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REVIEW

Chronic inflammatory demyelinating polyradiculoneuropathy: from pathology to phenotype

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ABSTRACT

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an inflammatory neuropathy, classically characterised by a slowly progressive onset and symmetrical, sensorimotor involvement. However, there are many phenotypic variants, suggesting that CIDP may not be a discrete disease entity but rather a spectrum of related conditions. While the abiding theory of CIDP pathogenesis is that cell-mediated and humoral mechanisms act together in an aberrant immune response to cause damage to peripheral nerves, the relative contributions of T cell and autoantibody responses remain largely undefined. In animal models of spontaneous inflammatory neuropathy, T cell responses to defined myelin antigens are responsible. In other human inflammatory neuropathies, there is evidence of antibody responses to Schwann cell, compact myelin or nodal antigens. In this review, the roles of the cellular and humoral immune systems in the pathogenesis of CIDP will be discussed. In time, it is anticipated that delineation of clinical phenotypes and the underlying disease mechanisms might help guide diagnostic and individualised treatment strategies for CIDP.

INTRODUCTION

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is the most common treatable chronic neuropathy worldwide, with a prevalence ranging from ~1 to 9 cases per 100 000.[1–6] CIDP typically presents as either a relapsing or progressive neuropathy with proximal and distal weakness which develops over at least an 8-week period.[7] Although CIDP is classed as an autoimmune disorder in which an aberrant immune response is directed towards components of the peripheral nerve causing demyelination and axonal damage, the exact mechanisms underlying the development of immunopathology remain to be defined. In addition, considerable variation in clinical presentation and multiple phenotypic variants make identification of the pathogenic mechanisms complicated, further accentuated by differential patient responses to treatment. While many patients can be successfully treated with current therapies aimed at arresting immunopathogenic mechanisms, some do not respond or have lasting disability. At present there remains no biomarker to aid diagnosis or to classify patients into subgroups. Further understanding of the correlations between immunopathology and clinical phenotype would assist in guiding diagnostic and treatment approaches for CIDP. This review will address the pathology of CIDP, the role of the cellular and humoral immune systems and their relationship to phenotypic expression in CIDP.

CIDP PHENOTYPIC VARIANTS

There are many phenotypic variants of CIDP. Indeed, CIDP may not be a discrete disease entity but rather a spectrum of discrete albeit related conditions in which immunogenetic variations drive individual phenotypic differences (table 1).

Typical CIDP involves motor and sensory nerve dysfunction, with motor deficits reported in up to 94% of patients and sensory deficits in up to 89%.[19] However, only 50% of patients with CIDP display the typical phenotype.

Sensory predominant CIDP occurs in 5–35% of patients,[9–11 20] often starting with lower limb numbness.[21] Despite purely sensory symptoms, patients often demonstrate prominent motor nerve conduction abnormalities consistent with demyelination.[21] Rarely, patients have been reported with purely sensory electrophysiological features.[22] However, many of these patients go on to develop motor weakness, sometimes many years after the onset of sensory symptoms.[23] Similarly, a small subset of patients with CIDP (~5%) present with progressive sensory ataxia and sensory symptoms,[8 12] termed *chronic immune sensory polyradiculopathy*. In contrast to sensory CIDP, these patients may demonstrate no evidence of demyelination in distal sensory nerves and are preferentially affected at the large fibres of the posterior roots.[24] However, somatosensory evoked potentials may confirm proximal sensory dysfunction.[25]

While typical CIDP is characterised by proximal and distal involvement, the *distal acquired demyelinating symmetric neuropathy* (DADS) variant is restricted to a distal, symmetrical distribution[26] with predominantly sensory symptoms, although there is often electrophysiological evidence of motor involvement.[26] In 50–70% of patients with the clinical picture of DADS phenotype, the cause is a distinctly separate condition in which an IgM paraprotein having antimyelin-associated glycoprotein (anti-MAG) antibody activity is responsible for the pathogenesis.[26 27] However, the DADS clinical picture may also be caused by a phenotypic variant of CIDP, with considerable overlap with sensory and sensory ataxic CIDP phenotypes.[28]

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Table 1 Major phenotypic variants of CIDP

CIDP phenotypic variant	Estimated prevalence within CIDP	Onset	Clinical symptoms	Distribution	References
Typical CIDP	51%	Chronic	Sensory and motor	Symmetrical, proximal and distal	8–10
Sensory CIDP	4–35%	Chronic	Sensory predominant; motor involvement may develop	As per typical CIDP	5, 9–11
Chronic immune sensory polyradiculopathy	5–12%	Chronic	Sensory ataxia	As per typical CIDP	8, 9, 12, 13
Lewis-Sumner syndrome/ MADSAM	6–15%	Chronic	Sensory and motor	Asymmetrical; often upper limb onset	5, 8, 9, 14
Focal CIDP	1%	Chronic	Sensory and motor	Focal; may progress to diffuse CIDP over time	9, 15
DADS	2–17%	Chronic	Sensory predominant, but may include motor involvement	Symmetrical, distal	5, 9, 10
Acute onset CIDP	2–16%	Acute onset	As per typical CIDP	As per typical CIDP	9, 16–18
Motor CIDP	4–10%	Chronic	Motor predominant	As per typical CIDP	5, 8, 9, 13

CIDP, Chronic inflammatory demyelinating polyradiculoneuropathy; DADS, distal acquired demyelinating symmetric; MADSAM, multifocal acquired demyelinating sensory and motor neuropathy.

Motor dominant CIDP has been reported, with patients demonstrating relapsing remitting weakness with minor or no sensory electrophysiological features or symptoms.[29 30] The motor dominant phenotype represents 7–10% of patients with CIDP,[8 9] with higher rates in patients <20 years age.[31] The major differential diagnosis of motor CIDP, particularly the rare instances of focal motor CIDP, is multifocal motor neuropathy (MMN, see below).[20]

Lewis-Sumner syndrome (LSS) or *multifocal acquired demyelinating sensory and motor neuropathy* (MADSAM) is characterised by asymmetry, presenting as a multifocal multiple mononeuropathy most commonly in the upper limbs.[32] It accounts for 6–15% of CIDP patients.[8 9] Patients demonstrate abnormal sensory and motor nerve conduction, with multifocal areas of conduction block predominating in one or both upper limbs.[14 33 34] The majority of patients eventually develop diffuse, typical CIDP spreading to the other limbs.[32 34]

Focal CIDP has also been reported with symptoms remaining restricted to one focal region for a prolonged period of time,[15] but may also precede the development of diffuse CIDP.[35] Focal sensory CIDP has been reported restricted to one upper limb for 30 years.[36]

While CIDP typically demonstrates a slowly progressive course with gradual worsening over more than 8 weeks,[37] *acute-onset CIDP* demonstrates a rapidly progressive onset within 8 weeks,[16 17] which may lead to diagnostic overlap with acute inflammatory demyelinating polyneuropathy (AIDP).[18] Two to 16% of patients with CIDP may demonstrate acute-onset CIDP.[9 16–18] Nerve excitability techniques have revealed differences between the profiles of AIDP and acute-onset patients with CIDP, potentially leading to improved diagnostic outcomes.[38] Although the onset phase of CIDP is usually defined as 8 weeks or more and that of AIDP as 4 weeks or less, some patients have an intermediate length of the initial progressive phase, termed subacute inflammatory demyelinating polyradiculoneuropathy.[39–41]

Differential diagnoses and mimic disorders

In addition to the wide range of CIDP phenotypes, there are several related immune-mediated neuropathies. Evidence of a paraprotein may signify a malignant haematological disorder or a monoclonal gammopathy of undetermined significance (MGUS).[42] Demyelinating neuropathy in the context of monoclonal gammopathy may be phenotypically similar to CIDP and has been termed paraproteinaemic demyelinating neuropathy (PDN). PDN associated with IgM paraprotein typically has a slowly progressive, distal, predominantly sensory phenotype.[26 42 43] More than 50% of patients with an IgM paraprotein have anti-MAG IgM antibodies.[44] Anti-MAG neuropathy is often associated with sensory ataxia and tremor.[43 45] Electrophysiological characteristics of anti-MAG neuropathy include reduced or absent sensory action potentials and disproportionately prolonged distal motor latencies.[46 47] While patients with PDN may meet diagnostic criteria for CIDP, the presence of high titres of anti-MAG antibodies precludes a diagnosis of CIDP.[7] IgG and IgA paraproteinaemic demyelinating neuropathies are less common and often resemble typical CIDP, particularly in their response to therapy.[48 49] It is uncertain whether the paraprotein is involved with the pathogenesis of these cases.

CANOMAD (Chronic ataxic neuropathy with ophthalmoplegia, M-protein, cold agglutinins and disialosyl antibodies) is a rare disorder with specific clinical features consisting of severe sensory ataxia and cranial nerve involvement including ophthalmoplegia, dysphagia or dysarthria and only minimal weakness.[50] It occurs in around 2% of patients with IgM PDN.[51] CANOMAD is associated with antibodies to ganglioside disialosyl moieties.[50] CANOMAD typically progresses over years and peripheral neuropathy may precede the development of other features such as ophthalmoplegia.[52]

Slightly less uncommon is the *POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinology, Monoclonal gammopathy and Skin changes)*, which is usually associated with plasma cell dyscrasia of an IgA or IgG paraprotein and a cluster of multisystem clinical features.[42] It often presents with neuropathy[53] typified by sensory and motor involvement with demyelinating and axonal features.[42] The onset is subacute and progression leads to severe motor weakness.[54] Neuropathic pain may be prominent.[53] High levels of the cytokine vascular endothelial growth factor[55] are helpful in diagnosis.

The major differential diagnosis of motor CIDP, particularly the rare instances of focal motor CIDP, is *MMN*.[56] MMN is a chronic, immune-mediated neuropathy with asymmetric, predominantly distal often upper limb weakness in the absence of objective sensory involvement.[57–59] MMN is characterised by multifocal conduction blocks in motor fibres of mixed nerves with normal sensory conduction through the same segments. Anti-GM1 IgM antibodies have been reported with varying prevalence in patients with MMN ranging from 30% to 85%[60 61] but most studies report between 40% and 50%.[62–64] This range is largely due to discrepancies in methodology[61 65] but it is widely accepted that anti-GM1 antibodies do occur in a

higher proportion of patients with MMN than in control groups and may correlate with severity of weakness and disability.[62] The asymmetry of presentation and motor involvement resemble those in the CIDP variants MADSAM and motor dominant CIDP, leading to potential for misdiagnosis. MMN usually responds to intravenous immunoglobulin (IVIg) immunotherapy but, unlike CIDP, not to plasma exchange or corticosteroid treatment.[56] However, motor CIDP has also been reported to be unresponsive to or deteriorate after treatment with steroids.[29 66]

Clinical diagnosis

The diagnosis of CIDP relies on a combination of clinical and electrophysiological criteria. A number of criteria have been proposed. The European Federation of Neurological Societies (EFNS)/Peripheral Nerve Society (PNS) guidelines were developed for clinical and research use.[7] The criteria combine clinical features and electrophysiological evidence to define CIDP, with supportive criteria including elevated cerebrospinal fluid (CSF) protein, gadolinium enhancement of nerve roots or plexus on MRI or nerve biopsy findings providing supplemental diagnostic evidence. Electrodiagnostic evidence of peripheral nerve demyelination in motor nerves is required for diagnosis, including distal latency prolongation, reduction of motor conduction velocity, prolongation of F-wave latency and partial motor conduction block and must be identified in at least two nerves for a diagnosis of 'definite' CIDP.[7] It should be noted that in some cases of pure sensory CIDP where routine motor conduction studies are normal, the EFNS/PNS guidelines may fail to diagnose the condition as CIDP. In these cases, if CIDP is suspected, the proximal region of the peripheral sensory nervous system should be carefully interrogated using sensory evoked potentials. Although other criteria have been proposed the EFNS/PNS criteria have good sensitivity and specificity for CIDP diagnosis and are currently the most commonly used.[6 67 68]

IMMUNOPATHOGENESIS OF CIDP

The abiding theory of CIDP pathogenesis is that cell-mediated and humoral mechanisms act synergistically to cause damage to peripheral nerves. There are several lines of evidence to support the conclusion that CIDP is an autoimmune disease mediated by humoral and/or cellular immunity against as yet undefined Schwann cell/myelin antigens (figure 1). Although some patients have reported antecedent infections prior to onset of neurological symptoms neither the target(s) nor the trigger for the autoimmune response has been identified and no infectious agent has been consistently linked with initiation of disease. However, the autoimmune aetiology is supported by the efficacy of treatments that target the immune system, including IVIg, plasma exchange and corticosteroids, and by evidence of an inflammatory response in the blood and peripheral nerves.

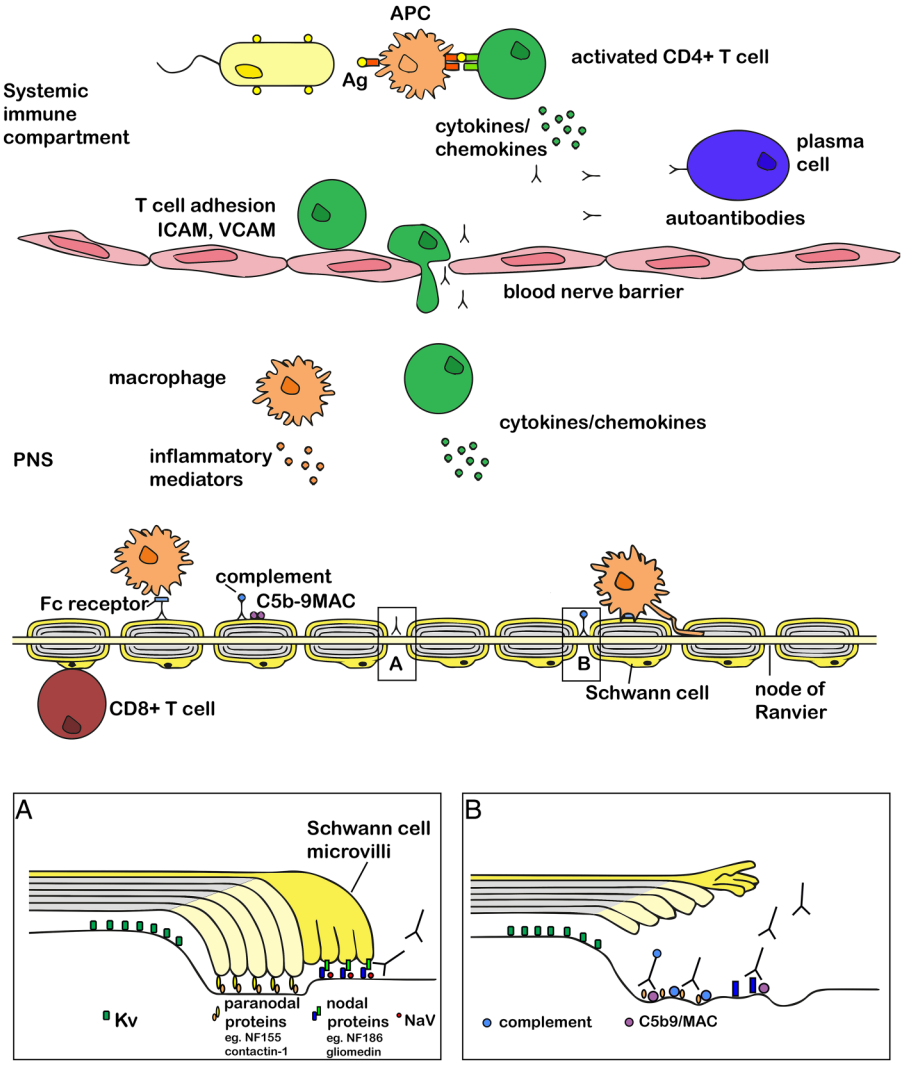

Figure 1 Immunopathogenesis of chronic inflammatory demyelinating polyneuropathy. The putative antigen is presented by antigen presenting cells to autoreactive T cells in the peripheral immune compartment. T cells become activated, undergo clonal expansion, release inflammatory mediators and cross the blood-nerve barrier (BNB). Breakdown of the BNB allows humoral factors such as autoantibodies access to the endoneurium. Further damage may be caused by macrophage-mediated demyelination, complement deposition, deposition of C5b-9/membrane attack complex (MAC), subsequent cell lysis and $CD8^+$ direct lysis of cells. Inset: Effects of antibody binding at the node of Ranvier. (A) Binding of an autoantibody to the node of Ranvier could block the function of nodal molecules interfering with saltatory conduction. (B) Binding of an antibody followed by fixation of complement and deposition of the MAC leading to disruption/destruction of the node and surrounding areas.

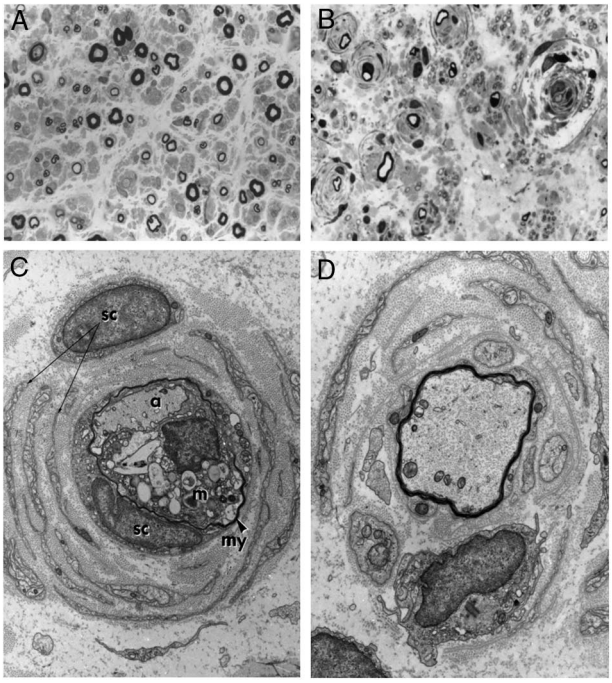

Figure 2 Semithin sections of biopsies from the (A) sural nerve and (B) brachial plexus in the same patient. Demyelination and small onion bulbs can be seen in the sural nerve biopsy whereas marked hypertrophic changes are also apparent in the plexus. Transmission electron micrographs from sural nerve show onion bulbs as well as (C) macrophage-mediated demyelination (D) and thinly remyelinated axons. Sc, Schwann cell; a, axon; m, macrophage; my, myelin.

Pathology of CIDP

A combination of autopsy, MRI and ultrasound studies has demonstrated that the inflammatory lesions in CIDP occur predominantly in the spinal roots, proximal nerve trunks and major plexuses but can also be disseminated throughout the PNS. However, due to the relative inaccessibility of the proximal nerves and nerve roots, most biopsies are taken from the sural nerve. Although this site is remote from the most prominent inflammatory activity, pathological changes in sural nerve biopsies nevertheless encompass a broad spectrum of changes which include no abnormalities, oedema, demyelination, formation of onion bulbs,[69] axonal degeneration and perivascular or endoneurial inflammatory infiltrates of macrophages[70] and T cells[71 72] (figure 2). Many of these pathological changes are also evident in an animal model of CIDP, experimental autoimmune neuritis (EAN), which is induced in susceptible strains of rodents or rabbits by immunisation with either whole myelin or specific myelin proteins and is the result of an autoimmune attack on peripheral nerve mediated by the cellular and humoral arms of the immune response.

Cellular mechanisms

Cellular immune mechanisms are implicated in the pathogenesis of CIDP based on the presence of inflammatory infiltrates in sural nerve biopsies,[73] changes in the frequencies/function of T cell subsets,[74 75] altered expression of cytokines[76–80] and other inflammatory mediators[81 82] in the blood and CSF of patients with CIDP, and the contribution of T cells to disease in EAN.[83–86]

Disruption of the blood nerve barrier

One of the critical precursors to inflammation of the nerve and subsequent nerve damage is the breakdown of the blood nerve barrier (BNB). Under normal physiological conditions the BNB maintains the homeostasis of the endoneurium by preventing free movement of soluble factors such as serum proteins from the blood into the nerve microenvironment. However, on activation, T cells are not only able to cross the BNB into the endoneurium but also affect BNB permeability so as to allow entry of usually restricted molecules. During active disease CD4+ T cells in the periphery up-regulate activation markers[87] such as t-bet and pstat1[75] and secrete proinflammatory cytokines including interleukin (IL)-2,[76 87] interferon γ (IFNγ)[75] and IL-17[75 88] as well as the chemokines interferon gamma-induced protein (IP)-10[81 82] and macrophage inflammatory protein 3 β (MIP3β).[81] This release of cytokines and chemokines into the circulation causes further activation of macrophages and induces upregulation of the adhesion molecules vascular cell adhesion molecule (VCAM)-1,[89] endothelial leukocyte adhesion molecule (ELAM)-1[90] and intercellular adhesion molecule (ICAM)-1[91] on endothelial cells lining the blood vessels of the nerve.

Activated T cells adhere to the endothelial cells by interacting with adhesion molecules, roll along the vessel surface and then migrate across the BNB (figure 3). Inflammatory mediators, such as matrix metalloproteinases[92] and proinflammatory cytokines/chemokines[76 80] continue to be secreted by these T cells as they transmigrate across the blood vessels, contributing to increased permeability of the BNB and upregulation of the immune response within the nerve. Breakdown of the BNB is a critical event as it allows soluble factors such as antibodies access to the endoneurium. It can be visualised by MRI gadolinium enhancement of nerve trunks or plexuses in patients with CIDP.[93]

Infiltration of inflammatory cells

CIDP sural nerve biopsies show that the infiltrating inflammatory cells include CD8+ T cells,[94] CD4+ T cells and macrophages.[73 95] Local reactivation of infiltrating T cells is facilitated by the upregulation of antigen presenting major histocompatibility complex (MHC) class II[72] molecules and the costimulatory molecules B7-1 and B7-2[96 97] not only by infiltrating macrophages but also by Schwann cells. Proinflammatory cytokines such as tumor necrosis factor α, IFNγ and IL-2 become expressed by a variety of cell types within the nerve[98] and amplify the immune response. Macrophages are the dominant infiltrating inflammatory cell and form clusters around endoneurial vessels.[70] Activated resident and recruited macrophages play an active role in many aspects of the immune response including antigen presentation and release of proinflammatory cytokines or toxic mediators. They also have an important role in the end stages of demyelination by stripping away and phagocytising myelin.[99] In ultrastructural studies of CIDP nerve biopsies macrophages can be seen insinuating themselves between the spirals of Schwann cell plasma membrane including the outer mesaxon and breaking down the myelin lamellae by extending elongated processes between the lamellae.[100]

The role of $CD8^+$T cells

The role of $CD8^+$ T cells in the pathogenesis of CIDP is contentious. In CIDP nerves[72] Schwann cells significantly up-regulate MHC class I molecules, potentially enabling recognition by and reactivation of cytotoxic ($CD8^+$) T cells. Reactivation of CD8+ cells within the endoneurium does occur in some conditions such as leprosy where Schwann cells infected with *Mycobacterium leprae* can be lysed by CD8+ T cells specific for the bacteria.[101] To date no foreign or self-antigen has been

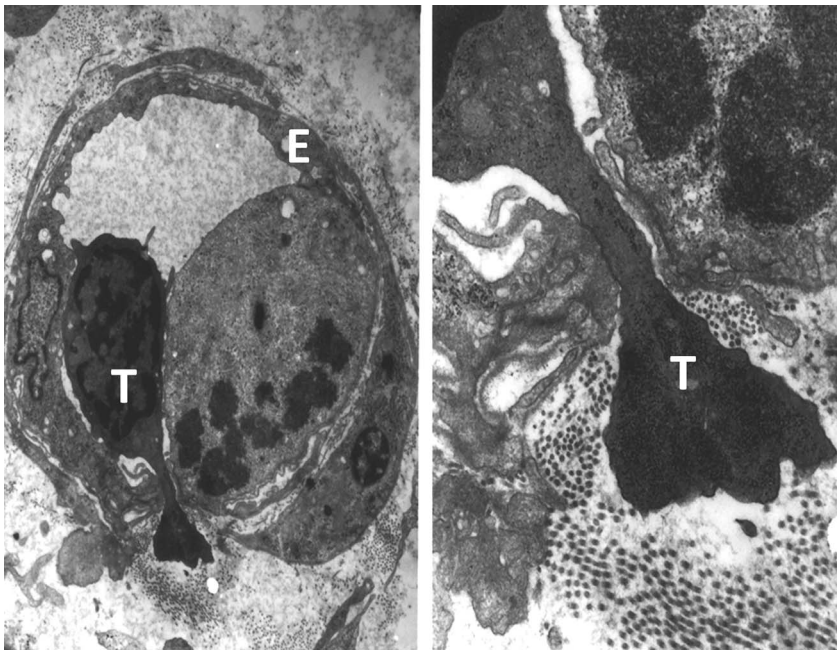

Figure 3 Transmission electron micrograph of rat nerve after adoptive transfer experimental autoimmune neuritis showing a lymphocyte leaving a blood vessel and infiltrating the endoneurium.

identified as a $CD8^+$ target in CIDP but there is evidence of similar clonal expansion of $CD8^+$ cells in sural nerve biopsies and peripheral blood.[94] These $CD8^+$ T cell clones are enriched in the nerve suggesting that an antigen-driven, $CD8^+$ cell mediated attack on the nerve contributes to the pathogenesis of CIDP. However, evidence of these CD8+ cells in direct contact between CD8+ T cells and their target cells in situ is lacking, limiting further conclusions about their role as cytotoxic effector cells in CIDP. A recent analysis of the T cell repertoire in patients with CIDP found a broader activation of $CD8^+$ than $CD4^+$ T cells that was reduced after treatment with IVIg.[102] Such oligoclonal activation of CD8+ cells is often regarded as evidence of a T cell response to chronic infection although no infectious agent has consistently been linked with CIDP. CD8+ T cells do not play a significant role in EAN.

Role of regulatory T cells and central tolerance

Although self-reactive T cells are largely eliminated during selection in the thymus a number escape into the periphery and have the capacity to cause autoimmune disease. These cells are kept in check by peripheral tolerance mechanisms such as the immunosuppressive action of regulatory T cells. In CIDP, there are indicators that the immunoregulatory cellular response involved in controlling excessive or inappropriate immune activation is impaired.[103 104] The numbers of circulating T regulatory cells, identified by the $CD4^+CD25^{high}Foxp3^+$ markers, are reduced[104] and, when isolated, are less effective in suppressing proliferative responses than those from healthy controls.[103 104] Dysregulation of the regulatory cell compartment could thus contribute to the immune dysfunction seen in CIDP.

The complexities of the interactions between autoreactive T cells, antigen-presenting cells and the inflammatory mediators released during an autoimmune reaction are emphasised in a mouse model of CIDP that develops spontaneously in non-obese diabetic mice (NOD) deficient in the costimulatory molecule B7-2.[105] The NOD mouse model was originally established to determine the role of T cell costimulation in the onset of diabetes mellitus. While blocking of B7-2 costimulation protected the mice from diabetes they unexpectedly developed a spontaneous autoimmune peripheral polyneuropathy (SAPP) similar to CIDP in terms of clinical signs, electrophysiology and histology. SAPP is mediated by myelin protein P0-specific $CD4^+$ T cells as demonstrated by the ability of hybridomas generated from CD4+ T cells nerve infiltrates to adoptively transfer disease.[106] Conversely, a P0T cell receptor transgenic mouse did not spontaneously develop disease unless crossed to a RAGKO background,[106] which had the effect of eliminating regulatory T cells leaving the pathogenic P0T cells unrestricted. Modulation of central tolerance mechanisms in NOD mice also has the effect of skewing the autoreactive immune response away from the pancreas towards the peripheral nerve resulting in spontaneous neuropathy. This can be demonstrated in NOD mice in which a point mutation in the autoimmune regulator (Aire) gene results in the reduced expression of P0 in the thymus and a concomitant increase of P0 specific T cells in the periphery.[107] Similarly, autoimmunity is shifted towards the peripheral nerve in another NOD model deficient for isoforms of ICAM-1.[108] Altered expression of ICAM-1 on thymic epithelial cells transforms selection of T cells from a diabetogenic into a neuritogenic repertoire.[108] Studies such as these highlight the critical role of regulatory mechanisms in maintaining immune homeostasis and the impact that changes to regulation can have on the development of disease.

Humoral mechanisms

Autoantibody responses to major myelin proteins

The efficacy of plasma exchange in the treatment of CIDP indicates that humoral mechanisms are critical to its pathogenesis. Furthermore, there is also a considerable amount of circumstantial evidence for the involvement of humoral immune mechanisms from biopsy and serological studies. Immunoglobulin and complement can be seen deposited on the outer surface of Schwann cells and the compact myelin in sural nerve biopsies from some patients with CIDP [109 110] while serum from some patients with CIDP can be shown to bind to normal nerve sections using indirect immunofluorescence[111] (figure 4). In a small proportion of patients who responded well to plasma exchange, serum that had been shown to bind to nerve sections caused demyelination[111] and a reduction of conduction velocity[111 112] following intraneural injection in the rat. Further experiments with this serum showed that the target antigen is compact

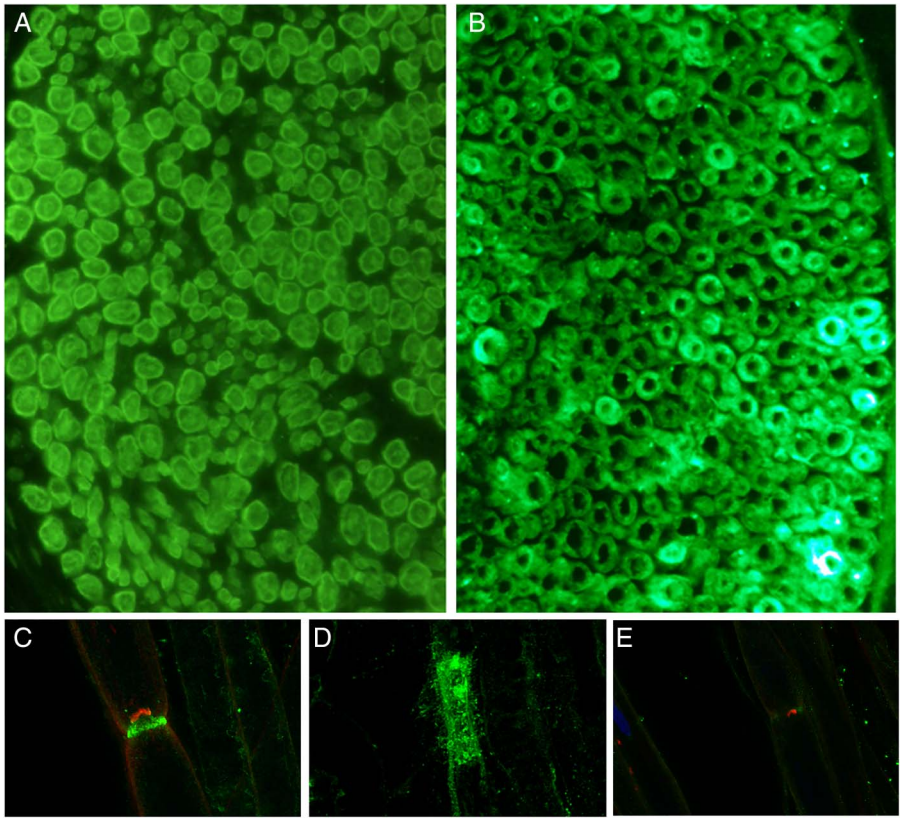

Figure 4 Indirect immunofluorescence staining of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) sera on transverse nerve sections (A and B) or teased nerve fibres (C and D). Antibodies (green) in the sera of patients with CIDP can be shown binding to the (A) non-compact regions of the Schwann cell, (B) compact myelin (C) nodes of Ranvier, as shown by staining for gliomedin (red) or (D) the paranodes. (E) Serum from a normal blood donor does not bind to teased nerve fibres, node of Ranvier stained for gliomedin (red).

myelin protein P0.[113] Nevertheless, for the majority of patients the specific target of the autoantibody response is unknown but due to the striking nature of the demyelination seen in the histopathological sections of CIDP nerve, these proteins located in the compact myelin have long been thought of as the most likely candidate autoantigens (table 2).

This view is supported by the animal model, EAN, which can be induced in rats using purified myelin proteins P0,[128] P2[129] and peripheral myelin protein (PMP)-22[130] demonstrating that an autoimmune response to these autoantigens has the potential to initiate disease and contribute to nerve damage and clinical symptoms. However, after many years of investigation there is little evidence for a pathogenic role of autoantibody responses to these major myelin proteins in the majority of patients with CIDP. Although some studies have detected autoantibody responses to P2[115], P0,[111 113 114 116] PMP-22[121] and connexin[119] in CIDP serum, others have not.[117] There is even more contention surrounding the pathogenicity of these autoimmune responses; of the myelin protein antibodies detected in patients with CIDP only those with specificity for P0 have been shown to be pathogenic in vivo by intraneural injection[113 131] and passive transfer.[113] The pursuit of autoantibodies reactive to the major compact myelin proteins in CIDP has thus far been somewhat unproductive and the search is now being diverted to other areas of the myelinated axon.

Autoantibody responses to the nodal regions of myelinated axons

Current studies on autoantibody specificity, not only in CIDP but also in some forms of GBS, are shifting their focus from the major myelin proteins to those located in the non-compact myelin, which includes the node of Ranvier, paranode and juxtaparanode.[124 126 132] Axoglial proteins are crucial to the formation and maintenance of the node of Ranvier and paranodal regions of myelinated axons. The nodal cell adhesion molecules (CAMs) gliomedin, neuron glia-related CAM (NrCAM) and neurofascin 186 (NF186) are vital for the initial clustering of Na^+ channels during development[133] and contribute to the long-term maintainence of Na^+ channel clustering at the node of Ranvier.[133] The adjacent paranode consists of axoglial junctions between paranodal loops and axonal membrane composed of contactin-1/caspr-1 complexes which bind to Schwann cell neurofascin 155 (NF155).[134] These proteins form and maintain the paranodal septate junctions. NF155 is essential for ion channel segregation, paranodal structure and efficient nerve conduction.[135] These regions are essential for effective saltatory conduction acting as a membrane barrier to limit lateral diffusion of ion channels, ensuring that Na^+ is concentrated at the node and K^+ at the juxtaparanode. This area comes under immune attack in several antiganglioside-mediated neuropathies which have recently been coined 'nodoparanodopathies'.[136] For example, in the AMAN form of GBS autoantibodies against glycolipids or glycolipid complexes bind to the nodal regions which results in complement fixation and injury to the node.[137 138] However, these antibodies are not consistently identified in the demyelinating form of GBS, AIDP,[139] nor in CIDP and the target(s) in these disorders remain elusive. In contrast, autoantibodies to a number of proteins located in the nodal regions have recently been described in a small minority of patients with AIDP and CIDP, and include antibodies to gliomedin,[126] neurofascin,[124 126] contactin-1,[127] caspr1[127] and moesin[140] (table 2). A recent study reported that 62% of patients with MMN had antibody reactivity to either gliomedin or NF186 and that 10% of sera without anti-GM1 IgM did have anti-NF186 antibodies.[141]

Indeed, in CIDP nerve biopsies nodal and paranodal regions are disrupted and the proteins vital for maintaining structural integrity are abnormally expressed and distributed.[142] Electron microscopic examination of nerve biopsies has revealed abnormalities in Schwann cell microvilli and paranodal glial loops with large

Table 2 Antibodies to myelin proteins and nodal antigens in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

Candidate antigen	Positive sera/total tested	Ig Class	Method	Reference
Myelin proteins				
P0	6/21	IgG	Western blotting	113
	4/21		IF on normal nerve	
	6/32	IgG (3), IgA (3)	Western blotting	114
	6/36*	IgG	ELISA	115
	5/32	IgM	ELISA	116
	0/32	IgG		
	7/30*	IgG	ELISA	117
	0/20*		ELISA	118
	1/24*		Western blotting	119
	3/40*	IgG	ELISA	120
	2/40*	IgM		
P2	11/32*	IgM	ELISA	116
	4/32*	IgG		
	4/36*	IgG	ELISA	115
	4/30	IgG	ELISA	117
	3/20*		ELISA	118
PMP22	3/30*	IgG	ELISA	117
	0/24*		Western blotting	119
	7/17	Ig (3), IgM (3), pan Ig (1)	ELISA	121
	6/17		Western blotting	
	3/6*		Western blotting	122
Cx32	1/24*		Western blotting	119
MBP	2/40*	IgG	ELISA	120
Nodal antigens				
Neurofascin 155	4/61	IgG4	ELISA	123
	5/117	IgG4, IgG3; IgM, IgA	ELISA	124
	CIDP 0/16*	IgG	Cell-based assay	125
	CCPD 5/7			
	CIDP 4/16*		ELISA	
	CCPD 6/7			
Neurofascin 186	1/50*	IgG	Cell-based assay	126
	0/117*		ELISA	124
Contactin-1	3/46†	IgG	Cell-based assay	127
	1/50*	IgG	Cell-based assay	126

*Frequency not significantly higher than in healthy controls or other neuropathy controls.
†Contactin-1/caspr-1 in one patient.
CCPD, combined central and peripheral demyelination; IF, immunofluorescence.

vacuoles in the Schwann cell outer cytoplasm and nodal axoplasm.[142] Further, punctate immunoreactivity for Na^+ and K^+ channels were distributed along the axon with diffuse distribution of caspr-1.[142] In addition, examination of cutaneous myelinated nerve fibres demonstrated elongated nodes of Ranvier and broadening of neurofascin and caspr staining compared to normal controls.[143] In EAN models induced by immunisation with PNS myelin, disruption of neurofascin and gliomedin occurred prior to paranodal demyelination and the dispersion of Na^+ channels.[144] Importantly, these changes were associated with the generation of serum autoantibodies to neurofascin and gliomedin, suggesting that these proteins may represent immune targets in some demyelinating neuropathies.[144]

Critically, there is now evidence to suggest that nodal antigens are important in some cases of CIDP. Devaux *et al*[126] found that 30% of patients with CIDP have serum IgG that binds to either the nodes of Ranvier or the paranodes in teased nerve fibres and in some cases identified the target antigens as neurofascin, gliomedin or contactin. Further, several studies have specifically identified autoantibodies against CAMs at the nodes of Ranvier and paranodal regions in patients with CIDP.[123 124 126 127 145]

Identified nodal and paranodal antigens in CIDP

Antibodies against the CAM neurofascin have been identified in 4% of patients with CIDP.[123 124] Interestingly, the majority of identified antibodies have been targeted against the glial neurofascin isoform NF155. While antibodies can be cross-reactive between glial NF155 and neuronal NF186 due to structural similarity,[146 147] neurofascin antibodies in patients with CIDP have been singularly targeted against NF155.[123 124] In two patients with high titres of anti-NF155 (IgG3 isotype) antibodies, plasma exchange was of clinical benefit.[124] In one of these patients anti-NF155 reactivity was monitored throughout the disease course and progressively declined over 4 years after which the patient went into remission and was weaned off plasma exchange treatment. Anti-NF155 antibodies have also been identified in 5/7 patients with combined central and peripheral demyelination.[125] In this study patients with anti-NF155 antibodies responded to either IVIg or PE after corticosteroids had only been partially effective. On the other hand, in combined central and peripheral demyelination patients without anti-NF155 antibodies, corticosteroids were effective for PNS and CNS lesions. The high frequency of anti-NF155 antibodies in combined central and peripheral demyelination and their relationship to treatment success makes them a possible marker for diagnosis and response to therapy: more investigation of these antibodies in this rare condition is needed.

A further subset of patients with CIDP has been identified with antibodies to NF155, with the dominant immunoglobulin subtype IgG4.[123] Initially, 2/53 CIDP and 0/204 patients with

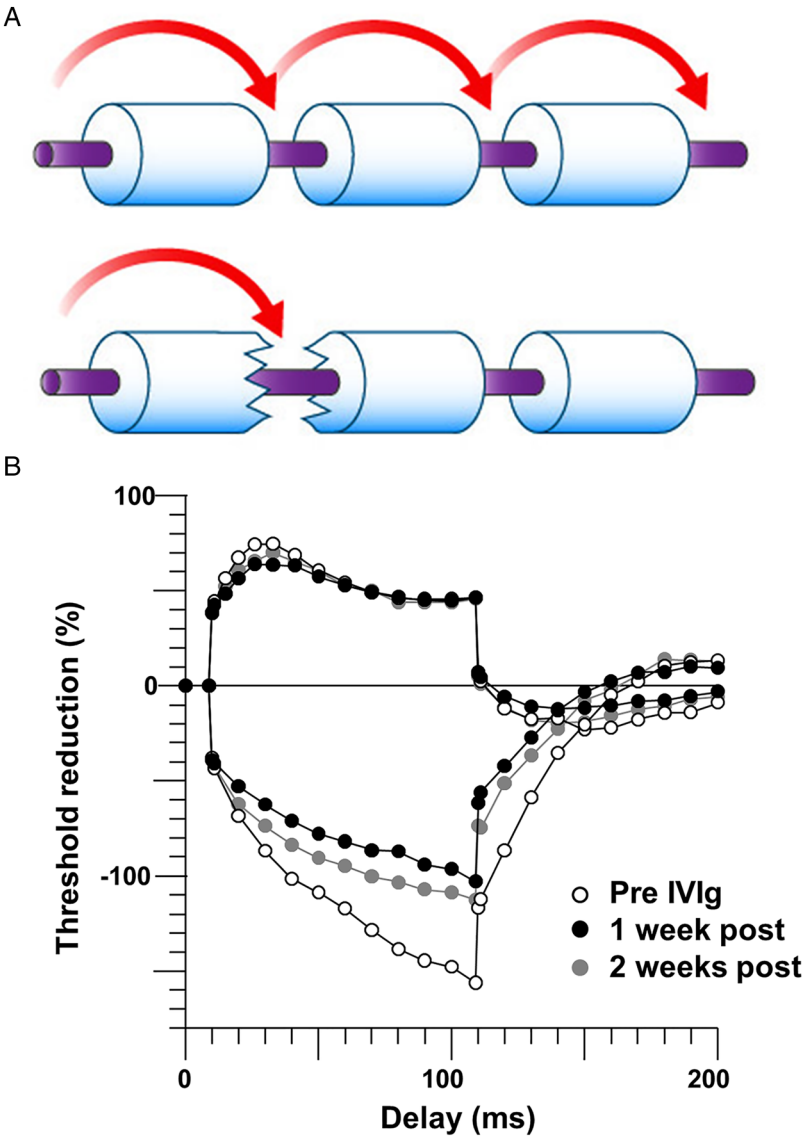

Figure 5 (A) Upper panel—saltatory conduction, with the nerve impulse jumping from a node of Ranvier to the next node along a myelinated axon; Lower panel—demyelination and alteration of nodal function may lead to conduction failure in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) (B) Restoration of conduction may be associated with excitability changes following maintenance intravenous immunoglobulin (IVIg) administration, as demonstrated in threshold electrotonus recordings. There is reduction in hyperpolarising threshold electrotonus from pre IVIg influsion (white) to 1 week post-IVIg infusion (black), which begins to return to pre IVIg values at 2 weeks post-IVIg infusion (grey).

other neuromuscular disorders were found to have anti-NF155 IgG4 antibodies. A further eight patients with CIDP refractory to IVIg treatment were then identified using a database and tested for anti-NF155 antibodies. Two of eight IVIg-refractory patients were found to have the anti-NF155 IgG4 antibody. These patients demonstrated similar clinical features including severe predominantly distal neuropathy, disabling tremor and poor response to treatment. The IgG4 subclass of IgG immunoglobulin has some distinctive properties that distinguish it from the other subclasses of IgG.[148] IgG4 antibodies have a reduced capacity to induce complement and cell activation due to their low affinity for C1q and Fc receptors. IgG4 antibodies are often considered to be anti-inflammatory because they can reduce complement-mediated damage and inflammation by completing with other IgG subclasses to bind antigen without activating immune effector mechanisms. However, in some instances IgG4 antibodies have been shown to be pathogenic via an 'antigen blocking' mechanism in which the antibody blocks critical functions of the bound target antigen.[124] This mechanism occurs in myasthenia gravis where anti-muscle-specific kinase (MuSK) IgG4 antibodies bind directly to MuSK and interfere with its function leading to disruption of synaptic structure and transmission.[149] Investigation of larger series of patients with CIDP for anti-NF155 IgG4 antibodies would be worthwhile.

An additional subset of patients with CIDP (3/46 vs 0/104 controls with other neurological diseases) have been identified with autoantibodies reactive to the axonal contactin-1/caspr complex in the paranode.[127] Cases positive for contactin-1 antibodies typically had an aggressive onset of disease, predominantly motor symptoms, early axonal involvement and were partially or not at all responsive to IVIg requiring further treatment with corticosteroids.[127] A pathogenic role for these contactin-1 antibodies has been supported by demonstrating disruption of paranodal junctions and interference with nodal structure, leading to nodal enlargement, decreased caspr immunostaining and reduced conduction velocity in myelinated neuronal cultures.[150]

Pathophysiological significance of autoantibodies

Despite recent advances in this area further studies are needed to scrutinise the pathophysiological significance of autoantibodies directed towards the nodal regions. It is now clear that the molecular and anatomical complexity of the node of Ranvier and surrounding paranodes and juxtaparanodes influences the ability of an antibody to bind in vivo and thus the likely pathogenicity of the response. In the case of autoimmunity to neurofascin, antibodies to both the NF155 and NF186 isoforms can bind to the proteins when expressed on the

surface of transfected cells using in vitro assays. However, experimental modelling suggests that nodal NF186 is the primary target[145 147] and antibodies to NF155 are unable to bind to either neurofascin isoform in vivo in EAE experimental models.[151] The ability of anti-NF155 antibodies to bind in vivo could be affected by steric hindrance caused by interacting proteins in close proximity[151] or due to limited accessibility of the paranode to circulating antibodies. The paranodal localisation of NF155 means that disruption of the paranodal structure may be necessary before autoantibodies are able to bind in vivo.[134] However, NF155 may become accessible following demyelination, suggesting that such antibodies may contribute to pathogenicity after the onset of demyelination rather than directly produce demyelination. In support of this, antibodies against NF155 have been demonstrated to inhibit myelination in vitro by disrupting the caspr/contactin/NF155 complex[152] and may have an important role in preventing remyelination.[152] This discrepancy highlights the need to fully consider the complex interactions between axons and Schwann cells at the molecular and anatomical level before meaningful conclusions as to the clinical impact can be drawn.

Similarly interactions at the molecular level could also impinge on the ability to detect autoantibody responses. Recent work on the detection of antibodies to gangliosides in the sera of patients with GBS has demonstrated that while patients with the axonal AMAN disease variant have reactivity against single glycolipid molecules, patients with GBS with demyelinating disease do not.[153] In some instances there is a better chance of detecting reactivity to complexes of two different glycolipids, which may reflect 'pattern recognition' of glycolipids as they are orientated in living neural membranes.[139 154] A similar phenomenon may also be operating in the recognition of or access to binding sites on proteins expressed at the node and paranode, particularly considering that many of the proteins in the axoglial junction form complexes with proteins in the apposing Schwann cell membrane. Indeed autoantibody reactivity to the paranodal protein contactin-1 has been described in 3/46 patients with CIDP as discussed above. In two of these patients reactivity was detected using contactin-1 alone whereas in other case it could only be detected when it was in complex with caspr1.[127]

In light of these studies full consideration must be given to the anatomical location and molecular interactions of potential autoantigens in order to develop assays to detect pathologically relevant antibodies responses. Further, differences in the assays used by various groups to detect autoantibody responses, that is, ELISA versus cell-based assays, protein complexes versus individual proteins, rat versus human protein, make interpretation and/or confirmation of findings more difficult. There is also the 'chicken or the egg' conundrum of whether these nodal proteins are the primary target of the immune response or whether autoantibodies to these molecules are an epiphenomenon generated when self-peptides are released after nerve damage due to an inflammatory response targeting something else entirely.

Functional significance of nodal disruption in CIDP

While further work is needed to examine the pathophysiological significance of nodal antigenic targets in CIDP, any disruption of nodal function is likely to interfere with normal nerve excitability and membrane potentials, contributing to conduction failure by interfering with saltatory conduction and ion channel function. In support of this, axonal excitability studies in patients with CIDP have revealed a range of findings demonstrating aberrant membrane excitability and membrane potential.[38 155 156] These studies provide evidence of altered axonal function in CIDP, which may reflect autoantibody interference with the node of Ranvier (figure 5A). Removal of antibodies from the circulation or interference with antibody effector mechanisms via immunotherapy may facilitate recovery from nodal disruption, providing a mechanism to account for the rapid recovery seen in some patients after treatment which is not consistent with demyelination.[112 157] Accordingly, cyclical modulation of axonal excitability has been demonstrated following successive IVIg maintenance treatments (figure 5B).[156]

While the safety factor of transmission typically ensures that the magnitude of current at the nodes of Ranvier is more than five times in excess of that required for action potential propagation,[158] demyelination reduces the safety factor, effectively reducing the ability of the axon to maintain charge.[159] The demands of a high impulse load during normal activity may further tip the balance towards conduction failure, leading to susceptibility to conduction failure during exercise. Accordingly maximal voluntary contraction has been demonstrated to reduce CMAP amplitude[160 161] and increase temporal dispersion[162] in patients with CIDP.

Motor axons demonstrate reduced accommodation to hyperpolarising membrane potential change and are more susceptible to conduction failure than sensory axons.[163] Motor axons also demonstrate reduced activation of the hyperpolarisation activated cation current I_h and a hyperpolarised membrane potential relative to sensory axons, making them less able to respond to additional hyperpolarisation and vulnerable to conduction failure.[164] These biophysical properties may influence treatment responsiveness. Patients with motor dominant CIDP as well as MMN may demonstrate clinical deterioration following corticosteroid treatment.[56 66] Patients with typical CIDP and evidence of focal demyelination and reduced sensory electrophysiological abnormalities were also more likely to deteriorate with corticosteroid treatment, although these associations need to be confirmed in a larger sample.[165] Corticosteroids have been demonstrated to modulate excitability in motor neurons, leading to hyperpolarisation of resting membrane potential via enhancement of Na^+/K^+ pump activity.[166–168] Steroid administration also increases Na^+/K^+ pump activity and expression in human skeletal muscle fibres.[169] Motor axons with focal demyelination or conduction block may be most vulnerable to this additional stress on normal membrane excitability produced by corticosteroid treatment and hence likely to be predisposed to further conduction failure and block.[165]

CONCLUSIONS

Despite extensive efforts, a unifying immunopathological mechanism remains to be established for either the acute or chronic inflammatory demyelinating neuropathies. On the other hand, there is significant phenotypic variability in the clinical spectrum of CIDP suggesting that there are differing immunopathological mechanisms at play. Further progress in the understanding of the pathogenesis of CIDP may come from a 'splitting' rather than 'lumping' approach as exemplified by the current interest in the recently defined antibodies targeting nodal and paranodal antigens. These antibodies while present in only a small number of cases, in the range of 2–5%, may allow us to understand the pathogenesis of CIDP and its variants, to define subtypes of CIDP that will respond to differing forms of immunomodulation and provide reproducible biomarkers that will allow disease and treatment monitoring. It was the recognition more than 20 years ago of differing subtypes of GBS which led to the major advances in the understanding of that disorder and the

more recent discovery of different pathogenic mechanisms underlying subtypes of the central demyelinating disorder MS has shown that unique treatment regimes are needed for these differing pathological processes. More work needs to be undertaken to explain the immunopathogenesis of the majority of CIDP cases, but significant progress has been made which should translate into better patient stratification and subsequently improved care.

All cases are unique, and very similar to others.

~T.S. Eliot, *The Cocktail Party*

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REFERENCES

1 McLeod JG, Pollard JD, Macaskill P, *et al*. Prevalence of chronic inflammatory demyelinating polyneuropathy in New South Wales, Australia. *Ann Neurol* 1999;46:910–13.
2 Chio A, Cocito D, Bottacchi E, *et al*. Idiopathic chronic inflammatory demyelinating polyneuropathy: an epidemiological study in Italy. *J Neurol Neurosurg Psychiatry* 2007;78:1349–53.
3 Iijima M, Koike H, Hattori N, *et al*. Prevalence and incidence rates of chronic inflammatory demyelinating polyneuropathy in the Japanese population. *J Neurol Neurosurg Psychiatry* 2008;79:1040–3.
4 Lunn MP, Manji H, Choudhary PP, *et al*. Chronic inflammatory demyelinating polyradiculoneuropathy: a prevalence study in south east England. *J Neurol Neurosurg Psychiatry* 1999;66:677–80.
5 Mahdi-Rogers M, Hughes RA. Epidemiology of chronic inflammatory neuropathies in southeast England. *Eur J Neurol* 2014;21:28–33.
6 Rajabally YA, Simpson BS, Beri S, *et al*. Epidemiologic variability of chronic inflammatory demyelinating polyneuropathy with different diagnostic criteria: study of a UK population. *Muscle Nerve* 2009;39:432–8.
7 Van den Bergh PY, Hadden RD, Bouche P, *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—first revision. *Eur J Neurol* 2010;17:356–63.
8 Busby M, Donaghy M. Chronic dysimmune neuropathy. A subclassification based upon the clinical features of 102 patients. *J Neurol* 2003;250:714–24.
9 Viala K, Maisonobe T, Stojkovic T, *et al*. A current view of the diagnosis, clinical variants, response to treatment and prognosis of chronic inflammatory demyelinating polyradiculoneuropathy. *J Peripher Nerv Syst* 2010;15:50–6.
10 Rotta FT, Sussman AT, Bradley WG, *et al*. The spectrum of chronic inflammatory demyelinating polyneuropathy. *J Neurol Sci* 2000;173:129–39.
11 Ayrignac X, Viala K, Koutlidis RM, *et al*. Sensory chronic inflammatory demyelinating polyneuropathy: an under-recognized entity? *Muscle Nerve* 2013;48:727–32.
12 Ohkoshi N, Harada K, Nagata H, *et al*. Ataxic form of chronic inflammatory demyelinating polyradiculoneuropathy: clinical features and pathological study of the sural nerves. *Eur Neurol* 2001;45:241–8.
13 Gorson KC, Allam G, Ropper AH. Chronic inflammatory demyelinating polyneuropathy: clinical features and response to treatment in 67 consecutive patients with and without a monoclonal gammopathy. *Neurology* 1997;48:321–8.
14 Lewis RA, Sumner AJ, Brown MJ, *et al*. Multifocal demyelinating neuropathy with persistent conduction block. *Neurology* 1982;32:958–64.
15 Thomas PK, Claus D, Jaspert A, *et al*. Focal upper limb demyelinating neuropathy. *Brain* 1996;119(Pt 3):765–74.
16 McCombe PA, Pollard JD, McLeod JG. Chronic inflammatory demyelinating polyradiculoneuropathy. A clinical and electrophysiological study of 92 cases. *Brain* 1987;110(Pt 6):1617–30.
17 Ruts L, Drenthen J, Jacobs BC, *et al*. Distinguishing acute-onset CIDP from fluctuating Guillain-Barré syndrome: a prospective study. *Neurology* 2010;74:1680–6.
18 Odaka M, Yuki N, Hirata K. Patients with chronic inflammatory demyelinating polyneuropathy initially diagnosed as Guillain-Barré syndrome. *J Neurol* 2003;250:913–16.
19 Said G, Krarup C. Chronic inflammatory demyelinative polyneuropathy. *Handb Clin Neurol* 2013;115:403–13.
20 Nobile-Orazio E. Chronic inflammatory demyelinating polyradiculoneuropathy and variants: where we are and where we should go. *J Peripher Nerv Syst* 2014;19:2–13.
21 Oh SJ, Joy JL, Kuruoglu R. "Chronic sensory demyelinating neuropathy": chronic inflammatory demyelinating polyneuropathy presenting as a pure sensory neuropathy. *J Neurol Neurosurg Psychiatry* 1992;55:677–80.
22 Rajabally YA, Wong SL. Chronic inflammatory pure sensory polyradiculoneuropathy: a rare CIDP variant with unusual electrophysiology. *J Clin Neuromuscul Dis* 2012;13:149–52.
23 van Dijk GW, Notermans NC, Franssen H, *et al*. Development of weakness in patients with chronic inflammatory demyelinating polyneuropathy and only sensory symptoms at presentation: a long-term follow-up study. *J Neurol* 1999;246:1134–9.
24 Sinnreich M, Klein CJ, Daube JR, *et al*. Chronic immune sensory polyradiculopathy: a possibly treatable sensory ataxia. *Neurology* 2004;63:1662–9.
25 Yiannikas C, Vucic S. Utility of somatosensory evoked potentials in chronic acquired demyelinating neuropathy. *Muscle Nerve* 2008;38:1447–54.
26 Katz JS, Saperstein DS, Gronseth G, *et al*. Distal acquired demyelinating symmetric neuropathy. *Neurology* 2000;54:615–20.
27 Saperstein DS, Katz JS, Amato AA, *et al*. Clinical spectrum of chronic acquired demyelinating polyneuropathies. *Muscle Nerve* 2001;24:311–24.
28 Larue S, Bombelli F, Viala K, *et al*. Non-anti-MAG DADS neuropathy as a variant of CIDP: clinical, electrophysiological, laboratory features and response to treatment in 10 cases. *Eur J Neurol* 2011;18:899–905.
29 Sabatelli M, Madia F, Mignogna T, *et al*. Pure motor chronic inflammatory demyelinating polyneuropathy. *J Neurol* 2001;248:772–7.
30 Kimura A, Sakurai T, Koumura A, *et al*. Motor-dominant chronic inflammatory demyelinating polyneuropathy. *J Neurol* 2010;257:621–9.
31 Hattori N, Misu K, Koike H, *et al*. Age of onset influences clinical features of chronic inflammatory demyelinating polyneuropathy. *J Neurol Sci* 2001;184:57–63.
32 Rajabally YA, Chavada G. Lewis-sumner syndrome of pure upper-limb onset: diagnostic, prognostic, and therapeutic features. *Muscle Nerve* 2009;39:206–20.
33 Saperstein DS, Amato AA, Wolfe GI, *et al*. Multifocal acquired demyelinating sensory and motor neuropathy: the Lewis-Sumner syndrome. *Muscle Nerve* 1999;22:560–6.
34 Viala K, Renie L, Maisonobe T, *et al*. Follow-up study and response to treatment in 23 patients with Lewis-Sumner syndrome. *Brain* 2004;127:2010–17.
35 Verma A, Tandan R, Adesina AM, *et al*. Focal neuropathy preceding chronic inflammatory demyelinating polyradiculoneuropathy by several years. *Acta Neurol Scand* 1990;81:516–21.
36 Ayrignac X, Rodrigues BS, Morales R, *et al*. Focal CIDP presenting as chronic progressive monomelic sensory neuropathy. *Muscle Nerve* 2013;47:143–4.
37 Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain-Barré syndrome. *Ann Neurol* 1990;27(Suppl):S21–4.
38 Sung JY, Tani J, Park SB, *et al*. Early identification of 'acute-onset' chronic inflammatory demyelinating polyneuropathy. *Brain* 2014;137:2155–63.
39 Hughes R, Sanders E, Hall S, *et al*. Subacute idiopathic demyelinating polyradiculoneuropathy. *Arch Neurol* 1992;49:612–16.

40 Oh SJ, Kurokawa K, de Almeida DF, *et al*. Subacute inflammatory demyelinating polyneuropathy. *Neurology* 2003;61:1507–12.
41 Rodriguez-Casero MV, Shield LK, Kornberg AJ. Subacute inflammatory demyelinating polyneuropathy in children. *Neurology* 2005;64:1786–8.
42 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* 2010;15:185–95.
43 Niermeijer JM, Fischer K, Eurelings M, *et al*. Prognosis of polyneuropathy due to IgM monoclonal gammopathy: a prospective cohort study. *Neurology* 2010;74:406–12.
44 Nobile-Orazio E, Manfredini E, Carpo M, *et al*. Frequency and clinical correlates of anti-neural IgM antibodies in neuropathy associated with IgM monoclonal gammopathy. *Ann Neurol* 1994;36:416–24.
45 Nobile-Orazio E, Meucci N, Baldini L, *et al*. Long-term prognosis of neuropathy associated with anti-MAG IgM M-proteins and its relationship to immune therapies. *Brain* 2000;123(Pt 4):710–17.
46 Rajabally YA. Neuropathy and paraproteins: review of a complex association. *Eur J Neurol* 2011;18:1291–8.
47 Kaku DA, England JD, Sumner AJ. Distal accentuation of conduction slowing in polyneuropathy associated with antibodies to myelin-associated glycoprotein and sulphated glucuronyl paragloboside. *Brain* 1994;117(Pt 5):941–7.
48 Suarez GA, Kelly JJ Jr. Polyneuropathy associated with monoclonal gammopathy of undetermined significance: further evidence that IgM-MGUS neuropathies are different than IgG-MGUS. *Neurology* 1993;43:1304–8.
49 Magy L, Chassande B, Maisonobe T, *et al*. Polyneuropathy associated with IgG/IgA monoclonal gammopathy: a clinical and electrophysiological study of 15 cases. *Eur J Neurol* 2003;10:677–85.
50 Willison HJ, O'Leary CP, Veitch J, *et al*. The clinical and laboratory features of chronic sensory ataxic neuropathy with anti-disialosyl IgM antibodies. *Brain* 2001;124:1968–77.
51 Nobile-Orazio E, Gallia F, Terenghi F, *et al*. How useful are anti-neural IgM antibodies in the diagnosis of chronic immune-mediated neuropathies? *J Neurol Sci* 2008;266:156–63.
52 Kam C, Balaratnam MS, Purves A, *et al*. Canomad presenting without ophthalmoplegia and responding to intravenous immunoglobulin. *Muscle Nerve* 2011;44:829–33.
53 Nasu S, Misawa S, Sekiguchi Y, *et al*. Different neurological and physiological profiles in POEMS syndrome and chronic inflammatory demyelinating polyneuropathy. *J Neurol Neurosurg Psychiatry* 2012;83:476–9.
54 Nobile-Orazio E. Neuropathy and monoclonal gammopathy. In: Said G, Krarup C, eds. *Handbook of clinical neurology*. Amsterdam: Elsevier, 2013:443–59.
55 Watanabe O, Maruyama I, Arimura K, *et al*. Overproduction of vascular endothelial growth factor/vascular permeability factor is causative in Crow-Fukase (POEMS) syndrome. *Muscle Nerve* 1998;21:1390–7.
56 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* 2010;15:295–301.
57 Arcila-Londono X, Lewis RA. Multifocal Motor Neuropathy. In: Said G, Krarup C, eds. *Handbook of clinical neurology*. Amsterdam: Elsevier, 2013:429–42.
58 Taylor BV, Dyck PJ, Engelstad J, *et al*. Multifocal motor neuropathy: pathologic alterations at the site of conduction block. *J Neuropathol Exp Neurol* 2004;63:129–37.
59 Taylor BV, Wright RA, Harper CM, *et al*. Natural history of 46 patients with multifocal motor neuropathy with conduction block. *Muscle Nerve* 2000;23:900–8.
60 Pestronk A, Choksi R. Multifocal motor neuropathy. Serum IgM anti-GM1 ganglioside antibodies in most patients detected using covalent linkage of GM1 to ELISA plates. *Neurology* 1997;49:1289–92.
61 van Schaik IN, Bossuyt PM, Brand A, *et al*. Diagnostic value of GM1 antibodies in motor neuron disorders and neuropathies: a meta-analysis. *Neurology* 1995;45:1570–7.
62 Cats EA, Jacobs BC, Yuki N, *et al*. Multifocal motor neuropathy: association of anti-GM1 IgM antibodies with clinical features. *Neurology* 2010;75:1961–7.
63 Galban-Horcajo F, Fitzpatrick AM, Hutton AJ, *et al*. Antibodies to heteromeric glycolipid complexes in multifocal motor neuropathy. *Eur J Neurol* 2013;20:62–70.
64 Nobile-Orazio E, Cappellari A, Priori A. Multifocal motor neuropathy: current concepts and controversies. *Muscle Nerve* 2005;31:663–80.
65 Willison HJ, Veitch J, Swan AV, *et al*. Inter-laboratory validation of an ELISA for the determination of serum anti-ganglioside antibodies. *Eur J Neurol* 1999;6:71–7.
66 Donaghy M, Mills KR, Boniface SJ, *et al*. Pure motor demyelinating neuropathy: deterioration after steroid treatment and improvement with intravenous immunoglobulin. *J Neurol Neurosurg Psychiatry* 1994;57:778–83.
67 Breiner A, Brannagan TH III. Comparison of sensitivity and specificity among 15 criteria for chronic inflammatory demyelinating polyneuropathy. *Muscle Nerve* 2014;50:40–6.
68 Rajabally YA, Fowle AJ, Van den Bergh PY. Which criteria for research in CIDP? An analysis of current practice. *Muscle Nerve* 2014. 10.1002/mus.24496 (In press).
69 Prineas JW, McLeod JG. Chronic relapsing polyneuritis. *J Neurol Sci* 1976;27:427–58.
70 Sommer C, Koch S, Lammens M, *et al*. Macrophage clustering as a diagnostic marker in sural nerve biopsies of patients with CIDP. *Neurology* 2005;65:1924–9.
71 Bosboom WM, van den Berg LH, De BL, *et al*. The diagnostic value of sural nerve T cells in chronic inflammatory demyelinating polyneuropathy. *Neurology* 1999;53:837–45.
72 Pollard JD, McCombe PA, Baverstock J, *et al*. Class II antigen expression and T lymphocyte subsets in chronic inflammatory demyelinating polyneuropathy. *J Neuroimmunol* 1986;13:123–34.
73 Schmidt B, Toyka KV, Kiefer R, *et al*. Inflammatory infiltrates in sural nerve biopsies in Guillain-Barré syndrome and chronic inflammatory demyelinating neuropathy. *Muscle Nerve* 1996;19:474–87.
74 Chi LJ, Xu WH, Zhang ZW, *et al*. Distribution of Th17 cells and Th1 cells in peripheral blood and cerebrospinal fluid in chronic inflammatory demyelinating polyradiculoneuropathy. *J Peripher Nerv Syst* 2010;15:345–56.
75 Madia F, Frisullo G, Nociti V, *et al*. pSTAT1, pSTAT3, and T-bet as markers of disease activity in chronic inflammatory demyelinating polyradiculoneuropathy. *J Peripher Nerv Syst* 2009;14:107–17.
76 Hartung HP, Reiners K, Schmidt B, *et al*. Serum interleukin-2 concentrations in Guillain-Barré syndrome and chronic idiopathic demyelinating polyradiculoneuropathy: comparison with other neurological diseases of presumed immunopathogenesis. *Ann Neurol* 1991;30:48–53.
77 Rentzos M, Angeli AV, Rombos A, *et al*. Proinflammatory cytokines in serum and cerebrospinal fluid of CIDP patients. *Neurol Res* 2012;34:842–6.
78 Gironi M, Saresella M, Marventano I, *et al*. Distinct cytokine patterns associated with different forms of chronic dysimmune neuropathy. *Muscle Nerve* 2010;42:864–70.
79 Sainaghi PP, Collimedaglia L, Alciato F, *et al*. The expression pattern of inflammatory mediators in cerebrospinal fluid differentiates Guillain-Barré syndrome from chronic inflammatory demyelinating polyneuropathy. *Cytokine* 2010;51:138–43.
80 Misawa S, Kuwabara S, Mori M, *et al*. Serum levels of tumor necrosis factor-alpha in chronic inflammatory demyelinating polyneuropathy. *Neurology* 2001;56:666–9.
81 Press R, Pashenkov M, Jin JP, *et al*. Aberrated levels of cerebrospinal fluid chemokines in Guillain-Barré syndrome and chronic inflammatory demyelinating polyradiculoneuropathy. *J Clin Immunol* 2003;23:259–67.
82 Kieseier BC, Tani M, Mahad D, *et al*. Chemokines and chemokine receptors in inflammatory demyelinating neuropathies: a central role for IP-10. *Brain* 2002;125:823–34.
83 Linington C, Lassmann H, Ozawa K, *et al*. Cell adhesion molecules of the immunoglobulin supergene family as tissue-specific autoantigens: induction of experimental allergic neuritis (EAN) by P0 protein-specific T cell lines. *Eur J Immunol* 1992;22:1813–17.
84 Pollard JD, Westland KW, Harvey GK, *et al*. Activated T cells of nonneural specificity open the blood-nerve barrier to circulating antibody. *Ann Neurol* 1995;37:467–75.
85 Spies JM, Westland KW, Bonner JG, *et al*. Intraneural activated T cells cause focal breakdown of the blood-nerve barrier. *Brain* 1995;118(Pt 4):857–68.
86 Spies JM, Pollard JD, Bonner JG, *et al*. Synergy between antibody and P2-reactive T cells in experimental allergic neuritis. *J Neuroimmunol* 1995;57:77–84.
87 van den Berg LH, Mollee I, Wokke JH, *et al*. Increased frequencies of HPRT mutant T lymphocytes in patients with Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy: further evidence for a role of T cells in the etiopathogenesis of peripheral demyelinating diseases. *J Neuroimmunol* 1995;58:37–42.
88 Mei FJ, Ishizu T, Murai H, *et al*. Th1 shift in CIDP versus Th2 shift in vasculitic neuropathy in CSF. *J Neurol Sci* 2005;228:75–85.
89 Archelos JJ, Previtali SC, Hartung HP. The role of integrins in immune-mediated diseases of the nervous system. *Trends Neurosci* 1999;22:30–8.
90 Oka N, Akiguchi I, Nagao M, *et al*. Expression of endothelial leukocyte adhesion molecule-1 (ELAM-1) in chronic inflammatory demyelinating polyneuropathy. *Neurology* 1994;44:946–50.
91 Musso AM, Zanusso GL, Bonazzi ML, *et al*. Increased serum levels of ICAM-1, ELAM-1 and TNF-alpha in inflammatory disorders of the peripheral nervous system. *Ital J Neurol Sci* 1994;15:267–71.
92 Leppert D, Hughes P, Huber S, *et al*. Matrix metalloproteinase upregulation in chronic inflammatory demyelinating polyneuropathy and nonsystemic vasculitic neuropathy. *Neurology* 1999;53:62–70.
93 Kuwabara S, Nakajima M, Matsuda S, *et al*. Magnetic resonance imaging at the demyelinative foci in chronic inflammatory demyelinating polyneuropathy. *Neurology* 1997;48:874–7.

94 Schneider-Hohendorf T, Schwab N, Uceyler N, *et al*. CD8+ T-cell immunity in chronic inflammatory demyelinating polyradiculoneuropathy. *Neurology* 2012;78:402–8.
95 Cornblath DR, Griffin DE, Welch D, *et al*. Quantitative analysis of endoneurial T-cells in human sural nerve biopsies. *J Neuroimmunol* 1990;26:113–18.
96 Kiefer R, Dangond F, Mueller M, *et al*. Enhanced B7 costimulatory molecule expression in inflammatory human sural nerve biopsies. *J Neurol Neurosurg Psychiatry* 2000;69:362–8.
97 Murata K, Dalakas MC. Expression of the co-stimulatory molecule BB-1, the ligands CTLA-4 and CD28 and their mRNAs in chronic inflammatory demyelinating polyneuropathy. *Brain* 2000;123(Pt 8):1660–6.
98 Mathey EK, Pollard JD, Armati PJ. TNF alpha, IFN gamma and IL-2 mRNA expression in CIDP sural nerve biopsies. *J Neurol Sci* 1999;163:47–52.
99 Kiefer R, Kieseier BC, Stoll G, *et al*. The role of macrophages in immune-mediated damage to the peripheral nervous system. *Prog Neurobiol* 2001;64:109–27.
100 Vital C, Vital A, Lagueny A, *et al*. Chronic inflammatory demyelinating polyneuropathy: immunopathological and ultrastructural study of peripheral nerve biopsy in 42 cases. *Ultrastruct Pathol* 2000;24:363–9.
101 Steinhoff U, Kaufmann SH. Specific lysis by CD8+ T cells of Schwann cells expressing Mycobacterium leprae antigens. *Eur J Immunol* 1988;18:969–72.
102 Mausberg AK, Dorok M, Stettner M, *et al*. Recovery of the T-cell repertoire in CIDP by IV immunoglobulins. *Neurology* 2013;80:296–303.
103 Sanvito L, Makowska A, Gregson N, *et al*. Circulating subsets and CD4(+)CD25(+) regulatory T cell function in chronic inflammatory demyelinating polyradiculoneuropathy. *Autoimmunity* 2009;42:667–77.
104 Chi LJ, Wang HB, Wang WZ. Impairment of circulating CD4+CD25+ regulatory T cells in patients with chronic inflammatory demyelinating polyradiculoneuropathy. *J Peripher Nerv Syst* 2008;13:54–63.
105 Salomon B, Rhee L, Bour-Jordan H, *et al*. Development of spontaneous autoimmune peripheral polyneuropathy in B7-2-deficient NOD mice. *J Exp Med* 2001;194:677–84.
106 Louvet C, Kabre BG, Davini DW, *et al*. A novel myelin P0-specific T cell receptor transgenic mouse develops a fulminant autoimmune peripheral neuropathy. *J Exp Med* 2009;206:507–14.
107 Su MA, Davini D, Cheng P, *et al*. Defective autoimmune regulator-dependent central tolerance to myelin protein zero is linked to autoimmune peripheral neuropathy. *J Immunol* 2012;188:4906–12.
108 Meyer zu HG, Mausberg AK, Cordes S, *et al*. Thymic epithelium determines a spontaneous chronic neuritis in Icam1tm1JcgrNOD Mice. *J Immunol* 2014;193:2678–90.
109 Dalakas MC, Engel WK. Immunoglobulin and complement deposits in nerves of patients with chronic relapsing polyneuropathy. *Arch Neurol* 1980;37:637–40.
110 Hays AP, Lee SS, Latov N. Immune reactive C3d on the surface of myelin sheaths in neuropathy. *J Neuroimmunol* 1988;18:231–44.
111 Yan WX, Taylor J, Ndrias-Kauba S, *et al*. Passive transfer of demyelination by serum or IgG from chronic inflammatory demyelinating polyneuropathy patients. *Ann Neurol* 2000;47:765–75.
112 Heininger K, Liebert UG, Toyka KV, *et al*. Chronic inflammatory polyneuropathy. Reduction of nerve conduction velocities in monkeys by systemic passive transfer of immunoglobulin G. *J Neurol Sci* 1984;66:1–14.
113 Yan WX, Archelos JJ, Hartung HP, *et al*. P0 protein is a target antigen in chronic inflammatory demyelinating polyradiculoneuropathy. *Ann Neurol* 2001;50:286–92.
114 Allen D, Giannopoulos K, Gray I, *et al*. Antibodies to peripheral nerve myelin proteins in chronic inflammatory demyelinating polyradiculoneuropathy. *J Peripher Nerv Syst* 2005;10:174–80.
115 Inglis HR, Csurhes PA, McCombe PA. Antibody responses to peptides of peripheral nerve myelin proteins P0 and P2 in patients with inflammatory demyelinating neuropathy. *J Neurol Neurosurg Psychiatry* 2007;78:419–22.
116 Khalili-Shirazi A, Atkinson P, Gregson N, *et al*. Antibody responses to P0 and P2 myelin proteins in Guillain-Barré syndrome and chronic idiopathic demyelinating polyradiculoneuropathy. *J Neuroimmunol* 1993;46:245–51.
117 Sanvito L, Makowska A, Mahdi-Rogers M, *et al*. Humoral and cellular immune responses to myelin protein peptides in chronic inflammatory demyelinating polyradiculoneuropathy. *J Neurol Neurosurg Psychiatry* 2009;80:333–8.
118 Quarles RH, Ilyas AA, Willison HJ. Antibodies to gangliosides and myelin proteins in Guillain-Barré syndrome. *Ann Neurol* 1990;27(Suppl):S48–52.
119 Kwa MS, van Schaik IN, Brand A, *et al*. Investigation of serum response to PMP22, connexin 32 and P(0) in inflammatory neuropathies. *J Neuroimmunol* 2001;116:220–5.
120 Melendez-Vasquez C, Redford J, Choudhary PP, *et al*. Immunological investigation of chronic inflammatory demyelinating polyradiculoneuropathy. *J Neuroimmunol* 1997;73:124–34.
121 Gabriel CM, Gregson NA, Hughes RA. Anti-PMP22 antibodies in patients with inflammatory neuropathy. *J Neuroimmunol* 2000;104:139–46.
122 Ritz MF, Lechner-Scott J, Scott RJ, *et al*. Characterisation of autoantibodies to peripheral myelin protein 22 in patients with hereditary and acquired neuropathies. *J Neuroimmunol* 2000;104:155–63.
123 Querol L, Nogales-Gadea G, Rojas-Garcia R, *et al*. Neurofascin IgG4 antibodies in CIDP associate with disabling tremor and poor response to IVIg. *Neurology* 2014;82:879–86.
124 Ng JK, Malotka J, Kawakami N, *et al*. Neurofascin as a target for autoantibodies in peripheral neuropathies. *Neurology* 2012;79:2241–8.
125 Kawamura N, Yamasaki R, Yonekawa T, *et al*. Anti-neurofascin antibody in patients with combined central and peripheral demyelination. *Neurology* 2013;81:714–22.
126 Devaux JJ, Odaka M, Yuki N. Nodal proteins are target antigens in Guillain-Barré syndrome. *J Peripher Nerv Syst* 2012;17:62–71.
127 Querol L, Nogales-Gadea G, Rojas-Garcia R, *et al*. Antibodies to contactin-1 in chronic inflammatory demyelinating polyneuropathy. *Ann Neurol* 2013;73:370–80.
128 Milner P, Lovelidge CA, Taylor WA, *et al*. P0 myelin protein produces experimental allergic neuritis in Lewis rats. *J Neurol Sci* 1987;79:275–85.
129 Kadlubowski M, Hughes RA. Identification of the neuritogen for experimental allergic neuritis. *Nature* 1979;277:140–1.
130 Gabriel CM, Hughes RA, Moore SE, *et al*. Induction of experimental autoimmune neuritis with peripheral myelin protein-22. *Brain* 1998;121(Pt 10):1895–902.
131 Hughes RA, Powell HC, Braheny SL, *et al*. Endoneurial injection of antisera to myelin antigens. *Muscle Nerve* 1985;8:516–22.
132 Devaux JJ. Antibodies to gliomedin cause peripheral demyelinating neuropathy and the dismantling of the nodes of Ranvier. *Am J Pathol* 2012;181:1402–13.
133 Amor V, Feinberg K, Eshed-Eisenbach Y, *et al*. Long-term maintenance of Na+ channels at nodes of Ranvier depends on glial contact mediated by gliomedin and NrCAM. *J Neurosci* 2014;34:5089–98.
134 Salzer JL, Brophy PJ, Peles E. Molecular domains of myelinated axons in the peripheral nervous system. *Glia* 2008;56:1532–40.
135 Thaxton C, Pillai AM, Pribisko AL, *et al*. In vivo deletion of immunoglobulin domains 5 and 6 in neurofascin (Nfasc) reveals domain-specific requirements in myelinated axons. *J Neurosci* 2010;30:4868–76.
136 Uncini A, Susuki K, Yuki N. Nodo-paranodopathy: beyond the demyelinating and axonal classification in anti-ganglioside antibody-mediated neuropathies. *Clin Neurophysiol* 2013;124:1928–34.
137 Chavada G, Willison HJ. Autoantibodies in immune-mediated neuropathies. *Curr Opin Neurol* 2012;25:550–5.
138 McGonigal R, Rowan EG, Greenshields KN, *et al*. Anti-GD1a antibodies activate complement and calpain to injure distal motor nodes of Ranvier in mice. *Brain* 2010;133:1944–60.
139 Shahrizaila N, Kokubun N, Sawai S, *et al*. Antibodies to single glycolipids and glycolipid complexes in Guillain-Barré syndrome subtypes. *Neurology* 2014;83:118–24.
140 Sawai S, Satoh M, Mori M, *et al*. Moesin is a possible target molecule for cytomegalovirus-related Guillain-Barré syndrome. *Neurology* 2014;83:113–17.
141 Notturno F, Di FT, Yuki N, *et al*. Autoantibodies to neurofascin-186 and gliomedin in multifocal motor neuropathy. *J Neuroimmunol* 2014;276:207–12.
142 Cifuentes-Diaz C, Dubourg O, Irinopoulou T, *et al*. Nodes of Ranvier and paranodes in chronic acquired neuropathies. *PLoS ONE* 2011;6:e14533.
143 Doppler K, Werner C, Sommer C. Disruption of nodal architecture in skin biopsies of patients with demyelinating neuropathies. *J Peripher Nerv Syst* 2013;18:168–76.
144 Lonigro A, Devaux JJ. Disruption of neurofascin and gliomedin at nodes of Ranvier precedes demyelination in experimental allergic neuritis. *Brain* 2009;132:260–73.
145 Yan W, Nguyen T, Yuki N, *et al*. Antibodies to neurofascin exacerbate adoptive transfer experimental autoimmune neuritis. *J Neuroimmunol* 2014;277:13–17.
146 Davis JQ, Lambert S, Bennett V. Molecular composition of the node of Ranvier: identification of ankyrin-binding cell adhesion molecules neurofascin (mucin+/third FNIII domain-) and NrCAM at nodal axon segments. *J Cell Biol* 1996;135:1355–67.
147 Mathey EK, Derfuss T, Storch MK, *et al*. Neurofascin as a novel target for autoantibody-mediated axonal injury. *J Exp Med* 2007;204:2363–72.
148 Nirula A, Glaser SM, Kalled SL, *et al*. What is IgG4? A review of the biology of a unique immunoglobulin subtype. *Curr Opin Rheumatol* 2011;23:119–24.
149 Huijbers MG, Zhang W, Klooster R, *et al*. MuSK IgG4 autoantibodies cause myasthenia gravis by inhibiting binding between MuSK and Lrp4. *Proc Natl Acad Sci USA* 2013;110:20783–8.
150 Labasque M, Hivert B, Nogales-Gadea G, *et al*. Specific Contactin N-glycans are implicated in neurofascin binding and autoimmune targeting in peripheral neuropathies. *J Biol Chem* 2014;289:7907–18.
151 Lindner M, Ng JK, Hochmeister S, *et al*. Neurofascin 186 specific autoantibodies induce axonal injury and exacerbate disease severity in experimental autoimmune encephalomyelitis. *Exp Neurol* 2013;247C:259–66.
152 Charles P, Tait S, Faivre-Sarrailh C, *et al*. Neurofascin is a glial receptor for the paranodin/Caspr-contactin axonal complex at the axoglial junction. *Curr Biol* 2002;12:217–20.

153 Rinaldi S, Brennan KM, Kalna G, *et al*. Antibodies to heteromeric glycolipid complexes in Guillain-Barré syndrome. *PLoS ONE* 2013;8:e82337.
154 Willison HJ, Goodyear CS. Glycolipid antigens and autoantibodies in autoimmune neuropathies. *Trends Immunol* 2013;34:453–9.
155 Cappelen-Smith C, Kuwabara S, Lin CS, *et al*. Membrane properties in chronic inflammatory demyelinating polyneuropathy. *Brain* 2001;124:2439–47.
156 Lin CS, Krishnan AV, Park SB, *et al*. Modulatory effects on axonal function after intravenous immunoglobulin therapy in chronic inflammatory demyelinating polyneuropathy. *Arch Neurol* 2011;68:862–9.
157 Dalakas MC. Advances in the diagnosis, pathogenesis and treatment of CIDP. *Nat Rev Neurol* 2011;7:507–17.
158 Tasaki I. Conduction of the nerve impulse. In: Field J, Magoun HW, Hall VE, eds. *Handbook of physiology, Section 1, neurophysiology*. Washington DC: American Physiological Society, 1959:75–121.
159 Bostock H, Grafe P. Activity-dependent excitability changes in normal and demyelinated rat spinal root axons. *J Physiol* 1985;365:239–57.
160 Cappelen-Smith C, Kuwabara S, Lin CS, *et al*. Activity-dependent hyperpolarization and conduction block in chronic inflammatory demyelinating polyneuropathy. *Ann Neurol* 2000;48:826–32.
161 Hitomi T, Kaji R, Murase N, *et al*. Dynamic change of proximal conduction in demyelinating neuropathies: a cervical magnetic stimulation combined with maximum voluntary contraction. *Clin Neurophysiol* 2007;118:741–50.
162 Straver DC, van den Berg LH, Franssen H. Activity-dependent conduction block in chronic inflammatory demyelinating polyneuropathy. *J Neurol Sci* 2011;300:33–8.
163 Kiernan MC, Lin CS, Burke D. Differences in activity-dependent hyperpolarization in human sensory and motor axons. *J Physiol* 2004;558:341–9.
164 Howells J, Trevillion L, Bostock H, *et al*. The voltage dependence of I(h) in human myelinated axons. *J Physiol* 2012;590:1625–40.
165 Eftimov F, Liesdek MH, Verhamme C, *et al*. Deterioration after corticosteroids in CIDP may be associated with pure focal demyelination pattern. *BMC Neurol* 2014;14:72.
166 Hall ED, Baker T, Riker WF Jr. Glucocorticoid effects on spinal cord function. *J Pharmacol Exp Ther* 1978;206:361–70.
167 Braughler JM, Hall ED. Acute enhancement of spinal cord synaptosomal (Na+ + K+)-ATPase activity in cats following intravenous methylprednisolone. *Brain Res* 1981;219:464–9.
168 Hall ED. Glucocorticoid effects on the electrical properties of spinal motor neurons. *Brain Res* 1982;240:109–16.
169 Nordsborg N, Thomassen M, Lundby C, *et al*. Contraction-induced increases in Na +-K+-ATPase mRNA levels in human skeletal muscle are not amplified by activation of additional muscle mass. *Am J Physiol Regul Integr Comp Physiol* 2005;289:R84–91.