tological dissociation, and 19% (white bar) had albuminocytological dissociation but no anti-ganglioside antibodies (Fig. 3B). In the second week, the frequencies did not differ statistically. During the third week, the frequency of antibody alone (5%) was lower than that of CSF albuminocytological dissociation alone (53%) ($p=0.01$, OR: 0.10, 95% CI: 0.00–0.70).

4. Discussion

In the first samples assayed at Massachusetts General Hospital (MGH), all taken during the first 3 weeks of GBS, 73% of 111 patients had raised CSF protein concentrations (Ropper et al., 1991). The incidence of raised protein found for the initial CSF sample increased from 66% in the first week to 82% in the second. The frequencies in our series showed a lower tendency, possibly because the former series was prospective and ours retrospective. Similar findings were obtained for our 123 patients with FS; 59% had CSF albuminocytological dissociation in the first 3 weeks of FS, and the incidence of this dissociation increased from the first to second weeks. CSF protein concentrations in the seven MGH patients with FS were lower and more often normal than those in patients with typical GBS who had CSF examinations during the first week (Ropper et al., 1991). This also was true in our larger study.

The positive anti-GQ1b IgG antibody frequency was 85% in our 123 patients with FS. The frequency was the same as in the diagnostic criteria for FS proposed by the Dutch group (van der Meché et al., 2001). To investigate whether the high frequency of anti-GQ1b IgG antibody in patients with FS reflected specific immune activation, anti-GQ1b IgG antibody test was studied in the control group. Anti-GQ1b IgG antibody test between FS and the control gave result as none false positive. Therefore, the comparisons performed in this study confirmed findings that the frequency of anti-GQ1b IgG antibody is high in FS, but low in GBS. GBS patients with ophthalmoplegia as well as FS often have anti-GQ1b IgG antibody (Chiba et al., 1993). In this study, all our GBS patients with anti-GQ1b IgG antibody showed ophthalmoplegia. FS and GBS are not distinct syndromes clinically and immunologically. Although the marginal and atypical cases were not eligible to enter our study, atypical FS such as unilateral ophthalmoparesis (Susuki et al., 2000), acute ophthalmoparesis without ataxia (Yuki et al., 2001), and ataxic form of GBS (Yuki et al., 2000) associated with anti-GQ1b IgG antibody have been reported. Anti-GQ1b antibody testing is considered to be useful for the investigation of nosological position of these conditions. In general, however, results of anti-ganglioside serology differ among laboratories, possibly because of differences in method and cutoff values (Willison et al., 1999). Standardization is required. In comparison with the findings for GBS, the McNemar test showed that anti-GQ1b antibody testing is superior to a CSF examination for supporting the diagnosis of FS during the first 3 weeks of illness. This does not necessarily mean that a CSF examination is inferior to autoantibody testing in the usual clinical setting. A physician can quickly obtain results of the former from the hospital laboratory, whereas it takes longer to obtain results of the latter. For example, serum samples from 1229 patients were referred to our neuroimmunological laboratory for anti-ganglioside antibody testing between December 2000 and November 2001. It took 3 days (median) from the day when the samples were received to the day when we reported the results by fax. It may take a similar period, or longer, for other laboratories, including commercial ones. If a rapid, standardized assay kit can be developed and made available to general hospitals, anti-GQ1b antibody testing could become more helpful for supporting the diagnosis of FS during the first 3 weeks.

Anti-GQ1b antibody testing in particular was much more useful than a CSF examination for supporting a diagnosis of FS during the first week. This was the most important finding of our study. A CSF examination is effective for supporting a diagnosis of FS, but combined with serum autoantibody testing it is even more efficacious. The CSF protein concentration is normal in some patients during the first week of FS but may rise due to serial lumbar punctures made in subsequent weeks. When a physician gets a positive anti-GQ1b IgG antibody result for an FS patient whose CSF protein level is normal during the first week, serial lumbar punctures may not be required. Anti-GQ1b IgG antibody was found in some GBS patients during each week after the onset of illness, but anti-GM1 and anti-GD1a IgG antibodies for the first week, and anti-GM1 IgG antibody for the second were present more frequently. Moreover, the frequencies of anti-GM1 and anti-GD1a IgG antibodies were higher in the GBS patients than in the FS patients. These frequencies were higher than those of raised CSF protein concentration in GBS patients during the first week. Anti-GM1 and anti-GD1a IgG antibody testing in GBS also may have clinical merit for patients and physicians in similar situations, even though it is inferior to anti-GQ1b antibody testing in FS.

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ORIGINAL COMMUNICATION

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Ataxic Guillain-Barré syndrome associated with anti-GM1b and anti-GalNAc-GD1a antibodies

Abstract Ataxic Guillain-Barré syndrome (GBS) associated with anti-GQ1b IgG antibody has been reported. We, however, have had a patient with ataxic GBS who had IgG antibodies to the minor gangliosides GM1b and GalNAc-GD1a, and we therefore retrospectively investigated the clinical features of patients who had antibodies to GM1b or GalNAc-GD1a, but not to GQ1b. Information on patients' antecedent illnesses, initial symptoms, neurological signs, and CSF findings was reviewed in those with ataxic GBS or Fisher syndrome (FS) with anti-GM1b or anti-GalNAc-GD1a IgG antibodies. We tested whether the anti-GM1b and anti-GalNAc-GD1a antibodies are cross-reactive and constructed three-dimensional structural models of GM1b and GalNAc-GD1a. Ataxic GBS was diagnosed in 1 of 65 patients who had both anti-GM1b and anti-GalNAc-GD1a antibodies and in 3 of 159 patients who had anti-GM1b antibody without anti-GalNAc-GD1a antibody: FS was diagnosed in 1 of the 159 patients and in 1 of 35 who had anti-GalNAc-GD1a antibody without anti-GM1b antibody. All the patients' antibodies to GM1b or GalNAc-GD1a were associated with the IgG isotype. The clinical features of patients with ataxic GBS associated with anti-GM1b or anti-GalNAc-GD1a IgG antibodies did not differ from those of patients who had anti-GQ1b IgG antibody. Absorption study findings for serum from the patient who had both anti-GM1b and anti-GalNAc-GD1a IgG antibodies showed significant absorbance of anti-GM1b IgG antibody by GalNAc-GD1a and of anti-GalNAc-GD1a IgG antibody by GM1b, indicating that these antibodies are cross-reactive. This is the first report of ataxic GBS or FS associated with anti-GM1b or anti-GalNAc-GD1a IgG antibodies. These autoantibodies, as well as anti-GQ1b IgG antibody, may function in the development of some patients with ataxic GBS and FS.

Key words ataxic Guillain-Barré syndrome · Fisher syndrome · anti-GM1b antibody · anti-GalNAc-GD1a antibody

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Introduction

Richter [13] proposed that ataxic Guillain-Barré syndrome (GBS) is characterized by severe ataxia of the cerebellar type at the onset of GBS without ophthalmoplegia or sensory ataxia due to proprioceptive loss. Distal paresthesias and sensory signs, areflexia, and elevated CSF protein suggest that the condition is a variant of GBS. Most patients with ataxic GBS experience some weakness, and the condition may progress to typical GBS, whereupon the ataxia may be obscured. In contrast, occasionally patients present with acute ataxia and areflexia without ophthalmoplegia who have neither limb weakness nor sensory loss. Seven patients with ataxic GBS who had anti-GQ1b IgG antibody that cross-reacts with GT1a have been reported [19]. The fact that ataxic GBS and Fisher syndrome (FS) both have an autoantibody with the same fine specificity suggests the probability that they form a continuous spectrum.

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Anti-GM1b or anti-GalNAc-GD1a IgG antibodies are reported to be associated with GBS [7, 8, 20, 21], but no association of either antibody with ataxic GBS or FS has been reported. We had a patient (*Patient 1* in the following section) with ataxic GBS who had IgG antibodies to the minor gangliosides GM1b and *N*-acetylgalactosaminyl GD1a (GalNAc-GD1a), whose IgG did not react with GQ1b. This led us to search for other patients with ataxic GBS or FS who had antibody activity to GM1b or GalNAc-GD1a but not to GQ1b. We then investigated whether anti-GM1b and anti-GalNAc-GD1a antibodies are cross-reactive, and constructed three-dimensional structural models of GM1b and GalNAc-GD1a.

Case Report

Patient 1, a 72-year-old man suffered diarrhea which was resolved within 3 days. Four days after its resolution (Day 1), he experienced diplopia which worsened, and on day 3 he developed unsteady gait. On day 8 (in April 2001) he was admitted to our hospital. Ocular movement was not markedly limited, but he complained of diplopia in all directions of gaze. His pupils were normal, and light reflexes prompt. Neither facial nor bulbar palsy was present. None of the 4 limbs showed weakness. Tendon reflexes were diminished or absent. Plantar responses were indifferent. Neither dysmetria nor decomposition was found in the finger-to-nose and heel-to-knee tests, whereas Mann's test was positive. Mono-pedal stance or tandem gait were not possible. Romberg's sign was negative. There was no impairment of sensation to pinprick, touch, vibration or of position sense. No paresthesias of the glove and stocking type were present. Tentatively, acute cerebellar ataxia was diagnosed. Protein CSF was 46 mg/dl on day 8 and 49 mg/dl on day 18 with normal cellularity. Anti-GM1b and anti-GalNAc-GD1a IgG antibodies titers respectively were 4,000 and 8,000 on day 8, but no antibodies against other gangliosides, including GQ1b, were detected. We speculated that his condition might be autoimmune-mediated. He did not receive plasma exchange or intravenous immunoglobulin because he had had aortocoronary bypass surgery for angina pectoris. Motor nerve conduction studies done by the conventional procedures on day 17 were normal for the median, ulnar, peroneal, and tibial nerves. F-wave conduction velocities and latencies were normal. His ataxia gradually lessened from day 15. On day 24 he was able to walk with tandem gait. On day 34 he was discharged, still with mild diplopia. Neither limb weakness nor marked gaze limitation was found during the course of his illness. Atypical FS was diagnosed on discharge. The respective anti-GM1b and anti-GalNAc-GD1a IgG antibodies titers had decreased to 1,000 and 2,000.

Patients and methods

Patients

Serum samples obtained from 1,713 patients who had various neurological disorders and had been referred to our neuroimmunological laboratory between July 1999 and May 2001 were used in the serum antiganglioside antibody tests. Normal control serum samples were taken from 59 healthy volunteers. Serum IgG and IgM antibodies to GM1, GM1b, GM2, GD1a, GalNAc-GD1a, GD1b, GD2, GT1a, GT1b, and GQ1b were measured routinely by an enzyme-linked immunosorbent assay, as described elsewhere [12]. The plane structure of each ganglioside is shown in Fig. 1. Absorbance values at 492 nm were calculated by subtracting the optical densities obtained for wells without antigen. Serum was considered positive for antiganglioside antibodies in this study when the absorbance value was 0.5 or higher at a dilution of 1:500 because this high cut-off level gives high specificity as reported elsewhere [14].

The patients' medical records at discharge sent from each physician were reviewed by one of the authors (M. T.). Clinical information on antecedent illnesses, initial symptoms, neurological signs, and CSF findings were obtained from patients with documented anti-GM1b or anti-GalNAc-GD1a antibodies-positivity. Patients who had ataxia of the cerebellar type, hypo- or areflexia, and occasional distal paresthesias, but no significant limb weakness (≥ 4 on the Medical Research Council scale), nor loss of proprioception or significant ophthalmo-

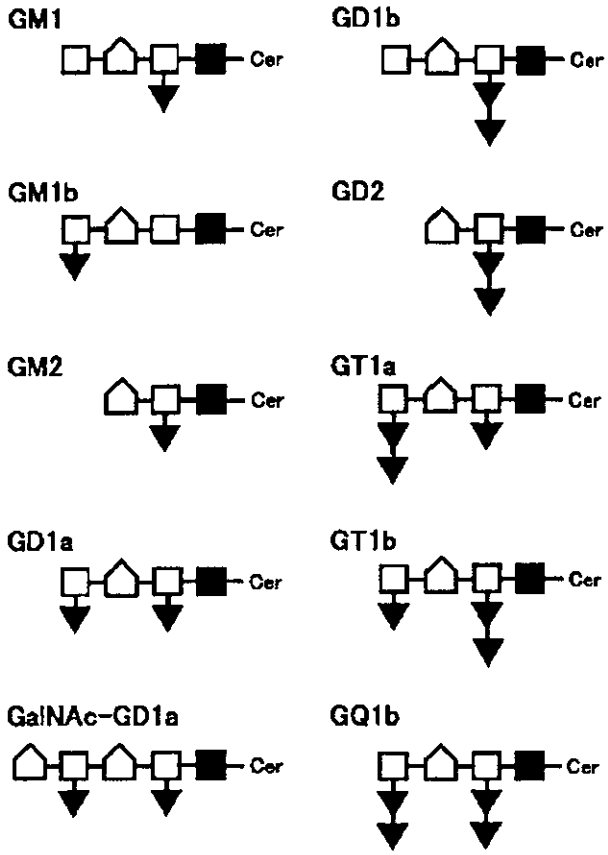

Fig. 1 Ganglioside plane structures. □ Galactose; ⌂ *N*-acetylgalactosamine; ■ Glucose; ▼ *N*-acetylneuraminic acid

plegia were considered to have ataxic GBS as proposed by Richter [13]. One of 2 original cases with ataxic form of GBS described by Richter [13] had bilateral partial blepharoptosis and right abducens palsy, whereas FS was characterized originally by total external ophthalmoplegia [3]. Ataxic GBS, not FS, was diagnosed for patients who showed no or minimal limitation of ocular movement with and without diplopia. FS diagnosis was based on our proposed criteria [11], the requirements being (1) progressive, relatively symmetric ophthalmoplegia and ataxia by 4 weeks, (2) hypo- or areflexia, and (3) limb strength graded 5 or 4 on the Medical Research Council scale. CSF albuminocytological dissociation was defined as a raised protein concentration (more than 45 mg/dl) associated with a count of 10 or fewer mononuclear leukocytes/μl. Although tentative diagnoses had been made by each primary physician, we made definite diagnoses based on the above criteria.

Anti-ganglioside antibodies titers and the absorption study

The patients' anti-GM1b, anti-GalNAc-GD1a, and anti-GD1b antibodies titers were measured as described previously [12]. Absorption studies of the serum from *Patient 1*, who had both anti-GM1b and anti-GalNAc-GD1a IgG antibodies, were made for GM1b, GalNAc-GD1a, GM1, GM2, GD1a, GD1b, GD2, GT1a, GT1b, and GQ1b as described elsewhere [12]. Antiganglioside antibodies were absorbed in microtiter wells coated with 5 picomole portions of ganglioside. Serum was added at the dilution that gave an optical density between 0.5 and 2.5. Absorption rates were expressed as percentages of the optical densities obtained with and without absorption.

Molecular modeling

The molecular display and molecular modeling for structural modification were done in a Silicon Graphics Indigo² workstation equipped with the Insight II® molecular graphics program [1]. The three-dimensional structures of the GM1b and GalNAc-GD1a molecules were modeled, and a manual search made of the computer graphics for the conformational spaces of their non-reducing ends.

Results

Antiganglioside antibodies

As shown in Table 1, patients were divided into 3 groups based on antibody activity: Anti-GM1b positive and anti-GalNAc-GD1a negative, anti-GM1b negative and anti-GalNAc-GD1a positive, or both anti-GM1b and anti-GalNAc-GD1a positive. Ataxic GBS was diagnosed in 1 (1.5%) of 65 patients who had both anti-GM1b and anti-GalNAc-GD1a antibodies and in 4 (2.5%) of 159 who had anti-GM1b antibody. One patient with anti-GM1b antibody, however, was excluded from the clinical analysis because the serum sample also reacted with GQ1b and GT1a. FS was diagnosed in 3 patients (4.6%) who had both anti-GM1b and GalNAc-GD1a antibodies, in 13 (8.2%) who had anti-GM1b antibody, and in 2 (5.7%) who had anti-GalNAc-GD1a antibody. All of the 3 patients with anti-GM1b and GalNAc-GD1a antibodies, 12 of the 13 with anti-GM1b antibody, and 1 of the 2 with anti-GalNAc-GD1a antibody were excluded because their sera also reacted with GQ1b. All the patients' antibodies to GM1b or GalNAc-GD1a were associated with the IgG isotype. Three patients (*Patients 2–4*) with ataxic GBS had anti-GD1b IgG antibody, their respective titers being 64,000, 32,000, and 4,000. One patient with ataxic GBS (*Patient 1*) and 2 patients with FS (*Patients 5 and 6*) carried no antibodies to the other gangliosides. Follow-up studies were possible for 3 patients (*Patients 1, 2, and 5*) whose titers decreased with clinical improvement. Anti-GM1b IgG antibody titer in *Patient 2* and anti-GalNAc-GD1a IgG antibody titer in *Patient 5*, had decreased respectively to 1,000 and 500.

Of the other patients with anti-GM1b or anti-GalNAc-GD1a antibodies, anti-GM1b IgG antibody was present in 140 who had GBS, in 14 who had acute motor axonal neuropathy associated with preserved tendon jerk, in 3 with overlapping GBS and FS, in 2 with overlapping GBS and Bickerstaff's brainstem encephalitis, in 1 with acute ophthalmoplegia, and in 1 with Charcot-Marie-Tooth disease. Anti-GalNAc-GD1a IgG antibody was present in 52 patients with GBS, in 3 with acute motor axonal neuropathy associated with preserved tendon jerk, and in 1 with overlapping GBS and FS. None of the other patients who had neurological disorders or the normal subjects had the anti-GM1b or anti-GalNAc-GD1a IgG antibody.

Clinical features

The clinical features of the 6 patients with ataxic GBS and FS who had the anti-GM1b or anti-GalNAc-GD1a IgG antibody without anti-GQ1b IgG antibody are given

Table 1 Ataxic GBS and FS associated with anti-GM1b and/or anti-GalNAc-GD1a antibodies

Diagnosis	Anti-GM1b positive		Anti-GM1b positive		Anti-GM1b negative	
	Anti-GalNAc-GD1a positive	with anti-GQ1b positive	Anti-GalNAc-GD1a negative	with anti-GQ1b positive	Anti-GalNAc-GD1a positive	with anti-GQ1b positive
n	65		159		35	
Ataxic GBS	1 (1.5%)	0	4 (2.5%)	1 (0.6%)	0	0
FS	3 (4.6%)	3 (4.6%)	13 (8.2%)	12 (7.5%)	2 (5.7%)	1 (2.9%)

GBS Guillain-Barré syndrome; *FS* Fisher syndrome

in Table 2. Age at onset was 28 to 88 years. Four of 6 patients had had an upper respiratory infection or diarrhea 2 weeks or less before the onset of neurologic symptoms. No serological evidence of recent *Campylobacter jejuni* infection was found in the 2 patients (*Patients 1 and 2*) who had had diarrhea. Initial symptoms were distal paresthesias in 3 patients, diplopia in 3, and unsteady gait in 1. On the basis of the diagnostic criteria for ataxic GBS, except for 2 patients with FS, no one had gaze limitation. *Patient 1* complained of diplopia, but as reported ocular movement was not markedly limited. *Patients 2* and *4* had blepharoptosis. *Patients 3* and *6* had nystagmus. Only *Patient 6* had facial palsy, and no one bulbar palsy. Four patients had no limb weakness, 1 insignificant weakness, and 1 mild weakness (4 on the Medical Research Council scale). Three patients (*Patients 2–4*) had glove and stocking type paresthesias, and CSF albuminocytologic dissociation was detected in 5 patients. Motor and sensory nerve conduction study findings of all the patients were normal except for 1 patient (*Patient 4*) who had reduced conduction velocities in sural nerve. Tentative diagnoses made by the primary physicians were FS (*Patients 2, 4, 5, and 6*), atypical FS (*Patient 3*), and acute cerebellar ataxia (*Patient 1*).

Molecular mimicry between GM1b and GalNAc-GD1a

Findings for the absorption of anti-GM1b and anti-GalNAc-GD1a IgG antibodies by GM1b, GalNAc-GD1a, GM1, GM2, GD1a, GD1b, GD2, GT1a, GT1b, and GQ1b are shown in Fig. 2. Anti-GM1b IgG antibody from *Patient 1* with ataxic GBS was absorbed more by GalNAc-GD1a and GM1b than by the other gangliosides, and anti-GalNAc-GD1a IgG antibody was absorbed more by GM1b and GalNAc-GD1a than by the others.

The three-dimensional structures of the non-reducing ends of the GM1b and GalNAc-GD1a molecules are similar (Fig. 3): (1) Steric clash was avoided in the modeling. (2) The stereo chemical configuration is retained. (3) The shapes of the molecular surfaces are similar. (4) The configurations of the hydrogen-bond acceptors and donors are similar. The sugar sequences of the non-reducing ends of the GM1b and GalNAc-GD1a molecules differ completely. In spite of that, these two molecules may have a three-dimensional structure in common in these regions.

Table 2 Clinical features of patients with ataxic GBS or FS who had anti-GM1b and/or anti-GalNAc-GD1a IgG antibodies without anti-GQ1b IgG antibody

Patient	1	2	3	4	5	6
Age/Sex	72/M	28/M	30/M	88/F	63/M	40/F
Antecedent illness	Diarrhea	Diarrhea	Sore throat	Cough	No	No
Initial symptoms	Diplopia	Paresthesias in hands and feet	Paresthesias in both hands unsteady gait	Paresthesias in hands and feet	Diplopia	Unsteady gait diplopia
Neurological signs						
Gaze limitation	No	No	No	No	Yes	Yes
Blepharoptosis	No	Yes	No	Yes	No	No
Nystagmus	No	No	Yes	No	No	Yes
Facial palsy	No	No	No	No	No	Yes
Bulbar palsy	No	No	No	No	No	No
Limb weakness	No	Insignificant	No	Mild*	No	No
Paresthesias	No	Glove and stocking	Glove and stocking	Glove and stocking	No	No
Ataxia						
cerebellar type						
limb ataxia	No	Yes	Yes	Mild	No	Mild
truncal ataxia	Yes	Yes	Yes	Yes	Yes	Yes
sensory type	No	No	No	No	No	No
vestibular type	No	No	No	No	No	No
CSF albuminocytologic dissociation	Yes	Yes	Yes	No	Yes	Yes
Anti-GM1b IgG titer	4,000	4,000	4,000	4,000	4,000	0
Anti-GalNAc-GD1a IgG titer	8,000	0	0	0	0	2,000
Tentative diagnosis	Acute cerebellar ataxia	Ataxic GBS	Atypical FS	Ataxic GBS	FS	FS
Final diagnosis	Ataxic GBS	Ataxic GBS	Ataxic GBS	Ataxic GBS	FS	FS

GBS Guillain-Barré syndrome; *FS* Fisher syndrome
* 4 on the Medical Research Council scale

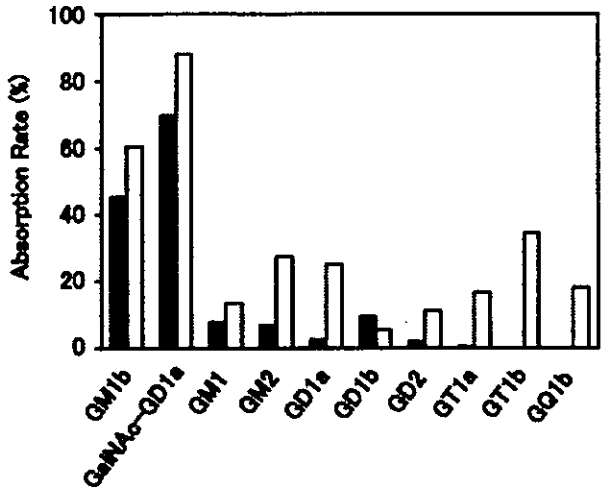

Fig. 2 Absorption study of serum from *Patient 1* who had both anti-GM1b and anti-GalNAc-GD1a IgG antibodies. Grey bars, absorption rates of anti-GM1b IgG antibody by GM1b, GalNAc-GD1a, GM1, GM2, GD1a, GD1b, GD2, GT1a, GT1b, and GQ1b. White bars, absorption rates of anti-GalNAc-GD1a IgG antibody by GM1b, GalNAc-GD1a, GM1, GM2, GD1a, GD1b, GD2, GT1a, GT1b, and GQ1b. Absorption rates were calculated from [1 – (optical densities in wells with sera for absorption-treatment)/(optical densities in reference wells with sera without absorption-treatment)] x 100

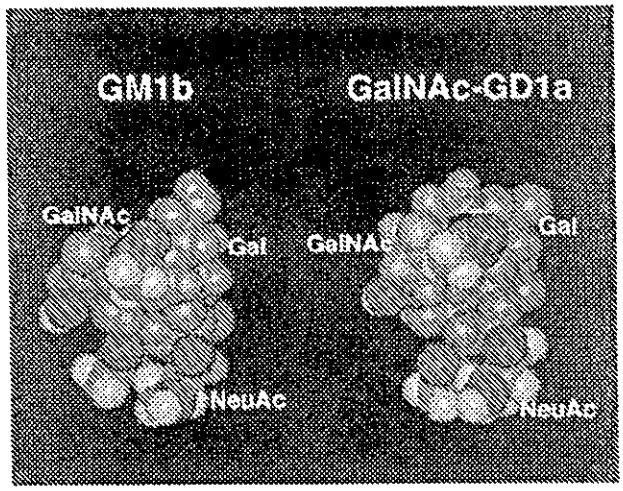

Fig. 3 Three-dimensional molecular display models of GM1b and GalNAc-GD1a. Carbon, green; oxygen, red; and hydrogen, grey

Discussion

Anti-GM1b or anti-GalNAc-GD1a IgG antibodies more frequently were positive in patients with such GBS-related conditions as ataxic GBS or FS than in those with other neurological disorders. This is the first report of ataxic GBS or FS associated with anti-GM1b or anti-GalNAc-GD1a antibodies. High anti-GM1b and anti-GalNAc-GD1a IgG antibody titers present during the acute phase decreased with clinical improvement. Anti-GM1b or anti-GalNAc-GD1a antibodies may function in the pathogenesis for some patients who have ataxic GBS or FS and may like anti-GQ1b IgG antibody. Confirmation by other investigators is needed to support this hypothesis.

Clinical features were analysed of the 6 patients with ataxic GBS or FS who had anti-GM1b or anti-GalNAc-GD1a IgG antibody but not anti-GQ1b IgG antibody. Of the 4 with ataxic GBS, all had had antecedent infections and 3 distal paresthesias. On the basis of our diagnostic criteria, none had significant limb weakness, gaze limitation, or proprioceptive impairment. Tendon jerks were absent in everyone. Acellular CSF with elevated protein was confirmed in 3. Internal ophthalmoplegia, facial palsy, and bulbar palsy were infrequent in our patients. The clinical features of those patients with ataxic GBS who had anti-GM1b or anti-GalNAc-GD1a IgG antibodies did not differ from those of reported patients who had ataxic GBS associated with anti-GQ1b IgG antibody [19]. FS, atypical FS, or acute cerebellar ataxia had been tentatively diagnosed by the primary physicians, but ataxic GBS was the final diagnosis. Two patients with FS had the triad of ophthalmoplegia, ataxia, and areflexia; 1 of whom had nystagmus and facial palsy, but neither had had an antecedent infection or distal paresthesias.

Antiganglioside antibody seems to recognize a common sugar sequence. Anti-GQ1b antibody cross-reacts with GT1a, which has a disialosyl residue linked to the external galactose common to GQ1b [2]. Anti-GalNAc-GD1a antibody cross-reacts with GM2, which has the terminal moiety [GalNAcβ1-4(NeuAcα2-3)Gal] [16]. Antibody to GM1, GD1b, and asialo-GM1 recognizes with the [Galβ1-3GalNAc] epitope common to those glycolipids [4]. The absorption study of the serum from *Patient 1* showed that anti-GM1b IgG antibody was absorbed by GalNAc-GD1a, indicative that anti-GM1b IgG antibody cross-reacts with GalNAc-GD1a. Moreover, anti-GalNAc-GD1a IgG antibody was absorbed by GM1b, indicative that it also cross-reacts with GM1b. Sera from some GBS patients who carried the anti-GM1b IgG antibody also have been reported to have IgG anti-GalNAc-GD1a antibody activity [8, 18]. In a preliminary report, Tatsumoto et al. [15] found that 4 of 175 patients with GBS who had high anti-GM1b IgG antibody titers also had anti-GalNAc-GD1a IgG antibody. Anti-GM1b IgG antibody titers in 2 patients were significantly decreased by absorption with GalNAc-GD1a. GM1b has a NeuAc that is α2-3 linked to a terminal galactose of the gangliotetraosyl core structure. In the plane structures, the terminal moiety of GalNAc-GD1a [GalNAc β1-4 (NeuAc β2-3) Gal β1-] is not present in GM1b (Fig. 1). There are no common sugar sequences at either of the non-reducing ends of the GM1b and GalNAc-GD1a molecules. In spite of that, our immunological findings indicate that the anti-GM1b IgG antibody recognizes the

GalNAc-GD1a molecule. We then examined the molecular mimicry between GM1b and GalNAc-GD1a. The GM1b and GalNAc-GD1a molecules are speculated to have common features in their three-dimensional structures. Our findings suggest the novel idea that the reactivities of the different non-reducing end epitopes with cross-reactive antibodies depend on the steric structure.

The lesion responsible for cerebellar ataxia in ataxic GBS and FS has yet to be clarified, but selective involvement of 1a neurons was suggested by Fisher in his original paper [3]. Postural body sway analysis findings also have suggested selective involvement of the group 1a afferent system in 10 patients with FS who had anti-GQ1b IgG antibody, as well as in a patient with ataxic GBS who had anti-GQ1b IgG antibody [9, 10]. Autopsy findings by Richter [13] for ataxic GBS showed outstanding degeneration of the fiber system of Clarke's column, but no lesions in the cerebellum. He concluded that cerebellar ataxia in ataxic GBS is a consequence of damage done to the spinocerebellar nucleus by afferent fibers. Human monoclonal antibody against b-series gangliosides, including GQ1b, immunostained muscle spindles and dorsal root ganglia in rodent peripheral nervous system [17], and murine anti-GQ1b monoclonal antibody immunostained some large neurons of human dorsal root ganglia [6]. The immunohistochemical localization of GM1b and GalNAc-GD1a also should be tested in humans. An immunochemical study of rat brain, which used an anti-GM1b monoclonal antibody, showed GM1b densely localized in the forebrain, midbrain, and cerebellum [5]. Interestingly, anti-GM1b monoclonal antibody-labeled granule cell bodies were present both in the external and inner granular layers of the cerebellum.

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Table 1 Comparison of clinical and serological features

	Initial symptoms				
	Hand weakness (n = 33)	Others (n = 431)	p Value	OR	95% CI
Age (median, (range))	43 (14 to 78)	44 (0 to 88)	NS		
Sex (M/F)	22/11	262/169	NS		
Preceding symptoms:					
Diarrhoea	19 (58%)	151 (35%)	<0.001	2.5	1.0 to 6.3
Upper respiratory tract infection	11 (33%)	174 (40%)	NS		
Cranial nerve involvement	9 (27%)	156 (36%)	NS		
Neck weakness	14 (42%)	221 (51%)	NS		
Sensory deficit	10 (30%)	211 (49%)	0.03	0.27	0.1 to 0.6
IgG antibodies against:					
All gangliosides tested	24 (73%)	182 (42%)	0.03	2.3	1.1 to 5.1
GM1	20 (61%)	106 (25%)	<0.001	3.4	1.4 to 3.8
GM1b	15 (45%)	111 (26%)	0.01	2.4	1.4 to 4.8
GM2	1 (3%)	2 (0.4%)	NS		
GD1a	10 (30%)	64 (15%)	0.01	2.5	1.1 to 4.7
GalNAc-GD1a	6 (18%)	37 (9%)	NS		
GD1b	9 (27%)	75 (17%)	NS		
GT1a	3 (9%)	41 (10%)	NS		
GT1b	1 (3%)	14 (3%)	NS		
GQ1b	1 (3%)	31 (7%)	NS		

Differences between groups were examined with the χ^2 or Fisher's exact test.
CI, confidence interval; F, female; M, male; NS, not significant (p value >0.05); OR, odds ratio.

Hand weakness onset Guillain–Barré syndrome

Landry's 19th century report gives the impression that Guillain–Barré syndrome (GBS) is characterised by ascending weakness. This clinical picture now is called "Landry's ascending paralysis."[1] Indeed, muscular weakness in GBS does usually begin in the legs, progressing to the trunk, arms, and cranial regions.[2] However, several clinical variants are now recognised in which weakness initially begins in other areas.[2] Four patients with acute polyneuropathy were reported initially to have had muscle weakness in the hands.[3] In two of these, *Campylobacter jejuni* infection had preceded the neurological symptoms, and serum anti-GM1 antibody was detected in the others.

To determine the frequency and clinical features of hand onset GBS, we reviewed the medical records of 464 consecutive patients with the disease. Eleven had been treated at our hospital, the others were referred to our laboratory from other hospitals for antiganglioside antibody tests. Hand onset GBS was diagnosed when the first symptom that a GBS patient recognised was hand weakness. Paraesthesiae and other sensory symptoms may have preceded hand weakness, but patients who developed weakness in both the hands and legs on the first day of illness were excluded.

We found that 33 (7%) of the patients reviewed had hand onset GBS. Frequent initial symptoms were weak hand grip and clumsy fingers. Paraesthesiae in the hands or all four limbs had preceded hand weakness in eight of them. Three patients presented with facial palsy, diplopia, or blurred vision on the day of hand weakness onset. Weakness was limited to the hands and arms throughout the acute phase of illness in four patients (12%), while it spread to the legs in the others. Assisted ventilation was required for four patients (12%). Compared with the other patients, those with hand onset GBS more often had a history of preceding diarrhoea, had antiganglioside IgG antibodies, and, less frequently, had sensory disturbance (table 1). Of the autoantibodies present, anti-GM1, anti-GM1b, and anti-GD1a IgG were significantly associated with hand onset GBS. Antecedent *C jejuni* infection was proven by serological assay (n = 19) or stool culture (n = 2) in 20 (61%) of the patients with hand onset GBS.

Hand onset GBS patients (n = 25) who had antiganglioside IgG, evidence of preceding *C jejuni* infection, or both often had a history of previous gastrointestinal symptoms but rarely cranial nerve involvement or sensory disturbance. Although most patients had received plasmapheresis or intravenous immunoglobulin within two weeks of onset, seven showed irreversible neurological damage at the last consultation. Moderate or mild weakness remained in the arms and legs of four patients (from four to 22 months after onset), and weakness mainly remained in the upper limbs of three (from two to four months after onset). Results of nerve conduction studies done within two weeks of weakness onset were available for 10 patients: five had predominant axonal disturbance and the others showed unclassified findings. In contrast, the eight patients who had neither antiganglioside IgG nor evidence of a preceding *C jejuni* infection often had a history of previous respiratory infection and sensory disturbance. All had received plasmapheresis or intravenous immunoglobulin and, except for one, had no or only mild weakness 12 months after onset. The exception required assisted ventilation at nadir and still had moderate distal weakness and amyotrophy in the legs six months after onset. Results of nerve conduction studies were available for four patients who had neither antiganglioside IgG nor evidence of a preceding *C jejuni* infection; all of these had a primary demyelinating disturbance.

In the larger population, we confirmed previous findings that hand onset GBS is related to *C jejuni* enteritis and anti-GM1 antibody,[3] although the cases reported had either *C jejuni* or anti-GM1 antibody. Furthermore, we found that hand onset GBS is characterised by pure motor symptoms and the presence of IgG antibodies against GM1b and GD1a, as well as those against GM1. Residual symptoms were frequent in the *C jejuni* or autoantibody related populations, but no statistical analysis was made of outcome. In contrast, one quarter of the patients with hand onset GBS had no evidence of previous *C jejuni* infection or antiganglioside IgG. Antecedent respiratory infection symptoms and sensory involvement were characteristic, and those patients tended to have better outcomes than the others.

It is noteworthy that motor deficit remained only in the arms during the course of the illness in the four hand

onset GBS patients, two of whom were positive for *C jejuni* serology and antiganglioside IgG. Another patient who developed acute pure motor neuropathy following *C jejuni* enteritis was reported to have localised weakness in his hands and anti-GM1 IgG.[4] Although that patient had preserved tendon reflexes in the four limbs, a serial electrophysiological study confirmed the diagnosis of an axonal variant of GBS, indicating that anti-GM1 IgG and *C jejuni* infection are related to hand-predominant weakness in GBS. It also is noteworthy that the six patients who had hand onset GBS had an initial diagnosis of cervical spondylosis (n = 4), lacunae infarction (n = 1), or brachial plexus neuritis (n = 1) on hospital admission. Frequent hand function problems have been reported even in mildly affected GBS patients who could walk unaided at nadir.[3] Early treatment has been suggested in such cases. Recognition of the clinical characteristics of hand onset GBS may lead to a good prognosis because individuals can be given specific treatment as early as possible.

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Lack of association between interleukin-1β polymorphism (−511) and ischaemic stroke

A growing body of evidence suggests an important role for interleukin 1 (IL-1) in the pathogenesis of brain damage following cerebral ischaemia. Central administration of IL-1 exacerbates brain damage, and overexpression of the IL-1 receptor antagonist (IL-1Ra) or blockade of IL-1 converting enzyme activity reduces infarct size dramatically (reviewed by Touzani *et al*[1]). Clinical studies suggest there is intrathecal IL-1 production early during stroke.[2]

Table 1 Distribution of risk factors and IL-1β genotypes in patients and controls

	Stroke patients (n = 183)	Controls (n = 180)	p Value
Age (years) (mean (SD))	65.2 (14.7)	64.8 (14.8)	0.80
Male	81 (44.3)	69 (38.3)	0.25
Hypertension	139 (76)	94 (52.2)	<0.01
Diabetes mellitus	33 (18)	32(17.8)	0.59
History of myocardial infarction	15 (8.21)	9 (5)	0.22
Current smoker	47 (25.7)	21 (11.7)	<0.01
IL-1β genotypes			0.37
CC	94 (51.4)	87 (48.3)	
CT	69 (37.7)	79 (43.9)	
TT	20 (10.9)	14 (7.8)	
T allele frequency (%)	29.8	29.7	0.97

Values are n.(%) unless stated otherwise.

A single nucleotide polymorphism in the promoter region of IL-1β at position −511 resulting in C–T transition influences the protein production, and IL-1β-511T carriers are reported to be higher producers of IL-1β than IL-1β-511C carriers.[5]

In the study described here we investigated whether IL-1β polymorphism (−511) can be involved in the genetic susceptibility to ischaemic stroke. We studied 183 consecutive patients with ischaemic stroke presenting to our stroke unit and 180 control subjects without a history of stroke. Control subjects were recruited from spouses of the patients, from individuals admitted to the university hospital for any reason other than neurological diseases, and from persons randomly selected from the community of our town. All patients, controls, and their parents had to be of white extraction.

Cerebral infarction was defined as a focal neurological deficit of sudden onset that persisted beyond 24 hours, documented by brain computed tomography or magnetic resonance imaging, indicating the presence of infarction or the absence of haemorrhage.

Stroke aetiology was defined according to the TOAST criteria[6]: 66 patients had large vessel disease, 50 had small vessel disease, 49 had cardioembolic stroke, and 18 had stroke of undetermined aetiology.

Arterial hypertension was diagnosed when its presence was documented in the medical records or if two or more readings of blood pressure were ⩾160 mm Hg (systolic) or ⩾95 mm Hg (diastolic) before the onset of stroke or three months later. Diabetes mellitus was diagnosed if the patient gave a history of diabetes that was confirmed by their medical records or was taking insulin or an oral hypoglycaemic agent. A patient was defined as a current smoker if there was a history of cigarette smoking during the last five years.

Genomic DNA was extracted from peripheral blood using a commercially available kit from Qiagen. Interleukin-1β polymorphism (−511) was detected using the polymerase chain reaction and restriction enzyme digestion as described elsewhere.[5]

All subjects gave informed consent and the local ethics committee approved the study protocol.

The sample size was calculated with a power of 80% at the 0.05 significance level. The sample size would allow detection of a relative risk by allele of 2.2. Differences between groups were examined using the χ^2 test or the unpaired Student *t* test as appropriate. Probability (p) values of less than 0.05 were considered statistically significant.

The characteristics of study subjects and distribution of IL-1 genotype are shown in table 1.

There was no significant difference between stroke patients and controls in age and sex.

Allele frequency in both controls and patients was in Hardy-Weinberg equilibrium (p = 0.32 for controls, p = 0.40 for stroke patients).

There was no significant difference between stroke patients and controls in IL-1β genotype distribution. There was also no relation between IL-1β polymorphism and any particular stroke subtype: large vessel disease, for TT, 7/66 (10.6%); small vessel disease, 6/50 (12.0%); cardioembolic stroke, 7/49 (14.3%) (p = 0.24, χ^2 test).

Comment

We failed to find a relation between IL-1β polymorphism (−511) and ischaemic stroke in this Polish population. Recently Seripa *et al* investigated the same polymorphism in an Italian population of 110 stroke survivors and 101 healthy controls[6] and also did not find any significant association between IL-1β polymorphism (−511) and stroke, although they showed a significantly higher frequency of the IL-1Ra 1/1 genotype in stroke survivors than in controls.

Several issues should be taken in account in interpreting the results of our study.

First, cytokines do not work alone, but in a network. Therefore a genetic predisposition to produce anti-inflammatory cytokines (for example, IL-10 or IL-1Ra) could interfere with the biological effects of IL-1.

Second, we did not examine another IL-1β polymorphism in exon 5 at position +3953 which could determine IL-1β synthesis.

Third, we cannot exclude the possibility that IL-1β polymorphism (−511) is associated with one particular stroke subtype; however, in our study we found no relation between IL-1 polymorphism and large vessel disease, small vessel disease, or cardioembolic stroke. From our point of view, there is currently a lack of strong evidence indicating a functional association between IL-1 and any particular stroke subtype.

Fourth, IL-1 may be linked to inflammatory mechanisms of atherogenesis. Hypertension and smoking play an important role in the pathogenesis of atherosclerosis. In our study the incidence of hypertension and smoking was higher in stroke patients than in controls, and the frequency of the TT allele was higher in smokers than in non-smokers (15.4% *v* 7.9%, p = 0.18) and in subjects with hypertension than in those without (10.3% *v* 7.7%, p = 0.48). Atherosclerosis is related to

Pharyngeal-brachial palsy after cytomegalovirus colitis

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Cytomegalovirus (CMV) is known to be associated with various central and peripheral neurologic disorders in patients with AIDS or after bone marrow or solid organ transplantation.[1] We report a patient with acute pharyngeal and brachial palsy after CMV colitis following bone marrow transplantation. This is the first report of regional neuropathy in a patient with CMV colitis.

Case report. A 37-year-old woman developed acute onset of progressive dysarthria, dysphagia, and distal weakness of bilateral upper extremities. She had chronic myeloid leukemia and received bone marrow transplantation. Two months later, she developed intractable watery diarrhea and pancytopenia. Stool cultures for common intestinal pathogens, including *Campylobacter jejuni*, were negative. Colonic biopsy showed swelling of mucosal epithelium with nuclear inclusion bodies with immunohistochemical evidence of CMV. Serum PCR for CMV was also positive. She was treated with anti-CMV immunoglobulins (Ig) (100 mg/kg/day three times per week) and ganciclovir (5 mg/kg/day twice a week). The diarrhea stopped and the serum CMV-PCR became negative on discharge.

Four weeks after CMV colitis, she developed acute distal weakness in bilateral upper extremities. The weakness progressed so rapidly that 2 days later she could not move her fingers. Dysarthria and dysphagia followed and she needed a nasogastric tube for feeding. The gag reflexes decreased bilaterally. The muscle power as graded by the Medical Research Council scale was 1/5 for the flexor and extensor muscles of hands and wrists bilaterally. The muscle strength of the biceps, triceps, and deltoid, as well as that of the lower extremities, was normal. Tendon reflexes of wrist flexors were absent bilaterally. Tendon reflexes of other limb muscles were preserved. Results of sensory examinations were normal. MRI of the head and cervical spinal cord had normal results. Initial nerve conduction studies (NCS, table) showed impersistence of F waves in the left median nerve. Two weeks later, NCS showed markedly decreased motor amplitudes and impersistence of F waves in bilateral median and ulnar nerves. The distal latencies and motor conduction velocities were normal, and there was no conduction block or temporal dispersion on any tested nerves. Diphtheria was excluded due to the lack of oropharyngeal pseudomembranes or tonsillitis and negative cultures for *Corynebacterium diphtheriae*. Botulism was excluded by the negative food intake history and negative stool culture for *Clostridium botulism*. At the peak of the neuropathy, serum CMV-IgM antibody and CMV-PCR were negative. Serum antiganglioside antibodies were measured by an established ELISA method for IgG and IgM against GM2, GM1, GM1b, GD1a, GalNAc-GD1a, GD1b, GT1a, GQ1b, and GT1b, and both IgG and IgM antibodies were negative.[2]

Pharyngeal-brachial palsy was diagnosed. IVIg were administered at the dose of 0.4 g/kg/day for 5 consecutive days. Dysarthria and dysphagia improved significantly 2 days after the IVIg. NCS 1 week after the completion of IVIg treatment showed restoration of F waves in the right median nerve with improvement of the strength in muscles of hands and wrists. The patient was free from hand weakness and swallowing disturbances 3 weeks after the treatment. However, she died of pancytopenia and refractory septic shock 5 months later.

Discussion. The constellation of the patient's clinical findings is reminiscent of pharyngeal-cervical-brachial palsy (PCB).[3-5] Ropper proposed that PCB is a regional variant of Guillain-Barré syndrome (GBS).[3] Interestingly, CMV had been known as one of the common antecedent infections of GBS.[6] Active CMV infections cause severe peripheral neuropathy in immunocompromised hosts and usually present with prominent sensory symptoms. In contrast, our patient developed acute painless pharyngeal-brachial palsy in the absence of active CMV disease. The prompt response to IVIg also suggests the presence of a postinfectious neuropathy rather than direct involvement of nerves or nerve roots by CMV.

Antibodies against certain ganglioside epitopes had been detected in patients with PCB and neuropathy with serologic evidence of antecedent CMV infections. Anti-GT1a IgG antibody had been reported to be associated with PCB,[4,5] and anti-GM2 IgM antibody was often detected in patients with GBS with CMV infections.[6,7] The serum IgM reactivity against GM2 from patients with GBS with CMV infections and high IgM anti-GM2 titers was decreased in a dose-dependent manner after incubation with fibroblasts infected by a CMV strain from a patient with GBS.[7] However, our patient did not have anti-GT1a, anti-GM2, or other antiganglioside antibodies during the acute phase of neuropathy. The prompt response to IVIg and lack of demyelinating features on NCS suggest that conduction failure, by some unidentified

Table Nerve conduction studies

Nerve	Distal latency, ms				Amplitude, mv or μv*				Conduction velocity, m/s			
	Day 6	Day 13	Day 22	Normal value	Day 6	Day 13	Day 22	Normal value	Day 6	Day 13	Day 22	Normal value
Motor nerve												
R median	4.0	3.9	4.0	<4.0	7.8	4.9	5.3	>5	51	51	53	>50
L median	3.9	4.3	3.9	<4.0	4.6	1.5	1.8	>5	58	54	51	>50
R ulnar	2.6	3.4	3.5	<3.5	4.5	1.2	0.9	>5	58	55	57	>50
L ulnar	2.8	3.1	3.2	<3.5	4.3	1.4	0.9	>5	57	52	59	>50
R tibial	3.4	3.8	5.2	<5.5	11.9	8.2	7.8	>5	45	41	42	>40
R peroneal	4.4	4.3	4.3	<5.5	3.9	2.8	2.7	>2.5	45	45	45	>40
Sensory nerve												
R median	2.6	2.5	2.6	<2.7	35.9	26.2	35.7	>10	54	56	54	>50
R ulnar	2.5	2.5	2.4	<2.7	26.4	19.5	26.4	>10	57	56	58	>50
R sural	2.9	2.6	2.6	<3.5	11.3	11.7	16.5	>5	48	54	54	>40

* Amplitude is expressed in mv for motor nerves and μv for sensory nerves.

serologic factors, may underlie the neurologic dysfunction in our patient.

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Short communication

Bickerstaff's brainstem encephalitis associated with IgM antibodies to GM1b and GalNAc-GD1a

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Abstract

This is the first report of a case of Bickerstaff's brainstem encephalitis (BBE) associated with IgM antibodies to GM1b and GalNAc-GD1a. Subsequent to *Campylobacter jejuni* enteritis, the patient rapidly developed consciousness disturbance and hyperreflexia in addition to external ophthalmoplegia and cerebellar-like ataxia. EEG showed transient 7 Hz monorhythmic θ activities, predominantly in the front-central area. He received high doses of immunoglobulin intravenously and had completely recovered 3 months later. High anti-GM1b and anti-GalNAc-GD1a IgM antibody titers present during the acute phase decreased with his clinical improvement. An absorption study showed the anti-GM1b and anti-GalNAc-GD1a IgM antibodies to be cross-reactive. Anti-GM1b and anti-GalNAc-GD1a antibodies have been detected in some patients who developed Guillain–Barré syndrome after *C. jejuni* enteritis, whereas the anti-GQ1b IgG antibody is associated with BBE. Infection by *C. jejuni* bearing a GM1b-like or GalNAc-GD1a-like lipooligosaccharide may trigger the production of anti-GalNAc-GD1a and anti-GM1b IgM antibodies. It is not clear why our patient developed BBE rather than Guillain–Barré syndrome. These antibodies may, however, prove useful serological markers for identifying BBE patients who do not have the anti-GQ1b IgG antibody.

Keywords: Bickerstaff's brainstem encephalitis; Anti-GM1b antibody; Anti-GalNAc-GD1a antibody; *Campylobacter jejuni*

1. Introduction

Bickerstaff's brainstem encephalitis (BBE) and Fisher syndrome (FS) are characterized by the acute onset of ophthalmoplegia and ataxia subsequent to an antecedent infectious illness [1,2]. For patients with consciousness disturbance or hyperreflexia, the diagnosis usually has been BBE rather than FS [3]. Because a history of prior infection is common in BBE, as in FS and Guillain–Barré syndrome (GBS), an autoimmune mechanism produced by microbial infection may trigger its pathogenesis [1–3]. Herpes simplex virus, cytomegalovirus, Epstein–Barr virus, varicella-zoster virus, measles virus, *Salmonella typhi*, and *Mycoplasma pneumoniae* have been reported as antecedent agents in BBE. One case of BBE subsequent to *Campylobacter jejuni* enteritis, the most frequently identified cause of GBS and FS, has been reported [4]. BBE, as well as FS, is associated with the anti-GQ1b IgG antibody [5,6] which was present in 66% of a population of patients who had BBE [7]. In contrast, anti-GM1b and anti-GalNAc-GD1a IgG (or IgM) antibodies have been found in patients who developed GBS after a *C. jejuni* infection [8–11]. This is the first report on BBE, in which the patient had anti-GalNAc-GD1a and anti-GM1b IgM antibodies after *C. jejuni* enteritis.

2. Case report

A 12-year-old boy had fever and watery diarrhea that lasted several days. Two weeks later, he developed unsteady gait (day 1). The next morning, he could not stand up and was admitted. He was apyrexial. There were no meningeal signs. Neurological examination showed drowsiness and mild bilateral blepharoptosis. Abducens gaze was

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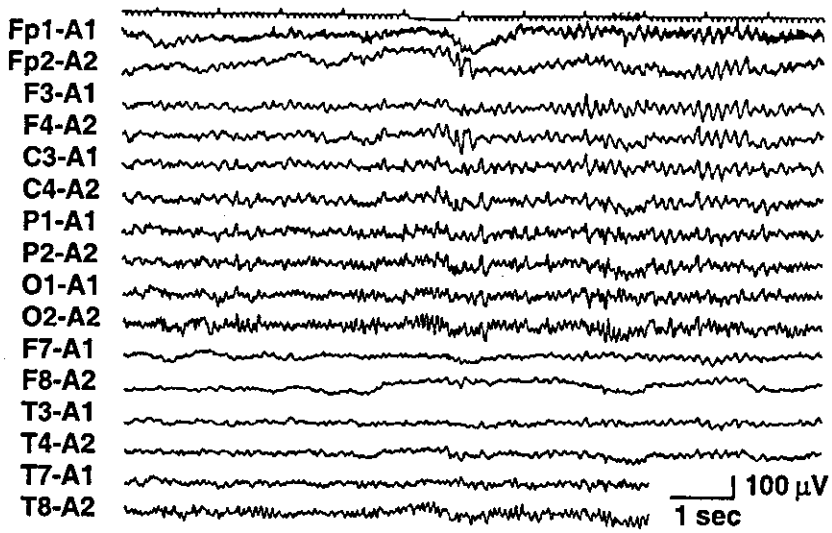

Fig. 1. EEG on day 2 showing regular 11 Hz basic rhythm with transient 7 Hz monorhythmic θ activities, predominantly in the front-central area.

limited in the right eye. Light reflexes were prompt, but the pupils were anisocoric (left 4 mm, right 2 mm). No nystagmus was present. There was no weakness in his four limbs, but because of severe truncal ataxia, he could not sit without support. Deep tendon reflexes were brisk in the legs, plantar responses indifferent. Routine hematological and biochemical test results were normal. C-reactive protein was normal. Serologic examinations for herpes simplex virus, cytomegalovirus, Epstein–Barr virus, and *M. pneumoniae* were negative. On day 2, CSF protein was 18 mg/dl with 3 cells/μl. EEG without sedative drugs detected a regular 11 Hz basic rhythm with transient 7 Hz monorhythmic θ activities, predominantly in the front-central area (Fig. 1). Brain MRI with and without gadolinium enhancement detected no abnormalities. Because the transient θ activities on the EEG were misinterpreted as hypnagogic hypersynchronous θ activities, initially we thought there was a discrepancy between his consciousness level and the EEG findings. The patient moaned loudly all day long, especially when someone was beside him. Although he reacted only to pain stimuli, he seemed to be aware of his circumstances. His parents told us that his situation had been stressful. Because he was apyrexial, and neither inflammatory nor abnormal MRI findings were present, a conversion reaction was suspected. Other possibilities were acute disseminated encephalomyelitis, herpetic brainstem encephalitis, and BBE. From day 2, he was given 1500 mg acyclovir intravenously daily for 2 days and 1 g methylprednisolone daily for 3 days. His neurological signs and symptoms, however, deteriorated rapidly after admission. During the evening of day 2, he became semicomatose. The eyeballs were fixed in the central position, and there was no eye movement in any direction. Both pupils were dilated and reacted sluggishly to light. Oculocephalic reflexes were negative. On day 10, consciousness began to return, and he was fully conscious on day 12. Repeated brain MRI on day 14 detected no abnormalities. On day 19, he could walk without support but had markedly ataxic gait. Another CSF examination on day 22 showed 18 mg/dl protein with 1 cell/μl.

On day 27, an enzyme-linked immunosorbent assay (ELISA) showed high IgM antibody titer against GM1b and GalNAc-GD1a in serum obtained on day 2 (described below). The patient had had an antecedent infection and had the CNS signs of consciousness disturbance and hyperreflexia in addition to ophthalmoplegia and ataxia. Based on his clinical features, which included EEG abnormalities and the presence of anti-ganglioside antibodies, BBE was diagnosed. As there had been no amelioration of his

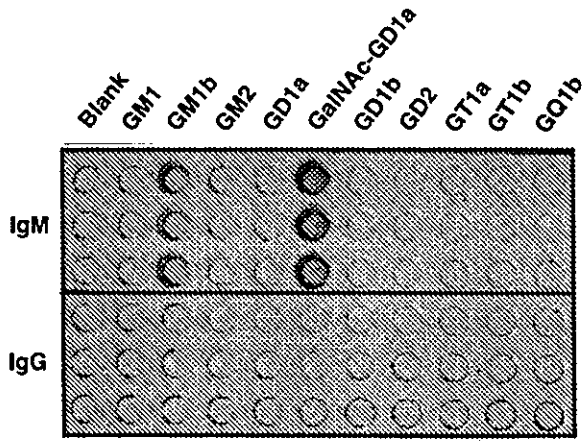

Fig. 2. Antigenic reactions against IgG and IgM class gangliosides. Antigens (top) with which the wells of each column were coated. Serum obtained on day 2 was assayed in triplicate. Strong IgM activities against GM1b and GalNAc-GD1a were detected. Anti-GM2 IgM activity was slightly elevated.

ophthalmoplegia up to this time, starting on day 28, he was given 0.4 g/kg immunoglobulin (Venilon-I®, Kaketsuken, Kumamoto, Japan) intravenously, daily for 5 days. Ataxic gait and gaze limitation disappeared, respectively, on days 44 and 102. Motor nerve conduction velocity in the left median nerve was normal on day 41. On day 49, EEG showed a return to normal.

3. Anti-*C. jejuni* and anti-ganglioside antibody titers and the anti-ganglioside antibody absorption study

Serum IgM, IgG, and IgA antibody titers to *C. jejuni* were measured by an ELISA [12]. Both the IgM and IgA antibody titers to *C. jejuni* were 1000 (normal, less than 500) on day 2, but they had decreased to the normal range by day 75. These decreases suggested a recent *C. jejuni* infection.

Serum IgG and IgM antibody activities against gangliosides GM1, GM1b, GM2, GD1a, GalNAc-GD1a, GD2, GD1b, GT1a, GT1b, and GQ1b were measured by an ELISA, as described elsewhere [13]. The anti-GM1b and anti-GalNAc-GD1a IgM antibodies titers were, respectively, 16,000 and 32,000 on day 2, whereas the other antibody titers were negative (Fig. 2). On day 75, these antibody titers had decreased, respectively, to 2000 and 1000. Absorption studies of the anti-GM1b and anti-GalNAc-GD1a IgM antibodies were made, using as absorbers GM1b, GalNAc-GD1a, GM1, GM2, and GQ1b, as described elsewhere [13]. Anti-GalNAc-GD1a IgM antibody was effectively absorbed by GM1b, as well as by GalNAc-GD1a, but not by GM1, GM2, or GQ1b, evidence that anti-GalNAc-GD1a IgM antibody cross-reacts with GM1b, and anti-GM1b IgM antibody with GalNAc-GD1a (Fig. 3).

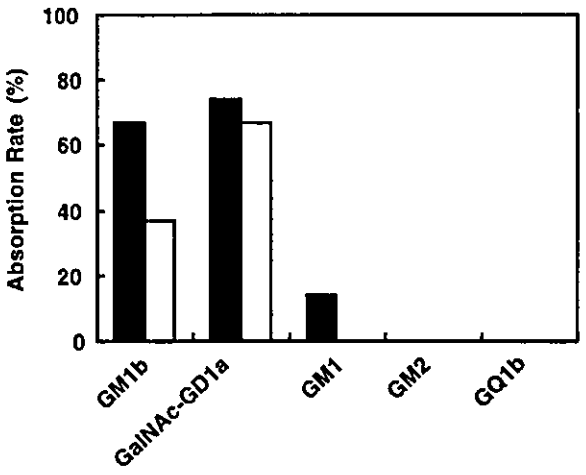

Fig. 3. Absorption study of the anti-GM1b and anti-GalNAc-GD1a IgM antibodies. Grey bars, anti-GM1b IgM antibody absorption rates. White bars, anti-GalNAc-GD1a IgM antibody absorption rates. The absorbers were GM1b, GalNAc-GD1a, GM1, GM2, and GQ1b. Absorption rates (%) were calculated from [1 − (optical densities in wells with sera for absorption − treatment)/(optical densities in reference wells with sera without absorption − treatment)] × 100.

4. Discussion

Subsequent to having watery diarrhea, our patient showed rapid, monophasic development of external ophthalmoplegia, cerebellar-like ataxia, and hyperreflexia. He also had consciousness disturbance (drowsiness and semicoma) and EEG abnormalities. We concluded that he had BBE. Serological results confirmed that there had been previous *C. jejuni* infection.

The patient in a previous report of BBE after *C. jejuni* enteritis had the anti-GQ1b IgG antibody [4], whereas our patient had the anti-GalNAc-GD1a and anti-GM1b IgM antibodies, serological markers of GBS [8–11]. This is the first report of BBE associated with the anti-GM1b and anti-GalNAc-GD1a IgM antibodies. Why our patient developed BBE rather than GBS is not clear. Possibly, the ganglioside composition of human nerves may vary in members of a population [14]. The correlation between the longitudinal antibody titers and clinical improvement suggests that the antibodies may be involved in BBE pathogenesis and that they may prove useful serological markers for diagnosing BBE without anti-GQ1b IgG antibody.

The etiology of BBE may be similar to that of GBS because of such common features as antecedent infection, areflexia, and CSF albuminocytological dissociation [1]. Moreover, the existence of overlapping cases of BBE and GBS [15,16] and BBE subsequent to *C. jejuni* enteritis [4] support the speculation that BBE is closely related to GBS, part of a continuous spectrum. The *C. jejuni* isolated from GBS patients had a lipo-oligosaccharide that bore the GM1b or GalNAc-GD1a epitope [10,11], whereas a considerable number of GBS patients who had the anti-GM1b or anti-GalNAc-GD1a antibody had a history of preceding *C. jejuni* infection [9,17]. These findings suggest there is a causative relationship between *C. jejuni* infection and GBS associated with anti-GM1b or anti-GalNAc-GD1a antibodies. Anti-GM1b and anti-GalNAc-GD1a antibodies frequently coexist in GBS patients [9,18]. Anti-GM1b IgG antibody titers in two GBS patients were significantly decreased by absorption with GalNAc-GD1a [18]. Furthermore, the absorption study done on our patient showed that the anti-GalNAc-GD1a and anti-GM1b IgM antibodies are cross-reactive.

An immunohistochemical study, done with an anti-GM1b monoclonal antibody, showed dense localization of GM1b in the forebrain, midbrain, and cerebellum [19]. Interestingly, anti-GM1b monoclonal antibody-labeled granule cell bodies were present in both the external and inner granular layers of the cerebellum. Infection by *C. jejuni* that bears an epitope of a GM1b-like or GalNAc-GD1a-like lipooligosaccharide may have induced the production of IgM antibodies to GM1b and GalNAc-GD1a and triggered our patient's cerebellar ataxia. The GM1b and GalNAc-

GD1a distributions in the human brain need to be studied in light of this speculation.

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ワークショップ4

ヒト外眼筋支配脳神経におけるGQ1b/GT1a糖鎖抗原のsubcellular localizationの検討

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目的

自己免疫性末梢神経障害における抗糖脂質抗体の病因的意義を支持する知見が集積されつつあるが、その作用部位と作用機序の詳細についてはまだ解明されていない点が多い。我々はヒトの外眼筋を支配する脳神経傍絞輪部へのGQ1b/GT1a糖鎖抗原の特異的集積を示したが、さらにその集積部位における局在をsubcellularレベルで検討する。

方法

剖検にて得られたヒトの動眼神経または外転神経の凍結切片を、アセトンあるいはアセトン-パラフォルムアルデヒド等で固定し、Fisher症候群患者血清血清抗GQ1b抗体と同じ微細反応性を有する抗GQ1b/GT1aモノクローナル抗体7F5で免疫染色し、共焦点顕微鏡・電子顕微鏡により観察した。電子顕微鏡用のサンプルはDABで発色を行った。

結果

共焦点顕微鏡の連続切片画像の3次元再構成では蛍光は絞輪部を頂点として広がる底面のない中空の円錐ー楕円筒状の分布を示した。免疫電顕による検討では、ミエリン周囲を取り囲む膜状の構造物に染色を認め、また軸索とミエリンの境界部にも染色を認めた。またミエリンの二重層構造が失われて泡沫様の膜構造物が集簇している部位において、その泡沫状の膜に染色を認めた。その部位での染色される部分の密度はミエリン最外層部でのものよりも高いように思われた。

考察

今回観察された免疫電顕像からは傍絞輪部だけではなくミエリン二重層の最外部にあるSchwann細胞の細胞膜にもGQ1b/GT1a糖鎖抗原が存在すると考えられた。ミエリンの最内層部と軸索の境界部の染色に関しては、その部位がミエリン側の最内層部か軸索膜側かは、今回の観察では識別できなかった。ミエリンの層構造が失われて泡沫様の膜構造物が集簇している部位はその位置関係からは恐らく、傍絞輪部においてミエリンの二重層構造が失われてSchwann細胞の細胞膜が細絨毛状に広がっている部位のではないかと考えられるが、その部位において染色の密度が高く見えるのは、単位面積当たりのSchwann細胞の細胞膜の密度が高いことによる可能性も考えられる。

7F5によるGQ1b/GT1a糖鎖抗原性の検出には切片のアセトン処理を要することから電顕による超微形態の評価には限界があるが、今回の検討からはGQ1b/GT1a糖鎖抗原はヒトの外眼筋を支配する脳神経のSchwann細胞の細胞膜に局在し、細胞膜の存在密度の高くなる傍絞輪部により集積して存在している可能性が高いと考えられた。

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A study on serum autoantibodies in post-infectious acute cerebellar ataxia

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Acute cerebellar ataxia (ACA) is characterised by an acute onset of self-limiting ataxia following a systemic viral infection. An autoimmune process has been suggested and some anti-neuronal antibodies were reported in ACA, but their antigen molecules have not been identified. We searched for serum antibodies in patients with ACA by Western blot (W/B) using a total protein fraction extracted from the cerebellar tissue with 2% SDS as the antigen. We found an IgM antibody that strongly reacted with a protein of approximately 28 kDa. The cerebellar cortex showed the strongest antigenicity among various nervous and non-nervous tissues based on the same amount of protein, and the strongest reaction was detected in the cytoplasmic fraction. The antigen protein was separated by 2D-electrophoresis and subjected to N-terminal amino acid sequencing. The sequence of 11 amino acid residues was shown to be identical with the N-terminal sequence of triose phosphate isomerase (TPI). Further, in 8 of 23 serum samples from patients with ACA, bands of the same mobility were detected by W/B. Anti-TPI IgM antibody titers were measured quantitatively using ELISA and the same 8 patients showed a significantly high antibody titer above mean +3SD of healthy controls (n=45), which decreased over time in patients checked in a time course evaluation. These findings suggest that the anti-TPI IgM antibody may be related to ACA.