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REVIEW

Chronic inflammatory demyelinating polyradiculoneuropathy: from pathology to phenotype

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ABSTRACT

Chronic inflammatory demyelinating polyradiculoneuropathy (CIPD) is an inflammatory neuropathy, classically characterised by a slowly progressive onset and symmetrical, sensorimotor involvement. However, there are many phenotypic variants, suggesting that CIPD may not be a discrete disease entity but rather a spectrum of related conditions. While the abiding theory of CIPD 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 CIPD 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 CIPD.

INTRODUCTION

Chronic inflammatory demyelinating polyradiculoneuropathy (CIPD) is the most common treatable chronic neuropathy worldwide, with a prevalence ranging from ~1 to 9 cases per 100 000.^{1–6} CIPD 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 CIPD 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 CIPD. This review will address the pathology of CIPD, the role of the cellular and humoral immune systems and their relationship to phenotypic expression in CIPD.

CIPD PHENOTYPIC VARIANTS

There are many phenotypic variants of CIPD. Indeed, CIPD 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 CIPD 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 CIPD display the typical phenotype.

Sensory predominant CIPD 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 CIPD (~5%) present with progressive sensory ataxia and sensory symptoms,^{8 12} termed *chronic immune sensory polyradiculopathy*. In contrast to sensory CIPD, 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 CIPD is characterised by proximal and distal involvement, the *distal acquired demyelinating symmetric neuropathy* (DADS) variant is restricted to a distal, symmetrical distribution²⁶ 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 CIPD, with considerable overlap with sensory and sensory ataxic CIPD 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 neuropathy⁵³ 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 factor⁵⁵ 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 macrophages⁷⁰ 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 markers⁸⁷ such as t-bet and pstat1⁷⁵ and secrete proinflammatory cytokines including interleukin (IL)-2,^{76–87} interferon γ (IFN γ)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 (MIP3 β).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)-1⁹⁰ and intercellular adhesion molecule (ICAM)-1⁹¹ 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 metalloproteinases⁹² and proinflammatory cytokines/chemokines^{76–80} continue to be secreted by these T cells as they transmute 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 II⁷² 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 , IFN γ and IL-2 become expressed by a variety of cell types within the nerve⁹⁸ 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 phagocytosing 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 nerves⁷² 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 reduced¹⁰⁴ 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 neurotogenic 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 immunofluorescence¹¹¹ (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 demyelination¹¹¹ 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 P2¹²⁹ and peripheral myelin protein (PMP)-22¹³⁰ 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 P2¹¹⁵, P0,^{111 113 114 116} PMP-22¹²¹ and connexin¹¹⁹ 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 development¹³³ and contribute to the long-term maintenance 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 'nodoparanopathies'.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 caspr¹²⁷ and moesin¹⁴⁰ (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
	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 infusion (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 competing 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 proximity¹⁵¹ 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 complex¹⁵² 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 dispersion¹⁶² 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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