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Review Article

The immunology and neuropathology of the autoimmune nodopathies☆

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ABSTRACT

The autoimmune nodopthies have recently emerged as a discrete subtype of inflammatory neuropathy. They are characterised by the presence of IgG class autoantibodies directed against structural components of the node of Ranvier, such as the axonal isoform of neurofascin (NF186), or flanking paranodes, where NF155, on the glial membrane, and the axonal complex of contactin-1 and contactin-associated protein-1 (Caspr1), are established targets. Although initially proposed to be atypical forms of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), many patients initially present with a clinical picture in keeping with the acute inflammatory neuropathy Guillain-Barré syndrome (GBS). Furthermore, compared to seronegative CIDP and GBS, the autoimmune nodopathies have distinct underlying immunological and neuropathogenic mechanisms. Crucially, the treatment response profile is also different, and patients often fail to respond to immunotherapies typically used in seronegative cases, such as immunoglobulin infusions and corticosteroids. However, responses to anti-CD20 B-cell depleting therapies are frequent and often long-lasting. This review provides on overview of the antigenic landscape of the node of Ranvier, and the broad concept of nodopathies, and summarises the immunology, neuropathology and clinical features of these disabling yet treatable disorders.

1. Introduction

Autoimmune nodopathy (AIN) is now considered to be a distinct type of inflammatory neuropathy (Van den Bergh et al., 2021). Although initially described as an atypical form of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), it is increasingly clear that the underlying immunology, pathology, and treatment response profile is substantially different. Herein, we review the concept and current pathological understanding of this disorder.

2. The node of Ranvier and the concept of nodopathies

The node of Ranvier is a highly specialised sub-domain of myelinated nerve fibres, critical for rapid and efficient saltatory conduction. It can be divided into three zones: the node proper, the paranode, and the juxtaparanode. Each sub-region is molecularly and functionally distinctive (Fig. 1) (Rasband and Peles, 2021). The node is the location at which the axolemma is most exposed to the extracellular fluid, covered only by the Schwann cell microvilli in the peripheral nervous system. It is here that the voltage-gated sodium channels responsible for the rapid inward depolarising phase of the action potential are clustered. This localisation and clustering are driven and maintained by two complementary sets of molecular mechanisms. Firstly, gliomedin, secreted from the Schwann cell microvilli at the node, interacts with extracellular domain of neurofascin-186 (NF186) in the underlying axolemma. NF186, in turn, binds ankyrin G via its intracellular domain. Ankyrin G then marshals a complex dependent on the cytoskeletal protein βIV-spectrin which links and clusters NF186, ankyrin G and the voltage-gated sodium channels. Secondly, the developing paranodes advance towards the node on either side during their development, acting as both a "plough" and barrier to further limit the lateral diffusion of the nodal components. Paranodal integrity, and the close opposition of non-compact myelin to the underlying axon in this region, crucial for this function, is maintained by a different set of molecular contacts. Here, septate-like junctions are formed by neurofascin-155 (on the glial membrane) interacting with a dimeric complex formed by contactin-1 (CNTN1) and contactin-associated protein 1 (Caspr1) within the axolemma. Finally, at the juxtaparanode, axonal Caspr2 interacts with glial contactin-2, which, mediated by PSD93/95 and 4.1B, link voltage-gated potassium channels to αII/βII spectrin. These voltage-gated potassium

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channels are involved in the repolarisation phase of action potentials. In addition, glycolipids, most notably of the sialylated glycosphingolipid family of gangliosides, are enriched at and play vital roles throughout the node. This includes contributing to the compartmentalisation of nodal/paranodal adhesion molecules as constituents of lipid rafts/microdomains, maintaining stability of paranodal junctions and ion channel clusters, assisting axo-glial interactions, and acting as receptors for both physiological (eg. myelin-associated glycoprotein, MAG) and pathological (eg. toxins and auto-antibodies) ligands.

The idea that the node of Ranvier might be an important site of immune-mediated pathology was first appreciated nearly 50 years ago, when an electron microscopy study of autoimmune allergic neuritis in rabbits demonstrated macrophage-mediated stripping of the paranodal myelin terminal loops from the underlying axon (Allt, 1975). Subsequently, clinical, electrophysiological and sero-pathological studies in Guillain-Barré syndrome (GBS) implicated the node in specific subtypes of this disorder, closely linked to the presence of ganglioside antibodies. Electrophysiology studies showed that presence of conduction block, more typically associated with segmental demyelination, could sometimes be found without other neurophysiological markers of demyelination, such as temporal dispersion. Critically, this could also be rapidly reversed following treatment, with parallel rapid clinical improvement, in a time frame incompatible with re-myelination, implicating a functional, nodally driven form of conduction block (Uncini et al., 2013).

Furthermore, experimental studies showed that at least some ganglioside antibodies target the node. Activation of the complement cascade then leads to insertion of membrane attack complex (MAC) into the axolemmal membrane, producing current leak and conduction block (McGonigal et al., 2010). Calcium influx through the MAC pore then activates calpain/caspases and leads to axonal degeneration. In this and other model systems, nodal conduction block can be parsed from axonal degeneration by the use of calpain inhibition. In the presence of these inhibitors, ganglioside antibodies remain able to bind their target antigen and fix complement, leading to current leak and a failure of action potential generation, but the structural integrity of the axon is preserved. This then facilitates more rapid recovery of conduction and nerve function during the recovery phase. (McGonigal et al., 2023)

It seems highly likely that axons in GBS pass through such a metastable state, where immunological injury has produced a functional deficit but the axon is not yet irreversibly committed to distal degeneration. This, in turn, may explain the dichotomous outcomes in "axonal" / nodal GBS, with rapid recovery from functional block on one hand and slow and incomplete recovery following axonal degeneration on the other. Whether the use of calpain inhibition in patients may help tip the metastable balance in favour of the former and improve outcomes remains to be seen, but is clearly a potentially beneficial approach ripe for exploration in future clinical trials.

3. Moving beyond gangliosides: Nodal/paranodal cell-adhesion molecules as autoantigens in peripheral nerve disease

The focus on the node produced by studies on ganglioside antibodies

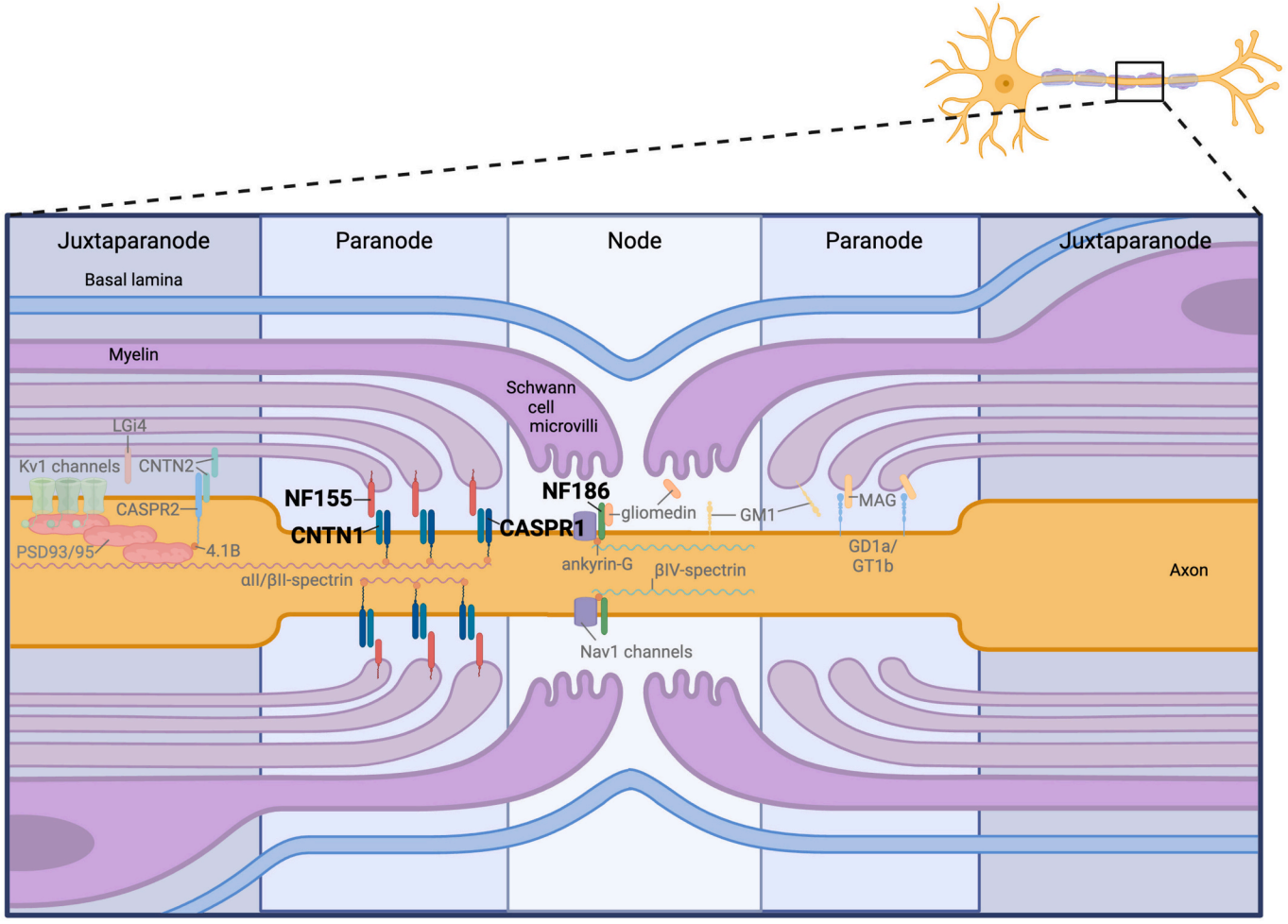

Fig. 1. Structure, sub-regions and molecular landscape of the node of Ranvier.
Established antigenic targets for the autoimmune nodopathies are shown in bold. (NF: neurofascin, CNTN: contactin, CASPR: contactin-associated protein, Nav: voltage0-gated sodium channel, Kv: voltage-gated potassium channel, MAG: myelin-associated glycoprotein).

prompted a search for other potential nodal autoantigens, initially in patients with clinical diagnoses of GBS (Prüss et al., 2011). Shortly after, IgG binding to nodal and/or paranodal regions of murine teased sciatic nerve fibres was demonstrated to be present in around 40 % of GBS and 30 % of CIDP sera (compared to 0 and 3.8 % in healthy and other disease controls). (Devaux et al., 2012) In a small number of these sera, nodal/paranodal reactivity was shown to be due to antibodies targeting specific adhesion molecules such as neurofascin-186, gliomedin or contactin-1. A subsequent series found neurofascin antibodies in 8/254 (3.1 %) inflammatory neuropathy patients but not in controls (Ng et al., 2012). Later, reactivity against cultured hippocampal neurons in 4/46 patients with CIDP was revealed to be due to autoantibodies against the CNTN1/Caspr1 complex, following immunoprecipitation/ mass-spectrometry proteomics and the development of a transiently-transfected, antigen-specific, cell-based assay (Querol et al., 2013). Similar approaches identified NF155, NF186, Caspr1 and the CNTN1/Caspr1 complex as autoantibody targets in distinct subsets of patients, and these targets have been confirmed and further explored in multiple subsequent studies (Querol et al., 2014; Doppler et al., 2016; Delmont et al., 2017; Pascual-Goñi et al., 2021; Fehmi et al., 2021). These have revealed a distinctive clinical, immunological and pathological signature which separates what are now known as autoimmune nodopathies from seronegative GBS/CIDP and other inflammatory/autoimmune neuropathies.

4. The immunology of autoimmune nodopathies

4.1. IgG subclass

The potential importance of certain IgG subclasses to autoimmune nodopathies initially emerged from a seminal study which showed neurofascin-155 antibodies in patients with clinical diagnoses of CIDP were rare, but predominantly of the IgG4 subclass in all identified cases (Querol et al., 2014). Later work suggested the variable presence of both IgG4 and other IgG subclasses in patients with NF155 and in those with other nodal/paranodal antibodies (Doppler et al., 2016; Delmont et al., 2017; Doppler et al., 2019; Cortese et al., 2020; Shelly et al., 2021). Notably, IgG1 and IgG3 may be prominent or exclusively present in patients with pan-neurofascin antibodies, in particular (Fehmi et al., 2021; Stengel et al., 2019).

This distinction is mechanistically important for several reasons, in part due to the distinctive characteristics of IgG4 antibodies (Table 1). IgG4 is the least abundant IgG subclass in circulation, but antigen-specific responses can be dominated by IgG4 (and may form a substantial portion of total IgG4), especially in the context of chronic antigenic stimulation. IgG4 antibodies are also typically highly mutated and of high affinity. However, they have a very limited capacity to engage activatory Fcγ receptors or bind C1q, and thus a limited scope to induce antibody-dependent cellular cytotoxicity (and probably antibody-dependent phagocytosis) or fix complement and activate the classical complement cascade. Furthermore, IgG4 class-switching is facilitated by T-helper 2 responses and type 2 cytokines (eg. IL-4 and/or IL-13), appears to more readily occur directly from naïve IgM+ B cells rather than indirectly from IgG1+ memory B cells, and is likely to require prolonged or repeated exposure to antigen (Rispens and Huijbers, 2023).

Table 1
Differential properties of the IgG subclasses.

Property	IgG1	IgG2	IgG3	IgG4
Molecular weight, kDa	150	150	170	150
Abundance in serum, g/L (%)	7 (60)	3.8 (31)	0.51 (4)	0.56 (4.5)
Half life, days	14–21	14–21	7	14–21
Hinge length, amino acids	15	12	62	12
C1q binding	+	+/−	++	−
Complement-mediated cytotoxicity	++	+/−	++	−
Antibody-dependent cell-mediated cytotoxicity	++	+/−	++	−
Antibody-dependent cell-mediated phagocytosis	+	+	+	−
FcRn binding	+	+	+/−	+
Fab arm exchange	−	−	−	++

In addition, compared to IgG1, IgG4-switched B cells have lower levels of expression of chemokine receptors involved in the generation of long-lived plasma cells. As such, there is a tendency for IgG4 production by antibody secreting cells (ASCs) to be shorter lived than for other IgG subclasses, a reduced tendency for the generation of long-lived plasma cells, and an increased reliance on continuous generation of new ASCs (short-lived plasmablasts) from differentiating B cells to maintain long-term IgG4 responses. Finally, IgG4 subclass antibodies have a unique ability to undergo Fab arm exchange. This is due to specific amino acid substitutions in the heavy chain which reduce the stability of the disulfide bond at the hinge region and reduce the strength of non-covalent interactions between the heavy chains. As a result, one half of a given IgG4 molecule is exchanged with another, producing monovalent, bispecific antibodies, with consequently lower avidity. This process is essentially random, such that if IgG4 antibodies of a certain specificity form a high proportion of the total IgG4 pool, some will be still exist in a bivalent, monospecific form (Rispens and Huijbers, 2023). The overall implication of these characteristics is that the potential pathological mechanisms of IgG4 antibodies are largely limited to the blockade of physiological interactions between the target antigen and its ligand(s). Complement fixation, recruitment or activation of inflammatory/immune effector cells, antigen cross linking (and the production of immune complexes) and target internalisation are all unlikely. Indeed, traditionally, IgG4 antibodies have been considered as “benign” and primarily involved in the resolution of immune responses. As discussed later, this is now being challenged by observations suggesting a pathogenic role in autoimmune nodopathies. There is, however, also evidence that IgG1 or IgG3 subclass antibodies found both exclusively or in addition to IgG4 in some patients may exert pathogenic effects though Fc-mediated effector functions, including complement activation via the classical pathway.

4.2. IgM

A small number of studies have also investigated the presence of IgM nodal/paranodal antibodies, with partially conflicting results. IgM antibodies against NF155 or NF186 were initially detected by cell-based assay in 5/59 (8 %) patients with inflammatory neuropathies (GBS/CIDP), in one case alongside IgG, but also in 2/111 (2 %) of patients with genetic neuropathies and 2/43 (5 %) with idiopathic neuropathies. (Shelly et al., 2021) However, a subsequent study in a different centre did not detect IgM NF155, NF186, or CNTN1 antibodies in any of 108 genetic neuropathy sera, and 1/108 with IgG NF155 reactivity by ELISA/CBA was ultimately considered negative following a teased-nerve fibre assay (Martín-Aguilar et al., 2020). A further study using ELISA reported NF155 IgM antibodies in 5/140 patients with GBS/CIDP and 0/143 controls (Doppler et al., 2018). Of interest, the presence of IgM antibodies was associated with tremor in all cases. Anti-CNTN1 IgM was not detected in any serum. Overall, IgM nodal/paranodal antibodies appear to be present in some patients with inflammatory neuropathies, and may also be present more widely. Their relevance to the pathological process or the immunological implications are, however, currently unclear.

4.3. HLA

In contrast to prior observations in seronegative GBS and CIDP, three studies to date have identified specific human leukocyte antigen (HLA) class II haplotypes as being associated with serologically defined subtypes of AIN. An initial study involving European centres showed that

HLA DRB1*15 alleles where significantly more common in NF155+ AIN patients, compared to seronegative CIDP and healthy controls (with odds ratios of around 20) (Martinez-Martinez et al., 2017), and a later Japanese study also found this association in addition to a link with DRB1*06 alleles (Ogata et al., 2020). More recently, a similar, albeit weaker (odds ratio ~ 2.6), association has been found between DRB1*11 alleles and CNTN1+ AIN. In all cases the identified HLA haplotypes were neither necessary not sufficient to generate the associated autoantibody and disease, but appear to act as a risk factor which increases the likelihood of a specific autoimmune response and thus AIN developing. These associations support the concept that antigen presentation to T-helper cells, which is dependent on class II HLA, is an important part of the immunopathological process in AIN. In support of this, in silico studies identified specific antigen peptides that are likely to be bound with high-affinity by the corresponding HLA alleles.

4.4. Autoantibody induction: Analysis of autoreactive B cells

There have, to date, only been limited, direct studies of the autoreactive B cells involved in the generation of autoantibodies in these disorders. Rohrbacher and colleagues isolated peripheral blood mononuclear cells from patients with NF155, panNF, CNTN1 and Caspr1 antibody-associated AIN (Rohrbacher et al., 2024). These cells were then cultured in the presence or absence of specific cytokines (IL-2 and R848) designed to induce circulating, earlier lineage B cells to differentiate into antibody secreting cells (ASCs) / plasmablasts in vitro. These studies revealed several different patterns of autoantibody production, which partially correlated with the serological classification, and which implicate different underlying immunological mechanisms in different patients. In a small number of cases, autoantibody production from unstimulated cells could be detected, consistent with the presence of pre-existing autoreactive ASCs. In all patients with CNTN1 and Caspr1 antibodies, and in most with NF155 antibodies, autoantibody production could be detected following stimulation, but this was not the case in patients with panNF antibodies. These results suggest that autoreactive circulating B cells are present in CNNT1 and Caspr1 positive patients, and in most with NF155 antibodies. In patients with high titre serum NF155 antibodies but no evidence of in vitro production from PBMCs, the implication is that production is largely driven by bone-marrow resident, long-lived plasma cells, although this has not, as yet, been directly demonstrated. The distinctly different pattern in panNF patients matches the distinctly different IgG subclass profile of this group (IgG1/3 v IgG4 dominant). It is possible that in this group large numbers of plasmablasts are generated without a correspondingly large pool of autoreactive precursor B cells being present or generated, that the optimal stimulation conditions required to generate these specific ASCs are different, or that the antibodies produced by in vitro stimulation of precursor B cell are of lower affinity than with other antigens.

Our own single B-cell studies revealed that IgM NF155/NF186 reactive, largely unmutated, CD19 + CD27 + IgD- memory B cells are present, albeit at low frequency, in patients with panNF antibody-associated AIN, and that circulating NF-reactive IgM antibodies are frequently found in such patients (Bergstrom Johnson et al., 2024). The implications of these observations for the immunopathological mechanisms in such patients remains to be determined. However, they suggest the potential for early tolerance defects to produce a pool of lower-affinity autoreactive B cells, which, under certain circumstances, can be induced to mature into higher-affinity, class switched, ASCs.

5. Autoantibody effector functions and pathological mechanisms

In contrast, there has been more extensive investigation of the effector mechanisms of nodopathy-associated autoantibodies. These have involved in vitro, ex vivo and in vivo studies. In keeping with the underlying immunobiology, data suggest that IgG1/3 antibodies induce complement-dependent effects whilst non-inflammatory/non-complement mediated “blocking” processes are crucial to the pathogenic effects of IgG4 antibodies, and reveal a differential importance of bispecific, monovalent and monospecific, bivalent IgG4 in NF155 versus CNTN1 antibody mediated disease (Fig. 2) (Doppler et al., 2019; Appeltshauser et al., 2023; Jentzer et al., 2022; Manso et al., 2016; Taieb et al., 2023).

5.1. EAN and passive transfer models

The potential for NF155 antibodies to contribute to autoimmune neuropathies was initially demonstrated by studies injecting monoclonal NF155-antibodies into Lewis rats previously immunised with P2 peptide to induce experimental autoimmune neuritis (EAN). In this paradigm, NF155 antibodies enhanced the severity and duration of EAN, whereas they had no effect in naive rats without EAN (Ng et al., 2012). However, as these antibodies were IgG2a and IgM mouse monoclonals, the relevance to human disease dominated by IgG4 antibodies was unclear. Similarly, Jerome Devaux demonstrated that passive transfer of gliomedin IgG exacerbated P2-EAN, and that immunisation with gliomedin-Fc produced a biphasic, demyelinating motor neuropathy. However, gliomedin antibodies have not been consistently associated with human neuropathies, and immunisation with NF186-Fc did not produce neurological signs or neuropathology (Devaux, 2012). However, when CNTN1 antibodies were isolated from the plasmapheresis fluid of 2 patients, injection of the IgG1 and especially the IgG4 fraction exacerbated and prolonged P2-EAN (Manso et al., 2016). A later study similarly purified IgG4 NF155 antibodies from patients. These were injected either into neonatal rats, where they impaired paranodal formation, or chronically administered via and intrathecal catheter in adult rats, where they disrupted the CNTN1/Caspr1 paranodal complex, most prominently in the ventral nerve roots, and led to conduction abnormalities and paralysis (Manso et al., 2019).

5.2. Contrasting pathogenic mechanisms of NF155 versus CNTN1 antibodies

A range of further studies highlight clear differences between the pathogenic mechanisms associated with NF155 versus CNTN1 antibodies. Firstly, CNTN1 antibodies appear to bind their target antigen at the paranode, whereas NF155 antibodies bind their cognate antigen at the node and on the abaxonal Schwann cell membrane. (Hecker et al., 2023) Furthermore, whilst CNTN1 antibodies have a direct blocking effect on the interaction between the axolemmal CNTN1/Caspr1 complex and glial NF155, directly leading to paranodal dehiscence and destruction (Manso et al., 2016), NF155 antibodies appear to prevent the incorporation of NF155 into the paranodal complex, leading to a failure of paranodal maintenance (Manso et al., 2019) (Fig. 2B,C).

In both cases, sera from affected patients contain various ratios of monospecific/bivalent and bispecific/monovalent antibodies (Jentzer et al., 2022; Taieb et al., 2023). The former have presumably not undergone Fab arm exchange, or have exchanged with other IgG4 molecules with the same antigen specificity. However, in the case of NF155, it is the bivalent/monospecific IgG4 antibodies that are pathogenic and disrupt paranodal maintenance (Jentzer et al., 2022). In contrast, monospecific CNTN1 IgG4 is rarer in circulation, and it is the bispecifc/monovalent fraction which interrupts paranodal interactions (Taieb et al., 2023).

5.3. Complement-mediated effects

Away from IgG4, there is also evidence to suggest that IgG1 and/or IgG3 antibodies may induce complement-dependent pathogenic effects, at least in some patients or at certain stages of the disease process (Doppler et al., 2019; Appeltshauser et al., 2023).

This was initially demonstrated for CNTN1 antibodies, using serum

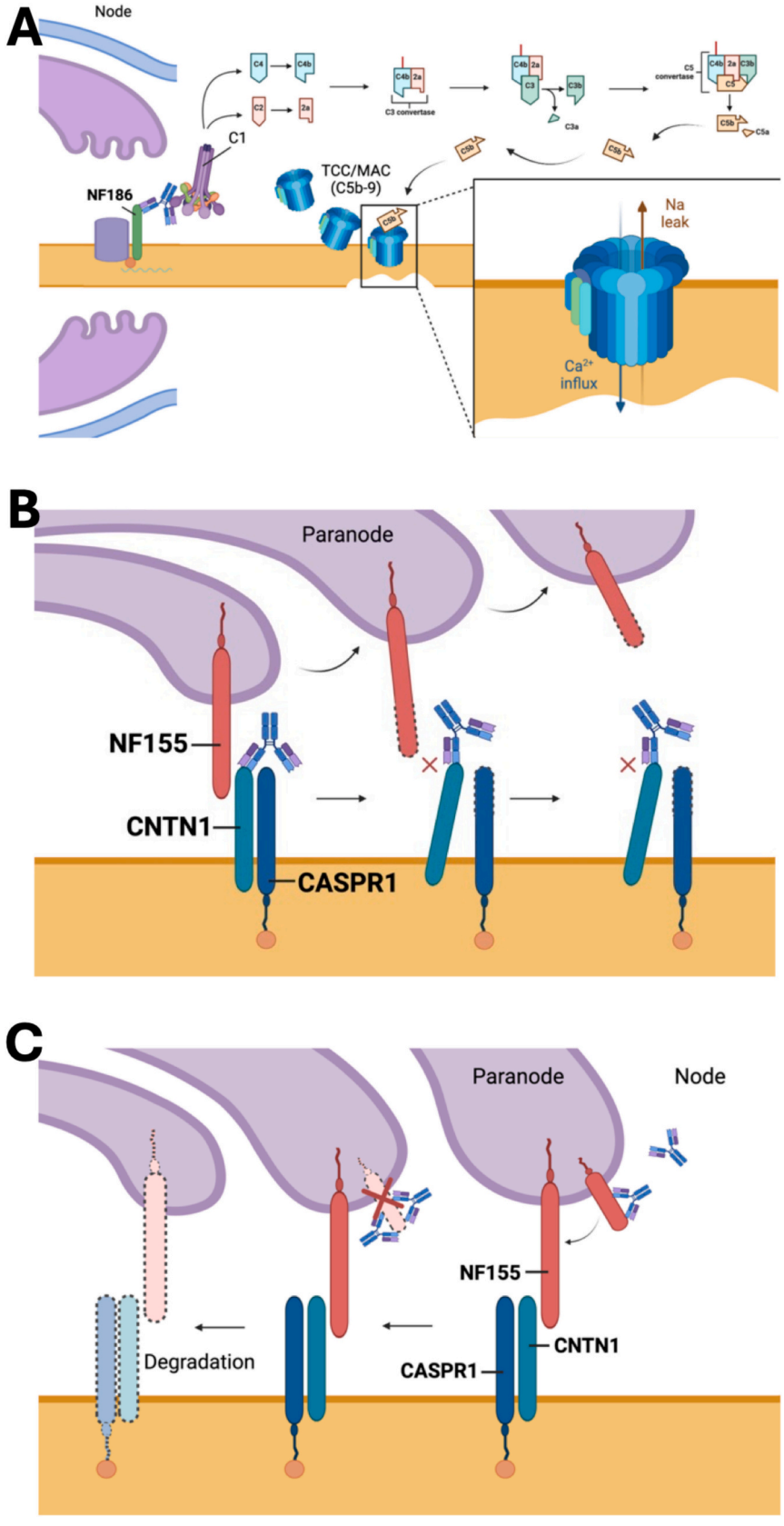

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Fig. 2. Pathogenic mechanism of nodal/paranodal antibodies.
(A) IgG1/3 subclass panNF antibodies likely target NF186 at the node where they are bound by C1q and activate the complement cascade, ultimately leading to formation of the terminal complement component (TCC) (previously known as the membrane attack complex, MAC) C5b-9. Inserted into the axolemma, this pore can act as a non-specific ion channel, causing reduced membrane resistance/current leak, leading to conduction block, and calcium influx, activating calcium dependent proteases and leading to axonal degeneration. (B) Monovalent / bispecific CNTN1 antibodies, created though the process of Fab arm exchange, bind to CNTN1 at the paranode, blocking interaction of the axonal CNTN1/Caspr complex with glial NF155, leading to paranodal dehiscence. (C) In contrast, bivalent / monospecific NF155 antibodies bind to their target antigen outside of the paranode, on the nodal/abaxonal Schwann cell membrane, and prevent integration into the paranodal complex, leading to its degradation.

collected from a patient during the acute phase of their disease, in which IgG3 dominated, and a patient with chronic disease, where the serum response was dominated by IgG4. Here, intraneural injection of the acute serum produced IgG3 paranodal binding, complement deposition and acute conduction block, with motor deficits, but without major structural changes to the node or evidence of axonal degeneration. Furthermore, conduction block could be reversed within a few days, paralleling the initial conception of nodo-paranodopathies in GBS associated with ganglioside antibodies (Fig. 2A). Such changes were rarely or not at all seen following injection of the chronic serum (Doppler et al., 2019).

In patients with panNF antibodies, the IgG1 or IgG3 subclasses are prominent and sometimes exclusively present (Fehmi et al., 2021; Stengel et al., 2019). Cell-based assays show that such antibodies, consistent with their canonical functions, are able to fix C1q, and in the presence of normal human serum as a source of complement, cause complement-dependent lysis of neurofascin-155 transfected HEK293 cells. Of note, this effect could be partially ameliorated by the presence of normal immunoglobulins (i.e. “intravenous” immunoglobulin (IVIg) used for the treatment of inflammatory neuropathies), which appeared to act by preventing complement activation rather than by inhibiting binding of antibody to antigen. Furthermore, in myelinating co-cultures, IgG3 antibodies in high-titre panNF sera bound to the node of Ranvier, disrupting the molecular architecture and leading to widening of the nodal gap, and causing a greater magnitude of disruption when compared to IgG4 NF155 antibodies. (Appeltshauser et al., 2023)

5.4. CNTN1-immune complexes and nephropathy

As further discussed below, one of the characteristic clinical features of AIN is their frequent co-occurrence with protein-losing nephropathy or nephrotic syndrome. Nephropathy is especially common in the presence of CNTN1 antibodies (Fehmi et al., 2023). Kidney biopsies from such patients typically show features in keeping with membranous nephropathy with IgG deposition around the glomerular basement membrane (Taieb et al., 2019). More detailed histological studies also revealed deposition of CNTN1 protein in glomeruli of affected patients, that was absent in controls, with ultrastructural evidence of immune-complex deposition below the glomerular basement membrane. Furthermore, patients with CNTN1-antibody-postive AIN were found to have much lower levels of serum CNTN1-protein than seronegative CIDP and healthy control subjects, but had evidence of circulating CNTN1-containing immune complexes during the acute phase of their illness (Fehmi et al., 2023). These changes can be seen to slowly reverse during remission, but typically lag months to years behind the fall in antibody titres (Fehmi et al., 2023). The implication is that the nephropathy is due to immune-complex deposition in the kidney, though whether these complexes form in the circulation or directly within the kidney remains to be determined.

6. Clinical features

6.1. Overview

The majority of patients ultimately diagnosed with an AIN are initially (mis)diagnosed as having GBS or CIDP. There are clearly overlapping clinical features, in particular a non-length-dependent, symmetrical, motor and sensory polyradiculoneuropathy.

The consistently reported ‘atypical’ features in AIN patients, such as aggressive onset and severe disease course, cranial neuropathies, tremor, pronounced sensory ataxia, respiratory and autonomic insufficiency, and little or no response to IVIg, provide increasing evidence that this group are phenotypically distinct. There are also differences at the group level in the relative frequencies of these features across the different serological subtypes (Fig. 3). Many of these features are also frequently observed in GBS patients, making them harder to clinically differentiate at the outset, than in CIDP patients, in whom these are rarely, if at all, present. It is essential to assess for each however, both to justify early antibody testing, and in order to select and initiate appropriate treatment; in the majority this is B-cell depleting treatment.

Typically AIN patients are male, in the 4th–6th decade of life, though paediatric patients can be affected. (Quinot et al., 2024; De Simoni et al., 2020; Harris et al., 2023) There seems to be a pattern emerging of associated syndromes, namely nephrotic syndrome, (Fehmi et al., 2021; Fehmi et al., 2023; Taieb et al., 2019; Miura et al., 2015; Delmont et al., 2020) paraproteinaemic or oncological associations. (Fehmi et al., 2021; Dubey et al., 2020)

6.2. Treatment response and outcome

A lack of treatment response to standard immunotherapies used in inflammatory neuropathies, in particular IVIg, seems to be a defining feature of AIN patients, though more variable response to plasma exchange (usually evident but transient) or steroids (occasionally inducing long-lasting remission) is seen. B-cell depletion therapy, (typically Rituximab and occasionally other anti-CD20 therapeutic monoclonal antibodies) on the other hand, has been repeatedly demonstrated to induce a good response, and often produces complete remission, both clinically and serologically (Querol et al., 2015; Liu et al., 2023a; Caballero-Ávila et al., 2025).

Published data on the longer-term outcome of AIN patients is still lacking, but in larger cohorts of NF155 patients (Shelly et al., 2021; Martín-Aguilar et al., 2022), at 3–5 years of follow up, the majority of those receiving Rituximab had good outcomes, though a significant proportion of patients relapsed. Morbidity and mortality (7.5–12 %), was variable but seemed more likely if effective treatment was delayed. This did not seem to be the case for panNF patients, who seem to make a remarkable recovery, even with many months between onset and Rituximab initiation (Appeltshauser et al., 2023), and in some cases apparently spontaneously.

6.3. Serological subtypes

There is some evidence that the specific serological subtype of AIN is relevant to the clinical phenotype, at least at the group level, and that this may also further influence treatment responses.

6.3.1. Pan-neurofascin

AIN patients with antibodies reactive to all neurofascin isoforms (155/186/140), termed ‘pan-neurofascin’ (panNF), present most dramatically, with a fulminant disease course characterised by quadriplegia, cranial neuropathies, and respiratory/autonomic insufficiency, requiring mechanical ventilation (Fehmi et al., 2021; Stengel et al., 2019). Nephrotic syndrome, initially detected more frequently in anti-

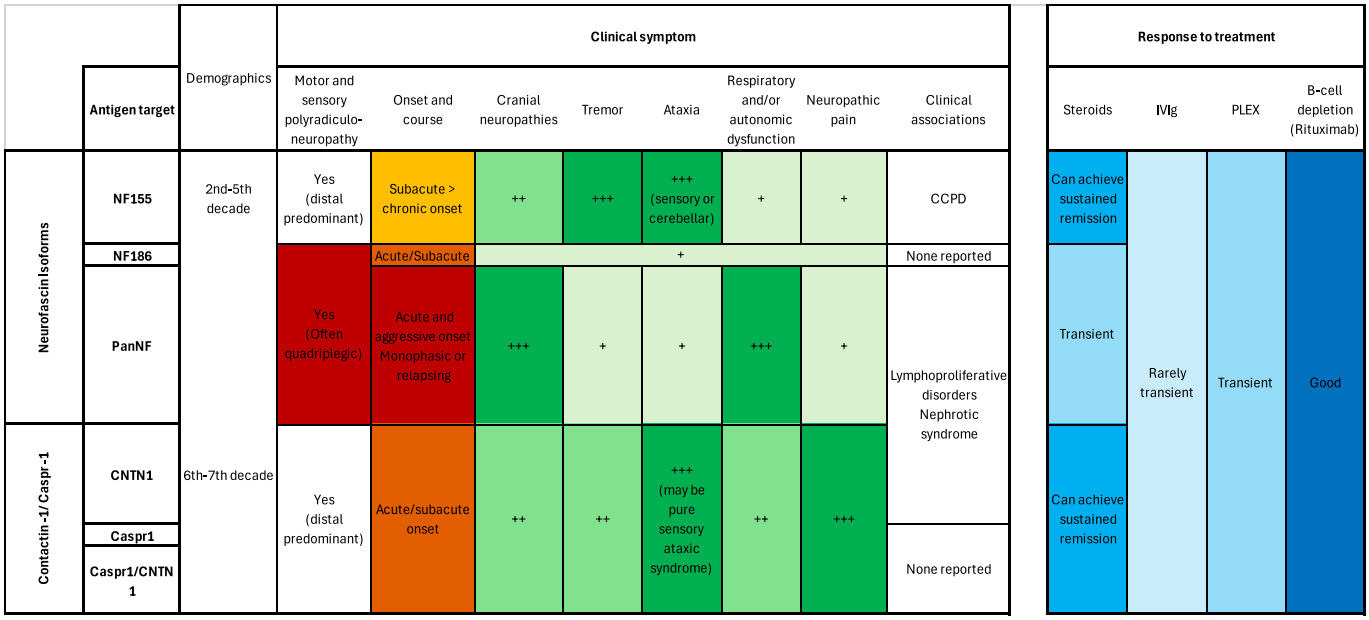

Fig. 3. Comparative clinical features and treatment responses of the serological subtypes of autoimmune nodopathies.
The overall frequency of reported clinical features is indicated as + (infrequent), ++ (frequent) and +++ (very frequent) for each AIN subtype. The most acute and aggressive onset neuropathies are highlighted in darker shades of orange/red, and better response to specific treatments in darker shades of blue.
Abbreviations: CCPD – Combined central and peripheral demyelination, IVIg – Intravenous Immunoglobulin, PLEX – Plasma exchange. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

CNTN1 positive patients, is now also increasingly recognised in panNF patients (Delmont et al., 2017; Fehmi et al., 2021). Despite having probably the highest early mortality, they can make a full and sustained recovery, mainly reported following B-cell depleting therapy (Fehmi et al., 2021; Appeltshauser et al., 2023).

6.3.2. *NF155*

Monospecific NF155 antibodies are the most frequently detected, and arguably represent a 'milder' form of AIN with relatively more insidious onset. Patients are most notably younger, clinically defined by a distal sensorimotor polyradiculoneuropathy, with ataxia and tremor (cerebellar or sensory ataxic) (Ng et al., 2012; Querol et al., 2014; Martín-Aguilar et al., 2022). There is also recognised involvement of the CNS in a small cohort of patients, with combined central and peripheral demyelination (CCPD). (Kawamura et al., 2013; Devaux et al., 2016)

6.3.3. *NF186*

Early studies reporting NF186 reactivity in AIN patients were not clearly monoreactive, so early clinical characterisation cannot be fully relied upon. More recently however, patients with NF186, but not NF155, reactive antibodies have emerged as mimicking NF155-AIN patients, including a minority with confirmed CNS involvement (Xie et al., 2021), but with a more acute onset and no tremor, resembling panNF patients (Delmont et al., 2017; Burnor et al., 2018; Liu et al., 2023b).

6.3.4. *CNTN1*

Anti-CNTN1 antibody positive AIN patients are reported to present at a slightly older age (6th–7th decade), with acute and aggressive-onset distal weakness and sensory ataxia, much like the original description by Querol in 2013 (Querol et al., 2013). Infrequently patients may present with a pure sensory ataxia (Dubey et al., 2020). Nephrotic syndrome has been found in at least half of patients (Fehmi et al., 2023; Taieb et al., 2019; Miura et al., 2015; Delmont et al., 2020). It is worth mentioning that steroids have, in earlier reports, been effective in treating anti-CNTN1-AIN patients (Miura et al., 2015), and even after follow up in a minority can demonstrate sustained remission (Caballero-Ávila et al., 2025).

6.3.5. *Caspr1 or CNTN1/Casp1 complex*

Patients with antibodies targeting anti-Caspr1 or the CNTN1/Caspr1 complex present similarly, possibly more likely to exhibit neuropathic pain, although this is based on small patient cohorts (Doppler et al., 2016; Pascual-Goñi et al., 2021; Delmont et al., 2020). Response to IVIg in this group may be more favourable in the context of early detection of IgG2 or 3 subclass antibodies (Appeltshauser et al., 2020).

7. Neurophysiology

Reported neurophysiological findings in AIN patients can be varied, in part due to the timing of the studies. They clearly, however, demonstrate surrogate markers of immune/antibody-mediated attack at the node (Uncini et al., 2013). Despite frequently exhibiting features typically associated with demyelination (conduction slowing and block, prolonged distal motor latencies, delayed F-waves), and commonly meeting the electrodiagnostic criteria for CIDP, there is no electrical evidence of de-remyelination (temporal dispersion of compound muscle action potentials) seen in the classical segmental demyelination which defines the most common inflammatory neuropathies.

Conduction block without temporal dispersion, otherwise known as 'axonal conduction block', can be seen to rapidly reverse (reversible conduction failure) on serial studies, thus avoiding the poor prognostic fate of axonal degeneration, from which any recovery will be much slower. Based upon earlier studies of the ganglioside antibodies in the axonal forms of GBS, this has long been understood to correlate with the pathological process of antibodies binding to and functionally disrupting the node and paranode ('nodo-paranodopathy') (Uncini et al., 2013; Kuwabara et al., 1998). Indeed, conduction block may be more common in AN than in CIDP, particularly at proximal sites (Niu et al., 2024).

Neurophysiology consistent with severe axonal degeneration can be seen in some cases weeks after initially appearing to be 'demyelinating' (Fehmi et al., 2021), and in others as an even earlier finding (Querol 2013, Pascual-Goni 2021) (Querol et al., 2013; Pascual-Goñi et al., 2021). This does not appear to prohibit clinical recovery however. (Liu

et al., 2023a) Taken together with the fact that neurophysiological findings do not always correlate with histological findings in the same patients (Doppler et al., 2016; Koike et al., 2017) this should discourage reliance on electrophysiology as a marker of poor prognosis, particularly early in the disease course.

8. Pathological and imaging features

When examined using standard histopathological techniques, nerve biopsies from patients with autoimmune tend to show non-specific findings of axonal dropout and little to nothing in the way of inflammation (Fehmi et al., 2021). However, skin biopsies from patients with autoimmune nodopathies have been demonstrated to show lengthening of the node and loss of paranodal NF155/Caspr1 staining (Cortese et al., 2020), consistent with nodal disruption, that is not seen in biopsies of patients with seronegative CIDP or in controls. Similarly, ultrastructural studies in AIN patients reveal dehiscence of the paranodal myelin loops from the underlying axolemma, and the absence of macrophage mediated stripping of internodal myelin which characterises CIDP (Koike et al., 2017).

The imaging features of AIN may also be different from CIDP, at least at the group level. The cross-sectional areas of proximal nerve roots and trunks of the brachial plexus are increased in patients autoimmune nodopathies, even when compared to CIDP, where values are themselves greater than in healthy controls (Niu et al., 2024). Similarly, nerve root enlargement or enhancement as detected by MRI appears to be more frequent in autoimmune nodopathies compared to CIDP (Liu et al., 2023b), and more frequent still in paediatric patients and with Caspr1 or CNTN1/Caspr1 complex antibodies (Doppler et al., 2016; Pascual-Goñi et al., 2021; De Simoni et al., 2020; Harris et al., 2023).

9. Outlook

The autoimmune nodopathies have emerged as clinically, pathologically and immunologically distinct forms of inflammatory neuropathy. It is likely that other nodal and extra-nodal antigens will also emerge as putative targets for autoantibodies in other patients in future. Indeed, recently antibodies against the juxtaparanodal molecule LGI4 were reported in a small number of patients meeting diagnostic criteria for CIDP. (Zhang et al., 2023) However, these findings remain to be more widely verified and the putative clinical associations confirmed.

Greater understanding of the pathological effector mechanisms should lead to more rapidly effective and targeted therapies. Similarly, greater knowledge of the underlying immunology should inform strategies to induce and maintain remission without the need for broad, non-specific and long-lasting immunosuppression.

CRediT authorship contribution statement

Claire Bergstrom Johnson: Writing – review & editing. **Janev Fehmi:** Writing – review & editing, Writing – original draft. **Simon Rinaldi:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Data availability

No data was used for the research described in the article.

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