PERIPHERAL NEUROPATHIES

Autoantibodies in chronic inflammatory neuropathies: diagnostic and therapeutic implications

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Abstract | The chronic inflammatory neuropathies (CINs) are rare, very disabling autoimmune disorders that generally respond well to immune therapies such as intravenous immunoglobulin (IVIg). The most common forms of CIN are chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy, and polyneuropathy associated with monoclonal gammopathy of unknown significance. The field of CIN has undergone a major advance with the identification of IgG4 autoantibodies directed against paranodal proteins in patients with CIDP. Although these autoantibodies are only found in a small subset of patients with CIDP, they can be used to guide therapeutic decision-making, as these patients have a poor response to IVIg. These observations provide proof of concept that identifying the target antigens in tissue-specific antibody-mediated autoimmune diseases is important, not only to understand their underlying pathogenic mechanisms, but also to correctly diagnose and treat affected patients. This state-of-the-art Review focuses on the role of autoantibodies against nodes of Ranvier in CIDP, a clinically relevant emerging field of research. The role of autoantibodies in other immune-mediated neuropathies, including other forms of CIN, primary autoimmune neuropathies, neoplasms, and systemic diseases that resemble CIN, are also discussed.

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The chronic inflammatory neuropathies (CINs) represent a clinically heterogeneous group of rare and disabling diseases characterized by motor and sensory symptoms of diverse severity[1,2]. Most CINs are diagnosed using clinical and electrophysiological criteria alone, except for polyneuropathy associated with monoclonal gammopathy of uncertain significance (MGUS-P), which also requires detection of an IgM monoclonal gammopathy[3–5]. Specific biomarkers are considered to be only supportive of the diagnosis. The diagnostic criteria for multifocal motor neuropathy (MMN) are restrictive and specific, and this disease is accordingly homogeneous in terms of its clinical presentation and treatment[4]. By contrast, the diagnostic criteria for chronic inflammatory polyradiculoneuropathy (CIDP) are sufficiently broad to include all patients who could benefit from immunomodulatory treatment[3]. This situation results in CIDP being a very heterogeneous disorder, in which typical (sensorimotor, symmetrical, predominantly proximal weakness) and atypical (predominantly distal weakness, focal presentations, pure sensory, pure motor and pure ataxic) variants are accepted to lie within the CIDP spectrum[1]. Moreover, some CIDP subtypes exhibit differences in disease progression (relapsing or progressive), associated clinical features (cranial involvement), concomitant disease (diabetes mellitus[6]) and paraclinical features (IgG or IgA monoclonal gammopathy) that further broaden the spectrum of this heterogeneous disease[7]. This complexity, and the inappropriate use of diagnostic criteria, has led to misdiagnosis of CIDP[8], thereby impeding the discovery of common pathophysiological pathways[9] and disease-specific biomarkers[10].

CIDP[9], MMN[11], and MGUS-P[12] (the latter with or without antibodies targeting myelin-associated glycoprotein (MAG)) together comprise an important subgroup of CINs that share an immune-mediated pathogenesis exclusively involving peripheral nerves[13]. The differential diagnosis includes non-CIN chronic immune-mediated neuropathies, such as vasculitic neuropathy, neuropathies associated with systemic diseases or paraneoplastic neuropathies, in which immune responses are not primarily directed against peripheral nerve components and other organs might be involved. These disorders are often difficult to differentiate from classic CIN[8].

The existence of pathological[14] and radiological[15,16] evidence of inflammation in nerves and nerve roots, the pathogenetic role of immune cells and, above all, the favourable response to immune therapies, support an

Key points

- Discovery of the antigenic targets associated with nerve-specific autoimmune diseases is a crucial step in understanding their pathogenesis
- The identification of highly disease-specific autoantibodies in patients with inflammatory neuropathies has considerable clinical utility, even when the proportion of antibody-positive patients is low
- IgG4 antibodies against contactin-1 and neurofascin splice variant 155 characterize a subtype of chronic inflammatory demyelinating polyradiculoneuropathy with distinct clinical features, including poor response to intravenous immunoglobulin
- Autoantibodies linked to multifocal motor neuropathy, polyneuropathy associated with monoclonal gammopathy of unknown significance and paraneoplastic peripheral nerve disorders provide important clinical information and their presence should be investigated in all patients with inflammatory neuropathies

immune-mediated pathogenesis for CIN[9]. The good responses to intravenous immunoglobulin (IVIg)[17] and plasma exchange[18] observed in most patients with CIN suggests a pathogenetic contribution of humoral factors, including autoantibodies[19]. The discovery of disease-specific autoantibodies would not only provide pathophysiological clues to deepen our understanding of CIN but also, more importantly, would provide biomarkers that can be useful for diagnosis, prognostication and appropriate selection of therapy. The search for autoantibodies has been partially successful in MGUS-P (anti-MAG)[20,21] and MMN[22] (anti-GM1 ganglioside), in which the target antigens are now known in 50% of patients[11,12,23]. However, despite intense efforts to discover disease-specific autoantibodies linked to CIDP, the target antigens in most patients with this condition remain unknown. IgG4 autoantibodies that target node of Ranvier proteins were only recently (since 2013) discovered in subsets of patients with CIDP[24–26].

In this state-of-the-art Review[27] we focus on the emerging evidence that specific autoantibodies are associated with particular types of CIDP. These advances provide proof of concept that antibodies can be used clinically to guide the diagnosis and management of CIDP, the paradigmatic CIN. In this context, we also describe what is known about specific autoantibodies associated with other CINs, with a particular focus on the clinical and pathogenic relevance of antibodies that target node of Ranvier structures, before considering how the principles learned from these conditions could be applied to other immune-mediated neuropathies. Of note, the term 'poor response to IVIg', as applied to seropositive patients with CIDP throughout this Review, should be construed as a reduced response rate or a suboptimal level of response relative to that obtained in patients with typical seronegative CIDP — and not as a complete absence of response in all patients. Furthermore, other therapies (such as steroids) can still provide very good and long-lasting responses in these individuals.

Autoantibodies in CIDP

The search for autoantibodies associated with CIDP dates from the early 1980s[28,29]. The excellent and fast response to IVIg or plasma exchange experienced by most patients with CIDP supported the hypothesis that CIDP is an antibody-mediated disease[19]. Further lines of evidence included the presence of immunoglobulin and complement deposits in sural nerve biopsy samples from patients with CIDP[30]; the association between polymorphisms in low affinity IgG Fc region receptor IIb (FcγRIIb, the inhibitory immunoglobulin receptor) and low levels of this receptor on the B-cell surface in such patients[31]; and the development of nerve demyelination in rats that were given IgG from patients with CIDP[32]. Despite this clinical and experimental evidence of a role for autoantibodies in the pathogenesis of CIDP, solid evidence of their existence has been found only in the past 5 years with the description of antibodies to nodal and paranodal antigens[33,34].

The node of Ranvier in CIDP

Nodes of Ranvier are critical structures for saltatory conduction of nerve impulses in myelinated nerve fibres[35]. Myelinated fibres are architecturally, molecularly and functionally complex structures consisting of four compartments — the node, paranode, juxtaparanode and internode — identified according to their molecular composition and function (FIG. 1). The paranodal regions immediately flank the nodes of Ranvier and are the sites where myelin sheath borders (paranodal loops) closely contact the axon via septate-like junctions (specialized adhesive junctions, also termed transverse bands)[36]. To date, three cell adhesion molecules are known to be involved in the formation of septate-like junctions: contactin-1 (CNTN1), contactin-associated protein-1 (CASPR1), and neurofascin splice variant 155 (NF155). CNTN1 and CASPR1 are expressed by neurons and form a complex that binds to NF155 (their glial counterpart) at the paranodal loops (FIG. 1). This complex enables compartmentalization of voltage-gated sodium channels (Nav1.6) at the nodes and voltage-gated potassium channels (Kv1.1/1.2/1.4/1.6) at the juxtaparanodes[37–40].

Given their importance for nerve conduction, nodes and paranodes are likely to be sites of pathology in CINs and related disorders[41]. Structural abnormalities and IgG deposition in nodes of Ranvier were described in early studies of patients with motor variants of Guillain–Barré syndrome (GBS)[42]. However, the identification of node of Ranvier pathology in CIDP is comparatively recent. In 2011, a study that compared node of Ranvier alterations in patients with CIDP and patients with idiopathic axonal neuropathies found node disruption and irregular or decreased expression of CASPR1 in patients with CIDP[43]. Elongated nodes, shortened internodes and irregular CASPR1 staining were also detected in myelinated fibres from skin biopsy samples from patients with CIDP[44]. In agreement with these observations, disruption of neurofascin splice variant 186 (NF186) and gliomedin (two other node of Ranvier proteins) preceded demyelination in animals with experimental allergic neuritis (EAN), a model of inflammatory neuropathies such as CIDP and GBS[45].

Antibodies against paranodal antigens

The earliest reports suggesting the presence of antibodies against node of Ranvier structures in patients with CINs were published in 2011, in two articles describing

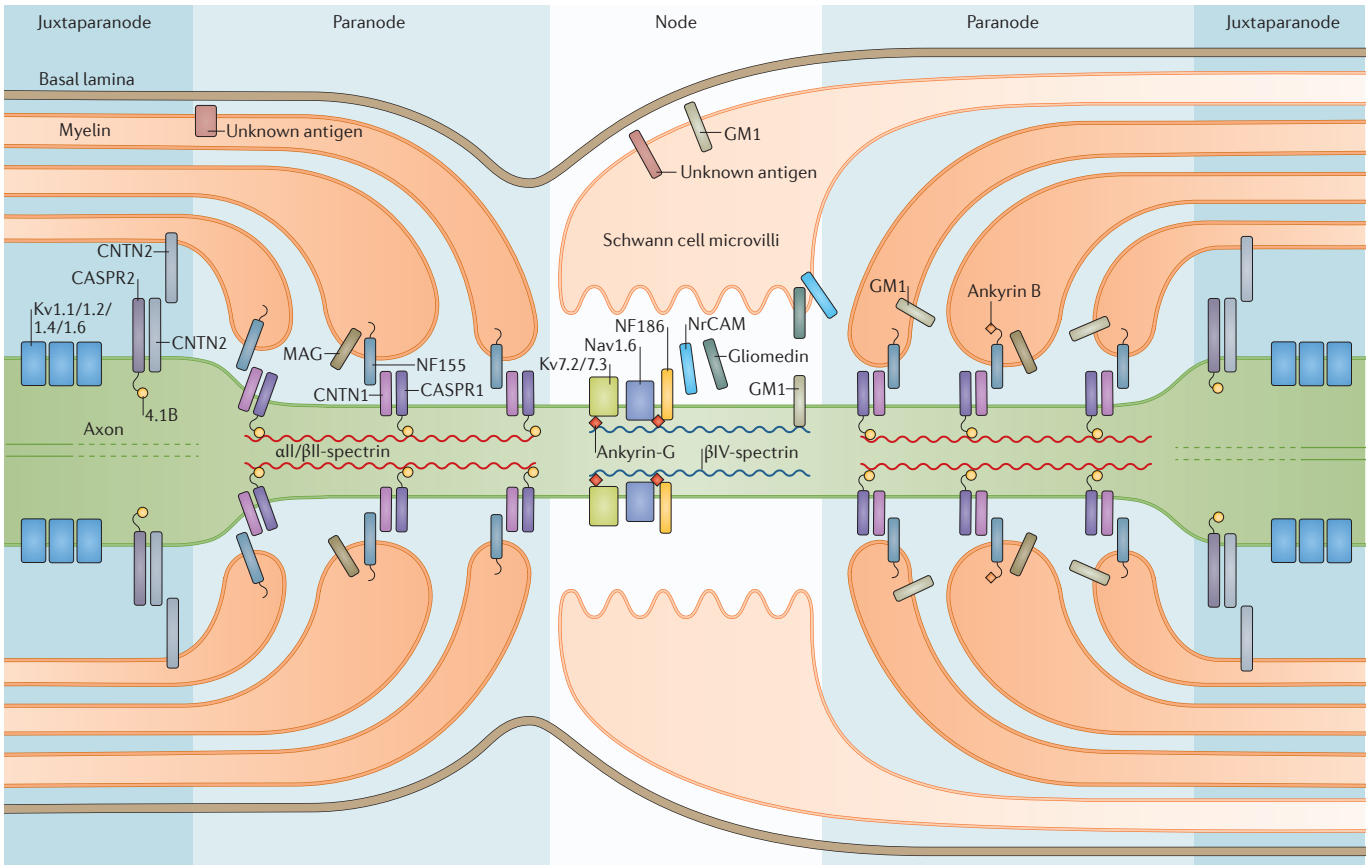

Figure 1 | **The node of Ranvier.** The figure shows the structure and key molecular components of the node of Ranvier, including those targeted by autoantibodies in autoimmune neuropathies. Adhesion molecules (NF186, NF155, NrCAM, CNTN1, CNTN2, CASPR1, CASPR2 and MAG) mediate axoglial attachment. Ion channels (Kv7.2/7.3, Kv1.1/1.2/1.4/1.6 and Nav1.6) mediate action potential propagation. Adhesion molecules and ion channels are all linked to the cytoskeleton by proteins, including ankyrins and spectrins. Gliomedin is an extracellular matrix constituent that stabilizes the structure of the nodal area. CASPR, contactin-associated protein; CNTN, contactin; Kv, voltage-gated potassium channel; MAG, myelin-associated glycoprotein; Nav, voltage-gated sodium channel; NF, neurofascin; NrCAM, neuronal cell adhesion molecule. Adapted with permission from Springer Nature © Stathopoulos, P., Alexopoulos, H. & Dalakas, M.C. Autoimmune antigenic targets at the node of Ranvier in demyelinating disorders. *Nat. Rev. Neurol.* **11**, 143–156 (2015).

increased titres of anti-neurofascin antibodies in patients with GBS and CIDP[46,47]. In 2012, our group found that up to one-third of patients with either GBS or CIDP showed evidence of IgG reactivity against node of Ranvier structures in teased nerve fibre preparations from mice[33]. The IgG staining patterns were diverse, with nodal and/or paranodal staining observed with sera from different patients[33]. We used a candidate-molecule approach, which revealed that the target antigens were also diverse, with antibodies reacting against CNTN1, gliomedin or NF186[33]. These results indicated that nodal and paranodal proteins can be the targets of autoimmune attack in CIDP, and that target antigens in patients with CIDP might be multiple and heterogeneous; however, no clear clinical conclusion could be drawn from these preliminary findings. Subsequently, electrophysiological patterns that did not fit within the traditional 'axonal versus demyelinating' paradigm were detected in patients with inflammatory neuropathies; since the patterns suggested node of Ranvier involvement, these neuropathies were called nodopathies or paranodopathies[48,49]. This pathological, electrophysiological and serological evidence laid the foundations for future studies focusing on the importance of the nodes of Ranvier as important sites for CIDP pathology and attempting to correlate clinical observations with immunological data.

Anti-CNTN1 antibodies. Our group used an unbiased proteomic approach to investigate the presence of antibodies against surface antigens on hippocampal neurons in a small subset of Spanish patients with CIDP (four of 46 patients)[24]. In one of these patients, the target antigen still remains unidentified, but the target antigen in the other three patients was identified as CNTN1 (two patients) or the CNTN1–CASPR1 complex (one patient). These three patients shared an aggressive disease phenotype with acute onset, predominantly motor involvement, older age at onset, evidence of denervation at first electromyography (EMG) and, importantly, a poor response to IVIg. This study was the first to report a clear association between specific autoantibodies and disease features in patients with CIDP. In a

Box 1 | **IgG4 antibodies in autoimmune disease**

A growing number of autoimmune diseases are now known to be mediated by IgG4 autoantibodies[54]. These autoantibodies are produced by regulatory B (B_{reg}) cells[139] and were originally considered to be immunomodulatory[140], as they cannot efficiently fix complement or bind to immunoglobulin receptors[141]. IgG4 antibodies are the last isotype to appear after affinity maturation[142]. They have the highest antigen affinity and show restricted oligoclonal expansions and epitope repertoires[142,143]. In the allergy setting they dampen inflammatory responses and tolerize individuals to allergens after repeated challenge; their levels correlate with allergen tolerance[144]. IgG4 antibodies have been studied in only a few non-allergic diseases: pemphigus; muscle-specific tyrosine kinase (MuSK)-related myasthenia gravis; and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) associated with antibodies to contactin-1 (CNTN1). In these settings, IgG4 antibodies disrupt the function of their target antigens without involving other effector mechanisms[55,145,146].

Another common feature of IgG4-mediated diseases is their positive response to B-cell depletion. In patients with CIDP, only case reports have been published[26,53,70,74], but B-cell depletion has proven effective in pemphigus[71], anti-phospholipase A2 receptor nephropathy[73] and MuSK-related myasthenia gravis[72], despite their very different target tissues. Responses to B-cell depletion are attenuated in patients with neuropathies who already have permanent nerve damage, but the scarce evidence available suggests that this treatment is effective in early disease. Thus, B-cell-depleting therapies can be used in patients with neuropathies who carry anti-CNTN1, anti-contactin-associated protein-1 or anti-neurofascin splice variant 155 antibodies and have not responded to conventional treatment. Our group and others have described poor responses to intravenous immunoglobulin (IVIg) in these diseases[24,25,52], although the underlying mechanisms remain unknown. The inhibitory immunoglobulin receptor low affinity IgG Fc region receptor IIb (FcγRIIB) is a major mediator of IVIg response[147]. Gene expression profiling suggests that IL-10$^+$ B_{reg} cells have reduced expression of FcγRIIB compared with IL-10$^-$ B_{reg} cells[139]. This difference could partly explain IVIg resistance, but other mechanisms or confounding factors might also contribute.

follow-up study, our group showed that the anti-CNTN1 antibodies were predominantly IgG4, an isotype that does not efficiently activate complement or inflammatory cells efficiently[50]. This finding might account for these patients' poor responses to IVIg[51] (BOX 1).

A replication study in more than 500 Japanese patients with CIDP confirmed the presence of anti-CNTN1 IgG4 antibodies in a small subset of patients[52]. The clinical presentation of these patients differed slightly from those we initially characterized, but all patients had IgG4 autoantibodies and poor responses to IVIg. These findings were further confirmed in a study of German patients with CIDP[53]. Interestingly, the paranode destruction observed in myelinated fibres from skin biopsies of patients with anti-CNTN1-positive CIDP identified in the German study suggested the pathogenic potential of these antibodies.

IgG4 antibodies are presumed to have anti-inflammatory functions, but have been implicated in the pathogenesis of several neurological syndromes[54]. In an exploratory study, using an *in vitro* myelinating model, our group found that anti-CNTN1 IgG4 antibodies disrupt binding of the CNTN1–CASPR1 complex to NF155, and thus to the paranodal structure, in the absence of complement[50]. These data suggested that anti-CNTN1 antibodies cause disease by dismantling the paranodal axoglial junction. Experiments in which anti-CNTN1 IgG4 antibodies were passively transferred to naive animals and into animals with EAN further confirmed their pathogenicity[55]. First, intraneural injections of anti-CNTN1 IgG4 indicated that these autoantibodies bind to and progressively invade paranodes *in vivo*, thereby disrupting paranodal axoglial junctions (FIG. 2). These effects were both antigen-specific and isotype-specific, as IgG1 or IgG4 reacting against other antigens (sham proteins or CASPR2) could not penetrate the paranodes. Second, the chronic infusion of IgG4 anti-CNTN1 antibodies induced a definite worsening of clinical status in animals with EAN, which was accompanied by nerve conduction defects consistent with those in the early acute phase in patients with CIDP. Last, a sural nerve biopsy sample from a patient with anti-CNTN1 antibodies showed transverse band loss and paranodal loop detachment, with morphological features supporting the progressive invasion of paranodes by anti-CNTN1 antibodies[56]. Similar findings are seen in animals after passive transfer of anti-CNTN1 antibodies[55], strongly suggesting that IgG4 anti-CNTN1 antibodies are themselves pathogenic without the need to involve inflammatory cells or complement (FIG. 2). These findings agree with those in *Cntn1* knockout or *Cntnap1* knockout mice, which both show loss of paranodal septate-like junctions and substantial slowing of nerve conduction[37,40].

Anti-NF155 antibodies. The first study reporting an immune reaction against neurofascin indicated that patients with GBS or CIDP have higher titres of antibodies against neurofascin than do healthy controls[46,47]. However, the exact neurofascin isoform was not specified in this study, and the clinical implications of these antibodies were not defined. A report published in 2012 found high titres of anti-NF155 antibodies in <3% of patients with CIDP[57]. Interestingly, in the two patients with the highest anti-NF155 titres, the antibody isotype was IgG4. Specific clinical features associated with these antibodies were not described in this initial report.

We tested patients from our Spanish cohort for IgG4 anti-NF155 antibodies, and found two antibody-positive patients with CIDP. These patients shared several clinical characteristics: predominant distal weaknesses, high-amplitude and low-frequency tremor, ataxia with cerebellar features, demyelinating features on EMG, and poor responses to IVIg[25]. We found that anti-NF155 IgG4 antibodies from these patients bound to the cerebellum — in particular, to cerebellar neurons — accounting for the action tremor and ataxia. We then tested eight additional IVIg-resistant patients with CIDP from other centres in Spain for the presence of anti-NF155 antibodies, and found an additional two patients with IgG4 anti-NF155 antibodies. These patients had similar clinical features to those from our own cohort.

The clinical–immunological association between this subtype of CIDP and IgG4 anti-NF155 antibodies was further confirmed in several independent cohorts. One of these studies showed that IgG from patients with CIDP possessed reactivity towards paranodes and myelinating glial cells *in vitro* (FIGS. 3,4), and was able to immunoprecipitate NF155 (REF. 58). In this large cohort study, anti-NF155 IgG4 antibodies were specifically detected in 38 patients with CIDP (7% of all patients with CIDP), and were not found in patients with GBS or multiple sclerosis. These 38 patients had a younger age at

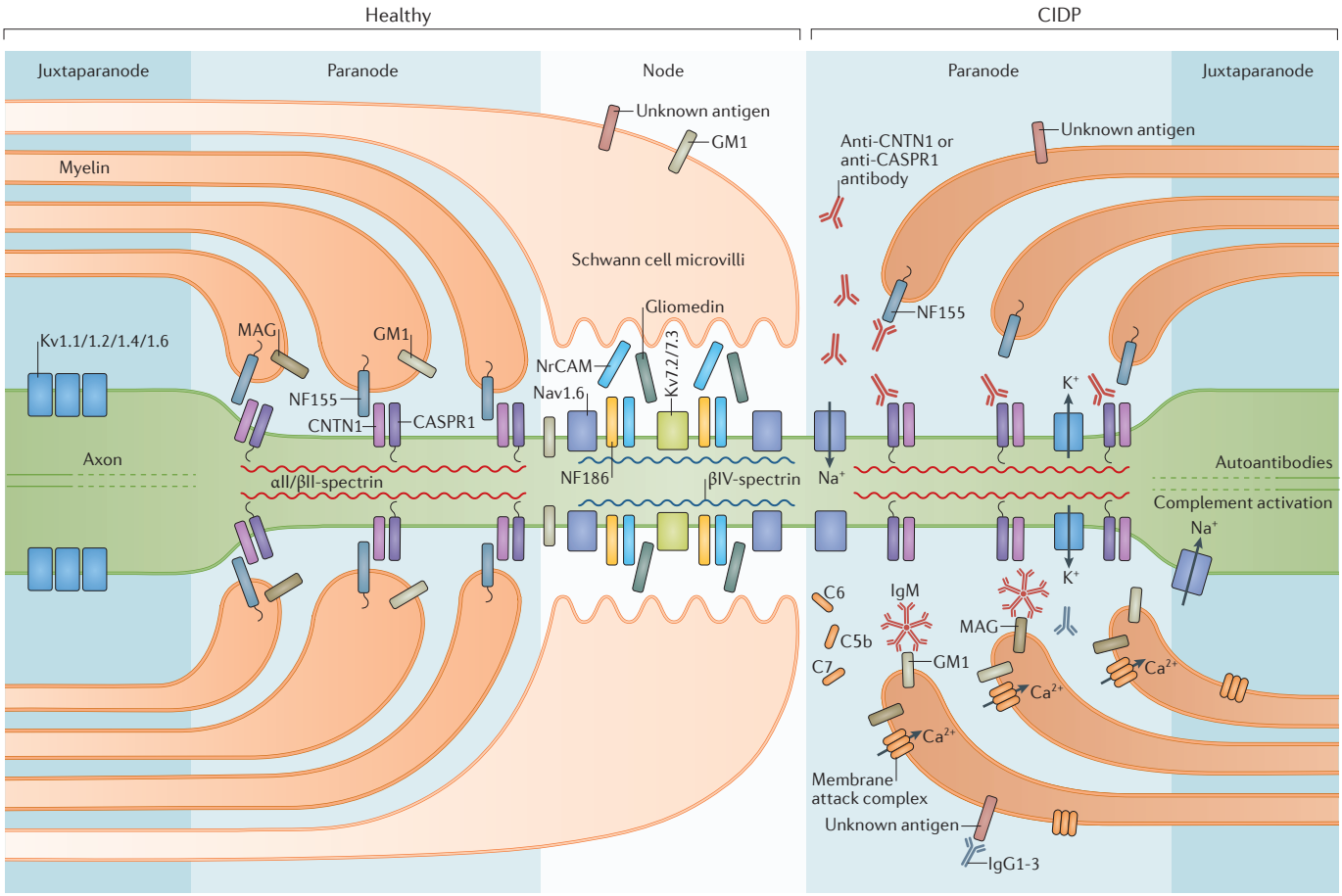

Figure 2 | **Pathogenic mechanisms involving antibodies associated with autoimmune neuropathies.** In chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), IgG4 autoantibodies that bind to contactin-1 (CNTN1) at the paranode disrupt the CNTN1–contactin-associated protein 1 (CASPR1)–neurofascin splice variant 155 (NF155) complex, and break the septate-like junctions and the axoglial junction. Although still not confirmed, indirect data (nerve biopsy studies) suggest that anti-NF155 antibodies have similar effects. IgM autoantibodies that bind to GM1 (monosialotetrahexosylganglioside) disrupt node of Ranvier function by activating complement, leading to formation of membrane attack complexes and, eventually, to axonal degeneration. Antibodies that target myelin-associated glycoprotein (MAG) are not well defined but induce separation of myelin layers in nerve biopsy tissue through an as-yet uncharacterized mechanism. NrCAM, neuronal cell adhesion molecule. Adapted with permission from Elsevier © Lim, J. P., Devaux, J. & Yuki, N. Peripheral nerve proteins as potential autoantigens in acute and chronic inflammatory demyelinating polyneuropathies. *Autoimmun. Rev.* **13**, 1070–1078 (2014).

onset of CIDP and a higher prevalence of ataxia, tremor or poor response to IVIg compared with seronegative patients. Two other reports found similar clinical features associated with anti-NF155 antibodies[59,60]. One of these reports described enlarged nerve roots and proximal nerve segments in MRI scans of the cervical and lumbosacral nerves of IgG4 anti-NF155-positive patients with CIDP, compared with seronegative patients[59].

Despite the presence of prominent tremor and ataxia with cerebellar features, the majority of anti-NF155-positive patients do not show abnormalities on brain MRI. These findings contradict a previous report suggesting that the presence of anti-NF155 antibodies was associated with combined central and peripheral demyelination (CCPD)[61]. A study in an independent cohort of patients with CCPD failed to detect anti-NF155 antibodies[62]. The features of patients with CCPD, along with their ethnic backgrounds and the antibody-detection techniques used, all differed substantially between the studies. Nonetheless, the available evidence supports the conclusion that the presence of anti-NF155 IgG4 has implications for the selection of treatment and defines a subset of patients with CIDP who share specific clinical features.

Some evidence indicates that anti-NF155 antibodies are pathogenic. The passive transfer of anti-neurofascin monoclonal antibodies (which recognized all neurofascin isoforms) into mice with EAN strongly exacerbated the severity of the pathology[63]. No studies have yet demonstrated that patient-derived anti-NF155 IgG4 antibodies are pathogenic; however, the few nerve biopsy samples obtained from patients with CIDP and anti-NF155 antibodies include features that differ from classic CIDP and are related to the nature and histological location of the antigen[56,59,64]. Sural nerve biopsy samples from patients with CIDP and IgG4 anti-NF155 antibodies show paranodal demyelination

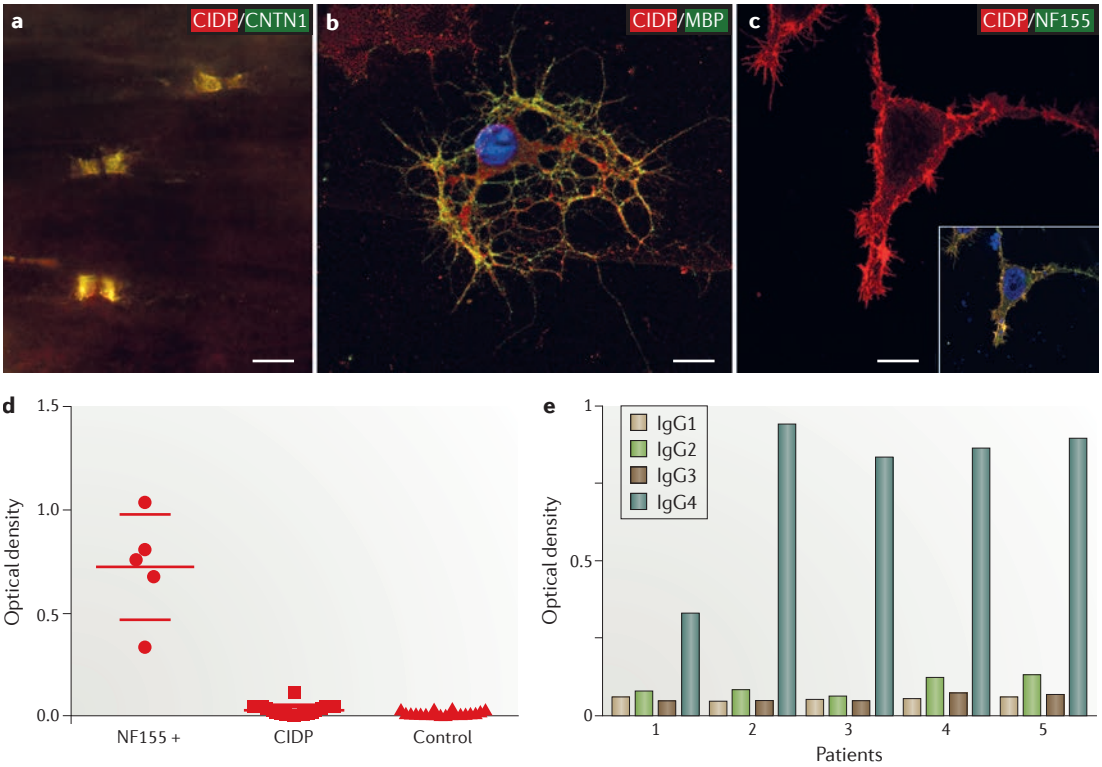

Figure 3 | **Immunological findings in patients with CIDP and anti-NF155 antibodies. a** | Serum from a patient with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) contains autoantibodies that target neurofascin splice variant 155 (NF155, red fluorescence), which co-localize at the paranode with a commercially available antibody targeting contactin-1 (CNTN1, green fluorescence). The merging of both fluorescent signals appears as yellow staining at the paranodes in teased nerve fibres, suggesting perfect co-localization of red (serum antibody) and green (commercial antibody). **a**–**c** | Cell nuclei are indicated by staining with 4',6-diamidino-2-phenylindole (DAPI; blue fluorescence). **b** | NF155 is expressed by myelinating oligodendrocytes *in vitro*. Serum from a patient with CIDP contains anti-NF155 autoantibodies (red fluorescence), which bind to oligodendrocytes expressing myelination markers such as myelin basic protein (MBP, green fluorescence). **c** | Transfection of an expression vector encoding human NF155 protein has become the gold standard for anti-NF155 detection. Main image: anti-NF155 antibodies (red fluorescence) from a patient with CIDP bind to the surface of NF155-transfected human embryonic kidney (HEK)293 cells. Inset image: patient-derived anti-NF155 autoantibodies (red fluorescence) co-localize with a commercially available anti-NF155 antibody (green fluorescence). Merger of both stains appears as a yellow signal. **d** | Enzyme-linked immunosorbent assay (ELISA) using human recombinant NF155 protein is a highly specific test to confirm anti-NF155 positivity in patients with CIDP. Only sera from anti-NF155^{+} patients will react with the recombinant NF155 protein; thus, optical density is close to zero in anti-NF155^{-} patients with CIDP as well as in healthy controls (of note, using other versions of NF155 protein (rat-derived, or fusion proteins) in such tests can lead to nonspecific binding and false positives). **e** | Finally, in patients with anti-NF155 antibodies, IgG isotype determination is achieved by ELISA. All patients tested had minor amounts of other IgG isotypes but IgG4 is clearly the predominant anti-NF155 isotype in these patients. All scale bars 10 μm; optical density, a measure of the intensity of the ELISA colorimetric reaction.

in the absence of inflammation[56,59]. A report published in 2016 described electron microscopy findings in sural nerve biopsy samples from two patients, showing loss of septate-like junctions and interposition of cellular processes between the paranodal loops and the axolemma[64] (FIG. 3). These alterations are reminiscent of those found in *Nfasc*-null mice[65] and in patients with mutations in *CNTNAP1* (the gene encoding CASPR1), suggesting that anti-NF155 antibodies might specifically disrupt the NF155–CNTN1–CASPR1 complex at paranodes.

Anti-CASPR1 antibodies. Compelling evidence for the presence of anti-CASPR1 antibodies has been reported in two patients with inflammatory neuropathies, one classified as having CIDP, the other as having GBS[26]. Serum from both patients contained antibodies that bound to paranodes in teased nerve fibre preparations but was negative for antibodies against CNTN1 or NF155. Several techniques confirmed the presence of anti-CASPR1 antibody reactivity, and an analysis of myelinated fibres in skin biopsy samples from both patients showed paranodal disruption. A sural nerve biopsy sample was available from one of the patients, which showed human IgG deposition at the paranode. Both patients also had intense neuropathic pain. Whether this pain was related to the presence of anti-CASPR1 antibodies needs further confirmation but, interestingly, the IgG in these patients

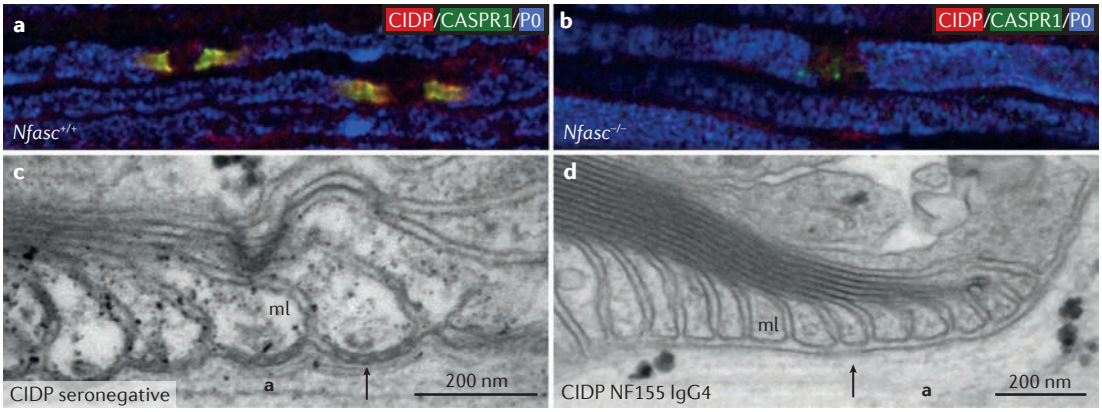

Figure 4 | **Features of CIDP associated with autoantibodies that target NF155. a,b** | The reactivity to paranodal antigens (seen here as a yellow signal resulting from the merger of red and green fluoresence) of serum from patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and anti-NF155 antibodies (red fluorescence) is lost in nerve preparations from neurofascin-null mice (part **b**) compared with those from wild-type mice (part **a**). Green fluorescence, CASPR1; blue fluorescence, P0 (myelin protein zero). **c,d** | Septate-like junctions, which link the Schwann cell paranodal loops to the axon, can be seen on sural nerve biopsy samples from seronegative patients with CIDP (part **c**) but are lost in patients with anti-NF155 antibodies (part **d**). ml, myelin loop; Nfasc, neurofascin. Reproduced with permission from Elsevier © Vallat, J.-M. *et al.* Paranodal lesions in chronic inflammatory demyelinating polyneuropathy associated with anti-neurofascin 155 antibodies. *Neuromuscul. Disord.* **27**, 290–293 (2016).

bound preferentially to transient receptor potential cation channel subfamily V-positive and isolectin B4-positive small neurons in dorsal root ganglia, a subtype of neurons implicated in pain[66]. The isotype of the anti-CASPR1 antibodies was IgG3 in the patient classified as having GBS and IgG4 in the patient diagnosed as having CIDP. The patient with GBS showed a characteristic postinfectious acute, monophasic course of disease, had anti-CASPR1 antibodies that fixed complement, and made a complete recovery after plasma exchange. In the patient with CIDP, however, complement activation was absent, and rituximab treatment was needed to achieve clinical stability and disappearance of the autoantibodies[26].

In our first report describing anti-CNTN1 antibodies in patients with CIDP, we did not find any patients with anti-CASPR1 antibodies, although we did find one patient with antibodies against the CNTN1–CASPR1 complex (but not against CNTN1 or CASPR1 alone)[24]. The latter antibodies reacted to a specific glycosylated form of CNTN1 (the high-mannose glycoform) obtained when CNTN1 and CASPR1 are co-expressed[50,67]. These observations imply that anti-CASPR1 antibodies have a low frequency in patients with CIDP[24], a suggestion that requires confirmation in large and well-characterized cohorts of patients with CIDP.

Other autoantibodies. In published reports and in our own experience, >40% of patients with CIDP show antibodies against components of myelinated nerves[33,68,69]. Within this group, patients who harbour well-characterized antibodies with a clear clinical–immunological correlation, such as anti-CNTN1 or anti-NF155 antibodies, account for <10% of all patients with CIDP. This disparity emphasizes that many additional antigen targets need to be characterized at the nodes, paranodes, Schwann cell microvilli, or myelin sheath. Some patients whose serum shows nodal or paranodal reactivity in teased nerve fibre preparations have antibodies against other nodal proteins, such as NF186 or gliomedin[33]. Moreover, our group has reported that up to one-third of patients with CIDP have serum reactivity against dorsal root ganglion neurons, Schwann cells or motor neurons *in vitro*[69]. Studying the antibodies responsible for this paranodal or nodal reactivity could enable the characterization of novel target antigens that have not yet been identified.

Our groups, in collaboration with others, have detected a subset of patients who harbour antibodies against the nodal isoforms of neurofascin (NF186 and NF140). These patients also share specific clinical features: two of five patients presented with concomitant focal segmental glomerulosclerosis, reinforcing the notion that within the CIDP spectrum, characterization of a patient's autoantibody profile will help to define more-homogeneous disease subgroups[70]. These findings need replication in other cohorts of patients to determine the clinical relevance of these antibodies and the disease features associated with them.

Clinical implications

Even though the proportion of patients in whom specific autoantibodies can be detected is low, recognition of these autoantibodies has several potentially important implications for diagnosis, prognostication, selection of treatment and follow-up. Diagnosis of CIDP still relies on use of standard diagnostic criteria. However, the presence of paranodal antibodies identifies a subset of patients with CIDP who share a particular phenotype and clinical features that diverge from those of seronegative patients. These markers might, therefore, aid prognostication and follow-up in these patients.

Autoantibodies to paranodal proteins. Patients with antibodies to paranodal proteins often show aggressive onset of disease, and might be initially diagnosed as having GBS[24]. Antibodies against CNTN1 seem to be associated with aggressive disease, denervation at onset and poor response to IVIg. Patients with anti-NF155 antibodies present with distal weakness and tremor, and also respond poorly to IVIg treatment.

Paranodal autoantibodies are almost all of the IgG4 isotype. Interestingly, the number of autoimmune diseases known to be mediated by IgG4 autoantibodies is increasing rapidly[54]. Thus, early detection of paranodal autoantibodies and monitoring of their titres is particularly important in patients with IgG4 paranodal autoantibodies, so as to predict clinical deterioration and aid tailoring of therapy. Although these patients are unlikely to respond to IVIg, they could still respond to steroids, other immunosuppressant drugs or plasma exchange[52,58]. In patients with IgG4-mediated diseases who do not respond to these conventional treatments, a very good response to B-cell-depleting therapies can be achieved. Drug-resistant patients with non-CIDP IgG4-mediated diseases in which the IgG4 antibodies are known to be pathogenic show excellent and long-lasting responses to rituximab, associated with a sharp decline in autoantibody titres[71–73]. Similarly favourable responses to rituximab occur in patients with CIDP and anti-CNTN1 or anti-NF155 IgG4 antibodies who do not respond to conventional therapies. In our rituximab-treated patients with CIDP, antibody titres decreased substantially or disappeared. Patients with short disease durations responded better than those with long disease durations, probably owing to the accrual of permanent axonal damage in the latter group[74]. Similar positive findings for rituximab treatment have been reported in individual patients with anti-CNTN1 or anti-CASPR1 IgG4 antibodies[26,53]. Although the efficacy of rituximab in patients with IgG4-related CIDP is supported only by limited evidence from case reports or small series, the strong effectiveness of B-cell depletion in other IgG4-mediated diseases with very diverse target organs[71,72] suggests that B-cell-depleting therapies could be beneficial in patients with CIDP and anti-CNTN1 or anti-NF155 antibodies who have not responded to conventional treatments.

In general, the presence of autoantibodies to paranodal structures should be suspected in patients with an acute, subacute or chronic acquired demyelinating polyradiculoneuropathy presenting with any of the described associated features, including distal involvement, prominent tremor and/or poor response to IVIg. Investigations to detect these antibodies should be considered in patients with CIDP who do not respond to standard treatments, because autoantibody-positive patients might respond well to B-cell-depleting therapies, which might prevent the accrual of permanent nerve damage, thereby improving the prognosis (BOX 2; TABLE 1).

Antibodies against compact myelin antigens and gangliosides. Considering the demyelinating nature of CIDP and the neuritogenic potential of some myelin proteins in animal models, researchers in the field of CIDP initially focused on identifying autoantibodies that target peripheral myelin components[28,75–77]. Antibodies against Schwann cells are present in up to 25% of patients with CIDP, but the molecular target of these antibodies remains elusive[68]. Some studies did find that antibodies against myelin proteins (P2, P0 and PMP22, among others) were associated with CIDP[76–79]. However, either the subsequent replication studies failed to confirm these associations or the antibodies identified were not strictly disease-specific, being also present in other neuropathies[80,81]. Their clinical utility, therefore, could not be established.

Glycolipids are well-known target antigens in immune neuropathies. Antibodies against gangliosides are associated with some subsets of GBS, MMN, and CANOMAD (chronic ataxic neuropathy with ophthalmoplegia, monoclonal IgM, cold agglutinins and disialosyl antibodies) syndrome[82]. Consequently, several groups have tried, generally without success, to demonstrate that antiganglioside antibodies were associated with CIDP. An exception to the unproductive nature of this search is the case of antibodies targeting LM1 ganglioside, which have been found in some subsets of patients with CIDP and GBS; these antibodies are associated with the presence of ataxia in patients with CIDP[83,84]. Independent confirmation of this association is pending.

Autoantibodies in other polyneuropathies

The research done in the field of autoantibodies in CIDP, as discussed above, clearly demonstrates that the presence of specific autoantibodies distinguishes different subsets of patients of CIDP, and can be used to guide the clinical management of these patients. Therefore, CIDP represents proof of concept in relation to the use of autoantibodies in other CINs and, by extrapolation, perhaps also in other autoantibody-mediated diseases. Below, we discuss the evidence that autoantibodies could be used to guide the management of patients with CINs other than CIDP, as well as data suggesting that autoantibodies have similar utility in patients with non-CIN secondary immune-mediated neuropathies, even if the autoantibodies do not specifically target neuronal antigens.

MMN

MMN is a highly stereotyped CIN syndrome characterized by asymmetric or focal weakness, absence of sensory involvement, and presence of motor nerve conduction blocks on EMG[11]. MMN is presumed to have an autoimmune origin involving B cells because it responds very well to IVIg[85]. By contrast, MMN does not respond to plasma exchange, and can even worsen with corticosteroid treatment[4].

In patients with the typical form of the syndrome, use of standardized diagnostic criteria quickly and easily leads to the diagnosis[4]. However, atypical forms of MMN can share clinical similarities with devastating and untreatable diseases, such as amyotrophic lateral sclerosis and lower motor neuron syndromes[86]. Moreover,

the existence of some patients with MMN who do not show overt conduction blocks or respond to IVIg makes the search for antibody biomarkers that could guide the diagnosis and management of patients with MMN important for everyday clinical practice[86–88].

Antiganglioside and antiganglioside-complex antibodies. Since its first description, MMN has been associated with the presence of IgM antibodies against GM1 ganglioside[22], which are present in around 50% of patients with this condition[89]. These IgM anti-GM1 antibodies are oligoclonal[90], activate complement, and might disrupt the function of nodes of Ranvier in motor axons (as has also been shown for IgG anti-GM1 autoantibodies)[85,91,92].

Several reports indicate that the diagnostic performance of testing for anti-GM1 antibodies in patients with MMN is improved when antibody reactivity to GM1–galactocerebroside complexes is also assessed[93,94]. Up to 70% of patients with MMN in these studies had antibodies that targeted either GM1 or GM1–galactocerebroside complexes, and the inclusion of anti-GM1–galactocerebroside complex antibodies did not compromise the specificity of anti-GM1 antibody

Box 2 | **When and for which autoantibody should I test?**

Patients with chronic inflammatory demyelinating polyradiculoneuropathy and the following features

- Aggressive disease onset
  - Anti-CNTN1 — especially if ataxia or prominent motor involvement are present, including signs of 'axonal' damage at onset
  - Anti-NF155 — especially if low-frequency tremor, prominent distal weakness or ataxia are present
- Poor or partial response to intravenous immunoglobulin
  - Anti-CNTN1 or anti-NF155
  - Anti-MAG — if IgM monoclonal gammopathy is present
- CNS demyelination
  - Consider anti-NF155
- Ataxia
  - Consider anti-LM1, anti-CNTN1 and anti-NF155
  - Anti-MAG and antiganglioside antibodies (disialosyl epitope) — if monoclonal gammopathy is present
- Tremor
  - Consider anti-NF155
  - Anti-MAG — if IgM monoclonal gammopathy is present
- Intense neuropathic pain (also in Guillain–Barré syndrome with intense neuropathic pain)
  - Consider anti-CASPR1 antibodies

Patients with slowly progressive, predominantly distal, sensory–ataxic, demyelinating neuropathy

- Anti-MAG — if IgM monoclonal gammopathy is present
- Consider anti-NF155 — if IgM monoclonal gammopathy is absent or if progression is faster than expected (at least one case has been reported of an associated IgM monoclonal gammopathy)

Patients with a purely motor, distal, asymmetric neuropathy, or no signs of upper motor neuron involvement

- Consider anti-GM1 and anti-GM1–galactocerebroside complex, even when conduction blocks are not detected

Patients with motor neuropathy and positive symptoms (myokymias, fasciculations, neuromyotonia)

- Consider anti-CASPR2

Patients with sensory neuropathy or neuronopathy

- Consider anti-Ro or anti-La
- Consider anti-Hu, especially if asymmetric
- Consider anti-FGFR3

Patients with systemic involvement

- Consider anti-neutrophil cytoplasmic antibodies (specifically anti-myeloperoxidase and anti-proteinase 3 antibodies) in multineuritis presentations
- Consider anti-FGFR3 in pure sensory neuropathies

Patients with neuropathy and constitutional syndrome or known neoplasm

- Consider CV2 (also known as anti-CRMP5) antibodies in sensory–motor neuropathies or in lung neoplasms and thymoma
- Consider anti-Hu in pure sensory neuropathies
- Consider anti-CASPR2 in pure motor neuropathies associated with neuromyotonia

CASPR, contactin-associated protein-like; CNTN1, contactin-1; CRMP5, dihydropyrimidinase-related protein 5 (DRP5), also known as collapsin response mediator protein 5; FGFR3, fibroblast growth factor receptor 3; GM1, monosialotetrahexosylganglioside; Hu, a family of four RNA-binding proteins: HuR, HuB, HuC, and HuD (also known as ELAV-like proteins 1–4); La, SSB (also known as lupus La protein); LM1, sialosylneolactotetraosylceramide; MAG, myelin-associated glycoprotein; NF155, neurofascin splice variant 155; Ro, SSA (also known as E3 ubiquitin-protein ligase TRIM21).

detection for the diagnosis of MMN[93,94]. Antibodies targeting GM1-bearing ganglioside complexes are highly sensitive and specific for MMN and, although their presence is not required by diagnostic criteria, these antibodies support the diagnosis in patients who have clinical features compatible with MMN. Antibody testing is particularly important for patients who have clinical syndromes that do not fulfil the diagnostic criteria for MMN[11,88], as the presence of anti-GM1 IgM antibodies might identify a subset of patients with atypical MMN (who might, therefore, respond to treatment with IVIg) despite lacking evidence of conduction blocks or demyelinating features on EMG[95]. Careful use of IgM anti-GM1 antibody testing might, therefore, avoid misdiagnosis and overtreatment of patients who actually have a degenerative lower motor neuron syndrome rather than atypical MMN.

An innovative study of human motor neurons obtained from induced pluripotent stem cells showed that IgM anti-GM1 antibodies cause pathology via a complement-dependent mechanism[96]. The anti-GM1 antibody pathogenicity was abrogated on complement inactivation or blockade of GM1. Interestingly, IgM obtained from patients with MMN who tested negative for anti-GM1 antibodies on enzyme-linked immunosorbent assay (ELISA) showed the same pattern of staining and pathogenic changes in motor neurons as was produced by IgM from ELISA-positive patients with anti-GM1 antibodies. The researchers concluded that IgM antibodies from both groups of patients recognized a similar epitope. However, other interpretations of these results are possible; for example, the researchers did not test for antiganglioside complex antibodies, and a subset of the patients categorized as anti-GM1 seronegative might have been positive for antibodies to GM1–galactocerebroside complexes. Alternatively, other glycans or proteins containing structurally similar epitopes might harbour the antigen detected in the anti-GM1 seronegative patients in this study.

In other studies, complement activity in plasma from patients with MMN correlated positively with anti-GM1 IgM antibody titres and, most importantly, with disease severity[97]. These findings suggest that complement inhibitors could be an effective treatment for MMN. However, the results of a small open-label trial of the complement inhibitor eculizumab in 13 patients with MMN were considered negative, as the addition of eculizumab did not result in a change in IVIg dosing frequency in the ten patients who were receiving maintenance IVIg. Nonetheless, eculizumab seemed to have a marginally positive effect on patient-rated subjective scores and several clinical and electrophysiological parameters (myometry), mostly in patients with the best motor function at baseline[98]. If these results were confirmed in controlled trials, measurement of IgM anti-GM1 antibody titres and assessment of their ability to activate complement might become essential to guide the choice of treatment before permanent axonal damage develops.

Antibodies against node of Ranvier proteins. Studies of the association between MMN and antibodies targeting node of Ranvier proteins have generated conflicting results. In theory, the enrichment of GM1 in nodes of Ranvier makes nodal glycoproteins good candidate antigens to explore in patients with MMN[99]. One study found that >60% of patients with MMN had autoantibodies against gliomedin or NF186, either alone or in combination with other autoantibodies such as anti-GM1 IgM[100]. Another study failed to replicate the association between MMN and anti-NF186 antibodies[101], and did not find

Table 1 | **Antibodies associated with chronic inflammatory neuropathies**

Antigen	Antibody isotype	Disease phenotype	Clinical implications
Chronic inflammatory demyelinating polyradiculoneuropathy			
Contactin-1 (CNTN1)	IgG4	Aggressive onset, axonal involvement at onset	Poor response to IVIg
Neurofascin splice variant 155 (NF155)	IgG4	Distal motor involvement, ataxia, prominent tremor	Poor response to IVIg
Contactin-associated protein 1 (CASPR1)	IgG4	Pain*	Poor response to IVIg
Sialosylneolactotetraosylceramide (LM1) ganglioside	IgG	Ataxia	None
Multifocal motor neuropathy			
Monosialotetrahexosylganglioside (GM1)	IgM	None	• Supports diagnosis • Supports treatment with IVIg when diagnostic criteria are not fulfilled
Polyneuropathy associated with MGUS			
Myelin-associated glycoprotein (MAG)	IgM	Distal motor involvement, ataxia, tremor	Identifies a subgroup of patients who are candidates for immune therapies
Disialosyl gangliosides	IgM	Ataxia ± ophthalmoparesis ± bulbar involvement	Identifies a subgroup of IVIg-responsive patients

MGUS, monoclonal gammopathy of uncertain significance; IVIg, intravenous immunoglobulin. *Anti-CASPR1 autoantibodies are also associated with pain in patients with Guillain–Barré syndrome.

any anti-NF155 or anti-CNTN1 antibodies either[101]. The potential association between MMN and an antibody response against gliomedin has not yet been replicated in any independent cohorts.

MGUS-P

Polyneuropathies frequently occur in the context of paraproteins or haematological malignancies[12]. The MGUS-P category specifically refers to demyelinating polyneuropathies in patients with monoclonal gammopathies of uncertain significance. As such, the diagnosis of MGUS-P specifically excludes the pure inflammatory neuropathies that develop in the context of haematological malignancies, cell dyscrasias that also show a monoclonal gammopathy, and CIDP associated with an IgG or IgA MGUS[5]. Most patients with MGUS-P show a characteristic, slowly progressive, predominantly sensory–ataxic, distal polyneuropathy with demyelinating features on EMG and wide-spaced myelin layers in myelinated fibres examined with electron microscopy. Thus, CIDP and polyneuropathies with haematological malignancies are often difficult to differentiate clinically from MGUS-P. This differential diagnosis is important, however: despite the similarity of their clinical features, the treatment and prognosis of these two conditions differs substantially. The key diagnostic features of MGUS-P include an IgM monoclonal gammopathy, and anti-MAG or antiganglioside antibodies[102].

Although IgG and IgA paraproteins can also be associated with polyneuropathy, whether a causal relationship exists is not clear. However, IgM monoclonal gammopathy is most frequently associated with a specific phenotype of demyelinating polyneuropathy, and particularly with anti-MAG-related MGUS-P. Serological testing reveals that 50% of patients with MGUS-P have anti-MAG IgM antibodies[20,103]. A subset of patients with IgM MGUS-P have antibodies against sulfatide (3-*O*-sulfogalactosylceramide, also known as sulfated galactocerebroside), although the clinical relevance of these antibodies and their associations with specific phenotypes are uncertain[104]. Anti-MAG antibody testing has high sensitivity and specificity for monoclonal IgM-associated demyelinating neuropathies[105,106]. Anti-MAG antibodies are not usually used to monitor response to therapy, and their titres do not seem to correlate with symptom severity. Nonetheless, titres of anti-MAG antibodies substantially and consistently decrease after successful treatment in diverse studies[107–110]. Patients with IgM MGUS-P often respond poorly to immunomodulatory or immunosuppressive treatment. A few studies have reported beneficial effects of treatment with plasma exchange, cyclophosphamide, IVIg and rituximab[20,102]. However, patients in randomized trials only show marginal benefits from these treatments (perhaps owing to a combination of poorly performing outcome measures[111], short follow-up, and inefficacy of B-cell depletion against anti-MAG producing cells[112]), despite reductions in anti-MAG antibody titres. The clinical utility of anti-MAG antibody detection is, therefore, restricted to diagnosis; these antibodies cannot be used for follow-up, prediction of prognosis or treatment selection. This situation might also reflect the fact that the pathogenicity of anti-MAG antibodies remains unclear. Nonetheless, the diagnostic utility of the antibodies in humans — in particular, their specificity, the homogeneity of the clinical syndrome, and the consistent pathological findings[113] — do suggest a pathogenetic role for anti-MAG antibodies in MGUS-P. Unfortunately, the interspecies differences in antigenicity of MAG and the lack of crossreactivity of human antibodies with mouse MAG proteins mean that polyneuropathy is difficult to elicit in animal models of anti-MAG-related disease[114–118].

A few patients with IgM monoclonal gammopathy present with a highly homogeneous phenotype characterized by chronic, severe large-fibre sensory polyneuropathy and IgM reactivity against gangliosides containing particular disialosyl groups, including GD1b, GD3, GQ1b and GT1b. A subset of these patients also exhibit ophthalmoparesis and, consequently, fulfil the diagnosis of CANOMAD syndrome[21,119,120]. Some patients might also have bulbar involvement, which is associated with antiganglioside antibody reactivity against GD1a, GM3 and GT1b, which all share the NeuNAc(α2,3)Gal terminal epitope[21,121].

An important clinical implication of the diagnosis of MGUS-P is that screening and follow-up for plasma-cell malignancies (including Waldenström macroglobulinaemia, in which B cells show a specific mutation profile that is not present in other MGUS[122], and other myeloma variants), should be part of the patient's routine work-up[12]. An increased risk of malignant transformation exists for patients with any MGUS, but is highest for those with IgM MGUS-P[123]. No studies have yet addressed whether the presence of a particular antibody reactivity (to either MAG or disialosyl gangliosides) promotes or protects against malignant transformation to myeloma. On the other hand, patients with IgM MGUS-P and anti-MAG antibodies show an oligoclonal B-cell population that displays clear IgM somatic hypermutation, suggestive of antigen-driven affinity maturation[112]. In patients who respond to rituximab treatment, the oligoclonal expansions are considerably reduced compared with those in patients who are receiving placebo or do not respond to rituximab[112]. Whether early B-cell-depleting treatment precludes disease progression (and, more importantly, the acquisition of malignant mutations such as those linked to Waldenström macroglobulinaemia) remains unknown.

In summary, although IgM MGUS-P is usually considered to be a homogeneous type of CIN, patients with this diagnosis display a variety of phenotypes, prognoses and responses to treatment; the specific autoantibodies borne by the patient can help to inform their management.

Non-CIN polyneuropathies

Regardless of the underlying cause, polyneuropathies display a restricted range of clinical features. As a consequence, identification and categorization of patients who require specific therapies is challenging. Accurate diagnosis is important not only for the polyneuropathies within the CIN spectrum already discussed above, but

also for all other polyneuropathies that might have an underlying immune pathogenesis but display neither acquired demyelination nor overt inflammatory involvement of other organs.

Polyneuropathies associated with systemic immune disorders. Polyneuropathies can develop in the context of various systemic disorders[124,125]. Neuropathies associated with systemic and nonsystemic vasculitides usually present as multineuritis; however, they can also resemble polyneuropathies. Detection of anti-neutrophil cytoplasmic antibodies (ANCA) facilitates recognition of these disorders, particularly when symptoms and EMG data show symmetric involvement. Anti-proteinase-3 (PR3) ANCA are associated with granulomatosis with polyangiitis (formerly Wegener granulomatosis), whereas anti-myeloperoxidase (MPO) ANCA are associated with microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis (formerly Churg–Strauss syndrome)[126]. Detection of anti-PR3-ANCA or anti-MPO-ANCA in the context of an axonal, rapidly progressing neuropathy should prompt initiation of appropriate treatment even when the patient's clinical presentation is not typical of vasculitis-related multineuritis. However, nerve biopsy is still considered the gold standard to detect neuropathies associated with vasculitis, and antibody testing is used only as a supportive test in patients who do not present with the typical phenotype.

Systemic immune disorders such as Sjögren syndrome, rheumatoid arthritis or systemic lupus erythematosus (and some treatments for these diseases, such as anti-tumour necrosis factor agents) are associated with polyneuropathy[124,127,128]. In some patients, diagnosis might be challenging because the systemic features are unclear or neuropathy precedes the development of the systemic syndrome. Thus, in patients with a polyneuropathy of unknown cause, a positive test for autoantibodies associated with an underlying systemic disease (such as antinuclear antibodies, anti-SSA-Ro or anti-SSB-La antibodies, or rheumatoid factor) should be followed by appropriate rheumatological evaluation[129]. In one report, the presence of antibodies against fibroblast growth factor receptor 3 (FGFR3) was associated with development of a sensory neuropathy in the context of various systemic immune disorders[130]. These anti-FGFR3 antibodies seem to be specific for the sensory neuropathy regardless of the underlying immunological disorder, but replication of this finding in other series is still needed.

Paraneoplastic polyneuropathies. As well as those polyneuropathies associated with haematological malignancies, solid tumours can also be associated with peripheral nerve disorders. The most typical syndrome is a rapidly progressing, purely sensory, asymmetric and disabling neuropathy associated with anti-Hu antibodies. Although these antibodies are probably not pathogenic, they are strongly associated with the presence of solid tumours, typically small-cell lung carcinoma. Thus, identification of these antibodies in the context of a purely sensory neuropathy should be followed by a thorough search for solid tumours and careful follow-up[131].

CV2 autoantibodies, which target dihydropyrimidinase-related protein 5 (DRP5, also known as CRMP5) are also associated with a variety of paraneoplastic neurological syndromes, including sensorimotor polyneuropathies[132–134]. Although the association of anti-CRMP5 antibodies with solid tumours is not as strong as that of anti-Hu antibodies, detection of these antibodies raises suspicion of an underlying neoplasm.

Finally, antibodies that target CASPR2 are associated with a peripheral motor syndrome with nerve hyperexcitability and neuromyotonia (with or without CNS involvement and dysautonomia) that can present as an idiopathic autoimmune or paraneoplastic syndrome. Patients with this syndrome respond very well to immune therapies or tumour removal[135,136].

Axonal neuropathies. Immune-mediated pathophysiology and classification as a CIN has been linked to the presence of acquired demyelinating features on EMG. However, some patients with CINs might not show overt demyelinating features on the initial EMG (including patients with axonal variants of GBS, ataxic CIDP, ataxic neuropathy with disialosyl antibodies or MGUS-P), and some non-CIN autoimmune disorders (such as rheumatological diseases or type 1 diabetes mellitus) are also associated with axonal neuropathies. Furthermore, in up to 40% of patients with axonal neuropathies, the cause of the neuropathy cannot be identified[129,137]. Despite this uncertainty, the search for autoantigens in patients classified as having axonal neuropathy has not been systematic, and no antibodies have been reliably associated with purely axonal neuropathies. Nonetheless, subgroups of patients with immune-mediated axonal neuropathies who could benefit from immune therapies might plausibly exist. Research efforts should aim to identify specific markers (including autoantibodies) in subsets of patients with idiopathic axonal neuropathies.

Conclusions

Autoantibodies have traditionally served as diagnostic biomarkers in very diverse autoimmune diseases. In some diseases, such as autoimmune encephalitis, identification of the target antigen(s) has had dramatic clinical implications from diagnosis to therapy[138]. In other diseases, even when the proportion of patients with a specific antibody is low, such as in myasthenia gravis, antibody characterization has helped to define distinct disease subsets, in which clinical features, prognosis, therapy and outcomes differ substantially depending on the associated autoantibody[72].

Tools such as electrophysiology and imaging techniques can undoubtedly identify patients with inflammatory neuropathies who are likely to respond to immune therapies. However, the discovery of paranodal autoantibodies in patients with CIDP revealed distinct subsets of disease that had remained unnoticed before these antibodies were described. These disease subsets differ in terms of clinical presentation (phenotypes), pathological features (paranodal dissection, myelin loop detachment and loss of transverse bands), pathophysiological mechanisms (CNTN1/CASPR1/NF155 complex

disruption) and therapeutic implications (efficacy of B-cell depletion). The discovery of other autoantigens such as MAG or gangliosides has been similarly illuminating in other CINs. These facts support the idea that detecting the specific antigens involved in tissue-specific autoimmune diseases, including neuropathies, is a key step towards understanding other important aspects of the disease and its treatment.

The crucial remaining research question is whether additional target antigens can be identified in apparently seronegative patients with CINs and other similar disorders. Answering this question might lead to fine phenotypic classification, and help untangle the pathogenesis of these diseases — something that has proven to be difficult in CIN, and is a prerequisite for precision medicine.

1. Latov, N. Diagnosis and treatment of chronic acquired demyelinating polyneuropathies. *Nat. Rev. Neurol.* **10**, 435–446 (2014).
2. Nobile-Orazio, E. 2013 Peripheral Nerve Society Meeting PNS Presidential Lecture. Chronic inflammatory demyelinating polyradiculoneuropathy and variants: where we are and where we should go. *J. Peripher. Nerv. Syst.* **19**, 2–13 (2014).
3. Van den Bergh, P. Y. *et al.* European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. *Eur. J. Neurol.* **17**, 356–363 (2010).
4. Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of multifocal motor neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society — first revision. *J. Peripher. Nerv. Syst.* **15**, 295–301 (2010).
5. Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of paraproteinemic demyelinating neuropathies. Report of a Joint Task Force of the European Federation of Neurological Societies and the Peripheral Nerve Society — first revision. *J. Peripher. Nerv. Syst.* **15**, 185–195 (2010).
6. Bril, V. *et al.* The dilemma of diabetes in chronic inflammatory demyelinating polyneuropathy. *J. Diabetes Complications* **30**, 1401–1407 (2016).
7. Viala, K. *et al.* A current view of the diagnosis, clinical variants, response to treatment and prognosis of chronic inflammatory demyelinating polyradiculoneuropathy. *J. Peripher. Nerv. Syst.* **15**, 50–56 (2010).
8. Allen, J. A. & Lewis, R. A. CIDP diagnostic pitfalls and perception of treatment benefit. *Neurology* **85**, 498–504 (2015).
9. Mathey, E. K. *et al.* Chronic inflammatory demyelinating polyradiculoneuropathy: from pathology to phenotype. *J. Neurol. Neurosurg. Psychiatry* **86**, 973–985 (2015).
10. Brannagan, T. H. Current diagnosis of CIDP: the need for biomarkers. *J. Peripher. Nerv. Syst.* **16** (Suppl. 1), 3–13 (2011).
11. Vlam, L. *et al.* Multifocal motor neuropathy: diagnosis, pathogenesis and treatment strategies. *Nat. Rev. Neurol.* **8**, 48–58 (2012).
12. Rojas-Garcia, R., Gallardo, E. & Illa, I. Paraproteinemic neuropathies. *Presse Med.* **42**, e225–e234 (2013).
13. Meyer zu Hörste, G., Hartung, H.-P. & Kieseier, B. C. From bench to bedside — experimental rationale for immune-specific therapies in the inflamed peripheral nerve. *Nat. Clin. Pract. Neurol.* **3**, 198–211 (2007).
14. Vallat, J.-M. Peripheral nervous system neuroimmunology seen by a neuro-pathologist. *Rev. Neurol. (Paris)* **170**, 564–569 (2014).
15. Shibuya, K. *et al.* Reconstruction magnetic resonance neurography in chronic inflammatory demyelinating polyneuropathy. *Ann. Neurol.* **74**, 1–5 (2014).
16. Ishikawa, T. *et al.* MR neurography for the evaluation of CIDP. *Muscle Nerve* **55**, 483–489 (2016).
17. Hughes, R. A. *et al.* Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial. *Lancet Neurol.* **7**, 136–144 (2008).
18. Mehndiratta, M. M., Hughes, R. A. & Pritchard, J. Plasma exchange for chronic inflammatory demyelinating polyradiculoneuropathy. *Cochrane Database Syst. Rev.* **8**, CD003906 (2015).
19. Berger, M., McCallus, D. E. & Lin, C. S.-Y. Rapid and reversible responses to IVIg in autoimmune neuromuscular diseases suggest mechanisms of action involving competition with functionally important autoantibodies. *J. Peripher. Nerv. Syst.* **296**, 275–296 (2013).
20. Dalakas, M. C. Pathogenesis and treatment of anti-MAG neuropathy. *Curr. Treat. Opt. Neurol.* **12**, 71–83 (2010).
21. Willison, H. J. *et al.* The clinical and laboratory features of chronic sensory ataxic neuropathy with anti-disialosyl IgM antibodies. *Brain* **124**, 1968–1977 (2001).
22. Pestronk, A. *et al.* A treatable multifocal motor neuropathy with antibodies to GM1 ganglioside. *Ann. Neurol.* **24**, 73–78 (1988).
23. Cats, E. A. *et al.* Multifocal motor neuropathy: association of anti-GM1 IgM antibodies with clinical features. *Neurology* **75**, 1961–1967 (2010).
24. Querol, L. *et al.* Antibodies to contactin-1 in chronic inflammatory demyelinating polyneuropathy. *Ann. Neurol.* **73**, 370–380 (2013).
25. Querol, L. *et al.* Neurofascin IgG4 antibodies in CIDP associate with disabling tremor and poor response to IVIg. *Neurology* **82**, 879–886 (2014).
26. Doppler, K. *et al.* Auto-antibodies to contactin-associated protein 1 (Caspr) in two patients with painful inflammatory neuropathy. *Brain* **139**, 2617–2630 (2016).
27. Grant, M. J. & Booth, A. A typology of reviews: an analysis of 14 review types and associated methodologies. *Health Info. Libr. J.* **26**, 91–108 (2009).
28. Zweiman, B., Rostami, A., Lisak, R. P., Moskovitz, A. R. & Pleasure, D. E. Immune reactions to P2 protein in human inflammatory demyelinative neuropathies. *Neurology* **33**, 234–237 (1983).
29. Pei, L. J., Devaux, J. & Yuki, N. Peripheral nerve proteins as potential autoantigens in acute and chronic inflammatory demyelinating polyneuropathies. *Autoimmun. Rev.* **13**, 1070–1078 (2014).
30. Dalakas, M. C. & Engel, W. K. Immunoglobulin and complement deposits in nerves of patients with chronic relapsing polyneuropathy. *Arch. Neurol.* **37**, 637–640 (1980).
31. Tackenberg, B. *et al.* Impaired inhibitory Fcγ receptor IIB expression on B cells in chronic inflammatory demyelinating polyneuropathy. *Proc. Natl Acad. Sci. USA* **106**, 4788–4792 (2009).
32. Yan, W. X., Taylor, J., Andrias-Kauba, S. & Pollard, J. D. Passive transfer of demyelination by serum or IgG from chronic inflammatory demyelinating polyneuropathy patients. *Ann. Neurol.* **47**, 765–775 (2000).
33. Devaux, J. J., Odaka, M. & Yuki, N. Nodal proteins are target antigens in Guillain–Barré syndrome. *J. Peripher. Nerv. Syst.* **17**, 62–71 (2012).
34. Querol, L. & Illa, I. Paranodal and other autoantibodies in chronic inflammatory neuropathies. *Curr. Opin. Neurol.* **28**, 474–479 (2015).
35. Huxley, A. F. & Stämpeli, R. Evidence for saltatory conduction in peripheral myelinated nerve fibres. *J. Physiol.* **108**, 315–339 (1949).
36. Bargmann, W. & Lindner, E. On the fine structure of the adrenal medulla of the hedgehog (*Erinaceus europaeus L.*) [German]. *Z. Zellforsch. Mikrosk. Anat.* **64**, 868–912 (1964).
37. Boyle, M. E. *et al.* Contactin orchestrates assembly of the septate-like junctions at the paranode in myelinated peripheral nerve. *Neuron* **30**, 385–397 (2001).
38. Charles, P. *et al.* Neurofascin is a glial receptor for the paranodin/Caspr-contactin axonal complex at the axoglial junction. *Curr. Biol.* **12**, 217–220 (2002).
39. Pillai, A. M. *et al.* Spatiotemporal ablation of myelinating glia-specific neurofascin (Nfasc NF155) in mice reveals gradual loss of paranodal axoglial junctions and concomitant disorganization of axonal domains. *J. Neurosci. Res.* **87**, 1773–1793 (2009).
40. Bhat, M. a *et al.* Axon–glia interactions and the domain organization of myelinated axons requires neurexin IV/Caspr/Paranodin. *Neuron* **30**, 369–383 (2001).
41. Stathopoulos, P., Alexopoulos, H. & Dalakas, M. C. Autoimmune antigenic targets at the node of Ranvier in demyelinating disorders. *Nat. Rev. Neurol.* **11**, 143–156 (2015).
42. Hafer-Macko, C. *et al.* Acute motor axonal neuropathy: an antibody-mediated attack on axolemma. *Ann. Neurol.* **40**, 635–644 (1996).
43. Cifuentes-Diaz, C. *et al.* Nodes of Ranvier and paranodes in chronic acquired neuropathies. *PLoS ONE* **6**, e14533 (2011).
44. Doppler, K., Werner, C. & Sommer, C. Disruption of nodal architecture in skin biopsies of patients with demyelinating neuropathies. *J. Peripher. Nerv. Syst.* **18**, 168–176 (2013).
45. Lonigro, A. & Devaux, J. J. Disruption of neurofascin and gliomedin at nodes of Ranvier precedes demyelination in experimental allergic neuritis. *Brain* **132**, 260–273 (2009).
46. Yan, W. X., Mathey, E., Yiannikas, C. & Pollard, J. Antineurofascin antibodies are present in patients with peripheral demyelinating neuropathies and mediate changes in nerve conduction in animals. *J. Peripher. Nerv. Syst.* **15**, 288–289 (2010).
47. Prüss, H., Schwab, J. M., Derst, C., Görtzen, A. & Veh, R. W. Neurofascin as target of autoantibodies in Guillain–Barré syndrome. *Brain* **134**, e173 (2011).
48. Uncini, A. & Kuwabara, S. Nodopathies of the peripheral nerve: an emerging concept. *J. Neurol. Neurosurg. Psychiatry* **86**, 1186–1195 (2015).
49. Uncini, A., Susuki, K. & Yuki, N. Nodo-paranodopathy: beyond the demyelinating and axonal classification in anti-ganglioside antibody-mediated neuropathies. *Clin. Neurophysiol.* **124**, 1928–1934 (2013).
50. Labasque, M. *et al.* Specific contactin N-glycans are implicated in neurofascin binding and autoimmune targeting in peripheral neuropathies. *J. Biol. Chem.* **289**, 7907–7918 (2014).
51. Tackenberg, B., Nimmerjahn, F. & Lünemann, J. D. Mechanisms of IVIg efficacy in chronic inflammatory demyelinating polyneuropathy. *J. Clin. Immunol.* **30** (Suppl. 1), S65–S69 (2010).
52. Miura, Y. *et al.* Contactin 1 IgG4 associates to chronic inflammatory demyelinating polyneuropathy with sensory ataxia. *Brain* **138**, 1484–1491 (2015).
53. Doppler, K. *et al.* Destruction of paranodal architecture in inflammatory neuropathy with anti-contactin-1 autoantibodies. *J. Neurol. Neurosurg. Psychiatry* **86**, 720–728 (2015).
54. Huijbers, M. G. *et al.* The expanding field of IgG4-mediated neurological autoimmune disorders. *Eur. J. Neurol.* **22**, 1151–1161 (2015).
55. Manso, C., Querol, L., Mekaouche, M., Illa, I. & Devaux, J. J. Contactin-1 IgG4 antibodies cause paranode dismantling and conduction defects. *Brain* **139**, 1700–1712 (2016).
56. Koike, H. *et al.* Paranodal dissection in chronic inflammatory demyelinating polyneuropathy with antineurofascin-155 and anticontactin-1 antibodies. *J. Neurol. Neurosurg. Psychiatry* **88**, 465–473 (2017).
57. Man, J. K. *et al.* Neurofascin as a target for autoantibodies in peripheral neuropathies. *Neurology* **79**, 2241–2248 (2012).
58. Devaux, J. J. *et al.* Neurofascin-155 IgG4 in chronic inflammatory demyelinating polyneuropathy. *Neurology* **86**, 800–807 (2016).
59. Ogata, H. *et al.* Characterization of IgG4 anti-neurofascin 155 antibody-positive polyneuropathy. *Ann. Clin. Transl. Neurol.* **2**, 960–971 (2015).

60. Kadoya, M. *et al.* IgG4 anti-neurofascin155 antibodies in chronic inflammatory demyelinating polyradiculoneuropathy: clinical significance and diagnostic utility of a conventional assay. *J. Neuroimmunol.* **301**, 16–22 (2016).
61. Kawamura, N. *et al.* Anti-neurofascin antibody in patients with combined central and peripheral demyelination. *Neurology* **81**, 714–722 (2013).
62. Cortese, A. *et al.* Neurofascin-155 as a putative antigen in combined central and peripheral demyelination. *Neurol. Neuroimmunol. Neuroinflamm.* **3**, e238 (2016).
63. Yan, W. *et al.* Antibodies to neurofascin exacerbate adoptive transfer experimental autoimmune neuritis. *J. Neuroimmunol.* **277**, 13–17 (2014).
64. Vallat, J.-M. *et al.* Paranodal lesions in chronic inflammatory demyelinating polyneuropathy associated with anti-neurofascin 155 antibodies. *Neuromuscul. Disord.* **27**, 290–293 (2016).
65. Sherman, D. L. *et al.* Neurofascins are required to establish axonal domains for saltatory conduction. *Neuron* **48**, 737–742 (2005).
66. Fitzgerald, M. The development of nociceptive circuits. *Nat. Rev. Neurosci.* **6**, 507–520 (2005).
67. Bonnon, C. *et al.* PGY repeats and N-glycans govern the trafficking of paranodin and its selective association with contactin and neurofascin-155. *Mol. Biol. Cell* **18**, 229–241 (2007).
68. Kwa, M. S. G. Autoimmunoreactivity to Schwann cells in patients with inflammatory neuropathies. *Brain* **126**, 361–375 (2003).
69. Querol, L. et al. Antibodies against peripheral nerve antigens in chronic inflammatory demyelinating polyradiculoneuropathy [poster abstract]. *J. Peripher. Nerv. Syst.* **21**, 202–203 (2016).
70. Delmont, E. *et al.* Autoantibodies to nodal isoforms of neurofascin in chronic inflammatory demyelinating polyneuropathy. *Brain* **140**, 1851–1858 (2017).
71. Joly, P. *et al.* A single cycle of rituximab for the treatment of severe pemphigus. *N. Engl. J. Med.* **357**, 545–552 (2007).
72. Díaz-Manera, J. *et al.* Long-lasting treatment effect of rituximab in MuSK myasthenia. *Neurology* **78**, 189–193 (2012).
73. Beck, L. H. *et al.* Rituximab-induced depletion of anti-PLA2R autoantibodies predicts response in membranous nephropathy. *J. Am. Soc. Nephrol.* **22**, 1543–1550 (2011).
74. Querol, L. *et al.* Rituximab in treatment-resistant CIDP with antibodies against paranodal proteins. *Neurol. Neuroimmunol. Neuroinflamm.* **2**, e149 (2015).
75. Kadlubowski, M. & Hughes, R. A. Identification of the neuritogen for experimental allergic neuritis. *Nature* **277**, 140–141 (1979).
76. Gabriel, C. M., Gregson, N. A. & Hughes, R. A. Anti-PMP22 antibodies in patients with inflammatory neuropathy. *J. Neuroimmunol.* **104**, 139–146 (2000).
77. Yan, W. X., Archelos, J. J., Hartung, H.-P. & Pollard, J. D. P0 protein is a target antigen in chronic inflammatory demyelinating polyradiculoneuropathy. *Ann. Neurol.* **50**, 286–292 (2001).
78. Inglis, H. R., Csurhes, P. A. & McCombe, P. A. Antibody responses to peptides of peripheral nerve myelin proteins P0 and P2 in patients with inflammatory demyelinating neuropathy. *J. Neurol. Neurosurg. Psychiatry* **78**, 419–422 (2007).
79. Rojas-Garcia, R., Gallardo, E., De La Torre, C., Sanvito, L. & Illa, I. Chronic sensorimotor polyradiculopathy with antibodies to P2: an electrophysiological and immunoproteomic analysis. *Muscle Nerve* **38**, 933–938 (2008).
80. Kwa, M. S., van Schaik, I. N., Brand, A., Baas, F. & Vermeulen, M. Investigation of serum response to PMP22, connexin 32 and P(0) in inflammatory neuropathies. *J. Neuroimmunol.* **116**, 220–225 (2001).
81. Ritz, M. F. *et al.* Characterisation of autoantibodies to peripheral myelin protein 22 in patients with hereditary and acquired neuropathies. *J. Neuroimmunol.* **104**, 155–163 (2000).
82. Willison, H. J. & Yuki, N. Peripheral neuropathies and anti-glycolipid antibodies. *Brain* **125**, 2591–2625 (2002).
83. Kuwahara, M., Suzuki, S., Takada, K. & Kusunoki, S. Antibodies to LM1 and LM1-containing ganglioside complexes in Guillain–Barré syndrome and chronic inflammatory demyelinating polyneuropathy. *J. Neuroimmunol.* **239**, 87–90 (2011).
84. Kuwahara, M. *et al.* Clinical features of CIDP with LM1-associated antibodies. *J. Neurol. Neurosurg. Psychiatry* **84**, 573–575 (2013).
85. Harschnitz, O. *et al.* MMN: from immunological cross-talk to conduction block. *J. Clin. Immunol.* **34**, 112–119 (2014).
86. Sanderson, A. B., Arnold, W. D., Elsheikh, B. & Kissel, J. T. The clinical spectrum of isolated peripheral motor dysfunction. *Muscle Nerve* **51**, 358–362 (2015).
87. Menkes, D. L. Multifocal motor neuropathy with and without conduction block: a single entity? *Neurology* **68**, 1161–1162 (2007).
88. Delmont, E. *et al.* Multifocal motor neuropathy with and without conduction block: a single entity? *Neurology* **67**, 592–596 (2006).
89. Nobile-Orazio, E., Giannotta, C., Musset, L., Messina, P. & Léger, J.-M. Sensitivity and predictive value of anti-GM1/galactocerebroside IgM antibodies in multifocal motor neuropathy. *J. Neurol. Neurosurg. Psychiatry* **85**, 754–758 (2014).
90. Cats, E. A. *et al.* Clonality of anti-GM1 IgM antibodies in multifocal motor neuropathy and the Guillain–Barré syndrome. *J. Neurol. Neurosurg. Psychiatry* **86**, 502–504 (2014).
91. Uncini, A., Santoro, M., Corbo, M., Lugaresi, A. & Latov, N. Conduction abnormalities induced by sera of patients with multifocal motor neuropathy and anti-GM1 antibodies. *Muscle Nerve* **16**, 610–615 (1993).
92. Paparounas, K., O'Hanlon, G. M., O'Leary, C. P., Rowan, E. G. & Willison, H. J. Anti-ganglioside antibodies can bind peripheral nerve nodes of Ranvier and activate the complement cascade without inducing acute conduction block *in vitro*. *Brain* **122**, 807–816 (1999).
93. Nobile-Orazio, E., Giannotta, C. & Briani, C. Anti-ganglioside complex IgM antibodies in multifocal motor neuropathy and chronic immune-mediated neuropathies. *J. Neuroimmunol.* **219**, 119–122 (2010).
94. Delmont, E. *et al.* Improving the detection of IgM antibodies against glycolipids complexes of GM1 and galactocerebroside in multifocal motor neuropathy using glycoarray and ELISA assays. *J. Neuroimmunol.* **278**, 159–161 (2015).
95. Strigl-Pill, N. *et al.* Prediction of response to IVIg treatment in patients with lower motor neurone disorders. *Eur. J. Neurol.* **13**, 135–140 (2006).
96. Harschnitz, O. *et al.* Autoantibody pathogenicity in a multifocal motor neuropathy induced pluripotent stem cell-derived model. *Ann. Neurol.* **80**, 71–88 (2016).
97. Vlam, L. *et al.* Complement activity is associated with disease severity in multifocal motor neuropathy. *Neurol. Neuroimmunol. Neuroinflamm.* **2**, e119 (2015).
98. Fitzpatrick, A. M. *et al.* An open label clinical trial of complement inhibition in multifocal motor neuropathy. *J. Peripher. Nerv. Syst.* **16**, 84–91 (2011).
99. Susuki, K. *et al.* Gangliosides contribute to stability of paranodal junctions and ion channel clusters in myelinated nerve fibers. *Glia* **55**, 746–757 (2007).
100. Notturno, F. *et al.* Autoantibodies to neurofascin-186 and gliomedin in multifocal motor neuropathy. *J. Neuroimmunol.* **276**, 207–212 (2014).
101. Doppler, K. *et al.* Contactin-1 and neurofascin-155/-186 are not targets of auto-antibodies in multifocal motor neuropathy. *PLoS ONE* **10**, e0134274 (2015).
102. Leger, J. M. *et al.* Placebo-controlled trial of rituximab in IgM anti-myelin-associated glycoprotein neuropathy. *Neurology* **80**, 2217–2225 (2013).
103. Magy, L. *et al.* Heterogeneity of polyneuropathy associated with anti-MAG antibodies. *J. Immunol. Res.* **2015**, 450391 (2015).
104. Giannotta, C., Di Pietro, D., Gallia, F. & Nobile-Orazio, E. Anti-sulfatide IgM antibodies in peripheral neuropathy: to test or not to test? *Eur. J. Neurol.* **22**, 879–882 (2015).
105. Kuijf, M. L. *et al.* Detection of anti-MAG antibodies in polyneuropathy associated with IgM monoclonal gammopathy. *Neurology* **73**, 688–695 (2009).
106. Nobile-Orazio, E. *et al.* How useful are anti-neural IgM antibodies in the diagnosis of chronic immune-mediated neuropathies? *J. Neurol. Sci.* **266**, 156–163 (2008).
107. Léger, J. M. *et al.* Placebo-controlled trial of rituximab in IgM anti-myelin-associated glycoprotein neuropathy. *Neurology* **80**, 2217–2225 (2013).
108. Benedetti, L. *et al.* Predictors of response to rituximab in patients with neuropathy and anti-myelin associated glycoprotein immunoglobulin M. *J. Peripher. Nerv. Syst.* **12**, 102–107 (2007).
109. Renaud, S. *et al.* Rituximab in the treatment of polyneuropathy associated with anti-MAG antibodies. *Muscle Nerve* **27**, 611–615 (2003).
110. Dalakas, M. C. *et al.* Placebo-controlled trial of rituximab in IgM anti-myelin-associated glycoprotein antibody demyelinating neuropathy. *Ann. Neurol.* **65**, 286–293 (2009).
111. Draak, T. H. P. *et al.* Changing outcome in inflammatory neuropathies: Rasch-comparative responsiveness. *Neurology* **83**, 2124–2132 (2014).
112. Maurer, M. A. *et al.* Rituximab induces sustained reduction of pathogenic B cells in patients with peripheral nervous system autoimmunity. *J. Clin. Invest.* **122**, 1393–1402 (2012).
113. Ritz, M. F. *et al.* Anti-MAG IgM penetration into myelinated fibers correlates with the extent of myelin widening. *Muscle Nerve* **22**, 1030–1037 (1999).
114. Willison, H. J. *et al.* Demyelination induced by intraneural injection of human antimyelin-associated glycoprotein antibodies. *Muscle Nerve* **11**, 1169–1176 (1988).
115. Ilyas, A. A., Gu, Y., Dalakas, M. C., Quarles, R. H. & Bhatt, S. Induction of experimental ataxic sensory neuronopathy in cats by immunization with purified SGPG. *J. Neuroimmunol.* **193**, 87–93 (2008).
116. Hays, A. P., Latov, N., Takatsu, M. & Sherman, W. H. Experimental demyelination of nerve induced by serum of patients with neuropathy and an anti-MAG IgM M-protein. *Neurology* **37**, 242–256 (1987).
117. Tatum, A. H. Experimental paraprotein neuropathy, demyelination by passive transfer of human IgM anti-myelin-associated glycoprotein. *Ann. Neurol.* **33**, 502–506 (1993).
118. Steck, A. J. *et al.* Passive transfer studies in demyelinating neuropathy with IgM monoclonal antibodies to myelin-associated glycoprotein. *J. Neurol. Neurosurg. Psychiatry* **48**, 927–929 (1985).
119. Willison, H. J., Paterson, G., Veitch, J., Inglis, G. & Barnett, S. C. Peripheral neuropathy associated with monoclonal IgM anti-Pr2 cold agglutinins. *J. Neurol. Neurosurg. Psychiatry* **56**, 1178–1183 (1993).
120. Jacobs, B. C. *et al.* Human IgM paraproteins demonstrate shared reactivity between *Campylobacter jejuni* lipopolysaccharides and human peripheral nerve disialylated gangliosides. *J. Neuroimmunol.* **80**, 23–30 (1997).
121. Rojas-Garcia, R. *et al.* Bulbar involvement in patients with antiganglioside antibodies against NeuNAc(α2–3) Gal. *J. Neurol. Neurosurg. Psychiatry* **81**, 623–628 (2010).
122. Treon, S. P. *et al.* MYD88 L265P somatic mutation in Waldenström's macroglobulinemia. *N. Engl. J. Med.* **367**, 826–833 (2012).
123. van de Donk, N. W. *et al.* The clinical relevance and management of monoclonal gammopathy of undetermined significance and related disorders: recommendations from the European Myeloma Network. *Haematologica* **99**, 984–996 (2014).
124. Bhattacharyya, S. & Helfgott, S. M. Neurologic complications of systemic lupus erythematosus, Sjögren syndrome, and rheumatoid arthritis. *Semin. Neurol.* **34**, 425–436 (2014).
125. Pavlakis, P. P. *et al.* Peripheral neuropathies in Sjögren syndrome: a new reappraisal. *J. Neurol. Neurosurg. Psychiatry* **82**, 798–802 (2011).
126. Gwathmey, K. G., Burns, T. M., Collins, M. P. & Dyck, P. J. B. Vasculitic neuropathies. *Lancet Neurol.* **13**, 67–82 (2014).
127. Kaltsonoudis, E., Voulgari, P. V., Konitsiotis, S. & Drosos, A. A. Demyelination and other neurological adverse events after anti-TNF therapy. *Autoimmun. Rev.* **13**, 54–58 (2014).
128. Stübgen, J.-P. Tumor necrosis factor-α antagonists and neuropathy. *Muscle Nerve* **37**, 281–292 (2008).
129. Farhad, K., Traub, R., Ruzhansky, K. M. & Brannagan, T. H. III. Causes of neuropathy in patients referred as 'idiopathic neuropathy'. *Muscle Nerve* **53**, 856–861 (2016).
130. Antoine, J.-C. *et al.* Antifibroblast growth factor receptor 3 antibodies identify a subgroup of patients with sensory neuropathy. *J. Neurol. Neurosurg. Psychiatry* **86**, 1347–1355 (2015).
131. Titulaer, M. J. *et al.* Screening for tumours in paraneoplastic syndromes: report of an EFNS task force. *Eur. J. Neurol.* **18**, 19–27 (2011).
132. Graus, F., Saiz, A. & Dalmau, J. Antibodies and neuronal autoimmune disorders of the CNS. *J. Neurol.* **257**, 509–517 (2010).
133. Hannawi, Y. *et al.* A case of severe chronic progressive axonal polyradiculoneuropathy temporally associated with anti-CV2/CRMP5 antibodies. *J. Clin. Neuromuscul. Dis.* **15**, 13–18 (2013).

134. Antoine, J. C. *et al.* Paraneoplastic anti-CV2 antibodies react with peripheral nerve and are associated with a mixed axonal and demyelinating peripheral neuropathy. *Ann. Neurol.* **49**, 214–221 (2001).
135. Lancaster, E. *et al.* Investigations of Caspr2, an autoantigen of encephalitis and neuromyotonia. *Ann. Neurol.* **69**, 303–311 (2011).
136. van Sonderen, A. *et al.* The clinical spectrum of Caspr2 antibody-associated disease. *Neurology* **87**, 521–528 (2016).
137. Hanewinckel, R. *et al.* Prevalence of polyneuropathy in the general middle-aged and elderly population. *Neurology* **87**, 1892–1898 (2016).
138. Graus, F. *et al.* A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol.* **15**, 391–404 (2016).
139. van de Veen, W. *et al.* IgG4 production is confined to human IL-10-producing regulatory B cells that suppress antigen-specific immune responses. *J. Allergy Clin. Immunol.* **131**, 1204–1212 (2013).
140. van der Neut Kolfschoten, M. *et al.* Anti-inflammatory activity of human IgG4 antibodies by dynamic Fab arm exchange. *Science* **317**, 1554–1557 (2007).
141. Aalberse, R. C., Stapel, S. O., Schuurman, J. & Rispens, T. Immunoglobulin G4: an odd antibody. *Clin. Exp. Allergy* **39**, 469–477 (2009).
142. Collins, A. M. & Jackson, K. J. A temporal model of human IgE and IgG antibody function. *Front. Immunol.* **4**, 235 (2013).
143. Huijbers, M. G. *et al.* Longitudinal epitope mapping in MuSK myasthenia gravis: implications for disease severity. *J. Neuroimmunol.* **291**, 82–88 (2016).
144. van de Veen, W. *et al.* Role of regulatory B cells in immune tolerance to allergens and beyond. *J. Allergy Clin. Immunol.* **138**, 654–665 (2016).
145. Di Zenzo, G. *et al.* Pemphigus autoantibodies generated through somatic mutations target the desmoglein-3 *cis*-interface. *J. Clin. Invest.* **122**, 3781–3790 (2012).
146. Huijbers, M. G. *et al.* MuSK IgG4 autoantibodies cause myasthenia gravis by inhibiting binding between MuSK and Lrp4. *Proc. Natl Acad. Sci. USA* **110**, 20783–20788 (2013).
147. Lünemann, J. D., Nimmerjahn, F. & Dalakas, M. C. Intravenous immunoglobulin in neurology — mode of action and clinical efficacy. *Nat. Rev. Neurol.* **11**, 80–89 (2015).

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Author contributions
L.Q. and J.J.D. contributed to researching data for the article, discussions of its content, writing and review or editing of the manuscript. L.Q. wrote the first draft of the manuscript focusing on chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and the clinical implications of autoantibodies. J.J.D. reviewed the basic aspects of the topic, molecular descriptions, animal models and pathogenicity. R.R.-G. researched data for the article, contributed to discussions of its content, and reviewed the sections on multifocal motor neuropathy and paraproteinaemic neuropathy. I.I. researched data for the article, contributed to discussions of its content and reviewed the clinical implications of antibodies in CIDP, as well as providing the general perspective and historical background.

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