

# Autoimmune nodopathies: treatable neuropathies beyond traditional classifications

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## Precise characterisation of the target antigens and autoantibody isotypes improves patient care in inflammatory neuropathies

Antibodies targeting all neurofascin isoforms (pan-neurofascin) have been associated with variants of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) that include ataxic presentations, cranial nerve involvement, respiratory failure and association with other autoimmune disorders.<sup>1,2</sup> Fehmi *et al* describe a severe, yet treatable, neuropathy associated with anti-pan-neurofascin antibodies of the IgG1 isotype.<sup>3</sup>

Nodo-paranodal antibodies have been described in neuropathies fulfilling CIDP diagnostic criteria. However, a significant proportion of patients harbouring any nodo-paranodal autoantibody (contactin-1, contactin-associated protein-1, neurofascin-155 or pan-neurofascin) presents as rapidly progressive, aggressive (including the need of intensive care unit admission and need of mechanical ventilation) neuropathies, often leading to an initial diagnosis of Guillain-Barré syndrome. Fehmi *et al* describe that anti-pan-neurofascin IgG1 antibodies associate with an aggressive (often fatal) neuropathy, leading to profound tetraplegia, intensive care unit admission and, interestingly, with normal cerebrospinal fluid protein levels. All patients presented with cranial nerve involvement, and most of them showed autonomic involvement and respiratory failure (features that rarely appear in typical CIDP). Two of them developed a haematologic malignancy but direct association of both conditions could not be confirmed. A previous report described patients with aggressive neuropathies associated with anti-pan-neurofascin antibodies of the IgG3 isotype (instead of the IgG1 described by Fehmi *et al*).<sup>2</sup> IgG1 and IgG3 isotypes display similar effector features: both activate complement and cell-mediated cytotoxicity while IgG2 and, especially, IgG4 do not<sup>4</sup>; it would then be expected that

different predominant isotypes associate with clinical and pathological differences, particularly when comparing patients with IgG1–3 versus IgG4 predominant autoantibodies. Since IgG1 and IgG3 are functionally homologous, anti-pan-neurofascin antibodies associate with similar clinical features regardless of the IgG isotype. However, why IgG1 or IgG3 predominates in different case series and whether this has clinical implications needs to be clarified.

Nephrotic syndrome is a frequent feature in patients with autoimmune nodopathies associated with anti-contactin-1 antibodies<sup>5</sup> and it was also described in the initial description of the anti-pan-neurofascin antibodies.<sup>1</sup> Nephrotic syndrome, however, is not present in patients with anti-contactin-associated-protein-1 and anti-neurofascin-155 antibodies, suggesting that it may be an antigen-specific feature. Fehmi *et al* confirm that almost 40% of patients with anti-pan-neurofascin antibodies present with nephrotic syndrome and, thus, this associated feature should prompt nodo-paranodal antibody testing in patients with an aggressive inflammatory neuropathy.

Different autoantibody isotypes have also been associated with different response to therapies in patients with autoimmune nodopathies: patients with predominantly IgG1–3 antibodies respond well to conventional therapies, while patients with predominantly IgG4 autoantibodies respond poorly to intravenous immunoglobulins and better to rituximab.<sup>6</sup> The patients described by Fehmi *et al* did not respond to conventional therapies (despite being IgG1-predominant), and the identification of the anti-pan-neurofascin antibodies led to successful use of rituximab in a subset of them. This is particularly important, since these patients, with a potentially fatal neuropathy, would have not had the chance to receive rituximab (or other immunosuppressant therapies) if the antibodies had not been tested.

In summary, Fehmi *et al* confirm that anti-pan-neurofascin antibodies identify

a potentially fatal, yet treatable, aggressive inflammatory neuropathy and support the idea that nodo-paranodal antibodies should be readily available to identify autoimmune nodopathies and treat them more effectively regardless of their presentation as an acute or chronic neuropathy.

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### REFERENCES

- 1 Delmont E, Manso C, Querol L, *et al*. Autoantibodies to nodal isoforms of neurofascin in chronic inflammatory demyelinating polyneuropathy. *Brain* 2017;140:1851–8.
- 2 Stengel H, Vural A, Brunder A-M, *et al*. Anti-pan-neurofascin IgG3 as a marker of fulminant autoimmune neuropathy. *Neurol Neuroimmunol Neuroinflamm* 2019;6. doi:10.1212/NXI.0000000000000603. [Epub ahead of print: 16 Aug 2019].
- 3 Fehmi J, Davies AJ, Walters J, *et al*. IgG pan-neurofascin antibodies identify a severe yet treatable neuropathy with a high mortality. *J Neurol Neurosurg Psychiatry* 2021;92:1089–95.
- 4 Nirula A, Glaser SM, Kalled SL, *et al*. What is IgG4? A review of the biology of a unique immunoglobulin subtype. *Curr Opin Rheumatol* 2011;23:119–24.
- 5 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;267:3664–72.
- 6 Vural A, Doppler K, Meinl E. Autoantibodies against the node of Ranvier in seropositive chronic inflammatory demyelinating polyneuropathy: diagnostic, pathogenic, and therapeutic relevance. *Front Immunol* 2018;9:1029.

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