Expert Review of Neurotherapeutics

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iern20

# Intravenous immunoglobulin in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP): mechanisms of action and clinical and genetic considerations

Marinos C. Dalakas, Norman Latov & Krista Kuitwaard

**To cite this article:** Marinos C. Dalakas, Norman Latov & Krista Kuitwaard (2022) Intravenous immunoglobulin in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP): mechanisms of action and clinical and genetic considerations, Expert Review of Neurotherapeutics, 22:11-12, 953-962, DOI: 10.1080/14737175.2022.2169134

**To link to this article:** https://doi.org/10.1080/14737175.2022.2169134

EXPERT REVIEW OF NEUROTHERAPEUTICS
2022, VOL. 22, NOS. 11–12, 953–962
https://doi.org/10.1080/14737175.2022.2169134

Taylor & Francis
Taylor & Francis Group

REVIEW



# Intravenous immunoglobulin in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP): mechanisms of action and clinical and genetic considerations

Marinos C. Dalakas[a], Norman Latov[b] and Krista Kuitwaard[c,d]

[a]Department of Neurology, Thomas Jefferson Neuroimmunology Unit, Philadelphia, PA and National and Department of Pathophysiology, Kapodistrian University of Athens, Greece; [b]Neuroimmunology Unit, Weill Cornell Medical College, New York, NY, USA; [c]Department of Neurology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands; [d]Department of Neurology, Albert Schweitzer Hospital, Dordrecht, The Netherlands

**ABSTRACT**

**Introduction:** Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an autoimmune peripheral nerve disorder that is characterized by subacute onset, progressive or relapsing weakness, and sensory deficits. Proven treatments include intravenous immunoglobulin (IVIg), corticosteroids, and plasma exchange. This review focuses on the mechanisms of action, pharmacodynamics, genetic variations, and disease characteristics that can affect the efficacy of IVIg.

**Areas covered:** The proposed mechanisms of action of IVIg that can mediate its therapeutic effects are reviewed. These include anti-idiotypic interactions, inhibition of neonatal Fc receptors (FcRn), anti-complement activity, upregulation of inhibitory FcγRIIB receptors, and downregulation of macrophage activation or co-stimulatory and adhesion molecules. Clinical and genetic factors that can affect the therapeutic response include misdiagnosis, degree of axonal damage, pharmacokinetic variability, and genetic variations.

**Expert opinion:** The mechanisms of action of IVIg in CIDP and their relative contribution to its efficacy are subject of ongoing investigation. Studies in other autoimmune neurological conditions, in addition, highlight the role of key immunopathological pathways and factors that are likely to be affected. Further investigation into the pathogenesis of CIDP and the mechanisms of action of IVIg may lead to the development of improved diagnostics, better utilization of IVIg, and more targeted and effective therapies.

**ARTICLE HISTORY**
Received 10 November 2022
Accepted 12 January 2023

**KEYWORDS**
Neurology; autoimmune disease; intravenous immunoglobulin; chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

## 1. Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is the most common autoimmune peripheral nerve disorder. It is characterized by subacute onset and progressive or relapsing weakness, sensory deficits, and areflexia [1]. The reported incidence ranges between 0.15 and 0.70 cases per 100,000 person-years and the prevalence between 0.67 and 7.7 cases per 100,000 persons [2].

The clinical presentation of CIDP is variable, and diagnostic guidelines have been proposed to delineate several subtypes [3]. First-line treatments with proven efficacy based on controlled trials include intravenous immunoglobulin (IVIg), corticosteroids, and plasma exchange [4]. The present review focuses on the proposed mechanisms of action of IVIg in CIDP, and the clinical and genetic factors that could affect its efficacy.

## 2. Mechanisms of action of IVIg in CIDP

The therapeutic effects of IVIg in CIDP are thought to be mediated by multiple mechanisms, including: 1) anti-idiotypic antibody activity; 2) saturation of neonatal Fc receptors (FcRn), 3) anti-complement activity; 4) upregulation of inhibitory FcγRIIb receptors that inhibit macrophage activation, and 5) downregulation of co-stimulatory and adhesion molecules.

### 2.1. Anti-idiotypic antibodies

CIDP is an autoimmune disease that targets the myelin in peripheral nerves. It is thought to be mediated by cellular and humoral mechanisms, although specific antigens have not been identified. IVIg, however, has also been shown to be effective in the treatment of other autoimmune neuropathies in which there are antibodies to specific nerve antigens, including multifocal motor neuropathy (MMN) with IgM antibodies to GM1 ganglioside, and acute motor axonal neuropathy with IgG antibodies to GM1 or GD1a gangliosides [5].

IVIg is manufactured from plasma collected from ≥ 1,000 donors and contains anti-idiotypic antibodies that bind through their $F(ab')_2$ regions. The greater the number of donors, the greater the idiotypic repertoire (Figure 1) [6]. The anti-idiotypic effect of IVIg on autoantibody binding was demonstrated in

CONTACT Norman Latov nol2002@med.cornell.edu Peripheral Neuropathy Clinical and Research Center, Weill Cornell Medical College, 1300 York Avenue, 10065, New York, NY, USA

**Article highlights**

- IVIg has multiple putative immunomodulatory effects that could contribute to its efficacy in the treatment of CIDP.
- The therapeutic effects of IVIg can be mediated by anti-idiotypic interactions, inhibition of FcRn, anti-complement activity, upregulation of inhibitory FcγRIIb receptors, and downregulation of macrophage activation and co-stimulatory and adhesion molecules.
- Clinical factors such as misdiagnosis, degree of axonal damage, and variability in pharmacokinetics or bioavailability can affect responsiveness in individual patients.
- Several genetic variations have been linked to responsiveness to IVIg.
- Additional studies to clarify the mechanism of IVIg in CIDP could lead to the development of improved diagnostics, better utilization of IVIg, and more targeted therapies.

several studies. One study reported that binging anti-GM1 antibodies on ELISA plates was inhibited by both IVIg and IVIg F(ab')$_2$ fragments to a similar degree [7]. In another study, IVIg inhibited the binding of patient sera containing anti-GD1a antibodies by immune-overlay on thin layer chromatography [8]. Similar inhibition was noted with serum from patients whose Guillain-Barré syndrome (GBS) improved after administration of IVIg [8].

The anti-idiotypic effect of IVIg was also demonstrated using autoantibody-positive sera from patients with GBS and Miller Fisher syndrome (MFS) by preventing the in vitro damaging effect of anti-GQ1b antibodies on motor nerve terminals [10], and by neutralizing the effect of GBS antibodies that block quantal release in a nerve muscle preparation [11]. Both serum from patients that improved after IVIg administration, and F(ab')$_2$ fragments from IVIg, neutralized blocking antibodies in a dose-dependent manner [11,12].

### 2.2. Saturation of neonatal Fc receptors (FcRn)

Treatment with IVIg for 3 months was shown to suppress the level of circulating autoantibodies [12,13]. This was demonstrated in controlled studies of anti-glutamic acid decarboxylase (GAD) antibodies in Stiff-person syndrome (SPS) [13] and of anti-voltage gated calcium channel (VGCC) antibodies in Lambert-Eaton myasthenic syndrome (LEMS) [14]. This effect seems likely related to saturation of the FcRn.

The FcRn protects circulating IgG from degradation by recycling it into the circulation [15]. After pinocytosis, FcRn-containing endosomes direct IgG away from lysosomes and back to the cell surface for release into the extracellular space. If the FcRn is blocked, the IgG is directed into the lysosomes for degradation instead. Administration of IVIg raises serum IgG to supraphysiological levels which saturates the FcRn and redirects the endogenous autoantibodies to the lysosomes for degradation, resulting in increased catabolism and lowering of the circulating autoantibody levels (Figure 2).

### 2.3. Anti-complement activity

A key effect of IVIg is to inhibit complement activation. Complement is involved in both antibody-mediated cytotoxicity and macrophage activation. The latter is thought to play a major role in CIDP which is considered to be a macrophage-mediated demyelinating neuropathy (Figure 3) [16].

The inhibition of complement by IVIg has been shown to occur at the C3ab level (Figure 4), with significant complement consumption observed at 2 days following administration of IVIg [17]. Inhibition of complement at the C3 level prevents the formation of membrane attack complex (MAC). After treatment with IVIg, C3b and MAC deposits disappeared in the muscle of dermatomyositis patients [17], an effect reflected in the muscle microvasculature of IVIg-treated patients. Microvascular pathology and perifascicular atrophy were reversed by effective IVIg therapy as evidenced by neovascularization and restoration of tissue architecture [17]. The effect of IVIg on complement activation was also shown with serum from patients with GBS and anti-GD1a antibodies, where IVIg was shown to inhibit complement fixation by the antibodies on sections of sciatic nerve [8].

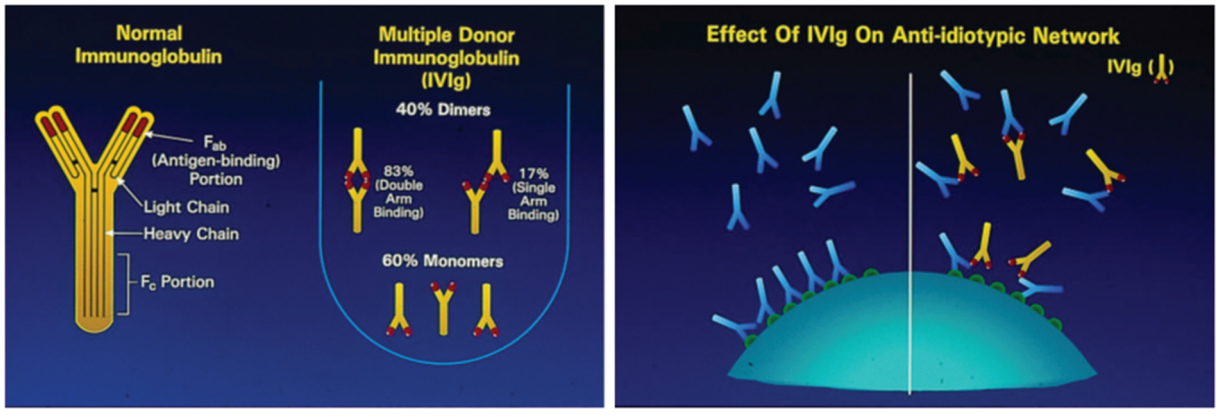


Figure 1. Illustration of idiotypes within the IVIg and their effect on pathogenic antibodies. The IgG's within the IVIg, derived from multiple donors, contain anti idiotypic antibodies that form dimers in F(ab')$_2$ pairs; the larger the pool of donors, the higher the number of F(ab')$_2$ pairs and wider the spectrum of idiotypic-anti-idiotypic antibody specificities [6]. Reprinted from Dalakas [9] with permission from Wolters Kluwer.

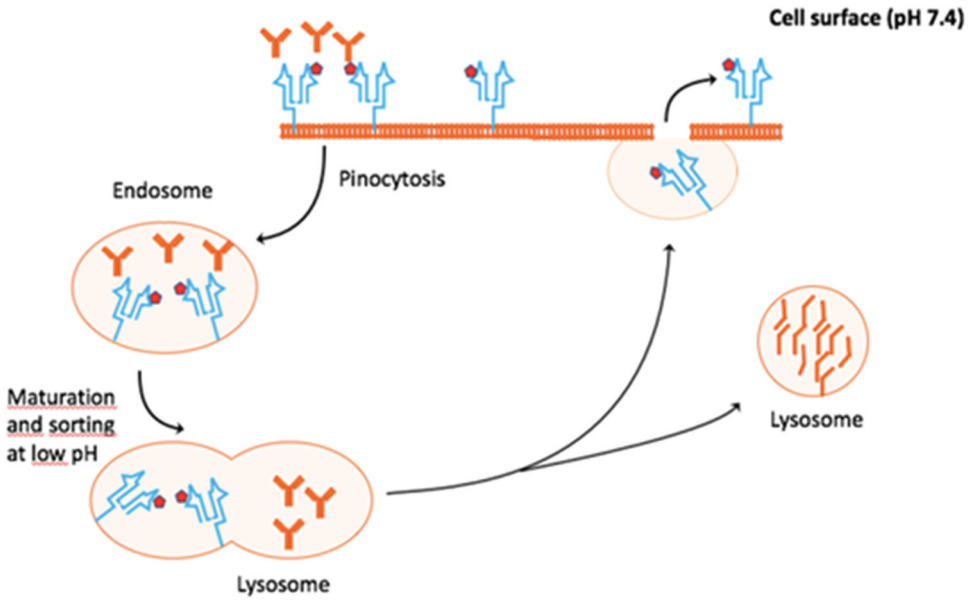


Figure 2. Supra-physiological IgG levels after IV infusion saturate the FcRn enhancing IgG catabolism. Reprinted from Dalakas and Spaeth [15] under open access license CC-BY-NC 4.0.

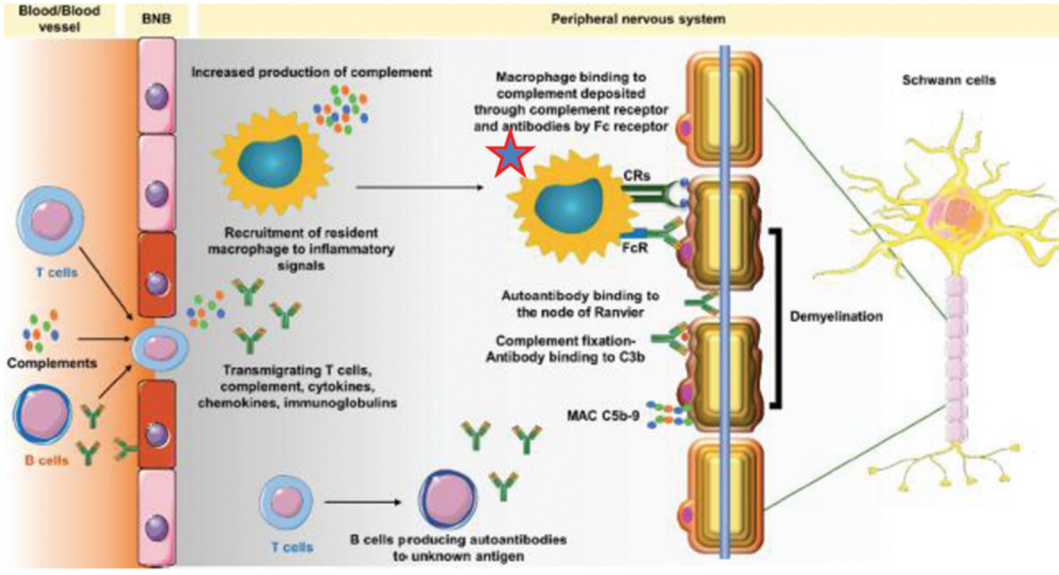


Figure 3. Role of complement in CIDP. Reprinted from Querol et al. [16] under open access license CC-BY-NC 4.0.

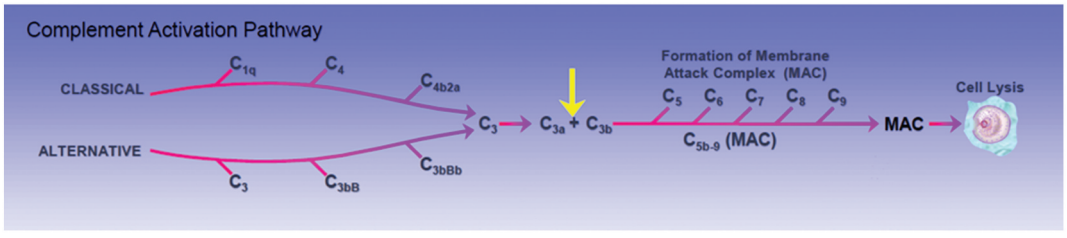


Figure 4. IVIg inhibits the complement pathway at the C3b level (arrow), intercepting the formation of MAC (Membranolytic Attack Complex) [17,18]. Reprinted from Dalakas [19].

### 2.4. Inhibitory FcγRIIB receptors and macrophage activation

IVIg also has a direct effect to inhibit macrophage activation. Macrophages have been shown to split the myelin lamellae in CIDP [20], and macrophage activation via Fc receptors has been shown to play a role in disease pathogenesis [21]. In tissue sections, Incubation with IVIg modulated 30–40% of the Fc receptors on invading macrophages in muscle fibers [15].

Among the Fcγ receptor families, the FcγRIIA activates while the FcγRIIB inhibits tyrosine-based motifs on monocytes and B-cells [6], and mice lacking FcγRIIB tend to develop autoimmune diseases [22,23]. The FcγRIIB receptors transduce inhibitory signals that prevent B-cells from transforming into IgG-producing plasma cells [6]. In mice, the administration of IVIg was shown to induce upregulation of FcγRIIB receptors [24]. CIDP patients have decreased FcγRIIB expression on naïve B cells and monocytes and fail to upregulate or maintain FcγRIIB during disease progression [25]. Administration of IVIg, however, upregulated FcγRIIB expression on monocytes and B cells including CD32+ monocytes, in patients with CIDP or MMN [26].

FcγRIIB expression can also be affected by sialylation of IgG. Nimmerjahn and Ravetch proposed that the anti-inflammatory activity of IVIg was attributable to a minor species of IgG modified with terminal sialic acids on the Fc-linked glycans acting through a unique receptor on macrophages, the activation of which leads to upregulation of FcγRIIB [27]. Normally, the sialic acid-containing isoform makes up 1–2% of IVIg but enriching this isoform up to 20% enhanced the anti-inflammatory effect of IVIg [28]. Analysis of samples from the Immune Globulin Intravenous CIDP Efficacy (ICE) trial [29] showed that induction of IgG Fc sialylation was associated with CIDP remission, with a significant correlation between improvement after 24 weeks of treatment and degree of Fc sialylation [30].

### 2.5. Co-stimulatory and adhesion molecules

Other effector molecules that can be affected by IVIg are the co-stimulatory molecules. The Dalakas laboratory demonstrated that Schwann cells and macrophages in nerves from CIDP patients express several co-stimulatory molecules [31]. Peter Hartung's group also demonstrated that the inducible co-stimulator (ICOS) on T lymphocytes, and the inducible co-stimulator ligand (ICOS-L) were expressed by macrophages within the peripheral nerve in inflammatory neuropathies (GBS, CIDP and vasculitic neuropathy) [32]. The same group also reported the expression of chemokines and chemokine receptors in sural nerve biopsies from patients with autoimmune demyelinating neuropathies [33]. The expression of the co-stimulated molecules can be suppressed by IVIg. As an example, the expressions of major histocompatibility class I (MHC-1), intercellular adhesion molecule 1 (ICAM-1), and transforming growth factor beta (TGF-beta) were downregulated after IVIg treatment in patients with dermatomyositis [18,34,35,36]. In muscle biopsies of patients with inflammatory myopathies, IVIg administration downregulated of mRNA expression of the adhesion molecules ICAM-1, Kallmann 1 (KAL-1, anosmin), and matrix metalloproteinase-9 (MMP-9) [37,38].

Administration of IVIg also inhibits the activity of the adhesion molecules. In mice with experimental autoimmune encephalomyelitis [39], IVIg was shown to inhibit the rolling and adhering of lymphocytes indicating a decrease in the recruitment of activated lymphocytes to the affected tissue. In another study, IVIg inhibited cytokine damage of cultured myotubes mediated by interleukin-1b [15].

## 3. Clinical factors that can affect the response to IVIg in CIDP

The dosage and frequency of administration of IVIg differs among CIDP patients [40], and some patients required two courses of IVIg to show an initial response [41]. In a retrospective study conducted by Kuitwaard et al. in collaboration with Angelika Hahn, the responses to IVIg were investigated in 281 treatment-naïve CIDP patients [42]. These patients met the diagnostic criteria for CIDP established by the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) [43], with responsiveness defined as an improvement of at least one grade in the modified Rankin scale [44]. The study showed that 76% of the patients were responsive to IVIg [42]. The group that was non-responsive to first-line IVIg treatment was likely to show good responses to second line or even third-line treatments (corticosteroids or plasma exchange) [42].

There are a number of possible reasons to explain the variability between patients in responsiveness to IVIg. These include misdiagnosis, degree of axonal damage, and differences in pharmacokinetics or pharmacogenetics. Further investigations into the variability of responses could shed light on the mechanistic effect of IVIg, improve treatment outcomes by selecting patients that are most likely to respond, and help expand our understanding of the immunopathogenesis of CIDP.

### 3.1. Diagnostic difficulties in CIDP

There is no gold standard for the diagnosis of CIDP and misdiagnosis is common [45,46]. The recent European Academy of Neurology/Peripheral Nerve Society (EAN/PNS) CIDP guideline was developed to avoid misdiagnosis and incorrect treatment, but not all neurologists in routine practice follow these guidelines, and it is not proven that adherence to the guidelines would improve diagnosis [3]. This update of the 2010 EFNS/PNS guideline [43] divides CIDP into (typical) CIDP and CIDP variants. [3,47] Among the disorders that are no longer classified as CIDP are autoimmune nodopathies [3], which include patients with specific clinical characteristics and antibodies against nodal-paranodal cell adhesion molecules (contactin-1 [CNTN1], neurofascin-155 [NF155], contactin-associated protein 1 [Caspr1], and neurofascin isoforms [NF140/186]). These nodopathies, which were included as CIDP variants in the 2010 guideline, are thought to comprise about 10% of CIDP cases [47].

The antibodies in nodopathy patients are mainly of the IgG-4 subclass which do not activate the complement cascade and have reduced capacity to bind to Fc receptors, rendering them

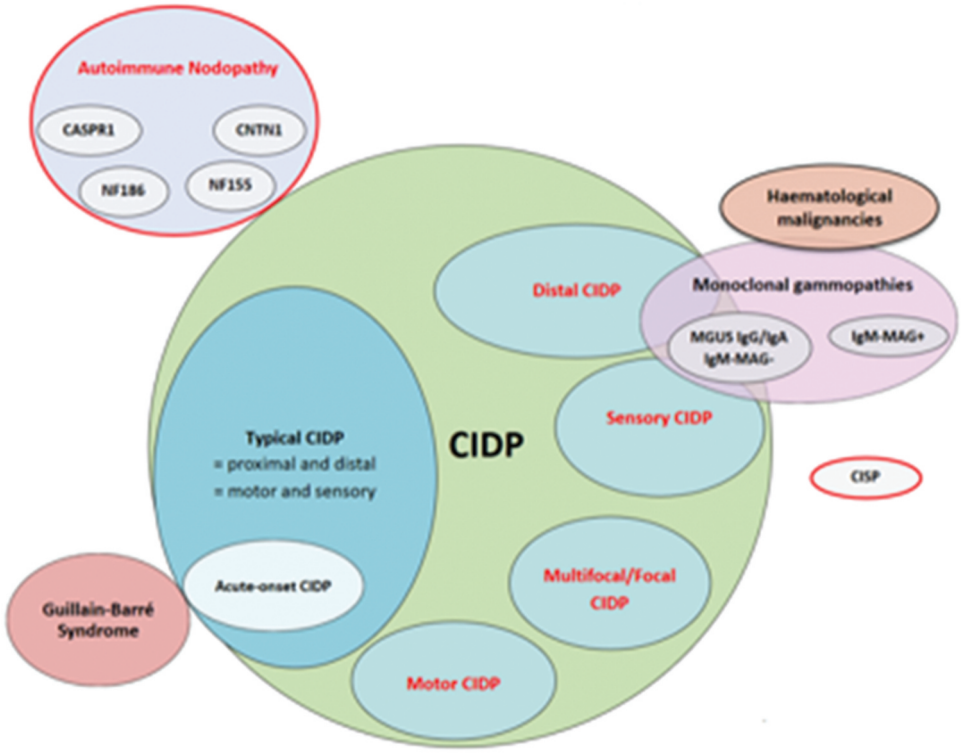


Figure 5. Proposed spectrum of CIDP according to the revised 2021 European Federation of Neurological Societies/Peripheral Nerve Society (EAN/PNS) CIDP guideline [3]. Changes in revised 2021 guideline compared to the 2010 [43] are displayed in red. This figure modified from Bunschoten et al. [47] with permission from Elsevier.

unable to activate cellular and complement-mediated immune responses that are inhibited by IVIg [48]. As a result, these patients do not respond to IVIg or their response is minimal and only if some of these antibodies are also of the IgG1-IgG3 subclass [49]. Differences in the proposed spectrum of CIDP between the 2010 EFNS/PNS guideline [43] and the new EAN/PNS guideline [3] are displayed in Figure 5 [47].

Typical CIDP is characterized by motor and sensory disturbances with proximal and distal muscles involved and accounts for more than 50% of CIDP cases. Additionally, there are sensory (<35% of the patients) and motor predominant (<10%) variants as well as multifocal (also termed asymmetric: <15%) and distal types (10–15%) of CIDP [47]. Patients with typical CIDP are very likely to be responsive to IVIg treatment (78%–87%) [50,51]. IVIg has been shown to be highly effective in pure motor and sensory variants as well (82% and 86%, respectively) [52]. Doneddu et al. [50] showed that patients with the distal and multifocal (also called multifocal acquired demyelinating sensory and motor neuropathy: MADSAM) variants of CIDP are less likely to be responsive to IVIg (50% and 42%, respectively). However, whether some of these patients had non-identified nodopathies is uncertain. Another study of IVIg treatment in multifocal CIDP showed that MADSAM patients had longer times to remission in addition to being less responsive to IVIg [51]. Of the multifocal CIDP patients, 23% were unresponsive to any of the treatments used (IVIg, corticosteroids, or plasmapheresis) [51]. The multifocal CIDP patients also had more frequent muscle atrophy than those with typical CIDP (50% vs. 22%, P = 0.005), probably due to greater axonal loss [51].

Table 1. Factors associated with IVIg response in CIDP.

| | Responsiveness to IVIg |
|---|---|
| Clinical Features | |
| Typical CIDP | ++++ |
| Distal CIDP | +++ |
| Multifocal CIDP | ++ |
| Pain | + |
| Difference in weakness between arms and legs | ++ |
| Muscle atrophy | ++ |
| Genotype | |
| CNTN2 p. Ala145Thr | ++ |
| PRF1 p. Ala91Val | +++ |
| FCGR2B Promoter 2B.4/2B.1 | ++++ |

Several clinical factors have been associated with a lack of responsiveness to IVIg (Table 1). These include: 1) the presence of pain [42]; 2) a difference in weakness between the arms and legs [42]; 3) muscle atrophy [51,52]; and reduced compound muscle action potentials (CMAPs) [52]. All these factors could be related to axonal damage. Some of the IVIg non-responders might have had a nodopathy, as older studies did not routinely test for IgG4 anti-nodal antigen antibodies.

In the recently issued guideline, responsiveness to treatment was a supportive criterion for the clinical diagnosis of CIDP [3].

Table 2. Genetic conditions that can mimic CIDP.

| Condition | Affected gene |
|---|---|
| CMT1X* | Gap junction β-1 – *GJB1* |
| CMT1A | Peripheral myelin protein 22 – *PMP22* |
| CMT1B* | Myelin protein zero – *MPZ* |
| CMT1C* | lipopolysaccharide-induced tumor necrosis factor – *LITAF* |
| CMT1D* | early growth response protein 2 -*EGR2* |
| CMT4C* | SH3 domain ant tetratricopeptide repeats-containing protein 2 – *SH3CT2* |
| CMT4J* | *FIG4* |
| Transthyretin-related familial polyneuropathy (TTR-FAP) | *TTR* |
| Hereditary sensory and autonomic neuropathy* (HSAN1) | Serine palmitoyltransferase long chain base subunits 1 and 2 – *SPTLC1, SPTLC2* |
| Hereditary neuropathy with liability to pressure palsies* (HNLPP) | *PMP22* |
| Ganglioside-induced differentiation-associated protein 1 (GDAP1)-related hereditary motor and sensory neuropathy | *GDAP1* |
| Mitochondrial neurogastrointestinal encephalopathy (MNGIE) | Thymidine phosphorylase -*TYMP* |

CMT = Charcot-Marie-Tooth
*Hereditary neuropathies that can show conduction block outside compression places

Patients, however, need to show an objective response as indicated by improvement on at least one disability scale and one impairment scale [3], based on the minimal clinically important difference (MCID) cutoff values. The disability scales include the inflammatory Rasch-built Overall Disability Scale (I-RODS) and Inflammatory Neuropathy Cause and Treatment (INCAT) disability score [3], and the impairment scales include the Medical Research Council (MRC) sum score, the Modified INCAT Sensory Sum scale (MISS), Neuropathy Impairment Score (NIS), and the Martin Vigorimeter [3]. With an objective treatment response, the diagnosis can be upgraded from possible CIDP to CIDP [3].

A potential reason for ineffectiveness of IVIg in CIDP is misdiagnosis. In patients that do not respond to treatment, it is important to consider whether the patient's disease is true CIDP, an IgG4-antibody associated autoimmune nodopathy, or another condition that can cause demyelination or mimics CIDP, such as hereditary demyelinating neuropathy, diabetes, anti-MAG antibodies, POEMS syndrome, or amyloidosis. A lack of response, however, does not exclude CIDP and an objective response does not prove the diagnosis, as it is not specific for CIDP. DNA testing, in particular, is not always done, even if there are a number of genetic conditions that can mimic CIDP [53] and show conduction block outside of compression places or temporal dispersion [53]. The genetic disorders that can mimic CIDP are listed in Table 2 [3,53,54].

In a retrospective study by Hauw et al. [55] of 1104 patients that fulfilled the EFNS/PNS 2010 criteria for definite or probable CIDP [43], 56 patients were suspected to have hereditary neuropathies, and genetic investigations confirmed the diagnosis of Charcot-Marie-Tooth (CMT) disease in 35 of the 56. When comparing the clinical characteristics of the CMT patients to a control group of patients with definite or probable CIDP by the EFNS/PNS criteria [43], the CMT patients were distinguished by early disease onset (<40 years old), a positive family history for CMT, and presence of muscle atrophy at the initial presentation [55]. The CMT patients that were misdiagnosed with CIDP were less responsive to IVIg than patients with CIDP (20% vs. 57% $p < 0.001$) [55]. Of interest, there was an objective improvement in muscle strength in 20% of the CMT patients, although the assessment was not standardized [55]. Three of the misdiagnosed patients had a *GJB1* mutation [55]. Misdiagnosis and ineffective treatment of these patients resulted in substantial expenditures, with the estimated cost of the IVIg treatment of 4.6 million euros [55]. It would have been substantially less expensive (2.7 million euros) to perform genetic testing on the entire cohort of 1104 patients [55]. In a study by Kuitwaard and colleagues looking at genetic biomarkers for IVIg responsiveness in patients diagnosed with CIDP, none of the 169 patients tested for *GJB1*, had CMT1X misdiagnosed as CIDP [56].

### 3.2. Axonal damage

Another reason for a lack of IVIg efficacy in CIDP is the occurrence of axonal loss. Studies showed that non-responsiveness to IVIg is associated with reduced CMAP amplitudes and a greater degree of muscle atrophy [52]. Greater axonal loss is also associated with a worse long-term prognosis [57]. Axonal damage has also been associated with decreased responsiveness to subcutaneous immunoglobulin (SCIg) [58]. Axonal loss is more likely to be irreversible, whereas remyelination can more readily occur.

### 3.3. Pharmacokinetics of IVIg

Another factor that could explain the variability of the response to IVIg is the difference in pharmacokinetics. A study in patients with GBS showed a considerable variation in serum IgG levels after standard (2 g/kg) treatment with IVIg [59]. Patients with GBS who had a low increase in serum IgG were less likely to be able to walk unaided after six months [56]. In CIDP, patients treated with the same dose and interval showed different peak and trough levels of IgG [60], although association with outcome was not evaluated.

## 4. Genetic variation affecting responsiveness to IVIg

The variability in responses to IVIg between patients can also be affected by pharmacogenomics. IVIg can affect the expression of many pathophysiologically relevant genes [37], and

there are known polymorphisms that can affect responsiveness to IVIg.

### 4.1. CNTN2

Transient axonal glycoprotein-1 (TAG-1 alias contactin-2) is a nerve-specific adhesion molecule that is present on the axon and myelin sheath of the juxtaparanode and has a role in maintaining axonal function [61]. In a study of 100 Japanese CIDP patients, a correlation was found between single-nucleotide polymorphisms (SNPs) in the *CNTN2* gene coding for contactin-2 and responsiveness to IVIg [62]. A small study in Chinese CIDP patients (n = 24) [63] and a larger study of Dutch patients (n = 172) [56] did not find this association, possibly due to the different genetic backgrounds of the patient populations.

### 4.2. PRF1

Perforin is a pore-forming protein found in cytotoxic T-lymphocytes and natural killer cells [64]. Perforin is responsible for creating pores in the cell membrane of target cells, triggering apoptosis [65]. Mutations leading to impairment of perforin function have been associated with autoimmune diseases [65]. SNPs in *PRF1* were studied in 94 CIDP patients and 158 controls and were found to be more common in the CIDP patients (21.3%) than in controls (5.7%, OR 4.47, $p < 0.0002$) [66]. A relapsing disease course (70% vs. 37%) and axonal damage (85% vs 51%) were more frequently found in CIDP patients with *PRF1* SNPs [66]. The most frequent variation found was the p.Ala91Val (OR 3.92) [66]. The p.Ala91Val variant was also found to be negatively associated with responsiveness to IVIg in a Dutch cohort of 157 CIDP patients [56].

### 4.3. FcRn

As previously noted, the FcRn protects IgG from degradation [15,67]. When patients are treated with IVIg, the FcRn is partially saturated and there is an increase in the catabolism of pathogenic IgG [15]. Polymorphisms in the FcRn have been studied in patients with GBS [68], MMN [69] and CIDP [56]. None of the studies identified an association between FcRn polymorphisms and response to IVIg treatment [56,68,69]. In myasthenia gravis (MG) however, a variable number of tandem repeat (VNTR) polymorphism in the *FCGRT* gene were associated with lower serum IgG levels and a lack of clinical benefit of IVIg [70].

### 4.4. FcγRIIB

FcγR are cellular receptors important for immunity against pathogens and the balance between immune responses and autoimmunity [71]. The 2B.4 variant of the inhibitory receptor FcγRIIB, has been associated with a transient disease course and a positive response to IVIg in immune thrombocytopenia (ITP) [72]. The same genetic variant was found more frequently in IVIg responders than in non-responders (15% vs. 5%, OR 3.23, $p = 0.01$) in patients with Kawasaki disease [73]. The 2B.4 variant was also associated with a better response to IVIg in 172 patients with CIDP [56].

The ADAPT trial investigated the effects of an FcRn blocker, efgartigimod, in MG patients [74]. More MG patients had a positive change in their MG-Activities of Daily Living (MG-ADL) score (≥2 points) in the efgartigimod treatment group than in the placebo group (68% versus 30%; OR 4.95, $p < 0.0001$) [74]. There are currently two ongoing or recently concluded trials looking at FcRn blockers in the treatment of CIDP. A randomized placebo control trial of rozanolixizumab in CIDP was recently completed [75], and a trial of efgartigimod is ongoing [76].

## 5. Conclusions

The proposed mechanisms of action of IVIg in altering the immunopathogenesis of CIDP include anti-idiotypic interactions, anti-complement activity, FcRn saturation, modulation of FcγRIIB receptors on macrophages, and downregulation of macrophage activation, and of inflammatory mediators. The relative contribution of these mechanisms to its therapeutic effect, and the role of pharmacokinetics, however, remain to be investigated. IVIg has limited efficacy in IgG4-mediated nodopathies, given that IgG4 is non-complement fixing, and has reduced capacity to bind to Fc receptors.

Patients with typical CIDP are more likely to be responsive to IVIg than patients with distal or multifocal CIDP variants. Patients with pain, differences in weakness between their arms and legs, or muscle atrophy are also less likely to respond to IVIg, probably due to greater axonal damage. Three genotypes have also been associated with differences in CIDP responsiveness to IVIg: the p. Ala145Thr variant of *CNTN2* and the p. Ala91Val variant of *PRF1* are associated with less responsiveness; the promoter 2B.4/2B.1 variant of *FCGR2B* is associated with greater responsiveness to IVIg.

## 6. Expert opinion

IVIg has been shown to exert its therapeutic effects via multiple immunomodulatory mechanisms, but their relative contributions, or whether some mechanisms are more important than others in patients with CIDP is not known. Further research into the affected pathways, and their role in the pathogenesis of CIDP would help to clarify the underlying pathogenic mechanisms and to develop more targeted therapies. For example, if the therapeutic effect of IVIg is primarily mediated by anti-complement activity, future studies might be directed at identifying the specific complement activation pathways involved, and the factors responsible for triggering activation of the complement cascade. Demonstration of a role for FcRn blockade would also be supportive of a role for the presence of humoral response or antibodies to the peripheral nerves, in which case future studies could focus on identifying the responsible autoantibodies and antigens. If macrophage activation, co-stimulatory factors, or cytokines are involved, then, agents that target macrophages, or block specific cytokines or their receptors could be tested as potential therapeutic agents. However, if IVIg is demonstrated to exert a substantial effect via anti-idiotypic antibody activity or

via multiple pathways, then treatment with IVIg alone, or in combination is likely to remain most effective given its multiple mechanisms of action. There may also be differences between subtypes of CIDP or individual patients.

Dosing of IVIg could also be a factor, as different pathways may be affected at different doses or concentrations. A recent study comparing three maintenance doses of IVIg revealed that a dose of 1 g/kg every 3 weeks was efficacious, but that some patients benefited from a dose of 0.5 g/kg whereas others required treatment with a 2 g/kg dose to show benefit [77]. In a study of dermatomyositis patients treated with IVIg [17], 2 g/kg IVIg produced an impressive inhibition of complement, but 600 mg/kg also produced a substantial effect, showing that even low doses of IVIg can exert immunomodulatory effects. Trials of IVIg to date have evaluated the rate of response to treatment, but not the magnitude of the response or underlying disease activity [78], which might also be affected by the dose of IVIg.

Misdiagnosis is an important problem. Given that there is no specific test for CIDP, and the overlap with other conditions that can present with similar phenotypes, CIDP can be over or underdiagnosed, with some patients not responding and others denied potentially effective treatment, respectively. Research into the underlying mechanisms of CIDP could help develop more reliable diagnostic tests that would help prevent misdiagnosis.

Genetic variations that predispose patients to the development or activity of CIDP or affect the pharmacokinetics or responsiveness to IVIg are also likely to exist. Collaborative large-scale studies such as a Genome Wide Association Study (GWAS) within the framework of an international genetics collaboration could provide more definitive information. International cooperation to recruit patients from different ethnic groups working through national and international projects such as the International CIDP Outcome Study (ICOS) and INCBase could be the ideal platforms to perform these crucial studies.

In conclusion, further studies are needed to advance our understanding of the pathogenesis of CIDP and the effects of IVIg on the specific immune pathways and mechanisms responsible for its therapeutic effects. Such studies would help reduce misdiagnosis and increase understanding of the differences in responses between patients, as well as how to optimize the use of IVIg, with the aim of preventing disease activity and irreversible axonal damage that can lead to permanent disability.

## Acknowledgments

The authors acknowledge Michael K James (Grifols) for medical writing, and Jordi Bozzo (Grifols) for editorial support.

## Funding

The material in this article was presented as a symposium at the Peripheral Nerve Society Annual Meeting, Miami, FL, USA on 16 May 2022. The symposium and generation of this review article were sponsored by Grifols.

## Declaration of interest

M Dalakas has received consultancy fees from Alexion, Sanofi, Grifols, Argenx, Dysimmmune Diseases Foundation, Elsevier and CSL. He serves as Deputy Editor for TAND and Associate Editor for Neurology. N Latov has received consultancy fees from Pfizer, Takeda, Grifols, Immunovant, Argenx, Ipsen, Sanofi, and Therapath. K Kuitwaard has received unrestricted research grants from Grifols, Takeda, and Baxter/Shire, consultancy fees from Takeda, and speaker's fees from Grifols and CSL. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

## Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

## References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Vallat JM, Sommer C, Magy L. Chronic inflammatory demyelinating polyradiculoneuropathy: diagnostic and therapeutic challenges for a treatable condition. Lancet Neurol. 2010 Apr;9(4):402–412.
2. Broers MC, Bunschoten C, Nieboer D, et al. Incidence and prevalence of chronic inflammatory demyelinating polyradiculoneuropathy: a systematic review and meta-analysis. Neuroepidemiology. 2019;52(3–4):161–172.
3. Van den Bergh PYK, van Doorn PA, Hadden RDM, et al. European Academy of Neurology/Peripheral Nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force-second revision. Eur J Neurol. 2021 Nov;28(11):3556–3583.
• **These are the current officiatn guidelines for diagnosis and treatment of CIDP.**
4. Oaklander AL, Lunn MP, Hughes RA, et al. Treatments for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP): an overview of systematic reviews. Cochrane Database Syst Rev. 2017 Jan 13;1(1):CD010369.
5. Lunemann JD, Quast I, Dalakas MC. Efficacy of intravenous immunoglobulin in neurological diseases. Neurotherapeutics. 2016 Jan;13(1):34–46.
6. Kazatchkine MD, Kaveri SV. Immunomodulation of autoimmune and inflammatory diseases with intravenous immune globulin. N Engl J Med. 2001 Sep 6;345(10):747–755.
7. Malik U, Oleksowicz L, Latov N, et al. Intravenous gamma-globulin inhibits binding of anti-GM1 to its target antigen. Ann Neurol. 1996 Jan;39(1):136–139.
8. Zhang G, Lopez PH, Li CY, et al. Anti-ganglioside antibody-mediated neuronal cytotoxicity and its protection by intravenous immunoglobulin: implications for immune neuropathies. Brain. 2004 May;127(5):1085–1100.
9. Dalakas MC. Mechanisms of action of IVIg and therapeutic considerations in the treatment of acute and chronic demyelinating neuropathies. Neurology. 2002 Dec 24;59(12 Suppl 6):S13–21.
10. Jacobs BC, O'Hanlon GM, Bullens RW, et al. Immunoglobulins inhibit pathophysiological effects of anti-GQ1b-positive sera at motor nerve terminals through inhibition of antibody binding. Brain. 2003 Oct;126(Pt 10):2220–2234.
11. Buchwald B, Ahangari R, Weishaupt A, et al. Intravenous immunoglobulins neutralize blocking antibodies in Guillain-Barre syndrome. Ann Neurol. 2002 Jun;51(6):673–680.
12. Dalakas MC. Blockade of blocking antibodies in Guillain-Barré syndromes: "unblocking" the mystery of action of intravenous immunoglobulin. Ann Neurol. 2002 Jun;51(6):667–669.

13. Dalakas MC. The role of IVIg in the treatment of patients with stiff person syndrome and other neurological diseases associated with anti-GAD antibodies. J Neurol. 2005 May;252(Suppl 1):I19–25.
14. Bain PG, Motomura M, Newsom-Davis J, et al. Effects of intravenous immunoglobulin on muscle weakness and calcium-channel autoantibodies in the Lambert-Eaton myasthenic syndrome. Neurology. 1996 Sep;47(3):678–683.
15. Dalakas MC, Spaeth PJ. The importance of FcRn in neuro-immunotherapies: from IgG catabolism, FCGRT gene polymorphisms, IVIg dosing and efficiency to specific FcRn inhibitors. Ther Adv Neurol Disord. 2021;14:1756286421997381.
16. Querol LA, Hartung HP, Lewis RA, et al. The role of the complement system in chronic inflammatory demyelinating polyneuropathy: implications for complement-targeted therapies. Neurotherapeutics. 2022;19(3):864–873. Apr 4
17. Basta M, Dalakas MC. High-dose intravenous immunoglobulin exerts its beneficial effect in patients with dermatomyositis by blocking endomysial deposition of activated complement fragments. J Clin Invest. 1994 Nov;94(5):1729–1735.
- **This paper demonstrates the mode of action of IVIg in dermatomyositis muscle biopsies.**
18. Dalakas MC. The use of intravenous immunoglobulin in the treatment of autoimmune neuromuscular diseases: evidence-based indications and safety profile. Pharmacol Ther. 2004 Jun;102(3):177–193.
19. Vital C, Vital A, Lagueny A, et al. Chronic inflammatory demyelinating polyneuropathy: immunopathological and ultrastructural study of peripheral nerve biopsy in 42 cases. Ultrastruct Pathol. 2000 Nov-Dec;24(6):363–369.
- **These authors describe the immunopatholgical changes in CIDP nerves.**
20. Dalakas MC. Inflammatory myopathies Recent advances in pathogenesis and therapy. Adv Neurol. 2002;88:253–271.
21. Boross P, Arandhara VL, Martin-Ramirez J, et al. The inhibiting Fc receptor for IgG, FcgammaRIIB, is a modifier of autoimmune susceptibility. J Immunol. 2011 Aug 1;187(3):1304–1313.
22. Nandakumar KS, Andren M, Martinsson P, et al. Induction of arthritis by single monoclonal IgG anti-collagen type II antibodies and enhancement of arthritis in mice lacking inhibitory FcgammaRIIB. Eur J Immunol. 2003 Aug;33(8):2269–2277.
23. Samuelsson A, Towers TL, Ravetch JV. Anti-inflammatory activity of IVIG mediated through the inhibitory Fc receptor. Science. 2001 Jan 19;291(5503):484–486.
24. Tackenberg B, Jelčić I, Baerenwaldt A, et al. Impaired inhibitory Fcγ receptor IIB expression on B cells in chronic inflammatory demyelinating polyneuropathy. Proc Nat Acad Sci. 2009;106 (12):4788.
25. Créange A, Gregson NA, Hughes RAC. Intravenous immunoglobulin modulates lymphocyte CD54 and monocyte FcγRII expression in patients with chronic inflammatory neuropathies. J Neuroimmunol. 2003;135(1–2):91–95.
- **This article reports that IVIg upregulates expression of inhbitory Fc receptors on monocytes in CIDP.**
26. Nimmerjahn F, Ravetch JV. The antiinflammatory activity of IgG: the intravenous IgG paradox. J Exp Med. 2007 Jan 22;204(1):11–15.
27. Kaneko Y, Nimmerjahn F, Ravetch JV. Anti-inflammatory activity of immunoglobulin G resulting from Fc sialylation. Science. 2006 Aug 4;313(5787):670–673.
28. Merkies IS, Bril V, Dalakas MC, et al. Health-related quality-of-life improvements in CIDP with immune globulin IV 10%: the ICE Study. Neurology. 2009 Apr 14;72(15):1337–1344.
29. Quast I, Keller CW, Maurer MA, et al. Sialylation of IgG Fc domain impairs complement-dependent cytotoxicity. J Clin Invest. 2015 Nov 2;125(11):4160–4170.
30. Murata K, Dalakas MC. Expression of the co-stimulatory molecule BB-1, the ligands CTLA-4 and CD28 and their mRNAs in chronic inflammatory demyelinating polyneuropathy. Brain. 2000 Aug;123 (Pt 8):1660–1666.
31. Hu W, Janke A, Ortler S, et al. Expression of CD28-related costimulatory molecule and its ligand in inflammatory neuropathies. Neurology. 2007 Jan 23;68(4):277–282.
32. Kieseier BC, Tani M, Mahad D, et al. Chemokines and chemokine receptors in inflammatory demyelinating neuropathies: a central role for IP-10. Brain. 2002 Apr;125(Pt 4):823–834.
33. Dalakas MC, Illa I, Dambrosia JM, et al. A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis. N Engl J Med. 1993 Dec 30;329(27):1993–2000.
34. Dalakas MC. Intravenous immunoglobulin in autoimmune neuromuscular diseases. Jama. 2004 May 19;291(19):2367–2375.
35. Amemiya K, Semino-Mora C, Granger RP, et al. Downregulation of TGF-beta1 mRNA and protein in the muscles of patients with inflammatory myopathies after treatment with high-dose intravenous immunoglobulin. Clin Immunol. 2000 Feb;94(2):99–104.
36. Dalakas MC. Update on Intravenous Immunoglobulin in neurology: modulating neuro-autoimmunity, evolving factors on efficacy and dosing and challenges on stopping chronic IVIg therapy. Neurotherapeutics. 2021 Oct;18(4):2397–2418.
37. Raju R, Dalakas MC. Gene expression profile in the muscles of patients with inflammatory myopathies: effect of therapy with IVIg and biological validation of clinically relevant genes. Brain. 2005 Aug;128(Pt 8):1887–1896.
38. Choi YC, Dalakas MC. Expression of matrix metalloproteinases in the muscle of patients with inflammatory myopathies. Neurology. 2000 Jan 11;54(1):65–71.
39. Lapointe BM, Herx LM, Gill V, et al. IVIg therapy in brain inflammation: etiology-dependent differential effects on leucocyte recruitment. Brain. 2004 Dec;127(Pt 12):2649–2656.
40. Rajabally YA, Seow H, Wilson P. Dose of intravenous immunoglobulins in chronic inflammatory demyelinating polyneuropathy. J Peripher Nerv Syst. 2006 Dec;11(4):325–329.
41. Latov N, Deng C, Dalakas MC, et al. Timing and course of clinical response to intravenous immunoglobulin in chronic inflammatory demyelinating polyradiculoneuropathy. Arch Neurol. 2010 Jul;67(7):802–807.
42. Kuitwaard K, Hahn AF, Vermeulen M, et al. Intravenous immunoglobulin response in treatment-naive chronic inflammatory demyelinating polyradiculoneuropathy. J Neurol Neurosurg Psychiatry. 2015 Dec;86(12):1331–1336.
43. Joint Task Force of the European Federation of Neurological Societies and the Peripheral Nerve Society, 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. J Peripher Nerv Syst. 2010 Mar;15(1):1–9.
44. van Swieten JC, Koudstaal PJ, Visser MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988 May;19(5):604–607.
45. Allen JA, Lewis RA. CIDP diagnostic pitfalls and perception of treatment benefit. Neurology. 2015 Aug 11;85(6):498–504.
46. Broers MC, Bunschoten C, Drenthen J, et al. Misdiagnosis and diagnostic pitfalls of chronic inflammatory demyelinating polyradiculoneuropathy. Eur J Neurol. 2021 Jun;28(6):2065–2073.
- **This paper describes the diagnostic difficulties in CIDP.**
47. Bunschoten C, Jacobs BC, Van den Bergh PYK, et al. Progress in diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy. Lancet Neurol. 2019;18(8):784–794.
48. Dalakas MC. IgG4-mediated neurologic autoimmunities. Neurol Neuroimmunol Neuroinflammat. 2021;9:1.
49. Dalakas MC. Autoimmune neurological disorders with IgG4 antibodies: a distinct disease spectrum with unique IgG4 functions responding to anti-B cell therapies. Neurotherapeutics. 2022 Apr;19(3):741–752.
50. Doneddu PE, Cocito D, Manganelli F, et al. Atypical CIDP: diagnostic criteria, progression and treatment response data from the Italian CIDP database. J Neurol Neurosurg Psychiatry. 2019 Feb;90(2):125–132.
51. Kuwabara S, Isose S, Mori M, et al. Different electrophysiological profiles and treatment response in 'typical' and 'atypical' chronic inflammatory demyelinating polyneuropathy. J Neurol Neurosurg Psychiatry. 2015 Oct;86(10):1054–1059.
52. Iijima M, Yamamoto M, Hirayama M, et al. Clinical and electrophysiologic correlates of IVIg responsiveness in CIDP. Neurology. 2005 Apr 26;64 (8):1471–1475.

53. Neligan A, Reilly MM, Lunn MP. CIDP: mimics and chameleons. Pract Neurol. 2014;14(6):399–408.
54. Verhamme C, Drenthen J. Wanneer is het een block? KNF Dagen, 2017, Lunteren, The Netherlands. Dutch Association for Clinical Neurophysiology; 2017. p. 51–60.
55. Hauw F, Fargeot G, Adams D, et al. Charcot-Marie-Tooth disease misdiagnosed as chronic inflammatory demyelinating polyradiculoneuropathy: an international multicentric retrospective study. Eur J Neurol. 2021 Sep;28(9):2846–2854.
56. Kuitwaard K, van Doorn PA, Bengrine T, et al. Genetic biomarkers for intravenous immunoglobulin response in chronic inflammatory demyelinating polyradiculoneuropathy. Eur J Neurol. 2021 May;28 (5):1677–1683.
57. Köller H, Kieseier BC, Jander S, et al. Chronic inflammatory demyelinating polyneuropathy. N Engl J Med. 2005;352(13):1343–1356.
58. Alcantara M, Hartung HP, Lawo JP, et al. Electrophysiological predictors of response to subcutaneous immunoglobulin therapy in chronic inflammatory demyelinating polyneuropathy. Clin Neurophysiol. 2021 Sep;132(9):2184–2190.
59. Kuitwaard K, de Gelder J, Tio-Gillen AP, et al. Pharmacokinetics of intravenous immunoglobulin and outcome in Guillain-Barré syndrome. Ann Neurol. 2009 Nov;66(5):597–603.
60. van Doorn PA, Kuitwaard K, Jacobs BC. Serum IgG levels as biomarkers for optimizing IVIg therapy in CIDP. J Peripher Nerv Syst. 2011 Jun;16(Suppl 1):38–40.
61. Iijima M, Koike H, Katsuno M, et al. Polymorphism of transient axonal glycoprotein-1 in chronic inflammatory demyelinating polyneuropathy. J Peripher Nerv Syst. 2011 Jun;16(Suppl 1):52–55.
62. Iijima M, Tomita M, Morozumi S, et al. Single nucleotide polymorphism of TAG-1 influences IVIg responsiveness of Japanese patients with CIDP. Neurology. 2009 Oct 27;73(17):1348–1352.
63. Pang SYY, Chan K-H, Mak WWW, et al. Single-nucleotide polymorphism of transient axonal glycoprotein-1 and its correlation with clinical features and prognosis in chronic inflammatory demyelinating polyneuropathy. J Peripheral Nerv Syst. 2012;17(1):72–75.
64. Voskoboinik I, Trapani JA. Perforinopathy: a spectrum of human immune disease caused by defective perforin delivery or function. Front Immunol. 2013. 12. Dec(4):441.
65. Voskoboinik I, Whisstock JC, Trapani JA. Perforin and granzymes: function, dysfunction and human pathology. Nat Rev Immunol. 2015 Jun;15(6):388–400.
66. Buttini S, Cappellano G, Ripellino P, et al. Variations of the perforin gene in patients with chronic inflammatory demyelinating polyradiculoneuropathy. Genes Immun. 2015 Jan-Feb;16(1):99–102.
67. Yu Z, Lennon VA. Mechanism of intravenous immune globulin therapy in antibody-mediated autoimmune diseases. N Engl J Med. 1999 Jan 21;340(3):227–228.
68. Fokkink WJ, Haarman AE, Tio-Gillen AP, et al. Neonatal Fc receptor promoter gene polymorphism does not predict pharmacokinetics of IVIg or the clinical course of GBS. Ann Clin Transl Neurol. 2016 Jul;3(7):547–551.
69. Vlam L, Cats EA, Willemse E, et al. Pharmacokinetics of intravenous immunoglobulin in multifocal motor neuropathy. J Neurol Neurosurg Psychiatry. 2014 Oct;85(10):1145–1148.
70. Su S, Liu Q, Zhang X, et al. VNTR2/VNTR3 genotype in the FCGRT gene is associated with reduced effectiveness of intravenous immunoglobulin in patients with myasthenia gravis. Ther Adv Neurol Disord. 2021;14:1756286420986747.
71. Nagelkerke SQ, Schmidt DE, de Haas M, et al. Genetic variation in low-to-medium-affinity fcgamma receptors: functional consequences, disease associations, and opportunities for personalized medicine. Front Immunol. 2019;10:2237.
72. Schmidt DE, Kmj H-P, Laarhoven AG, et al. Transient and chronic childhood immune thrombocytopenia are distinctly affected by Fc-gamma receptor polymorphisms. Blood Adv. 2019 Jul 9;3(13):2003–2012.
73. Shrestha S, Wiener HW, Olson AK, et al. Functional FCGR2B gene variants influence intravenous immunoglobulin response in patients with Kawasaki disease. J Allergy Clin Immunol. 2011 Sep;128(3):677–680.
74. Howard JF, Bril V, Vu T, et al. Safety, efficacy, and tolerability of efgartigimod in patients with generalised myasthenia gravis (ADAPT): a multicentre, randomised, placebo-controlled, phase 3 trial. Lancet Neurol. 2021;20(7):526–536.
75. A study to assess the efficacy, safety and tolerability of rozanolixizumab in subjects with chronic inflammatory demyelinating polyradiculoneuropathy (MyCIDPchoice): NCT03861481 [updated 23 May 2022; cited 2022 June 7]. Available from: https://www.clinicaltrials.gov/ct2/show/results/NCT03861481?term=NCT03861481%2C+Rozanolixizumab&draw=2&rank=1
76. A study to assess the safety and efficacy of a subcutaneous formulation of efgartigimod in adults with Chronic Inflammatory Demyelinating Polyneuropathy (CIDP, an Autoimmune Disorder That Affects the Peripheral Nerves) (ADHERE): NCT04281472 [updated 3 May 2022; cited 2022 June 7]. Available from: https://www.clinicaltrials.gov/ct2/results?cond=&term=NCT04281472%3A+Efgartigimod&cntry=&state=&city=&dist=
77. Cornblath DR, van Doorn PA, Hartung HP, et al. Randomized trial of three IVIg doses for treating chronic inflammatory demyelinating polyneuropathy. Brain. 2022;145(3):887–896. Jan 17
78. Chin RL, Deng C, Bril V, et al. Follow-up nerve conduction studies in CIDP after treatment with IGIV-C: comparison of patients with and without subsequent relapse. Muscle Nerve. 2015 Oct;52(4):498–502.