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# A review on Chronic Inflammatory Demyelinating Polyradiculoneuropathy

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**ABSTRACT:** Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a kind of inflammatory neuropathy that has a gradual start and symmetrical sensory involvement. However, there are several clinical variances, suggesting that CIDP may represent a spectrum of linked disorders rather than a single disease entity. While the prevailing idea of CIDP pathogenesis is that cell-mediated and humoral processes interact in an abnormal immune response to damage peripheral neurons, the proportional roles of T cell and autoantibody responses are yet unknown. T cell responses to specified myelin antigens are responsible in animal models of spontaneous inflammatory neuropathy. Antibodies to Schwann cell, compact myelin, and nodal antigens have been found in different human inflammatory neuropathies. The roles of the cellular and humoral immune systems in the development of CIDP are discussed in this review. It is believed that, in the future, the identification of clinical phenotypes and the underlying disease processes would aid in the development of diagnostic and therapy options for CIDP.

**KEYWORDS:** Myelin, Neuroimmunology, Neuropathy, Neurophysiology, Schwann cell

## INTRODUCTION

The most prevalent treated chronic neuropathy is chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), which has an incidence of 1 to 9 cases per 100000 people globally [1–6]. CIDP manifests as a recurrent or progressive neuropathy with proximal and distal weakness that lasts at least eight weeks [7]. Although CIDP is classified as an autoimmune condition in which an abnormal immune response is directed towards peripheral nerve components, causing demyelination and axonal destruction, the specific processes behind immunopathology development are unknown. Furthermore, the wide range of clinical presentations and various phenotypic variations confound the identification of pathogenic pathways, which is exacerbated by differing patient responses to therapy. While modern medicines focused at stopping immunopathogenic pathways can help many people, others do not respond or have long-term disabilities. There is currently no biomarker that can be used to help diagnosis or categorise individuals into subgroups. A better knowledge of the relationships between immunopathology and clinical phenotype might aid in the development of CIDP diagnostic and therapy strategies. The pathogenesis of CIDP, the function of the cellular and humoral immune systems, and their link to phenotypic manifestation in CIDP will be discussed in this review.

### CIDP Phenotypic Variants

CIDP has several phenotypic variations. Indeed, CIDP might represent a spectrum of distinct but linked diseases in which immunogenetic variances drive individual phenotypic disparities.Motor and sensory nerve dysfunction are common in CIDP, with motor impairments recorded in up to 94 percent of patients and sensory abnormalities reported in up to 89 percent of patients [19]. On the other hand only 50% of CIDP patients have the classic phenotype. Sensory dominant CIDP affects 5-35 percent of patients, with lower limb numbness being the most common symptom [9-11, 20, 21]. Despite the absence of sensory complaints, individuals with demyelination frequently have severe motor nerve conduction problems [21].Sometimes patients with just sensory electrophysiological characteristics have been observed [22]. Many of these individuals, however, go on to develop motor weakness

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years after the start of sensory symptoms [23]. Similarly, a small percentage of CIDP patients (5%), known as chronic immune sensory polyradiculopathy, suffer with increasing sensory ataxia and sensory complaints [8-12]. In contrast to sensory CIDP, these individuals may show little signs of demyelination in distal sensory nerves and are damaged mostly in the posterior root's fibres [24]. Somatosensory evoked potentials may be used to confirm proximal sensory impairment [25].While conventional CIDP involves both proximal and distal involvement, the distal acquired demyelinating symmetric neuropathy (DADS) variety is limited to a distal, symmetrical distribution [26], with mostly sensory complaints, but electrophysiological evidence of motor involvement is common [26]. The cause is a unique disorder in which an IgM paraprotein with antimyelin-associated glycoprotein (anti-MAG) antibody activity is responsible for the pathogenesis in 50–70% of individuals with the clinical picture of DADS phenotype [26, 27]. On the other hand, the DADS clinical picture might be produced by a phenotypic variety of CIDP that shares a lot of similarities with the sensory and sensory ataxic CIDP phenotypes [28]. Patients with recurrent remitting weakness with limited or no sensory electrophysiological characteristics or symptoms have been documented to have motor dominant CIDP [29, 30]. The motor dominant phenotype affects 7-10% of CIDP patients [8, 9] with rates greater in those under the age of 20 years [31]. Multifocal motor neuropathy is the most common differential diagnosis for motor CIDP, especially in the rare cases of focal motor CIDP [20]. Asymmetry characterises Lewis-Sumner syndrome (LSS), also known as multifocal acquired demyelinating sensory and motor neuropathy (MADSAM), which manifests as a multifocal multiple mononeuropathy, most typically in the upper limbs [32]. It affects 6-15 percent of people with CIDP [8,9]. Patients have impaired sensory and motor nerve conduction in one or both upper limbs [14, 33, 34]. The majority of individuals develop diffuse, classic CIDP that spreads to the other limbs [32,34]. Focal CIDP has also been recorded, with symptoms confined to a single focal location for an extended length of time [15], but it may also occur before diffuse CIDP develops [35]. For the past 30 years, focal sensory CIDP has been observed to be limited to one upper limb [36]. Acute-onset CIDP has a fast progression beginning within 8 weeks [16,17], which may cause diagnostic overlap with acute inflammatory demyelinating polyneuropathy (AIDP) [18]. Acute-onset CIDP affects 2 to 16 percent of CIDP patients [9, 16-18]. Nerve excitability approaches have indicated variations in the profiles of AIDP and acute-onset CIDP patients, potentially resulting in better diagnostic results [38]. Although the onset phase of CIDP is normally defined as 8 weeks or more, and the onset phase of AIDP is usually defined as 4 weeks or less, some individuals have a subacute inflammatory demyelinating polyradiculoneuropathy with an intermediate duration of the initial progressive phase [39-41].

**Differential Diagnoses and Mimic Disorders**

There are various immune-mediated neuropathies that are associated to the vast variety of CIDP symptoms. Evidence of a paraprotein might indicate a malignant haematological illness or an unexplained monoclonal gammopathy [42]. Paraproteinaemic demyelinating neuropathy (PDN) refers to demyelinating neuropathy that occurs in the context of monoclonal gammopathy and is phenotypically similar to CIDP. The phenotype of PDN linked with IgM paraprotein is often sluggish, distant, and largely sensory [26, 42, 43]. Anti-MAG IgM antibodies are seen in more than half of IgM paraprotein patients [44]. Sensory ataxia and tremor are common symptoms of Anti-MAG neuropathy [43, 45]. Reduced or missing sensory action potentials, as well as excessively long distal motor latencies, are electrophysiological features of anti-MAG neuropathy [46, 47]. While individuals with PDN may satisfy diagnostic criteria for CIDP, strong anti-MAG antibody rule out CIDP diagnosis [7]. IgG and IgA paraproteinaemic demyelinating neuropathies are less prevalent, although they can look a lot like CIDP, especially in terms of treatment response [48,49]. CANOMAD (Chronic ataxic neuropathy with ophthalmoplegia, M-protein, cold agglutinins, and disialosyl antibodies) is an uncommon illness characterised by severe sensory ataxia and cranial nerve involvement, which includes ophthalmoplegia, dysphagia, or dysarthria, and very little weakening [50]. It affects around 2% of people with IgM PDN [51]. Antibodies to gangliosidedisialosylmoieties are linked to CANOMAD [50]. CANOMAD usually takes years to develop, and peripheral neuropathy may appear before other symptoms such as ophthalmoplegia [52]. POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinology, Monoclonal gammopathy, and Skin Changes) is a little less frequent condition marked by plasma cell dyscrasia of an IgA or IgGparaprotein and a slew of multisystem clinical symptoms [42]. It is frequently associated with neuropathy [53], which is characterised by sensory and motor involvement as well as demyelinating and axonal characteristics [42]. In the initial phase it remains as subacute, and the disease progresses to leave the patient with significant motor weakness [54]. This condition might be a lot of neuropathic pain [53]. The cytokine vascular endothelial growth factor [55] is useful in determining the diagnosis.MMN is the most common differential diagnosis for motor CIDP, especially in the rare cases of focused motor CIDP [56]. In the absence of

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objective sensory involvement, MMN is a chronic, immune-mediated neuropathy characterised by asymmetric, mostly distal, and typically upper limb weakness [57-59]. Multifocal conduction blockages in mixed nerve motor fibres with normal sensory conduction along the same segments characterize MMN. Anti-GM1 IgM antibodies have been found in individuals with MMN at varied levels of prevalence, ranging from 30% - 85% [60,61] but most studies report the ranges between 40% - 50% [62-64]. This broad range is partly owing to methodological differences [61,65] , but it is commonly agreed that anti-GM1 antibodies are present in a larger proportion of individuals with MMN than in control groups, and that they may be associated with the degree of weakness and impairment [62]. The asymmetry of presentation and motor involvement are similar to those seen in the CIDP subtypes MADSAM and motor dominant CIDP, making misdiagnosis a possibility. MMN generally responds to immunotherapy with intravenous immunoglobulin (IVIg), but not to plasma exchange or corticosteroid treatment, unlike CIDP [56]. Motor CIDP, on the other hand, has been observed to be resistant to or worsen in steroid therapy [29,66].

**Clinical Diagnosis**

A combination of clinical and electrophysiological criteria is used to diagnose CIDP. There have been a few criteria proposed. The recommendations were created by the European Federation of Neurological Societies (EFNS) and the Peripheral Nerve Society (PNS) for clinical and scientific purposes [7]. To identify CIDP, the criteria incorporate clinical and electrophysiological evidence, with supportive criteria such as high CSF protein, gadolinium elevation of nerve roots or plexus on MRI, or nerve biopsy results giving further diagnostic evidence. For a diagnosis of 'definite' CIDP, electrodiagnostic evidence of peripheral nerve demyelination in motor nerves, such as distal latency prolongation, reduction of motor conduction velocity, prolongation of F-wave latency, and partial motor conduction block, must be identified in at least two nerves [7]. It should be highlighted that the EFNS/PNS criteria may fail to diagnose pure sensory CIDP in some patients where regular motor conduction testing is normal. If CIDP is suspected in these situations, sensory evoked potentials should be used to probe the proximal area of the peripheral sensory nerve system. Although alternative criteria have been presented, the EFNS/PNS criteria for CIDP diagnosis have high sensitivity and specificity and are now the most often utilized [6,67,68].

**Immunopathogenesis of CIDP**

The prevailing idea of CIDP pathophysiology is that cell-mediated and humoral processes work together to generate peripheral nerve injury. Several lines of evidence point to CIDP being an autoimmune illness mediated by humoral and cellular response to as-yet-unidentified Schwann cell/myelin antigens. Despite the fact that some patients have reported antecedent infections prior to the development of neurological symptoms, no target(s) or trigger for the autoimmune response has been identified and no infectious agent has been reliably associated to illness onset. The success of therapies that target the immune system, such as IVIg, plasma exchange, and corticosteroids, as well as indications of an inflammatory response in the blood and peripheral nerves, support the autoimmune etiology.

**Pathology of CIDP**

Inflammatory lesions in CIDP are seen mostly in the spinal roots, proximal nerve trunks, and major plexuses, but can also be found throughout the PNS, according to autopsy, MRI, and ultrasound investigations. However, because the proximal nerves and nerve roots are relatively inaccessible, most biopsies are performed from the sural nerve. Despite the fact that this site is far from the most active inflammatory activity, pathological changes in sural nerve biopsies include no abnormalities, oedema, demyelination, onion bulb formation, axonal degeneration, and perivascular or endoneurial inflammatory infiltrates of macrophages and T cells [69, 70, 71,72]. Many of these pathological changes are also seen in an animal model of CIDP called experimental autoimmune neuritis (EAN), which is caused by an autoimmune attack on peripheral nerve mediated by the cellular and humoral arms of the immune response and is induced in susceptible strains of rodents or rabbits by immunization with either whole myelin or specific myelin proteins.

**Cellular Mechanisms**

Based on the presence of inflammatory infiltrates in sural nerve biopsies, [73] changes in the 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 CIDP patients, and the

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contribution of T cells to disease in EAN, cellular immune mechanisms are implicated in the pathogenesis of CIDP [83-86]. The blood-nervous-system barrier is disrupted. The disruption of the blood-nerve barrier (BNB) is one of the key antecedents of nerve inflammation and subsequent nerve injury. The BNB maintains endoneurium homeostasis under normal physiological settings by restricting free passage of soluble substances such as serum proteins from the blood into the neuron microenvironment.On the other hand, T cells can not only cross the BNB into the endoneurium when activated, but they may also change the permeability of the BNB, allowing substances that are normally prohibited to enter. During active disease, $CD4^+$ T cells in the periphery upregulate activation markers [87] such as t-bet and pstat1 [75] and secrete proinflammatory cytokines such as interleukin-2 (IL-2) [76,87] interferon γ (IFNγ) [75] and IL-17 [75,88] as well as the chemokines interferon gamma-induced protein-10 (IP-10) [81,82] and macrophage inflammatory protein-3β (MIP-3β) [81]. The up-regulation of the adhesion molecules vascular cell adhesion molecule-1 (VCAM-1) [89], endothelial leukocyte adhesion molecule-1 (ELAM-1) [90], and intercellular adhesion molecule-1 (ICAM-1) [91] on endothelial cells lining the blood vessels of the nerve is caused by the release of cytokines and chemokines into the circulation.Activated T cells connect with adhesion molecules on endothelial cells, roll along the vessel surface, and then travel across the BNB. These T cells continue to release inflammatory mediators such as matrix metalloproteinases [92] and proinflammatory cytokines/chemokines [76, 80] as they travel through the blood arteries, adding to greater BNB permeability and activation of the immune response inside the nerve. The BNB's breakdown is crucial because it permits soluble factors like antibodies to enter the endoneurium. In individuals with CIDP, MRI gadolinium augmentation of nerve trunks or plexuses might be seen [93]. Inflammatory cells infiltrate Infiltrating inflammatory cells in CIDP sural nerve biopsies include $CD8^+$ T cells, [94] $CD4^+$ T cells, and macrophages [73,95]. The increase of antigen-presenting major histocompatibility complex (MHC) class II [72] molecules as well as the costimulatory molecules B7-1 and B7-2 [96, 97] by invading macrophages and Schwann cells facilitates local reactivation of infiltrating T cells. Tumor necrosis factor, interferon, and IL-2 are proinflammatory cytokines that are produced by a range of nerve cell types [98] and exacerbate the immunological response. Macrophages are the most common inflammatory cells that infiltrate endoneurial arteries and form clusters surrounding them [70]. Many components of the immune response are influenced by activated resident and recruited macrophages, including antigen presentation and the production of proinflammatory cytokines and toxic mediators. They also play a key role in the last phases of demyelination by phagocytizing and taking away myelin [99]. Macrophages may be detected infiltrating between the spirals of the Schwann cell plasma membrane, including the outer mesaxon, and breaking down the myelin lamellae by extending elongated processes between the lamellae in ultrastructural investigations of CIDP nerve biopsies [100].

The involvement of $CD8^+$ T cells in CIDP pathogenesis is debatable [72]. In CIDP nerves Schwann cells greatly upregulate MHC class I molecules, presumably allowing cytotoxic ($CD8^+$) T lymphocytes to be recognised and reactivated. $CD8^+$ cells can be reactivated inside the endoneurium in some circumstances, such as leprosy, where $CD8^+$ T lymphocytes specific for the bacteria can lyse Schwann cells infected with Mycobacterium leprae[101]. Although no foreign or self-antigen has been identified as a $CD8^+$ target in CIDP, sural nerve biopsies and peripheral blood have shown comparable clonal proliferation of $CD8^+$ cells [94]. The presence of these $CD8^+$ T cell clones in the nerve suggests that CIDP is caused by an antigen-driven, $CD8^+$ cell-mediated assault on the nerve. However, there is little evidence of these $CD8^+$ cells in direct contact with their target cells in situ, which limits any inferences concerning their involvement as cytotoxic effector cells in CIDP. A recent study of the T cell repertoire in CIDP patients discovered that $CD8^+$ T cells were more activated than $CD4^+$ T cells, which was decreased following treatment with IVIg[102].Despite the fact that no infectious agent has been reliably associated to CIDP, oligoclonal activation of $CD8^+$ cells is frequently interpreted as evidence of a T cell response to chronic infection. In EAN, $CD8^+$ T lymphocytes play no involvement.Central tolerance and regulatory T cells although self-reactive T cells are mostly destroyed during thymus selection, a small number escape and can cause autoimmune illness. Peripheral tolerance mechanisms, such as the immunosuppressive effect of regulatory T cells, keep these cells in check. There are signs that the immunoregulatory cellular response that controls excessive or inappropriate immune activation is disrupted in CIDP [103,104]. The number of circulating T regulatory cells, as measured by $CD4^+CD25(high)Foxp3^+$ markers is decreased [104], and when isolated, they are less efficient in inhibiting proliferative responses than healthy controls [103,104]. The immunological dysfunction found in CIDP might possibly be linked to dysregulation of the regulatory cell compartment.

In a mouse model of CIDP that develops spontaneously in non-obese diabetic (NOD) mice deficient in the costimulatory molecule B7-2, the complexities of the interactions between autoreactive T cells, antigen-presenting cells, and the inflammatory mediators

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released during an autoimmune reaction are highlighted [105]. The NOD mouse model was created to investigate the function of T cell costimulation in the development of diabetes. While suppressing B7-2 costimulation protected the mice against diabetes, they developed a spontaneous autoimmune peripheral polyneuropathy (SAPP) that was clinically, electrophysiologically, and histologically comparable to CIDP. This may be seen in NOD mice with a point mutation in the autoimmune regulator (Aire) gene, which results in decreased P0 expression in the thymus and an increase of P0 specific T cells in the peripheral blood [107]. In another NOD model lacking for isoforms of ICAM-1, autoimmunity is transferred to the peripheral nerve [108]. Changed ICAM-1 expression on thymic epithelial cells shifts T cell selection from a diabetogenic to a neuritogenic repertoire [108]. These studies emphasize the importance of regulatory systems in maintaining immunological homeostasis, as well as the influence that alterations in regulation might have on disease development.

**Humoral Mechanisms**

Responses of autoantibodies to myelin proteins Plasma exchange's success in the treatment of CIDP suggests that humoral processes are important in the disease's etiology. Furthermore, there is a lot of evidence from biopsy and serological investigations that humoral immune systems are involved. Sural nerve biopsies from certain individuals with CIDP exhibit immunoglobulin and complement deposited on the outer surface of Schwann cells and compact myelin [109,110] and blood from some patients with CIDP may be demonstrated to bind to normal nerve sections using indirect immunofluorescence [111]. Following intraneural injection in the rat serum that had been proven to bind to nerve sections induced demyelination [111] and a decrease in conduction velocity [111,112] in a small fraction of patients who reacted well to plasma exchange. Further tests with this serum revealed that compact myelin protein P0 is the target antigen [113]. However, the specific target of the autoantibody response in the majority of patients is unknown, but due to the striking nature of the demyelination seen in histopathological sections of CIDP nerve, these proteins found in compact myelin have long been thought to be the most likely candidate autoantigens. The EAN animal model, which can be induced in rats using purified myelin proteins P0, [128], P2 [129], and peripheral myelin protein (PMP)-22 [130], supports this viewpoint, demonstrating that an autoimmune response to these autoantigens has the potential to initiate disease and contribute to nerve damage and clinical symptoms. However, after years of research, there is scant evidence that autoantibody reactions to these main myelin proteins have a pathogenic role in the majority of CIDP patients. Although autoantibody reactions to P2 [115], P0 [111,113,114,116], PMP-22 [121], and connexin [119] have been found in CIDP serum in some investigations [117]. Even more controversy surrounds the toxicity of these autoimmune reactions; only those myelin protein antibodies specific for P0 have been demonstrated to be harmful in vivo by intraneural injection [113, 131] and passive transfer [113]. The hunt for autoantibodies reactive to the primary compact myelin proteins in CIDP has been fruitless thus far, and the focus has shifted to other aspects of the myelinated axon.Studies on autoantibody specificity are changing their attention from key myelin proteins to those found in the non-compact myelin, which includes the node of Ranvier, paranode, and juxtaparanode, not just in CIDP but also in some cases of GBS [124,126,132]. The creation and maintenance of the node of Ranvier and paranodal areas of myelinated axons are dependent on axoglial proteins. Gliomedin, neuron glia-related CAM (NrCAM), and neurofascin 186 (NF186) are nodal cell adhesion molecules (CAMs) that are required for the first clustering of $Na^+$ channels during development [133] and contribute to the long-term maintenance of $Na^+$ channel clustering in the node of Ranvier [133]. Axoglial junctions between paranodal loops and axonal membrane formed of contactin-1/caspr-1 complexes that bind to Schwann cell neurofascin 155 (NF155) make up the neighbouringparanode[134]. The paranodalseptate connections are formed and maintained by these proteins. Ion channel segregation, paranodal structure, and effective neuronal conduction all need NF155 [135]. These areas are necessary for successful saltatory conduction because they operate as a membrane barrier that prevents ion channel lateral diffusion, ensuring that $Na^+$ is concentrated at the node and $K^+$ is concentrated at the juxtaparanode. In numerous antiganglioside-mediated neuropathies, known as 'nodoparanodopathies,' this region is targeted by the immune system [136]. Autoantibodies against glycolipids or glycolipid complexes attach to the nodal areas in the AMAN variant of GBS, causing complement fixation and node damage [137,138]. However these antibodies have not been consistently found in the demyelinating variant of GBS, AIDP [139], or in CIDP, and the target(s) in these illnesses remain unknown. Autoantibodies to a variety of proteins found in the nodal areas, such as gliomedin [126],neurofascin [124, 126], contactin-1 [127], caspr1 [127], and moesin [140], have recently been reported in a small percentage of individuals with AIDP and CIDP. According to a recent research, 62 percent of patients with MMN exhibited anti-gliomedin or anti-NF186 antibodies, while 10% of sera lacking anti-GM1IgM had anti-NF186 antibodies [141].Indeed, nodal and paranodal areas

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are disturbed in CIDP nerve biopsies, and proteins essential for structural integrity are improperly produced and distributed [142]. Schwann cell microvilli and paranodal glial loops with extensive vacuoles in the Schwann cell outer cytoplasm and nodal axoplasm were found aberrant on electron microscopy of nerve samples [142]. Furthermore, punctate immunoreactivity for $Na^+$ and $K^+$ channels was dispersed along the axon, whereas caspr-1 was diffusely distributed [142]. In addition, as compared to normal controls, cutaneous myelinated nerve fibres had enlarged nodes of Ranvier and broadened neurofascin and caspr staining [143].Neurofascin and gliomedin disruption occurred before paranodal demyelination and the dispersion of $Na^+$ channels in EAN models caused by vaccination with PNS myelin [144]. Importantly, these alterations were linked to the production of serum autoantibodies against neurofascin and gliomedin, indicating that these proteins might be immunological targets in some demyelinating neuropathies [144]. Importantly, there is now evidence that nodal antigens have a role in some instances of CIDP. Devaux et al. [126] discovered that 30% of individuals with CIDP have serum IgG that binds to either the nodes of Ranvier or the paranodes in strained nerve fibres, and that the target antigens are neurofascin, gliomedin, or contactin in certain instances. Furthermore, autoantibodies against CAMs have been found in the nodes of Ranvier and paranodal areas of individuals with CIDP in various investigations [123,124,126,127,145]. In CIDP, nodal and paranodal antigens have been identified. Antibodies against the CAM neurofascin have been discovered in 4% of CIDP patients [123,124]. Surprisingly the majority of antibodies discovered were directed against the NF155 isoform of glialneurofascin. While antibodies to glial NF155 and neuronal NF186 can cross-react due to structural similarities [146, 147]neurofascin antibodies in CIDP patients have been specifically targeted against NF155 [123,124]. Plasma exchange proved beneficial in two patients with elevated anti-NF155 (IgG3 isotype) antibody titres [124]. Anti-NF155 reactivity was evaluated in one of these patients throughout the course of the disease and gradually decreased over four years, following which the patient went into remission and was weaned off plasma exchange medication. Antibodies to NF155 have also been found in 5/7 patients with both central and peripheral demyelination [125]. Patients with anti-NF155 antibodies reacted to IVIgafter corticosteroids were only partially effective in this trial. On the other hand, corticosteroids were efficacious for PNS and CNS lesions in individuals with mixed central and peripheral demyelination who did not have anti-NF155 antibodies. The high prevalence of anti-NF155 antibodies in combined central and peripheral demyelination, as well as their link to treatment success, suggests that they might be used as a diagnostic and treatment response marker; nevertheless, additional research into these antibodies in this unusual syndrome is needed.Antibodies against NF155 have been found in a subgroup of individuals with CIDP who have the dominant immunoglobulin subtype IgG4 [123]. Anti-NF155 IgG4 antibodies were identified in 2/53 CIDP patients and 0/204 individuals with other neuromuscular illnesses at first. A database was used to identify eight more individuals with CIDP who were resistant to IVIg therapy and were tested for anti-NF155 antibodies. Anti-NF155 IgG4 antibodies were detected in two of eight IVIg-refractory individuals. These individuals had clinical characteristics such as severe distal neuropathy, debilitating tremor, and poor response to therapy. The IgG4 subtype of IgG immunoglobulin has certain unique characteristics that set it apart from the other IgG subclasses [148]. Because of their limited affinity for C1q and Fc receptors, IgG4 antibodies have a lower ability to generate complement and cell activation. Anti-inflammatory IgG4 antibodies are thought to minimise complement-mediated damage and inflammation by combining with other IgG subtypes to bind antigen without activating immunological effector pathways. However, IgG4 antibodies have been proven to be harmful in some cases due to 'antigen blocking' process in which the antibody prevents the bound target antigen from performing crucial activities [124]. In myasthenia gravis, anti-muscle-specific kinase (MuSK) IgG4 antibodies bind directly to MuSK and interfere with its activity, causing synaptic structure and transmission to be disrupted [149]. It might be good to look for anti-NF155 IgG4 antibodies in a bigger group of CIDP patients. Autoantibodies reactive to the axonal contactin-1/caspr complex in the paranode have been found in an additional subgroup of CIDP patients (3/46 vs 0/104 controls with other neurological disorders) [127]. Contactin-1 antibody-positive cases showed an aggressive start of illness, primarily motor symptoms, early axonal involvement, and were either partially or not at all responding to IVIg, necessitating further corticosteroid therapy [127]. In myelinated neuronal cells, disruption of paranodal connections and interference with nodal structure led to nodal enlargement, decreased casprimmunostaining, and lower conduction velocity, indicating a pathogenic function for these contactin-1 antibodies [150].

**Pathophysiological Significance of Autoantibodies**

Despite recent progress, further research is needed to fully understand the pathophysiological implications of autoantibodies directed towards nodal areas. The molecular and anatomical complexity of the node of Ranvier and adjacent paranodes and juxtaparanodes

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now clearly impacts an antibody's capacity to bind in vivo, and therefore the response's potential pathogenicity. Antibodies against both the NF155 and NF186 isoforms of neurofascin can bind to the proteins when produced on the surface of transfected cells utilising in vitro experiments in the event of neurofascin autoimmunity. Antibodies to NF155 are unable to bind to either neurofascin isoform in vivo in EAE experimental models, suggesting that nodal NF186 is the predominant target [145,147,151]. Anti-NF155 antibodies' ability to bind in vivo might be hampered by steric hindrance produced by nearby interacting proteins [151] or by the paranode's limited accessibility to circulating antibodies. Because NF155 is located at the paranodal level, it may be essential to damage the paranodal structure before autoantibodies may bind in vivo [134]. NF155 may become accessible after demyelination, implying that such antibodies may contribute to pathogenicity after demyelination rather than directly cause demyelination. Antibodies against NF155 have been shown to suppress myelination in vitro by disrupting the caspr/contactin/NF155 complex [152], suggesting that they may play a role in inhibiting remyelination[152]. This disagreement emphasizes the need of thoroughly understanding the intricate interactions between axons and Schwann cells at the molecular and anatomical levels before drawing significant conclusions about the therapeutic consequences.Interactions at the molecular level might affect the capacity to identify autoantibody reactions. Individuals with the axonal AMAN disease variety show reactivity to single glycolipid molecules, while patients with GBS with demyelinating illness do not, according to recent research on the identification of antibodies to gangliosides in the sera of GBS patients [153]. There is a greater possibility of finding response to complexes of two distinct glycolipids in some cases, which might indicate glycolipid 'pattern recognition' as they are oriented in live brain membranes [139,154]. Given that many proteins in the axoglial junction form complexes with proteins in the Schwann cell membrane, a similar process might be at work in the identification or access to binding sites on proteins produced at the node and paranode. As previously mentioned, autoantibody reactivity to the paranodal protein contactin-1 has been reported in 3/46 individuals with CIDP. Reactivity was discovered using contactin-1 alone in two of these individuals, but it could only be detected when it was in combination with caspr1 in the other [127]. In light of these findings, tests to detect pathologically relevant antibody responses must take into account the anatomical location and molecular interactions of possible autoantigens. Furthermore, discrepancies in the autoantibody response detection techniques utilised by different researchers, such as ELISA versus cell-based assays, protein complexes versus individual proteins, and rat versus human protein, make interpretation and confirmation of data more challenging. The question of whether these nodal proteins are the primary target of the immune response or whether autoantibodies to these molecules are an epiphenomenon produced when self-peptides are released after nerve damage due to an inflammatory response.

**Functional Significance of Nodal Disruption in CIDP**

While more research on the pathophysiology of nodal antigenic targets in CIDP is needed, any disturbance of nodal function is likely to alter normal nerve excitability and membrane potentials, contributing to conduction failure by interfering with saltatory conduction and ion channel function. Axonal excitability investigations in individuals with CIDP have revealed a variety of data revealing abnormal membrane excitability and membrane potential, supporting this theory [38,155,156]. These findings show that CIDP patients have altered axonal function, which might be due to autoantibody interaction with the Ranvier node. Immunotherapy may aid recovery after nodal disruption by removing antibodies from circulation or interfering with antibody effector mechanisms, giving a mechanism to account for the quick recovery reported in certain patients following treatment that is not consistent with demyelination [112,157]. As a result of the IVIg maintenance treatments, cyclical regulation of axonal excitability has been established [156]. While the safety factor of transmission normally guarantees that the magnitude of current at the nodes of Ranvier is more than five times that necessary for action potential propagation [158], demyelination diminishes the safety factor, lowering the axon's capacity to hold charge [159]. The demands of a high impulse load during regular activity may shift the balance even further towards conduction failure, making more susceptible to it during exercise. In individuals with CIDP, maximum voluntary contraction has been shown to diminish CMAP amplitude [160,161] and increase temporal dispersion [162]. Motor axons are more prone to conduction failure than sensory axons because they have less tolerance to hyperpolarising membrane potential changes [163]. In comparison to sensory axons, motor axons have a lower activation of the hyperpolarisation triggered cation current $I_h$ and a hyperpolarised membrane potential, rendering them less able to react to subsequent hyperpolarization and more susceptible to conduction failure [164]. Treatment response may be influenced by these biophysical features. Following corticosteroid therapy, patients with motor dominant CIDP and MMN may have clinical deterioration [56,66]. Patients with typical CIDP, focused demyelination, and decreased sensory electrophysiological abnormalities were also more likely to worsen with corticosteroid

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therapy, albeit these findings need to be verified in a larger sample [165]. Corticosteroids have been shown to increase the activity of the $Na^+/K^+$ pump in motor neurons, resulting in hyperpolarization of the resting membrane potential [166-168]. In human skeletal muscle fibres, steroid treatment enhances $Na^+/K^+$ pump activity and expression [169]. Motor axons with localised demyelination or conduction block may be more sensitive to the extra load on normal membrane excitability caused by corticosteroid therapy, and hence more prone to conduction failure and block [165].

## CONCLUSIONS

Despite substantial research, a unifying immunopathological mechanism for acute or chronic inflammatory demyelinating neuropathies has yet to be discovered. On the other hand, the clinical spectrum of CIDP shows substantial phenotypic diversity, indicating that several immunopathological processes are at work. As seen by the present interest in newly characterized antibodies targeting nodal and paranodal antigens, further progress in understanding the pathophysiology of CIDP may come from a'splitting' rather than a 'lumping' strategy. While these antibodies are only found in a small percentage of patients (2–5%), they may help us understand the pathophysiology of CIDP and its variations, establish subtypes of CIDP that react to different methods of immunomodulation, and offer repeatable biomarkers for disease and therapy monitoring. The discovery of different pathogenic mechanisms underlying subtypes of the central demyelinating disorder MS, which occurred more than 20 years ago, led to major advances in our understanding of that disorder, and the more recent discovery of different pathogenic mechanisms underlying subtypes of GBS has shown that unique treatment regimes are required for these different pathological processes. Although more research is needed to fully understand the immunopathogenesis of the majority of CIDP patients, substantial progress has been achieved, which should lead to better patient categorization and in turn better therapy.

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