AINO JOURNAL, Vol. 6, 2007, pp. 19–23

Review

Anti-GM1 antibodies in Guillain-Barré syndrome

Toshifumi TANAKA *Professor, Department of Nursing, Aino Gakuin College, Aino Institute for Aging Research*

Key words: Guillain-Barré syndrome, anti-GM1 antibodies, acute motor axonal neuropathy, ganglioside GM1

Introduction

In Guillain-Barré syndrome (GBS) there are miscellaneous antibodies against certain gangliosides. The kind of antibody is closely related to the disease type and removal of these antibodies by plasmapheresis is an effective treatment to improve the diseases. Therefore these antibodies have been postulated as effecter molecules in these peripheral neuropathies. However it is still unclear how to raise the auto-antibodies and how the antibodies injure neuronal tissue in GBS. In this short review, I will try to touch on a new aspect to understand the pathophysiological mechanisms of GBS.

Clinical feature of GBS

GBS is a typical postinfectious autoimmune polyradiculoneuropathy. Characteristically, it presents in a previously healthy person with the rapid onset of symmetrical limb weakness and loss of tendon reflexes. Additional findings include cranial nerve, gait ataxia, respiratory compromise, and autonomic involvement (Burns et al., 2005; Ropper, 1992). GBS has become the most frequent cause of acute flaccid paralysis, with 0.4–4.0 cases per 100,000 population (Hughes and Rees, 1997).

Clinical symptoms often occur 1–3 weeks after a precedent bacterial or viral infection, most frequently, *Campylobacter jejuni (C. jejuni)* (23%), *Cytomegalovirus* (10%), *Mycoplasma pneumoniae* (6%), or *Epstein-Barr virus* (3%), raising the possibility that GBS may be a consequence of infection from these agents (Ogawara et al., 2000). Typically, the symptoms become worse within 1–2 weeks of initial onset. In general most patients recuperate satisfactorily 2–3 months after predicating infection. Some patients may experience lingering motor disturbances and 8% of patients die within 1 year of disease onset (Ariga and Yu, 2005). Cerebrospinal fluid findings are albuminocytologic dissociation with increased protein and fewer than 50 white blood cells (Burns et al., 2005).

Nerve conduction study may demonstrate prolonged distal latencies, conduction slowing, conduction block, and temporal dispersion of compound action potential in demyelinating cases. In primary axonal damage, the findings include reduced amplitude of the action potentials without conduction slowing and fibrillations in electromyography (Burns et al., 2005; Ropper, 1992). Plasma exchange therapy shortens the time required for artificial ventilation and the period of inability to walk, thereby providing significant savings in health care. Intravenous infusion with a human immunoglobulin preparation has equivalent clinical effects (Hughes et al., 2007).

Currently GBS is divided into several subtypes based on electrodiagnostic, pathological, and immunological criteria (Hughes and Cornblath, 2005). Acute inflammatory demyelinating polyneuropathy (AIDP) is a multifocal demyelinating disorder of the peripheral nerves. This is the most common type in Europe and North America. Acute motor axonal neuropathy (AMAN) shows axonal degeneration and sparing of the myelin. In China and Japan, AMAN occurs in more than 40% of persons with GBS (Ho et al., 1995; Ogawara et al., 2000). Other cases appear to involve both sensory and motor axons and such cases are termed acute motor

and sensory axonal neuropathy (AMSAN). The incidence of AMSAN is very low (less than 10% of that of AMAN) (Hughes and Cornblath, 2005). Miller Fisher syndrome (MFS) is another GBS variant that occurs in about 5% of people affected by GBS. It is characterized by ophthalmoplegia, areflexia, ataxia, and, in some cases, facial and bulbar palsy (Paparounas, 2004).

Monosialotetrahexosylganglioside; GM1

Gangliosides, compounds composed of a glycosphingolipid (ceramide and oligosaccharide) with one or more sialic acids, are predominantly distributed on the cell surface membrane and anchored in the external leaflet of the lipid bilayer by a ceramide moiety (Fig. 1).

The ganglioside GM1 is a ubiquitous glycosphingolipid, exposed on the surface of a variety of human cells including motor neurons (Corbo et al., 1992), lymphocytes (Nashar et al., 1996), capillary endothelial cells (Kanda et al., 1994) , and bone marrow cells (Ackerman et al., 1980). GM1 has been generally regarded as an authentic raft molecule. The raft is a cholesterol and glycosphingolipid-enriched microdomain in cell membranes and works as a platform for the attachment of proteins during signal transduction (Simons and Ikonen, 1997). Many proteins are associated to the raft on the cells of nervous system, for example, adhesion molecules, ion channels, protein kinases and receptors (Kasahara and Sanai, 2002).

From the aspect of biological function, GM1 has neuritogenic and neurotrophic properties (Ferrari et al., 1983; Gorio, 1986), but in a broad sense, it has come to be regarded as a modulator of various receptors (Yates and Rampersaud, 1998) such as TrkA (nerve growth factor [NGF] receptor) which is attached to the raft (Mutoh et al., 1995; Wu et al., 1997) and EGFR (epidermal growth factor receptor) (Bremer et al., 1984). GM1 is also well known as a receptor of the cholera toxin B-subunit and has been used to probe its distribution in many microscopic studies (Nichols, 2003) (Fig. 2).

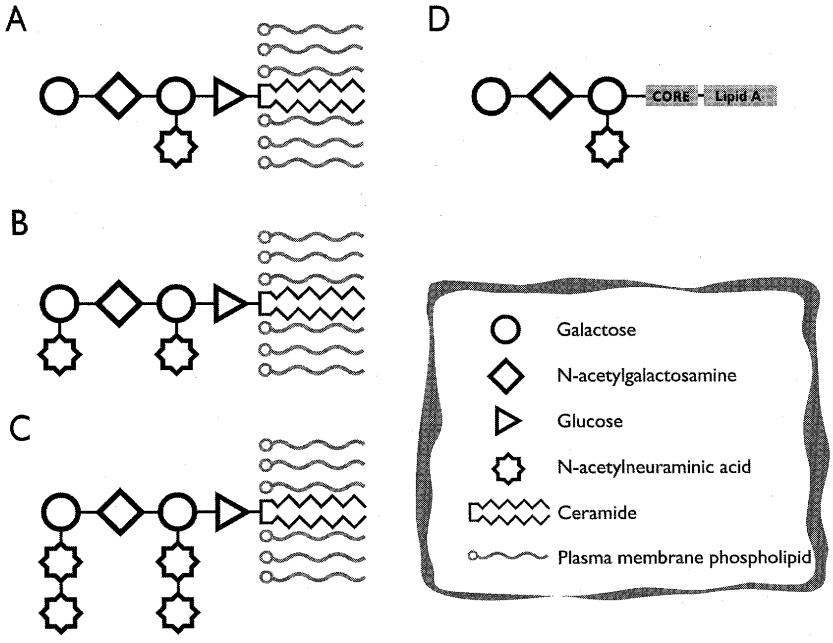

Fig. 1 Schematic structures of the membrane gangliosides and a bacterial lipooligosaccharide
A. GM1 ganglioside. GM1 consists of a pentasaccharide moiety exposed at the surface of the cell membrane and anchored by a ceramide tail which is inserted into the outer leaflet of the plasma membrane.
B. GD1a ganglioside, C. GQ1b ganglioside, D. GM1-like lipooligosaccharide (LOS) on *C. jejuni* cell surface(Yuki et al., 1993).

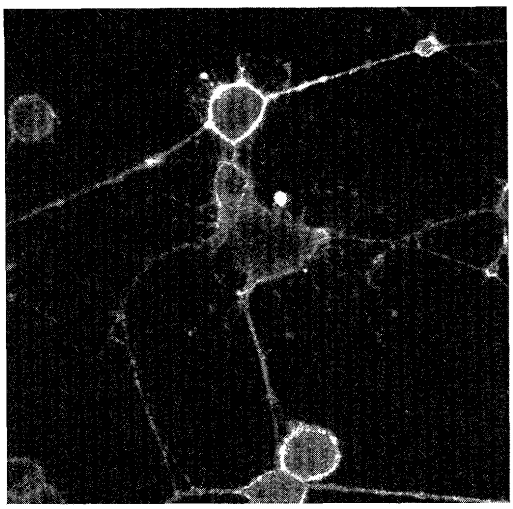

Fig. 2 Localization of GM1 in PC12 cells
This is a immunofluorescence image using cholera toxin B subunit-FITC. PC12 cells had been previously differentiated by NGF.

Anti-ganglioside antibodies in GBS

The relevance between anti-ganglioside antibodies and neuropathies was first suggested in the 1980s, when monoclonal immunoglobulins recognizing GM1 were found in some patients with gammopathy-associated neuropathy and motor neuron disease (Ilyas et al., 1985).

Antibodies that recognize gangliosides have been associated with GBS (Table 1). Some antibodies, which are shown in Table 1, have type-specificities, such as anti-GM1 (Kornberg and Pestronk, 1994) and anti-GD1a (Ho et al., 1999) antibodies of the IgG class are associated with AMAN. And a high titer of IgG type anti-GQ1b antibodies are found in the sera of patients with MFS (Chiba et al., 1992). Particularly IgG class anti-GM1 antibodies are the best-studied example for autoimmune anti-ganglioside antibodies in neuropathies.

Table 1 Relationship between antibodies against gangliosides, antibody isotypes and clinical syndromes

Polyclonal antibodies against	Antibody isotype	Clinical syndromes
GM1	IgG	AMAN
	IgM	MMN
GM1b	IgG	AMAN
GM2	IgM	GBS*
GD1a	IgG	AMAN
GQ1b	IgG	Fisher syndrome
	IgM	SAN

AMAN: acute motor axonal neuropathy; GBS*: GBS with sensory and clanial nerve disturbance; MMN: multifocal motor neuropathy; SAN: sensory ataxic neuropathy.

The roles of anti-GM1 antibodies

In GBS, the first reports of anti-GM1 antibodies appeared in the early 1990s. The anti-GM1 antibodies were strongly associated with AMAN (Kornberg and Pestronk, 1994) and the predominant immunoglobulin class was IgG rather than IgM (Walsh et al., 1991). Correlations were sought between the presence of these antibodies and the prognosis in terms of long-term disability (Kornberg and Pestronk, 1994). Rees et al. showed that patients who were anti-GM1 antibody positive were more likely to have axonal degeneration than anti-GM1 antibody-negative patients (Rees et al., 1995). In a subgroup analysis of GBS cases from another large series of patients, it was also found that patients with anti-GM1 antibodies had a more severe neuropathy with predominantly distal weakness and no sensory involvement (Jacobs et al., 1996).

Gangliosides are typical self-glycans, and it is difficult to raise high-affinity anti-ganglioside antibodies (Kawashima et al., 1992). When purified GM1 was applied for treatment of various diseases, a few patients developed GBS (Illa et al., 1995) in combination with anti-GM1 antibodies, indicating that in certain conditions GM1 can be immunogenic in humans. However, most researchers believed that GM1 immunization produces minor electrophysiological and pathological alterations (Thomas et al., 1991), but no clinical symptoms (Lopez et al., 2002). On the other hand, high titers of anti-GM1 antibodies can be produced in rabbits by inoculation of GM1 or bovine brain with proper adjuvant, accompanied by a flaccid limb weakness of acute onset with a monophasic illness course (Yuki et al., 2001). It is considered that the antibodies must have high affinity for GM1 to cause neuropathies and, in GBS, high-affinity antibodies are generated by certain mechanisms (Nores et al., 2007). The "molecular mimicry" hypothesis (Yuki, 2005) is one of the widely accepted hypotheses for the mechanism. Anti-GM1 antibodies have been found in patients with GBS subsequent to C. *jejuni*-associated diarrhea (Yuki et al., 1993). The surface of C. *jejuni* contains lipooligosaccharides that resemble GM1 (Fig. 1). This resemblance has been termed "molecular mimicry", which is defined as the dual re-

cognition of a microbe's structure and an antigen of the host, and is the mechanism by which infections trigger cross-reactive antibodies or T cells that can lead to autoimmune diseases (Ang et al., 2004).

As mentioned above, IgG class anti-GM1 antibodies have been implicated as potential pathogenic agents for GBS, especially AMAN. However the roles of the antibody in the pathophysiology of GBS and molecular mechanisms to impair the nerve tissues are still unclear.

Autopsy studies of AMAN patients have indicated that immunoglobulins and complement deposits are frequently located at the nodes of Ranvier where sodium channels are clustered (Hafer-Macko et al., 1996). Anti-GM1 antibodies may cause nerve dysfunction and injury by interfering with ion channel function at the nodes of Ranvier and may contribute to the pathogenic mechanisms of some neuropathies (Susuki et al., 2007; Takigawa et al., 1995).

Anti-GM1 antibodies containing IgG from GBS patients inhibit the potentiating effect of GM1 to NGF-TrkA signaling dose-dependently and interfered with the NGF induced neurite outgrowth in a sympathetic nerve cell line (Tanaka et al., 2007). This result suggests two important viewpoints. First, anti-GM1 antibodies may affect the pathogenesis of the recovery phase of GBS because NGF plays important roles in nerve regeneration and its repair. Second, anti-GM1 antibodies prohibit the potentiating effect of GM1, in other words, modify the function of GM1. It can be speculated that anti-GM1 antibodies interfere with the NGF-TrkA signaling by functional modification of the raft, because the rafts are GM1 enriched microdomain and TrkA attaches to the raft as already described. If this speculation is true, anti-GM1 antibodies could affect other signal transduction not only in neural cells but also in immune cells, for example brain derived nerve growth factor (BDNF) signaling (Fujitani et al., 2005) in motor neurons and T cell receptor signaling (Razzaq et al., 2004) in lymphocytes. These modulations could contribute to the immunological pathophysiology in GBS.

Conclusion

The anti-GM1 antibodies clearly have effects on the pathophysiology in anti-GM1-antibody-positive GBS but it is necessary to perform further studies focusing on the functional aspect of ganglioside.

References

Ackerman GA, Wolken KW, Gelder FB. Differential expression of surface monosialoganglioside GM1 in various hemic cell lines of normal human bone marrow. A quantitative immunocytochemical study using the cholera toxin-gold-labeled anti-cholera toxin procedure. J Histochem Cytochem 1980; 28: 1334–42.

Ang CW, Jacobs BC, Laman JD. The Guillain-Barre syndrome: a true case of molecular mimicry. Trends Immunol 2004; 25: 61–6.

Ariga T, Yu RK. Antiglycolipid antibodies in Guillain-Barre syndrome and related diseases: review of clinical features and antibody specificities. J Neurosci Res 2005; 80: 1–17.

Bremer EG, Hakomori S, Bowen-Pope DF, Raines E, Ross R. Ganglioside-mediated modulation of cell growth, growth factor binding, and receptor phosphorylation. J Biol Chem 1984; 259: 6818–25.

Burns TM, Russell JA, Royden Jones Jr H. Acquired demyelinating polyradiculoneuropathies: Guillain-Barré syndrome and chronic inflamatory demyelinating polyradiculoneuropathy. In: Royden Jones Jr H, editor. Netter's neurology. U. S. A.: Icon Learning Systems LLC, 2005: 818–26.

Chiba A, Kusunoki S, Shimizu T, Kanazawa I. Serum IgG antibody to ganglioside GQ1b is a possible marker of Miller Fisher syndrome. Ann Neurol 1992; 31: 677–9.

Corbo M, Quattrini A, Lugaresi A, Santoro M, Latov N, Hays AP. Patterns of reactivity of human anti-GM1 antibodies with spinal cord and motor neurons. Ann Neurol 1992; 32: 487–93.

Ferrari G, Fabris M, Gorio A. Gangliosides enhance neurite outgrowth in PC12 cells. Brain Res 1983; 284: 215–21.

Fujitani M, Honda A, Hata K, Yamagishi S, Tohyama M, Yamashita T. Biological activity of neurotrophins is dependent on recruitment of Rac1 to lipid rafts. Biochem Biophys Res Commun 2005; 327: 150–4.

Gorio A. Ganglioside enhancement of neuronal differentiation, plasticity, and repair. CRC Crit Rev Clin Neurobiol 1986; 2: 241–96.

Hafer-Macko C, Hsieh ST, Li CY, Ho TW, Sheikh K, Cornblath DR, et al. Acute motor axonal neuropathy: an antibody-mediated attack on axolemma. Ann Neurol 1996; 40: 635–44.

Ho TW, Mishu B, Li CY, Gao CY, Cornblath DR, Griffin JW, et al. Guillain-Barre syndrome in northern China. Relationship to Campylobacter jejuni infection and anti-glycolipid antibodies. Brain 1995; 118 (Pt 3): 597–605.

Ho TW, Willison HJ, Nachamkin I, Li CY, Veitch J, Ung H, et al. Anti-GD1a antibody is associated with axonal but not demyelinating forms of Guillain-Barre syndrome. Ann Neurol 1999; 45: 168–73.

Hughes RA, Cornblath DR. Guillain-Barre syndrome. Lancet 2005; 366: 1653–66.

Hughes RA, Rees JH. Clinical and epidemiologic features of Guillain-Barre syndrome. J Infect Dis 1997; 176 Suppl 2: S92–8.

Hughes RA, Swan AV, Raphael JC, Annane D, van Koningsveld R, van Doorn PA. Immunotherapy for Guillain-Barre syndrome: a systematic review. Brain 2007; 130: 2245–57.

Illa I, Ortiz N, Gallard E, Juarez C, Grau JM, Dalakas MC. Acute axonal Guillain-Barre syndrome with IgG antibodies against motor axons following parenteral gangliosides. Ann Neurol 1995; 38: 218–24.

Ilyas AA, Quarles RH, Dalakas MC, Brady RO. Polyneuropathy with monoclonal gammopathy: glycolipids are frequently antigens for IgM paraproteins. Proc Natl Acad Sci U S A 1985; 82: 6697–700.

Jacobs BC, van Doorn PA, Schmitz PI, Tio-Gillen AP, Herbrink P, Visser LH, et al. Campylobacter jejuni infections and anti-GM1 antibodies in Guillain-Barre syndrome. Ann Neurol 1996; 40: 181–7.

Kanda T, Yoshino H, Ariga T, Yamawaki M, Yu RK. Glycosphingolipid antigens in cultured bovine brain microvascular endothelial cells: sulfoglucuronosyl paragloboside as a target of monoclonal IgM in demyelinative neuropathy [corrected]. J Cell Biol 1994; 126: 235–46.

Kasahara K, Sanai Y. [Neural cell membrane rafts and signal transduction]. Tanpakushitsu Kakusan Koso 2002; 47: 333–7.

Kawashima I, Nakamura O, Tai T. Antibody responses to ganglio-series gangliosides in different strains of inbred mice. Mol Immunol 1992; 29: 625–32.

Kornberg AJ, Pestronk A. The clinical and diagnostic role of anti-GM1 antibody testing. Muscle Nerve 1994; 17: 100–4.

Lopez PH, Villa AM, Sica RE, Nores GA. High affinity as a disease determinant factor in anti-GM (1) antibodies: comparative characterization of experimentally induced vs. disease-associated antibodies. J Neuroimmunol 2002; 128: 69–76.

Mutoh T, Tokuda A, Miyadai T, Hamaguchi M, Fujiki N. Ganglioside GM1 binds to the Trk protein and regulates receptor function. Proc Natl Acad Sci U. S. A 1995; 92: 5087–91.

Nashar TO, Williams NA, Hirst TR. Cross-linking of cell surface ganglioside GM1 induces the selective apoptosis of mature CD8+ T lymphocytes. Int Immunol 1996; 8: 731–6.

Nichols BJ. GM1-containing lipid rafts are depleted within clathrin-coated pits. Curr Biol 2003; 13: 686–90.

Nores GA, Lardone RD, Comin R, Alaniz ME, Moyano AL, Irazoqui FJ. Anti-GM1 antibodies as a model of the immune response to self-glycans. Biochim Biophys Acta 2007.

Ogawara K, Kuwabara S, Mori M, Hattori T, Koga M, Yuki N. Axonal Guillain-Barre syndrome: relation to anti-ganglioside antibodies and Campylobacter jejuni infection in Japan. Ann Neurol 2000; 48: 624–31.

Paparounas K. Anti-GQ1b ganglioside antibody in peripheral nervous system disorders: pathophysiologic role and clinical relevance. Arch Neurol 2004; 61: 1013–6.

Razzaq TM, Ozegbe P, Jury EC, Sembi P, Blackwell NM, Kabouridis PS. Regulation of T-cell receptor signalling by membrane microdomains. Immunology 2004; 113: 413–26.

Rees JH, Gregson NA, Hughes RA. Anti-ganglioside GM1 antibodies in Guillain-Barre syndrome and their relationship to Campylobacter jejuni infection. Ann Neurol 1995; 38: 809–16.

Ropper AH. The Guillain-Barre syndrome. N Engl J Med 1992; 326: 1130–6.

Simons K, Ikonen E. Functional rafts in cell membranes. Nature 1997; 387: 569–72.

Susuki K, Rasband MN, Tohyama K, Koibuchi K, Okamoto S, Funakoshi K, et al. Anti-GM1 antibodies cause complement-mediated disruption of sodium channel clusters in peripheral motor nerve fibers. J Neurosci 2007; 27: 3956–67.

Takigawa T, Yasuda H, Kikkawa R, Shigeta Y, Saida T, Kitasato H. Antibodies against GM1 ganglioside affect K+ and Na+ currents in isolated rat myelinated nerve fibers. Ann Neurol 1995; 37: 436–42.

Tanaka T, Furutama D, Sakai R, Fujita A, Kimura F, Tagami M, et al. Biological roles of anti-GM1 antibodies in patients with Guillain-Barre syndrome for nerve growth factor signaling. Biochim Biophys Acta 2007; 1772: 543–8.

Thomas FP, Trojaborg W, Nagy C, Santoro M, Sadiq SA, Latov N, et al. Experimental autoimmune neuropathy with anti-GM1 antibodies and immunoglobulin deposits at the nodes of Ranvier. Acta Neuropathol 1991; 82: 378–83.

Walsh FS, Cronin M, Koblar S, Doherty P, Winer J, Leon A, et al. Association between glycoconjugate antibodies and Campylobacter infection in patients with Guillain-Barre syndrome. J Neuroimmunol 1991; 34: 43–51.

Wu C, Butz S, Ying Y, Anderson RG. Tyrosine kinase receptors concentrated in caveolae-like domains from neuronal plasma membrane. J Biol Chem 1997; 272: 3554–9.

Yates AJ, Rampersaud A. Sphingolipids as receptor modulators. An overview. Ann N Y Acad Sci 1998; 845: 57–71.

Yuki N. Carbohydrate mimicry: a new paradigm of autoimmune diseases. Curr Opin Immunol 2005; 17: 577–82.

Yuki N, Taki T, Inagaki F, Kasama T, Takahashi M, Saito K, et al. A bacterium lipopolysaccharide that elicits Guillain-Barre syndrome has a GM1 ganglioside-like structure. J Exp Med 1993; 178: 1771–5.

Yuki N, Yamada M, Koga M, Odaka M, Susuki K, Tagawa Y, et al. Animal model of axonal Guillain-Barre syndrome induced by sensitization with GM1 ganglioside. Ann Neurol 2001; 49: 712–20.