Anti-ganglioside Antibodies in Guillain-Barré Syndrome; Useful Diagnostic Markers as Well as Possible Pathogenetic Factors

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Guillain-Barré syndrome (GBS) is an acute motor-dominant monophasic polyneuropathy usually preceded by an infection. It has been considered that GBS is a demyelinating neuropathy, which is caused by the damage to myelin. Recently, in addition, the presence of an axonal form of GBS is recognized. There are also some variants of GBS, including Miller Fisher syndrome (MFS), characterized by the triads of ophthalmoplegia, ataxia and areflexia. Considering the effectiveness of plasmapheresis for the treatment of GBS, some humoral factors such as autoantibodies should have an important role in its pathogenesis.

Gangliosides are sialic-acid containing glycolipids, which are rich in the nervous system and are localized on the cell surface membrane. Among the gangliosides, there are diverse molecular species according to the carbohydrate sequence. Each ganglioside has a unique localization in the nervous system. Recent investigations have indicated that the increased titer of antibodies against glycolipids, including gangliosides, in sera is characteristic of autoimmune neuropathies, such as GBS, multifocal motor neuropathy, and IgM paraproteinemic neuropathy (1). The titer of the anti-ganglioside antibodies in GBS is highest in the acute-phase serum and decreases with time. This suggests that the production of anti-ganglioside antibodies is closely associated with the pathogenesis of GBS. Anti-ganglioside antibody therefore is a possible humoral factor that plays an important role in the pathogenesis.

Molecular mimicry between the microorganism of the antecedent infection and gangliosides is considered to be an important mechanism of the antibody production in GBS. The lipopolysaccharide of Campylobacter jejuni has been reported to have a ganglioside-like structure (2). In addition to gangliosides, galactocerebroside, a major myelin glycolipid, also is a target for serum antibody in some GBS patients. Most of GBS patients with anti-galactocerebroside antibody have an antecedent infection with Mycoplasma pneumoniae, which has been shown to have a glycolipid with a galactocerebroside-like carbohydrate structure (3).

Most of the anti-ganglioside antibodies are known to be associated with a certain clinical features. Anti-GQ1b IgG antibody is closely associated with ophthalmoplegia and ataxia (MFS) (4, 5). Anti-GM1 IgG antibody (6), anti-GalNac-GD1a IgG antibody (7), and anti-GM1b IgG antibody (8) are associated with pure motor type of GBS. Anti-GD1a IgG antibody is associated with GBS of acute motor axonal neuropathy type (9). GBS patients with anti-GD1b IgG antibody have sensory as well as motor disturbance and are of demyelinating type (10). IgG antibody against LM1 is present in the sera from patients with demyelinating type of GBS. The association between anti-GT1a IgG antibody and the pharyngeal-cervical-brachial variant of GBS has been reported.

Some of these relationships can be explained by the distribution of target antigens in human peripheral nerves; that is, GQ1b is densely localized in the paranodal region of the three cranial nerves (oculomotor, trochlear, and abducens nerves) innervating extraocular muscles (4) and in some primary sensory neurons (5), GD1b is localized in the large primary sensory neurons and in the paranodal region of the peripheral nerves (11). LM1 is known to be the predominant ganglioside in human peripheral nervous system myelin. Anti-ganglioside antibodies may therefore determine the distribution of the damage by binding to the regions where respective ganglioside antigens are densely localized.

The pathogenetic role of anti-ganglioside antibodies has been confirmed by rabbit experimental sensory ataxic neuropathy induced by sensitization with GD1b ganglioside (12). GD1b is localized in large primary sensory neurons, which convey deep sensation. Disturbance in deep sensation cause sensory ataxia. Anti-GD1b antibody therefore may bind to those GD1b-positive sensory neurons to cause ataxia. In addition, motor neuropathy has been reported by sensitization with GM1 (13). The effect of anti-GQ1b antibody to the neurotransmitter release from the presynaptic terminal of neuromuscular junction of mouse diaphragm has also been reported (14). Thus, data suggesting that anti-ganglioside antibody is involved in the pathogenesis of autoimmune neuropathies have recently accumulated.

Anti-ganglioside antibodies also can be used as a diagnostic marker of autoimmune neuropathies, especially GBS and MFS, because early diagnosis is essential for appropriate therapy for the patients with GBS and MFS. For example, acute ophthalmoplegia or ataxia can be caused by many dis-
orders of various etiologies; cerebrovascular diseases, acute cerebellitis, brainstem encephalitis, multiple sclerosis, aneurysm, tumor, Tolosa-Hunt syndrome, diabetic ophthalmoplegia, myasthenia gravis, etc. In such cases, anti-GQ1b IgG antibody can be used as a diagnostic marker of MFS and GBS with ophthalmoplegia or ataxia.

The presence of anti-ganglioside antibodies is usually examined by enzyme-linked immunosorbent assay (ELISA) or thin-layer chromatogram (TLC) immunostaining procedure. Although those assays could be performed within one day, they need technical skill and are not included in the routine laboratory examination in most hospitals. Considering the usefulness of the antibody assay for the diagnosis of GBS, it is of importance to develop a method that can be easily performed by clinicians. Alaedini and Latov reported the latex agglutination assay for detection of anti-ganglioside antibodies (15). In this issue, Irie et al reported the results of anti-ganglioside antibody assay by the use of the above method with some modifications and compared the results with those of ELISA (16).

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This method is easy to perform and the results can be obtained within only a few minutes. The problem is its sensitivity. Anti-ganglioside antibodies with a high titer on ELISA were detected by this method, while those with medium or low titer were undetectable. Because this agglutination assay is a hopeful method for easy and rapid examination of anti-ganglioside antibody activities, further investigation is necessary to increase the sensitivity of this assay.

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References


