

Subtype-specific therapy for autoimmune neuropathies?

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Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP) are the most common autoimmune neuropathies. In both disorders, different variants have been described, reflecting the types of axons that are affected (motor and/or sensory), the nature of the injury (axonal vs demyelinating), and the response to treatment. Because most patients respond to therapies that target autoantibodies (plasmapheresis and IV immunoglobulin [IVIg]), these disorders are thought to be antibody-mediated. Consistent with this, autoantibodies to different peripheral nerve glycolipids, especially complexes of multiple gangliosides, are found in specific subtypes of patients.¹ Moreover, high titers of antibodies against GM1 and GQ1b gangliosides are highly associated with multifocal motor neuropathy² and Miller Fisher syndrome/Bickerstaff encephalitis,³ respectively. There is strong evidence from both human and animal models that the binding of autoantibodies to their cognate lipid antigens fixes complement that in turn damages myelinated motor and/or sensory axons.

More recently, autoantibodies to protein antigens—neurofascins (axonal NF186 and glial NF155), gliomedin, and contactin—have been described in a small proportion of patients with GBS and/or CIDP.^{4,5} These are cell adhesion molecules important for glial-axonal interactions at nodes (NF186 and gliomedin) and paranodes (contactin-1 and NF155). Patient antibodies target surface epitopes in their large extracellular domains and are plausibly directly pathogenic, but what is the evidence?

In animal models, autoantibodies against these proteins are sufficient to cause neuropathy. In the case of gliomedin, an active immunization produces acute peripheral neuropathy, and transfer of the antibodies to other animals can worsen autoimmune neuropathy.⁶ In the case of NF186, active immunization did not cause neuropathy in 1 animal model,⁶ but injecting 2 pan-neurofascin monoclonal antibodies worsened experimental neuritis in a different animal model.⁵

The data from humans are more circumstantial. Querol et al.⁷ previously found IgG4 autoantibodies to NF155 in 4 patients with CIDP who were unresponsive to IVIg (but some responded partially to plasmapheresis) and often had pronounced tremor. In the current issue of *Neurology® Neuroimmunology & Neuroinflammation*, Querol et al.⁸ expand on this finding by examining the clinical effects of rituximab in 2 of the patients with IgG4 antibodies against NF155 as well as another patient with IgG4 antibodies against contactin-1 (who also had aggressive motor CIDP and a poor response to immune therapy). Rituximab substantially lowered IgG4 titers against NF155 or contactin-1 in all 3 patients. The 2 patients (1 with IgG4 antibodies against NF155 and 1 with IgG4 antibodies against contactin-1) who had dramatic clinical responses to rituximab had been affected for less than a year. The authors note that the 1 patient who responded minimally had had CIDP for 15 years, so axonal loss may have precluded recovery.

IgG4 has several distinct features that pertain to the current study (for an excellent review see reference 9).

1. IgG4 does not effectively cross-link target antigens or fix complement, both of which mediate other autoimmune diseases.
2. Direct functional effects of IgG4 on target proteins are plausible. Thus, autoantibodies to contactin-1 bind to specific surface epitopes on contactin-1 and prevent contactin-1 from interacting with NF155.¹⁰ Conversely, it is possible that antibodies to NF155 block the interaction between NF155 and contactin-1, a finding that might help us understand the similarities of the 2 phenotypes.
3. B cell depletion with rituximab is remarkably effective in many IgG4-mediated diseases (including anti-muscle-specific tyrosine kinase myasthenia gravis [MUSK]).

The previous antibody studies therefore lead to the recognition of a particular subset of patients with

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refractory CIDP and also suggested a rational treatment strategy. The current study provides additional motivation to study rituximab treatment for CIDP associated with IgG4 antibodies to nerve proteins.

Although the study by Querol et al.⁸ should be considered preliminary, the possibility of an additional effective therapy for some patients with CIDP is welcome news for patients and clinicians. In the short term, we should be able to determine whether IgG4 antibodies mediate some forms of CIDP and whether rituximab is better than current conventional treatments. The work also motivates efforts to identify more autoantibodies associated with autoimmune neuropathy. These may lead to a better understanding of the pathogenesis of CIDP, increasingly useful panels of diagnostic tests, and individualized therapy for every patient with autoimmune neuropathy.

AUTHOR CONTRIBUTIONS

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