Anti-GQ1b Ganglioside Antibody in Peripheral Nervous System Disorders

Pathophysiologic Role and Clinical Relevance

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The recent literature about autoimmune peripheral neuropathies has been dominated by the discovery of antibodies to a variety of glycosphingolipids. Gangliosides are important carbohydrate determinants for autoimmune activity, and several studies have suggested that serum antibodies against gangliosides are responsible for some forms of acute and chronic neuropathy syndromes. However, this view is disputable, and despite substantial progress in understanding the potential pathogenic effects of antiganglioside antibodies, many central issues remain unresolved across the whole pathogenic process. Miller Fisher syndrome has been classified as a variant of Guillain-Barré syndrome that comprises the clinical triad of ataxia, areflexia, and ophthalmoplegia. It has been considered the archetypal antiganglioside antibody–mediated human neuropathy because anti-GQ1b ganglioside antibody is detected in most patients with Miller Fisher syndrome, decays rapidly with clinical recovery, and is not found in normal and disease control serum samples. The only other case in which this antibody is found is in patients with related conditions, which might share the same pathogenic mechanism, such as Bickerstaff brainstem encephalitis. The strength of this close serologic-clinical association is such that measurement of anti-GQ1b antibody in suspected cases of Miller Fisher syndrome is a useful diagnostic marker for clinicians. This article reviews the occurrence, the pathophysiologic role, and the clinical background of anti-GQ1b ganglioside antibody in Miller Fisher syndrome and related disorders.

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During the past 2 decades, the autoimmune peripheral neuropathies have been an intense field of research, and substantial bibliographic evidence implicates gangliosides as major targets for antibody responses in these syndromes. However, the precise role that these antibodies play in the disease process is not fully understood, and the key question still remains unanswered: Can antiganglioside antibodies initiate the neuropathy process, and are they indicators of a primary immune attack, or does their existence signify a nerve tissue breakdown epiphenomenon by another, still unidentified, mechanism(s)? Much of the research on the pathogenic effects of antiganglioside antibodies has emphasized the role of anti-GQ1b antibody in Miller Fisher syndrome (MFS), and this antibody provides the best example of the close association between antibodies to gangliosides and neuropathy.

GANGLIOSIDES IN PERIPHERAL NERVE

It has been known for several decades that peripheral nerves contain gangliosides. Gangliosides are complex glycosphingolipids that contain at least 1 sialic acid residue (N-acetylneuraminic acid) attached to the internal or the terminal galactose of an oligosaccharide core composed of up to 4 sugars. Gangliosides reside in the outer layer of plasma membrane and have an amphipathic structure, with their hydrophilic sugars on the outer surface of the membrane. They are linked to the cell by the hydrophobic lipid moiety ceramide, which is immersed into the membrane. There is an abundance of literature suggesting that gangliosides may play a role in
membrane and cell functions. The binding of cholera toxin to GM1 ganglioside is well documented, and gangliosides on nerve terminals may also act as receptors for tetanus and botulinum toxin.

The abundance of gangliosides in the nervous system and the extracellular display of their sugars makes them attractive potential antigenic targets in peripheral neuropathies. Many attempts have been made to link anti-ganglioside antibody responses with the pathogenesis of these diseases and to explain their specific features: whether they are entirely motor or sensory in presentation, demyelinating or axonal on electrophysiologic study or pathological examination, or associated with a particular regional distribution of deficits.

**ANTI-GQ1b ANTIBODY: AN IMMUNOLOGIC MARKER FOR MFS**

Miller Fisher syndrome is characterized by the clinical triad of ophthalmoplegia, ataxia, and areflexia, and it was first reported in 3 patients in 1956. Most patients initially have diplopia followed by gait and limb ataxia. Ocular signs range from complete ophthalmoplegia with unreactive pupils to external ophthalmoplegia with or without ptosis. Cranial nerves other than ocular motor nerves may also be affected, most notably the facial nerves. Motor strength is usually preserved, although overlap with Guillain-Barré syndrome (GBS) can occur, and some patients may develop quadriplegia. In his original description, Miller Fisher noticed that the cause of this disorder was obscure but that the rise in the protein level of the cerebrospinal fluid in the late stages of the disease indicated a close relation to GBS. Since then, MFS has been described as an unusual variant of GBS with a benign prognosis.

Guillain-Barré syndrome is an acute, symmetrical, rapidly evolving flaccid paralysis that has now been classified on a pathological basis into demyelinating and axonal forms. Axonal GBS has been further subclassified into acute motor axonal neuropathy and acute motor and sensory axonal neuropathy. The pathologic features of these subclassifications are similar, and several data suggest that they are part of the spectrum of a single type of immune attack on the axon. Both conditions may follow *Campylobacter jejuni* enteritis, and anti-GM1, anti-GM1b, and anti-GD1a IgG antiganglioside antibodies could be used as immunologic markers to differentiate axonal forms of GBS from demyelinating GBS.

The first study involving antiganglioside antibodies in the pathogenesis of MFS was published in 1992 by Chiba et al. They found increased serum anti-GQ1b IgG activity in all 6 patients with MFS in the early phase of the illness. The titer of the antibody reduced with the clinical course of the disease. They suggested an association between anti-GQ1b antibodies and MFS, and since then several studies have found increased anti-GQ1b antibody titers in MFS, with the immunoglobulin being of IgG class rather than IgM. The complete absence of anti-GQ1b antibody from normal and disease control groups suggests a high level of specificity for this antibody.

As in GBS, a wide range of pathogenic organisms have been reported as antecedent agents in MFS. In particular, the frequency of *C jejuni* antecedent infection was lower in patients with MFS (18%) than in patients with GBS (31%). Cross-reactivity of anti-GQ1b IgG antibody with surface epitope on *C jejuni* strains from patients with MFS supports the hypothesis of molecular mimicry between bacteria and neural tissue.

In some anti-GQ1b IgG antibody–positive serum samples, additional anti-GT1a IgG antibody activity has been detected. This finding indicates that anti-GQ1b and anti-GT1a antibodies cross-reacted with each other’s antigen, suggesting that the same IgG antibody binds to both antigens, which are structurally similar. The IgG anti-GT1a antibody may be associated with the pharyngeal-cervical variant or oropharyngeal palsy in GBS.

Some studies showed that anti-GQ1b IgG antibody was related to the severity of the cerebellarlike ataxia of the syndrome. Selective staining of the human cerebellar molecular layer by serum IgG anti-GQ1b antibodies from patients with MFS or GBS with ophthalmoplegia and ataxia gave further evidence that anti-GQ1b antibody was related to ophthalmoplegia and ataxia in MFS and similar syndromes and supported the hypothesis for a central origin of ataxia in MFS.

Also, extensive investigations that included large numbers of patients have confirmed the close association of IgG anti-GQ1b antibody with ataxia and ophthalmoplegia. Other studies suggest that anti-GQ1b IgG antibody is not necessarily associated with ophthalmoplegia. These studies included patients with acute oropharyngeal palsy, acute demyelinating polyradiculoneuropathy, or Miller Fisher–like syndrome with high titers of anti-GQ1b IgG antibody activity without ophthalmoplegia.

In contrast, several studies suggest the close correlation between anti-GQ1b IgG antibody and acute ophthalmoplegia in typical MFS, in atypical (without ataxia) MFS, in GBS with ophthalmoplegia, and in Bickerstaff brainstem encephalitis (BBE), which is a nosologic condition with which MFS has clinical similarities. Bickerstaff described 8 patients who had a clinical syndrome of gradual onset with almost total paralysis of all motor function originating in the brainstem but without cardiac or respiratory abnormality; characteristically, drowsiness was a prominent symptom of the syndrome. Seven of the 8 original patients had ophthalmoplegia, all 8 had ataxia, and 4 had areflexia or hyporeflexia, features that are suggestive of MFS. All these patients had a prodromal infection. Seven patients had a dramatic total recovery without neurologic sequelae. Bickerstaff characterized it as “a grave syndrome with benign prognosis.”

Some authors recommend that diseases that show external ophthalmoplegia be labeled “IgG anti-GQ1b antibody syndrome,” and this proposal is supported by the fact that the anti-GQ1b antibody activity reflects the se-
verity of patients’ symptoms, especially ophthalmoplegia.\textsuperscript{29} Immunohistochemical studies\textsuperscript{16} have shown staining in the paranodal regions of the extramedullary portions of human oculomotor, trochlear, and abducens nerves; such an accumulation of GQ1b epitope was not present in the other cranial nerves or in the peripheral and central nerve tissues examined. The same authors\textsuperscript{30} investigated the ganglioside composition of all human cranial nerves and found a significantly higher percentage of GQ1b gangliosides in the optic nerve and all 3 ocular motor nerves than in all the other cranial nerves.

**BBE AND ANTI-GQ1b ANTIBODY**

The nosologic relationship of BBE to MFS remains controversial, and it is not clear whether they are distinct or related conditions. One of the 3 patients reported by Fisher had drowsiness, and 4 of the 8 patients originally described by Bickerstaff had areflexia. Moreover, whether the lesions responsible for the clinical findings of these diseases are in the peripheral or central nervous system has been a matter of disagreement as well.\textsuperscript{31,32} Serum samples taken from patients with BBE and ophthalmoplegic poliomyelitis have increased titers of anti-GQ1b IgG antibody during the acute phase of the syndrome. The antibody titers decrease during the clinical course of the disease.\textsuperscript{33} These findings suggest that a common autoimmune mechanism is likely in MFS and BBE and that both illnesses possibly represent a distinct disease with a wide spectrum of symptoms involving the peripheral and the central nervous systems.\textsuperscript{34} From a clinical-diagnostic perspective, the brainstem involvement in patients with BBE is responsible for the disturbance of consciousness, and patients with MFS or GBS with drowsiness should be diagnosed as having BBE. Further studies are needed to clarify the clinical and pathophysiologic overlap of MFS and BBE and to demonstrate whether they are distinct disorders or closely related conditions.

**ANTI-GQ1b ANTIBODY: INCONSISTENCIES AND PERSPECTIVES**

Although several neurologic disorders are believed to have an autoimmune etiology, myasthenia gravis remains the classic antibody-mediated neurologic disease. In this disease, circulating autoantibodies to acetylcholine receptors are found in more than 80% of patients, and their pathogenicity has been demonstrated by “passive transfer” of the disease into experimental animals, resulting in impairment of neuromuscular transmission postsynaptically with weakness and loss of muscle acetylcholine receptors.\textsuperscript{35} Myasthenia gravis fulfills Witebsky’s postulates that establish a human disease as autoimmune in origin.\textsuperscript{36}

In MFS, although several different studies have suggested that GQ1b is the candidate antigen, the pathogenic role of this antibody remains speculative, and important issues are still unanswered. The clinical and neurophysiologic findings in MFS do not match entirely with the distribution of GQ1b ganglioside: GQ1b ganglioside is not present in high quantities in the lower cranial nerves that may be affected in atypical MFS or in MFS variants, whereas its concentration is high in optic nerves that are not affected.\textsuperscript{30} Thus, the tissue distribution of GQ1b ganglioside cannot sufficiently explain the regional localization of the clinicopathologic features because key gangliosides are also present at sites unaffected by the disease process.

During the past few years, the distal motor nerve terminal has been intensely studied in the investigation of the effects of anti-GQ1b antibody, and several studies\textsuperscript{37-40} suggested that this antibody can mediate pathophysiologic changes at the mouse neuromuscular junction. However, other studies\textsuperscript{41} concluded that neuromuscular block is not a primary effect of anti-GQ1b antibody but results from complement activation. Electrophysiologic studies\textsuperscript{41,42} showed that serum without any detectable anti-GQ1b activity was as effective as serum containing GQ1b antibody in blocking evoked quantal release at the mouse neuromuscular junction. It cannot be excluded that circulating factors other than the anti-GQ1b antibody may cause or contribute to the clinicopathologic phenotype of MFS, and the presence of anti-GQ1b antibody might be a secondary phenomenon due to destruction of neurons and after exposure of neuronal antigens to the immune system.

The different results of experimental studies or the divergent findings between in vitro and in vivo studies may have many explanations. The experimental models are not identical to human disease. The pathophysiologic environment, the duration of antibody exposure to the target sites, the affinity of antibody, and its ability to fix complement are likely to be different in experimental models than in human disease. Technical factors also may contribute to some discrepancies that arise from different experimental studies. For example, the effect of osmotic pressure changes on transmitter release from mammalian motor nerve terminals is well known. Hyperosmotic solutions initially increase miniature end plate potential transmitter release from motor nerve terminals and then block neuromuscular transmission.\textsuperscript{44}

Detailed clinical-electrophysiologic studies in patients with MFS may help the investigation of the status of the neuromuscular junction, and, maybe, biopsy samples of motor point from affected patients may determine the anti-GQ1b antibody binding and the disruption of the integrity of the neuromuscular junction in patients with MFS. On the other hand, most studies, so far, have addressed the role of humoral factors in MFS and related disorders. However, cellular cytotoxicity may be of pathogenic importance in these syndromes, or humoral and cellular immune responses may contribute to the pathogenesis. The study by Kusunoki et al\textsuperscript{45} has established a well-defined animal model of autoimmune neuropathy mediated by an antiganglioside antibody. They pioneered a model of experimental sensory ataxic neuropathy induced by sensitization with GD1b ganglioside and provided clear evidence that GD1b antibodies can mediate injury to sensory neurons in dorsal root ganglia and cause sensory ataxic neuropathy in rabbits.\textsuperscript{45} Overall, the ultimate proof that the anti-GQ1b ganglioside antibody mediates MFS requires an animal model in which passive transfer of this antibody can induce the clinical and pathologic features of the disease.\textsuperscript{46} This experiment represents the cardinal demonstration of antigenspecific autoimmunity,\textsuperscript{47} but it has not been achieved. The existence of a reproducible animal disease model would
be useful to broaden our knowledge about the implicated immune mechanisms and to further explain the facts occurring in MFS pathogenesis. Above all, a reproducible animal disease model may offer an opportunity to explore and develop future therapies.

CONCLUSIONS

The extent of immune processes that are responsible for MFS is not completely defined. Although increasing evidence suggests the key role of anti-GQ1b antibody, the pathogenesis of this syndrome cannot be explained on the basis of GQ1b antibody alone. The existing data about the role of anti-GQ1b antibody is suggestive but not conclusive evidence, and this can provide an incentive for further research. However, the frequent occurrence of the IgG antibody to ganglioside GQ1b in MFS and related anti-GQ1b–positive syndromes is of great diagnostic and therapeutic significance to clinicians. In particular, on diagnostic grounds, the measurement of this antibody in serum samples from patients with suspected MFS seems equivalent to estimating antibodies against acetylcholine receptors in myasthenia gravis. In addition, patients with acute ophthalmoparesis, occurring alone or with weakness or ataxia, should be screened for the presence of anti-GQ1b antibody. If anti-GQ1b antibody is present, intravenous immunoglobulin may be an effective therapy in these patients, and further clinical studies may substantiate this view.

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REFERENCES