Elucidating autoimmune nodopathies and the CIDP spectrum

This scientific commentary refers to 'Antibodies to the Caspr1/contactin-1 complex in chronic inflammatory demyelinating polyradiculoneuropathy', by Pascual-Goñi *et al.* (doi:10.1093/brain/awab014).

Clinicians treating patients with immune-mediated polyradiculoneuropathies such as Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) know that some patients respond poorly to standard treatments like intravenous immunoglobulin (IVIg) or corticosteroids.[1] An exciting new era in our understanding of these disorders began with the discovery that some of these poor responders have antibodies directed against membrane proteins located at or around the node of Ranvier. These include contactin-1 (CNTN1), contactin-associated protein-1 (Caspr1) and neurofascin 155 (NF155) located at the paranode, as well as neurofascin (NF140/186) located at the node.[2,3]

This is of interest not only because these patients may belong to a pathophysiological subgroup, but also because studies suggest that they may respond favourably to rituximab after failure of standard treatments.[2-4] For the approximately 2–15% of patients with a CIDP or GBS phenotype (depending on the cohort of patients tested) thought to harbour these antibodies, the consequences for treatment could thus be very significant. However, it is not yet certain which patients suspected to have GBS or CIDP should be tested for nodal-paranodal protein antibodies or which detection assay is most sensitive and specific. In this issue of *Brain*, Pascual-Goñi and colleagues[5] present the results of a rigorous characterization of serum antibodies from 15 patients who showed enhanced immunoreactivity against Caspr1/CNTN1, compared to CNTN1 alone, during routine testing for nodal-paranodal antibodies.

The spectrum of CIDP is expanding and patients with antibodies against nodal or paranodal antigens seem to constitute a distinct group, referred to as the autoimmune nodopathies.[6] These patients overlap traditional classifications of the spectrum, such as acute onset as in GBS or in acute-onset CIDP (A-CIDP) versus chronic onset as in CIDP; by 'axonal' versus 'demyelinating' electrophysiology (which we now know does not always correlate with pathology), and the distinction between the clinical phenotype of typical CIDP versus that of the distal or ataxic variants. Although patients with autoimmune nodopathies usually meet the clinical and electrodiagnostic criteria for CIDP or its variants, they may be considered to have a disease different from CIDP because they lack classical demyelination and overt signs of inflammation on nerve biopsy, and respond differently to treatment.

These paranodal protein antibodies are likely to contribute to pathophysiology. NF155, Caspr1 and CNTN1 are cell adhesion molecules that help secure the axo-glial junction at the paranode, which is essential for saltatory nerve conduction. The Caspr1/CNTN1 complex on the paranodal axolemma associates with NF155 on the terminal myelin loops to form septate-like junctions, acting as a membrane barrier to limit lateral diffusion of ion channels (Fig. 1). Antibodies cause detachment of these terminal myelin loops from the paranodal axolemma, allowing aberrant expression of juxtaparanodal potassium channels, and leading to conduction block and conduction slowing. These antibodies are thus potential targets for immunotherapy.

The clinical phenotypes associated with individual nodal-paranodal antibodies are becoming clearer. Antibodies against CNTN1 have been reported in patients presenting with acute or subacute onset (as GBS or A-CIDP), a severe disease course with predominant distal weakness and ataxia, and no or poor response to IVIg.[2–4] Antibodies against Caspr1 were initially found in a patient with GBS and in a patient with a CIDP phenotype.[7] Additional studies have indicated that patients with these antibodies have predominant distal weakness, neuropathic pain, occasionally cranial nerve involvement and respiratory failure, and lack responsiveness to IVIg. Antibodies against NF155 have been observed mainly in young adults with a subacute or chronic disease course, distal more than proximal weakness, ataxia, tremor, and poor response to IVIg.[2–4] Antibodies against NF140/186 were initially reported in patients with a subacute disease onset and sensory ataxia. It appears that most of these patients have motor and sensory, cranial nerve and bulbar involvement, which may lead to quadriplegia and respiratory failure. Some of these patients, however, may have a relatively good response to IVIg or corticosteroids.[8]

The study by Pascual-Goñi *et al.*[5] is important for several reasons. First, the authors provide new information on relatively rare patients with antibodies targeting Caspr1 or the Caspr1/CNTN1 complex. They calculated the prevalence of Caspr1/CNTN1 complex antibodies in cases that fulfilled the European Federation of Neurological Societies/Peripheral Nerve Society criteria for definite CIDP, finding it to be 1.9% in the Sant Pau cohort and 4.3% in a German cohort of acute-onset CIDP.[9] Second, from a clinical perspective, they noted that of the 15 patients, 47% were initially diagnosed with GBS (A-CIDP), 80% had ataxia, 40% had cranial nerve and respiratory involvement, and 53% reported

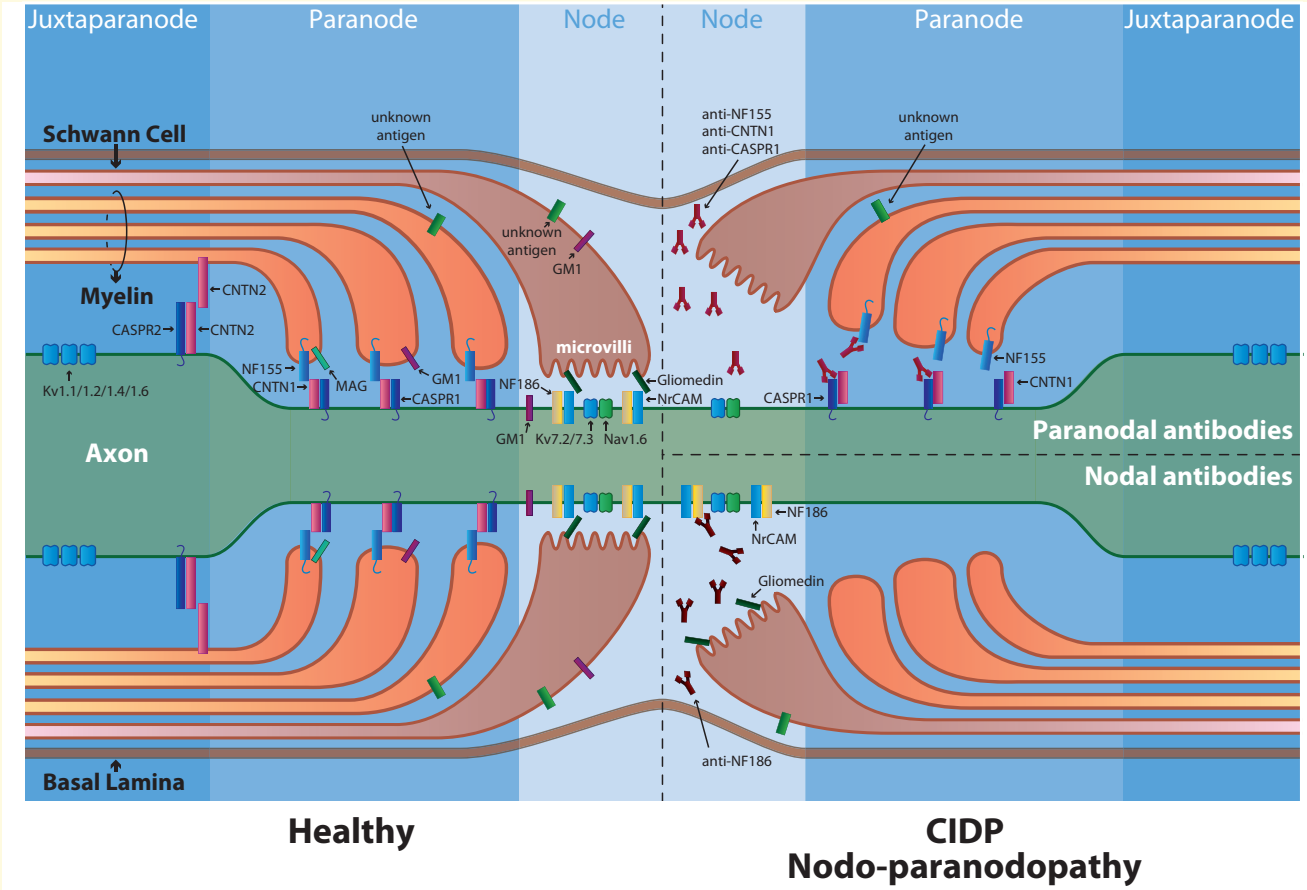

Figure 1 Pathogenic mechanisms in autoimmune nodopathies. The figure shows the structure and key molecular components of the node of Ranvier, the paranodes and the juxtaparanodes. *Left*: Healthy situation. *Right*: Autoimmune nodopathies with detachment of myelin loops. *Top*: Paranodal targets. *Bottom*: Nodal targets. Components targeted by IgG4 antibodies include: Caspr1 (contactin-associated protein-1), CNTN1 (contactin-1) and NF155 (neurofascin-155) at the paranode, and NF186 (neurofascin-186) at the node. Reproduced with permission from Bunschoten *et al.*[1]

neuropathic pain. Few responded well to standard treatments, while almost all responded to rituximab. Therefore, if a patient diagnosed with GBS or A-CIDP responds poorly to standard treatment, the treating neurologist should be alert to the potential presence of nodal-paranodal antibodies. Third, the researchers carefully studied the patients' sera, which targeted the Caspr1/CNTN1 complex, and showed that the primary reactivity against Caspr1 was enhanced when CNTN1 was added, both in ELISA and cell-based assays.

It is of particular interest that the sera of patients with autoimmune nodopathies displayed better antibody staining against the Caspr1/CNTN1 complex than against either or both proteins separately. In demyelinating GBS, antibodies against complexes of two glycolipids were much more frequent than antibodies against the single gangliosides in traditional highly purified assays. It has been hypothesized that antibody specificities reliant on the *cis* interactions of neighbouring membrane glycolipids could explain this discrepancy.[10]

One limitation of the study by Pascual-Goñi *et al.*[5] is the small number of patients; the reported prevalence of the antibodies may also have been affected by selection bias. However, the study provides substantial new information on the clinical characteristics of patients with these antibodies, irrespective of whether they are directed against Caspr1 or the Caspr1/CNTN1 complex.

It remains to be determined why the response to conventional treatment is so limited or even absent. However, this may be related to the fact that the nodal-paranodal antibodies are predominantly of the IgG4 subclass. These antibodies have unique functional and structural properties, such as a poor ability to activate complement because of low affinity for C1q and Fc receptors, which may explain why IVIg is less effective in these patients. The response to treatment with rituximab usually appears to be good, but patient numbers are small and randomized controlled trials have not been

performed. The response to rituximab may be slower if there is severe axonal degeneration and muscle wasting, and in some patients the onset of improvement may be delayed by months. Not all centres have rapid access to nodal-paranodal antibody testing meeting quality standards. However, if available, testing of nodal and paranodal antibodies is strongly recommended in CIDP populations with particular clinical features, especially if the patients have not responded well to proven effective treatments.

Competing interests

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References

1. Bunschoten C, Jacobs BC, Van den Bergh PYK, Cornblath DR, van Doorn PA. Progress in diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy. *Lancet Neurol*. 2019;18(8):784–794.
2. Querol L, Devaux J, Rojas-Garcia R, Illa I. Autoantibodies in chronic inflammatory neuropathies: Diagnostic and therapeutic implications. *Nat Rev Neurol*. 2017;13(9):533–547.
3. Delmont E, Brodovitch A, Kouton L, et al. Antibodies against the node of Ranvier: A real-life evaluation of incidence, clinical features and response to treatment based on a prospective analysis of 1500 sera. *J Neurol*. 2020;267(12):3664–3672.
4. Cortese A, Lombardi R, Briani C, et al. Antibodies to neurofascin, contactin-1, and contactin-associated protein 1 in CIDP: Clinical relevance of IgG isotype. *Neurol Neuroimmunol Neuroinflamm*. 2020;7(1):e639.
5. Pascual-Goñi E, Fehmi J, Lleixà M, et al. Antibodies to the Caspr1/contactin-1 complex in chronic inflammatory demyelinating polyradiculoneuropathy. *Brain*. 2021;144(4):1183–1196.
6. Van den Bergh PYK, van Doorn PA, Jacobs BC, Querol L, Bunschoten C, Cornblath DR. Boundaries of chronic inflammatory demyelinating polyradiculoneuropathy. *J Peripher Nerv Syst*. 2020;25(1):4–8.
7. Doppler K, Appeltshauser L, Villmann C, et al. Auto-antibodies to contactin-associated protein 1 (Caspr) in two patients with painful inflammatory neuropathy. *Brain*. 2016;139(Pt 10):2617–2630.
8. Delmont E, Manso C, Querol L, et al. Autoantibodies to nodal isoforms of neurofascin in chronic inflammatory demyelinating polyneuropathy. *Brain*. 2017;140(7):1851–1858.
9. Van den Bergh PY, Hadden RD, Bouche P, et al.; Peripheral Nerve Society. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society - first revision. *Eur J Neurol*. 2010;17(3):356–363.
10. Rinaldi S, Brennan KM, Kalna G, et al. Antibodies to heteromeric glycolipid complexes in Guillain-Barre syndrome. *PLoS One*. 2013;8(12):e82337.