ORIGINAL ARTICLE

Prospective study on anti-ganglioside antibodies in childhood Guillain-Barré syndrome

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Background: Antiganglioside antibodies have been reported to play a part in the pathophysiology of Guillain-Barré syndrome (GBS).

Aims: To investigate the prevalence and correlation of anti-ganglioside antibodies with clinical data in children with GBS in a multicentre clinical trial.

Methods: Immunoglobulin (Ig)G and IgM to GM1, GM1b, GD1a, GalNAc-GD1a, GD1b, GT1a, and GQ1b were measured by ELISA in sera obtained before treatment. In addition, serological testing for *Campylobacter jejuni* was carried out. In parallel, a group of adults with GBS and a control group of children without GBS or other inflammatory diseases were evaluated.

Results: Sera from 63 children with GBS, 36 adults with GBS and 41 children without GBS were evaluated. Four of the children with GBS showed positive IgG to GM1, in one case combined with anti-GalNAc-GD1a and in one with anti-GD1b. Two others showed isolated positive IgG to GD1b and GT1a. One showed increased anti-GalNAc-GD1a IgM. In 5 of the 63 children, serological evidence of a recent infection with *C. jejuni* was found, and this correlated significantly with the raised antibodies ($p=0.001$). In the control group without GBS, no child showed positive IgG, but one showed anti-GalNAc-GD1a IgM. Compared with the adults with GBS, the frequency of antibodies in children was insignificantly lower. In our study, patients with positive antibodies did not show a more severe GBS course or worse outcome than those who were seronegative, and we could not show an increased incidence of axonal dysfunction.

Conclusions: In some children with GBS, one can detect raised IgG against various gangliosides, similar to that in adults. A recent infection with *C. jejuni* is markedly associated with the presence of these antibodies. However, in contrast with what has been reported in adults, in this study we were unable to show a negative effect of these findings on the clinical course.

Guillain-Barré syndrome (GBS) is an acute immunemediated polyneuropathy occurring mainly in adults, but with a lower incidence of 0.4–0.6/100 000 in children as well.¹ The disease often gives rise to severe, life-threatening disability, but in childhood after a variable course most patients recover without residual disability. A large number of studies in the past few years have shown that antiganglioside antibodies can play an important part in the pathophysiology and outcome of GBS and its variants.^{2–3} Most importantly, antibodies to GM1, GM1b, GD1a and GalNAc-GD1a gangliosides are associated with preceding diarrhoea, *Campylobacter jejuni* aetiology, axonal injury, a more severe course and a worse outcome.^{4–6} Other antiganglioside antibodies correlate specifically with different subtypes of the disease, such as anti-GQ1b immunoglobulin (Ig)G in Fisher's syndrome and anti-GT1a in the pharyngeal-cervical-brachial variant.^{7–8} These data have usually been obtained from studies on adults. We aimed to prospectively investigate the prevalence of these anti-ganglioside antibodies in children with GBS, in comparison with healthy children and adults with GBS. Furthermore, we tried to clarify their association with electrophysiological findings, clinical course and outcome.

PATIENTS AND METHODS

Patients

German, Swiss and Austrian paediatric hospitals were invited by personal contact, by announcements at scientific meetings and on the homepage of the German Society of Neuropediatrics to enrol patients. During the 40-month recruitment period, 63 hospitals included one or more patients. Children and adolescents from the age of independent walking to 18 years

were eligible. Inclusion and exclusion criteria were based on published research diagnostic criteria, including the results of cerebrospinal fluid examinations.⁹ Testing of nerve conduction velocity (NCV), F wave and electromyogram (EMG), as well as spinal magnetic resonance imaging, were not considered mandatory, because many paediatric hospitals were not able to conduct these investigations within a short time. Patients were removed from the study if the diagnosis in the later course turned out to be incorrect. Another inclusion criterion was the informed consent of the parents and—as far as possible according to age—the patient. The study was approved by the ethics committee of the University of Freiburg, Freiburg, Germany (register number 140/98).

Methods

Preceding events and diseases during the 6 weeks before the onset of GBS were recorded prospectively. Nearly all children were treated with intravenous immunoglobulins (IVIGs). The functional ability of patients, during the course of the disease was scored using an ordinal disability score similar to that used in published studies on treatment of GBS (0, normal; 1, able to run; 2, able to walk 5 m unaided; 3, able to walk with aids; 4, not able to walk, bedbound or chairbound; 5, intubated, on artificial ventilation). Cranial nerve involvement was scored as none (0), present (1) and requiring intervention (2; ie, lagophthalmus or tube feeding). Pain was recorded using a

Abbreviations: AMAN, acute motor axonal neuropathy; EMG, electromyogram; GBS, Guillain-Barré syndrome; IQR, interquartile range; IVIG, intravenous immunoglobulin; LOS, lipo-oligosaccharides; NCV, nerve conduction velocity

six-point score (0–5, Smiley scale). The available electrophysiological data were scored as follows: normal, not excitable, demyelinating neuropathy (at least one of the following: motor NCV <80% of lower limit of normal, distal latency >110% of upper limit of normal, ratio of amplitudes at proximal and distal stimulation <0.5, F wave latency >120% of upper limit of normal), purely axonal neuropathy (amplitude at distal stimulation <80% of normal, EMG with signs of acute denervation and no signs of demyelination), and mixed neuropathy (combined signs of demyelination and axonal dysfunction).

Anti-ganglioside antibody testing

Antibodies to various gangliosides were tested in sera obtained from the acute phase of the disease before treatment with IVIG. After blood sampling and centrifugation, the sera were shipped to the coordinating study centre (Freiburg) where they were deep frozen at -80°C . For comparison, we used the sera of a control group of children admitted to Freiburg Children's Hospital (Freiburg, Germany) for non-infectious and non-inflammatory diseases. As a second parallel control group, sera from adults with GBS treated at the Neurological University Hospital Wuerzburg (Wuerzburg, Germany) were examined. All the sera were lyophilised and sent to Dokkyo University School of Medicine, Dokkyo, Japan, and analysed blindly.

Serum IgG and IgM to GM1, GM1b, GD1a, GalNAc-GD1a, GD1b, GT1a and GQ1b were measured routinely by ELISA as reported elsewhere.¹⁰ Absorbance values at 492 nm were calculated by subtracting the optical densities obtained for wells without antigen. Serum was considered positive for anti-ganglioside antibodies when the absorbance value was ≥ 0.5 at a dilution of 1:500, because this high cut-off value gives high specificity.¹¹ Concurrent with the antiganglioside antibody testing, the serum samples were examined, as reported elsewhere, to detect recent infection with *C jejuni* and *Haemophilus influenzae*.^{12–13} Moreover, in the children with GBS, further serological tests for 24 infective agents were carried out prospectively.¹⁴

Statistical evaluation was carried out using the program package SPSS V.11.0.1. Correlations of the serological findings with clinical data were investigated with contingency table analysis (Fisher's exact test for 2×2 tables and χ^2 test for $n \times k$ tables) and non-parametric Mann–Whitney U test, as appropriate. A *p* value <0.05 was considered significant.

RESULTS

Over a 40-month period, 95 children fulfilling the diagnostic criteria of GBS were included in the clinical study.¹⁵ Prospective serological testing for antiganglioside antibodies was carried out on 63 patients. In all, 29 were male and 34 female. Their age ranged from 12 months to 16 years (mean 7.3 years). Electrophysiological testing was carried out in 42 of these children, usually during the first 3 weeks of the disease and without later repetition. The NCV findings in 20 were scored as demyelinating neuropathy. Three were scored as purely acute motor axonal neuropathy (AMAN) and 11 as mixed polyneuropathy. The findings were normal in five and no responses could be obtained in three. When the disease was at its peak, 18% of patients were still able to walk without aid and another 22% were able to walk with aid. A total of 60% were unable to walk, of whom 13% had to be artificially ventilated, and 41% had cranial neuropathy. Neuropathic pain was reported by 79% of children, in half of whom it was severe. All but five patients were treated with IVIG (2 g/kg twice weekly in 2 or 5 days). The first improvement by 1 point on the GBS score occurred after a median time of 15 days (interquartile range (IQR) 11–25). Children who had been unable to walk regained the ability

to walk unaided at a median time of 25 days after onset of GBS (IQR 13–50 days), and symptoms disappeared during the follow-up period in 46 patients at a median time of 121 days after onset (IQR 77–188). The total duration of follow-up was a median of 288 days (range 119–505 days). At the last follow-up, 73% of the children were symptom free. Another 19% could run, and 5% were able to walk unaided. In all, 68% of children had no complaints. However, 10 of 50 still had dyscoordination and fatigability, 2 had foot drop and 3 had dysaesthesias.

For the parallel investigations, we obtained sera from 41 children without GBS or other inflammatory and infectious diseases. The mean age of this patient group was 9.8 (range 1–24) years; 24 of them were male and 17 female.

The adult group of patients with GBS consisted of 39 consecutively treated patients whose sera were available in the Wuerzburg laboratory; clinical data were extracted retrospectively from the files (missing data in six). Their mean age was 56.4 (range 26.7–90.9) years; 16 were male and 20 female. Electrophysiological testing showed demyelinating neuropathy in 18, AMAN in 4 and mixed neuropathy in 11 patients; 8 were treated with immunoglobulin, 14 with plasma exchange and 6 with both measures. When the disease was at its peak, 21% were able to run and 6% were able to walk independently. A total of 70% were unable to walk, of whom 27% had to be artificially ventilated; 67% showed cranial nerve involvement and 93% reported neuropathic pain. Adults who were unable to walk, were able to walk independently after 32 (IQR 14–73) days. Only the frequency of cranial nerve involvement differed considerably from the children with GBS.

Anti-ganglioside antibodies

Four children in the study group showed positive IgG to GM1, in one case in combination with anti-GalNAc-GD1a and in one with anti-GD1b antibodies. Two others showed IgG reactive only to GD1b or GT1a (table 1). Another child showed increased IgM reactive to GalNAc-GD1a without IgG. None showed anti-GQ1b antibodies. In the control group without GBS, no child showed positive IgG reactive to the investigated antigens, but one showed positive IgM to anti-GalNAc-GD1a. This patient had a metabolic disease without apparent peripheral nerve involvement (ornithine aminotransferase deficiency with gyrate atrophy). In the adult GBS group, five patients were positive for anti-GM1 IgG, one of them in combination with anti-GD1a and anti-GD1b, one with anti-GalNAc-GD1a and two with anti-GD1b. Comparing the antibody frequencies between the groups, there was a significant difference between the children with GBS and controls, as well as between the controls and the adults with GBS (Fisher's exact test, *p* = 0.04 and *p* = 0.02, respectively).

Table 2 shows the clinical features, electrophysiological findings and infectiological data of children and adults with GBS, and of children with and without IgG to GM1, GM1b, GD1a or GalNAc-GD1a. The cranial nerves were affected more often in adults than in children, but the other clinical features, neurographical findings, preceding illnesses and *Campylobacter* positivity were similar between the age groups. Comparing the patients with and without antibodies, a recent *C jejuni* infection was considerably more frequent in children with antibodies. On the other hand, anti-GM1, anti-GM1b, anti-GD1a or anti-GalNAc-GD1a IgG were never found in the children with preceding *Mycoplasma pneumoniae* or cytomegalovirus infection. We could not show differences between those with and without antibodies with regard to the clinical features, neurographical findings and preceding symptoms.

Table 1 Positive anti-ganglioside immunoglobulin G antibodies

IgG antibodies	Child		Adults GBS n = 39	p Value	
	GBS n = 63	Other diseases n = 41		Child GBS v child other diseases	Child GBS v adult GBS
Total*	6 (9.5%)	0	5 (13%)	0.04	NS
GM1	4 (6.3%)	0	5 (13%)	NS	NS
GM1b	0	0	0	—	—
GD1a	0	0	1 (2.6%)	NS	NS
GalNAc-GD1a	1 (1.6%)	0	1 (2.6%)	NS	NS
GD1b	2 (3.2%)	0	3 (7.7%)	NS	NS
GT1a	1 (1.6%)	0	0	NS	NS
GQ1b	0	0	0	—	—

GBS, Guillain-Barré syndrome; NS, not significant ($p > 0.05$).

*Including GM1, GM1b, GD1a, GalNAc-GD1a, GD1b, GT1a and GQ1b gangliosides.

DISCUSSION

We investigated antiganglioside antibodies in childhood GBS— to our knowledge for the first time in a large prospective study. Raised IgG already reported to be associated with axonal GBS and *C jejuni* aetiology (GM1, GM1b, GD1a and GalNAc-GD1a) were detected in 4 of 63 children. Isolated anti-GD1b or anti-GT1a antibodies were detected in two children; 5 of the 63 children with GBS showed serological evidence of a recent *C jejuni* infection, and there was a definite correlation between the presence of raised antibodies and this aetiology.

Gangliosides are a family of chemical compounds located in neural tissues on axonal membranes and especially at synapses where antiganglioside antibody binding is possible.^{16–17} Many studies in recent years have shown that the presence of antiganglioside antibodies correlates with specific clinical phenotypes of GBS.^{2–3} Anti-GM1, anti-GD1a, anti-GM1b and anti-GalNAc-GD1a IgG are associated with AMAN.^{4–6} Other IgG such as anti-GQ1b and anti-GT1a have shown a correlation with Fisher's syndrome.⁷ Anti-GM1 IgG and IgM were also associated with signs of axonal damage in acute inflammatory demyelinating polyneuropathy and chronic demyelinating clinical phenotypes such as multifocal motor neuropathy.^{18–19}

Intestinal infections with *C jejuni* are among the most often reported antecedent diseases in GBS. In adults, *C jejuni* has repeatedly been reported to be a triggering agent for about 30% (14–72%) of patients with GBS.^{19–21} It was found to be associated with a higher rate of ganglioside antibodies, axonal damage and worse prognosis.^{6–20} Molecular mimicry between *C jejuni* lipo-oligosaccharides (LOS) and GM1, GD1a and GT1a gangliosides has been shown to be one of the mechanisms for ganglioside antibody formation in GBS. There is structural similarity between microbial glycans and the carbohydrate part of the gangliosides. The most frequently involved microbial antigens in this respect are the LOS of *C jejuni* and *H influenzae*.^{22–25} Antibodies to these microbial LOS can also bind to peripheral nerve gangliosides, resulting in autoimmune injury.^{26–27} Further pathogenetic pathways are thought to involve other glycolipids located in axonal membranes, Schwann cells and myelin sheaths and their microbial counterparts.^{2–28}

A large number of cases with *C jejuni*-associated GBS and AMAN have also been reported in children from China, South America, Turkey and South Africa.^{29–33} However, this organism does not seem to occur so frequently as an aetiological agent in

Table 2 Comparison of clinical and laboratory data

	Child GBS			Adult GBS	p Value	
	Total	Positive abs	Negative abs		Child GBS with abs v child GBS without Abs	Child GBS v adult GBS
Preceding illness	n = 63	n = 4	n = 59	n = 39		
Diarrhoea	10 (16%)	1 (25%)	9 (15%)	4 (10%)	NS	NS
RTI	23 (37%)	1 (25%)	22 (37%)	14 (36%)	NS	NS
Clinical features	n = 63	n = 4	n = 59	n = 39		
Median max severity (IQR)	4 (3–4)	3.5 (2.2–4.0)	4 (3–4)	4 (2–5)	NS	NS
Median cranial nerve involvement score (IQR)	0 (0–2)	0 (0–0.7)	0 (0–2)	1 (0–2)	NS	0.04
Median pain score (IQR)	3 (1–4)	3 (0–5)	3 (1–4)	2 (1–5)	NS	NS
Median days to walk (IQR)	25 (13–50)	14 (6–29)	26 (13–51)	32 (14–73)	NS	NS
Infection serology	n = 63	n = 4	n = 59	n = 39		
<i>C jejuni</i>	5 (7.9%)	3 (75%)	2 (3.4%)	4 (10%)	0.001	NS
<i>H influenzae</i>	0	0	0	0	—	—
Cytomegalovirus	8 (13%)	0	8 (14%)	ND	NS	—
<i>M pneumoniae</i>	6 (9.5%)	0	6 (10%)	ND	NS	—
NCS	n = 42	n = 3	n = 39	n = 33	NS	NS
Demyelinating	20 (48%)	0	20 (51%)	18 (55%)		
Axonal	3 (7.1%)	0	3 (7.7%)	4 (12%)		
Mixed	11 (26%)	1 (33%)	10 (26%)	11 (33%)		
No response	3 (7%)	1 (33%)	2 (5.1%)	0		
Normal	5 (12%)	1 (33%)	4 (10%)	0		

Abs, antibodies; GBS, Guillain-Barré syndrome; IQR, interquartile range; max, maximum; NCS, nerve condition study; RTI, respiratory tract infection.

The one child with monospecific anti-GT1a IgG had an especially severe course of GBS with ocular and bulbar involvement, associated with a recent *C jejuni* gastroenteritis. Two years later, after a protracted recovery, the antibody was no longer detected.

What is already known on this topic

- Antibodies to various gangliosides may have a role in the pathophysiology of Guillain-Barré syndrome (GBS) and its variants. Their presence is associated with *Campylobacter jejuni* enteritis, a preceding infection in some adults with GBS.
- *C jejuni* enteritis and the presence of anti-ganglioside antibodies correlate to axonal damage and a worse prognosis in adults.

What this study adds

- Raised anti-ganglioside antibodies were found in a proportion of German children with GBS similar to previous reports in adults. Their presence correlated considerably with *Campylobacter jejuni* infection.
- In this study, *C jejuni* enteritis and raised antibodies did not necessarily predict a worse prognosis.

childhood GBS in Western countries, as is also evident in our study. From our data, we can calculate an annual incidence of recent *C jejuni* infections in children with GBS of 24/1000. This is twice as high as has been estimated for the general population, indicating an aetiological role of *C jejuni* also in children with GBS.^{34–35} Moreover, we confirm that *C jejuni* aetiology can be associated with raised anti-ganglioside antibodies in children as well. However, in our study, we found no apparent association between clinical features or electrophysiological findings and raised antibodies. There can be various reasons for this: differently from adults, AMAN in children has been reported not to have a worse prognosis than the acute demyelinating variant of GBS.^{33–36} On the other hand, electrophysiological investigations in our children were not carried out systematically according to a prospective protocol. Kuwabara *et al*³⁷ showed that in the early phase of *C jejuni*-associated GBS, demyelinating features can predominate, whereas the axonal damage is not discernible until later on. To verify this finding, repeated investigations including EMG would have been necessary.

Despite the large amount of clinical and experimental data supporting the concept of a specific microbial aetiology, molecular mimicry, induced anti-ganglioside antibodies and axonal damage, the aetiology and pathogenetic pathways remain obscure for a large number of patients with GBS. Only a certain percentage of patients show a specific aetiology, and anti-ganglioside antibodies have rarely been shown in >30% of them. In their large European study including 229 patients, Hadden *et al*¹⁹ showed that although there was a statistical association between *C jejuni* infection, anti-GM1 antibodies, axonal damage and prognosis, the same agent could also give rise to a completely different clinical, neurophysiological and immunological constellation, suggesting as yet unknown immunological host factors. Alternative pathways that have been shown to be active in the pathophysiology of GBS include cellular factors and functional changes induced by sodium channel-blocking antibodies whose effect can be reversed by the addition of 7S-immunoglobulins.^{19–38–39}

In conclusion, similar to adults with GBS, IgG to GM1 and various other gangliosides can be detected in some paediatric patients with GBS. As in adults, their presence is associated with *C jejuni* aetiology in some patients. In this study, the

children who had antiganglioside antibodies and *C jejuni* enteritis did no worse than the children who did not. However, due to the small sample size this cannot be generalised, and larger studies with more patients are needed to safely conclude this.

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Being a contributor involves:

- Selecting from a validated, screened search (performed by in-house Information Specialists) epidemiologically sound studies for inclusion.
- Documenting your decisions about which studies to include on an inclusion and exclusion form, which we keep on file.
- Writing the text to a highly structured template (about 1500-3000 words), using evidence from the final studies chosen, within 8-10 weeks of receiving the literature search.
- Working with *Clinical Evidence* editors to ensure that the final text meets epidemiological and style standards.
- Updating the text every 12 months using any new, sound evidence that becomes available. The *Clinical Evidence* in-house team will conduct the searches for contributors; your task is simply to filter out high quality studies and incorporate them in the existing text.

If you would like to become a contributor for *Clinical Evidence* or require more information about what this involves please send your contact details and a copy of your CV, clearly stating the clinical area you are interested in, to CECommissioning@bmjgroup.com.

Call for peer reviewers

Clinical Evidence also needs to recruit a number of new peer reviewers specifically with an interest in the clinical areas stated above, and also others related to general practice. Peer reviewers are healthcare professionals or epidemiologists with experience in evidence-based medicine. As a peer reviewer you would be asked for your views on the clinical relevance, validity, and accessibility of specific topics within the journal, and their usefulness to the intended audience (international generalists and healthcare professionals, possibly with limited statistical knowledge). Topics are usually 1500-3000 words in length and we would ask you to review between 2-5 topics per year. The peer review process takes place throughout the year, and out turnaround time for each review is ideally 10-14 days.

If you are interested in becoming a peer reviewer for *Clinical Evidence*, please complete the peer review questionnaire at www.clinicalevidence.com/ceweb/contribute/peerreviewer.jsp