Close to the node but far enough
What nodal antibodies tell us about CIDP and its therapies

Chronic inflammatory demyelinating polyneuropathy (CIDP) is the most common and gratifying chronic autoimmune neuropathy because it is treatable in the majority of cases. The demyelination is multifocal, accounting for the variable distribution of symptoms and signs, clinically expressed as CIDP variants. Although histologically the demyelination is associated with macrophages, complement-fixing immunoglobulin G (IgG) antibodies have been implicated for more than 30 years but never clearly identified, probably because we had focused on compact myelin molecules as antigenic targets. Overwhelming evidence over the last 5 years indicates that molecules associated with saltatory conduction at the nodes of Ranvier may be more meaningful targets, as functional blockade in these regions can best account for the rapid improvement noticeable within days after plasmapheresis or IV immunoglobulin (IVIg). Likely antigenic targets include the following: neurofascin-186, moesin, and glomedin (at the node); neurofascin-155 (NF155), contactin/Caspr 1 (CNTN1), and connexins (at the paranode); and transient axonal glycoprotein-1 or potassium channels (at the juxtaparanode). Using standardized techniques such as proteomics, transfected cell lines, teased-nerve fibers, immunocytochemistry, and ELISA, many laboratories have reported evidence that supports paranodal NF155 and CNTN1 as the most consistent and clinically relevant targets, at least in a small patient subset. In this issue of Neurology® and a companion publication, Devaux et al. confirm these antibodies in a large CIDP cohort.

Anti-NF155 antibodies, mostly of the IgG4 isotype, were first demonstrated with molecular immunopathologic correlations by Ng et al. in 4 patients with CIDP (4% of total) and seemed pathogenic, exacerbating experimental allergic neuritis. This original observation was later confirmed in 4 Spanish patients with CIDP (3.7%), demonstrating an aggressive sensory-motor neuropathy, tremor, and resistance to IVIg. A Japanese group also found NF155 antibodies, but their patients with CIDP had concurrent CNS demyelination and were IVIg-responsive. Parallel studies identified anti-CNTN1 antibodies in another small CIDP subset, with phenotype similar to anti-NF155, responding poorly to IVIg.

This observation was confirmed in 4 of 53 patients with CIDP, who exhibited paranodal alterations in their skin biopsies; their anti-CNTN1-positive sera disrupted paranodes in myelinating Schwann cell cultures.

The present study provides further information in the largest-ever CIDP cohort. Screening 533 patients, Devaux et al. found 38 (7%) with IgG4 anti-NF155 antibodies and a phenotype similar to that previously reported but having in addition cerebellar ataxia, dysarthria, nystagmus, and CNS demyelination; 80% of them were IVIg-unresponsive. Their seropositive sera reacted with CNS tissues and peripheral paranodes, regardless of coexisting CNS demyelination, and targeted a fibronectin epitope. Furthermore, 13 of 533 patients (2.4%) had IgG4 antibodies against CNTN1 with phenotype similar to that previously reported.

What do the 2 Devaux studies tell us, in conjunction with the prior original reports? Anti-NF155 and CNTN1 antibodies, although infrequent, seem pathogenic. The strength of the present studies is in numbers, providing information on antibody prevalence in a largest-ever CIDP cohort; however, the study has limitations. The patients were drawn from multiple centers with retrospectively applied diagnostic criteria and nonuniform definition of response to therapies. This concern, also applicable to previous studies when testing archived sera, is greater here because of the larger-sized study and the inclusion of atypical patients with cerebellar ataxia, dysarthria, and nystagmus, which are not typical features of CIDP. What is retrospectively called CIDP may represent a variety of misdiagnoses with inappropriate therapies, reaching up to 47% in a recent US study.

The anti-NF155 anti-CNTN1 CIDP phenotype, despite similarities across series, shows substantial variability, perhaps because of ethnicity, degree of axonal involvement, electrophysiology, and response to variably applied therapies. It is unclear whether the...
IVlg-unresponsive patients received sufficient courses of therapy and, as in other series, some patients improved with steroids and plasmapheresis. Conduction block and denervation were present in the patients in the studies by Devaux et al. but not in the study by Querol et al. despite severe weakness and axonal disease; concurrent CNS demyelination was present only in the Japanese cohorts. Apart from these limitations, anti-NF155 and CNTN1-positive patients seem overall to have more severe disease, axonal involvement, tremors, sensory ataxia, and suboptimal response to IVlg, supporting the suggestion of distinct phenotypes.

Although these antibodies probably contribute to immunopathogenesis in small CIDP subsets, questions remain. The IgG4 isotypes are atypical in causing autoimmune disease because they do not activate complement and do not bind to Fc receptors or cross-link with their antigen to cause functional disruption. NF155 is a Schwann cell adhesion protein at the paranodal terminal myelin loops that binds to CNTN1, forming a complex critical for maintenance of nodal structures and rapid impulse propagation. The hypothesis that the antibodies disrupt the NF155/CNTN1 complex, in the absence of complement and inflammatory cells, is fundamentally novel in antibody-mediated demyelination and requires further investigation. Because they seem to bind to distinct epitopes associated with cell adhesion, such as N-glycosylated Fn1–4 domain of NF155, they may cause disadhesion of NF155/CNTN1 components by affecting glycosylation. Although unresponsiveness to IVlg may relate to lack of complement involvement, this is a partial explanation; IVlg not only works by inhibiting complement but also by affecting idiotypes and inflammatory mediators.

So what is the message for clinicians? Even though the clinical utility of discovered antibodies is evolving, only about 10% of patients with CIDP have paraneoplastic antibodies and a seemingly distinct phenotype. If a patient with CIDP who has distal involvement, tremors, and ataxia does not respond to IVlg, steroids, or plasmapheresis, alternate therapies may now be more seriously considered, especially anti–B cell agents such as rituximab; sending sera to centers with expertise in exploring nodal antibodies is advisable. Should such patients be excluded from enrollment in future CIDP trials? There is no good answer because only a small proportion (2/8) of patients refractory to IVlg have these antibodies. Collectively, this important work has brought us closer to the node, but we are still far away from understanding the pathogenesis of most CIDP cases.

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REFERENCES