Invited Minireview

Pathogenesis of Guillain-Barré and Miller Fisher Syndromes Subsequent to *Campylobacter jejuni* Enteritis

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SUMMARY: Some patients developed Guillain-Barré syndrome (GBS) after the administration of bovine gangliosides. Patients with GBS subsequent to *Campylobacter jejuni* enteritis frequently have IgG antibody to GM1 ganglioside. Miller Fisher syndrome (MFS), a variant of GBS, is associated with IgG antibody to GQ1b ganglioside. We showed the existence of molecular mimicry between GM1 and lipopolysaccharide of *C. jejuni* isolated from patients with GBS, and that between GQ1b and *C. jejuni* lipopolysaccharides from patients with MFS. The molecular mimicry between infectious agents and gangliosides may function in the production of anti-ganglioside antibodies. This sugar mimicry is one possible cause for GBS and MFS, and unidentified host factor may contribute to the development of these syndromes.

1. Introduction

The term Guillain-Barré syndrome (GBS) covers a set of clinical syndromes in which idiopathic peripheral neuropathy causes acute or subacute weakness of at least 2 limbs, which progresses for up to 4 weeks and then reaches a plateau (1). The neuropathy usually affects the motor, sensory, and autonomic nerves supplying the limbs and may involve the respiratory muscles and facial, bulbar, and ocular motor nerves. The symptoms may be caused by inflammatory demyelination, axonal degeneration, or both. GBS occurs throughout the world, with a median incidence of 1.3 cases/100,000 population (range, 0.4-4.0), and is the most common cause of acute neuromuscular paralysis in persons in developed countries. Males are more commonly affected than females, and there are peaks in young adults and the elderly. Infection due to gram-negative bacterium *Campylobacter jejuni*, a leading cause of acute diarrheal illness, is the most frequently identified the cause of GBS, which is associated with more severe disease and prolonged disability. Multivariate analysis by Jacobs et al. (2) showed that in GBS patients, infection with *C. jejuni* (32%),

cytomegalovirus (13%), and Epstein-Barr virus (10%) were significantly more frequent than in controls. *Mycoplasma pneumoniae* infections occurred more often in GBS patients (5%) than in controls in univariate analysis.

The value of plasma exchange in GBS is well established (3). The therapeutic effect of plasma exchange presumably is related to the removal of circulating factors. Plasma concentrations of IL-2, IL-6, IFN- γ , and TNF- α are elevated in GBS, but because their circulating half-lives are only a few hours, the effect of plasma exchange on their plasma levels would be short term. Complement depletion is also brief. The respective half-lives of IgM and IgA are 5 and 6 days. In contrast, the half-life of IgG, except the IgG3 subclass, is 21 days, much longer than that of other plasma proteins. Plasma IgG levels may be reduced for up to 5 weeks following a course of plasma exchange. Because plasma exchange is beneficial, autoantibodies to peripheral nerves may function in the development of GBS. An immunohistochemical study showed the presence of IgG and that the complement activation product binds to motor fibers in an axonal variant of GBS (4). This indicates that IgG binding effectively with complements and macrophages is the most important factor in the development of GBS. The possible significance of cytokines and cellular immunity is detailed elsewhere (5).

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2. Guillain-Barré syndrome

2.1. Autoantibody to GM1 ganglioside

Gangliosides are highly expressed in the nervous tissues

and are considered as cell surface molecules implicated in various biological cellular functions. There were several reports of motor neuron disease and multifocal motor neuropathy associated with IgM antibody to GM1 ganglioside (6,7). Ilyas et al. (8) and Inuzuka et al. (9) reported that several GBS patients who showed sensory dysfunction had autoantibodies to gangliosides except for GM1 ganglioside.

GBS patients often have sensory impairment; however, patients with GBS subsequent to *C. jejuni* enteritis show no or minimal sensory disturbance. We reported that 2 patients with GBS following *C. jejuni* infection had high IgG anti-GM1 antibody titers in the acute phase of the illness (10). No anti-GM1 antibody was detected in patients who had *C. jejuni* enteritis that was not followed by GBS. The association of IgG anti-GM1 antibody with GBS subsequent to *C. jejuni* enteritis was established elsewhere (11-13).

2.2. Molecular mimicry between GM1 and *C. jejuni* lipopolysaccharide

Ganglioside extracted from bovine brain tissue was widely given throughout Western Europe and South America for several neurologic disorders. Since we first reported on amyotrophic lateral sclerosis-like disorder following ganglioside therapy (14), there has been an increasing number of reports about patients who developed GBS after receiving bovine brain ganglioside (15,16). This development suggests an antecedent infectious agent with a ganglioside-like structure as a cause of GBS. By Penner's method, *C. jejuni* is serotyped on the difference in the lipopolysaccharide (LPS). Kuroki et al. and we showed that a specific Penner's serotype (PEN), PEN 19, was frequently isolated from GBS patients (17,18). Thus, we investigated whether GM1 epitope is present in the LPS from PEN 19 *C. jejuni*.

LPS was extracted from PEN 19 *C. jejuni* that had been isolated from a GBS patient by use of the hot phenol-water technique. Thin-layer chromatography with immunostaining showed that cholera toxin which specifically recognizes the GM1-oligosaccharide reacted with the LPS fraction (19), indicating that the LPS has the GM1 epitope. The LPS showing the binding activity of the cholera toxin was purified by silica-bead column chromatography. Gas-liquid chromatography-mass spectrometric analysis showed that the purified LPS contained galactose (Gal), *N*-acetylgalactosamine (GalNAc), and *N*-acetylneuraminic acid (NeuAc), which are sugar components of GM1 ganglioside. ¹H nuclear magnetic resonance methods revealed that the oligosaccharide structure (Gal β 1-3 GalNAc β 1-4 [NeuAc α 2-3] Gal β) protruded from the LPS core. We showed that this terminal structure (Gal β 1-3 GalNAc β 1-4 [NeuAc α 2-3] Gal β) is identical to the terminal tetrasaccharide of the GM1 ganglioside (Fig. 1) (20), and our study was the first to demonstrate the existence of molecular mimicry between nerve tissue and the infectious agent isolated from a GBS patient. Moreover, its findings supported the probability of there being an adverse reaction after ganglioside administration. Wirguin et al. (21) reported that IgM anti-GM1 monoclonal antibody reacted with LPS of *C. jejuni*. Oomes et al. (22) showed that IgG anti-GM1 antibody was absorbed by *C. jejuni*.

Willison and Veitch (23) showed that the IgG subclass distribution of anti-GM1 antibodies is limited mainly to IgG1 and IgG3 in GBS. Because IgG antibodies to bacterial polysaccharide are generally restricted to the IgG2 subclass, they assumed that either the general rules for the immune response to LPS were broken in the GBS patients or that an alternative

Fig. 1. Molecular mimicry between GM1 ganglioside and *Campylobacter jejuni* lipopolysaccharide. Terminal tetrasaccharide occupies the nonreducing end of GM1 and the lipopolysaccharide. Cer, ceramide; $\square$, Galactose; $\square$, *N*-acetylgalactosamine; $\blacksquare$, Glucose; $\blacktriangledown$, *N*-acetylneuraminic acid.

antigen had yet to be identified. To clarify whether the LPS participates in the production of IgG anti-GM1 antibody, we investigated the subclasses of IgG antibody to the LPS that bears GM1-like structure (24). They were predominantly restricted to IgG1 and IgG3. Therefore, the GM1-like LPS may be an immunogen that functions in the production of IgG anti-GM1 antibody. Subclasses IgG1 and IgG3 are characteristic of a T-cell dependent antibody response, and helper T-cells may be associated with the production of IgG anti-GM1 antibody.

2.3. Association of PEN 19 *C. jejuni* with IgG anti-GM1 antibody

Aspinall et al. (25) reported that LPS from PEN 4 has GD1a-like structure, and that LPSs from PENs 1, 23, and 36 have GM2-like structures. They concluded that these differences in sugar sequences and linkage types are sufficient to account for the serological differences. In contrast, we showed that monoclonal anti-GM1 and anti-GD1a antibodies reacted with PENs 1, 4, and 19 *C. jejuni* LPSs (26). We therefore proposed that Penner's serotyping system is not dependent on differences in the ganglioside-like oligosaccharide structures of the LPSs. Aspinall et al. (27) reached the same conclusion as they noted that the LPSs of PENs 4 and 19 have the same ganglioside-like structure and that there is structural variability among the low-molecular-weight LPSs from 3 PEN 19 strains.

Kuroki et al. (28) reported that 10 of 12 isolates (83%) from GBS patients belonged to PEN 19, while this serotype accounts for fewer than 2% of *C. jejuni* strains in Japan. The association of PEN 19 with GBS, however, is controversial (28,29). Therefore, we serotyped *C. jejuni* isolates from GBS and enteritis patients. PEN 19 was more frequently isolated from the GBS patients (16/31 isolates, 52%) than from the enteritis patients (11/215 isolates, 5%) (30). Next, we investigated whether PEN 19 *C. jejuni* is associated with IgG anti-GM1 antibody. The frequency of IgG anti-GM1 antibody titers of 500 or more among GBS patients with PEN 19 *C. jejuni* was significantly higher (12/14 patients, 86%) than that among GBS patients with non-PEN 19 *C. jejuni* (9/20 patients, 45%). Aspinall et al. (31) reported that a hyaluronic acid-like repeat unit of LPS is an antigenic determinant of PEN 19. Glycosami-

Fig. 2. Pathogenesis of Guillain-Barré syndrome associated with IgG anti-GM1 antibody subsequent to *Campylobacter jejuni* enteritis. (1) Infection by *C. jejuni* that bears the GM1-like lipopolysaccharide associated with the serotypic determinant of PEN 19 induces high production of IgG anti-GM1 antibodies with help of T cells. (2) IgG anti-GM1 antibodies bind to motor nerve terminal axons, inhibits motoneuron excitability, and produces the development of muscular weakness.

noglycans, including hyaluronic acid, may play an important role in the development of autoimmune diseases (32). It is possible that the hyaluronic acid-like structure may help the GM1-like LPS to induce the production of the IgG anti-GM1 antibody and the subsequent development of GBS (Fig. 2).

Nackamkin et al. (33) showed that 26.2% of 275 random enteritis-associated isolates of *C. jejuni* were positive for the GM1 epitope using a cholera toxin-binding assay. Of the 36 different O serotypes in the sample, 21 (58.3%) contained no strains positive for GM1, whereas in 6 serotypes (16.7%), >50% of isolates were positive for GM1. GBS-associated serotypes were more likely to contain strains positive for GM1 than were non-GBS-associated serotypes (37.8% vs. 15.1%). These results suggest that humans are frequently exposed to strains exhibiting GM1-like mimicry and, while certain serotypes may be more likely to possess GM1 epitope, the presence of GM1 epitope on *C. jejuni* strains does not itself trigger GBS.

2.4. Pathogenic role for anti-GM1 antibodies

GM1 epitope is present at the neuromuscular junction (34) and the nodes of Ranvier (35). Immunization of rabbits with GM1 resulted in elevated serum anti-GM1 antibody titers and induced a neuropathy with conduction block and immunoglobulin deposits at the nodes of Ranvier (36). IgM anti-GM1-positive sera from patients with multifocal motor neuropathy induced a block of conduction when injected, either with or without additional complement, intraneurally into rat sciatic or tibial nerve (37,38). A partial conduction block was induced by anti-GM1 antibody-positive human and rabbit sera in an in vitro rat sciatic nerve preparation (39). Sera from patients with multifocal motor neuropathy and IgM anti-GM1 antibody blocked distal motor nerve conduction in mice (40). Rabbit anti-GM1 antibody alters the kinetics of K⁺ channels and suppresses voltage-sensitive Na⁺ currents, thereby interfering with the function of the Na⁺ channels at the nodes of Ranvier (41). However, other studies failed to show the electrophysiological effects in their assay systems (42,43). In our co-culture

system of rat motoneurons and human muscle cells, mouse IgM anti-GM1 MAb (GMB16) as well as human IgG anti-GM1 antibody rapidly suppressed spontaneous firing, end-plate potentials, and muscle contraction (44). Their rapid recovery, when the anti-GM1 antibodies were removed, is the evidence that this antibody has the ability to inhibit motoneuron excitability without producing morphological changes.

2.5. Molecular mimicry between *C. jejuni* LPSs and minor gangliosides (GalNAc-GD1a and GM1b)

Kusunoki et al. (45) suggested that *N*-acetylgalactosaminyl GD1a (GalNAc-GD1a) is a target molecule for serum antibody in some patients with GBS subsequent to *C. jejuni* enteritis. We confirmed this relationship. An absorption test indicated the presence of the GalNAc-GD1a epitope in *C. jejuni* LPS (46). Some patients have developed GBS after being administered the GM1 fraction isolated from bovine brain (47). Hirabayashi et al. (48) purified a minor ganglioside GM1b from the bovine brain GM1 fraction. Kusunoki et al. (49) proposed GM1b to be a new antigen for serum antibody in GBS. To clarify the pathogenesis of GBS associated with, and without, a preceding monosialoganglioside injection, we investigated the presence of anti-GM1b antibody in sera from GBS patients. We showed that IgG anti-GM1b antibody is associated with GBS after *C. jejuni* enteritis (50). To evaluate the hypothesis that GM1b is an immunogen, we determined whether the GM1b epitope was present in *C. jejuni* isolated from a patient with GBS associated with anti-GM1b antibody. Immunostaining with anti-GM1b MAb NA-6 indicated that the LPS of the *C. jejuni* strain does have the GM1b epitope.

2.6. Pathogenesis of GBS after *C. jejuni* infection

Some autoimmune diseases are related to particular human leukocyte antigens (HLA), but it is controversial whether a particular HLA is associated with the development of GBS after *C. jejuni* enteritis. Rees et al. (51) showed that GBS patients in the United Kingdom who showed evidence of

Fig. 3. Pathogenesis of Miller Fisher syndrome associated with IgG anti-GQ1b antibody subsequent to *Campylobacter jejuni* enteritis. (1) Infection by *C. jejuni* that bears GQ1b-like lipopolysaccharide associated with the serotypic determinant of PEN 2 induces high production of IgG anti-GQ1b antibodies with help of T cells. (2) IgG anti-GQ1b antibodies bind to the oculomotor, trochlear, and abducens nerves, and to deep cerebellar nuclei causing external ophthalmoplegia and cerebellar ataxia.

prior *C. jejuni* infection frequently had (HLA)-DQB1*03. We reported that GBS and MFS subsequent to *C. jejuni* enteritis were associated with HLA-B54 and Cw1 (52). Ma et al. (53) failed to reveal a significant association between HLA and GBS with serologic evidence of *C. jejuni* infection. A particular immunogenetic background has yet to be identified.

The neuropathy in chickens was found to occur spontaneously in animals on farms owned by Chinese patients with GBS (54). In addition, chickens fed PEN 19 *C. jejuni* from one of the patients developed a paralytic neuropathy. In their nerves, Wallerian-like degeneration similar to that seen in the human form of GBS subsequent to *C. jejuni* infection was observed (55). Illa et al. (56) showed that purified IgG from GBS patients with high IgG anti-GM1 antibody titers who had been treated with bovine brain gangliosides recognized epitopes at the nodes of Ranvier and distal motor nerve terminals that lack the blood-nerve barrier. IgG anti-GM1 antibodies are associated with reversible conduction failure and axonal degeneration in GBS (57), as well as anti-GM1b and anti-GalNAc-GD1a IgG antibodies (Ogawara et al., unpublished).

It is possible that the pathogenesis of GBS after *C. jejuni* enteritis to be as follows: (58) Infection by *C. jejuni* that bears a GM1-, GM1b-, or GalNAc-GD1a-like LPS induces high production of IgG1 and IgG3 anti-GM1, anti-GM1b, or anti-GalNAc-GD1a antibodies with the help of T cells in patients who have a particular immunogenetic background (Fig.2). IgG anti-GM1 antibody binds to the motor nerve terminal, inhibits motoneuron excitability, and produces muscular weakness. IgG1 and IgG3 are much more effective than the other two IgG subclasses for triggering effector functions. Binding of the IgG1 and IgG3 anti-GM1, anti-GM1b, or anti-GalNAc-GD1a antibodies readily causes degeneration of the motor axon from its terminals. In addition, the anti-GM1, anti-GM1b, or anti-GalNAc-GD1a antibodies, which can bind at nodes of Ranvier, might produce failure of conduction.

3. Miller Fisher syndrome

Miller Fisher syndrome (MFS) is characterized by the acute onset of ophthalmoplegia, ataxia, and areflexia. It is considered a variant of GBS because some patients who present with MFS then progress to GBS. This suggests that

an autoimmune mechanism similar to that of GBS is involved in the pathogenesis of MFS. Chiba et al. (59) found that MFS is associated with IgG anti-GQ1b antibody, which was later confirmed by Willison et al. and our study (60,61). Chiba et al. (62) then showed that anti-GQ1b monoclonal antibody strongly stains the paranodal regions of the extramedullary portion of the oculomotor, trochlear, and abducens nerves, and weakly stains the deep cerebellar nuclei.

Some patients develop MFS subsequent to *C. jejuni* infection (63). We isolated 2 *C. jejuni* strains from patients who had anti-GQ1b antibody in the acute phase of MFS (64). To clarify the pathogenesis of MFS and to test the molecular mimicry hypothesis, we investigated whether the GQ1b epitope is present in *C. jejuni* LPSs. Anti-GQ1b monoclonal antibodies (GMR13 and 7F5) reacted with both LPS fractions, indicating that the LPSs extracted from *C. jejuni* bear the GQ1b epitope (65). This was the first report of molecular mimicry between GQ1b and an antecedent infectious agent of MFS. Jacobs et al. (66) reported that anti-GQ1b IgG antibody recognized surface epitope on *C. jejuni* from patients with MFS. The subclasses of IgG antibodies to the GQ1b-like LPS were restricted to IgG1 and IgG3 in MFS patients, as were the antibodies to GM1-like LPS in GBS patients (23). We showed that 5 out of 7 isolates from patients with MFS patients belonged to PEN 2; (30) moreover, PEN 2 *C. jejuni* was isolated from 2 GBS patients, both of whom initially had presented as having MFS. The frequency of IgG anti-GQ1b antibody in PEN 2-isolated GBS and MFS was significantly higher than that in non-PEN 2-isolated GBS and MFS. The serotypic determinant of PEN 2 may help the GQ1b-like LPS to produce the IgG anti-GQ1b antibody.

It is possible that infection by *C. jejuni* that bears GQ1b-like LPS associated with the serotypic determinant induces excessive production of IgG anti-GQ1b antibody with the help of T-cells; moreover, that this autoantibody binds to the oculomotor, trochlear, and abducens nerves, and to the deep cerebellar nuclei causing external ophthalmoplegia and cerebellar ataxia in patients with MFS (58) (Fig.3).

4. Conclusion

Molecular mimicry between *C. jejuni* LPSs and gangliosides

was shown in GBS and its variant MFS. This sugar mimicry is one possible cause for GBS and MFS, and unidentified host factor may contribute to the development of these syndromes.

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