

After the observation that monoclonal IgM reacting with the myelin-associated glycoprotein (MAG) from patients with neuropathy cross-reacted with a complex glycolipid, sulfate-3-glucuronyl paragloboside (SGPG), it was found that MAG/SGPG-negative monoclonal antibodies from patients with neuropathy and IgM gammopathy frequently reacted with gangliosides or other glycolipid antigens (1). Subsequently, high titers of polyclonal antibodies reacting with various gangliosides were found in other forms of neuropathy including multifocal motor neuropathy (MMN) and subsets of Guillain-Barré syndrome (GBS). As described in a recent detailed review of this area (2), a strong correlation was soon established between IgM antibodies to GM1 ganglioside and motor nerve disorders.

In the past several years, a new correlation has emerged between clinical presentation and antibody specificity concerning patients that have sensory ataxic neuropathy (SAN) in association with IgM gammopathy in which the monoclonal antibody reacts with GD1b and other gangliosides containing disialosyl moieties such as GD2, GD3, GT1b, and GQ1b. The first patient of this type was described by Ilyas et al. (3), and at least six similar cases have appeared in the literature establishing this correlation (cited in references 2 and 4). SAN is characterized by a severe loss of kinesthetic sensation (proprioception and vibration) with a notable preservation of muscle strength (5). Primary lesions in this disorder are in the dorsal root ganglia causing loss of large ganglionic neurons. The paper by Willison et al. (4) in this issue of *The Journal* provides the first direct passive transfer data showing that the monoclonal IgM from a patient with SAN can cause neurophysiological malfunction.

Whereas passive transfers of human anti-MAG/SGPG antibodies to experimental animals have essentially established their causal role in this type of neuropathy (2), the pathogenic roles of anti-ganglioside antibodies have remained more enigmatic. The monoclonal IgM from one patient with SAN was reported to be cytotoxic to dorsal root ganglion neurons in culture (6). However, the current findings that anti-ganglioside IgM from a patient with SAN impairs nerve excitability and release of neurotransmitter in a mouse phrenic nerve–hemidiaphragm preparation (4) suggest that anti-ganglioside antibodies may exert their pathogenic effect, at least in part, by interfering with the physiology of nerve excitability and synaptic transmission. Although the mechanism by which the antibody causes the pathophysiological effects is unknown, gangliosides have long been known to be concentrated in neuronal surface membranes and at synaptic endings, and there is abundant evidence to suggest that they may modulate the activity of receptors, ion channels, or other membrane constituents (7).

The sensory ataxia in chronic SAN associated with gammopathy is very similar to that in a variant of GBS known as Miller-Fisher syndrome (MFS). Furthermore, nearly all patients with MFS have polyclonal IgG antibodies reacting with

gangliosides containing disialosyl moieties including GQ1b, implying that immune-mediated pathogenic mechanisms in MFS and SAN in association with gammopathy are probably similar. Indeed, serum factors from three patients with MFS had similar physiological effects on the phrenic nerve–hemidiaphragm preparation (8). However, a drawback to this model for investigating SAN and MFS is that it is a neuromuscular preparation, and, as noted by the authors, future work on sensory nerve preparations will be needed to draw more clinically relevant pathophysiological conclusions. In this regard, it is noteworthy that sera positive for anti-GM1 ganglioside antibodies from patients with MMN also impair neuronal activity in these preparations, but the nature of the effects is somewhat different (9).

GD1b is quantitatively the most important antigen when whole ganglioside fractions from human nerve are tested for reactivity with IgM from SAN (3). However, it is curious that many of the anti-GM1 antibodies in patients with motor nerve disorders recognize the Gal $\beta$ 1-3GalNAc epitope and also react with GD1b, yet these patients do not exhibit sensory deficits. This suggests that gangliosides different from GD1b may be more significant for the pathogenic effects exerted by the antibodies to disialosyl moieties that are found in SAN. In spite of the specific clinical symptomatology in SAN, the present study (4) demonstrated ubiquitous binding of IgM to areas such as motor end plate regions, endomysial spaces, blood vessels, and neuronal cell bodies, without causing tissue destruction even in the putative target cells. Since most anti-ganglioside antibodies from neuropathy patients cross-react with several gangliosides sharing carbohydrate configurations, important areas for future research will be to establish the identity of the target antigens in clinically relevant tissues and demonstrate if there are cell-specific toxic effects beyond functional blockade. The current results (4) combined with other reports indicating that anti-ganglioside antibodies found in various human neuropathies have the capacity to exert pathogenic effects in vitro and in vivo (2, 6) suggest that the antibodies are not epiphenomena, but may indeed cause some or all aspects of the disorders. To the extent that their effects are pathophysiological as reported here and do not involve irreversible cellular damage, the prospects for future therapies that remove or inactivate the anti-ganglioside antibodies are enhanced.

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