REVIEW

# Chronic inflammatory demyelinating polyneuropathy: update on diagnosis, immunopathogenesis and treatment

Helmar Christoph Lehmann,[1] David Burke,[2] Satoshi Kuwabara[3]

[1]Neurology, University Hospital of Cologne, Köln, Germany
[2]Institute of Clinical Neurosciences, University of Sydney, Sydney, New South Wales, Australia
[3]Neurology, Chiba University School of Medicine, Chiba, Japan

**Correspondence to**
Dr Helmar Christoph Lehmann, Neurology, University Hospital of Cologne, Köln 50937, Germany; helmar.lehmann@uk-koeln.de

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## ABSTRACT

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an immune-mediated neuropathy typically characterised by symmetrical involvement, and proximal as well as distal muscle weakness (typical CIDP). However, there are several 'atypical' subtypes, such as multifocal acquired demyelinating sensory and motor neuropathy (Lewis-Sumner syndrome) and 'distal acquired demyelinating symmetric neuropathy', possibly having different immunopathogenesis and treatment responses. In the absence of diagnostic and pathogenetic biomarkers, diagnosis and treatment may be difficult, but recent progress has been made in the application of neuroimaging tools demonstrating nerve hypertrophy and in identifying subgroups of patients who harbour antibodies against nodal proteins such as neurofascin and contactin-1. Despite its relative rarity, CIDP represents a significant economic burden, mostly due to costly treatment with immunoglobulin. Recent studies have demonstrated the efficacy of subcutaneous as well as intravenous immunoglobulin as maintenance therapy, and newer immunomodulating drugs can be used in refractory cases. This review provides an overview focusing on advances over the past several years.

## INTRODUCTION

Chronic inflammatory demyelinating polyneuropathy (CIDP) is the most common chronic immune-mediated inflammatory polyneuropathy, and includes several subtypes that belong to the spectrum of causally treatable neuropathies. According to the definition of the European Federation of Neurological Societies and the Peripheral Nerve Society (EFNS/PNS), CIDP is progressive or relapsing for over 2 months, has electrophysiological or pathological evidence of peripheral nerve demyelination, and responds to immunesuppressive or immune-modulating therapies.[1 2]

Clinically CIDP is classified into 'typical' and 'atypical' cases; typical CIDP is a symmetrical polyneuropathy affecting proximal and distal muscles equally, whereas atypical CIDP includes 'distal acquired demyelinating symmetric' (DADS), and multifocal acquired demyelinating sensory and motor neuropathy (MADSAM, or Lewis-Sumner syndrome [LSS]). DADS is a symmetrical length-dependent sensory or sensorimotor neuropathy, often associated with an IgM paraprotein and markedly increased distal motor latencies. The features are characteristic of demyelinating neuropathy with antimyelin-associated glycoprotein (MAG) antibodies, but in the EFNS/PNS criteria anti-MAG neuropathy is excluded from CIDP, largely because of the presence of a specific antibody and different treatment response. LSS has a multifocal distribution, and the electrophysiological hallmark of the disease is the presence of conduction block. In addition, pure motor and sensory CIDP variants have been reported, the latter sometimes restricted to sensory nerve roots (chronic immune sensory polyradiculopathy). A rare *c*hronic *a*taxic *n*europathy associated with *o*phthalmoplegia, Ig*M* paraprotein, cold *a*gglutinins and *d*isialosyl (ganglioside) antibodies is known by the acronym CANOMAD (figure 1). Recognition of the clinical phenotypes is critical for management of patients because the subtypes probably have different clinical/electrophysiological profiles and immunopathogenesis, and thereby different responses to treatment. In this regard, each atypical CIDP subtype, and even typical CIDP, should be more strictly defined clinically.[3] The European Academy of Neurology/PNS (formerly EFNS/PNS) Task Force has just started the second revision of the CIDP guidelines which is expected to define clinical criteria for CIDP subtypes.

Over the past years significant progress has been made in elucidating novel aspects of the immunopathogenesis of the disease, including antibodies against nodal and paranodal proteins in subgroups of patients with CIDP. Regarding clinical management, neuroimaging tools that demonstrate nerve hypertrophy have now been established and tested as potential diagnostic biomarkers and surrogate measures in the disorder. Moreover, recent clinical trials have demonstrated efficacy of new management protocols such as subcutaneous immunoglobulin. In this review we provide an overview of recent developments in improving diagnosis and in optimising treatment of CIDP.

### Epidemiology and economic burden

CIDP is considered an orphan disease with different prevalence rates in different geographical regions (figure 2).[4–7] In a study from England, Mahdi-Rogers and Hughes[5] reported a prevalence rate of 2.84 per 100 000 for CIDP. In this study male patients outnumbered female patients by 2:1, and CIDP was more prevalent in advanced age. Reported prevalence rates from previous studies range from 0.8 in Tottori, Japan[8] to 8.9 per 100

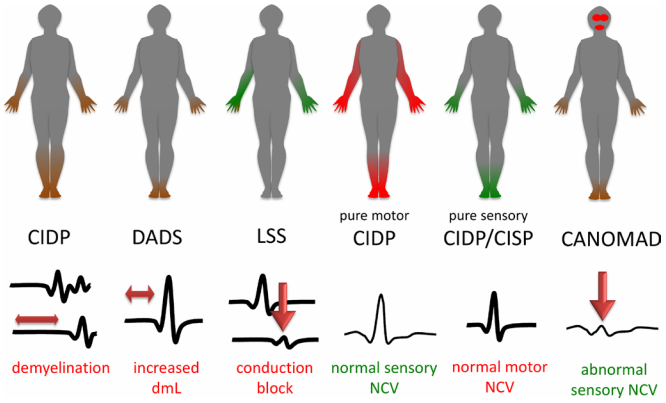


**Figure 1** Variants of CIDP: clinical and electrophysiological hallmarks of CIDP subtypes. Motor deficits are drawn in red, sensory deficits in green and sensorimotor in brown colour. Classical CIDP presents often with proximal and distal sensorimotor deficits. Demyelination should be present as defined by the the EFNS/PNS criteria.[1] 'Distal acquired demyelinating symmetric neuropathy' (DADS) shows typically distal symmetrical, sensory or sensorimotor symptoms and is often associated with abnormally increased distal motor latencies (dmL). Patients with Lewis-Sumner syndrome (LSS) display multifocal distributed sensory and motor symptoms, and nerve conduction studies frequently show conduction blocks. Pure sensory and motor CIDP show exclusively sensory or motor deficits and may have normal respective nerve conduction studies. Chronic immune sensory polyradiculopathy (CISP) is restricted to sensory nerve roots only (after ref 11). CANOMAD (chronic ataxic neuropathy associated with ophthalmoplegia, IgM paraprotein, cold agglutinins and disialosyl antibodies) presents as chronic ataxic neuropathy associated with oculomotor and/or bulbar symptoms. CIDP, chronic inflammatory demyelinating polyneuropathy; EFNS/PNS, European Federation of Neurological Societies and the Peripheral Nerve Society;NCV, nerve conduction velocity.

000 inhabitants in Olmsted County, USA.[9] Recent epidemiological data from Ireland report the prevalence of CIDP as 5.87 per 100 000 adults.[10] The reason for the different prevalence in various different geographical regions is not known. Apart from methodological differences, true geographical differences as described for other autoimmune disorders or differently applied diagnostic criteria are potential explanations.

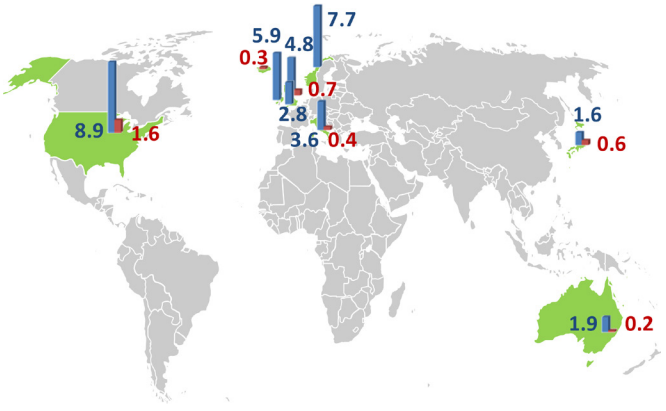


**Figure 2** Epidemiology of chronic inflammatory demyelinating polyneuropathy: overview about prevalence (per 100 000/year, blue) and incidence (per 100 000/year, red) in different geographical regions in the world (after refs 4 5 7 10).

The frequency of CIDP subtypes (figure 1) varies considerably between studies. The Italian CIDP Database study group analysed data from 460 patients with CIDP, and found that 82% had typical CIDP and the remaining 18% had atypical CIDP; the atypical CIDP included DADS (7%), LSS (4%), pure motor (4%) and pure sensory CIDP (3.5%).[11] In a Japanese study, 100 consecutive patients with CIDP were classified as having typical CIDP (60%), MADSAM (34%), DADS (5%) or pure sensory CIDP (1%).[12] The differences may be dependent on clinical criteria for atypical CIDP. Nevertheless, it is notable that, in both studies, patients with atypical CIDP were less responsive to intravenous immunoglobulin (IVIg), and this points to a different underlying pathophysiology.[3 12]

Separately, recent studies also highlight the economic burden of CIDP: the annual costs for CIDP are calculated at around €45 000 in Germany,[13] above £22 000 (£49 000 for patients on IVIg) in the UK[14] and more than $50 000 in the USA, mostly due to repeated or maintenance IVIg treatment.[15]

## Clinical diagnosis and electrophysiology

The diagnostic criteria for CIDP that were developed by the EFNS/PNS[1] are most commonly used and distinguish CIDP from other neuropathic conditions with high sensitivity and specificity. Nevertheless, misdiagnosis of CIDP is not uncommon and occurred in up to 50% of patients in recent studies.[16–19] Alternative diagnoses included motor neuron disease, diabetic and inherited polyneuropathy, and even conditions clearly distinguishable clinically such as fibromyalgia or multiple sclerosis. None of these patients had 'typical CIDP'; all were atypical phenotypes.

The diagnostic challenge of CIDP is accentuated by the fact that more than half of patients with alternate diagnoses have clinical features that are compatible with CIDP, and some may even fulfil the criteria for typical CIDP. Accordingly, in patients with suspected CIDP, particularly those who are refractory to immunotherapy, re-evaluation of the diagnosis is advised. Attention should be paid to features such as motor predominance, proximal and distal weakness, lack of pain, distal leg weakness and generalised areflexia, all of which are significant features of typical CIDP (table 1).[18] Conversely, typical CIDP is defined by these features. Rare conditions that may be confused clinically with CIDP and may even occasionally fulfil the EFNS/PNS criteria are transthyretin familial amyloid polyneuropathy (TTR-FAP) and POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes) syndrome.[20–22] In TTR-FAP, symptoms that may point to this important differential diagnosis are pain, dysautonomia and small fibre sensory loss, in addition to pronounced axonal damage in nerve conduction studies.[20] A recent study emphasises the need for the correct interpretation of nerve conduction studies when applying diagnostic criteria for CIDP to avoid misdiagnosis.[17] Particularly slowing of motor conduction for small compound muscle action potentials, slowing across sites of compression and slowing in diseases such as diabetes may be misinterpreted as demyelinating features. Moreover, reliance on supportive criteria such as elevations in CSF protein and subjective improvement of symptoms subsequent to immunotherapy are also common mistakes in patients who are misdiagnosed as having CIDP.[19] In POEMS syndrome, patterns of nerve conduction abnormalities are useful for differentiation from CIDP; POEMS syndrome is characterised by less prolonged distal motor latency and higher terminal latency index in the median nerves and unrecordable tibial and sural responses, suggesting demyelination predominately in the nerve

**Table 1** Pitfalls in the diagnosis of CIDP

| Category | Compatible with CIDP | Pitfall | Alternative explanation to be considered | References |
|---|---|---|---|---|
| Clinical | Widespread loss of reflexes. | Only absence of ankle reflexes. | Length-dependent neuropathy. | 18 |
| | Loss of vibration sense. | Vibration sense not reduced. | Motor neuron disease. | 18 |
| | Treatment response assessed by objective scales. | Subjective or non-specific response to immunotherapy. | Placebo effect, confounding factors such as fatigue, depression. | 19 |
| | Consistent and objective improvement in muscle strength by reducing IVIg infusion interval or by other immunotherapies. | No response to immunotherapy is considered 'refractory'. | Non-immunoneuropathy, motor neuron disease. | 18 |
| CSF | High elevation (often >100 mg/dL). | No or only mild elevation of CSF protein. | Non-specific, occurs also in, for example, spinal stenosis. | 18 19 |
| Electrophysiology | Significantly (<80% LLN) reduced conduction slowing. Conduction slowing independent of compression sites. | Misinterpretation of conduction slowing. | Conduction slowing for small potentials. Conduction slowing at compression sites. | 17 |
| | Upper limb segmental demyelination. | Abnormalities exclusively in lower extremity nerves. | Length-dependent neuropathy. | 17 |
| | Heterogeneous motor conduction slowing. | Homogeneous nerve conduction slowing. | Hereditary neuropathy. | 16 |

CIDP, chronic inflammatory demyelinating polyneuropathy; CSF, cerebrospinal fluid; IVIg, intravenous immunoglobulin; LLN, lower limit of normal values.

trunk rather than in the distal nerve terminals, and axonal loss in the lower limb nerves.[21]

## Autoantibodies

The diagnosis of CIDP can be improved by testing for specific autoantibodies that are directed against isoforms of neurofascin (NF155 and NF186) or against contactin-1 (CNTN1), a protein expressed at the axonal site in the paranodal region (table 2).

Anti-CNTN1 antibodies are found in 2.2%–8.7% of patients with CIDP.[23–26] Notably, anti-CNTN1 antibody-positive patients are clinically distinct with predominant involvement of motor fibres and axonal damage. An exception to this clinical-serological correlation is a finding observed in a cohort from Japan.[25] These patients presented primarily with sensory ataxia, which could be explained by different epitope recognition and hence preferential binding to either motor or sensory fibres in the different cohorts. In all cohorts, anti-CNTN1 antibody-positive patients tended to respond poorly to IVIg.

Other autoantibody targets that have been detected in CIDP are isoforms of neurofascin, namely NF155 and NF186. NF155 is expressed by the Schwann cells in the paranodal region, whereas NF186 is expressed on the axon in the nodal region. Serological studies have demonstrated that between 4% and 18% of patients with CIDP harbour serum antibodies against NF155.[27–29] The highest frequency was found in a Japanese cohort, in which 18% of patients with CIDP were positive for anti-NF155 antibodies.[30] The variability in the frequency can best be explained by different sensitivities of the cell-based assays that were used to detect these antibodies. A way to facilitate antibody testing and to increase comparability could lie in the establishment of conventional ELISA-based testing. The utility of using recombinant human rather than rat NF155 has been demonstrated by Kadoya and colleagues.[31] Clinical features that are associated with NF155 seropositivity are younger onset, tremor and sensory ataxia. Nerve conduction studies show more pronounced prolongation of distal and F-wave latencies in those patients.[30] Like anti-CNTN1-positive patients, NF155-positive patients show a poor response to IVIg. A case series suggests that these patients may benefit from treatment with rituximab.[32]

More recently, antibodies against another neurofascin isoform, NF140/NF186, have been described, occurring in less than 2% of patients with CIDP. Most of these patients had associated autoimmune disorders, were severely affected, presented with sensory ataxia but not tremor, and generally responded to IVIg or corticosteroids.[33]

Anti-CNTN1, anti-NF155 and anti-NF140/NF186 antibodies belong to the infrequent subtype IgG4, which does not activate complement and binds less well to activating Fc gamma receptors, pointing to a specific role of IgG4 autoantibodies in the pathogenesis of CIDP and other IgG4 antibody-associated autoimmune disorders. The response to IVIg in NF140/NF186-positive patients indicates that complement abrogation is not the primary mechanism of action of IVIg in these patients.

IgM antibodies against NF155, with antibody titres ranging between 1:100 and 1:400, have recently been described

**Table 2** Frequency of antibodies against nodal proteins

| Country | Patients (n) | CNTN1-positive (n) | NF155-positive (n) | NF186-positive (n) | References |
|---|---|---|---|---|---|
| Spain | 46 | 2 | – | – | 23 |
| Germany | 53 | 4 | – | – | 24 |
| Japan | 533 | 13 | | | 25 |
| Spain | 53 | – | 2 | – | 27 |
| Australia | 44 | 3 | 3 | 0 | 26 |
| Japan Germany Sweden | 117 | – | 5 | 1 (cobinding) | 69 |
| Japan | 50 | – | 9 | 0 | 30 |
| Japan | 533 | – | 38 | – | 28 |
| USA | 40 | – | 4 | 0 | 29 |
| Australia | 144 | – | 32 | – | 70 |
| Japan | 191 | – | 15 | – | 31 |
| France Spain Italy | 246 | 2 | 9 | 1/5 (NF140/NF186) | 33 |

CNTN1, contactin-1; NF, neurofascin.

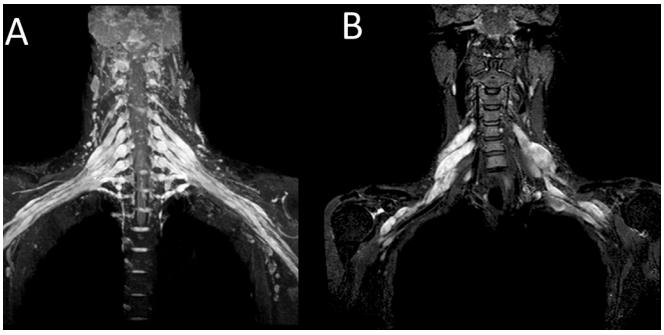


**Figure 3** Nerve hypertrophy in typical and atypical CIDP. (A) Coronal STIR reconstruction MRI reveals symmetrical bilaterally enlarged brachial plexus in a patient with typical CIDP. (B) Multifocal fusiform hypertrophy of the left cervical roots in a patient with MADSAM (coronal STIR weighted MRI). The symmetrical, root-dominant nerve hypertrophy in typical CIDP suggests an antibody-mediated immune attack primarily on the nerve roots, where the blood–nerve barrier is anatomically deficient, whereas the multiple sclerosis-like multifocal involvement in MADSAM could be caused by cell-mediated immunity.[3 12] CIDP, chronic inflammatory demyelinating polyneuropathy; MADSAM, multifocal acquired demyelinating sensory and motor neuropathy; STIR, short tau inversion recovery

independently in two cohorts, in 4%–8% of patients with CIDP.[29 34] The majority of patients presented with tremor and substantial axonal damage in nerve biopsies, thus resembling 'classical' NF155-IgG-positive patients with CIDP. Electron micrographs of sural nerve biopsies in CNTN1-positive and NF155-positive patients with CIDP indicate a pathological role for these antibodies since the paranodal architecture in those patients is severely compromised with widened myelin loops as well as widened space between adjacent myelin in the absence of macrophage-mediated demyelination.[35] Evidence for the pathogenicity of CNTN1 antibodies is provided by cell culture experiments in which autoantibodies induce alteration of paranodal architecture.[36] Further, passive transfer of purified anti-CNTN1 IgG to rats immunised with P2 can replicate the clinical features of antibody-positive patients. Notably these clinical changes went along with destruction of CNTN1-containing paranodal structures, whereas myelin and axon structures remained largely unaffected.[37]

These clinical, laboratory and pathological findings support the concept that CNTN1-positive and NF155-positive CIDP are '(para)nodopathies', different from classical CIDP.

## Neuroimaging

Imaging techniques that have been assessed as tools for diagnosis and to measure the response to treatment in CIDP are nerve ultrasound and MRI. Nerve ultrasound in CIDP usually shows enlarged cross-sectional areas (CSA) in affected nerves. In treatment-naïve patients with inflammatory chronic neuropathies, including CIDP, enlarged CSAs in the proximal median nerve and brachial plexus are highly discriminative features compared with axonal neuropathies and amyotrophic lateral sclerosis.[38] This pattern is not specific and also occurs in other hereditary or inflammatory neuropathies, such as multifocal motor neuropathy. Application of ultrasound scores can increase diagnostic sensitivity for CIDP compared with other chronic immune-mediated,[39] hereditary[40] or diabetic neuropathies.[41]

MRI techniques that have been evaluated in CIDP include magnetic resonance neurography[42–44] and diffusion tensor imaging (DTI).[45–47] DTI-based fractional anisotropy (FA) values are significantly lower in the nerves of the upper and lower extremities in CIDP, with the largest differences in ulnar and sciatic nerves compared with those of controls.[45–48] Discrepant results have been reported regarding correlation with electrophysiological changes. Preclinical studies suggest that FA is rather a marker of axonal damage than of demyelination.[49] Kronlage *et al*[46] reported that FA and radial diffusivity (another DTI-based parameter that influences FA) correlated strongly with demyelinating changes in nerve conduction studies whereas others did not find such a correlation.[45 48] A general limitation of this technique is that it is not specific for inflammatory neuropathies and requires comparison with a set of normal controls: different acquisition parameters and analysis procedures including different acquisition software and hardware may result in small but significant changes in DTI parameters.

The brachial and lumbar plexus represent more challenging anatomical sites for MRI due to angle artefacts and lung movement. However, by conventional MRI, plexus enlargement (figure 3) or T2 hyperintensity can be observed in typical and atypical CIDP variants. Recent studies that used an advanced MRI technique called 'three-dimensional nerve-sheath signal increased with inked rest-tissue rapid acquisition of relaxation imaging'[50] also demonstrated increased sizes of ganglia and roots in patients with CIDP, at the lumbar plexus almost twice the size of healthy controls.[51] Enlarged ganglia are occasionally visible on clinical examination as enlargement of the neck and upper trapezius region.[52]

Two recently published studies also evaluated neurogenic muscle atrophy by MRI. Gilmore and colleagues[53] assessed areas, volume and composition (contractile vs non-contractile muscle tissue) of the tibialis anterior muscle in patients with CIDP and found smaller volume and larger non-contractile tissue volume in patients with CIDP compared with age-matched controls. In a study from our group, we evaluated muscle fat fractions and could demonstrate significantly higher fat fractions in the thigh muscles of patients with CIDP.[45] These changes are not specific for CIDP, but serial studies might confirm worsening of disease.

## Treatment

Treatment of patients with CIDP is complex and requires individualised treatment strategies. First-line therapies that have been shown to be efficacious include corticosteroids, IVIg and plasma exchange.[54–56]

It is assumed that IVIg exerts anti-inflammatory activity in autoimmune neuropathies by several mechanisms of actions. These include Fc-dependent and Fab-dependent mechanisms such as neutralisation of autoantibodies, inhibition and abrogation of activated complement, alteration of FcR expression, and redressing altered cytokine patterns (reviewed in ref 57). The effects of IVIg on the humoral immune response in CIDP are less well researched, due to the lack of specific antigen epitopes that could be used in experimental models. Indirect evidence is provided that IVIg alters serum levels of the cytokine B cell activating factor (BAFF)[58] and that IVIg infusion leads to the formation of novel IgG dimers.[59]

Currently, the standard maintenance treatment regimen with IVIg in CIDP is 1.0 g/kg intravenously every 3 weeks. This treatment has been shown to be effective in randomised controlled trials in CIDP over 24 weeks. A recently published open-label study also reported high response rates (almost 70%) after 52 weeks for this maintenance regimen.[60]

Disease heterogeneity and subtypes of CIDP, different time, and the degree of response to IVIg may require individualised

**Table 3** Randomised controlled studies in CIDP published in 2015–2018

| Study | Intervention | Design | Patients (n) | Primary endpoint | Results | Duration | References |
|---|---|---|---|---|---|---|---|
| PATH | SCIg (2 dosage levels) vs placebo | Randomised controlled, double-blind | Definite or probable CIDP, IVIg-responsive, n=172 | Proportion with relapse or withdrawn for other reason | 63% on placebo, 39% on low-dose SCIg and 33% on high-dose SCIg (p=0.0007) | 24 weeks | 62 |
| FORCIDP | Fingolimod vs placebo | Randomised, controlled, double-blind, | Definite or probable CIDP, n=106 | Time to worsening (≥1 adjusted INCAT score) | Ended for futility, fingolimod (42%) vs placebo (43%) | Flexible | 66 |
| Lieker *et al* | IA vs PE | Randomised, controlled, not blinded | CIDP, n=18 of 20 | Improvement in adjusted INCAT score and MRCss | IA: 6/9 vs PE: 4/9 | 6 sessions | 65 |
| Danish CIDP and MMN study group | SCIg vs IVIg | Randomised, controlled, crossover, single-blinded | Definite CIDP (EFNS/PNS), n=20 | cIKS | cIKS 7.4 (SCIg) vs 6.9 (IVIg) (p=0.80) | 20 weeks (10/treatment) | 63 |

CIDP, chronic inflammatory demyelinating polyneuropathy; EFNS/PNS, European Federation of Neurological Societies and the Peripheral Nerve Society; IA, immunoadsorption; IVIg, intravenous immunoglobulin; MMN, Multifocal motor neuropathy; MRCss, Medical Research Council sum score; PE, plasma exchange; SCIg, subcutaneous immunoglobulin; cIKS, combined isokinetic muscle strength.

treatment regimens. Lunn and colleagues[61] tested a feasible dosing algorithm by which patients with CIDP were treated initially with one or two courses of 2 g/kg IVIg. Subsequently treatment was discontinued until the patient showed clinical deterioration. This time period was then considered the optimal dose interval. Patients were then restabilised and the dose was subsequently reduced by 20% per treatment cycle. By this algorithm a mean IVIg dose of 1.4 g/kg was found to be optimal as maintenance therapy, administered at a mean interval of 4.3 weeks.[61]

IgG peak/trough levels that occur with intravenous administration can be avoided by administration of subcutaneous immunoglobulin (SCIg). Small case series and retrospective studies had suggested beneficial effects, including high adherence, and this led to the recently published PATH study, which demonstrated that SCIg is efficacious and well tolerated in CIDP (table 3).[62]

The PATH trial included 172 patients who underwent a two-tier treatment protocol. First, patients had to demonstrate IVIg dependency after IVIg withdrawal within a 12-week time frame. Those patients that deteriorated after withdrawal and restabilised again after IVIg treatment were eligible for the second phase of the study. Eligible patients were then randomised into three treatment arms that included weekly treatment for 24 weeks with either 0.2 g/kg, or 0.4 g/kg (20% SCIg) or placebo (2% human albumin solution). The primary outcome was a little unusual: it comprised the proportion of patients with a relapse or withdrawn from treatment for another reason during those 24 weeks. Thirty-six patients (63%) on placebo, but only 22 (39%) on low-dose and 19 (33%) on high-dose SCIg had a relapse or were withdrawn from the study for other reasons. 'Withdrawal because of other reasons' occurred in less than 10%; most patients reached the primary endpoint because of a relapse. Seven per cent in the placebo group, 5% in the low-dose group and 16% in the high-dose group withdrew for reasons other than relapse. Common reasons were mild local reactions or withdrawal of consent. Overall the withdrawals did not influence the primary endpoint outcome. Secondary outcomes included hand force assessed using a Vigorimeter, and clinical scores such as 'Medical Research Council sum score' and 'Inflammatory Neuropathy-Rasch-Built Overall Disability Scale' (I-RODS), and INCAT Overall Disability Sum Score. These measures were also in favour of SCIg treatments except the I-RODS score in the low-dose group. Causally related adverse events were higher in the two treatment groups (30% and 34% vs 18%). These were mostly local reactions, with decreasing frequency over the treatment period, and they did not result in discontinuation of the therapy. The PATH study eventually led to approval of SCIg in the European Union, and this form of administration represents a therapeutic alternative for patients who suffer wear-off phenomena with cyclic deterioration at an interval following an IVIg infusion. Arguments against a switch to SCIg are reduced hand function and reservation from the patient because of the increase in self-responsibility for treatment.

The Danish CIDP study group further reported results of a randomised, single-blind, crossover trial in treatment-naïve patients with CIDP who received SCIg (0.4 g/kg/week) for 5 weeks or IVIg (0.4 g/kg/day) for 5 days and, after 10 weeks the opposite treatment.[63] The two regimens had similar effects on muscle strength, and this suggests that these two regimens are equally effective. Further it questions the necessity of the usually recommended double dose (2 g/kg/day) induction treatment of IVIg in some patients with CIDP.

With regard to corticosteroids, a retrospective study compared different regimens (daily oral prednisolone, pulsed oral dexamethasone or pulsed intravenous methylprednisolone) in 125 patients with CIDP. Overall, 60% responded to corticosteroids, with no significant difference in safety and efficacy between the three treatment regimens.[64]

The third first-line treatment, plasma exchange, is used less frequently, but can still be very effective, especially in patients who have a relapsing disease course. Due to a better side effect profile and a shortage of replacement compound albumin, immunoadsorption is employed frequently (ie, in Germany and Japan), although its efficacy has never been demonstrated in randomised controlled trials in CIDP. A small prospective randomised trial recently compared the two treatments. Twenty patients with CIDP were randomised to receive either plasma exchange or immunoadsorption (six sessions). The authors reported a similar rate of clinical improvement and side effects, and this is in line with retrospective studies indicating that there is little difference between the two treatments.[65]

Immunosuppression may be required particularly in atypical CIDP variants or in long-term cases, using agents such as azathioprine, mycophenolate mofetil or methotrexate, although evidence from randomised controlled trials is lacking for these agents. A randomised controlled study that evaluated the utility of fingolimod in CIDP did not show any beneficial effect and was stopped for futility.[66] A retrospective case series reported beneficial effects of treatment with the proteasome inhibitor bortezomib subcutaneously in a group of severely affected (INCAT

score 6 or 7) treatment-refractory patients with CIDP. Six of the ten patients improved, and neurotoxicity did not occur.[67] The same authors also reported mixed outcomes of stem cell transplantation in this cohort: two deaths within 2 years and disease progression in a third transplanted patient. Regarding monoclonal antibodies, several case series report a beneficial effect of rituximab in patients with CIDP, particularly in patients positive for anti-CNTN1 and anti-NF155 antibodies.[32 68] However, other case reports have also shown no obvious efficacy following rituximab administration. The efficacy of rituximab in patients with antibodies against the paranodal proteins should be investigated in future clinical trials.

### Monitoring response to therapy

There is no substitute for a well-documented careful clinical examination, and a number of functional scales are available, as detailed above under the discussion of clinical trials of SCIg.

The jury is out on whether diagnostic tests are suitable surrogate measures to follow a patient's course. Nerve ultrasound and MRI have diagnostic value, but their sensitivity for following patients is still being assessed. Nerve conduction studies are often used as a simple non-invasive follow-up test, but the findings need to be interpreted with caution because of the variability inherent in the tests. Changes in conduction velocities without significant recovery of the size of motor potentials are usually not clinically significant and are commonly operator-dependent. Whether changes in antibody levels subsequent to treatment may serve as surrogate is currently unknown, but would only be feasible in subsets of patients with CIDP.

## CONCLUSION

Although clinical research in CIDP has addressed important issues in the management of patients with CIDP, there is still a potpourri of unresolved questions. These include foremost diagnosis and treatment, but also related aspects such as epidemiology and economic burden of the disease. CIDP is still by definition an orphan disease, but with significant costs. The increasing shortage of IVIg in many countries necessitates further studies that aim to optimise treatment algorithms to avoid overtreatment. The high rate of misdiagnosis emphasises the need for careful review of patients' clinical and electrophysiological parameters, as well as the thorough application of the diagnostic criteria by trained neuromuscular experts. It is to be hoped that the establishment of novel diagnostic biomarkers such as antibodies, MRI and ultrasound may facilitate diagnosis and discrimination from other neuropathic conditions. Second-line treatments in patients who do not respond to IVIg need to be further developed and tested in randomised controlled trials, and there is a need for surrogate markers of disease progression for both clinical practice and clinical trials.

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