Complex antibodies in the Guillain Barré syndromes provide a simple explanation for the plurality of clinical presentations

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A strong argument can be made for using the plural of the eponymous term when referring to the acute post infectious polyradiculoneuropathies. The Guillain Barré syndromes thus (GBS) include axonal, demyelinating and paranodopathy forms, defined electrophysiologically or pathologically. Clinically recognised variants can be limited to specific body regions (such as facial diplegia or paraplegic GBS) and preferentially or exclusively affect specific nerve types (pure motor, sensory, acute pandysautonomia). Antibodies directed against the ganglioside GQ1b are strongly associated with the GBS variant known as Miller Fisher syndrome (MFS), yet are also found in forms of MFS, Bickerstaff's brainstem encephalitis, and the regional pharyngeal-cervical-brachial variant. An explanation for the plurality of clinical presentations associated with this single antibody has thus far proved elusive.

The idea that distinct epitopes might be formed by "clustered saccharide patches" composed of different oligosaccharide chains is not a new one (*Varki, 1994*). Indeed the related observation that the presence of a second ganglioside in the cell membrane can prevent binding to the first was initially made over 20 years ago in melanoma cell lines (*Lloyd et al., 1992*). Following the detection of ganglioside complex (GSC) antibodies in the serum of patients with GBS by Kusunoki and colleagues (*Kaida et al., 2004*), interest in this area has grown. Such 'complex enhanced' antibodies were demonstrated to recognise overlapping portions of 2 different gangliosides, binding weakly or not at all in the presence of only one. Ganglioside complexes were subsequently shown to have a significant influence on the binding affinity of other lectins such as bacterial toxins and the sialic acid binding immunoreceptor family known as SIGLECs (*Rinaldi et al., 2009*). Furthermore, anti-GM1 antibodies which additionally interact with GM1-complexes ('complex independent') are able to cause nerve injury in a model system, whereas those with GM1 reactivity alone ('complex attenuated') are pathologically inert (*Greenshields et al., 2009*). When applied to clinical cohorts, immunoassays using complexes can provide increased sensitivity and/or have revealed associations between specific anti-complex antibodies and certain clinical features (*Kaida et al., 2007; Galban-Horcajo et al., 2012; Rinaldi et al., 2013*).

The current study from Professor Yuki's prolific group has collected a very impressive 915 serum samples, from over 10,000 tested, with anti-GQ1b or anti-GT1a ganglioside reactivity. Attesting to the specificity of these antibodies, all positive samples were drawn from patients with an ultimate

diagnosis of MFS or one of the related anti-GQ1b syndromes. The authors sought to determine whether the fine specificity of these antibodies, with respect to their ganglioside complex binding capabilities, was associated with specific clinical features of the anti-GQ1b syndromes. Applying a statistical definition to both the definition of complex enhanced or attenuated binding, as well as to the serological-clinical associations, a large number of different neurological signs have been shown to be associated with specific anti-complex antibodies. Whilst the number of new associations demonstrated is initially somewhat bewildering, and the serological segregation between patients with and without specific features incomplete, the underlying concept is as clear as it is thought provoking.

As the authors point out, the implication is that neural membranes at different regions within the nervous system have distinct, ganglioside-complex antigenic profiles. It has so far been unclear why anti-GM1 antibodies are associated with pure motor syndromes, despite sensory nerves containing abundant GM1 antigen. The current study suggests that this might also relate to a difference in GM1 complexes between the nerve types. Localised differences and inter-subject variations in ganglioside-complex expression may also be of relevance to the breakdown in self-tolerance required to induce GBS. If specific complexes are only generated in immunologically privileged parts of the nervous system they may not be recognised as self and thus predisposed to autoimmune attack. The challenges now are to demonstrate the variability of ganglioside-complex expression in different tissues, and to understand the factors governing their differential formation. Whilst immunohistochemical studies have been proposed, the power of cutting-edge membrane imaging techniques may be required to effectively address this first question.

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