# Neurofascin antibodies in inflammatory neuropathy

## How many needles make a haystack?

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Guillain-Barré syndrome and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) punch above their epidemiologic weight because they need early diagnosis and treatment, can be severely disabling or fatal, and incur very high health care costs. Despite accrual of substantial information about their clinical and pathophysiologic features, the precise cause and immune targets of the commoner demyelinating form of Guillain-Barré syndrome, acute inflammatory demyelinating polyneuropathy (AIDP), and of CIDP, remain largely undiscovered. In this issue of *Neurology*®, Ng et al.[1] focus on autoantibody responses to a key protein in the nodal complex, neurofascin. Interest in this protein in inflammatory neuropathy extends earlier studies identifying neurofascin as a key target for pathogenic autoantibodies in multiple sclerosis.[2]

What evidence supports a possible autoantibody target in AIDP or CIDP? In early lesions, macrophages penetrate the Schwann cell basal lamina and outer cytoplasm, and invade the outer myelin sheath layers. In biopsy material, the myelin sheath segments ingested by the macrophages are morphologically intact, resembling the changes in T-cell–mediated animal model experimental autoimmune neuritis.[3] At autopsy, the spinal roots of patients with AIDP show immunoglobulin and complement deposition and vesicular dissolution of myelin in the absence of cell infiltration, suggesting an antibody-mediated process.[4] Removal of antibodies by plasma exchange is beneficial in both diseases.

The first searches for candidate protein antigens focused on the compact myelin proteins P2, PMP22, and especially P0, which induce the active immunization model of AIDP and CIDP, experimental autoimmune neuritis. Searches for antibodies to these targets in the human diseases have given inconsistent results. In the most positive report, antibodies to P0 were found in 6 of 21 patients with CIDP, and immunoglobulin G (IgG) from CIDP sera induced demyelination following intraneural injection into rat sciatic nerves, a somewhat artificial experiment.[5,6] However, this observation has not been replicated and others have not consistently identified antibodies or T-cell–mediated immunity to any of these protein antigens in AIDP or CIDP.[7,8]

Recent interest has focused on a wide range of proteins localized to the nodal complex including neurofascin.[9,10] Neurofascin exists in neuronal (NF186) and glial (NF155) isoforms, which maintain the highly organized structure of the node of Ranvier required for impulse propagation. Their function and localization make them possible candidates as immune targets in AIDP and CIDP. Neurofascin and another paranodal protein, gliomedin, are disrupted in experimental autoimmune neuritis when induced by immunization with peripheral myelin, but not by P2; peripheral myelin immunization also induces anti-neurofascin antibodies.[9]

Animal data fall short of providing evidence for involvement in human disease. Prüss et al.[11] reported antibodies to rat neurofascin by ELISA in Guillain-Barré syndrome more than in normal controls. The current study searched more rigorously for antibodies to the extracellular portions of both neurofascin isoforms; it used recombinant human (rather than rat) proteins for ELISA and confirmed the presence of antibodies with a sophisticated cell-bound assay that more faithfully recapitulates the molecular orientation seen in vivo. Antibodies to one or the other human neurofascin isoform were found in 3 of 65 patients with AIDP and 5 of 119 patients with CIDP, and in none of 50 patients with acute motor axonal neuropathy, 20 patients with other neuropathies, 63 patients with other neurologic diseases, or 77 healthy donors. Immunohistology and experimental autoimmune neuritis studies added strong evidence for the authentic and pathogenic nature of some of the detected anti-neurofascin antibodies. There was no obvious common clinical denominator between the patients with antibodies and those without, and little information about the time course of the antibodies in individual patients except that the antibodies persisted over several years in one patient. Nevertheless, the authors have rigorously demonstrated the presence of IgG antibodies to neurofascin in AIDP and CIDP, albeit in a tiny minority of patients.

Ng et al. have now shown that anti-neurofascin monoclonal antibodies exacerbate experimental autoimmune neuritis induced with P2, thus establishing that anti-neurofascin antibodies have the potential to contribute to the severity of AIDP and CIDP. It would

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not be surprising if this were a general property of many molecules expressed at the Schwann cell surface, including, for example, galactocerebroside.[12] While the neurofascin isoforms investigated were credible target antigens based on the experimental autoimmune neuritis data, the absence of antibodies from the vast majority of patients with AIDP or CIDP makes them unlikely to be important primary target autoantigens. Furthermore, without data about their appearance during the development of the disease and disappearance with treatment or recovery, there is no evidence to indicate cause or effect.

The search will continue for the antigens responsible for AIDP and CIDP. They are likely to be expressed at the Schwann cell surface. They are also likely to be found preferentially in the peripheral rather than CNS myelin, like P0 but not a feature of neurofascin. However, the current evidence for P0 being an important target antigen is unconvincing. Gangliosides and related nerve glycolipids remain alternative candidates. They are antigenic targets in the axonal forms of Guillain-Barré syndrome, Fisher syndrome, multifocal motor neuropathy, and certain paraproteinemic neuropathies. Although results from assays for antibodies to single glycolipids in AIDP and CIDP have been unrewarding so far, novel methods for detecting both glycolipid and protein antigens presented in a complex microenvironment resembling their physiologic domains are promising and likely to be more rewarding.[13] A key element of antibody screens in clinical cohorts is that they should include meticulous case definitions and cross-referencing with screens in the same cohorts for other candidate antigens. This is the aim of the recently started International Guillain-Barré syndrome Outcome Study (IGOS; www.gbsstudies.org).

## DISCLOSURE

The authors report no disclosures relevant to the manuscript. **Go to Neurology.org for full disclosures.**

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