992-1999 een incidentie van 3.10, RR 5.22 (95%CI 2.5-10.2, p=0.02). De incidentie over het jaar volgde een duidelijke seizoensgebondenheid. De patiënten groep werd gekarakteriseerd door een ernstig beloop met een hoge mortaliteit en een hoog percentage van de pure motore vorm van GBS. Deze bevindingen, samen met het hoge percentage gevonden voorafgaande gastro-enteritis infecties en het hoge percentage gevonden positieve *C.jejuni* serologie, maken een rol voor *C.jejuni* in de stijging van de incidentie van GBS, zeer waarschijnlijk.

In **hoofdstuk** 3 worden de klinische studies van dit proefschrift beschreven. **Paragraaf 3.1 en 3.2** gaan over de GBS patiënten bij wie de ziekte mild verloopt, d.w.z. patiënten die nog in staat zijn zelfstandig te lopen op het dieptepunt van hun ziekte. Tot nu toe zijn de meeste studies betreffende GBS gebaseerd op ernstige patiënten. Theorieën over het pathofysiologische mechanisme en resultaten van therapeutische trials zijn dan ook voornamelijk gebaseerd op deze ernstige patiënten terwijl in de retrospectieve studie, beschreven in paragraaf 3.1, 28% van de GBS patiënten slechts mild aangedaan is. De patiënten uit deze studie zijn afkomstig van de survey beschreven paragraaf 2.2. Omdat de verdeling van de voorafgaande klinische infecties niet verschilde tussen de ernstige en milde patiënten, in tegenstelling tot de serologisch bewezen voorafgaande infecties, is het mogelijk dat er voor het ontstaan van milde GBS andere pathogenen verantwoordelijk zijn. Om dit te onderzoeken is een prospectieve studie verricht waarvan de resultaten beschreven staan in paragraaf 3.2. In deze studie werden bijna alle GBS patiënten in Nederland gedurende 2 jaar geïncludeerd. Dit resulteerde in 139 GBS patiënten van wie 14% mild

aangedaan was. In de verzamelde serum monsters werden significant meer voorafgaande infecties gevonden met het EBV virus in milde patiënten. Verder werden er significant minder anti-ganglioside antilichamen gevonden in de milde groep. Wij concludeerden dan ook dat dit een factor zou kunnen zijn die betrokken is bij het bepalen van de ernst van de ziekte. In **paragraaf 3.3** wordt de behandeling van Miller Fisher patiënten geëvalueerd aan de hand van de bestudering van het beloop van de ziekte en herstel in 12 patiënten die includeerd werden in de prospectieve studie beschreven in paragraaf 3.2. Daar het beloop van de ziekte veel overeenkomsten vertoonde met GBS en een therapeutische trial niet haalbaar geacht wordt vanwege de lage incidentie, werd er geconcludeerd dat ernstige MFS patiënten behandeld zouden kunnen worden met IVIg.

Hoofdstuk 4 beschrijft studies die betrekking hebben op therapeutische trials en GBS. Allereerst worden in **paragraaf 4.1** de resultaten beschreven van de gerandomiseerde dubbelblinde trial naar het additionele effect van methylprednisolon naast standaard IVIg therapie. Tweehonderdvijfentwintig ernstige patiënten werden geincludeerde. Zesenvijftig procent in de placebo groep en 68% in de MP-groep behaalden het primaire eindpunt, p=0.06, p=0.05 na correctie voor leeftijd. Na inclusie van de prognostische factoren in de analyse (leeftijd, aantal dagen tussen begin van de zwakte en randomisatie, MRC-score ten tijde van inclusie en een voorafgaande infectie met het CMV virus), bereikte het verschil tussen de MP groep en de placebo groep een p waarde van 0.015.
Paragraaf 4.2 beschrijft een studie naar het effect van publicatie van een eerdere therapeutische trial in GBS op het verwijzingspatroon van de patiënten. Doordat deze trial aantoonde dat IVIg minstens zo effectief was als plasmaferese, was het nu mogelijk patiënten in kleine centra te behandelen daar IVIg in deze centra beschikbaar is in tegenstelling tot plasmaferese. Dit zou kunnen leiden tot een slechter herstel in deze patiënten omdat GBS kan resulteren in autonome disfunctie en behoefte aan mechanische beademing. Beide zijn complicaties waar kleinere centra weinig ervaring mee hebben. In deze studie werd aangetoond dat er inderdaad minder patiënten verwezen worden van kleine naar grote centra na de introductie van IVIg als therapeuticum. Echter dit resulteerde niet in een stijging van de mortaliteit en morbiditeit in kleine centra. Het bleek dat patiënten met een hoog risico op complicaties nog steeds adequaat worden doorverwezen naar grotere centra. Er werd geconcludeerd dat de introductie van IVIg in Nederland heeft geleid tot een meer optimaal gebruik van zorginstellingen.

Hoofdstuk 5 is de algemene discussie. Hierin is getracht de bevindingen in dit proefschrift te vertalen naar epidemiologische concepten wat betreft het ontstaan van het Guillain-Barré syndroom. Allereerst worden enkele methodologische aspecten besproken. Verder worden suggesties gedaan voor eventueel toekomstig onderzoek.

List of abbreviations

AIDP	acute inflammatory demyelinating polyneuropathy
AMAN	acute motor axonal neuropathy
AMSAN	acute motor-sensory axonal neuropathy
CDC	centers for disease control and prevention
CIDP	chronic inflammatory demyelinating polyneuropathy
C.jejuni	Campylobacter jejuni
CMV	Cytomegalovirus
CSF	cerebrospinal fluid
EBV	Epstein-Barr virus
EMG	electromyogram
F-score	functional grading score
GBS	Guillain-Barré syndrome
ICD	international classification of disease
IR	incidence rate
IVIg	intravenous immunoglobulin
PE	plasmapheresis
MFS	Miller Fisher syndrome
MP	methylprednisolone
Mpneu	Mycoplasma pneumoniae
MRC	medical research council
NINCDS	National Institute of Neurological Disorders and Stroke
PCB	pharyngo-cervico-brachial
RCT	randomised controlled trial

PIETER VAN DOORN,
Ik begon als student vol bewondering en onder de indruk van je kennis en heldere communicatie. Geen student meer, maar nog wel onder de indruk. In de loop der jaren is er voor het éénrichtingsverkeer, een tweerichtingsverkeer in de plaats gekomen waarbij je het gevoel geeft dat mijn ervaring en kennis waarde hebben. Dat is een waardevolle eigenschap voor een "baas". Verder heb je grote input geleverd aan mijn proefschrift. Het feit dat milde patiënten aandacht krijgen is dankzij jou. Tot slot, voor mij één van de belangrijkste eigenschappen die een mens kan bezitten:
Je hebt humor!

MONICA,
Voor hulp bij mijn werk kon ik altijd bij je aan kloppen, en belangrijker, ook daarbuiten. Met sommige mensen klikt het gewoon .....

PROFESSOR FRANS VAN DER MECHÉ,
Grote vrijheid binnen duidelijke grenzen! Vrijheid om de opleiding tot Klinisch Epidemioloog te volgen, om het Curaçao project te starten. Uw complete overzicht van het onderzoek, zowel inhoudelijk, methodologisch als statistisch zorgde voor consistentie en heeft bijgedragen aan de kwaliteit van dit proefschrift.

ERIK,
Liefde
Fenne
Humor
Steun
De man achter deze vrouw
Dat jij jij bent
Computerheld!

Dit proefschrift werd mede mogelijk gemaakt door.....

SIGRID & SONIA
Bedankt!

Sieg, ook voor de jaren lange vriendschap.
Sonia, ook voor de pas korte vriendschap.

NEUROLOGEN EN GBS PATIËNTEN IN NEDERLAND EN CURAÇAO,
Zonder uw medewerking was het onderzoek niet mogelijk geweest. Dankzij u kunnen we meer betekenen voor de GBS patiënten van de toekomst.

MAMA,
Altijd was je betrokken bij de dingen die ik ondernam, vol belangstelling en trots, zonder je verwachtingen op te leggen. Je bent daarin mijn voorbeeld. Dat geldt ook voor je optimisme en (veer) kracht!

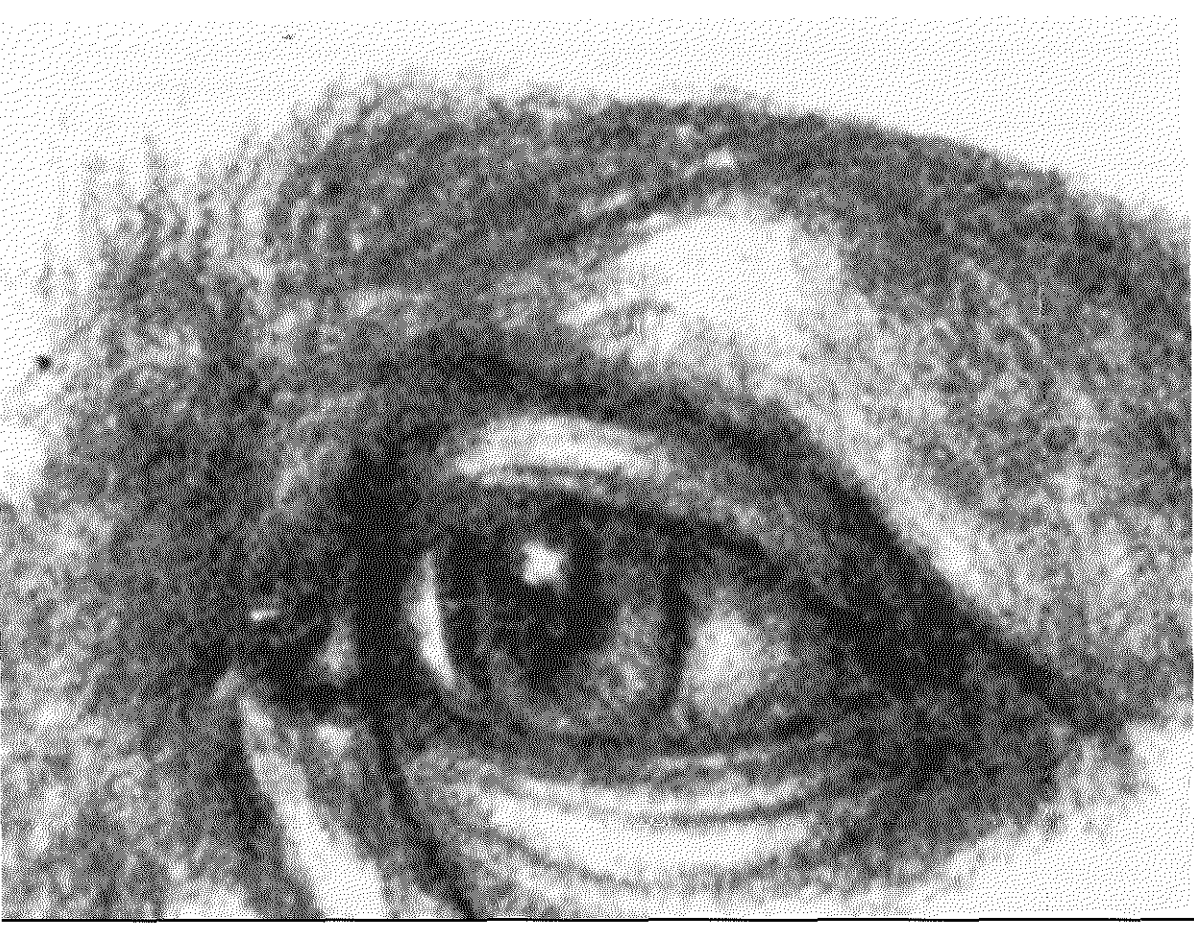
MANNEN VAN DE NEURO-IMMUNOLOGIE,
Bart; voor je discussies, al dan niet wetenschappelijk verantwoord.
Dragan; voor je puurheid en vriendschap
Ingemar; voor je introductie en begeleiding op je mooie eiland, jouw innerlijke rust is een voorbeeld.
Marcel; jaren achter de rug en nog jaren te gaan samen, jij bent lol met een ruggengraat.
Wim; mijn wetenschappelijk wederhelft, wij zijn zó verschillend in alle opzichten, dat zal wel de formule zijn geweest voor onze goede samenwerking en pret.

COLLEGA'S VAN DE 22E,
In de afgelopen 4 jaar heb ik typische gevallen van leed maar ook van lief meegemaakt. Jullie hebben daar veel van meegemaakt en meebeleefd. Het heeft mij veel steun gegeven, heel erg bedankt. Het is een raar, samengeraapt kluppie bij elkaar op de 22e, die de betonnen omgeving en de TL-verlichting waarschijnlijk allang niet meer bewust is. Gelukkig is er wel altijd oog en oor voor elkaar, een soort gekke Familie Knots met Hanneke, Monica en Dirk als mama en papa.

ARTS-ASSISTENTEN EN STAFLEDEN, NEUROLOGIE ERASMUS MC,
Voor de tijd en ruimte die ik heb gekregen om mijn proefschrift af te maken en de goede en inspirerende begeleiding die ik tot nu toe heb gekregen in mijn prille bestaan als assistent-in-opleiding.

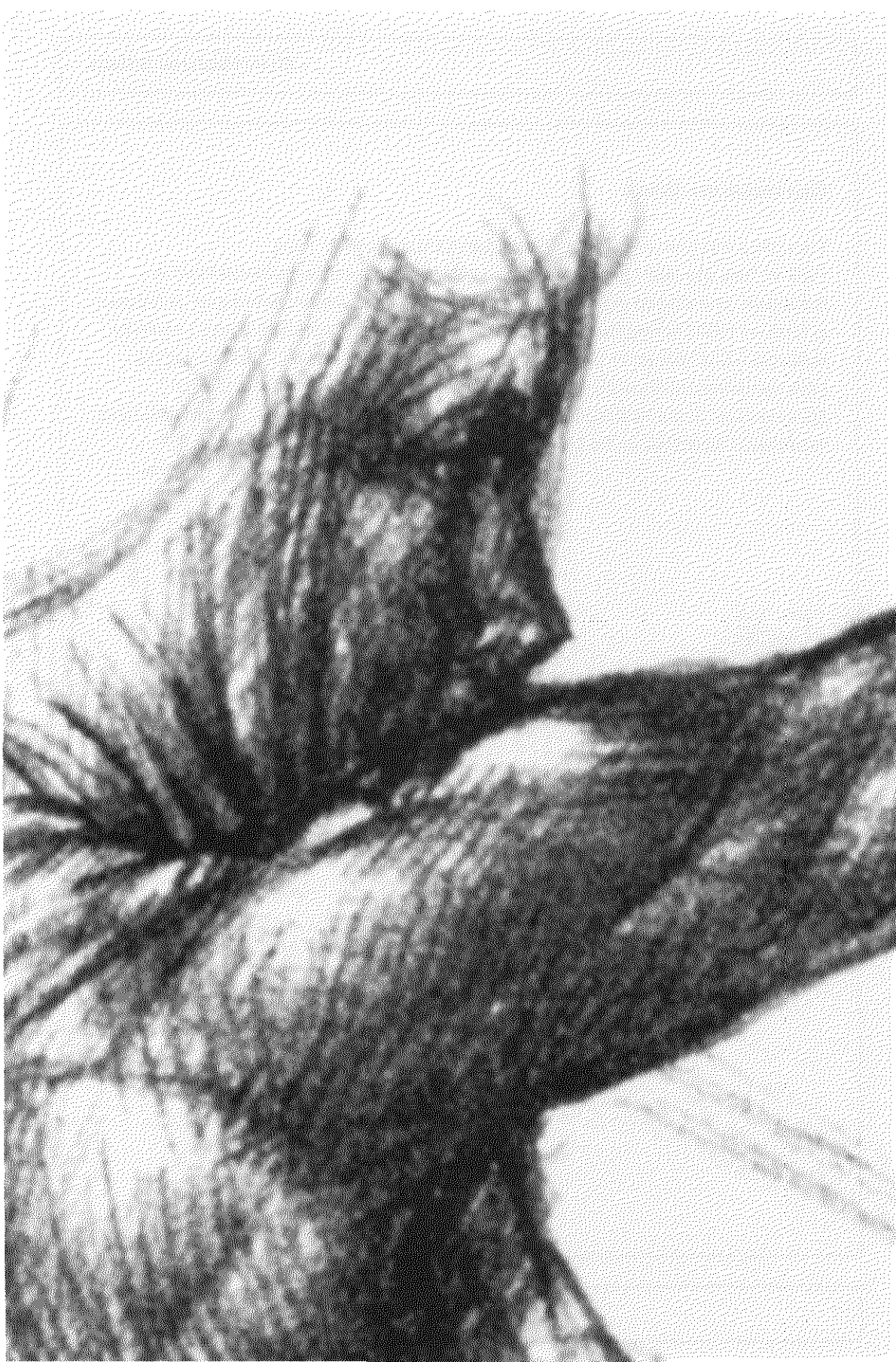
PAUL SCHMITZ,
Ongelooflijk veel middagen hebben wij samen doorgebracht! Ik zat erbij en keek ernaar en heb geleerd.
Je hebt niet alleen door je statistische bijdrage mijn onderzoeken vaak op een hoger plan gebracht maar ook mij methodologisch scherp en altijd op het juiste ogenblik aan de tand gevoeld.

STUDIO EIGENWIJS,
Lieve Ellen bedankt voor het strak en eigenwijs maken van mijn levenswerk.



Curriculum Vitae

The author was born in Bemmel on the 15th of February 1970. From 1983 to 1988 she attended the "Christelijke Scholengemeenschap Melanchthon" in Rotterdam. She studied medicine at the "Rijksuniversitair Centrum Antwerpen" in Belgium in 1988. In 1989 she returned to Rotterdam to study medicine at the Erasmus University Rotterdam. She finished in 1996 and started the research underlying this thesis at the Erasmus University Rotterdam. In 2000 she finished the study "Master of Clinical Epidemiology" at the Netherlands Institute for Health Sciences. In May 2001 she started a residency in Neurology at the Erasmus Medical Center Rotterdam.



List of publications

van Koningsveld R, van Doorn PA , Schmitz PI, Ang CW, van der Meché FG. Mild forms of Guillain-Barré syndrome in an epidemiologic survey in The Netherlands.
Neurology 2000;54:620-625.

van Koningsveld R, van Doorn PA , Schmitz PI, van der Meché FG. Changes in referral pattern and its effect on outcome in patients with Guillain-Barré syndrome.
Neurology 2001;56:564-566.

Van Koningsveld R, Rico R, Gerstenbluth I, Schmitz PI, Ang CW, Merkies IS, Jacobs BC, Halabi Y, Endtz HP, van der Meché FG, van Doorn PA. Gastroenteritis-associated Guillain-Barré syndrome on the Caribbean island Curaçao.
Neurology 2001;56:1467-1472.

van Koningsveld R, Schmitz PIM, Ang CW, Groen J, Osterhaus ADME, Van der Meché FGA, Van Doorn PA. Infections and course of the disease in mild forms of Guillain-Barré syndrome.
Accepted for publication by Neurology

Martina IS, van Koningsveld R, Schmitz PI, van der Meché FG, van Doorn PA. Measuring vibration threshold with a graduated tuning fork in normal aging and in patients with polyneuropathy. European Inflammatory Neuropathy Cause and Treatment (INCAT) group.
J Neurol Neurosurg Psychiatry 1998;65:743-747.

van der Pol WL, van den Berg LH, Scheepers RH, van der Bom JG, van Doorn PA, van Koningsveld R, van den Broek MC, Wokke JH, van de Winkel JG. IgG receptor IIa alleles determine susceptibility and severity of Guillain-Barré syndrome.
Neurology 2000;54:1661-1665.

Ang CW, van Doorn PA, Endtz HP, Merkies IS, Jacobs BC, de Klerk MA, van Koningsveld R, van der Meché FG, van der Pol WL, van den Berg LH, Scheepers RH, van der Bom JG, van den Broek MC, Wokke JH, van de Winkel JG. A case of Guillain-Barré syndrome following a family outbreak of Campylobacter jejuni enteritis.
J Neuroimmunol 2000;111:229-233.

Havelaar AH, de Wit M, van Koningsveld R, van Kempen E. Health burden in the Netherlands due to infection with thermophilic Campylobacter spp.
Epidemiol Infect 2000;125:505-522.