Antiganglioside antibody in patients with Guillain-Barré syndrome who show bulbar palsy as an initial symptom

Michiaki Koga, Nobuhiro Yuki, Koichi Hirata

Abstract

Objectives—To identify valuable antiganglioside antibodies that support the diagnosis of Guillain-Barré syndrome (GBS) and its variants in patients showing bulbar palsy as an initial symptom.

Methods—Medical records of 602 patients with GBS or its variants were reviewed. Fifteen patients had bulbar palsy as an initial symptom. Serum antibodies against GM1, GM1b, GD1a, GalNAc-GD1a, GT1a, and GQ1b were examined in 13 of them.

Results—Serum antiganglioside antibodies were positive in 11 (85%) patients. IgG anti-GT1a (n=8; 62%) and anti-GM1b (n=7; 54%) antibodies were often present, whereas all the patients had low or no anti-GM1 antibody activity. High anti-GD1a and anti-GQ1b IgG antibody titres were also present in some patients, but most had higher IgG antibody titres to GM1b or GT1a. All five patients with high IgG antibody titre to GM1b or GT1a only had had antecedent diarrhoea. Some patients with pharyngeal-cervical-brachial weakness (PCB) had IgG antibody to GT1a which did not cross react with GQ1b. Other patients with PCB had antibody to GT1a which cross reacted with GQ1b or antibody to GM1b, but anti-GM1b and anti-GT1a antibodies were not associated with the presence of bulbar palsy. All the patients who had no IgG antiganglioside antibodies recovered completely.

Conclusions—Measurement of serum IgG anti-GT1a and anti-GM1b antibodies gives helpful support for the diagnosis of GBS and its variants when there is early involvement of the oropharyngeal function independently of other neurological findings which appear as the illness progresses.

Keywords: Guillain-Barré syndrome; bulbar palsy; antiganglioside antibody

Bulbar palsy may be an initial clinical sign in several neurological or non-neurological disorders. Dysphagia and dysarthria often appear at the beginning of botulism and diphtheria. Myasthenia gravis, brainstem vascular disturbance, multiple sclerosis, and tumour invasion to the vagus nerve sometimes show oropharyngeal dysfunctions early in the clinical course. Guillain-Barré syndrome (GBS) also may have the initial neurological sign of bulbar palsy, although very rarely. Patients with GBS should be treated with plasmapheresis or intravenous immunoglobulin as soon as possible to shorten the duration of disability. It is therefore important to differentiate GBS and its variants, which show early oropharyngeal dysfunctions, from other disorders. Physiological studies and CSF testing, however, may detect no abnormalities in some patients with GBS who show bulbar palsy early.

Measurement of serum antiganglioside antibodies should prove useful for supporting the diagnosis of GBS or its variants. The major gangliosides GM1 and GD1a are target molecules for the autoantibodies found in GBS and its variants. The presence of IgG anti-GM1 antibody, strong supportive evidence for the diagnosis of GBS, however, is not common in patients with GBS with cranial nerve involvement. Furthermore, there are only a few reports on serum antiganglioside antibodies in patients with GBS or its variants who show bulbar palsy as an initial symptom, and it is not clear which antiganglioside antibodies are useful for differentiating GBS with early oropharyngeal dysfunction from other disorders. To assess the diagnostic value of the antiganglioside antibodies present in patients with GBS and its variants who had bulbar palsy as an initial symptom, we examined the frequencies of detectable serum antibodies to various gangliosides, including minor ones, in these patients and the relation of antiganglioside antibodies to clinical features.

Patients and methods

Patients
Medical records were reviewed of 387 patients with GBS, 156 with Fisher’s syndrome (FS), 36 with Bickerstaff’s brainstem encephalitis (BBE), and 23 with acute ophthalmoparesis, all...
of whom had been referred to our neuroimmunological laboratory between June 1994 and March 1998 for tests for serum antiganglioside antibodies. Diagnoses of GBS, FS, and acute ophthalmoplegias were based on established clinical criteria. Patients with BBE fulfilled all the following: (1) presence of external ophthalmoplegia and cerebellar ataxia; (2) consciousness disturbance or presence of long tract signs such as pyramidal signs and hemisensory disturbance; (3) recovery from neurological deficits beginning within 4 weeks of onset; and (4) ability to rule out the diagnosis of cerebral vascular disease, brain tumour, Wernicke’s encephalopathy, botulism, multiple sclerosis, or herpes simplex virus encephalitis. Our review of current illness and neurological signs on the day of admission indicated that 15 patients (mean age 34; nine males; six females) had bulbar palsy as an initial symptom (11 patients with GBS, two with FS, one with BBE, and one with acute ophthalmoplegias). Of these 15 patients, serum samples were taken within 4 weeks of the onset of neurological symptoms from 13 (87%) (mean age 34; seven males; six females, table 1), who therefore were included in the present study. The details of patients 5 and 6 have been reported elsewhere. To monitor the functional prognosis of the patients, follow up faxes were sent when possible to the physicians who treated the patients during the recovery phase of the illness. Because serum antibodies against GM1b were frequent in patients with GBS with early involvement of the lower cranial nerves, we also examined 175 consecutive patients with GBS (n=124) or FS (n=51) to determine whether the presence of bulbar palsy is significantly related to serum anti-GM1b IgG and IgM antibodies.

**ENZYME LINKED IMMUNOSORBENT ASSAY**

We measured the serum antibodies to GM1, GM1b, GD1a, GalNAc-GD1a, GT1a, and GQ1b using the enzyme linked immunosorbent assay (ELISA) described elsewhere. Serum was considered positive when the antibody titre was $\geq 500$

**ABSORPTION STUDY**

This study was done as described elsewhere with minor modifications. Antiganglioside antibodies were absorbed in microtitre wells coated with 10 pmole portions of ganglioside. Absorption rates were expressed as percentages of the optical densities obtained with and without absorption treatment.

**Results**

**CLINICAL FEATURES (TABLE 1)**

Eleven (92%) of 12 patients for whom clinical data were available had had antecedent symptoms, of which upper respiratory infection was the most frequent (n=7; 58%) and diarrhoea the second (n=6; 50%). The patients often complained of dysesthesia in the distal extremities at the time bulbar palsy appeared. Facial palsy and ophthalmoplegia were frequent (facial palsy, 77%; ophthalmoplegias, 69%). Muscle weakness was present in some or all limbs in 10 (77%) patients, of whom seven (54%) had arm dominant weakness but no leg dominant weakness. Only one (patient 5), as reported elsewhere, met the clinical criteria for pharyngeal-cervical-brachial weakness (PCB) proposed by Ropper. The other six (patients 2, 6, 8, 10, 12, and 13) with arm dominant weakness also had severe weakness for neck flexion, but did not fulfill the criteria for PCB because areflexia and/or muscle weakness were present throughout the lower limbs. Babinski’s sign, drowsiness, ophthalmoplegias, and ataxia were present temporarily in patient 8, in whom the diagnosis of BBE was made. Assisted ventilation was required in five patients (2, 3, 8, 11, and 12). Four patients (6, 11, 12, and 13) made complete recoveries within 3 to 12 months after onset, whereas moderate or severe limb weakness remained in patients 1, 3, 10 to 4 months after onset. Bulbar palsy disappeared in all the patients for whom clinical progosis data were available. Mild ophthalmoplegias were present in six patients (3, 4, 5, 7, 8, and 9) from 3 weeks to 18 months after onset, but they had no problems in carrying out daily activities.

**ANTIGANGLIOSIDE ANTIBODIES**

Serum antiganglioside antibodies were positive in 11 (85%) of 13 patients (table 2). IgG anti-GT1a (n=8; 62%) and anti-GM1b (n=7; 54%) antibodies were frequent, whereas anti-GM1 antibody activity was low or not detected. High anti-GD1a and anti-GQ1b IgG antibody titres were found in some patients, but all except one (patient 10) had higher IgG antibody titres to GM1b or GT1a.

Patients were classified into four groups (groups A-D) according to their IgG antigen-ganglioside antibodies (table 2). Group A (patients...
Table 2  Antiganglioside antibody titres in GBS patients with the initial symptom of bulbar palsy

<table>
<thead>
<tr>
<th>No</th>
<th>GM1</th>
<th>GM1b</th>
<th>GD1a</th>
<th>GalNAc-GD1a</th>
<th>GT1a</th>
<th>GQ1b</th>
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<tbody>
<tr>
<td>1</td>
<td>500</td>
<td>25600</td>
<td>64000</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>500</td>
<td>12800</td>
<td>1000</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>12800</td>
<td>-</td>
<td>500</td>
<td>4000</td>
<td>500</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>4000</td>
<td>-</td>
<td>-</td>
<td>500</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1000</td>
<td>32000</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>32000</td>
<td>500</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>4000</td>
<td>64000</td>
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<td>102400</td>
<td>25600</td>
</tr>
<tr>
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<td>-</td>
<td>500</td>
<td>-</td>
<td>32000</td>
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<td>-</td>
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<td>-</td>
<td>-</td>
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<td>500</td>
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<tr>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>32000</td>
<td>500</td>
</tr>
<tr>
<td>13</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>500</td>
<td>500</td>
</tr>
</tbody>
</table>

Only titres of ≥500 are shown.

Table 3  Absorption rate of IgG anti-GM1b antibody and IgG anti-GT1a antibody

<table>
<thead>
<tr>
<th>Absorber</th>
<th>GM1</th>
<th>GM1b</th>
<th>GD1a</th>
<th>GalNAc-GD1a</th>
<th>GT1a</th>
<th>GQ1b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>Absorption rate of IgG anti-GM1b Ab(%)</td>
<td>Absorption rate of IgG anti-GT1a Ab(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>96</td>
<td>2</td>
<td>82</td>
<td>1</td>
<td></td>
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<tr>
<td>2</td>
<td>25</td>
<td>55</td>
<td>0</td>
<td>2</td>
<td>0</td>
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</tr>
<tr>
<td>3</td>
<td>13</td>
<td>82</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Patient</td>
<td>Absorption rate of IgG anti-GT1a Ab(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0</td>
<td>75</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>0</td>
<td>80</td>
<td>0</td>
<td></td>
<td></td>
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<tr>
<td>8</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>0</td>
<td>0</td>
<td>81</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>3</td>
<td>14</td>
<td>78</td>
<td>11</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1–4) had a marked increase in IgG anti-GM1b antibody, which was not absorbed by GT1a or GQ1b, but in some patients were absorbed by GD1a or GM1 (table 3). In group B (patients 5–7), IgG anti-GT1a antibodies that did not cross react with GQ1b were detected as described elsewhere. Group C (patients 8–10) had IgG anti-GT1a antibodies which cross reacted with GQ1b and sometimes with GD1a (table 3). Group D (patients 11–13) had no IgG antibodies to the gangliosides used in this study. Thin layer chromatography (TLC) with immunostaining was performed using serum samples from two patients (1 and 8). Serum IgG from patient 1 reacted with GM1b ganglioside but not with others such as GM1, GD1a, GT1a, or GQ1b on TLC (data not shown). The IgG from patient 8 reacted strongly with GT1a and more weakly with GQ1b (data not shown).

Three (75%) of the four patients in group A had antecedent diarrhoea, and all showed facial palsy. Two had moderate to severe residual muscle weakness 10 to 16 weeks after onset, and one made a complete recovery, except for mild ophthalmoparesis, 5 months after onset. In groups B and C, ophthalmoparesis and arm dominant limb weakness were often present, and minimal residual symptoms of ophthalmoparesis remained. In Group D, ophthalmoparesis was less common and all three patients made a complete recovery. Five (71%) of the seven patients 2, 5, 6, 8, 10, 12, and 13 with PCB-like symptoms had high IgG antiganglioside antibody titre; two had IgG anti-GT1a antibodies which did not cross react with GQ1b (group B), two had IgG anti-GT1a and GQ1b antibodies which cross reacted with each other (group C), and one had a marked increase in IgG anti-GM1b antibodies (group A).

Discussion

We often found serum antiganglioside antibodies in patients with GBS or its variants in whom bulbar palsy appeared early in the illness. Measurement of these autoantibodies should be useful to distinguish GBS with early involvement of oropharyngeal functions from such other disorders as botulism and myasthenia gravis. Of the antiganglioside antibodies, IgG anti-GT1a and anti-GM1b seem to be particularly valuable as diagnostic markers for GBS and its variants in which there is early appearance of bulbar palsy, because five (38%) of 13 patients (patients 2–6) had very high antibody activity to GT1a or GM1b, and low or no activity to other gangliosides. Conversely, measurement of anti-GM1 and anti-GalNAc-GD1a antibodies does not seem useful for distinguishing GBS from other diseases when bulbar palsy appears early in the clinical course. All five patients (2–6) with high IgG antibody titre only to GM1b or GT1a had had antecedent diarrhoea, whereas patients 1, 8, 9, and 10, with high antibody titres to other gangliosides as well as GM1b and GT1a, often had a history of prior upper respiratory infection. In patients with a history of antecedent diarrhoea in particular, measurement of serum IgG antibodies to gangliosides other than GM1b and GT1a may give false negative results in serological examinations.

GT1a and GM1b are minor human brain gangliosides, that also seem to be present on human peripheral nerves. The gram negative bacterium Campylobacter jejuni, a leading agent of antecedent infection in GBS, was isolated from a stool specimen of one patient (3), who had increased IgG antibody titre against GM1b and GT1a. Some strains of C jejuni that had been isolated from patients with GBS have lipopolysaccharides bearing sugars...
that mimic those of GT1a\textsuperscript{15,26,27} and GM1b.\textsuperscript{15} Molecular mimicry therefore may function in the induction of anti-GT1a and anti-GM1b antibodies which cause neurological deficits such as bulbar palsy in some patients with GBS or its variants, but anti-GT1a\textsuperscript{15,16} and anti-GM1b antibodies are not associated with the presence of bulbar palsy in most patients.

Unlike patients with classic ascending GBS, seven (54%) of the 13 patients in this study showed neck and arm dominant muscle weakness, originally described by Ropper in PCB,\textsuperscript{2} whereas the tendon reflex was preserved in the legs of only one patient. Although most of the patients with PCB described by Ropper et al.\textsuperscript{14} made slow recoveries, the bulbar palsy in most of the patients in our study completely disappeared. Limb weakness rather than bulbar palsy remained as a residual symptom in some patients who had early bulbar palsy.

Mizoguchi et al.\textsuperscript{2} and ourselves\textsuperscript{17,21} reported the detection of IgG anti-GT1a antibody which does not cross react with GQ1b in PCB. We have now confirmed that anti-GT1a antibody which cross reacts with GQ1b and anti-GM1b antibody is also present in some patients with PCB-like symptoms. In three patients with acute oropharyngeal palsy as described by O’Leary et al.\textsuperscript{29} serum IgG antibodies against GT1a and GQ1b were found during the acute phase of the illness. None of the patients had ophthalmoplegia during the clinical course, even though IgG anti-GQ1b and anti-GT1a antibodies are closely associated with the presence of ophthalmoplegia.\textsuperscript{20} In another patient with GBS, described by Mizoguchi et al.,\textsuperscript{22} who had bulbar palsy and generalised muscle weakness but no ophthalmoplegia, the IgG anti-GQ1b and anti-GT1a antibody titres were also raised. We have confirmed that patients who initially had bulbar palsy and later ophthalmoparesis also had raised IgG antibody titres to GQ1b and GT1a as do patients with “typical” FS. We speculate that the involvement of the oculomotor nerves in acute oropharyngeal palsy depends on the severity of the illness and that acute oropharyngeal palsy with increased serum IgG antibody titres to GQ1b and GT1a can be defined as an early clinical stage of FS, BBE, or PCB.

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