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REVIEW

Antiganglioside antibodies and their pathophysiological effects on Guillain–Barré syndrome and related disorders—A review

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Guillain–Barré syndrome (GBS) is an acute immune-mediated polyradiculoneuropathy which can cause acute quadriplegia. Infection with micro-organisms, including *Campylobacter jejuni* (*C. jejuni*), *Haemophilus influenzae*, and *Cytomegalovirus* (*CMV*), is recognized as a main triggering event for the disease. Lipooligosaccharide (LOS) genes are responsible for the formation of human ganglioside-like LOS structures in infectious micro-organisms that can induce GBS. Molecular mimicry of LOSs on the surface of infectious agents and of ganglioside antigens on neural cells is thought to induce cross-reactive humoral and cellular immune responses. Patients with GBS develop antibodies against those gangliosides, resulting in autoimmune targeting of peripheral nerve sites, leading to neural damage. Heterogeneity of ganglioside expression in the peripheral nervous system (PNS) may underlie the differential clinical manifestation of the GBS variants. Recent studies demonstrate that some GBS sera react with ganglioside complexes consisting of two different gangliosides, such as GD1a and GD1b, or GM1 and GD1a, but not with each constituent ganglioside alone. The discovery of antiganglioside complex antibodies not only improves the detection rate of autoantibodies in GBS, but also provides a new concept in the antibody–antigen interaction through clustered carbohydrate epitopes. Although ganglioside mimicry is one of the possible etiological causes of GBS, unidentified factors may also contribute to the pathogenesis of GBS. While GBS is not considered a genetic disease, host factors, particularly human lymphocyte antigen type, appear to have a role in the pathogenesis of GBS following *C. jejuni* infection.

Keywords: Guillain-Barré syndrome/peripheral neuropathy/molecular mimicry/llipopolysaccharides/bacterial infection/inflammation

GBS and antiganglioside antibody: heterogeneity of ganglioside expression in the peripheral nervous system

Gangliosides, sialic acid containing glycosphingolipids (GSLs), are diverse and highly complex molecules located primarily on plasma membranes and are particularly abundant in the nervous system. Gangliosides are known to play important roles in biological functions, such as cellular growth and differentiation, modulation of signal transduction, and immune reactions. Variation of their functional roles may depend on their carbohydrate, and sometimes on their ceramide structures (Hakomori 2002; Yu et al. 2004). Antibodies to gangliosides have been found in autoimmune neuropathies, especially in Guillain-Barré syndrome (GBS) and in motor-dominant acute polyradiculoneuropathy (Kusunoki 2000; Ariga et al. 2001; Willison and Yuki 2002; Ariga and Yu 2005; Yu et al. 2006). Approximately 60% of patients with GBS have antiganglioside antibodies in sera during the acute clinical phase of the disease (Kusunoki, Iwamori, et al. 1996; Ariga and Yu 2005; Yu et al. 2006). Recent studies have clarified that the clinical features of GBS are composed of different pathological subtypes and that each subtype is closely associated with specific antiganglioside antibodies (Table I). It has been recognized that diversity in ganglioside expression can influence development of the subtype and the symptomatology of GBS. In this review, we will focus on recent studies on the clinical and pathophysiological roles of antiganglioside antibodies in GBS and related disorders. Much of the work on antiganglioside antibodies in GBS has been covered in several review articles published previously (Ariga and Yu 2005; Yu et al. 2006).

Classification of GBS: acute inflammatory demyelinating polyneuropathy and acute motor axonal neuropathy

GBS is classified into two primary subtypes: demyelinating and axonal.

The demyelinating form, acute inflammatory demyelinating polyneuropathy (AIDP), is the most prevalent form of GBS in Western countries and is characterized by segmental demyelination of peripheral nerves. The putative target antigens have been reported to be GD1b and LM1 (Kusunoki et al. 1997; Yako et al. 1999; Miyazaki et al. 2001). A subtype of GBS characterized by primary axonal degeneration with preserved sensory function is known as acute motor axonal neuropathy (AMAN). AMAN is less frequently encountered in North America and Europe, accounting for only about 5% of the total GBS cases, than is demyelinating GBS, but AMAN is more common in China and Japan (McKhann et al. 1993; Griffin, Li, Ho, et al. 1996; Hadden et al. 1998; Kuwabara et al. 1998). This primary axonal GBS almost overlaps with a pure motor variant of GBS, but it rarely leads to sensory deficits. Primary axonal GBS that leads to sensory deficits is called acute motor and sensory axonal neuropathy (AMSAN) (McKhann et al. 1993; Griffin, Li, Ho, et al. 1996). The main clinical method for distinguishing among subtypes is electrodiagnostic examination. According to pathological studies in autopsy cases of AMAN (Griffin, Li, Macko,

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Table I. Target antigens of anti-ganglioside antibodies, their localization in human peripheral nerves, and associated clinical features

Antigens	Clinical features	Localization in human PNS	References
GM1	AMAN, Pure motor GBS	Not determined	
		Animals: axolemma at node and paranode of motor nerve, myelin of motor nerve, dorsal root ganglia, motor nerve terminals	Sheikh et al. (1999) O'Hanlon et al.(1996);(1998) Gong et al. (2002) Susuki, Baba, et al. (2007); Suzuki, Rasband, et al. (2007) Buchwald et al. (2007)
GD1a	AMAN	Not determined	
		Animals: motor nerve terminal	Goodfellow et al. (2005) Buchwald et al. (2007)
GalNAc-GD1a	AMAN, Pure motor GBS	Periaxonal membrane of motor nerve at node and paranode, axolemma of small fibers in sural nerve	Kaida et al. (2003)
		Animals: axon, motor nerve terminal	Taguchi et al. (2004) Nakatani et al. (2007)
GM1b	Pure motor GBS	Not determined	
GD1b	Ataxia in GBS	Large neurons in DRG, paranodal myelin	Kusunoki et al. (1993); (1997)
		Animals: large neurons in DRG, paranodal myelin	Kusunoki, Shimizu, et al. (1996)
GD3	AIDP, CIDP	Not determined	
		Animals: NMJ	Usuki et al. (2005)
GQ1b	MFS, GBS with ophthalmoplegia	Paranodal myelin of oculomotor, trovhlear, and abducens nerves	Chiba et al. (1993) Kusunoki, Chiba, et al. (1999)
		A part of DRG neurons	
		Animals: large neurons in DRG and motor nerve terminals	Willison et al. (1996) Goodyear et al. (1999) Plomp et al. (1999) O'Hanlon et al. (2001); (2003) Halstead et al. (2004)
GT1a	Bulbar palsy in GBS PCB-GBS	Not determined	

AMAN, acute motor axonal neuropathy; GBS, Guillain-Barré syndrome; CIDP, chronic inflamatory demyelinating polyneuropathy; AIDP, acute inflammatory demyelinating polyradiculoneuropathy; MFS, Miller Fisher syndrome; PCB, pharyngeal-cervical-brachial; DRG, dorsal root ganglion; NMJ, neuromuscular junction.

et al. 1996; Hafer-Macko et al. 1996), IgG and complement deposits on the axolemma at the nodes of Ranvier of motor fibers are found early in the course of the disease with little demyelination and lymphocytic infiltration, followed by macrophage recruitment. These findings indicate that an antibody-mediated response to the axonal membrane is the primary pathophysiology in AMAN, rather than a T-cell mediated response. Some antiganglioside antibodies are considered to play a crucial role in the development of AMAN. GM1, *N*-acetylgalactosaminyl GD1a (GalNAc-GD1a), GD1a, and GM1b are the most potent target antigens in AMAN (Gregson et al. 1991; van den Berg et al. 1992; Kusunoki et al. 1994; Kusunoki, Iwamori, et al. 1996; Ho et al. 1997, 1999; Kaida et al. 2000; Ogawara et al. 2000; Yuki 2000).

Anti-GM1 Antibody. An anti-GM1 antibody is commonly associated with a pure motor variant of GBS, characterized by no sensory loss, sparing of the cranial nerves, and predominant distal weakness (Rees, Gregson, et al. 1995; Visser et al. 1995; Jacobs et al. 1996). Some studies, however, have found no correlation between anti-GM1 antibodies and electrophysiologic findings that are indicative of axonal neuropathy (Enders et al. 1993; Ho et al. 1995; Rees, Gregson, et al. 1995; Rees, Vaughan, et al. 1995; Vriesendorp et al. 1995). Pathological findings in the peripheral nerves of patients with AMAN suggest the possibility that antigens associated with AMAN are expressed in the axolemma of motor nerves, especially at the nodes of Ranvier (Hafer-Macko et al. 1996). GM1 exists in the axolemma at the nodes of Ranvier (Sheikh et al. 1999), whereas GM1 also locates on the myelin of motor nerves and dorsal root ganglia (DRG) (O'Hanlon et al. 1996, 1998; Gong et al. 2002). Thus, immunohistochemical studies of normal human peripheral nerves have not provided conclusive evidence for the association between the distribution of the GM1 antigen and the development of AMAN. Recent studies using rabbits sensitized with a GM1-mimic antigen suggest the distribution of GM1 antigen at the nodes of Ranvier of motor nerves (Yuki et al. 2001, 2004; Susuki et al. 2003). Yuki et al. (2001, 2004) have succeeded in producing an AMAN model by inoculating rabbits with LOS from *C. jejuni* or a ganglioside mixture containing GM1. Pathological studies in rabbits with a GM1-specific IgG antibody show IgG deposition on axons at the nodes of Ranvier of the ventral roots as well as at internodal axolemma (Susuki et al. 2003). Interestingly, in experiments using β1,4-*N*-acetylgalactosaminyltransferase (GalNAc-T; GM2/GD2 synthase)-knockout or wild-type mice, Susuki et al. have shown that GM1 is enriched in the lipid-raft fraction at paranodes and that GM1 plays a role in maintaining the paranodal architecture and clusters of voltage-gated sodium channels (Nav) (Susuki, Baba, et al. 2007). In the rabbit AMAN model, sensitized with a bovine brain ganglioside mixture that includes GM1, nodes of the ventral roots were lengthened, Nav channel clusters at the nodes were disrupted, and paranodal axoglial junctions, nodal cytoskeleton, and Schwann cell microvilli were impaired in a complement-mediated manner (Susuki, Rasband, et al. 2007). The anti-GM1 monoclonal antibody and the cholera toxin-B subunit stained nodes and axons, consistent with IgG deposition (Susuki, Rasband, et al. 2007). These findings indicate that the Nav channel at the nodes of

Ranvier of motor nerves is linked to GM1, and that anti-GM1 antibodies may directly impair the function of the Nav channel. Interestingly, complement inhibitor, nafamostat mesilate, prevents sodium channel disruption in a rabbit model of GBS (Phongsisay et al. 2008).

On the other hand, the presynaptic axonal membrane is also a candidate for targets directed by the anti-GM1 antibody (Buchwald et al. 2007). In ex vivo experiments using mouse hemidiaphragmas, interaction between the anti-GM1 antibody and the presynaptic membrane of motor nerves induces a decrease in the presynaptic-transmitter release in a complement-independent manner, probably because depolarization-induced calcium influx is inhibited (Buchwald et al. 2007). Thus, the functional blockade of motor nerve terminals can explain limb weakness in AMAN with anti-GM1 antibodies. Considering that presynaptic sites in the neuromuscular junction are outside the blood–nerve barrier, are rich in gangliosides (Martin 2003), and can act as receptors for toxins such as botulinum toxins (Bullens et al. 2002), it is possible that presynaptic membranes are susceptible to antiganglioside antibody attack. However, impairment of neuromuscular junctions has never been confirmed by clinical electrophysiological tests in GBS patients with anti-GM1 antibodies.

In addition, anti-GM1 antibodies from GBS patients have been shown to inhibit Cav2.1 voltage-dependent Ca^{2+} channel current (Nakatani et al. 2007, 2009). This finding suggests that in some cases of GBS, particularly of AMAN patients with IgG anti-GM1 antibodies, muscle weakness may be induced by dysfunction of Ca^{2+} channel at the motor nerve terminal.

Anti-GalNAc-GD1a Antibody. GalNAc-GD1a, a minor ganglioside in the human brain and peripheral nerves (Svennerholm et al. 1973; Yu et al. 1983; Ilyas et al. 1988), is a target molecule for serum antibodies in GBS (Kusunoki et al. 1994). Patients who develop IgG anti-GalNAc-GD1a antibodies are characterized by preserved sensory function, infrequent cranial nerve deficits, and distal-dominant weakness, characteristics that are identical to [those in patients with] a pure motor variant of GBS (Ang et al. 1999; Hao et al. 1999; Kaida et al. 2000, 2001). Electrodiagnostic results generally showed a primary axonal neuropathy pattern characteristic of AMAN (Kaida et al. 2000). An immunohistochemical study using human peripheral nerves showed localization of GalNAc-GD1a in the vicinity of the nodes of Ranvier in motor nerves (Kaida et al. 2003). IgG anti-GalNAc-GD1a antibodies purified from the sera of rabbits that had been sensitized with GalNAc-GD1a immunostained an inner part of compact myelin and additionally a periaxonal axolemma-related region in the ventral roots and intramuscular nerves (Kaida et al. 2003). In teased ventral fibers, the nodal and paranodal axolemmae are immunostained by the anti-GalNAc-GD1a antibodies.

Moreover, a biochemical study using human ventral and dorsal roots showed that GalNAc-GD1a is localized specifically in ventral spinal roots (Yoshino et al. 2005). It is likely that the IgG anti-GalNAc-GD1a antibody attacks the axolemma at nodes or nerve terminals and causes the conduction failure of motor nerves. Recent studies demonstrated that the IgG anti-GalNAc-GD1a antibody blocked neuromuscular transmission in rat muscle-spinal cord co-cultured cells and inhibited voltage-gated Ca channel currents of PC12 pheochromocytoma cells (Taguchi et al. 2004; Nakatani et al. 2007, 2008). The IgG anti-GalNAc-GD1a antibody may block neurotransmitter release by its presynaptic inhibitory effect of voltage-gated Ca channel currents through its binding to motor nerve terminals and cause limb weakness. Neuromuscular transmission failure, however, has never been confirmed by clinical electrophysiological tests also in GBS patients with anti-GalNAc-GD1a antibodies.

Anti-GD1a Antibody. An IgG anti-GD1a antibody, rather than anti-GM1 antibody, is thought to be closely associated with the AMAN subtype of GBS (Ho et al. 1999). GD1a is expressed both in human motor and sensory nerves, although the precise cellular and subcellular localization of GD1a in motor nerves has not yet been confirmed. Recent ex vivo studies using monoclonal anti-GD1a antibodies indicated that the interaction between the anti-GD1a antibodies and GD1a in the presynaptic membrane of motor nerves might cause muscle weakness through inhibition of presynaptic transmitter release (Goodfellow et al. 2005; Buchwald et al. 2007). Anti-GD1a antibodies from mice sensitized with GD1a-mimicking antigens from *C. jejuni* bound to motor nerve terminals and produced destructive changes at mouse neuromuscular junctions in a complement-dependent manner (Goodfellow et al. 2005). As speculated in the mechanism of limb weakness in cases of patients with AMAN with anti-GM1 and -GD1a antibodies, a presynaptic block of calcium influx at motor nerve terminals may play an important role in the development of limb weakness in patients with AMAN (Buchwald et al. 2007). Moreover, anti-GD1a-mediated injury was found in GD3-synthase knockout mice that overexpressed GD1a but not found in normal mice, suggesting that the high level of expression of GD1a at neuromuscular junctions is required for developing an anti-GD1a-mediated disorder (Goodfellow et al. 2005). According to a recent study, monoclonal anti-GD1a antibodies that selectively immunostained ventral roots recognized GD1a-derivatives with some chemical modifications of the *N*-acetylneuraminic (NeuAc) acid residues, such as GD1a-NeuAc ethylester, GD1a-NeuAc 1-alcohol, or GD1a-NeuAc 1-metylester, but another monoclonal anti-GD1a antibody that immunostained both ventral and dorsal roots did not react with such derivatives (Lopez et al. 2008). Thus, fine structural differences of GD1a between motor and sensory nerves may explain why motor nerves are selectively injured by anti-GD1a antibodies in GBS. An inhibitory effect against regeneration of injured peripheral nerves may be associated with delayed or poor recovery in patients with AMAN (Lehmann et al. 2007).

Anti-GM1b Antibody. Kusunoki, Iwamori, et al. (1996) first reported that a minor ganglioside, GM1b, is one of the target antigens for serum antibodies in GBS. They pointed out that 36% of GBS patients with anti-GM1b antibodies had IgG anti-GalNAc-GD1a antibodies and that 32% had anti-GM1 antibodies; no association was found, however, between anti-GM1b antibodies and the development of AMAN. Subsequent collaborative studies in Japan and the Netherlands confirmed that anti-GM1b antibody-positive GBS is preceded by an antecedent gastrointestinal infection, such as *C. jejuni* enteritis, and characterized by infrequent cranial nerve involvement, pure motor neuropathy, rapid progression, and good response to treatment with immunoglobulin (Yuki, Ang, et al. 2000). The researchers also found no correlation, however, between the presence of the anti-GM1b antibody and the electrodiagnostic

findings that are indicative of axonal neuropathy, although 56% of anti-GM1b-positive patients with GBS had anti-GM1 antibodies (Yuki, Ang, et al. 2000). The precise tissue localization of GM1b in human PNS remains to be determined.

Anti-GD3 Antibody. Recently Usuki et al. (2005) described the presence of antiganglioside antibodies against GM3, GD3, and GT3 in two patients that appear to be rare cases of CIDP and AIDP. In the CIDP patient, the IgG antibody titer to GD3 was remarkably elevated, indicating that the highest activities was directed toward the NeuAcα2-8 NeuAcα2-3Galβ1-4Glc- structure. There were weak antibody titers toward GM4 and GM2, indicating that the antibody was not specific. In contrast, the antiserum from the AIDP case showed similar avidity toward GM3, GD3, and GT3. Interestingly, the antiserum from the AIDP patient produced an inhibitory effect on the spontaneous muscle action potential in the neuromuscular junctions (NMJs) in vitro, but the antiserum from the CIDP case did not. Thus, in AIDP the common epitope of GM3, GD3, and GT3 may be shared with certain antigens localized in the PNS and may participate in a component of conduction-related molecules in the NMJ. High-titer anti-GD3 antibodies and the distortion of antibody recognition in the CIDP case seem to have no immediate effect on the electrophysiologic function in the PNS.

Miller Fisher syndrome

Miller Fisher syndrome (MFS) is characterized by a clinical triad of ophthalmoplegia, ataxia, and areflexia, and is considered a variant of GBS (Fisher 1956; Willison and O'Hanlon 1999). A serum IgG anti-GQ1b antibody, frequently cross-reacting with GT1a, is an excellent diagnostic marker for MFS and is pathophysiologically associated with ophthalmoplegia or ataxia in MFS and GBS (Chiba et al. 1992, 1993; Kusunoki, Chiba, et al. 1999; Yuki et al. 2000a). The distribution of the GQ1b antigen is critical for the symptomatology of MFS. An immunohistochemical study using a monoclonal anti-GQ1b antibody indicated the dense distribution of GQ1b at paranodal myelin of cranial nerves innervating extraocular muscles (Chiba et al. 1993). Biochemical investigations on human cranial nerves and roots showed that oculomotor, trochlear, and abducens nerves contained more GQ1b than did other nerves, a finding that supports the hypothesis that ophthalmoplegia results from conduction failure by binding of the anti-GQ1b antibody to paranodal myelin in cranial nerves (Chiba et al. 1997). Some large neurons in human DRG were immunostained by the same monoclonal anti-GQ1b antibody, and GQ1b in the DRG may also be one of the target antigens responsible for the development of ataxia in patients with MFS (Kusunoki, Chiba, et al. 1999).

As stated above, presynaptic membranes are susceptible to antibody attack. Some immunohistochemical ex vivo or in vitro studies using a monoclonal anti-GQ1b antibody have shown a neuroparalytic action of the anti-GQ1b antibody, such as conduction block at motor nerve terminals (Roberts et al. 1994; Willison et al. 1996; Goodyear et al. 1999; Plomp et al. 1999; O'Hanlon et al. 2001, 2003; Halstead, Morrison, et al. 2005; Halstead, O'Hanlon, et al. 2005). An anti-GQ1b antibody induces an α-latrotoxin-like effect, electrophysiologically characterized by an increase in spontaneous neurotransmitter release. The activity of the anti-GQ1b antibody in the neuromuscular junction appears to be caused by direct presynaptic membrane damage through classic complement pathway activation, irrespective of activation of α-latrotoxin receptors (Bullens et al. 2005). Halstead, Morrison, et al. (2005) showed that GD3-reactive antibodies induced perisynaptic Schwann cell death and that GT1a-reactive antibodies correlated with the extent of nerve terminal injury. That finding suggests that the ganglioside composition in presynaptic membranes is critical for antibody-mediated dysfunction in the NMJ. Thus, there is a prevailing hypothesis that the pore-forming membrane attack complex of complement induced by antibody-binding against gangliosides, such as GQ1b, in the presynaptic membranes causes neuronal and perisynaptic Schwann cell injury at the motor nerve terminals (Halstead et al. 2004). A recent intriguing study demonstrated that a novel therapeutic inhibitor of complement activation, APT070 (Mirococept, Inflazyme Pharmaceuticals, British Columbia, Canada), thoroughly precludes membrane attack complex formation and has a neuroprotective effect at the nerve terminal (Halstead, O'Hanlon, et al. 2005), a finding that raises hope for a novel therapeutic modality. Halstead et al. (2008) have confirmed that the humanized monoclonal antibody eculizumab, which blocks the formation of human C5a and C5b-9, has a similar neuroprotective effect at motor nerve terminals in a novel mouse model of MFS. They succeeded in producing a mouse model suffering from respiratory paralysis through intraperitoneal injection of anti-GQ1b antibody and normal human serum. Intravenous eculizumab injection prevented the respiratory paralysis in the animal model and complement-mediated destruction of nerve terminals in the diaphragm in in vivo and in vitro mouse systems. These elegant results should provide promising therapeutic strategies. As for the pathophysiologic role of the anti-GQ1b antibody in motor nerve terminals, a recent study using axonal-stimulating single fiber electromyography showed that an anti-GQ1b antibody did not affect neuromuscular transmission in limb muscles of patients with MFS or Bickerstaff brainstem encephalitis who have an IgG anti-GQ1b antibody and no other antiganglioside antibodies (Kuwabara et al. 2007). They have pointed out that in five previous reports showing neuromuscular transmission failure in MFS or GBS patients antiganglioside antibodies were not systematically examined, and tested muscles were variable. It is important to consider that the expression of GQ1b on the motor nerve terminals may be different between humans and animals, or between extraocular muscles and limb muscles. Systematic examination for various antiganglioside antibodies is also required to analyze a real effect of an anti-GQ1b antibody on neuromuscular transmission.

Pharyngeal-cervical-brachial variant of GBS

Since Ropper (1986) described patients with acute neuropathy characterized by pharyngeal-cervical- brachial (PCB) weakness as being a variant of GBS, some case reports and clinical studies have pointed out a close correlation between IgG anti-GT1a antibody and a PCB variant of GBS (Mizoguchi et al. 1994; Ilyas et al. 1998; Kashihara et al. 1998; Koga, Yuki, Ariga, et al. 1998; Koga et al. 2002; Okuda et al. 2002; Nagashima et al. 2004, 2007). A recent expanded study on PCB clarifies that PCB, GBS, MFS, and Bickerstaff brainstem encephalitis form a continuous spectrum (Nagashima et al. 2007). In these cases, an IgG anti-GT1a antibody often cross-reacts with GQ1b, while a monospecific anti-GT1a antibody without GQ1b

reactivity is considered more essential for the development of bulbar palsy in patients with GBS (Koga et al. 2002; Nagashima et al. 2004). Using the anti-GT1a-positive serum from a patient with GBS, researchers using thin-layer chromatography-overlay have shown that human glossopharyngeal and vagal nerves contain both GQ1b and GT1a (Koga et al. 2002); the localization of GT1a in human peripheral nerves, however, has not yet been confirmed. Interestingly, *C. jejuni* strains isolated from patients with GBS and with MFS carry a GT1a-like epitope in their lipooligosaccharides (LOSs) (Koga, Gilbert, et al. 2005; Koga et al. 2006). A large clinical study has identified a high frequency of *C. jejun*i infection in patients with PCB (31%) (Nagashima et al. 2007). Taken together, molecular mimicry between bacterial LOSs and nerve gangliosides may also account for the pathogenesis of PCB variants.

Ataxia in GBS

At the onset of disease, patients with GBS occasionally suffer from severe ataxia but not ophthalmoplegia (Ropper et al. 1991). IgG anti-GD1b antibodies are thought to be closely associated with ataxia in patients with GBS (Wicklein et al. 1997; Yuki et al. 2000b; Pan et al. 2001; Sugimoto et al. 2002). Some case reports described sensory ataxia (Wicklein et al. 1997; Pan et al. 2001), whereas others describe cerebellar-like ataxia (Yuki et al. 2000b; Sugimoto et al. 2002). A study of experimental ataxic neuropathy in rabbits sensitized with GD1b provides support for the close association of antibody titers with this disorder (Kusunoki, Shimizu, et al. 1996; Kusunoki, Hitoshi, et al. 1999) and indicates that monospecific anti-GD1b IgG plays a pathogenic role in the development of experimental ataxic neuropathy (Kusunoki, Hitoshi, et al. 1999).

Immunohistochemical studies on human peripheral nerves have shown that GD1b is localized on DRG neurons (Kusunoki et al. 1993, 1997), especially neurons of large diameter. These findings may explain that antibodies monospecific to GD1b cause ataxic neuropathy. In clinical studies on patients with GBS with only IgG anti-GD1b antibodies, only four of nine patients exhibited ataxia (Miyazaki et al. 2001). Differential specificity of anti-GD1b antibodies in each of those nine cases may account for that clinical diversity. A recent study that compared anti-GD1b activity to a mixture of GD1b and another ganglioside in patients with GBS with and without ataxia indicates that GD1b-specific antibody induces ataxia in patients with GBS (Kaida, Kamakura, et al. 2008). This study suggests that complex lipid environments in nerve membranes could affect accessibility of antiganglioside antibodies against target glycoepitopes in nerve tissue (Kaida, Kamakura, et al. 2008).

Ganglioside complexes: new target antigens in GBS and related disorders

After antiganglioside antibodies were discovered in sera from patients with autoimmune neuropathy, screening for antiganglioside antibodies in patients' sera based on the solid-phase immunoassay has relied primarily on using purified single ganglioside antigens. Surprisingly, we have demonstrated the presence of antibodies specifically reacting with ganglioside complexes (GSCs) that consist of two different gangliosides (Kaida et al. 2004). Eight of 100 patients with GBS had IgG antibodies to the GD1a–GD1b complex (GD1a/GD1b), and their sera showed

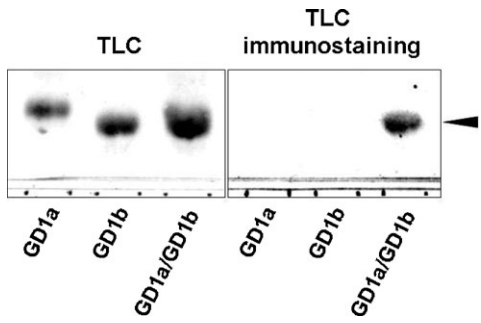

Fig. 1. High-performance thin-layer chromatogram (TLC)-immuno-overlay of a serum sample from a patient with GBS. TLC bands were visualized with orcinol reagent in the left panel. TLC-immunostaining study shows that overlapping portions between GD1a and GD1b are strongly stained (right panel, arrowhead). The serum antibody is shown to react with a ganglioside complex, GD1a/GD1b, but not with GD1a or GD1b alone. Serum was diluted to 1:100. A horseradish peroxidase-conjugated anti-human IgG antibody was used as a secondary antibody. Three micrograms of each ganglioside was applied to each lane on the TLC plate. The developing solvent system was chloroform/methanol/0.2% $CaCl_2.H_2O$ (55/40/10, v/v).

sharp and strong immunostaining in the overlapping portion of GD1a and GD1b on a thin-layer chromatographic plate (Figure 1) (Kaida et al. 2004). The antibody activity to GD1a/GD1b became maximal when the mixture consisted of an equal amount of GD1a and GD1b. Interestingly, the anti-GSC antibodies had little or no reactivity with individual gangliosides of the GSC, indicating that novel glycoepitopes are formed in the GSC and may function as target molecules in antibody-mediated events. This finding implies that it may be insufficient to state that sera are antiganglioside antibody-negative until the anti-GSC antibodies are examined. Two of the eight patients with GBS had anti-GD1a/GD1b antibodies, but not antibodies to single ganglioside antigens using conventional screening methods (Kaida et al. 2004). A study using a larger population of GBS patients, however, showed that 39 of 234 (17%) GBS patients had IgG antibodies to GSCs consisting of two of the four major ganglio-series gangliosides, GM1, GD1a, GD1b, and GT1b, and that patients with anti-GD1a/GD1b or anti-GD1b/GT1b antibodies are significantly predisposed to severe disability (Kaida et al. 2007). In patients with MFS for which GQ1b is considered to be a prime antigen, half of patients have IgG antibodies to GSLs containing GQ1b, such as GQ1b/GM1 and GQ1b/GD1a (Kaida et al. 2004). MFS-associated antibodies are likely to be subdivided into three types based on antibody specificity: GQ1b-specific, GQ1b/GM1-reactive, and GQ1b/GD1a-reactive (Kaida et al. 2006). Similarly, approximately half of GBS patients with ophthalmoplegia have antibodies to GSCs containing GQ1b or GT1a (Kanzaki et al. 2008). Recently, antibodies specifically reacting with GM1/GalNAc-GD1a, a complex consisting of GM1 and GalNAc-GD1a, were found in certain GBS patients (Kaida, Sonoo, et al. 2008). The anti-GM1/GalNAc-GD1a-positive patients were categorized into pure motor variant of GBS, whose electrophysiological findings featured early conduction block at intermediate nerve segments. GM1 and GalNAc-GD1a may form a complex in the axolemma at nodes of Ranvier or paranodes of the motor nerves, and may be target antigens in pure motor GBS, especially in the form of acute motor conduction block neuropathy (Kaida, Sonoo, et al. 2008). Thus, examination of anti-GSC antibodies may increase the spectrum of

antiganglioside antibodies in GBS and related disorders, enhancing their value as diagnostic markers.

Specific bacterial genes and ganglioside-mimicking structures in the LPSs/LOSs of pathogens causing antecedent infection are critical for inducing antiganglioside antibodies and regulating antibody specificity (Ang et al. 2002; Godschalk et al. 2004, 2007; Yuki 2007a, 2007b). Taking that finding into account, we propose that microbial LPS/LOS may possess ganglioside-complex-like structures responsible for inducing anti-GSC antibodies. This hypothesis received support in a recent study demonstrating cross-reactivity between the LOSs of *C. jejuni* and anti-GSL antibodies, such as anti-GM1/GD1a and anti-GD1a/GQ1b (Kuijf et al. 2007). The homogeneous GD1c-like LOS of *C. jejuni* isolated from GBS patients induced anti-GD1a/GQ1b antibodies with higher activity than anti-GQ1b antibody (Kuijf et al. 2008), indicating the complexity of molecular mimicry in the production of anti-GSL antibodies. Oligosaccharides, including gangliosides, are organized in clusters in the plasma membrane and are wrapped closely together to create rigid structures with multivalency in clustered saccharide patches (Varki 1994; Hakomori 2002; Willison 2005). Highly dense epitopes and distribution of charges in the saccharide patches may exert an enormous influence on configuration of the oligosaccharide moieties and involve the induction of antigenic GSLs, whose structure is difficult to predict.

Risk factors in the pathogenesis of GBS and related diseases

Ganglioside molecular mimicry and bacterial risk factors following Campylobacter jejuni (C. jejuni) enteritis

As stated above, GBS arises as a result of autoimmune attack due to structural similarities between certain LOS molecules of *C. jejuni* strains and human nerve tissue gangliosides. GBS is related to antecedent infections, and the identification of various antiganglioside serum antibodies in patients with GBS is crucial in understanding the etiology of this disorder. Antibodies formed against ganglioside-like epitopes in LOSs of certain infectious bacteria have been shown in both histopathological data (Griffin, Li, Ho, et al. 1996; Kaida et al. 2000) and animal studies (Yuki et al. 2004; Usuki et al. 2006) to cross-react with the ganglioside surface molecules of the PNS, providing strong evidence that molecular mimicry serves as a most-likely pathogenic mechanism for the disease (Willison and Yuki 2002; Yu et al. 2006). Sensitization of rabbits with the LOS of *C. jejuni* induces AMAN, similar to that in rabbits sensitized with GM1 ganglioside. The paralyzed rabbits have pathological changes in their peripheral nerves identical to the changes seen in humans with GBS. *C. jejuni* infection may induce antiganglioside antibodies by molecular mimicry, causing AMAN (Komagamine and Yuki 2006). The LOS of *C. jejuni* is a major surface molecule consisting of two parts, the core oligosaccharide and lipid A. A number of genes are involved in core oligosaccharide synthesis in LOS (Fry et al. 2000) and in the induction of GBS (Yuki 2007b).

Previous studies of the complete genomic sequence of *C. jejuni* revealed that the locus for *Campylobacter* LOS biosynthesis is 16 kb in length and contains 12 genes encoding proteins, open reading frames (ORFs) (designated *galE* and *wlaBCDEFGHIKLM*), and two incompletely present ORFs (*waaC and orf′*) (Fry et al. 1998; Szymanski et al. 1999). In the LOS structure, the backbone of the lipid A moiety is substituted at position 6′ with a 2→4-linked disaccharide of 3-deoxy-α-*d-manno*-octulosonic acid (Kdo). Gene *waaC* serves as an acceptor for transfer of the first heptose residue to position 5 of the first Kdo residue, which is accomplished by heptosyltransferase I (Klena et al. 1998; Kanipes et al. 2006). Fry et al. (1998, 2000) reported that the *C. jejuni galE* gene encoding a UDP-galactose-4-epimerase, which catalyzes interconversion of UDP-galactose and UDP-glucose, is indispensable to the formation of a ganglioside-like structure of the LOS-core oligosaccharide. Shu et al. (2006) performed immunization experiments in a guinea pig model using *C. jejuni* HS:19 and its *galE* mutant, and showed the development of high-titer anti-GM1 IgG and axonal degeneration only in animals sensitized with *C. jejuni* but not in animals sensitized with the *galE* mutant. Houliston et al. (2006) identified a sialate *O*-acetyltransferase, *orf11*, in the LOS biosynthesis locus of *C. jejuni*. Strains possessing this locus are known to produce sialylated outer core structures that mimic host gangliosides and have been implicated in triggering the onset of GBS. In recent studies of the *C. jejuni* strain HB 93-13, ORFs contain 13 consecutive genes: *waaC, htrB, wlaNC, wlaND, cgtA, cgtB, cstII, neuB, neuC, neuA, wlaVA, wlaQA,* and *waaF* (Phongsisay and Fry 2007), which are involved in lipid A and LOS synthesis (Stintzi 2003; Phongsisay et al. 2006; Yuki 2007b). These genes are essential for the formation of human ganglioside-like LOS structures that can potentially induce GBS. Functionally, the *C. jejuni htrB* gene encodes a putative acyltransferase involved in lipid A synthesis (Gilbert et al. 2000, 2002; Parkhill et al. 2000; Phongsisay et al. 2007). The *waaF* encodes a heptosyltransferase II that catalyzes the transfer of the second Kdo residue to the core oligosaccharide moiety of LPS (Misawa et al. 2001; Oldfield et al. 2002). Interestingly, Oldfield et al. (2002) constructed a waaF mutant in *Campylobacter* strains to examine the role of *waaF*. Loss of heptosyltransferase activity results in production of a truncated core oligosaccharide, failure to bind specific ligands, and loss of serum reactive GM1, asialo-GM1, and GM2 ganglioside epitopes. Linton, Gilbert, et al. (2000) have demonstrated that the *C. jejuni wlaN* gene, which encodes β1,3-galactosyltransferase, is responsible for converting GM2-like LOS structures to GM1-like structures and for producing a ganglioside GM1-mimicking LOS. In addition, phase-variable expression of the C. jejuni *wlaN* gene results in alternate ganglioside-mimicking LOS structures. The *wlaND* and *wlaQA (waaV)* genes encode a putative glucosyltransferase and a putative glycosyltransferase, respectively (Parkhill et al. 2000; Gilbert et al. 2002). In addition, several genes involved in the biosynthesis of LOSs in GBS have been cloned: genes encoding a β-1, 4-*N*-acetylgalactosaminyl transferase (*cgtA*) (Gilbert et al. 2000; Nakamikin et al. 2002), a β-1, 3-galactosyl transferase (*cgtB*) (Gilbert et al. 2000; Linton, Gilbert, et al. 2000; Nakamikin et al. 2002), and a bifunctional sialyltransferase (*cst-II*) (Gilbert et al. 2000, 2002; Nachamkin et al. 2002; Chiu et al. 2004; Koga, Takahashi, et al. 2005). Guerry et al. (2000) cloned three genes involved in biosynthesis of the LOS core of *C. jejuni* MSC57360, whose structure mimics GM2 ganglioside. These genes have been characterized as encoding proteins with homology to a sialyltransferase (*cstII*), a putative *N*-acetylmannosamine synthetase (*neuC1*), and a putative β-1,4-*N*-acetylgalactosaminyltransferase (*Cgt*).

The *Cgt* enzyme is capable of transferring GalNAc to an acceptor with or without NeuAc. The *Cst* enzyme is involved in transferring *N*-acetylneuraminic acid (NeuAc) to an acceptor with or without GalNAc. In addition, the genome of *C. jejuni* NCTC 11168 has a *neuB* gene, which encodes proteins with sequence similarity to NeuAc synthases, the enzymes that condense *N*-acetylmannosamine and phosphenopyruvate to form NeuAc (Linton, Karlyshev, et al. 2000). Analysis of the *C. jejuni* NCTC 11168 genomic sequence identified three putative NeuAc synthetase genes, called *neuB1*, *neuB2*, and *neuB3* (Linton, Karlyshev, et al. 2000). The *neuB* genes of *C. jejuni* appear to be involved in the biosynthesis of at least two distinct surface structures: LOS and flagella (flagellin protein). The *neuB1* encodes NeuAc synthetase, which is required for the synthesis of NeuAc of *C. jejuni* LOS (Xiang et al. 2006). After the neuB1 mutant was constructed from a *C. jejuni* HS:19 wild strain, mutant LOS could not bind the cholera toxin B subunit, failed to induce anti-GM1 antibodies, and did not cause pathological changes in the PNS. These data suggest that the NeuAc residue in LOS is a crucial epitope in realization of ganglioside molecular mimicry. Similarly, the *neuA* gene is also essential for the formation of human ganglioside-like LOS (Phongsisay et al. 2007). NCT 11168, in addition to possessing *cj1143* (*neuA1*), contains two other copies of *neuA* alleles, *cj1311* (*neuA2*) and *cj1331* (*neuA3 or ptmB*). The neuA3 or ptmB allele is involved in posttranslational modification of the flagellin of *C. coli* VC167 (Guerry et al. 2000). The *cstII* is involved to transfer NeuAc to the O-3 position of galactose and to the O-8 position of NeuAc that is α2,3-linked to a galactose from *C. jejuni* (Gilbert et al. 2000). The cst-I was shown to be absent from certain strains that have been involved in transferring a NeuAc on the inner β1,3-Gal residue of their LOS outer core (Gilbert et al. 2000), and consequently, cst-l is unlikely to be responsible for LOS sialylation (Gilbert et al. 2002). Godschalk et al. (2006) identified three markers, located in the LOS biosynthesis genes *cj1136*, *cj1138*, and *cj1139c*, that were significantly associated with GBS ($P = 0.024$, $P = 0.047$, and $P < 0.001$, respectively). The study further suggests that bacterial GBS markers are limited in number and located in the LOS biosynthesis genes, which corroborates the current consensus that LOS mimicry may be the prime etiologic determinant of GBS.

The LOS synthesis gene clusters contain several additional ORFs with similarity to genes involved in biosynthesis of the LOS inner core, including *gmhA* (Cj1149), *gmhD* (Cj1151), and *gmhE* (*Cj1150*) (Oldfield et al. 2002). The *gmhA* (formerly called *lpcA*) encodes phosphoheptose isomerase, which converts sedoheptulose 7-phosphate into D-*glycero*-D-*manno*-heptose 7-phosphate (Brooke and Valvano 1996). The second characterized gene, *rfaD* (recently designated *gmhD*), encodes ADP-L-*glycero*-D-*manno*-heptose epimerase, which converts ADP-D-*glycero*-D-*manno*-heptose to ADP-L-*glycero*-D-*manno*-heptose (Pegues et al. 1990), the substrate for the heptosyltransferase reaction, but the roles of other inner core biosynthesis genes still require confirmation (Oldfield et al. 2002).

Godschalk et al. (2007) demonstrated that specific bacterial genes are crucial for the induction of antiganglioside antibodies, determining the class of LOS loci (classes A–E) in a collection of 26 neuropathy-associated and 21 control *C. jejuni* strains isolated from patients with uncomplicated enteritis. Analyzing the expression of ganglioside-like structures in relation to the class of LOS locus, they found that GM1-like structures were associated with the class A locus, whereas GQ1b-like structures were predominantly expressed in strains with the class B locus. In 8 of 11 strains with class D or E locus, ganglioside-like structures were not detected, which is in accordance with the absence of genes involved in the biosynthesis or transfer of NeuAc. These results indicate that genes unique to class A and B loci and genes involved in NeuAc biosynthesis or transfer may be crucial for the induction of neuropathogenic cross-reactive antibodies and may be considered GBS marker genes. Koga et al. (2006) reported bacterial risk factors for developing GBS. These factors include genotypes, serotypes, and ganglioside mimics on the LOS in *C. jejuni* strains from Japanese patients with GBS. Clearly, bacterial strains isolated from patients with GBS had LOS biosynthesis locus class A more frequently (72/106; 68%) than did the strains from patients with enteritis (17/103; 17%). Class A strains were predominantly serotype HS:19 and had the *cstII* (Thr51) genotype; the latter is responsible for biosynthesis of GM1-like and GD1a-like LOSs. Both anti-GM1 and anti-GD1a monoclonal antibodies regularly bind to class A LOSs, whereas no antibody binds to other LOS locus classes. Mass spectrometric analysis showed that a class A strain carried GD1a-like LOS as well as GM1-like LOS. The class A locus and serotype HS:19 seem to be linked to *cstII* polymorphism, resulting in the synthesis of both GM1-like and GD1a-like structures on LOS and, consequently, an increase in the risk of producing antiganglioside autoantibodies and predicatively developing GBS. Interestingly, there are no apparent differences in gene frequency between strains from patients with GBS or MFS versus the control strain (van Belkum et al. 2001). However, 8/8 (100%) strains displaying a GQ1b epitope have *cstII*, whereas among the GQ1b-negative strains only 14/26 (54%) are *cstII* positive ($P = 0.03$). This result indicates that the *cstII* NeuAc transferase is a necessary determinant for the synthesis of GQ1b-like epitopes, but that it is itself not sufficient to produce the epitopes and consequently trigger GBS or MFS. In this regard, Gilbert et al. (2002) showed that one of the variable residues among the *Cst-II* versions results in either a monofunctional *Cst-II* (Thr-51) or a bi-functional *Cst-II* (Asn-51).

There is strong evidence for frequent cross-contamination during slaughtering and meat-product processing. Some studies have indicated that slaughter processes have an influence on the risk for human campylobacteriosis (Usuki et al. 2006b). Schmidt-Ott et al. (2006) developed a serological assay for the diagnosis of *C. jejuni* infections that involved two purified recombinant *C. jejuni* antigens encoded by *C. jejuni* genes *Cj0017* and *Cj0113*, thereby greatly improving *Campylobacter* serology. They found serological evidence of a preceding *C. jejuni* infection in 80.6% of the patients but in only 3.5% of the controls. This study presents strong evidence that prior *C. jejuni* infection in GBS patients is far more frequent than previously reported (Table II).

Familial cases of GBS

Generally, GBS is considered a complex multifactorial disorder caused by both genetic and environmental factors rather than a disorder following simple Mendelian inheritance (Geleijns, Brouwer, et al. 2004). Nonetheless, several rare familial cases have been reported. Saunders and Rake (1965) first reported a brother and a sister with muscle weakness that developed 4 years apart. Bar-Joseph et al. (1991) reported three siblings, all

Table II. Proposed functions for GBS-related genes in the LOS biosynthesis locus of various *C. jejuni* strains

Factors	Proposed function	Strain	Class	References
ORFs				
waaA	Kdo-transferase	F38011; clinical isolate		Klena et al. (1998)
waaC	Heptosyltransferase I	81-176		Kanipes et al. (2006)
waaF	Heptosyltransferase II	NCTC11828		Oldfield et al. (2002)
galE	UDP-glucose 4-epimerase	HS:6 (81116)	E	Fry et al. 1998, 2000
wlaNA (htrB)	Putative. Lipid A biosynthesis acyltransferase	OH4382; OH4384; NCTC11168		Gilbert et al. (2002)
		NCTC11168		Parkhill et al. (2000)
wlaB	Polysaccharide involvement			
	Expert hemolysin			
wlaNC	Putative glucosyltransferase	OH4382; OH4384; NCTC11168		Gilbert et al. (2002)
		NCTC11168		Parkhill et al. (2000)
wlaC	Glycosyltransferase			
wlaND	Putative glucosyltransferase	OH4382; OH4384; NCTC11168		Gilbert et al. (2002)
		NCTC11168		Parkhill et al. (2000)
wlaD	Abequosyltransferase			
	Glycosyltransferase			
wlaE	Glycosyltransferase			
wlaF	Oligosaccharyltransferase			
	O-Antigen polymerase			
wlaG	Glycosyltransferase			
	Galactantransferase			
wlaH	Galactosyltransferase first step			
	Galactosyltransferase			
wlaI	Polysialic acid capsule synthesis			
	Acyltransferase			
wlaJ	*O*-acetyltransferase			
wlaK	Perosamine synthetase			
	Transamination			
wlaL	Capsule synthesis			
	Acetylgalactosamine synthesis			
wlaM	Accessory colonization factor			
wlaVA	Putative acetyltransferase	OH4382; OH4384; NCTC11168		Gilbert et al. (2002)
		NCTC11168		Parkhill et al. (2000)
wlaQA (waaV)	Putative glycosyltransferse	OH4382; OH4384; NCTC11168		Gilbert et al. (2002)
		NCTC11168		Parkhill et al. (2000)
wlaN	β-1,3-Galactosyltransferase	NCTC11168	C	Linton, Gilbert, et al. (2000)
orf11	O-Acetyltransferase	HS:19	A	Houliston et al. (2006)
Cst-I	α2,3-Sialylltransferase	HS:19 (OH4384)	A	Gilbert et al. (2000)
Cst II	α2,3/α2,8-Sialyltransferase	HS:19 (OH4384)	A	Gilbert et al. 2000, 2002
	α2,3/α2,8-Sialyltransferase	HS:19 (OH4384)	A	Chiu et al. (2004)
	α2,3/α2,8-Sialyltransferase	HS:19	A	Nachamkin et al. (1998)
		HS:1(MSC57360)		Guerry et al. (2000)
Cst-II (Thr51)	α2,3-Sialyltransferase	HS:19(OH4382/OH4384)	A	Koga, Takahashi, et al. (2005)
Cst-II (Asn51)	α2,3/α2,8-Sialyltransferase	HS:19(OH4382/OH4384)	A	Koga, Takahashi, et al. (2005)
Cst III	α2,3-Sialyltransferase	HS:1(MSC57360)	A	Guerry et al. (2000)
CgtA	β-1,4-*N*-Acetylgalactosaminyltransferase	HS:19 (OH4384)	A	Gilbert et al. (2000)
	β-1,4-*N*-Acetylgalactosaminyltransferase	HS:23/HS:36(81176)	B	Guerry et al. (2000)
	β-1,4-*N*-acetylgalactosaminyltransferase	HS:19	A	Nachamkin et al. (1998)
CgtB	β-1,3-Galactosyltransferase	HS:19 (OH4384)	A	Gilbert et al. (2000)
	β-1,3-galactosyltransferase	HS:19	A	Nachamkin et al. (1998)
		NCTC11168		Linton, Gilbert, et al. (2000)
neuA (neuA1)	CMP-NeuAc synthetase	OH4382; OH4384; NCTC11168		Gilbert et al. (2002)
NeuB1 (neuB1)	Sialic acid synthetase	HS:19	A	Xiang et al. (2006)
NeuC1 (neuC1)	ManAc synthesis	HS:1(MSC57360)	A	Guerry et al. (2000)

ORFs, open reading frames; Kdo, 3-deoxy-D-*manno*-octulosonic acid.

of whom developed GBS when less than 2 years old. Davidson et al. (1992) reported the disorder in a father and a son. The onset of the father's illness was at the age of 58, and that of the son's illness was diagnosed 9 years later at the age of 43. They had remarkably similar HLA typing. Yuki and Tsujino (1995) reported two Japanese sisters who developed MFS, after infection by *C. jejuni* enteritis. The 19-month-old girl first developed diarrhea that resolved during a period of eight days after *C. jejuni* enteritis. On the next day, she was unable to stand up or sit down by herself. On day 2, muscle weakness developed in the upper limbs, and she was admitted to the hospital. Neurological examination showed flaccid tetraplegia and areflexia without sensory impairment. After 10 days, her 3.5-year old sister developed similar clinical signs and symptoms. Both patients met the clinical criteria for MFS. Geleijns, Brouwer, et al. (2004) described 12 Dutch families in which at least two members have had GBS. The researchers also observed an earlier onset of GBS in successive generations. The occurrence of GBS within families may suggest a role of genetic factors in the pathogenesis of GBS.

Host factors involved in the pathogenesis of GBS and related diseases, especially in non-antiganglioside antibodies

Infection with certain strains of *C. jejuni* induces antibodies specific for the LOS of certain strains that cross-react with peripheral nerve antigens, resulting in production of antiganglioside antibodies in the sera of some patients with GBS (Willison and Yuki 2002; Usuki et al. 2005). Biochemical and serological studies have revealed that many *C. jejuni* strains express ganglioside-like structures in their LOSs. Molecular mimicry has been proposed as a pathogenetic mechanism for autoimmune diseases, as well as a probe useful in uncovering its etiologic agents (Willison and Yuki 2002; Yu et al. 2006). That hypothesis is based in part on the abundant epidemiological, clinical, and experimental evidence of an association of infectious agents with autoimmune diseases and the observed cross-reactivity of immune reagents with host "self"-antigens and microbial determinants (Oldstone 1998). Some *C. jejuni* strains isolated from patients with diarrhea, however, contain GM1 ganglioside-like epitopes (Sheikh et al. 1998), and yet those patients do not develop antiganglioside antibodies (Nachamkin et al. 1998). In this regard, ganglioside-mimics do not induce GBS in more than 40% of patients, and the etiology of GBS, including in those cases, remains unknown (Godschalk et al. 2006). In addition, McCarthy and Giesecke (2001) estimated that only 0.01% of patients with *C. jejuni* enteritis subsequently developed GBS. Therefore, there must be unidentified factors influencing the onset of GBS after infection, which include host genetic factors or other host-related factors (Yuki 2000; Godschalk et al. 2006).

De Libero et al. (2005) have reported that bacterial infection may promote the activation of T cells reactive to self-glycosphingolipids (self-GSLs) and that, after infection, $CD1^+$-antigen-presenting cells (APCs) increase endogenous GSL synthesis and stimulate GSL-specific T cells in a CD1- and T-cell receptor-dependent manner. This stimulation may contribute to inflammatory responses during bacterial infections and may predispose individuals to autoimmune diseases. It is especially important to determine whether bacterial antigens activate T cells that cross-react with peripheral nerve antigens. CD1 molecules can present bacterial GSL-like epitopes to T cells, raising the question whether peripheral nerve gangliosides could be recognized by CD1-restricted T cells (Porcelli et al. 1998). In addition, APCs may be involved in the induction of T-cell- and B-cell-mediated autoaggressive immunity in GBS and CIDP (Press et al. 2005). The recruitment of dendritic cells to the cerebrospinal fluid of patients with GBS and CIDP may be important in capturing antigens released from inflamed spinal nerve roots into the cerebrospinal fluid (CSF) and in transferring those antigens from CSF to local lymph nodes, where native T and B cells may be activated. Caporale et al. (2006) reported the association between GBS and CD1 molecules that are MCH-like glycoproteins specialized in capturing and presenting a variety of glycolipids to antigen-specific T cells. The combination of CD1A*01/02 and CD1E*01/02 reduces by one-fifth the risk of developing GBS. CD1 genes are known to be located in human chromosome 1 (named CD1A, B, C, D, and E). The susceptibility of developing disease is associated with polymorphisms of CD1A and CD1E genes found in an Italian population with GBS (Aureli et al. 2007) and CIDP (De Angelis et al. 2007). In this regard, Kuijf et al. (2008) recently indicated that susceptibility to GBS is not associated with CD1A and CD1E polymorphisms. In immunohistochemical studies of the CD1 molecules in peripheral nerves, CD1B expressed on the myelinated nerve fibers in patients with AIDP (Khalili-Shirazi et al. 1998) and on the Schwann cells in those with CIDP (van Rhijn et al. 2000). However, Geleijns, Jacobs, et al. (2004) reported that the LPS receptors CD14 and the Toll-like receptor 4 (TLR4) did not confer GBS susceptibility and were not associated with *C. jejuni* infection. The reduction of circulating $CD4^+CD25^+$cells in GBS has been reported in GBS (Chi et al. 2007; Pritchard et al. 2007; Harness and McCombe 2008).

In certain rare cases, there are shared major histocompatibility complex (MHC; called HLA in human) types, consistent with either a common exposure to environmental factors or a genetic influence on an individual's susceptibility to infectious and autoimmune diseases (Hartung and Toyka 1990; Yuki et al. 1991; Wucherpfennig 2001). These cases demonstrate an increased frequency of HLA B35 in patients with GBS following *Campylobacte*r infection. In HLA typing for class II alleles, Rees, Vaughan, et al. (1995) reported an association between HLA-DQB1*03 and preceding *C. jejuni* infection in GBS and MFS. In patients with AIDP, the DRB1*1301 allele shows a significant increase but not in patients with AMAN. Preliminary studies on patients in China with either an AMAN or AIDP form of GBS indicate that certain HLA alleles, DRB1*1301-03 and DRB1*1312, are overrepresented in the different forms of AMAN but not in the control groups (Monos et al. 1997). Using DNA-based typing methods, 47 patients with AMAN, 25 patients with AIDP, and 97 healthy controls were studied for the distribution of class II alleles (Magira et al. 2003). The DQ β RLD(55-57)/ED(70-71) and DR β E(9)V(11)H(13) epitopes were associated with susceptibility to AIDP ($P = 0.009$ and $P = 0.004$, respectively), and the DQ β RPD (55–57) epitope was associated with protection ($P = 0.05$) from AIDP. Class II HLA associations, however, were not identified with AMAN, suggesting a different immunological mechanism of disease induction in those two forms of GBS. T-cell recognition was associated with AIDP but not with AMAN. Those findings provide immunogenetic evidence for differentiating the two disease entities (AMAN and AIDP) and for focusing on particular DRβ/DQβ residues that may be instrumental in understanding the pathophysiology of AIDP. Gorodezky et al. (1983) reported a possible association of DR3 with patients with GBS in Mexico that may play some role in susceptibility to GBS. HLA-B54 and -Cw1 antigens were found in GBS and Miller Fisher patients from whom *C. jejuni* had been isolated more often than from healthy controls (Koga, Yuki, Kashiwase, et al. 1998). HLA-DR2 was reported to be associated with recurrent MFS (Chida et al. 1999). A more recent study indicated that HLA-DRB1 and HLA-DQB1 alleles did not differ between GBS patients and control subjects although the frequency of HLA-DRB1*01 was increased in patients with GBS (McCombe et al. 2006). HLA-B35 and HLA-DR8 antigens also have been found to be increased in patients with GBS (Chatzipanagiotou et al. 2003). Interestingly, HLA associations are found to differ with the gender of the patients in some autoimmune diseases (McCombe et al. 2006). Gender-related HLA-DR2 associations in patients with GBS and CIDP occur more frequently in female patients than in males, suggesting that gender-related factors may interact with the risk factor(s) associated with carriage of HLA-DR

for developing CIDP, but not for developing GBS. Oligoclonal expansion of T cells bearing particular types of T-cell receptor Vβ and Vδ genes frequently occurs in patients with GBS and with MFS (Koga et al. 2003). Overall, Vβ and Vδ spectra types are expanded more frequently in patients with GBS (Vβ in 77%, Vδ in 53%) or MFS (Vβ in 75%, Vδ in 65%) than they are in healthy controls (Vβ in 59%, Vδ in 38%). No particular spectra type was significantly associated with GBS or MFS. However, Ma et al. (1998) did not find significant differences in HLA DRB1 or DQB1 alleles in Japanese cases of GBS and concluded that the roles of TCRAC, T-cell receptor beta-chain variable (TCRBV), HLA class I or class II are not critical in the development of GBS. In addition, HLA class II alleles, HLA-DQA, -DQb, and -DRB, may not be a determinant in distinct subgroups of GBS (Geleijns, Schreuder, et al. 2005). No association has been found in HLA-DR, -DQ or -DP alleles or in HLA-DR-DQ haplotypes in GBS (Hillert et al. 1991). Those data suggest that HLA class II genes do not confer susceptibility to GBS. Schonberger et al. (1981) also reported that no specific HLA antigen was significantly associated with GBS, although HLA AW 30 and AW 31 were associated with chronic relapsing polyneuropathies. Chiba et al. (1995) reported serologic analysis of HLA class I antigens (A, B, and C) and class II antigens (DR and DQ) in patients with GBS and MFS, but HLA types were not found to be associated with an anti-GQ1b IgG antibody in MFS and GBS. That finding points to an area that needs more careful study involving additional numbers of patients (Geleijns, Schreuder, et al. 2005).

The intricate balance of the numerous factors involved in immune responses determines the outcome of the interaction between the microbe and the host. Recent studies focusing on the role of cytokines, chemokines, and their networks of related mediators and/or receptors suggest that any imbalance may make a significant contribution to the pathogenesis of the infectious disease process (Tsang and Valdivieso-Garcia 2003). Macrophages infiltrate peripheral nerves and may contribute to neural damage in GBS (Geleijns et al. 2007). Ma et al. (1998) studied genetic polymorphisms in the tumor necrosis factor (TNF) in Japanese patients with GBS. A significantly higher frequency of the 100-base pair (bp) (TNF-2α) allele of the TNF-α microsatellite marker, which is associated with high TNF-α production, exists in *C. jejuni*-positive (Cj+) GBS patients than in the control groups, suggesting the involvement of a genetic predisposition to high TNF-α secretion in the development of *C. jejuni*-related GBS. Similar studies indicate the involvement of TNF-α and/or soluble TNF-α receptors in GBS (Creange et al. 1996; Putzu et al. 2000; Radhakrishnan et al. 2003; Zhang et al. 2007). Molecular analysis has revealed a duplication at chromosome 17p11, 2-12, which is a genetic risk factor for GBS (Munch et al. 2008). Intravenous immunoglobulin (IVIG) therapy may play a protective role by inhibiting elevated levels of serum or peripheral nerve TNF-α and soluble TNF-α receptors (Radhakrishnan et al. 2003, 2004; Reuben et al. 2003). The A(-670)GSNP in the promoter region of Fas and levels of sFas may be involved in the pathogenesis of GBS (Geleijns, Laman, et al. 2005). The −592 CC and −819 CC genotypes associated with increased interleukin-10 (IL-10) response are more frequent in the patients with GBS than in the controls ($P = 0.027$), but the polymorphisms do not influence the clinical course of the disease (Myhr et al. 2003). The serum concentrations of IL-2 and soluble IL-2 receptor are elevated in patients with GBS (Hartung and Toyka 1990). Kieseier et al. (1998) reported that matrix metalloproteases MMP-9 and MMP-7 are expressed in the nerve cells of patients with GBS that may contribute to the pathogenesis of this disease. Geleijns et al. (2007) determined that single nucleotide polymorphisms (SNPs) in genes encoding macrophage-mediators are related to the susceptibility and severity of GBS. Although the frequencies of SNPs in the TNF-α, MMP-9, IL10, and NOS2a genes did not differ between 263 GBS patients and 210 healthy subjects, the MMP-9 C(-1562)T and TNF-α C(-863)A SNPs are associated with severe weakness and poor outcomes, indicating that these SNPs may be one of the factors predisposing individuals to a severe form of GBS. Infiltration of spinal nerve roots and peripheral nerves by macrophages and T cells are rather consistent immunopathologic findings in patients with GBS and CIDP. The level of spontaneous IFN-γ and IL-5 secretions increases in patients with GBS and is especially increased in those with CIDP as compared with healthy controls and patients with nonimmune mediated neuropathies (Csurhes et al. 2005). In patients with CIDP, increased numbers of spontaneous IFN-γ- and IL-5-secreting cells and increased IFN-γ secretion in response to PMP-22 (51-64) provide further evidence for a role of myelin-specific T cells in CIDP. Deng et al. (2008) reported enhanced IL-12, IL-12R1 in AIDP, and TNF-α in AMAN during the acute phase, as well as increased TNF-αR1 during the plateau phase of AIDP. In addition, chemokines may play a central role in the recruitment of leukocytes to inflamed tissues. Press et al. (2003) reported the involvement of chemokines, monocyte chemoattractant protein 1 (MCP-1), and IFN-γ-inducible protein-10 (IP-10) in the pathogenesis of GBS, and IP-10 and macrophage-inflammatory protein-3β (MIP-3β) in the pathogenesis of CIDP. MCP-1 and its receptor (CCR2) may participate in the recruitment of circulating mononuclear cells in nerve tissue in patients with GBS, in which the number of circulating CCR2-positive cells is lower in patients with GBS than in healthy subjects.

In addition to the above findings, involvement of leukocyte immunoglobulin (IgG) receptor (FcγR) IIa, IIIA, and IIIB polymorphisms in patients with GBS has been reported (Vedeler et al. 2000). The FcγR genotype has high affinity for IgG1 and IgG3, and clearance of circulating autoantibodies and immune complexes may be of importance in the pathogenesis of GBS (Vedeler et al. 2000). FcγRIII genotypes may represent mild disease-modifying factors in GBS (van Sorge et al. 2005). FcγRIIa allotypes capable of initiating efficient cellular-effector functions are associated with increased risk for GBS and a more severe disease course. FcγR alleles may constitute novel genetic risk markers for GBS (van der Pol et al. 2000). However, immunoglobulin KM allotypes, a genetic marker of immunoglobulin kappa chains, are not risk factors for developing GBS but do contribute to the generation of autoimmune responses to GD1a ganglioside in patients with the disease (Pandey et al. 2005).

Interestingly, molecular analysis revealed duplication at chromosome 17p11, 2-12, which is a genetic risk factor for GBS (Munch et al. 2008). Hadden et al. (2001) reported the involvement of soluble intercellular adhesion molecule-1 (sICAM-1) in GBS. In addition, significantly higher IgG antibody titers against heat-shock proteins (HSPs) HSP27, HSP60, HSP70, and the HSP90 family, including mycobacterial HSP65 and *Escherichia coli* GroEL, have been found in the CSF of patients with GBS as compared with patients with motor neuron

Table III. Host risk factors for GBS and related diseases

Host factors	Patients	Reference
Antigen-presenting cells		
$CD1^+$APCs	GBS/CIDP	Press et al. (2005)
CD1A, CD1E	GBS	Caporale et al. 2006; Kuijf et al. 2008; Aureli et al. 2007
CD1A, CD1E	CIDP	De Angelis et al. (2007)
CD1E	AIDP	Khalili-Shirazi et al. (1998)
CD1E	CIDP	van Rhijn et al. (2000)
CD14, Toll-like receptor4 (TLR4)	GBS	Geleijns, Jacobs, et al. (2004)
$CD4^+$, $CD25^+$	GBS	Pritchard et al. (2007)
HLA Class-I		
B35	GBS	Chatzipanagiotou et al. (2003)
B54	GBS/MFS	Koga, Yuki, Kashiwase, et al. (1998)
Cw1	GBS/MFS	Koga, Yuki, Kashiwase, et al. (1998)
HLA Class-II		
DR3	GBS (Mexican)	Gorodezky et al. (1983)
DR2	MFS	Chida et al. (1999)
DR2	CIDP (Female)	McCombe et al. (2006)
DR	GBS	Hartung and Toyka (1990)
DR8	GBS	Chatzipanagiotou et al. (2003)
DRB1*1301	AIDP	Monos et al. (1997)
DRB1*1301-03	AMAN	Monos et al. (1997)
DRB2*1312	AMAN	Monos et al. (1997)
DQB1*1	GBS	McCombe et al. (2006)
DQB1*3	GBS/MFS	Rees, Vaughan, et al. (1995)
DQβRLD(55-57)ED(70-71)	AIDP	Magira et al. (2003)
DQβE(9)V(11)H(13)	AIDP	Magira et al. (2003)
T-cell receptors		
TCRVβ, TCRVδ	GBS/NFS	Koga et al. (2003)
Apoptosis		
TNF-2α	GBS (in Japan)	Ma et al. (1998)
TNF-α and/or TNF-α receptor	GBS	Creange et al. 1996; Zhang et al. 2007; Putzu et al. 2000; Radhakrishnan et al. 2003, 2004; Deng et al. 2008
A(-670)GSNP (promoter region of Fas)/sFas	GBS	Geleijns, Laman, et al. (2005)
Cytokines, Chemokines		
IL-10	GBS	Myhr et al. (2003)
IL-5, IFN-γ	GBS/CIDP	Csurhes et al. (2005)
Matrix metalloproteins, MMP-9 and MMP-7	GBS	Kieseier et al. (1998)
SNP in MMP-9, IL-10, TNFA, NOS2a	GBS	Geleijns et al. (2007)
Chemoattractant protein 1 (MCP-1) and its receptor (CCR2)	GBS	Press et al. (2003)
IFN-γ-inducible protein-10 (IP-10)	CIDP	Press et al. (2003)
Macrophage-inflamatory protein-3β (MIP-3β)	CIDP	Press et al. (2003)
Leukocyte immunoglobulin (IgG) receptor (Fc receptor)		
FcγRIIa, IIIA, IIIB	GBS	Vedeler et al. (2000)
FcγRIII	GBS	van Sorge et al. (2005)
FcγRIII-H131	GBS	van der Pol et al. (2000)
Others		
Chromosome 17p11, 2-12	GBS	Munch et al. (2008)
Soluble intercellular adhesion molecule-1 (sICAM-1)	GBS	Hadden et al. (2001)
Heat shock proteins, HSP27, HSP60, HSP70, and HSP90	GBS	Yonekura et al. (2004)

diseases (Yonekura et al. 2004). The CSF antibodies against HSPs may modify the immune responses and/or cell-protective functions of HSPs in the pathophysiology of GBS. These host factors are summarized in Table III.

Other risk factors in the pathogenesis of GBS

Increasing evidence supports the concept that GBS comprises a group of heterogeneous disorders with different immunological pathogeneses. Most cases of GBS are triggered by infection, vaccination, or other factors (D'Alessandro et al. 1999; Tam et al. 2007), such as bacterial or viral infection with the latter consisting of cytomegalovirus, Epstein–Barr virus, herpes, encephalitis virus, hepatitis B, HIV, and mononucleosis. Infection by *Mycoplasma pneumoniae* is also considered a potential cause for the development of GBS. In rare cases of GBS, infective endocarditis, *rubella* virus infection, *Haemophlus influenzae*, and *Legionnella* infection may be associated (Akyildiz et al. 2008; Baravelli et al. 2008; Condon and Tobin 2008; Figueiredo et al. 2008). Vaccinations, including flu vaccine, immunization against group A streptococcus, rabies, and swine flu, may also trigger GBS (Ropper et al. 1991; Yuki and Hirata 1998; Nachamkin et al. 2008; Sivadon-Tardy et al. 2009). In addition, administration of meningococcal conjugate vaccine may have a risk factor for inducing GBS (De Wals et al. 2008). Other causal factors triggering GBS include systemic lupus erythematosus, blood cancers, especially Hodgkin lymphoma, pregnancy, surgery, and certain drugs, such as streptokinase, heroin, danazol, and captopril (Ropper et al. 1991), Trauma (Yardimci et al. 2009), stem cell plantation (Zhang et al. 2008), and barium poisoning (Talwar et al. 2007) may also mimic GBS.

Conclusion

GBS and related disorders are autoimmune neuropathies that frequently occur as a result of enteritis resulting from an infectious event from agents such as *C. jejuni* and that are characterized by an immune-mediated attack on the peripheral nerves, particularly in the myelin sheath of sensory and motor nerves. Increased antibody titers in GBS and variants are thought to be a result of the production of antibodies to bacterial carbohydrate-containing surface antigen(s) that cross-react with gangliosides (ganglioside mimicry) of the myelin sheath and the axons of nerve cells. For this reason, the most-common diagnostic test of GBS is detection of circulating antiganglioside antibodies in patients who may have GBS. These antiganglioside antibodies in turn damage the nerve fibers that are enriched in gangliosides. The identification of antiganglioside antibodies in GBS has directed therapeutic research efforts on either eliminating these antibodies or countering their pathologic effects. Although detection of antiganglioside antibodies and glycobiological analysis of pathogens causing antecedent infection have contributed to elucidation of the pathophysiology of GBS and related disorders, many questions remain. Investigation of anti-GSL antibodies in patients' sera and biochemical analysis of glycoepitopes of gangliosides or GSL antigens in peripheral nerves should enhance the understanding of the pathogenesis of GBS. On the other hand, relatively little is known about the complex host factors associated with the development of GBS. Innovative molecular biological techniques and further advances in research on the immune network may be required to determine the host factors. It is imperative to confirm the role of host factors, and such knowledge will undoubtedly improve the opportunity to develop a novel treatment for GBS and related disorders.

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Conflict of interest statement

None declared.

Abbreviations

AIDP, acute inflammatory demyelinating polyradiculoneuropathy; AMAN, acute motor axonal neuropathy; AMSAN, acute motor and sensory axonal neuropathy; *cgtA*, β-1,4-*N*-acetylgalactosaminyltransferase; *cgtB*, β-1.3-galactosyltransferase; CIDP, chronic inflammatory demyelinating polyneuropathy; CMV, cytomegalovirus; CN, cranial nerve; *cst-I*, α-2,3-sialyltransferase-I; *cst-II*, α-2,3-sialyltransferase-II; DRG, dorsal root ganglia; EBV, Epstein–Barr virus; *galE*, UDP-galactose-4-epimerase; GBS, Guillain–Barré syndrome; GSC, ganglioside complex; GSL, glycosphingolipid; Kdo, 3-deoxy-α-D-*manno*-octulosonic acid; KLH, keyhole limpet hemocyanin; LOS, lipooligosaccharide; LPS, lipopolysaccharide; MFS, Miller Fisher syndrome; Nav, voltage-gated sodium channel; *neu*, NeuAc-synthetase; NeuAc, sialic acid; NMJ, neuromuscular junction; ORF, open reading frame; PCB, pharyngeal-cervical-brachial; PNS, peripheral nerve system.

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