Serum anti-GQ\textsubscript{1b} IgG antibody is associated with ophthalmoplegia in Miller Fisher syndrome and Guillain-Barré syndrome: Clinical and immunohistochemical studies

A. Chiba, MD; S. Kusunoki, MD; H. Obata, MD; R. Machinami, MD; and I. Kanazawa, MD

**Article abstract**—To determine the significance of serum anti-GQ\textsubscript{1b} IgG antibody, we studied the disease spectrum associated with this antibody and GQ\textsubscript{1b} epitope in the human nervous system. We examined sera from 19 patients with typical Miller Fisher syndrome (MFS), five patients with acute postinfectious ophthalmoplegia without ataxia (atypical MFS), six patients with Guillain-Barré syndrome (GBS) with ophthalmoplegia (GBS-OP\textsubscript{+}), and 23 patients with GBS without ophthalmoplegia (GBS-OP\textsubscript{-}). We also examined sera from 84 patients with other neurologic or non-neurologic disorders and from 16 normal control subjects. Eighteen of the 19 patients with typical MFS, all the patients with atypical MFS, and five of the six patients with GBS-OP\textsubscript{+} had increased anti-GQ\textsubscript{1b} IgG activity in ELISA, but none of the patients in the other groups, including GBS-OP\textsubscript{-}, had it. All the patients’ sera that had anti-GQ\textsubscript{1b} IgG antibody showed anti-GT\textsubscript{m} IgG activity. Results of absorption studies suggested that the same antibody reacted with GQ\textsubscript{1b} and GT\textsubscript{m}. An anti-GQ\textsubscript{1b} mouse monoclonal antibody immunostained the paranodal regions of the extramedullary portion of the human oculomotor, trochlear, and abducens nerves. Biochemical analysis showed that the human oculomotor nerve contained a larger amount of GQ\textsubscript{1b} than did the ventral and dorsal roots of the spinal cord. We conclude that serum IgG antibody against GQ\textsubscript{1b} is very closely associated with acute postinfectious ophthalmoplegia in MFS and GBS.

C. Miller Fisher described\textsuperscript{1} a syndrome consisting of ophthalmoplegia, ataxia, and areflexia (Miller Fisher syndrome [MFS]). Although, on the basis of common clinical features, he regarded it as a variant of Guillain-Barré syndrome (GBS), the relation between MFS and GBS and the pathogenesis for the features unique to MFS are unknown.

Serum antiganglioside antibodies are present in GBS.\textsuperscript{2-5} Recently, we reported\textsuperscript{6} the presence of serum IgG antibody against ganglioside GQ\textsubscript{1b} in patients with MFS in the acute phase and pointed out an immunologic feature common to MFS and GBS: the presence of antiganglioside antibody. Serum antiganglioside antibodies also are present in, and possibly involved in the pathogenesis of, motor neuron disease (MND) and multifocal motor neuropathy (MMN).\textsuperscript{7,11}

To evaluate the significance of serum anti-GQ\textsubscript{1b} IgG antibody in detail, we investigated whether this antibody is present in larger groups of patients that included those with atypical MFS and GBS with ophthalmoplegia. We also investigated the distribution of the epitope for anti-GQ\textsubscript{1b} antibody immunohistochemically using a mouse monoclonal antibody (mAb).

**Methods.** Examination of anticylgolipid antibody in patients’ sera. **Patients.** Serum samples were obtained from 19 patients with typical MFS, all of whom had the triad of the syndrome (ophthalmoplegia, ataxia, and hyporeflexia) but no major limb weakness or other signs suggestive of CNS involvement. We also examined five patients who experienced acute ophthalmoplegia after an infectious prodrome (four infected with common cold and one with diarrhea) who recovered without specific therapy. They all had a relatively mild bilateral abducens palsy; two had hyporeflexia, two a mild decrease of vibration sense in the lower extremities, and two a mild albuminocytologic dissociation in the cerebrospinal fluid, but...
none had ataxia or any other neurologic sign. This group was designated "atypical MFS."

Serum samples also were taken from six patients who had GBS and ophthalmoplegia (GBS-OP(+)). Twenty-three patients with GBS but without ophthalmoplegia (GBS-OP(-)) also were examined, three of whom showed ataxia that was considered to be due to loss of position sense. In the others, ataxia was absent or could not be assessed because of limb weakness. The clinical features of these patients are given in the table. Neurologists examined them in the acute phase. The first serum samples were taken in the acute phase, except for one patient with atypical MFS and one patient with GBS-OP(+), from whom samples were obtained 60 days (atypical MFS) and 53 days (GBS-OP(+)) after neurologic onset.

As disease controls, serum samples were taken from two patients with brainstem encephalitis, 24 with MS, five with MMN, 12 with chronic inflammatory demyelinating polyneuropathy (CIDP), and 23 with MND, as well as 18 patients with other immunologic disorders, nine of whom had systemic lupus erythematosus, seven polymyositis, and two mixed connective tissue disorder. Except for MND, the samples were taken in the acute, active, or relapse phases of the disorders. Samples also were taken from 16 normal control subjects. Both patients with brainstem encephalitis had lesions in the brainstem, as confirmed by MRI, showing abnormal ocular movement (conjugate gaze palsy in one, coarse horizontal gaze nystagmus in the other), ataxia, and hyporeflexia, as well as consciousness disturbance and dysarthria. They eventually recovered. Serologic examinations suggested herpes simplex virus infection in one of them, but the causative agent in the other is not known. Of the 24 patients with MS, nine had ataxia and four ophthalmoplegia or diplopia. All five patients with MMN had the serum anti-GM1, IgM antibody. None of the patients with CIDP had ophthalmoplegia.

Table. Clinical features of patient groups

<table>
<thead>
<tr>
<th>No. pts</th>
<th>Ophthalmoplegia</th>
<th>Hypo- or areflexia</th>
<th>Limb weakness</th>
<th>First serum examination*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical MFS</td>
<td>Ext</td>
<td>Int</td>
<td>Ataxia</td>
<td>+</td>
</tr>
<tr>
<td>Atypical MFS</td>
<td>5</td>
<td>+</td>
<td>or +</td>
<td>or +</td>
</tr>
<tr>
<td>GBS-OP(+)</td>
<td>6</td>
<td>+</td>
<td>or +</td>
<td>or</td>
</tr>
<tr>
<td>GBS-OP(-)</td>
<td>23</td>
<td>–</td>
<td>–</td>
<td>9-40</td>
</tr>
</tbody>
</table>

* Range in days. |
| Ext | External ophthalmoplegia. |
| Int | Internal ophthalmoplegia. |
| MFS | Miller Fisher syndrome. |
| GBS-OP(+) | Guillain-Barre syndrome (GBS) with ophthalmoplegia. |

GBS-OP(-) GBS without ophthalmoplegia. |
| Present. |
| Absent. |
| Minimal. |
| ? Unable to be assessed because of limb weakness. |

diluted serially from 1:10 with blocking solution was added in duplicate to the antigen-coated and -uncoated wells, after which the plates were incubated overnight at 4 °C. The wells then were washed three times with the blocking solution and incubated for 2 hours at room temperature with 50 µl of peroxidase-conjugated goat anti-human IgG antibody (y-chain specific; Cappel, West Chester, PA) diluted 1:500 with blocking solution. Next, they were washed three times then incubated with 200 µl of 40 mg/ml of o-phenylenediamine dihydrochloride and 0.006% H2O2 in phosphate-citrate buffer, pH 5.0, as the enzyme substrate. The reaction was stopped by the addition of 50 µl of 8N H2SO4. The color reaction was read at 492 nm with an ELISA reader (BioRad, Hercules, CA). Readings for the GQ1b-uncoated wells were subtracted from those for the GQ1b-coated wells. The titer for each patient was taken as the highest dilution factor at which the mean OD of the duplicate wells exceeded the cutoff value. This corresponded to the mean + 3 SD of the normal control sera at the dilution of 1:10. Taking into account the variations of the OD values in the different experiments, we determined the cutoff value for each assay by using serially diluted positive standard serum on the same plate. This value ranged from 0.215 to 0.350 in the anti-GQ1b IgG antibody assay. Serum anti-GQ1b IgM antibody and the IgM and IgG antibodies against other glycolipids (GM1, GM2, GM3, GD1a, GD1b, GD3, GT1b, GA1, galactocerebroside) also were examined by ELISA, as described earlier, at a serum dilution of 1:40. For the second antibody in the IgM class, we used peroxidase-conjugated goat antihuman IgM antibody (µ-chain specific; Cappel) diluted 1:200. The cutoff value also corresponded to the mean + 3 SD of the normal control sera for each glycolipid.

Thin-layer chromatography (TLC) and enzyme immunoassays. GM1, GD1a, GD1b, GT1b, GQ1b, and GT1a were the test antigens used. GT1a was the gift of Dr. Susumu Ando, Tokyo Metropolitan Institute of Gerontology. A 500-ng sample of each purified ganglioside was loaded on a plastic-backed TLC plate (Macherey-Nagel, Düren, Germany) and developed with chloroform:methanol:0.2% CaCl2 (45:55:10). The plate then was air-dried, dipped in a solution of 0.4% polysobutylmethacrylate in n-hexane, and air-dried again. Nonspecific protein-binding sites were saturated with 10% normal goat serum in PBS. The different lanes on the plate were overlaid with sera from the patients or normal control subjects diluted with 10% normal goat serum in PBS: 1:40 for patients with anti-GQ1b IgG antibody titers above 1:160 in ELISA and 1:20 for subjects with titers
below 1:80. The plate then was incubated overnight at 4 °C, after which it was washed with PBS and incubated for 2 hours at room temperature with peroxidase-conjugated goat antihuman IgG antibody diluted 1:200. Immunoreactants were made visible with PBS containing 50 mg/ml 3,3’-diaminobenzidine tetrahydrochloride and 0.01% H2O2.

**Absorption study.** Antiglycolipid antibodies were absorbed in the antigen-coated ELISA wells. Each well of the microtiter plate was coated with 500 ng of purified glycolipid. Nonspecific protein-binding sites were saturated with 10% normal goat serum in PBS, in the same ratio used for the TLC-enzyme immunoassay, was added to both the antigen-coated and -uncoated wells, after which the plates were incubated overnight at 4 °C. The residual antiglycolipid activities of the supernatants were assayed by TLC-enzyme immunoassay, and the activities absorbed in the wells were assayed by ELISA. We confirmed there were no significant differences in the protein concentrations of the materials absorbed by this method.

**Immunohistochemical and biochemical studies.** We used tissue specimens obtained from autopsied patients with no known neurologic disorders. These specimens were frozen within 18 hours of death and kept at −80 °C until used.

**Immunohistochemical study.** Human nerve tissues were studied immunohistochemically with a monoclonal antibody, mAb 7F5, that reacts with both GQ1b and GT1b and belongs to the IgG2 subclass of the mouse. This antibody was provided by Mecto (Tokyo, Japan). We examined all 12 cranial nerves and the ventral and dorsal roots of the lumbar spinal cord, as well as the femoral nerve, dorsal root ganglion (DRG), thoracic spinal cord, cerebellum, and brainstem. Specimens were frozen in isopentane cooled in liquid nitrogen. Sections of 10 μm were cut on a cryostat at −25 °C, then mounted on gelatin-coated slide glasses, air dried, and fixed in cold acetone for 5 minutes, after which they were immunostained with Vectastain ABC kit (Vector Laboratories, Burlingame, CA). After incubating them with 1.5% normal horse serum, the sections were incubated overnight at 4 °C with mAb 7F5 diluted 1:400 (corresponding to 15 μg of IgG2, per ml), after which they were washed twice with PBS (10 minutes each), then incubated for 2 hours at room temperature with biotinylated horse antimouse IgG antibody (1:200). After two washings with PBS, the sections were incubated for 1 hour at room temperature with the avidin-biotin complex. After two more PBS washes, the immunoreactants were made visible with 3% BSA for 6 hours at room temperature, the membrane was incubated overnight at 4 °C with the first antibody diluted with Tris-buffered saline (pH 8.0) containing 0.05% Tween 20. After being washed, the membrane was incubated for 2 hours at room temperature with alkaline phosphatase-conjugated antihuman IgG antibody (1:200). The second antibody for mAb 7F5 was peroxidase-conjugated goat antimouse IgG antibody (1:200) (Cappel) and, for the patient’s serum, peroxidase-conjugated goat antihuman IgG antibody (1:200).

**Western blot analysis.** Specimens were homogenized in ice-cold modified Laemmli’s sample buffer containing 0.08 M Tris-HCl (pH 6.8), 2% sodium dodecyl sulfate (SDS), 10% glycerol, and 0.1 M dithiothreitol. After the samples had been immersed in boiling water for 1.5 minutes, insoluble precipitates were removed by centrifugation at 10,000 × g and 4 °C for 15 minutes. The protein concentrations then were measured by the method of Lowry et al., as modified by Ross and Schatz, with BSA as the standard. Twenty μg of protein per lane was separated by electrophoresis on a 15% SDS-polyacrylamide slab gel, then transferred electrophoretically to a nitrocellulose membrane.16,17 The blots were immunostained by enzyme-immunoassay with ProtBlot (Promega, Madison, WI). After incubation with 3% BSA for 6 hours at room temperature, the membrane was incubated overnight at 4 °C with the first antibody diluted with Tris-buffered saline (pH 8.0) containing 0.05% Tween 20. After being washed, the membrane was incubated for 2 hours at room temperature with alkaline phosphatase-conjugated antihuman IgG diluted 1:750. The immunoreactants were made visible with nitroblue tetrazolium and 5-bromo-4-chloro-3-indolyl phosphate as the enzyme substrates. MAb 7F5 and purified mouse IgG2a (the control) were used as the first antibodies at 15 μg of IgG2a per ml.

**Results.** Examination of antiglycolipid antibody in patients’ sera. Eighteen of the 19 patients with typical MFS, all five of those with atypical MFS, and five of the six with GBS-OP(+) had increased anti-GQ1b IgG antibody titers ranging from 1:40 to 1:640 in ELISA (figure 1). In three of these patients, we could examine their sera as early as 1 or 2 days after neurologic onset, and they all had high titer of 1:320. None of the 23 patients with GBS-OP(−), the 84 disease control subjects, or the 16 normal control subjects had titers above 1:10.

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Figure 1. Anti-GQ\textsubscript{1b} IgG antibody titers. Eighteen of the 19 patients with typical Miller Fisher syndrome (MFS), all five patients with atypical MFS, and five of the six patients with Guillain-Barré syndrome with ophthalmoplegia (GBS-OP[+]) show increased titers ranging from 1:40 to 1:640. The titers of patients with GBS without ophthalmoplegia (GBS-OP[−]) and those of the normal subjects are all less than 1:10.

In all 28 patients with anti-GQ\textsubscript{1b} IgG antibody, anti-GT\textsubscript{1a} IgG antibody also was detected in the TLC-enzyme immunoassay. The other antiglycolipid activities were detected in five of them: anti-GD\textsubscript{1b} IgG activity in two (one with typical MFS, the other with GBS-OP[+]); anti-GD\textsubscript{3} IgG activity in one with GBS-OP[+]; anti-GD\textsubscript{1b} and relatively weak anti-GD\textsubscript{3} IgG activities in one with typical MFS (who also had IgM activities against GQ\textsubscript{1b}, GM\textsubscript{1}, and GD\textsubscript{1b}); and anti-GQ\textsubscript{1b} IgM activity in one with atypical MFS.

To investigate the cross-reactivity of the anti-GQ\textsubscript{1b} and anti-GT\textsubscript{1a} IgG antibodies, we did absorption studies on four patients: two with typical MFS, one with atypical MFS, and one with GBS-OP[+]. Preliminary incubation with GQ\textsubscript{1b} or GT\textsubscript{1a} reduced the antibody activities against both GQ\textsubscript{1b} and GT\textsubscript{1a} in the sera of all the patients.

Serial studies of anti-GQ\textsubscript{1b} IgG were done on 18 patients, five of whom were given prednisolone orally and three of whom received plasmapheresis therapy. The first serum samples had the highest anti-GQ\textsubscript{1b} IgG activities, which decreased with time whether or not prednisolone or plasmapheresis treatment had been used. No patient showed a reincrease in anti-GQ\textsubscript{1b} IgG activity except for one who showed a little reincrease in the activity without clinical exacerbation in association with the nonspecific rebound of the total serum IgG concentration after extensive plasmapheresis. Profiles of the anti-GQ\textsubscript{1b} IgG activity and the clinical manifestations of one patient from whom sera could be obtained at short intervals from 2 days after neurologic onset are shown in figure 2. Although his clinical manifestations worsened during the first 6 days after onset, anti-GQ\textsubscript{1b} IgG antibody activity was highest in the first sampling taken 2 days after onset, decreasing even in the phase when his clinical signs were exacerbated before prednisolone administration.

Immunohistochemical and biochemical studies. Binding characteristics of mAb 7F5 are shown in

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Figure 2. Profiles of the clinical manifestations and anti-GQ\textsubscript{1b} IgG activity, at a serum dilution of 1:80, of a patient with typical MFS. Ophthalmoplegia represents the degree of diplopia in lateral gaze, and ataxia, unsteadiness of gait. The ophthalmoplegia was bilateral abducens palsy. Anti-GQ\textsubscript{1b} IgG activity is present 2 days after neurologic onset but decreases during the progression phase before the administration of prednisolone.

Figure 3. Binding characteristics of mAb 7F5. MAb 7F5 has the same specificity as the patient's sera. It reacts with GQ\textsubscript{1b} and GT\textsubscript{1b} but not with GM\textsubscript{1}, GD\textsubscript{1a}, GD\textsubscript{1b}, or GT\textsubscript{1a}.
Figure 4. Oculomotor nerve immunostained with an anti-GQβ₁ monoclonal antibody, mAb 7F5. (A) Cross section. The many doughnut-shaped stainings appear to consist of unstained axoplasm surrounded by a stained portion. The entire surrounding portion is stained in some of them (arrows) and the inner part only in others (arrowheads). (Bar = 25 µm.) (B) Longitudinal section. The paranodal regions of Schwann cells mainly appear to be stained. (Bar = 10 µm.)

Figure 3. This mAb recognizes GQβ₁ and GT₁₂ but not GM₁, GD₁₃, GD₁₉, or GT₁₉. Purified mouse IgG₃ used as the isotype control did not react with any of the gangliosides.

Unique immunostaining by mAb 7F5 was seen in the oculomotor, trochlear, and abducens nerves in both the proximal portion of the subarachnoid space and the distal portion adjacent to the external ocular muscles. Doughnut-shaped stainings were present in cross section (figure 4A). In longitudinal sections, the paranodal regions were immunostained (figure 4B). These stainings were lessened by prior treatment of a section with chloroform:methanol (1:1) for 1 minute. Similar stainings were not, or only rarely, present in the other peripheral nerve tissues. Some large DRG cells had granular stainings in their cytoplasms. In the CNS, the gray matter in the spinal cord and brainstem and the deep cerebellar nuclei generally had faint stains, but these were much weaker than the staining of the oculomotor, trochlear, and abducens nerves. No nerve fiber bundles in the spinal cord and brainstem, including the intramedullary portions of the oculomotor and abducens nerves, were stained.

Analysis of the total ganglioside fractions showed that the human oculomotor nerve had GQβ₁, but no GT₁₉ detectable in this condition (figure 5). Although GQβ₁ was present in both the ventral and dorsal roots, its content was greater in the oculomotor nerve for the same wet weight of tissue. In the TLC-enzyme immunoassay of the total ganglioside fractions, both mAb 7F5 and the patient's serum immunostained only GQβ₁ among the gangliosides. No specific bands were detected by the Western blot analysis.

Discussion. We confirmed the previously reported serum anti-GQβ₁ IgG antibody in patients in the acute phase of typical MFS. Moreover, we found anti-GQβ₁ IgG antibody in patients with atypical MFS and those with GBS-OP(+), whereas no patient with GBS-OP(−) had it. Although the grouping of these patients was arbitrary, the correlation with the clinical manifestations suggests that this antibody is most closely associated with acute ophthalmoplegia in MFS and GBS.

We detected anti-GT₁₉ IgG activity in all patients with anti-GQβ₁ IgG activity. The absorption studies showed that the anti-GQβ₁ and anti-GT₁₉ antibodies cross-reacted with each other's antigen, which suggested that the same IgG antibody bound to both antigens.

Serum anti-GQβ₁ activities were present in patients with IgM paraproteinemia and sensory-dominant neuropathy, but presumably without ophthalmoplegia, the anti-GQβ₁ activities possibly being derived from IgM M proteins binding to a broad spectrum of polysialogangliosides. In our series, the IgG antibodies against GQβ₁ and GT₁₉ in patients with typical and atypical MFS and with GBS-OP(+) reacted with none of the other gangliosides examined or, at most, only with a very few...
Ganglioside patterns. Ganglioside fractions corresponding to 4.0 mg wet weight of tissue were chromatographed on an HPTLC plate then stained with resorcinol. The oculomotor nerve (OM) has more GQ₁b than do the ventral root (VR) and dorsal root (DR) of the lumbar spinal cord for the same wet weight (arrowhead). ST = mixture of known standard gangliosides (500 ng each).

In the typical MFS, atypical MFS, and GBS-OP(+) groups, two patients (one with typical MFS, the other with GBS-OP(+)) did not have the anti-GQ₁b antibody. Both of these anti-GQ₁b-negative patients had isolated complete unilateral abducens palsy, whereas the patients with anti-GQ₁b IgG antibody had bilateral ophthalmoplegia: 14 total external ophthalmoplegia, 13 bilateral abducens palsy with or without other impairment, and one bilateral palsy of adduction and infraduction. Although abducens palsy is the most common early extraocular sign in MFS and GBS, isolated complete unilateral abducens or oculomotor palsy, as in the two patients in our series, is rare. The underlying mechanism of ophthalmoplegia in these two patients without anti-GQ₁b antibody may differ from that in patients with the antibody.

The immunohistochemical study with the anti-GQ₁b mAb showed prominent staining in the oculomotor, trochlear, and abducens nerves that was not present elsewhere in the nervous system examined. Biochemical analysis showed that the oculomotor nerve had a higher content of ganglioside GQ₁b than did the ventral and dorsal roots of the lumbar spinal cord for the same wet weight of tissue. Taking into account the negative results of Western blot analysis and the positive results of the TLC-enzyme immunoassay, we suspect that the mAb recognized ganglioside GQ₁b in the oculomotor nerve. The unique distribution of GQ₁b is compatible with the clinical association of anti-GQ₁b antibody with ophthalmoplegia.

The GQ₁b epitope was expressed mainly in the paranodal regions of the extramedullary portion of the three cranial nerves involved in ocular movement. The paranodal regions of Schwann cells have special features indicative of their involvement in impulse generation and damage to these regions blocks impulse generation at the nodes of Ranvier. These findings suggest the probable attack site of the anti-GQ₁b antibody and the cause of the conduction block. The extramedullary distribution of the attack site is compatible with the neuropathologic findings in a patient with GBS with ophthalmoplegia who had demyelinating lesions in the extramedullary portions of the oculomotor and abducens nerves.

Although anti-GQ₁b antibody might be elevated as a result of tissue destruction, we feel it is involved in pathogenesis because of the high titer as early as 1 or 2 days after neurologic onset. Close serial examination of one patient showed that the peak of anti-GQ₁b IgG activity preceded the maximum neurologic manifestations. In another patient, anti-GQ₁b IgG antibody reincreased transiently, without clinical exacerbation, in association with the nonspecific rebound of the total serum IgG concentration after extensive plasmapheresis, suggesting that the damage was not dependent on the intensity of the antibody activity alone. A time lag
between the peaks of antibody activity and the symptoms would be expected if the antibody is responsible for the initiation of damage.

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