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The Discovery of Autoimmune Nodopathies and the Impact of IgG4 Antibodies in Autoimmune Neurology

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Abstract

In the past decade, significant progress has been made on the understanding of IgG4-mediated autoimmune diseases, of both the central and the peripheral CNS. In addition to the description of diverse antigenic targets, the description of IgG subclasses associated with specific pathogenic autoantibodies has provided useful insights into the pathophysiology and, more importantly, into the therapeutic implications of the autoantibody subclasses. This understanding has affected how myasthenia gravis, autoimmune encephalitis, and autoimmune neuropathies are treated. In the case of autoimmune neuropathies, the discovery of antigenic targets located at the node of Ranvier has led to the definition of a new diagnostic category, the autoimmune nodopathies, which differentiate them from the classical forms of Guillain-Barré syndrome and chronic inflammatory demyelinating polyradiculoneuropathy. These neuropathies including those caused by autoantibodies targeting contactin-1, contactin-associated protein 1, and neurofascin are mainly, though not always exclusively, mediated by IgG4 antibodies, and respond to therapies similarly to other IgG4-mediated neurologic and non-neurologic diseases, providing evidence that not only the antigenic target but also the autoantibody subclass play a role in understanding both the disease pathophysiology and response to therapies. In this article, we describe the history and main findings on autoimmune nodopathies; highlight the particularities and similarities of IgG4-mediated neurologic diseases, including autoimmune nodopathies and neuromuscular junction and certain CNS disorders; elaborate on the unique functional properties of IgG4 in influencing their specific response to immunotherapies stressing the rationale of the most suitable present and future targeted therapies; and discuss how best to apply and monitor maintenance therapies for inducing disease stability in all IgG4 neurologic autoimmunities including the need for potential future biomarkers.

Introduction

IgG4 is the fundamental antibody subclass in 5 autoimmune neurologic diseases, referred here as IgG4-NDs, which include the autoimmune nodopathies, muscle-specific kinase (MuSK) antibody–positive myasthenia, leucine-rich glioma-inactivated-1 (LGI1) and CASPR2-associated syndromes, anti-IgLON5 disorder, and anti-DPPX encephalitis. Because the IgG4 antibodies exert pathogenicity not by an inflammatory-mediated tissue destruction, as the IgG1-3 antibody subclasses do, but by interfering with protein-protein interactions affecting cell adhesion or signal transduction pathways as discussed later, they have unique characteristics in reference to immunotherapies, especially their response to anti-inflammatory agents or IVIg.

Among the IgG4-NDs, the autoimmune nodopathies are extensively discussed in this review not only because they had been overlooked until the past decade but also because, in contrast to the other 4 IgG4-NDs which can be suspected from the outset and confirmed with specific

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Glossary

CASPR1 = contactin-associated protein-1; **CIDP** = chronic inflammatory demyelinating polyradiculoneuropathy; **CNTN1** = contactin-1; **GBS** = Guillain-Barré syndrome; **LGI1** = leucine-rich glioma-inactivated-1; **MuSK** = muscle-specific kinase; **sNfL** = serum neurofilament light chain; **VGKC** = voltage-gated potassium channel.

antibody testing, nodopathies always present as Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and are only diagnosed in retrospect, when they do not respond to IVIg and clinicians search for nodal antibodies in special laboratories, highlighting the importance of high level of suspicion for early recognition.

Although the typical variants of GBS and CIDP are easy to diagnose, there are patient subsets presenting with atypical features that do not fit into the canonical definitions. Among those, the most common include acute CIDP (developing in less than 8 weeks); CIDP or GBS associated with nephrotic syndrome; "refractory CIDP" that responds to B-cell–depleting therapies or GBS not recovering after treatment; and CIDP associated with pain or tremor. All these phenotypic patterns were considered variants that deviated from the archetypal presentation of GBS and CIDP, but not independent entities. Guidelines updating the diagnostic criteria for both GBS and CIDP have been recently published[1,2] and include a novel category of disorders termed "autoimmune nodopathies," defined by the presence of antibodies targeting cell adhesion molecules located at the node and paranode of Ranvier. Autoimmune nodopathies have clinical and pathophysiologic features that simultaneously overlap and differ from the typical GBS and CIDP cases, and they are defined by the presence of distinct antibodies targeting cell adhesion molecules at the node of Ranvier.

This review describes the discovery of and main research on autoimmune nodopathies including clinical implications and pathophysiologic mechanisms and highlights the unique immunobiological properties of IgG4 antibodies in destructing targeted antigens in IgG4-NDs, the reasons IVIg is generally ineffective or rarely effective in IgG4-NDs, and why IgG4-NDs specifically respond to anti–B-cell agents.

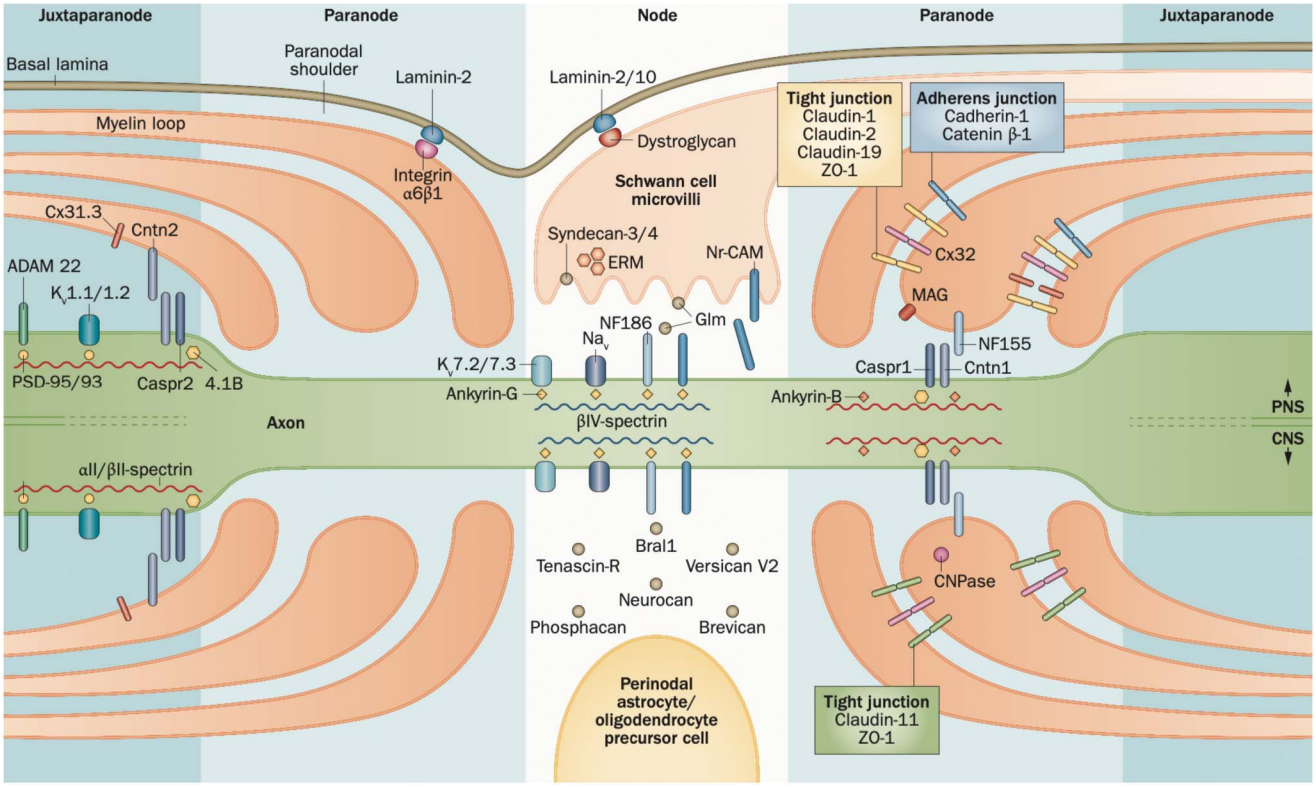
The Node of Ranvier as the Target of Autoimmunity

The node of Ranvier is a functionally and structurally important domain essential for saltatory nerve conduction in myelinated nerve fibers. Different cell adhesion molecules, such as the canonical isoform of neurofascin (NF186), contribute to maintain voltage-gated sodium channels ensuring saltatory conduction at the node of Ranvier. Other cell adhesion molecules—the axonal complex formed by contactin-1 (CNTN1) and contactin-associated protein-1 (CASPR1) and the glial isoform of neurofascin (NF155)—form septate-like structures linking the Schwann cell paranodal loops to the axon to isolate the sodium channels at the node from the voltage-gated potassium channels at the juxtaparanode. The diverse molecules that could be potential candidate antigens in the nodal, paranodal, and juxtaparanodal regions are illustrated in Figure 1.[3]

The node of Ranvier had been identified as a site of autoimmune attack in patients with GBS triggered by parenteral gangliosides when their IgG recognized GM1 at the nodes of Ranvier and distal motor nerve terminals.[4] Then, the group of Johns Hopkins elucidated antibody and complement deposition and macrophage infiltration with paranodal demyelination in nerve roots and peripheral nerves in patients with GBS.[5] The GM1 ganglioside, the most frequent target of autoantibodies in GBS, is enriched in the nodal axolemma and paranodal myelin.[6] In addition, paranodal disruption is one of the first events happening in the experimental autoimmune neuritis, the animal model of GBS.[7] Autoantibodies causing other autoimmune peripheral nerve diseases, such as myelin-associated glycoprotein or contactin-associated protein-2, are also enriched at the paranode and juxtaparanode, supporting the view that structures of the Ranvier node are vulnerable to autoimmune attack.

Segmental demyelination was traditionally considered the histopathologic hallmark of CIDP, and evidence for pathology at the Ranvier node was scarce. Autoantibodies targeting compact myelin or Schwann cells had been described,[8] but disruption of nodo-paranodal molecules in pathologic specimens was described just recently.[9] In 2012, Devaux et al.[10] provided the first evidence that IgG from patients classified as GBS or CIDP targeted the node, the paranode, or both and the targeted antigens included cell adhesion molecules, such as CNTN1 or NF186, later associated with specific clinical syndromes. In this landmark article, the only clinical feature identified to associate with the presence of nodo-paranodal antibodies was respiratory disturbance. The same year, Edgar Meinl's group described antibodies targeting both the axonal (NF186) and the glial (NF155) isoforms of neurofascin binding to the paranodes in a small subset of patients with GBS and CIDP.[11] The antibodies targeting NF155 in 2 patients with CIDP were described for the first time to be IgG4, a finding proven later to have therapeutic implications. Finally, our group, led by Isabel Illa, following the idea that antigenic search in CIDP had been largely unsuccessful by focusing on myelin as the targeted antigen and inspired by the recent discovery of NMDA receptor antibodies in

Figure 1 Molecular Anatomy of the Node of Ranvier



Adhesion molecules (NF186, Nr-CAM, CNTN1, NF155, CASPR1, CNTN2, CASPR2, and MAG) mediate axoglial attachment. Ion channels (KV7.2/7.3, KV1.1/1.2, and NaV1.6) mediate action potential propagation. Both adhesion molecules and ion channels are linked to the cytoskeleton; these proteins include ankyrin-G/B, PSD-95/93, 4.1B, and spectrins. Glm, versican V2, brevican, phosphacan, neurocan, Bral1, and tenascin-R are extracellular matrix constituents and stabilize the structure of the nodal area. Syndecan-3/4, dystroglycan, laminin-2/10, and ADAM 22 are involved in cell signaling. Connexins are gap junction proteins, claudins and ZO-1 are tight junction proteins, and cadherin-1 and catenin β-1 are adherens junction proteins. ADAM 22 = disintegrin and metalloproteinase domain-containing protein 22; Bral1 = brain link protein 1; CASPR = contactin-associated protein; CNTN = contactin; Cx = connexin; ERM = ezrin-radixin-moesin; Glm = gliomedin; KV = voltage-gated potassium channel; MAG = myelin-associated glycoprotein; NaV = voltage-gated sodium channel; NF = neurofascin; Nr-CAM = neuronal cell adhesion molecule; PSD = postsynaptic density protein (adapted from Stathopoulos et al.[3])

autoimmune encephalitis,[12] used hippocampal neurons to screen for autoantibodies in patients with CIDP.[13] We found that 4 patients presented strong reactivity against hippocampal neurons. Immunoprecipitation experiments detected antibodies against CNTN-1 in 2 patients and against the CNTN1-CASPR1 complex in another. Those 3 articles, published within a brief time frame, helped boost the discovery and characterization of other autoantibodies associated with distinct clinical characteristics within the spectrum of autoimmune neuropathies.

The Clinical Description of Autoimmune Nodopathies/ Paranodopathies

An important finding in our anti-CNTN1 report was that patients had clinical features different from classical CIDP or GBS.[13] Patients were older and had more aggressive course, early axonal involvement, and, most importantly, "poorer responses" to conventional therapies than those with typical CIDP. Confirmatory studies, including a large Japanese cohort[14] and smaller case reports, expanded the phenotype associated with anti-CNTN1 antibodies: patients may present with severe ataxia[14] in pediatric age and, most characteristically, with concomitant nephrotic syndrome.[15]

In 2013, Kawamura et al. described the association of antiNF155 antibodies with combined central and peripheral demyelination (CCPD) in patients fulfilling diagnostic criteria for CIDP that also had CNS demyelination.[16] Although the association of anti-NF155 antibodies with CCPD was not confirmed in European cohorts,[17] other authors confirmed the association of these antibodies with CNS demyelinating lesions or optic neuropathies that, for unknown reasons, seem more frequent in patients of Asiatic ancestry.[18]

In our anti-NF155 antibody series, patients presented with subacute CIDP-like disorder, with predominantly distal motor involvement, prominent ataxia, and high-amplitude, low-frequency tremor with cerebellar features.[19] As in patients with CNTN1, response to IVIg was poor. Larger cohorts confirmed the initial description of this phenotype, incorporated radiologic features, and described a human

leukocyte antigen (HLA) haplotype present in up to 90% of patients,[20,21] suggesting a strong genetic risk factor in anti-NF155, that is likely the most frequent autoimmune nodopathy.

Doppler et al.[22] in 2016 described anti-CASPR1 antibodies in 2 patients initially diagnosed with GBS and CIDP, both with severe neuropathic pain. The authors presented clear evidence of anti-CASPR1 antibodies and paranodal staining with the patient-derived IgG. These antibodies are associated with a very aggressive, often painful, neuropathy, frequently indistinguishable from GBS.[23] Again, patients harboring these antibodies do not respond well to IVIg but respond to B-cell depletion.

The group from Marseille identified one patient with a severe neuropathy and electrophysiologic findings suggestive of nodo-paranodopathy (as described by Uncini and Kuwabara)[24] with strong nodal reactivity when incubating the serum with teased nerve fibers[25]; neurofascin was identified as the target antigen by immunoprecipitation, targeting mainly the nodal isoforms (186 and 140), but also the paranodal NF155. This combined reactivity pattern, now termed pan-neurofascin (panNF),[26,27] differs from the pure anti-NF155 reactivity because, in this case, the antibodies target the third fibronectin domain of NF155 that is absent in the nodal isoforms; other patients, including 2 (of 5) with nephrotic syndrome, were also described.[25] The phenotype associated with anti-panNF antibodies often is an extremely severe and potentially fatal neuropathy that does not respond to conventional therapies but responds to B-cell–depleting agents.[26,27] Antibodies targeting only NF186 have also been described and need validation in other cohorts.[28]

Nodopathies: Neither Inflammatory nor Demyelinating

Although autoimmune nodopathies were initially identified within CIDP cohorts, a significant proportion is initially diagnosed with GBS because the disease presents aggressively, requiring increased awareness that patients with autoimmune nodopathy can be misclassified as CIDP or GBS. From the electrophysiologic view, these patients, except for some of those with anti-panNF, display nerve conduction studies that fulfil CIDP criteria with significantly prolonged distal latencies, decreased conduction velocities, conduction blocks, and temporal dispersion, all features traditionally assimilated to segmental demyelination, the pathologic hallmark of CIDP. However, distinct pathologic findings characterized by a variable degree of axonal loss with a milder or absent myelin disruption with thinner myelin sheath or myelin ovoids rule out segmental demyelination and inflammation.[29,30] The ultrastructural analysis also displays specific findings that include loss of the septate-like structures formed by the CNTN1/CASPR1/NF155 complex and the detachment of the Schwann cell paranodal loops from the axon (in patients with anti-CNTN1 and anti-NF155), and loss of Schwann cell nodal microvilli (in patients with anti-panNF).[31] These findings question the assimilation of electrophysiologic "demyelination" with histopathologic demyelination that, at least in autoimmune nodopathies, is not equivalent.

Are Nodal/Paranodal Antibodies Pathogenic?

After the initial reports, it was unclear whether nodo-paranodal antibodies were pathogenic or just an epiphenomenon resulting from nerve damage. Although the location and function of the target antigens made them pathogenic candidates, studies describing their pathogenicity were unavailable and the only reports describing the role of these nodo-paranodal proteins in disease were the descriptions of the "Compton-North myopathy," a lethal congenital "myopathy" that appeared in patients homozygous for CNTN1 pathogenic variants.

Labasque et al.[32] provided the first in vitro evidence that anti-CNTN1 antibodies could be pathogenic because they were predominantly of IgG4 subclass targeting functionally important glycans of CNTN1; furthermore, patient-derived IgGs interfered with the binding of CNTN1/CASPR1-expressing cells with NF155-expressing cells and disrupted paranodal formation in myelinating co-cultures. Considering that anti-CNTN1 antibodies were IgG4, they proposed that this paranodal disruption should happen in the absence of complement or inflammatory cells. Other reports, however, demonstrated that anti-CNTN1 antibodies can also mediate damage in a complement-dependent fashion when the subclass is not IgG4.[33,34] Formal confirmation that anti-CNTN1 antibodies are pathogenic was published by Manso et al.[35] Using in vitro experiments, intraneural injections, and a passive transfer model in rats, they demonstrated that anti-CNTN1 pathogenicity is independent from inflammatory cells and complement and does not cause axonal damage or demyelination in the model, that the pathogenicity is higher with IgG4 anti-CNTN1 antibodies than with other subclasses, and that the antibodies cause clinical and electrophysiologic alterations similar to those identified in patients by slowly penetrating and diffusing into the paranodes.[35] The same group recently described that pathogenicity of these autoantibodies is dependent on the valency of the antibodies because Fab antibody portions cause pathology to the same extent as fully formed IgGs and F(ab)2 portions.[36] CNTN1 is also expressed in the CNS and neuromuscular junctions, but, so far, syndromes associated with these locations have not been described, probably because of the presence of postraductional modifications of CNTN1. Nevertheless, anti-CNTN1 antibodies can also alter the surface expression of CNTN1 and sodium currents on dorsal root ganglia neurons.[37]

The ultrastructural findings in nerve biopsies of patients with anti-NF155 antibodies suggested that these antibodies could also be pathogenic. Manso et al.[38] in 2019 described that intrathecal injection of IgGs derived from patients with anti-

NF155 to rats caused clinical and electrophysiologic features resembling those seen in patients with anti-NF155. These functional alterations are not related to interference of the antibodies with the CNTN1/CASPR1/NF155 complex but due to depletion of NF155 from the Schwan cell surface, preventing its incorporation into the complex. Again, all these alterations appeared in the absence of overt demyelination.[38] A recent report by the same group described that valency also influences antibody pathogenicity. In this case, and contrary to what happens in anti-CNTN1 antibodies, bivalent anti-NF155 antibodies (or F(ab)2 fragments) need to be present to cause pathologic alterations in the animals while monovalent antibodies are innocuous.[39] These 2 examples demonstrate that not only the antigenic target but also the subclass and the valency influence the pathogenicity of nodo-paranodal antibodies.

Definitive evidence demonstrating the pathogenicity of anti-panNF or anti-CASPR1 antibodies in vivo is not yet available. In vitro studies by Appeltshauser et al.[40] showed that anti-panNF antibodies cause destruction of the nodo-paranodal architecture and axonal damage through complement-mediated mechanisms. While it would be logical to consider anti-CASPR1 antibodies pathogenic, the only evidence comes from a report describing the interference of IgG4 anti-CASPR1 antibodies in a cell aggregation assay performed with cells expressing the CNTN1/CASPR1 complex and cells expressing NF155,[41] but more elaborated pathogenicity studies have not yet been developed.

Key Clinical Messages for Autoimmune Nodopathies: Suspect, Identify, Treat, Monitor

Autoimmune nodopathies account for no more than 10% of patients fulfilling CIDP diagnostic criteria. However, their prompt identification is crucial because the response to first-line therapies is often insufficient and B-cell depletion, not routinely used in GBS or CIDP, is very effective.[20,23] Ideally, these antibodies should be tested in patients in whom GBS and CIDP are suspected to avoid diagnostic and therapeutic delays. However, testing for these antibodies systematically may not be feasible at all centers and the CIDP/GBS guidelines recommend testing when some key clinical features appear.[2] Patients fulfilling CIDP diagnostic criteria with aggressive presentation, cranial nerve involvement or ventilatory failure, and very high CSF protein (frequently over 1.5 g/L) and especially if they do not respond to IVIg should be tested.[42] In addition, patients presenting at a young age (late childhood to early adulthood) with severe ataxia or high-amplitude tremor and a predominantly distal motor involvement should be considered for anti-NF155 testing; patients with nephrotic syndrome should be considered for anti-CNTN1 or anti-panNF testing; patients with severe tetraplegia should be considered for anti-panNF testing; and patients with a subacute, severe, and painful sensory motor neuropathy should be considered for anti-CASPR1 testing.[42]

Identification of these autoantibodies is crucial to properly select treatment. Some patients may respond transiently or partially to IVIg and half of them to corticosteroids, but rituximab is frequently a better option. Most patients treated with rituximab respond well and in a long-lasting fashion.[20,43] This improvement occurs in parallel with a significant reduction or complete disappearance of the autoantibodies. Serum neurofilament light chain (sNfL) levels, which are high in these patients, also decrease with clinical improvement and autoantibody reduction.[20,40,43] Considering the long-lasting effect of B-cell depletion, we propose that the autoantibody levels and sNfL levels could be used to monitor reappearance of the disease and optimize the use of rituximab.

Considering the low frequency of the nodo-paranodal antibodies, the broad population that will eventually be tested, and the therapeutic implications, it is crucial to have a specific test with an optimal positive predictive value to avoid misdiagnoses and inappropriate treatment.[42] The CIDP diagnostic guidelines recommend the use of cell-based assays and encourage the use of a second confirmatory technique. An interlaboratory study performed in 4 of the most experienced laboratories analyzing different tests supports the use of cell-based assays (preferable with live cells) or a specific ELISA for screening of these antibodies (pending publication). The use of other techniques, such as western blot analysis, is not backed by evidence and, in our experience, is subject to substantial false-positivity rates.

The Impact of IgG4 Antibody Subclass in Autoimmune Neurology: From Autoimmune Nodopathies and Beyond

The mechanism by which IgG4 subclass of nodal/paranodal antibodies disrupts their targeted antigens exemplifies the need to appreciate the uniqueness of IgG4 antibodies not only in nodopathies but also in the 4 other IgG4-NDs described further because like the nodopathies, most of them also do not respond to anti-inflammatory agents and IVIg, either from the outset or sometime during their disease course.[44,45] They include the following:

1. *MuSK antibody–positive myasthenia* presents with IgG4 antibodies against MuSK, a postsynaptic transmembrane polypeptide of the neuromuscular junction.[46] MuSK IgG4 can passively transfer disease, and the antibody titers correlate with disease severity, being reduced when patients are in remission.[46,47] MuSK-MG, although may have a similar phenotype to AChR-MG, also has a unique presentation with selective weakness and atrophy of

the neck, tongue, shoulder, and bulbar muscles. In MuSK-MG, the thymus is not involved and IVIg does not substantially help in a crisis.[44,45]

2. *LGI1 and CASPR2-associated autoimmune CNS or PNS syndromes* present with diverse symptomatology of encephalitis, autoimmune epilepsy, faciobrachial dystonic seizures, Morvan syndrome, neuromyotonia, or autoimmune pain, associated with 2 specific antibodies against LGI1 or CASPR2 (contactin-associated protein 2). LGI1 and CASPR2 stabilize the voltage-gated potassium channel (VGKC) complex into the membrane with LGI1 bridging the presynaptic VGKC Kv1.1 with the postsynaptic AMPA receptor by interaction with synaptic anchor molecules ADAM22/23.[48,49] The LGI1 and CASPR2 antibodies are mostly of the IgG4 subclass but, in some patients, may also coexist with IgG1 and IgG2 antibody subclasses. Both are expressed in the CNS and PNS, including peripheral nerves and dorsal root ganglia, which explains their wide spectrum and overlapping symptomatology. Of interest, small fiber sensory neuropathy with reduced intraepidermal nerve fiber densities and autonomic symptoms such as postural orthostatic tachycardia syndrome (POTS) are increasingly recognized in CASPR2-positive patients defining a distinct autoimmune pain syndrome responding to immunotherapies.[48]
3. *Anti-IgLON5 disorder* presents with sleep disturbance, cognitive decline, abnormal eye movements, bulbar dysfunction, gait instability, craniofacial dyskinesias, dystonia, and chorea.[50] IgLON5 is a cell adhesion molecule attached to the neuronal cell membrane by a glycosyl-phosphatidylinositol anchor protein that plays a key role in adhesion of cellular proteins and signaling pathways through their interaction with other cytoskeletal proteins (50). Anti-IgLON5 antibodies are mostly of the IgG4 subclass causing disruption of cytoskeletal proteins, resulting in axonal swellings and abnormal neurofilament accumulation resembling neurodegenerative process linked to autoimmunity.[51]
4. *Anti-DPPX encephalitis* is characterized by gastrointestinal symptoms, cognitive dysfunction, and neurologic hyperexcitability, sometimes resembling progressive encephalopathy with rigidity and myoclonus (PERM). The targeted antibody is against the dipeptidyl-peptidase–like protein (DPPX), a regulatory subunit of the neuronal Kv4.2 potassium channel complex, which is associated with generation of inhibitory currents regulating the repetitive firing rates into dendritic processes.[52] The DPPX antibodies are of the IgG4 and IgG1 subclass exerting a combined pathogenic effect by reducing neuronal cell membrane protein expression of DPPX and Kv4.2 potassium channels inducing neuronal excitability in not only CNS but also the myenteric neuronal plexus, being responsible for the dysautonomic manifestations and diarrhea.[52]The disease responds better to rituximab with more frequent relapses when rituximab is stopped, pointing to effects more related to IgG4 rather than IgG1 antibodies.

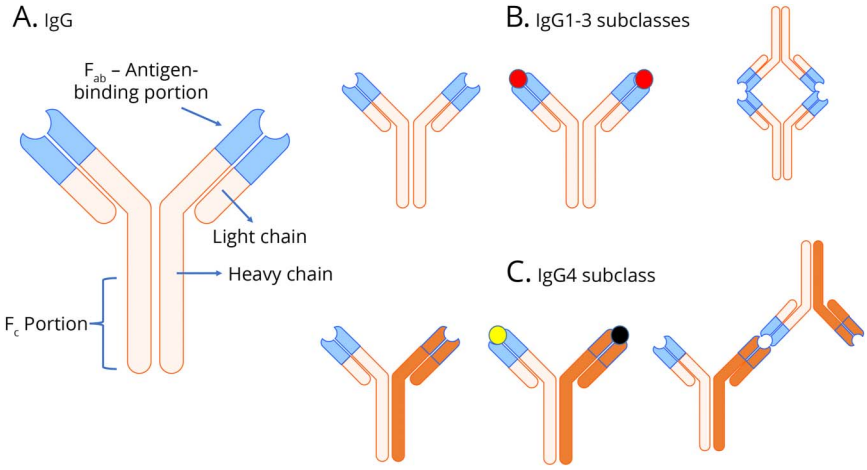
The Distinct Anti-inflammatory Functions of IgG4 Antibodies

The IgG4 subclass comprises less than 5% of IgGs, and, although the least common, the IgG4 antibodies have evolved as an anti-inflammatory response against allergic inflammations, owing to their unique structure.[44,45,53,54] The 2 heavy and light chains of IgG4 are joined by noncovalent bonds, being unable to crosslink identical antigens; as a result, they recognize antigens only with one arm, undergoing half-antibody "Fab-arm exchange," being *functionally monovalent and bispecific*; this is in distinct contrast with the IgG1-3 antibody subclasses that have 2 identical antigen-binding sites binding to the same antigen, being *bivalent and monospecific* (Figure 2).[45] Because the IgG4 antibodies recognize antigens only with one Fab-arm, they result in very low concentration of antigen-bound molecules at their targets; consequently, IgG4 is unable to bind C1q to activate complement and has reduced binding capacity for the proinflammatory, cell-mediated cytotoxicity promoting inhibitory FcγRIIB receptors.[44,45,53,54] It is because of these 2 unique binding qualities that the IgG4 antibodies exhibit noninflammatory properties, being unable to crosslink immune complexes to degrade an antigen by activating cellular or complement-mediated immune factors; their pathogenicity is instead exerted by blocking protein-protein interactions affecting directly the structure and function of antigenic proteins.[44,45,53,54]

Why IVIg Is Ineffective in IgG4 "Neuroautoimmunities"?

The effectiveness of IVIg is based on the following fundamental functions, either alone or in combination[44,55]: (1) inhibition of complement binding, preventing the formation of membranolytic attack complex; (2) upregulation of the inhibitory FcγRIIB receptors on macrophages, dendritic cells, and B cells that inhibit phagocytosis and cytokine production intercepting antibody-dependent cell-mediated cytotoxicity; (3) suppression of pathogenic cytokines; (4) partial saturation of the FcRn receptors, enhancing the catabolism of IgG1-3 antibodies; and (5) neutralization of pathogenic autoantibodies by idiotypic antibodies of the IgG1-3 subclass. Most of these IVIg actions are, however, irrelevant in inhibiting the pathogenic effects of IgG4 antibody subclass because the IgG4 antibodies (1) do not fix complement; (2) do not bind or upregulate the inhibitory FcγRIIB receptors, an effect very relevant to CIDP where the FcγRIIB receptors are substantially underexpressed on B cells and monocytes[44,45];

Figure 2 Structural and Functional Features of IgG4 Antibodies



(A) The IgG has 2 heavy and 2 light chains, both with a constant fragment (Fc), identical for all antibodies of the same isotype that binds to FcR of cells of innate immunity allowing phagocytosis. IgG has 2 antigen-binding fragments (Fab) that bind to a specific antigen. (B) The IgG1-3 antibody subclasses have 2 identical antigen-binding sites (in blue) binding to the same antigen (both depicted in red) with both arms; they are, therefore, *bivalent and monospecific*. (C) The IgG4s have unique structure in the hinge region, and their 2 heavy and light chains are joined by noncovalent bonds; as a result, they cannot crosslink identical antigens as the IgG1-3 do (depicted one in black and the other in yellow). Instead, the IgG4s continuously undergo half-antibody "Fab-arm exchange" recognizing the same antigen only with one arm; they are, therefore, functionally *monovalent and bispecific* (adapted from Dalakas[45]).

(3) do not recruit immune cells through Fc receptors, not inducing phagocytosis or triggering cytokines and inflammatory responses; and (4) are not neutralized by idiotypes because the IVIg does not contain idiotypic IgG4 antibody subclass.

There are, however, rare exceptions where IVIg can be partially effective for short periods in some IgG4-NDs, such as autoimmune nodopathies and MuSK-MG, mainly because of aberrant complement activation or IgG subclass switch. In rare autoimmune nodopathies, anti-panNF antibodies can cause destruction of the nodo-paranodal architecture and axonal damage through complement-mediated mechanisms,[40] although IgG4 does not bind C1q and can even reduce the affinity of IgG1 subclass to bind C1q. Such rare IgG4 complement activation may be triggered by either the other IgG subclasses or the IgG4 subclass itself when it is aberrantly glycosylated because it may activate complement through the lectin pathway, as shown in experimental membranous nephropathy.[56]

The Insidious IgG4 Subclass Switch and Its Therapeutic Consequences

Immunoglobulin subclass switch can normally occur late in the immune response because of the dynamic process of maturation and hypermutation but is routinely inconsequential. In IgG4-NDs, however, an insidious subclass switch from IgG1-3 to IgG4 is highly relevant because it affects response to immunotherapies, especially IVIg, reverting a previously IVIg-responding patient to IVIg-unresponsive. This has been noted in a patient with autoimmune nodopathy, when the antibody subclass was switched from IgG3 against CNTN1/CASPR1 to IgG4 against CASPR1 and the patient stopped responding to IVIg[57]; the reverse has also occurred in a patient with MuSK-MG when the anti-MuSK IgG4 was switched from IgG4 to IgG1 and the patient clinically reverted to a stable remission.[58] Awareness of IgG subclass switch is, therefore, essential when a previous IVIg-responsive patient does not respond anymore; this may be also relevant for consideration when enrolling patients with CIDP or MuSK-MG in randomized trials.

In some IgG4-NDs, more often LGI1 and CASPR2, but also in DPPX and rarely in some nodopathies, the antibodies may not be predominantly or exclusively of IgG4 subclass but the IgG4 may coexist with IgG1 and IgG2 enhancing the chances for a potential subclass switch due to chronic antigenic stimulation.[44,45,53] Although antibody-antigen internalization and antigen crosslinking are mediated only by the bivalent IgG1-3 antibody subclasses, experimentally, if confirmed, these might rarely occur even with the monovalent IgG4.[59]

Why B-Cell–Depleting Therapies Are the Treatment of Choice in IgG4-NDs?

Immunoglobulins are produced by long-lived plasma cells, but IgG4 is likely produced by CD20-positive short-lived plasma cells stimulated by IL-4 and IL-21.[60] The IgG4 production is more specifically enhanced by IL-10 that, in IgG4-rheumatological diseases (IgG4-RDs), plays a key role in B-cell subclass switching to IgG4 production.[53,54] T follicular regulatory cells expressing IL-10 and follicular helper T cells producing IL-4, IL-10, and IL-21 are also involved in subclass switch and may be relevant to IgG4 production.[61] Memory B cells and expanded IgG4-producing plasmablasts are also increased in the peripheral blood being associated with disease activity, collectively supporting a pathogenic role of B cells and justifying the rationale for B-cell–depletion therapies.[44,45] Rituximab, which targets B cells before their differentiation into non–CD20-expressing plasma cells,

reduces IgG4 levels by targeting IgG4-producing CD20-positive short-lived plasma cells and plasmablasts.[62,63]

In IgG4-NDs, the impressive success of rituximab is undisputed. In a multicenter study of 24 patients with MuSK-MG, 58% of rituximab-receiving patients reached the primary outcome compared with 16% of controls (p = 0.002), after a median 3.5-year follow-up period with significant reduction in their mean prednisone dose.[44,45,64] IgG4 MuSK antibodies were markedly reduced 2–7 months after rituximab initiation, being even undetectable within 2 years coinciding with long-term sustained remission[64]; this has also been our experience with a number of patients.

In NF155 and CASPR1/CNTN1 nodopathies, the unresponsiveness to IVIg is overwhelming because <10% partially or transiently respond, in contrast to >80% responding to rituximab.[41,43] Among patients with NF155-IgG4, 45% had neuropathic pain because of small fiber neuropathy and autonomic symptoms, suggesting rituximab effectiveness also in NF155-IgG4–positive painful neuropathy.

In several retrospective small series of patients with *LGI1/CASPR2*-associated and *DPPX*-associated autoimmunities, the first-line immunotherapy for the patient with encephalitis, epilepsy, and pain has been steroids and IVIg with good, although variable, benefits,[45,48,65] considering that in some patients, the antibodies are of IgG1-3 subclasses. In patients with LGI1/CASPR2-associated encephalitis with worse outcomes when more frequently treated with IVIg and steroids, increased LGI1-specific plasmablasts/plasma cells were noted in the CSF, justifying anti-CD19/CD20-specific immunotherapies from the outset.[65] In DPPX autoimmunity with the IgG1-3 or IgG4 antibody subclass, many patients with poor benefit from other agents often responded to rituximab, exhibiting relapses when rituximab is discontinued,[52] highlighting the need for increased awareness for an insidious subclass switch and consideration for early rituximab initiation if response to conventional immunotherapies is inconsistent or suboptimal.

Rituximab Maintenance and Potential Biomarkers: Enhanced Experience From IgG4-RDs to IgG4-NDs

In several IgG4-RDs, the risk of relapse has been lower while on rituximab maintenance, compared with only one rituximab induction therapy[53,54,63] with rising serum IgG4 levels considered a risk factor of relapse. In our view, the IgG4 is not a reliable biomarker because IgG4 levels can increase nonspecifically during immune activation periods. In IgG4-NDs, the total IgG4 levels are irrelevant because, based on a series of patients with CIDP with IgG4-nodal antibodies we have examined, the IgG4 concentration was normal (<1,350 mg/L, the limit used for active IgG4-RD: unpublished observations by Dalakas et al.). In contrast to other autoimmune neurologic diseases where antibody titers are not reliable biomarkers (like anti-MAG-ab, AChR-ab, and anti-GAD-ab), in IgG4-NDs, the IgG4 antibody titers can serve as biomarkers because they correlate with disease activity, as shown for MuSK-MG[64] and autoimmune nodopathies,[37] but their predictive value needs to be assessed in long-term trials.

The role of follow-up rituximab infusions for long-term remissions in IgG4-NDs remains empirical, but reassuring. In contrast to IgG1-3-NDs where patients have more labile disease and may require 2 grams every 6 months or 1 g every 3 months to ensure stability,[62] some patients with IgG4-NDs, based on our experience with MuSK-MG and autoimmune nodopathies[41-43,64], may remain free of disease for long periods. Until controlled studies are, however, performed and biomarkers evaluated, the main factors guiding future infusions remain the clinical status, imminent signs of early relapse, and the IgG-4 antibody–specific titers.[45] A reliable biomarker for the need of reinfusion remains the reemergence of $CD27^+$ memory B cells because their resurgence is associated with clinical relapses.[62] Regarding future disease-specific biomarkers, of interest is the observation in IgG4-RD where the enhanced liver fibrosis score, used to assess the impact of rituximab on fibroblast activation, was a clinically useful indicator suggesting that B-cell depletion has the potential to halt continued collagen deposition[66]; this may be equivalent to sNfL levels, proposed earlier in monitoring response to the patients with nodopathy.

The Future

The description of the nodo-paranodal antibodies has reinvigorated the search for antigenic targets in other patients fulfilling CIDP or GBS diagnostic criteria, and despite not been confirmed in large cohorts or specific clinical phenotypes, it exemplifies strong ongoing interest. Examples of recently described autoantibodies in CIDP include those targeting LGI4,[67] a protein located at the juxtaparanodes and dorsal root ganglia, in a subset of typical or multifocal CIDP variants responding to IVIg; dihydrolipoamide S-acetyltransferase in CIDP with predominantly sensory features[68]; and the leukemia inhibition factor, a protein we found in 2 patients with CIDP[69] and playing a role in central and peripheral myelination. The impact of nodo-paranodal antibody discovery redefining what it means to have CIDP supports the need for such a continuing effort because CIDP is not anymore a disease but a syndrome with diverse pathophysiologic mechanisms, different phenotypes, and therapeutic responses; the recent data that IgG-lowering therapies are effective in patients with CIDP[70] support the view that other autoantigens (some among those depicted in Figure 1) need to be identified.

Regarding the future of immunotherapies applicable to all IgG4-NDs, the extensive somatic hypermutation shown by immunoglobulin sequencing of expanded plasmablast clones

in IgG4-RD, in conjunction with the effect of rituximab in B-cell depletion, provides strong rationale that the newer anti–B-cell therapies may be highly promising in providing more effective or long-lasting benefits. As recently discussed,[45] controlled studies with anti-CD19/20 monoclonals, including those that also activate FcγRIIB such as *obexelimab and obinutuzumab* that target CD19/FcγRIIB or CD20/FcγRIIB, may be even more relevant in treating IgG4-NDs, especially the nodopathies.[45] Finally, the CD19 CAR T-cell therapies now ongoing in various refractory neurologic autoimmunities, such as progressive MS, myasthenia gravis, stiff person syndrome, or MOGAD, should be considered for refractory IgG4-NDs. At the molecular level, examining somatic hypermutation by immunoglobulin sequencing of expanded plasmablast clones after anti–B-cell treatments may shed light on understanding IgG4-secreting B-cell clones as recently highlighted.[44,62]

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