Campylobacter jejuni Infections and Anti-GM1 Antibodies in Guillain-Barré Syndrome

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The group of patients with Guillain-Barré syndrome (GBS) is very heterogenous with regard to antecedent infections, immunological parameters, clinical manifestations, and response to treatment. In this study, the presumed pathogenic factors anti-GM1 antibodies and *Campylobacter jejuni* infections were related to the clinical characteristics. Serum from 154 patients with GBS, 63 patients with other neurological diseases (OND), and 50 normal controls (NC) were tested for the presence of antibodies against GM1 and *C. jejuni*. Anti-GM1 antibodies were detected in 31 (20%) GBS patients, 5 (8%) OND patients, and in none of the NC. Evidence for a recent *C. jejuni* infection was found in 49 (32%) GBS patients and less often in OND patients (11%) or NC (8%). In GBS patients, the presence of anti-GM1 antibodies was significantly associated with *C. jejuni* infections. The subgroup of GBS patients with anti-GM1 antibodies suffered more often from a rapidly progressive and more severe neuropathy with predominantly distal distribution of weakness, without deficits of cranial nerves or sensory disturbances. The subgroup with *C. jejuni* infection also more often had a severe pure motor variant of GBS. Recovery of the patients with anti-GM1 antibodies and *C. jejuni* infections was not as good after plasma exchange compared with intravenous immunoglobulins.

Jacobs BC, van Doorn PA, Schmitz PIM, Tio-Gillen AP, Herbrink P, Visser LH, Hooijkaas H, van der Meché FGA. *Campylobacter jejuni* infections and anti-GM1 antibodies in Guillain-Barré syndrome. Ann Neurol 1996;40:181–187

The Guillain-Barré syndrome (GBS) is a subacute polyradiculoneuropathy resulting in progressive weakness and areflexia [1]. Although GBS is accepted as a disease entity, a large heterogeneity exists between individual GBS patients with regard to the severity and distribution of weakness, the degree of sensory deficit, the extent of demyelination and axonal degeneration, and the response to treatment [2, 3]. The clinical and electrophysiological manifestations may, to some extent, be determined by biological factors like age, antecedent infections, and immunological parameters. Therefore, laboratory characteristics added to clinically defined cases may help to delineate specific subgroups [3].

Campylobacter jejuni has recently been identified as a major cause of antecedent infections in GBS patients [4–14]. Some reports suggest that GBS patients with *C. jejuni* infections suffer from a more severe form of GBS [4, 6, 10], with less sensory deficit [6, 13, 14] and with poorer recovery [6, 10, 13], although this has not been found by others [8, 11].

Antibodies against the ganglioside GM1 have been demonstrated in different proportions (9–78%) of GBS patients [6, 7, 10–19]. The presence of serum anti-GM1 antibodies was found to be associated with a more severe [6, 13], pure motor variant of GBS [6, 14, 15, 19], with more extensive axonal degeneration [6, 15, 16, 19] and worse recovery [6, 7, 13, 15, 17, 19], although others have not found these associations [10, 11]. There is also still controversy on whether GBS patients with anti-GM1 antibodies suffer more frequently from an antecedent *C. jejuni* infection [6, 7, 12, 13] or not [10, 11].

In this retrospective study, we determined the presence of antibodies against *C. jejuni* and GM1 in the serum of 154 GBS patients and analyzed whether the presence of these antibodies is related to a subgroup of patients with distinct clinical manifestations and response to treatment.

Patients and Methods

Serum samples were obtained from GBS patients who were included either in the Dutch GBS trial, comparing the therapeutic effect of plasma exchange (PE) and intravenous immunoglobulins (IVIg) [20], or in the pilot study, evaluating

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Received Sep 20, 1995, and in revised form Dec 20, 1995, and Feb 28, 1996. Accepted for publication Feb 28, 1996.

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the effect of methyl prednisolone and IVIg (MP-IVIg) [21]. All patients fulfilled the criteria for GBS [1], were unable to walk 10 m independently, and were admitted within 2 weeks of onset of weakness. The functional score and the Medical Research Council (MRC) sum score [22], ranging from 60 (normal) to 0 (tetraparalytic), were determined at study entry and subsequently at 16 time points during a follow-up period of 6 months. The rapidity of progression was indicated by the number of days from the onset of weakness to the moment of maximal weakness. The severity of weakness was indicated by the lowest MRC sum score. From the 172 GBS patients who participated in these two studies, pretreatment serum samples of 154 patients were available for serological testing. The 18 excluded cases did not differ from the other patients regarding their clinical manifestations and course of disease. Sixty-seven patients were treated with PE, 66 with IVIg, and 21 with MP-IVIg. Serum samples from 63 patients with other neurological diseases (OND) and from 50 normal controls (NC) were also tested. The group of OND included patients with chronic inflammatory demyelinating polyneuropathy (CIDP) (16), multiple sclerosis (MS) (17), chronic polyneuropathy (PNP) other than CIDP (15) [PNP and paraproteinemia (5), hereditary motor and sensory neuropathy (2), pure sensory PNP (3), pure motor PNP (3), sensory motor PNP (2)], and 15 patients with various other disorders [CVA (3), myasthenia gravis (3), amyotrophic lateral sclerosis (ALS) (3), others (6)]. All samples were taken from patients within their active phase of disease before treatment was started and were tested without knowledge of the clinical data.

Detection of Antibodies Against C. jejuni

Serum antibodies against *C. jejuni* were determined by an indirect enzyme-linked immunosorbent assay (ELISA) for IgG [23] and by antibody class capture ELISA for IgM and IgA antibodies [24]. The presence of anti–*C. jejuni* antibodies was expressed as a ratio of OD between a test sample and the cutoff serum sample, which was included in all tests. A ratio for IgM and/or IgA antibodies higher than 1.0 was considered as evidence for a recent *C. jejuni* infection [23]. A ratio of IgG antibodies higher than 7.0, indicating a high titer, was considered suggestive for a recent *C. jejuni* infection [23].

Detection of Antibodies Against GM1

ENZYME-LINKED IMMUNOSORBENT ASSAY. IgM, IgG, and IgA antibodies against GM1 were tested in an ELISA as described previously [25]. For each isotype a serum sample from a GBS patient with a high titer of anti-GM1 antibodies was used as a positive control in each assay. To correct for interassay variations all extinctions were normalized against the positive control serum. Serum samples with an OD of more than 3 SD above the mean value of 50 NC sera were tested in a thin-layer chromatography (TLC) overlay to exclude antibody binding to contaminants in the GM1 preparation. Positive serum samples were tested again in ELISA, using serial dilutions starting at 1:100. The reciprocal of the highest dilution that resulted in an OD higher than the cutoff value was then taken to be the titer.

THIN-LAYER CHROMATOGRAPHY OVERLAY. TLC was performed on aluminum-backed Kieselgel 60 $WF_{254}S$ high-performance TLC plates (Merck, Darmstadt, Germany) that were coated with 500 pmol of GM1 and developed in chloroform/methanol/0.25% $CaCl_2$ in water (50:40:10, by volume). After chromatography, the plates were air dried and dipped in a solution of 0.1% polyisobutylmethacrylate in *n*-hexane. The plates were air dried and blocked with phosphate-buffered saline (PBS)/1% bovine serum albumin (BSA) for 1 hour and incubated with serum diluted 1:100 in PBS/0.1% BSA for 4 hours at 4°C. After washing with PBS, the plates were incubated for 2 hours at 4°C with peroxidase-conjugated goat anti-human IgM (μ-chain specific) or IgG (γ-chain specific) or IgA (α-chain specific) (Sigma) diluted 1:2,500 in PBS/0.1% BSA and washed with PBS. The plates were developed for 10 to 150 seconds using an enhanced chemiluminescence procedure (Amersham, UK).

Statistical Analysis

Differences in proportions were tested with the χ^2 test without continuity correction and differences in medians were tested with the Wilcoxon–Mann–Whitney *U* test. The time for patients to reach independent locomotion was analyzed by the Kaplan–Meier method and the log-rank test.

Results

IgM and/or IgA antibodies and/or high titers of IgG antibodies against *C. jejuni* were detected in 32% of 154 GBS patients, 11% of 63 OND patients, and 8% of 50 NC (Table 1). According to this criterion, recent *C. jejuni* infections were significantly more often present in GBS patients than in patients with OND and NC. The OND patients with a recent *C. jejuni* infection suffered from CIDP (2), MS (3), pure sensory PNP (1), or CVA (1). Moreover, IgM and/or IgA antibodies, a more specific but less sensitive criterion for recent infection, were also more often found in GBS patients than in OND patients and NC (see Table 1).

Elevated titers of anti-GM1 antibodies were detected in the serum of 31 (20%) of the 154 GBS patients. IgM anti-GM1 antibodies were found in 16 (10%), IgG in 22 (14%), and IgA in 11 (7%) GBS patients (Fig 1). Twelve patients had elevated titers of two or three classes and 6 patients of three classes. GBS patients with anti-GM1 IgA antibodies, but without IgM or IgG antibodies, were not found. Anti-GM1 antibodies were found in 5 (8%) of 63 OND patients but not in NC (see Fig 1). Anti-GM1 IgM antibodies were present in 1 patient with CIDP and 3 patients with a chronic pure motor PNP other than CIDP and IgA antibodies in another patient with CIDP.

Serological evidence for a recent *C. jejuni* infection was more often found in the GBS patients with anti-GM1 antibodies (65%) than in the patients without anti-GM1 antibodies (24%) ($p < 0.001$) (Table 2). Anti-GM1 antibodies of the IgM, IgG, and IgA isotype were all associated with *C. jejuni* infection ($p < 0.001$)

Table 1. Prevalence of Elevated Titers of IgM and IgA and High Titers of IgG Antibodies Against C. jejuni *in Patients with Guillain-Barré Syndrome (GBS), Patients with Other Neurological Diseases (OND), and Normal Controls (NC)*

Anti–*C. jejuni* Antibodies	GBS (n = 154)	OND (n = 63)	p_1	NC (n = 50)	p_2
IgM	28 (18%)	5 (8%)	0.056	1 (2%)	**0.004**
IgA	34 (22%)	4 (6%)	**0.006**	2 (4%)	**0.004**
IgG	29 (19%)	2 (3%)	**0.003**	3 (6%)	**0.03**
IgM and/or IgA	42 (27%)	7 (11%)	**0.01**	2 (4%)	**0.001**
IgM, IgA, and/or IgG	49 (32%)	7 (11%)	**0.002**	4 (8%)	**0.001**
Two or three isotypes	29 (19%)	4 (6%)	**0.02**	1 (2%)	**0.004**

p_1 = p value for GBS patients versus OND patients.
p_2 = p value for GBS patients versus NC.

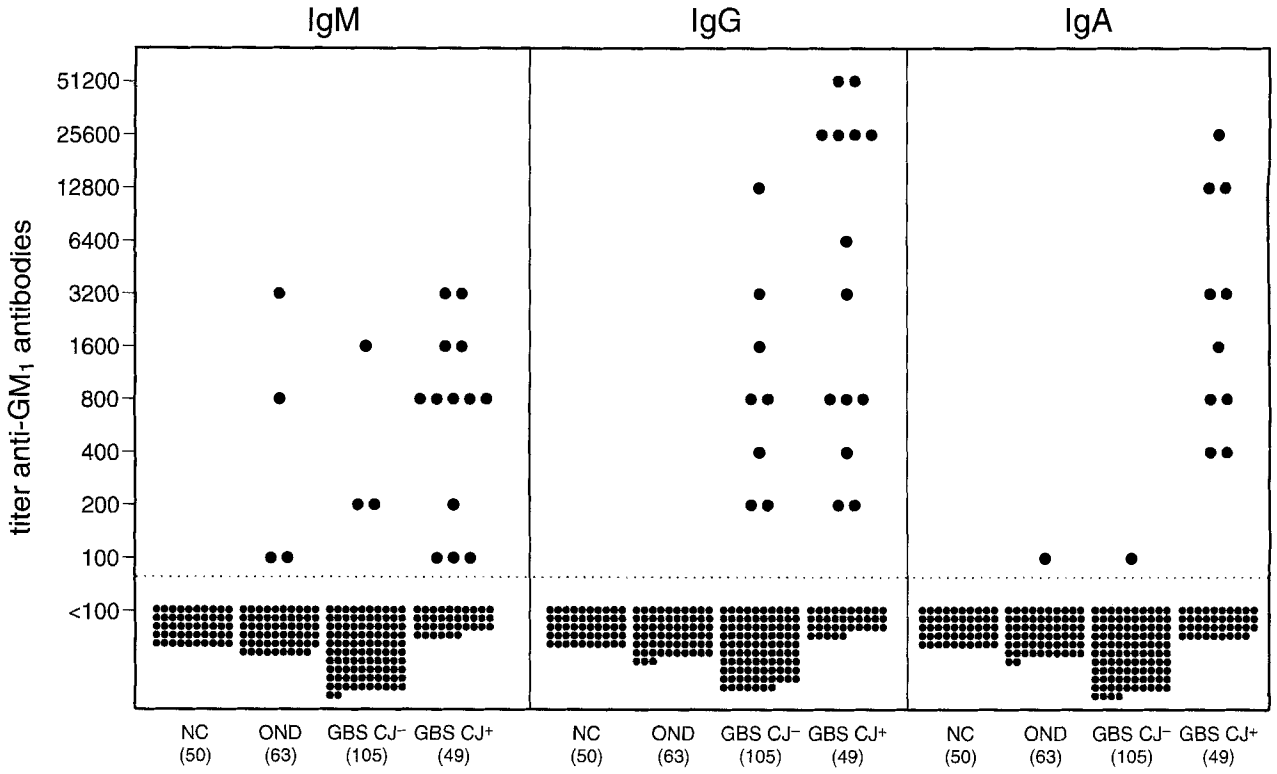

Fig 1. Titer of serum anti-GM1 antibodies in patients with Guillain-Barré syndrome (GBS), other neurological diseases (OND), and normal controls (NC). GBS patients were subdivided in patients with Campylobacter jejuni *infection (CJ+) and without (CJ−).*

(see Fig 1). IgM and/or IgA antibodies against *C. jejuni* were also associated with anti-GM1 antibodies ($p < 0.001$). In OND patients, no association was found between anti-GM1 antibodies and *C. jejuni* infections. In additional experiments, it was demonstrated that anti-GM1 antibodies are not absorbed by the *C. jejuni* protein extract used to determine the *C. jejuni* serology (data not shown).

The clinical characteristics of GBS patients associated with antecedent *C. jejuni* infection and anti-GM1 antibodies are given in Table 2. No differences were found in sex and age between the GBS patients with or without *C. jejuni* infections or anti-GM1 antibodies. The presence of IgM and/or IgA antibodies against *C. jejuni* only was associated with a predominantly distal weakness without cranial nerve impairment in addition to a more severe maximal weakness with less paresthesias and sensory deficits (data not shown).

The clinical manifestations associated with the presence of anti-GM1 antibodies were predominantly re-

Table 2. Clinical Characteristics of GBS Patients Associated with C. jejuni *Infection and Anti-GM1 Antibodies*

	C. jejuni Infections			Anti-GM1 Antibodies		
	+ (n = 49)	− (n = 105)	*p*	+ (n = 31)	− (n = 123)	*p*
Diarrhea	19 (39%)	6 (6%)	**<0.001**	12 (39%)	13 (11%)	**<0.001**
MRC sum score at entry[a]	36 (0–52)	41 (8–56)	**0.049**	32 (0–50)	41 (12–56)	**0.001**
Days to lowest MRC sum score[a]	7 (2–21)	9 (2–21)	0.48	6 (1–18)	9 (3–21)	**<0.001**
Lowest MRC sum score[a]	30 (0–50)	35 (0–55)	**0.03**	20 (0–50)	36 (0–55)	**0.01**
Tetraplegia	13 (27%)	12 (11%)	**0.02**	10 (32%)	15 (12%)	**0.007**
Predominantly distal weakness	23/48 (48%)	32/101 (32%)	0.055	19 (61%)	36/118 (31%)	**0.002**
Cranial nerve impairment	25 (51%)	67 (64%)	0.13	12 (39%)	80 (65%)	**0.008**
Sensory deficit at entry	23 (47%)	66/100 (66%)	**0.03**	13/30 (43%)	76/119 (64%)	**0.04**
Paresthesias	32 (65%)	92 (88%)	**0.001**	17 (55%)	107 (87%)	**<0.001**
Anti-GM1 antibodies	20 (41%)	11 (10%)	**<0.001**	—	—	—
C. jejuni infections	—	—	—	20 (65%)	29 (24%)	**<0.001**

[a]Median (2.5–97.5% percentile). The MRC sum score ranges from 60 (normal) to 0 (tetraparalytic).

GBS = Guillain-Barré syndrome; MRC = Medical Research Council.

lated to the IgG and IgA class. GBS patients with anti-GM1 IgM antibodies did not differ from patients without these antibodies with respect to days to peak severity, tetraplegia, distribution of weakness, and cranial and sensory nerve impairment.

In the group of GBS patients with a recent *C. jejuni* infection, 24 patients were treated with PE, 22 with IVIg, and 3 with MP-IVIg. A longer median time to recover in the subgroup with *C. jejuni* infection was only found in the patients treated with PE ($p = 0.003$), and not in the patients treated with IVIg or MP-IVIg. The patients with *C. jejuni* infections had a significantly shorter median time to reach independent locomotion after IVIg or MP-IVIg than after PE (Fig 2b). In the patients without *C. jejuni* infections, there was no difference between the treatment modalities (Fig 2a). Patients with only IgM and/or IgA antibodies against *C. jejuni* also had a better prognosis after IVIg or MP-IVIg than after PE (data not shown).

In the group of GBS patients with anti-GM1 antibodies, 10 were treated with PE, 13 with IVIg, and 8 with MP-IVIg. In the subgroup treated with PE, the median time to recover was longer in the patients with anti-GM1 antibodies (>181 days) than in those without (69 days) ($p = 0.03$). In the group of patients treated with IVIg alone, recovery was not associated with the presence of anti-GM1 antibodies. The patients with anti-GM1 antibodies had a significantly shorter median time to recover after IVIg or MP-IVIg than after PE (Fig 2d). In patients without anti-GM1 antibodies, there was no difference between the treatment modalities (Fig 2c). The presence of anti-GM1 antibodies of the IgM, IgG, and IgA class were all negative prognostic factors in the patients treated with PE.

Discussion

In this study on 154 patients with GBS, the presence of *C. jejuni* infections and anti-GM1 antibodies seems to define a clinically distinct subgroup of patients. These patients more often had a severe and predominantly distal weakness without sensory deficits or cranial nerve impairment. This clinical picture resembles, at least in part, multifocal motor neuropathy (MMN) and the acute motor axonal neuropathy (AMAN) in China, two disorders with predominantly distal weakness and, in general, without sensory or cranial nerve involvement that are also associated with the presence of anti-GM1 antibodies [26, 27]. Such similarity indicates a possible role for anti-GM1 antibodies in the pathogenesis of motor nerve impairment. This is supported by the finding of a higher concentration of GM1 in myelin of human motor nerves compared with sensory nerves [28] and by the binding of anti-GM1 antibodies with peripheral nerves at the node of Ranvier [29]. In addition, monoclonal antibodies against GM1 from patients with MMN can induce conduction block in a mouse phrenic nerve/diaphragm preparation leading to unresponsiveness [30]. However, even in the subgroup of GBS patients with anti-GM1 antibodies, heterogeneity of clinical manifestations exists. This clinical diversity may be related to the heterogeneity of anti-GM1 antibodies regarding the fine specificity, titer, avidity, isotype, and capacity to bind complement.

The presence of *C. jejuni* infections and anti-GM1 antibodies seems to define a distinct subgroup of patients in which PE is less effective than IVIg or MP-IVIg. This parallels MMN, since these patients also do not respond to PE [26] and are claimed to recover after

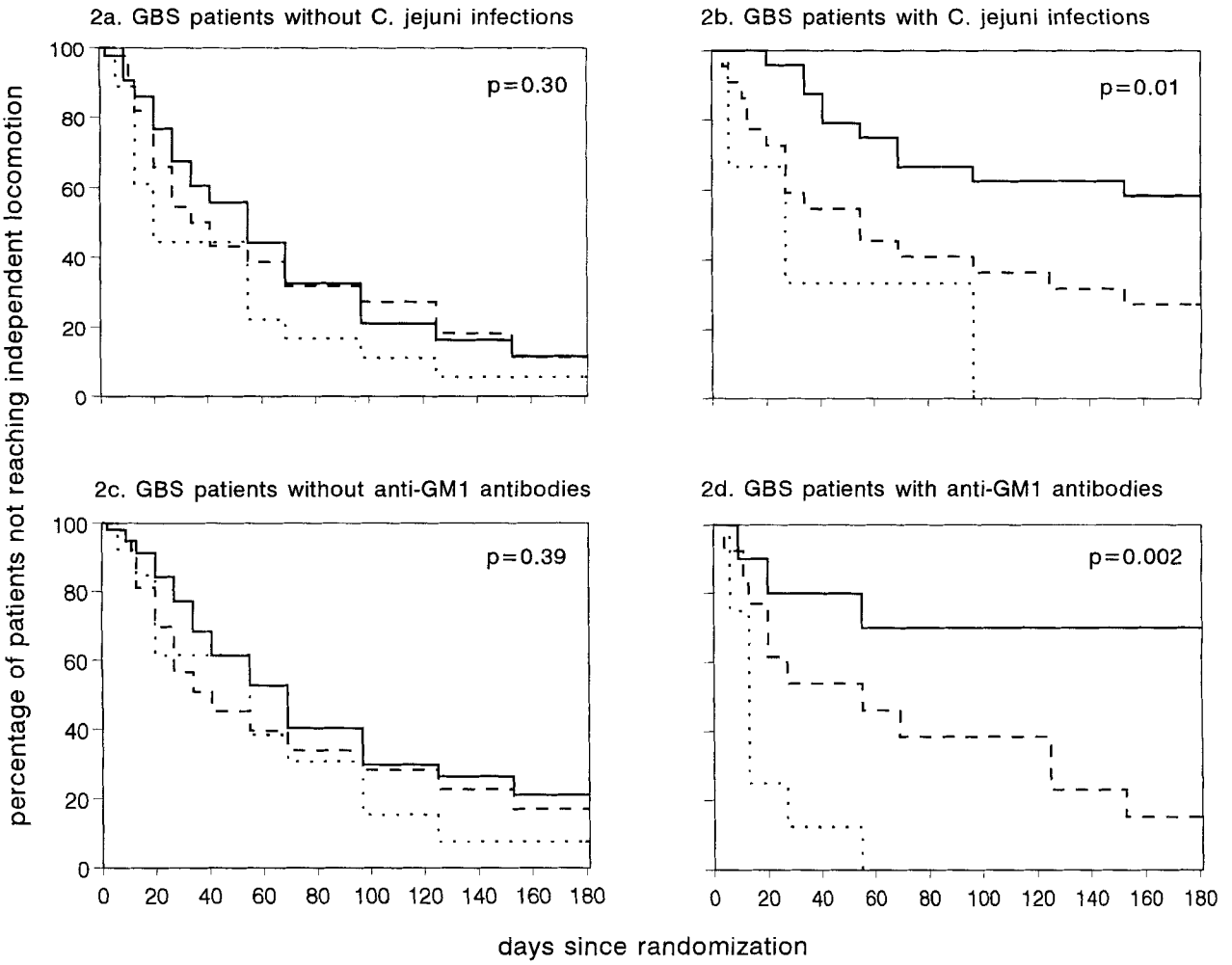

Fig 2. Kaplan–Meier curves indicating the percentage of patients who were not able to walk independently for 10 m. Follow-up during 181 days of patients treated with plasma exchange (_____), intravenous immunoglobulins (IVIg) (_ _ _), or methyl prednisolone and IVIg (. . . . .).

IVIg [31, 32]. However, our analysis is retrospective and includes only a small group of patients treated with MP-IVIg. Prospective studies are needed to confirm these findings.

In the GBS patients, the presence of anti-GM1 antibodies was significantly associated with antecedent *C. jejuni* infections ($p < 0.001$). This finding supports the hypothesis that antibodies against GM1 in GBS patients are induced during the antecedent infection with *C. jejuni*. The high percentage (91%) of recent *C. jejuni* infections in GBS patients with IgA anti-GM1 antibodies further strengthens the relation with enteric infections. Recently, it has been shown that lipopolysaccharides from a *C. jejuni* isolate from a GBS patient with anti-GM1 antibodies express a GM1-like structure [33]. Also, only specific *C. jejuni* strains are recognized by anti-GM1 antibodies from the serum of GBS patients [34]. A similar observation has been made in *C. jejuni* isolates from patients with Miller Fisher syndrome (MFS) that bind specifically with anti-GQ1b antibodies [25].

The association between anti-GM1 antibodies and recent *C. jejuni* infections has been demonstrated in some studies [6, 7, 12, 13] but not in others [10, 11]. In our study, involving a large group of GBS patients, the association is significant but not absolute. This may explain why a significant association was not found in studies investigating smaller groups of GBS patients. Besides, the patients in our study suffered from a relatively severe variant of GBS. Since anti-GM1 antibodies and *C. jejuni* infections are both more frequently found in patients with severe GBS, the association between anti-GM1 antibodies and *C. jejuni* infections could more easily be demonstrated in this group of

patients. The association also depends on the sensitivity and specificity of the assays used to detect the antibodies.

There are several explanations for the finding that not all GBS patients with anti-GM1 antibodies had a *C. jejuni* infection. First, some GBS patients may have the same epiphenomenic or nonpathogenical anti-GM1 antibodies that are also found in low titers in some normal controls. Second, it is possible that other infectious agents also express GM1-like structures. Anti-GM1 IgG antibodies have been demonstrated in a patient with a chronic PNP after *Mycoplasma pneumoniae* infection [35]. Third, mechanisms other than infections may be involved in the induction of anti-GM1 antibodies.

Some GBS patients have *C. jejuni* infections without having anti-GM1 antibodies. There are several explanations for this. First, the recent *C. jejuni* infections in these patients may be unrelated to GBS, since these were also found in 8% of NC. Second, the particular *C. jejuni* may not express a GM1-like structure, since the presence of this epitope is strain specific [34]. These GBS patients could have had an infection with a *C. jejuni* strain expressing structures that mimic neural components other than GM1. In these patients, T lymphocytes or antibodies against other neural epitopes can be involved in the pathogenesis of GBS. This is supported by the finding in animals that antibodies against peripheral nerve proteins are induced after immunization with *C. jejuni* [36, 37]. Other infections and antibodies against other glycolipids may further delineate the clinical heterogeneity in GBS.

This research project was supported by grants from the Prinses Beatrix Fonds (no. 90-3161), the Willem H. Kröger Stichting (no. 92-011), and Baxter, Hyland Division.

We gratefully thank M. A. de Klerk for his technical assistance.

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