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Current cases in which epitope mimicry is considered a component cause of autoimmune disease: Guillain-Barré syndrome

N. Yuki

Department of Neurology, Dokkyo University School of Medicine, Kitakobayashi 880, Mibu, Shimotsuga, Tochigi 321-0293 (Japan), Fax + 81 282 86 5884, e-mail: yuki@dokkyomed.ac.jp

Abstract. Some patients develop 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. Molecular mimicry between GM1 and lipopolysaccharide of *C. jejuni* isolated from patients with GBS, and between GQ1b and *C. jejuni* lipopolysaccharides from patients with MFS have been demonstrated. The molecular mimicry between infectious agents and gangliosides may function in the production of anti-ganglioside antibodies. This sugar mimicry is one possible cause of the Guillain-Barré and Miller Fisher syndromes; however, unidentified host factors may contribute to the development of these syndromes.

Key words. Molecular mimicry; Guillain-Barré syndrome; Miller Fisher syndrome; *Campylobacter jejuni*; lipopolysaccharide; ganglioside.

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 two limbs, which progresses for up to 4 weeks and then reaches a plateau [reviewed in ref. 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 of increased frequency in young adults and the elderly. Infection by the 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 disablity. Multivariate analysis by Jacobs et al. [2] showed that in GBS patients, infections 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 [reviewed in ref. 3]. The therapeutic effect of plasma exchange is presumably related to the removal of circulating factors. Plasma concentrations of interleukins 2 and 6, tumor necrosis factor-α, and interferon-γ 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 level may be reduced for up to 5 weeks following a course of plasma exchange. Because plasma exchange is beneficial, autoantibody to peripheral nerve may function in the development of GBS. An immunohistochemical study demonstrated the presence of IgG, and that

the compliment activation product binds to motor fibers in an axonal variant of GBS [4]. This indicates that IgG binds effectively complement and macrophages are the most important factor in the development of GBS. The possible significance of cytokines and cellular immunity is detailed elsewhere [5].

Guillain-Barré syndrome

Autoantibody to GM1 ganglioside

Gangliosides are highly expressed in 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.

Patients with GBS often have sensory impairment; however, patients with GBS subsequent to *C. jejuni* enteritis show no or minimal sensory disturbance. We reported that two 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 has been confirmed by others [11–13].

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 of 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 the Penner method, *C. jejuni* is serotyped on the difference in the lipopolysaccharide (LPS). We, and others, have shown that a specific Penner serotype (PEN), PEN 19, is frequently isolated from GBS patients [17, 18]. Thus, we investigated whether the 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 patient with GBS using the hot phenol-water technique. Immunostaining of thin-layer chromatograms showed that cholera toxin which specifically recognizes the GM1-oligosaccharide reacts 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. ^{1}H nuclear magnetic resonance methods revealed that the oligosaccharide structure (Gal β1–3 GalNAc β1–4 [NeuAc α2–3] Galβ) protruded from the LPS core. We showed that this terminal structure is identical to the terminal tetrasaccharide of the GM1 ganglioside (fig. 1); this study was the first to demonstrate the existence of molecular mimicry between nerve tissue and the infectious agent isolated from a GBS [20]. 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 patients with GBS, or an alternative 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.

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 PEN 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 PEN 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 three PEN 19 strains.

Kuroki et al. [28] reported that 10 of 12 isolates (83%) from patients with GBS 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 patients with GBS (16/31 isolates, 52%) than from the patients with enteritis (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 ≥ 500 among GBS patients with PEN 19 *C. jejuni* was significantly higher (12/14 patients, 86%) than 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. Glycosaminoglycans, including hyaluronic acid, may play an important role in the development of autoimmune diseases [32]. I speculate 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). However, the results of Nackamkin et al. [33] suggest that humans are frequently exposed to strains exhibiting GM1-like mimicry and, while certain serotypes may be more likely to possess the GM1 epitope, the presence of the GM1 epitope on *C. jejuni* strains does not itself trigger GBS.

Pathogenic role for anti-GM1 antibodies

The GM1 epitope is present at the neuromuscular junction [34] and the nodes of Ranvier [35]. Immunization of rabbits with GM1 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 conduction block when injected, either with or without additional complement, intraneurally into rat sciatic or tibial nerve [37, 38]. Partial conduction block was induced by anti-GM1 antibody-positive human and rab-

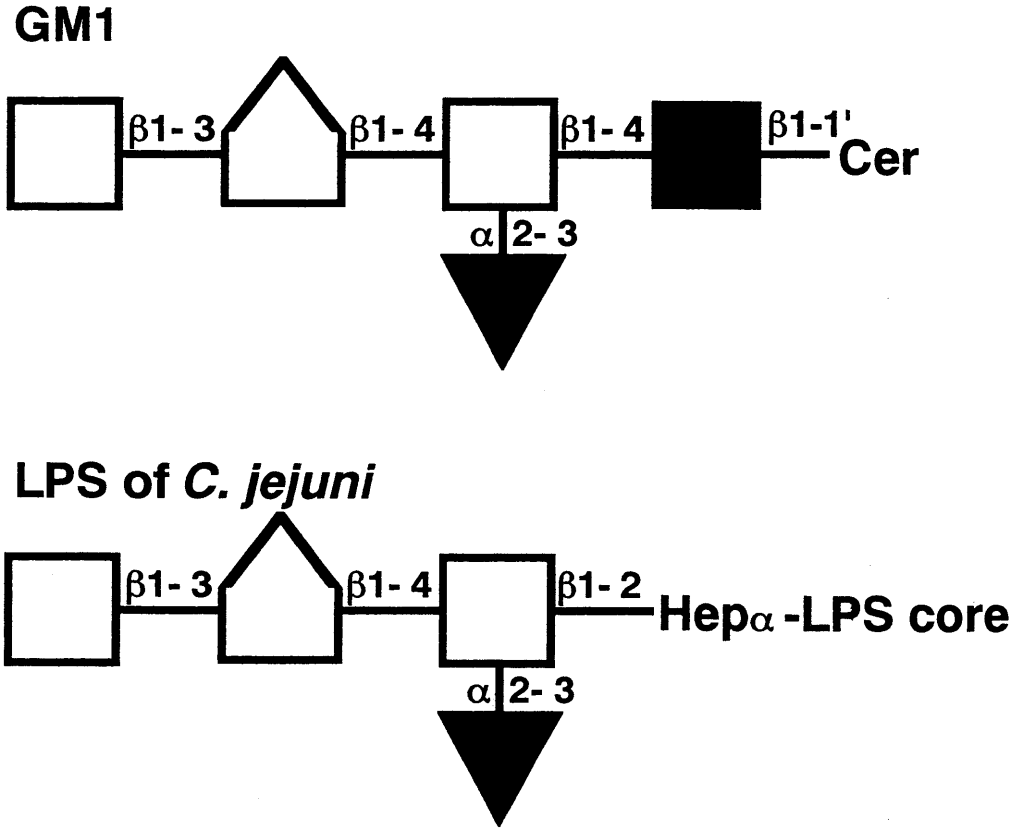

Figure 1. Molecular mimicry between GM1 ganglioside and *Campylobacter jejuni* lipopolysaccharide. The terminal tetrasaccharide occupies the nonreducing end of GM1 and the lipopolysaccharide. Cer, ceramide; open space, galactose; pentagon, *N*-acetylgalacosamine; filled square, Glucose; filled triangle, *N*-acetylneuraminic acid.

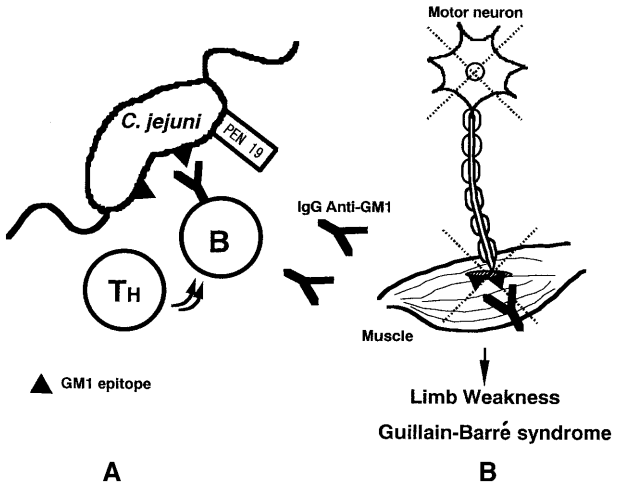

Figure 2. Pathogenesis of Guillain-Barré syndrome associated with IgG anti-GM1 antibody subsequent to *C. jejuni* enteritis. (*A*) Infection by *C. jejuni* bearing the GM1-like lipopolysaccharide associated with the serotypic determinant of PEN 19 induces high production of IgG anti-GM1 antibodies with the help of T cells. (*B*) IgG anti-GM1 antibodies bind to motor nerve terminal axons, inhibit motoneuron excitability, and produce the development of muscular weakness.

bit 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 electrophysiolocal effects in their assay systems [42, 43]. In our co-culture system of rat motoneurons and human muscle cells, mouse IgM anti-GM1 monoclonal antibody (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 evidence that this antibody can inhibit motoneuron excitability without producing morphological changes.

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 as 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 patients with GBS. 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.

Pathogenesis of GBS after *C. jejuni* Infection

Many autoimmune diseases occur more frequently in subjects with particular human leukocyte antigens (HLA), and not with other HLA, but whether a particular HLA is associated with the development of GBS after *C. jejuni* enteritis is disputed. Rees et al. [51] showed that patients with GBS in the United Kingdom who had evidence of prior *C. jejuni* infection frequently had HLA-DQB1*03. We reported GBS and Miller Fisher syndrome (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 serologically confirmed *C. jejuni* infection. A particular immunogenetic background has yet to be identified.

The neuropathy was found to occur spontaneously in chickens from 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. Their nerves, demonstrated Wallerian-like degeneration similar to that seen in the human form of GBS subsequent to *C. jejuni* infection [55]. Illa et al. [56] showed that purified IgG from patients with GBS with high-titer anti-GM1 IgG 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 data].

I speculate 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 antibody, which can bind at nodes of Ranvier, might cause conduction failure.

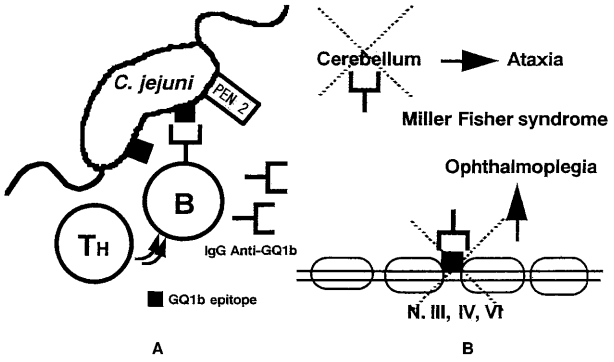

Figure 3. Pathogenesis of Miller Fisher syndrome associated with IgG anti-GQ1b antibody subsequent to *C. jejuni* enteritis. (*A*) Infection by *C. jejuni* bearing GQ1b-like lipopolysaccharide associated with the serotypic determinant of PEN 2 induces high production of IgG anti-GQ1b antibodies with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

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 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 Willison et al. [60] and we [61] later confirmed. Chiba et al. [62] then showed that anti-GQ1b mAb 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 two *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 mAbs (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 IgG anti-GQ1b antibody recognized a 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 five out of seven isolates from patients with MFS belonged to PEN 2 [30]; moreover, PEN 2 *C. jejuni* was isolated from two GBS patients, both of whom initially had presented with 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.

I speculate 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, 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 (fig. 3) [58].

Conclusion

Molecular mimicry between *C. jejuni* LPSs and gangliosides was shown in GBS and its variant MFS. This sugar mimicry is one possible cause of GBS and MFS; however, unidentified host factors may also contribute to the development of these syndromes.

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