REVIEW

Chronic inflammatory demyelinating polyradiculoneuropathy: from pathology to phenotype

Emily K Mathey,¹ Susanna B Park,¹,² Richard A C Hughes,³ John D Pollard,¹ Patricia J Armati,¹ Michael H Barnett,¹ Bruce V Taylor,⁴ P James B Dyck,⁵ Matthew C Kiernan,¹ Cindy S-Y Lin⁶

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 abnormally immune response to cause damage to peripheral nerves, the relative contributions of T 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.

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%. However, only 50% of patients with CIDP display the typical phenotype.

Sensory predominant CIDP occurs in 5–35% of patients, often starting with lower limb numbness. Despite purely sensory symptoms, patients often demonstrate prominent motor nerve conduction abnormalities consistent with demyelination. Rarely, patients have been reported with purely sensory electrophysiological features. However, many of these patients go on to develop motor weakness, sometimes many years after the onset of sensory symptoms. Similarly, a small subset of patients with CIDP (~5%) present with progressive sensory ataxia and sensory symptoms, 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. However, somatosensory evoked potentials may confirm proximal sensory dysfunction.

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 with predominantly sensory symptoms, although there is often electrophysiological evidence of motor involvement. 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 anti-myelin-associated glycoprotein (anti-MAG) antibody activity is responsible for the pathogenesis. 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.

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.

Correspondence to
Dr Cindy S-Y Lin, Faculty of Medicine, Department of Physiology, Translational Neuroscience Facility, School of Medical Sciences, University of New South Wales, Sydney, NSW 2052 Australia

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

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. It accounts for 6–15% of CIDP patients. Patients demonstrate abnormal sensory and motor nerve conduction, with multifocal areas of conduction block predominating in one or both upper limbs. The majority of patients eventually develop diffuse, typical CIDP spreading to the other limbs.

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

While CIDP typically demonstrates a slowly progressive course with gradual worsening over more than 8 weeks, acute-onset CIDP demonstrates a rapidly progressive onset within 8 weeks, which may lead to diagnostic overlap with acute inflammatory demyelinating polyneuropathy (AIDP). Two to 16% of patients with CIDP may demonstrate acute-onset CIDP. Nerve excitability techniques have revealed differences between the profiles of AIDP and acute-onset patients with CIDP, potentially leading to improved diagnostic outcomes. 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.

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). 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. More than 50% of patients with an IgM paraprotein have anti-MAG IgM antibodies. Anti-MAG neuropathy is often associated with sensory ataxia and tremor. Electrophysiological characteristics of anti-MAG neuropathy include reduced or absent sensory action potentials and disproportionately prolonged distal motor latencies. While patients with PDN may meet diagnostic criteria for CIDP, the presence of high titres of anti-MAG antibodies precludes a diagnosis of CIDP. IgG and IgA paraproteinaemic demyelinating neuropathies are less common and often resemble typical CIDP particularly in their response to therapy. 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 axania and cranial nerve involvement including ophthalmoplegia, dysphagia and dysarthria and only minimal weakness. It occurs in around 2% of patients with IgM PDN. CANOMAD is associated with antibodies to ganglioside disialosyl moieties. CANOMAD typically progresses over years and peripheral neuropathy may precede the development of other features such as ophthalmoplegia.

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. It often presents with neuropathy, typified by sensory and motor involvement with demyelinating and axonal features. The onset is subacute and progression leads to severe motor weakness. Neuropathic pain may be prominent. High levels of the cytokine vascular endothelial growth factor are helpful in diagnosis.

The major differential diagnosis of motor CIDP, particularly the rare instances of focal motor CIDP, is MMN. MMN is a chronic, immune-mediated neuropathy with asymmetric, predominantly distal upper limb weakness in the absence of objective sensory involvement. 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%. but most studies report between 40% and 50%. This range is largely due to discrepancies in methodology but it is widely accepted that anti-GM1 antibodies do occur in a

| 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-Summer syndrome/ MADSAM | 6–15%                            | Chronic | Sensory and motor | Asymmetrical; often upper limb onset | 9, 8, 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, 9, 13 |

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

Table 1 Major phenotypic variants of CIDP
higher proportion of patients with MMN than in control
groups and may correlate with severity of weakness and disability. 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. However, motor CIDP has also been reported to
be unresponsive to or deteriorate after treatment with steroids.

**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 devel-
oped for clinical and research use. The criteria combine clinical
features and electrophysiological evidence to define CIDP with
supportive criteria including elevated cerebrospinal fluid (CSF)
gprotein, gadolinium enhancement of nerve roots or plexus on
MRI or nerve biopsy findings providing supplemental diagnostic
evidence. Electrodiagnostic evidence of peripheral nerve demye-
lination in motor nerves is required for diagnosis, including
distal latency prolongation, reduction of motor conduction vel-
ocity, prolongation of F-wave latency and partial motor conduc-
tion block and must be identified in at least two nerves for a
diagnosis of ‘definite’ CIDP. 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 sus-
pected, 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.

**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 neuro-
logical 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 ef-
cacy 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.
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, axonal degeneration and perivascular or endoneurial inflammatory infiltrates of macrophages and T cells (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 myelin basic protein.\(^{69}\) In EAN, Schwann cells\(^{70}\) and macrophages\(^{71}\) are infiltrated 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.

Cellular mechanisms
Cellular immune mechanisms are implicated in the pathogenesis of CIDP based on the presence of inflammatory infiltrates in sural nerve biopsies. Changes in the frequencies/function of T cell subsets, altered expression of cytokines and other inflammatory mediators in the blood and CSF of patients with CIDP, and the contribution of T cells to disease in EAN.\(^{73-78}\)

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 such as T-bet and psat1\(^{79}\) and secrete proinflammatory cytokines including interferon \(\gamma (IFN\gamma)\), interleukin (IL)-2, IL-4, IL-5 and IL-17\(^{80-88}\) as well as the chemokines interferon gamma-induced protein (IP)-10\(^{81}\), and macrophage inflammatory protein 3 \(\beta (MIP3\beta)\).\(^{89}\) 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\(^{90}\), endothelial leukocyte adhesion molecule (ELAM)-1\(^{91}\) and intercellular adhesion molecule (ICAM)-1\(^{92}\) 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\(^{93}\) and proinflammatory cytokines/chemokines\(^{94,95}\) 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.\(^{96}\)

Infiltration of inflammatory cells
CIDP sural nerve biopsies show that the infiltrating inflammatory cells include CD8\(^+\) T cells, CD4\(^+\) T cells and macrophages.\(^{97-99}\) Local reactivation of infiltrating T cells is facilitated by the upregulation of antigen presenting major histocompatibility complex (MHC) class II\(^{99}\) molecules and the costimulatory molecules B7-1 and B7-2 not only by infiltrating macrophages but also by Schwann cells. Proliferative inflammatory cytokines such as tumor necrosis factor \(\alpha (TNF\alpha)\), IFN\gamma 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.\(^{100}\) 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.\(^{95}\) 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\(^{101}\) 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.\(^{102}\) To date no foreign or self-antigen has been...
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. 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. 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. The numbers of circulating T regulatory cells, identified by the CD4+CD25highFoxp3+ markers, are reduced and, when isolated, are less effective in suppressing proliferative responses than those from healthy controls. 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. The NOD mouse model was originally established to investigate 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. Conversely, a P0T cell receptor transgenic mouse did not spontaneously develop disease unless crossed to a RAGKO background, 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. Similarly, autoimmunity is shifted towards the peripheral nerve in another NOD model deficient for isoforms of ICAM-1. Altered expression of ICAM-1 on thymic epithelial cells transforms selection of T cells from a diabetogenic into a neuritogenic repertoire. 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 while serum from some patients with CIDP can be shown to bind to nerve sections caused demyelination and a reduction of conduction velocity following intraneural injection in the rat. Further experiments with this serum showed that the target antigen is compact
myelin protein P0. 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, P2, and peripheral myelin protein (PMP)-22 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, P0, P0, and PMP-22 and connexin in CIDP serum, others have not. 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 and passive transfer. 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. 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 and contribute to the long-term maintenance of Na+ channel clustering at the node of Ranvier. 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). These proteins form and maintain the paranodal septate junctions. NF155 is essential for ion channel segregation, paranodal structure and efficient nerve conduction. 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’. 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. However, these antibodies are not consistently identified in the demyelinating form of GBS, AIDP, 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, neurofascin, contactin-1, caspr1, and moesin (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.

Indeed, in CIDP nerve biopsies nodal and paranodal regions are disrupted and the proteins vital for maintaining structural integrity are abnormally expressed and distributed. Electron microscopic examination of nerve biopsies has revealed abnormalities in Schwann cell microvilli and paranodal glial loops with large nodal expansions.
vacuoles in the Schwann cell outer cytoplasm and nodal axoplasm. Further, punctate immunoreactivity for Na+ and K+ channels were distributed along the axon with diffuse distribution of caspr-1. In addition, examination of cutaneous myelinated nerve fibres demonstrated elongated nodes of Ranvier and broadening of neurofascin and caspr staining compared to normal controls. 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. 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. Critically, there is now evidence to suggest that nodal antigens are important in some cases of CIDP. Devaux et al 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. Identified nodal and paranodal antigens in 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     | ELISA  | 117       |
|                   | 7/30*                     | IgG     | ELISA  | 118       |
|                   | 0/20*                     |         | ELISA  | 119       |
|                   | 1/24*                     | IgG     | Western blotting | 120 |
|                   | 3/40*                     | IgM     | ELISA  | 116       |
|                   | 2/40*                     |         | ELISA  | 117       |
| P2                | 11/32*                    | IgM     | ELISA  | 116       |
|                   | 4/32*                     | IgG     | ELISA  | 117       |
|                   | 4/36*                     | IgG     | ELISA  | 118       |
|                   | 4/30*                     | IgG     | ELISA  | 117       |
|                   | 3/20*                     |         | ELISA  | 118       |
| PMP22             | 3/30*                     | IgG     | ELISA  | 117       |
|                   | 0/24*                     |         | ELISA  | 118       |
|                   | 7/17*                     | Ig (3), IgM (3), pan Ig (1) | Western blotting | 121 |
|                   | 6/17*                     |         | Western blotting | 122 |
|                   | 3/6*                      |         | Western blotting | 123 |
| Cx32              | 1/24*                     |         | Western blotting | 120 |
| MBP               | 2/40*                     | IgG     | ELISA  | 119       |

Nodal antigens

| Candidate antigen | Positive sera/total tested | Ig Class | Method | Reference |
|-------------------|---------------------------|---------|--------|-----------|
| Neurofascin 155   |                           |         |        |           |
|                   | 4/61                      | IgG4    | ELISA  | 123       |
|                   | 5/117                     | IgG4, IgG3, IgM, IgA | Cell-based assay | 125 |
|                   | CDP 0/16*                 | IgG     | ELISA  | 124       |
|                   | CDP 5/7*                  |         | ELISA  | 125       |
|                   | CDP 4/16*                 |         | ELISA  | 126       |
|                   | CDP 6/7*                  |         | ELISA  | 127       |
| Neurofascin 186   |                           |         |        |           |
|                   | 1/50*                     | IgG     | Cell-based assay | 126 |
|                   | 0/117*                    |         | ELISA  | 127       |
| Contactin-1       |                           |         |        |           |
|                   | 3/46*                     | IgG     | Cell-based assay | 126 |
|                   | 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.

Identified nodal and paranodal antigens in CIDP

Antibodies against the CAM neurofascin have been identified in 4% of patients with CIDP. 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, neurofascin antibodies in patients with CIDP have been singularly targeted against NF155. In two patients with high titres of anti-NF155 (IgG3 isotype) antibodies, plasma exchange was of clinical benefit. 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. 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.
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. 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. 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. 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. 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. 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 neural cultures.

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

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).
surface of transfected cells using in vitro assays. However, experimental modelling suggests that nodal NF186 is the primary target and antibodies to NF155 are unable to bind to either neurofascin isoform in vivo in EAE experimental models. The ability of anti-NF155 antibodies to bind in vivo could be affected by steric hindrance caused by interacting proteins in close proximity 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. 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 casp/contactin/NF155 complex and may have an important role in preventing remyelination. 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. 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. 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 casp.

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-antigens 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.

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. Accordingly, cyclical modulation of axonal excitability has been demonstrated following successive IVIg maintenance treatments (figure 5B).

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, demyelination reduces the safety factor, effectively reducing the ability of the axon to maintain charge. 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 and increase temporal dispersion in patients with CIDP.

Motor axons demonstrate reduced accommodation to hyperpolarising membrane potential change and are more susceptible to conduction failure than sensory axons. Motor axons also demonstrate reduced activation of the hyperpolarisation activated cation current I_S and a hyperpolarised membrane potential relative to sensory axons, making them less able to respond to additional hyperpolarisation and vulnerable to conduction failure. These biophysical properties may influence treatment responsiveness. Patients with motor dominant CIDP as well as MMN may demonstrate clinical deterioration following corticosteroid treatment. 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. Corticosteroids have been demonstrated to modulate excitability in motor neurons, leading to hyperpolarisation of resting membrane potential via enhancement of Na\(^+/K^+\) pump activity. Steroid administration also increases Na\(^+/K^+\) pump activity and expression in human skeletal muscle fibres. 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.

**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 IG, Pollard JD, Macaskill P, et al. Prevalence of chronic inflammatory demyelinating polyradiculoneuropathy 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;66:671–80.
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, Beni 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 PT, 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 Vialia K, Maisonneuve T, Stojilovic T, et al. A current view of the diagnosis, clinical variants, response to treatment and prognosis of chronic inflammatory demyelinating polyneuropathy. 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;179:129–39.
11 Aygriegrak A, Vialia K, Koutsidis RM, et al. Sensory chronic inflammatory demyelinating polyneuropathy: an under-recognised entity? Muscle Nerve 2015;48:727–32.
12 Ohkoshi N, Harada K, Nagata H, et al. Ataxic form of chronic inflammatory demyelinating polyneuropathy: clinical features and pathological study of the sural nerves. Eur Neurol 2001;45:241–8.
13 Gorson KC, Alam G, Ropper AH. Chronic inflammatory demyelinating polyneuropathy: clinical features and response to treatment in 67 consecutive patients with and without a monomodal gamopathy. 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, Jasper 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 Rut K, Drenten 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, Krupaj C. Chronic inflammatory demyelinating polyneuropathy. Handb Clin Neurol 2013;115:403–13.
20 Rajabally YA, Wong SL. Chronic inflammatory pure sensory polyneuropathy: a rare CIDP variant with unusual electrophysiology. J Clin Neuromuscul Dis 2012;13:149–52.
21 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.
22 Sinneveij M, Klein CJ, Daube JR, et al. Chronic immune sensory polyradiculopathy: a possibly treatable sensory ataxia. Neurology 2004;63:1662–9.
23 Yianikis C, Vucic S. Utility of somatosensory evoked potentials in chronic acquired demyelinating neuropathy. Muscle Nerve 2008;38:1447–54.
24 Katz JS, Saperstein DS, Grosset GS, et al. Distal acquired demyelinating symmetric neuropathy. Neurology 2000;54:615–20.
25 Saperstein DS, Katz JS, Amato AA, et al. Clinical spectrum of chronic acquired demyelinating polyneuropathies. Muscle Nerve 2001;24:311–24.
26 Lateu S, Bombelli F, Vialia K, et al. Non-ant-MAG DADS neuropathy as a variant of CIDP. clinical, electrophysiological, laboratory features and response to treatment in 10 cases. Eur J Neurol 2011;18:899–903.
27 Sabatelli M, Madia F, Mignogna T, et al. Pure motor chronic inflammatory demyelinating polyneuropathy. J Neurol 2001;248:772–7.
28 Kimura A, Sakurai T, Kouruma A, et al. Motor-dominant chronic inflammatory demyelinating polyneuropathy. J Neurol 2010;257:621–9.
29 Hattori N, Minu K, Koike H, et al. Age of onset influences clinical features of chronic inflammatory demyelinating polyneuropathy. J Neurol Sci 2001;184:57–63.
30 Rajabally YA, Chavada G. Lewis–sumner syndrome of pure upper-limb onset: diagnostic, prognostic, and therapeutic features. Muscle Nerve 2009;39:206–20.
31 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.
32 Vialia K, Renie L, Maisonneuve T, et al. Follow-up study and response to treatment in 23 patients with Lewis–Sumner syndrome. Brain 2004;127:2010–17.
33 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.
34 Aygriegrak X, Rodrigues BS, Morales R, et al. Focal CIDP presenting as chronic progressive monosymptomatic sensory neuropathy. Muscle Nerve 2013;47:143–4.
35 Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain–Barré syndrome. Ann Neurol 1990;27(Suppl):S21–4.
36 Sunn WJ, Tanf J, Park SB, et al. Early identification of ‘acute-onset’ chronic inflammatory demyelinating polyneuropathy. Brain 2014;137:2155–63.
37 Hughes R, Sanders E, Hall S, et al. Subacute idiopathic demyelinating polyradiculoneuropathy. Arch Neurol 1992;49:612–16.
38 Oh SJ, Kurokawa S, de Almeida DF, et al. Subacute inflammatory demyelinating polyneuropathy. Neurology 2003;61:1507–12.
39 Rodriguez-Casero MV, Shield LK, Kornberg AJ, Subacute inflammatory demyelinating polyneuropathy in children. Neurology 2005;64:1786–8.
40 Joint Task Force of the EFNS and the PNS: European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of parapareptic 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.
41 Niermeijer JM, Fischer K, Eurellings M, et al. Prognosis of polyneuropathy due to IgM monoclonal gamopathy: a prospective cohort study. Neurology 2010;74:406–12.
42 Noble-Orazi E, Manfredini E, Carpo M, et al. Frequency and clinical correlates of anti-neural IgM antibodies in neuropathy associated with IgM monoclonal gamopathy. Ann Neurol 1994;36:416–24.
45 Nobile-Orazio E, Meucci N, Baldini L, et al. Long-term prognosis of neuropathy associated with anti-NGM IgM 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. J Neurol 2011;18:1291–8.

47 Kaku DA, England B, Munner AJ. Distal accentuation of conduction slowing in polyneuropathy associated with antibodies to myelin-associated glycoprotein and sulphated glucuronil paragloboside. Brain 1994;117(Pt 5):941–7.

48 Suarez GA, Kelly JJ Jr. Polyneuropathy associated with monoclonal gamopathy of undetermined significance: further evidence that IgM-MGUS neuropathies are different than IgG-MGUS. Neurology 1992;43:1304–8.

49 Marq J, Chassande B, Maisonnéte B, et al. Polyneuropathy associated with IgG anti-GM1 monoclonal gamopathy: 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-disialyl 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. Canadom 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 1994;57:317–21.

54 Nobile-Orazio E. Neuropathy and monoclonal gamopathy. In: Said G, Krarup C, eds. Handbook of clinical neurology. Amsterdam: Elsevier; 2013:434–59.

55 Watanabe O, Manuyama A, Aminura K, et al. Overproduction of vascular endothelial growth factor/vascular permeability factor is causative in Caw-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 Ar et al

58 Taylor BV, Dyck PJ, Englestad 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 Pestrkova 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. Anti-GM1 IgM antibodies with clinical features. J Neurol Neurosurg Psychiatry 1986;13:123–34.

62 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.

63 Chi Li, Xu WH, Zhang ZW, et al. Distribution of Th17 cells and Th1 cells in peripheral blood and cerebrospinal fluid in chronic inflammatory demyelinating polyradiculoneuropathy. Brain 2010;133(Pt 8):1660–9.

64 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.

65 Hartung HP, Reiners K, Schmidt B, et al. Serum interleukin-2 concentrations in Guillain-Barré syndrome and chronic idiopathic demyelinating polyradiculoneuropathy: correlation with other neurological diseases of presumed immunopathogenesis. Ann Neurol 1991;30:48–53.

66 Donaghy M, Mills KR, Boniface SJ, et al. Multifocal motor neuropathy with conduction block: association with other neurological diseases of presumed immunopathogenesis. J Neurol Neurosurg Psychiatry 2010;15:345–56.

67 Breiner A, Brannagan TH III. Comparison of sensitivity and specificity of sural nerve biopsies in Guillain-Barré syndrome and chronic inflammatory demyelinating polyradiculoneuropathy. Brain 2011;134:3596–607.

68 Rajabally YA, Cila-Londono X, Lewis RA. Multifocal Motor Neuropathy. In: Said G, Krarup C, eds. Handbook of clinical neurology. Amsterdam: Elsevier; 2013:434–59.

69 Kaku DA, England B, Munner AJ. Distal accentuation of conduction slowing in polyneuropathy associated with antibodies to myelin-associated glycoprotein and sulphated glucuronil paragloboside. Brain 1994;117(Pt 5):941–7.

70 Pollard JD, McCombe PA, Baverstock J, et al. Class II antigen expression and T lymphocyte subsets in chronic inflammatory demyelinating polyneuropathy. J Neuromuscul Disord 1986;13:123–34.
Neuro-inflammation

100 Vital C, Vital A, Laguerre 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. *Ear J Immunol* 1988;18:969–72.

102 Zemlin F, Faissol ML, Matthey EK, 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 Li, Wang HB, Wang WZ. Impairment of circulating CD4+CD25+ regulatory T cells in patients with chronic inflammatory demyelinating polyradiculoneuropathy. *J Periodin Neurol Surv* 2008;13:54–63.

105 Salomon B, Rhee B, Bae JS, et al. Development of autoimmune peripheral anti-PMP22 antibodies in patients with chronic inflammatory demyelinating polyradiculoneuropathy. *Hum Immunol* 2009;70:516–22.

106 Devaux J. Antibodies to glialin cause peripheral demyelinating neuropathy and the dismantling of the nodes of Ranvier. *J Am Physiol* 2012;181:1402–13.

107 Amor V, Feinberg K, Eshel-Ishai Y, et al. Long-term maintenance of Na+ channels at nodes of Ranvier depends on glial contact mediated by glialin and XLNAT2. *J Neurol Sci* 2014;340:589–98.

108 Meyer zu Hagen AK, Mausberg AK, Cordes S, et al. Neuronal membrane protein P0 increases in chronic inflammatory demyelinating polyneuropathy patients. *J Peripher Nerv Sys* 2013;18:136–40.

109 Dalakas MC, Engel WK. Immunoglobulin and complement deposits in nerve myelin proteins P0 and P2 in patients with inflammatory neuropathy of the anterior horn cell type. *Ann Neurol* 2000;47:765–75.

110 Hays AP, Lee SS, Latov N. Immune reactive C3d on the surface of myelin sheaths in chronic inflammatory demyelinating polyneuropathy. *Ann Neurol* 1987;21:392–8.

111 Shahrizaila I, Kokubun N, Sawai S, et al. Antibodies to single glycolipids and glycolipid complexes in Guillain-Barré syndrome subtypes. *Neurology* 2014;83:118–24.

112 Heininger U, Liebert UG, Tokaya KV, et al. Chronic inflammatory polyneuropathy. Reduction of nerve conduction velocities in monkeys by systemic passive transfer of immunoglobulin G. *J Neurol Sci* 1984;66:11–14.

113 Mathey EK, Derfuss T, Storch MK, et al. P0 protein is a target antigen in chronic inflammatory demyelinating polyradiculoneuropathy. *Neurol Sci* 2001;14:269–76.

114 Yan WX, Taylor J, Ntasi-Kauba S, et al. Passive transfer of demyelination by serum or IgG from chronic inflammatory demyelinating polyneuropathy patients. *Ann Neurol* 2000;47:765–75.

115 Inglis HR, Crottes PA, McCombe PA. Antibody responses to peptides of peripheral nerve myelin proteins P0 and P2 in patients with inflammatory demyelinating polyneuropathy. *J Neurol Neurosurg Psychiatry* 2007;78:419–22.

116 Khalili-Shirazi A, Atkinson P, Gregson N, et al. Development of spontaneous chronic inflammatory polyneuropathy: Immunopathological and ultrastructural study of peripheral nerve biopsy in 42 cases. *Neuro-Immuno-Pathol* 2012;61:59–68.

117 He J, Li L, Kang Z, et al. Antibodies to peripheral nerve myelin protein 22 induce axonal injury and exacerbate disease severity in experimental autoimmune neuritis. *J Neurol Sci* 2013;328:66–73.

118 Hays AP, Liebert UG, Tokaya KV, et al. Chronic inflammatory polyneuropathy. Reduction of nerve conduction velocities in monkeys by systemic passive transfer of immunoglobulin G. *J Neurol Sci* 1984;66:11–14.

119 Mathey EK, Derfuss T, Storch MK, et al. P0 protein is a target antigen in chronic inflammatory demyelinating polyradiculoneuropathy. *Neurol Sci* 2001;14:269–76.

120 Urban N, Derfuss T, Storch MK, et al. Antibodies to peripheral nerve myelin protein 22 induce axonal injury and exacerbate disease severity in experimental autoimmune neuritis. *J Neurol Sci* 2013;328:66–73.

121 He J, Li L, Kang Z, et al. Antibodies to peripheral nerve myelin protein 22 induce axonal injury and exacerbate disease severity in experimental autoimmune neuritis. *J Neurol Sci* 2013;328:66–73.

122 Mathey EK, Derfuss T, Storch MK, et al. P0 protein is a target antigen in chronic inflammatory demyelinating polyradiculoneuropathy. *Neurol Sci* 2001;14:269–76.

123 He J, Li L, Kang Z, et al. Antibodies to peripheral nerve myelin protein 22 induce axonal injury and exacerbate disease severity in experimental autoimmune neuritis. *J Neurol Sci* 2013;328:66–73.

124 Mathey EK, Derfuss T, Storch MK, et al. P0 protein is a target antigen in chronic inflammatory demyelinating polyradiculoneuropathy. *Neurol Sci* 2001;14:269–76.

125 He J, Li L, Kang Z, et al. Antibodies to peripheral nerve myelin protein 22 induce axonal injury and exacerbate disease severity in experimental autoimmune neuritis. *J Neurol Sci* 2013;328:66–73.
160 Cappelen-Smith C, Kuvabara 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, Trevillon 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.