Isotyping paranodal antibodies in inflammatory neuropathies

One step closer to precision care

Cinta Lleixà, BSc, and Luis Querol, MD, PhD

Correspondence
Dr. Querol
lquerol@santpau.cat

The discovery of autoantibodies against paranodal proteins such as neurofascin-155 (NF155), contactin-1 (CNTN1), or contactin-associated protein-1 (CASPR1) in inflammatory neuropathies has led to the description of subsets of patients with specific phenotypic features.[1] These antibodies mostly belong to the immunoglobulin G (IgG)4 subclass, but IgG1, IgG2, or IgG3 autoantibodies have also been described.[2–4] Different autoantibody isotypes are associated with different effector mechanisms causing nerve damage[5,6]; testing them may have implications to inform therapeutic choices or to predict prognosis.

In this issue of *Neurology: Neuroimmunology & Neuroinflammation*, an article entitled *Antiparanodal antibodies and IgG subclasses in acute autoimmune neuropathy*[7] by Luise Appeltshauser et al. provides evidence that IgG2/3 antibodies can be found in acute onset inflammatory neuropathies associated with paranodal antibodies and suggests a correlation between the clinical features and therapeutic response and the IgG isotypes associated to the disease.

The authors screened for anti-CNTN1 and anti-CASPR1 antibodies in a cohort of patients with Guillain-Barré syndrome (GBS) and acute chronic inflammatory demyelinating polyradiculoneuropathy (A-CIDP), including follow-up autoantibody testing in some patients. The frequency of the detected antibodies (around 4% of GBS/A-CIDP patients) confirms data from previous reports published by this and other groups. They found 5 patients with IgG2 or IgG3 autoantibodies against CNTN1, CASPR1, or both proteins, and 1 patient with IgG4 autoantibodies against CNTN1 and suggest that IgG3 antibodies may associate with a better response to IVIg. A recent study in CIDP does not find a relationship of IVIg efficacy and terminal complement inhibition in CIDP without paranodal antibodies.[8] However, the authors of this study have previously reported that complement deposition mediated by IgG3 autoantibodies targeting paranodal proteins can be modulated by IVIg.[6] Thus, the mechanisms through which IVIg exert their effect in CIDP may differ depending on the subtype of CIDP and associated autoantibodies. Other mechanisms may explain the poorer response to IVIg in diseases caused by autoantibodies of the IgG4 isotype. For example, IgG4-producing plasma cells have been reported to have regulatory phenotypes (IL10+) and lower expression levels of the inhibitory immunoglobulin receptor FcGRIIb.[9] Further studies should clarify the underlying mechanisms explaining this differential response to IVIg of autoimmune diseases depending on the autoantibody isotype; apart from the role of complement inhibition induced by IVIg proposed by the authors, it seems reasonable to assume that the antibody-producing cells that produce antibodies that have antagonistic functions (i.e., proinflammatory IgG1-3 vs anti-inflammatory IgG4) may respond differently to the immunomodulatory effects of IVIg.

The authors also describe an interesting patient with A-CIDP in which the autoantibody subclass switches from IgG3 in the acute phase of the disease to IgG4 in the chronic stage; the target of the autoantibody also shifts over time from CNTN1 and CASPR1 to CASPR1 alone. This simultaneous change in the antigenic target and the isotype, which should be confirmed in

other patients, may be explained by 2 related facts: first, IgG4 antibodies appear late in the immune response, after several rounds of affinity maturation and somatic hypermutation have occurred.[10] Second, this fine tuning of the affinity may drive the autoantibody response toward the CASPR1 epitope. Whether this epitope is a immunodominant epitope driving the affinity selection in all CIDP patients in which an anti-CASPR1 IgG4 response is detected, as it happens in other diseases such as anti-MusK myasthenia gravis,[11] and whether this phenomenon occurs in other CIDP or GBS patients with anti-CASRP1 antibodies, remains to be elucidated. In most of the studies regarding paranodal antibodies in CIDP, samples were acquired in the chronic phase of the disease, and there are few longitudinal studies in the field. Therefore, data on the appearance and features of paranodal autoantibodies in the acute phase of CIDP are scarce. For this reason, although larger prospective studies are still needed, the association of IgG isotypes and disease progression and treatment response described in this study could be important for optimal patient care in each moment of the disease.

The report also describes 2 patients with antibodies against both CNTN1 and CASPR1 proteins in the acute phase of the disease. There is uncertainty in the field as to whether the immune response in patients with antibodies against the CNTN1/CASPR1 complex is targeting an epitope arising from the binding of both CNTN1 and CASPR1, or separately against each of CNTN1 and CASPR1 proteins. Authors provide descriptive data suggesting that the latter may be happening. Considering the changes that authors report in the antigenic specificity over time in some patients, it could well be that this uncertainty can be clarified by studying longitudinally (as the authors did in this report) the IgG isotypes in all patients and analyzing epitope changes over time in patients previously classified as having antibodies only against the CNTN1/CASPR1 complex. Because technical issues can also explain some of these discrepancies, collaborative, interlaboratory validation studies are needed to elucidate the true antigenic target and assess the diagnostic accuracy of each test in all nodo/paranodal autoantibodies.

In conclusion, detection of antibodies against paranodal proteins, followed by IgG isotype testing in seropositive cases and their longitudinal monitoring during disease course should be considered in the diagnostic workup in inflammatory neuropathies to improve pathophysiologic knowledge, diagnostic accuracy, and treatment selection.

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Disclosure

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

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