Antibodies to GM2 Ganglioside in Neurological Disorders

**Key words:** anti-GM2 antibody, motor neuropathy, amyotrophic lateral sclerosis, Guillain-Barré syndrome

Anti-ganglioside antibodies can be detected in several immune-mediated neuropathies. Anti-GQ1b IgG antibodies which cross-react with GT1a are frequently present in patients with Fisher syndrome, Bickerstaff’s brainstem encephalitis, acute ophthalmoparesis without ataxia, and ataxic Guillain-Barré syndrome (GBS) (1). Anti-GM1, anti-GM1b, anti-GD1a, and anti-GalNAc-GD1a IgG antibodies are associated with axonal GBS. Anti-GT1a IgG antibodies with and without anti-GQ1b reactivity are found in pharyngeal-cervical-brachial variant of GBS. High anti-GM1 IgM antibody titers are detected in some patients with multifocal motor neuropathy. Anti-GD1b IgM antibodies with reactivity against other b-series gangliosides are associated with chronic sensory ataxic neuropathy. In contrast, anti-GM2 IgM antibodies have been found in patients with chronic motor neuropathy (2–7), amyotrophic lateral sclerosis (ALS)-like disorder after ganglioside therapy (8), chronic demyelinating neuropathy with sensory ataxia (9), and demyelinating GBS subsequent to cytomegalovirus (CMV) infection (10).

With respect to anti-ganglioside antibodies in CMV-associated GBS, Me et al (10) first detected anti-GM2 IgM and IgG antibodies in three patients. None of 48 GBS patients without preceding CMV infection had anti-GM2 antibodies, although one of six non-GBS control patients with acute CMV infection had anti-GM2 antibodies. Jacobs et al (11) also reported that anti-GM2 IgM antibodies were present more frequently in patients with GBS with CMV infection (22%) than in patients without the infection (2%), and others have reported similar observations (12). It remains, however, that acute CMV infection, with and without GBS, is clearly associated with anti-GM2 IgM antibodies (13). This calls into question whether anti-GM2 IgM antibodies play a role in the development of GBS or represent an epitope phenomenon related to CMV infection, and whether CMV exerts its neuritogenic effects through other mechanisms.

In one recent study, two chronic neuropathy cases were identified with highly elevated anti-GM2 IgM titers (6). One case with GM1/GM2 cross-reactive antibodies had multifocal motor neuropathy with conduction block of 20 years duration, principally affecting the distal right arm. The second case, with GM2/GalNAc-GD1a/GalNAc-GM1b cross-reactive antibodies, had a demyelinating motor neuropathy of 8 years duration, principally affecting the proximal lower limbs. In view of their association with motor neuropathy, anti-GM2 antibodies have also been sought extensively in motor neuron disease. Occasional patients are identified with an apparent relationship (6, 8), but similar antibodies are also found occasionally in control subjects (6). Thus, there is a relationship between anti-GM2 IgM antibodies and chronic neuropathy syndromes that remains to be clarified fully. Another issue to consider is that GM2 cannot be detected in human peripheral nerves by the standard immunohistochemical techniques using anti-GM2 IgM anti-serum (6). These studies raise some doubts about the pathophysiological significance of anti-GM2 IgM antibody in human autoimmune neuropathy including GBS associated with CMV infection.

Gangliosides extracted from bovine brain tissue have been widely administered to patients with various neurological disorders. GBS cases following ganglioside administration have been reported, and the number of affected subjects has increased (14–16). One interesting patient studied in Japan where gangliosides were also used as therapy developed limb weakness after the intramuscular administration of gangliosides (8). At first, this patient was considered to have ALS because of the gradual progression of weakness over a period of 6 months, the presence of upper motor neuron signs and the absence of sensory or autonomic dysfunction. This patient’s serum contained anti-GM2 IgM that was capable of killing GM2-containing neuroblastoma cells in the presence of complement (17). These findings suggested that anti-GM2 IgM antibody might be responsible for the patient’s muscular weakness. GM2 is expressed in motor neurons and is a major ganglioside in an immortalized mouse motor neuron-like cell line (18). Cytotoxicity studies by another investigators also demonstrated that GM2 antisera from patients with neuropathy subjects were capable of complement-mediated lysis of GM2-containing neural membranes in neuroblastoma cells (6, 19). Complement-mediated cell lysis induced by anti-GM2 IgM antibodies may be a possible mechanism of neural damage in patients with immune-mediated neuropathies.

The serum anti-GM2 IgM antibody titers (1:640) in the ALS patient reported by Mizutani et al (20) were not significantly higher than those of GBS patients subsequent to CMV infection (1:40 to 1:640). The serum of a patient with ALS-
like disorder after ganglioside therapy contained very high titers (>1:32,000) of IgM antibody against GM2, while antibody titers of sera from control subjects, patients with ALS, and patients with diabetic neuropathy who had received treatment with gangliosides were all less than 128 (8). Moreover, the weakness improved strikingly after plasmapheresis, and the serum did have killing activity in the presence of complement. In contrast, the pathogenetic role of anti-GM2 IgM antibodies in the ALS patient reported by Mizutani et al (20) is unclear. Cytotoxicity studies using the patient serum and larger studies using age-matched control sera are need to determine the pathogenetic role of the disease development.

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References