Chronic inflammatory demyelinating polyradiculoneuropathy

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Summary

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is the most common autoimmune neuropathy. The diagnosis depends on the clinical presentation with a progressive or relapsing course over at least 2 months and electrophysiological evidence of primary demyelination. Whereas typical CIDP is quite easily recognizable because virtually no other neuropathies present with both distal and proximal motor and sensory deficit, atypical CIDP, focal and multifocal variants in particular, may represent a difficult diagnostic challenge. CIDP very likely is an underdiagnosed condition as suggested also by a positive correlation between prevalence rates and sensitivity of electrophysiological criteria. Since no ‘gold standard’ diagnostic marker exists, electrophysiological criteria have been optimized to be at the same time as sensitive and as specific as possible. Additional supportive laboratory features, such as increased spinal fluid protein, MRI abnormalities of nerve segments, and in selected cases nerve biopsy lead to the correct diagnosis in the large majority of the cases. Objective clinical improvement following immune therapy is also a useful parameter to confirm the diagnosis. The pathogenesis and pathophysiology of CIDP remain poorly understood, but the available evidence for an inflammatory origin is quite convincing. Steroids, intravenous immunoglobulin (IVIG), and plasma exchange (PE) have been proven to be effective treatments. IVIG usually leads to rapid improvement, which is useful in severely disabled patients. Repeat treatment over regular time intervals for many years is often necessary. The effect of steroids is slower and the side-effect profile may be problematic, but they may induce disease remission more frequently than IVIG. An important and as of yet uncompletely resolved issue is the evaluation of long-term outcome to determine whether the disease is still active and responsive to treatment.
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired demyelinating neuropathy of presumed autoimmune origin. Starting with the publication of a case of recurrent polyneuritis in 1890 [1], a number of case reports can be found in the scientific literature of the first half of the 20th century [2]. In 1958, Austin [3] described a patient with 20 consecutive episodes of relapsing steroid-responsive polyneuritis, thereby providing evidence for a treatable inflammatory origin. However, the characterization of CIDP as a distinct disease entity with well-defined clinical, electrophysiological, and pathological features had to await the seminal papers by Dyck et al. [4] and Prineas and McLeod [5] in the mid-1970s. The current name of the disorder was first used by Dyck et al. in 1982 [6], when they reported improvement with prednisone. The diagnosis of CIDP is based on a combination of clinical features, nerve conduction studies, spinal fluid analysis, and, in selected cases, nerve biopsy [7]. As there is no definitive biologic diagnostic marker and as clinical and laboratory features are heterogeneous, recognition of CIDP may not be straightforward in all cases [8]. This review aims to provide an update on the diagnostic and therapeutic management of CIDP.

**Clinical features**

**Typical chronic inflammatory demyelinating polyradiculoneuropathy**

The clinical picture comprises symmetric proximal and distal muscle weakness, sensory loss, and decreased or absent deep tendon reflexes. Most commonly, the disease begins with paresthesias and weakness in the distal limbs as well as difficulty walking. The disease course is steadily or stepwise progressive over at least 2 months, but can also be relapsing. In contrast with Guillain–Barré syndrome (GBS), cranial nerves are rarely affected and respiratory or autonomic involvement is exceptional [9–15]. Typical CIDP can occur at any age, but most commonly between 40 and 60 years. Onset during infancy and childhood has been repeatedly documented [16–19]. As compared to adult-onset CIDP, the initial disease progression in childhood-onset CIDP is often faster, response to steroid treatment is more favourable, and the prognosis as to recovery appears to be better. Typical CIDP may present acutely (acute-onset CIDP) with the nadir of symptoms and signs reached within 4 weeks in up to 13% of patients [20,21]. Therefore, distinguishing acute-onset CIDP from GBS can be challenging as shown by Ruts et al. [22], who found that 5% of patients initially diagnosed with GBS eventually had acute-onset CIDP. In contrast with GBS patients, acute-onset CIDP patients continue to deteriorate more than 8 weeks after onset or relapse at least 3 times. Often, these patients remain able to walk independently, they are less likely to have facial weakness, respiratory or autonomous nervous system involvement, and they are more likely to have sensory signs [22,23].

**Atypical chronic inflammatory demyelinating polyradiculoneuropathy**

The total clinical spectrum is much wider, including predominantly distal or proximal weakness, pure motor or sensory forms, and asymmetric or focal presentations. Even if some clinical features are different from typical CIDP, the various presentations of atypical CIDP share the common pathogenic mechanism of inflammatory demyelination and response to immune therapy [24–26]. Asymmetric CIDP has been reported in 1982 by Lewis et al. [27] as “multifocal demyelinating neuropathy with persistent conduction block” to become known as Lewis-Sumner syndrome. The condition is characterized by slowly progressive, asymmetric, sensorimotor symptoms and signs in the distribution of two or more peripheral nerves, usually first in the upper limbs. Later on, lower limbs may become involved and sometimes these are affected at the onset of the disease [27–29]. In the distribution of the affected nerves, deep tendon reflexes are reduced or absent. Cranial nerves, including oculomotor, trigeminal, facial, vagal, and genioglossal nerves, may rarely be involved [27–32]. Lewis-Sumner syndrome is very similar to multifocal motor neuropathy (MMN) but may be distinguished from it by the presence of sensory involvement, the absence of serum anti-GM1 antibodies and, in some cases, a positive response to steroids [33]. Focal CIDP affects the brachial or lumbosacral plexus or one or more peripheral nerves in an upper or lower limb [34,35]. Although it can remain focal, the condition may precede typical CIDP by many years [36]. Pure motor CIDP is characterized by selective involvement of motor fibres and absence of sensory symptoms or signs [37,38]. Sensory nerve conductions and sural nerve biopsy are normal. Usually, patients do not improve and may even deteriorate with steroid treatment. Pure sensory CIDP causing gait ataxia, large fiber sensory loss, and paresthesias, responding to immune therapy has been reported as chronic immune sensory polyradiculopathy (CISP) [39]. Although clinical involvement is purely sensory, motor nerve conduction slowing and conduction block have been reported in some cases [40–42]. A long-term follow-up study has shown that CIDP with only sensory symptoms is a transient clinical stage that precedes the appearance of weakness in about 70% of patients [43]. Predominantly distal CIDP has been described as distal acquired demyelinating symmetric neuropathy (DADS) [44]. The phenotype is mainly sensory. In approximately 2 thirds of the cases, DADS neuropathy is an IgM paraproteinemic neuropathy with antibodies against myelin-associated glycoprotein (MAG), which are thought to be causal. IgM anti-MAG DADS neuropathy is different from CIDP and responds poorly to treatment. Patients without anti-MAG...
antibodies, however, improve with immune therapy similar to typical CIDP patients [45,46].

Both typical and atypical CIDP are rarely associated with multifocal central nervous system demyelination, resembling multiple sclerosis [47–49]. Clinical presentations include optic neuritis, internuclear ophthalmoplegia, cerebellar and pyramidal signs. Prolonged central motor conduction times and white matter lesions, usually periventricularly, on brain imaging studies are found and can occur subclinically in up to 50% of CIDP patients [50,51].

Diseases concomitant with chronic inflammatory demyelinating polyradiculoneuropathy

Based on case reports, numerous diseases have been associated with CIDP. These include IgG or IgA monoclonal gammopathy of undetermined significance [52,53], IgM monoclonal gammopathy without antibodies to MAG [45,46], HIV infection, chronic active hepatitis, systemic lupus erythematosus [54,55] or other connective tissue diseases [56,57], sarcoidosis, thyroid disease, inflammatory bowel disease [58], membranous glomerulonephritis [59], bone marrow or solid organ transplantation [60]. There is insufficient evidence to consider CIDP associated with these diseases different from idiopathic CIDP. Several authors have reported an increased occurrence of CIDP in diabetes mellitus with a range from 9 to 26% of diabetic patients being affected [61,62]. Sharma et al. [63] found the odds of occurrence to be 11 × higher among diabetic versus non-diabetic patients. However, rigorous epidemiological studies did not find an increased prevalence of typical CIDP in diabetes [64,65] and, therefore, do not support a pathogenic relationship. Differentiation of CIDP from demyelinating CMT is not difficult in most cases because of the family history, skeletal deformities, distal involvement, early onset and slow disease progression. Nerve conduction velocities are markedly and homogeneously slowed without abnormal temporal dispersion or conduction block, whereas in most CIDP patients the latter findings are frequent and slowing is heterogeneous [66]. Difficulties may arise in sporadic (or recessive) cases with early onset in particular since childhood CIDP may provoke foot deformities [67]. Also, in CMTX, nerve conduction velocities are often intermediate, slowing can be heterogeneous, and abnormal temporal dispersion can occur [66,68–70], therefore rendering the differential diagnosis with CIDP sometimes difficult. To complicate matters, coexistent hereditary neuropathy and CIDP has been reported in families with PMP22 (CMT1A), MPZ (CMT1B), CMTX (connexin 32), HSAN (SPLTC1), and CMT4C (SH3C2), often responding to steroid or IVIG treatment [67,71–73].

Laboratory features

Electrophysiology

Since by definition CIDP is a primary demyelinating neuropathy, the definitive diagnosis depends on electrophysiological or pathological studies. As CIDP is a heterogeneous, multifocal disease, nerve conduction studies are an excellent diagnostic tool because they allow to comprehensively and extensively evaluate the peripheral nervous system. Primary demyelination leads to nerve conduction velocity slowing, distal latency prolongation, and F-wave latency prolongation or absence. Buchthal and Behse [74] were the first to show that the degree of histopathologically determined demyelination in sural nerve quite precisely correlated with sensory and motor nerve conduction slowing when comparing demyelinating Charcot-Marie-Tooth disease (CMT1) with peroneal muscular atrophy (PMA). Other features are abnormal temporal dispersion of the compound muscle action potential (CMAP), because of differential conduction slowing, and conduction block, which is an amplitude and area reduction of the CMAP proximal to a focal area of demyelination in a certain number of axones as compared to the distal CMAP [75,76] (figure 1A). The electrophysiological recognition of primary demyelination, in chronic neuropathies in particular, is not always straightforward because secondary demyelination may occur in primary axonopathies and because some conduction slowing can be explained by loss of large, fast-conducting axones and slow conduction in regenerating or atrophic axones [77]. The sensitivity of electrophysiology for motor nerves may be improved by exhaustive four limb studies and proximal stimulation in the upper limbs [78,79], by studying distal CMAP duration [80,81], and by analysing F-wave latency, chronodispersion, and persistence [82]. Examination of sensory nerves [83,84] may be helpful and somatosensory evoked potentials can be useful to demonstrate abnormal proximal sensory conduction, particularly in sensory CIDP [39,85].

Spinal fluid studies

Increased spinal fluid protein with white blood cell counts less then 10/mm³ occurs in most but not all patients (91% [4]; 95%, [86]; 90.9% in chronic progressive CIDP and 94.1% in relapsing CIDP [45]). Pleocytosis is indicative of infection and warrants further investigation to diagnose alternative or concomitant diseases such as Lyme disease, HIV infection, sarcoidosis. Moreover, lymphomatous or leukemic nerve root infiltration also may need to be excluded.

MRI of spinal root, plexus, and peripheral nerve

MRI may demonstrate gadolinium enhancement and/or hypointensity of the cauda equina and lumbosacral nerve roots [87–91] and of brachial and lumbosacral plexuses [89,92,93] in CIDP. MRI at the site of conduction block or abnormal temporal dispersion has shown nerve enlargement and high signal intensity and gadolinium enhancement in median and ulnar nerves in CIDP [94] (figure 1B). Inversion recovery MR images (STIR) have been reported to show abnormalities in up to 66.7% of CIDP patients as opposed to 50% on T1-weighted
images and on gadolinium enhancement in up to 31.6%. Interestingly, diffusion-weighted images (DWI) showed abnormalities in 55.6% of the cases [95]. The feasibility of demonstrating cervical nerve root hypertrophy in CIDP by ultrasound has also been demonstrated [96]. The differential diagnosis, especially in focal CIDP, is broad and includes benign peripheral nerve tumours (intraneural perineurioma, neurofibroma, schwannoma, neurofibromatosis, sarcoidosis, lymphoma, leukemia, leptomeningeal carcinomatosis) [97]. Differentiation from demyelinating CMT types may be difficult but there is little or no contrast enhancement in these [91].

Peripheral nerve biopsy

Ideally, the nerve considered for biopsy should be clinically and electrophysiologically affected. Usually the sural sensory nerve, but occasionally the superficial peroneal, superficial radial, or gracilis motor nerve is selected. Supportive features for the diagnosis of CIDP are macrophage-associated demyelination, onion bulb formation, demyelinated and to a lesser extent remyelinated nerve fibres, endoneurial oedema, endoneurial mononuclear cell infiltration, and variation between fascicles [7]. Demyelinating lesions were found retrospectively on nerve teasing in 48%, 50%, and 72% of cases by Barohn et al. [86], Haq et al. [98] and Bouchard et al. [99], respectively, and in ultrastructural studies in 79% of cases [98]. Interestingly, lack of agreement between electrodiagnostic and histological criteria was observed. Vallat et al. [100] found histological evidence of de- and remyelination and/or cellular infiltrates in eight of 44 patients with CIDP, who did not meet electrophysiologic criteria. In a prospective study, Gabriel et al. [101] showed an alteration of the diagnosis in 14% of the patients after sural nerve biopsy. These observations are indicative of the added value of nerve biopsy in reaching a final diagnosis. However, when Krendel et al. [102] compared histological features of sural nerve biopsies of patients with CIDP and patients with other neuropathies, no abnormalities were specific, but cellular infiltrates and onion bulbs appeared to be diagnostically helpful when considered together with clinical information. Retrospective studies have shown that sural nerve biopsy is of limited value [103–106]. Bosboom et al. [104,105] compared sural nerve biopsies from patients with CIDP and chronic idiopathic axonal polyneuropathy (CIAP) and from normal controls. Although significant differences of features of demyelination, axonal degeneration, and inflammation were found, there was a considerable overlap of abnormalities in CIDP and CIAP. Attempts to identify more specific diagnostic signs of inflammation (upregulation of matrix metalloproteinases 2 and 9 [105,107] and of specific chemokine receptors and interferon-gamma inducible protein of 10 kDa, IP-10 [108]) have been made. The available evidence indicates that sural nerve biopsy can provide supportive evidence for the diagnosis of CIDP in carefully selected difficult cases, but positive findings are not specific and negative findings do not exclude the diagnosis. Moreover, qualified neuropathological laboratory facilities for peripheral nerve biopsy analysis are rare and histological techniques time-consuming, which makes the requirement of nerve biopsy criteria for a definite diagnosis problematic.
Chronic inflammatory demyelinating polyradiculoneuropathy

Diagnostic criteria

CIDP is a syndrome with a broad spectrum of clinical presentations and laboratory features only give indirect evidence of the key pathological features, peripheral nerve inflammation and demyelination, except nerve biopsy, which, because of its inherent problems as discussed above, is helpful only in selected cases. As there is no gold standard for the diagnosis [8], diagnostic criteria have been proposed and adapted to accommodate advancing insight and understanding over the last two decades [109]. The first set of diagnostic clinical criteria was published by Dyck et al. [4,6] and included progressive course of 6 months, usually slowed nerve conduction velocities (and occurrence of conduction block), spinal fluid cyto-albumic dissociation, and nerve biopsy demonstrating segmental de- and remyelination and perivascular inflammation. This descriptive set was the basis for a formalized set of criteria, proposed by Barohn et al. [86]. The required time period of disease progression was reduced to 2 months. Laboratory criteria consisted of nerve biopsy abnormalities, motor conduction slowing to < 70% in two nerves, and spinal fluid protein > 45 mg/dl. Fulfillment of all criteria was necessary for a definite diagnosis; fulfillment of only two and one laboratory criteria led to the diagnostic categories of probable and possible, respectively. Of 60 patients with a clinical diagnosis of CIDP by the authors, 30% had all three laboratory abnormalities, 48% had two, and 22% had one; however, 95% responded to treatment, mainly prednisone. Research criteria for CIDP were proposed by an Ad Hoc Subcommittee of the AAN [110]. Fulfillment of clinical, physiological, pathological, and spinal fluid criteria led to three diagnostic categories (definite, probable, possible). Fulfillment of pathological criteria was necessary for a definite diagnosis. Electrophysiological criteria for primary demyelination were quite restrictive as three of four conduction parameters were required to be abnormal, even for the diagnosis of possible CIDP. On the other hand, the criteria for partial motor conduction block and abnormal temporal dispersion were probably not restrictive enough, as suggested by AAEM consensus criteria for the diagnosis of partial conduction block [111]. To increase sensitivity, Saperstein et al. [112] proposed a modified criteria set, based on the AAN and Barohn et al. criteria [86,110]. The differences were nerve biopsy was not mandatory for a definite diagnosis; spinal fluid protein > 45 mg/dl was mandatory; modification of AAN physiological criteria such that abnormality of two of four nerve conduction parameters was sufficient and a change in criteria for conduction block to match the AAEM consensus. Criteria were developed by the Inflammatory Neuropathy Cause and Treatment (INCAT) group for inclusion of CIDP patients in a trial comparing intravenous immunoglobulin and prednisolone [113]. Both clinical and electrophysiological criteria were modified from the AAN criteria. Requirements included testing of four motor nerves bilaterally and demyelinating abnormalities in three nerves or a confirmatory nerve biopsy if only in two nerves.

Since electrophysiology plays a key role in the diagnosis of demyelinating neuropathies, many investigators have attempted to develop electrophysiological criteria with high sensitivity and specificity for primary acquired demyelination in CIDP (for review, see Van den Bergh and Piéret [114]). Bromberg [115] compared three sets [86,110,116] and found maximal sensitivity of 50% (66% after modification) with 100% specificity with regard to ALS and diabetic neuropathy. Van den Bergh and Piéret [114] (and unpublished observations) confirmed 100% specificity of only two of these three sets for ALS and diabetic neuropathy with sensitivity levels of 68% [116], 29% [86], and 39% [110]. In three additional sets [112,113,117], sensitivity of 43, 50 and 57% was observed without full specificity with regard to diabetic neuropathy and ALS. Therefore, to increase sensitivity and specificity, Van den Bergh and Piéret [114] constructed a criteria set at both the motor nerve and patient levels. Criteria at the motor nerve level were based on scientific evidence for cut-off values for the basic motor conduction parameters to distinguish demyelination from axonal degeneration (e.g., at least 30% of motor nerve conduction slowing according to Buchthal and Behse [74] and van Asseldonk et al. [118]), whereas criteria on the patient level did consider empirical evidence for the number of abnormal parameters, required to distinguish CIDP from other disorders, diabetic neuropathy and ALS in particular. This resulted in the requirement for only 1 abnormal parameter in each of at least two different nerves (table I). The high diagnostic sensitivity of these criteria was initially demonstrated in the original series (75% sensitivity with 100% specificity) and in a multicentre study by Rajabally et al. [119], showing a sensitivity of 79.5% and specificity of 96.9%. Dispersion of the distal CMAP is an additional parameter, which may significantly enhance sensitivity. Thaisetthawatkul et al. [80] reported 78% sensitivity with 94% specificity for ALS and diabetic neuropathy by using only this parameter. Combination of the distal CMAP dispersion parameter with criteria proposed by Nicolas et al. [117] increased sensitivity from 61 to 87% but specificity decreased from 91 to 85% for ALS and from 100 to 94% for diabetic polyneuropathy [80].

In 2006, a task force of the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) published a CIDP management guideline [109] with clearly defined criteria. Clinical criteria were proposed for typical and atypical CIDP and the electrophysiological component criteria included the set originally described by Van den Bergh and Piéret [114] with addition of the distal CMAP dispersion criterion published by Thaisetthawatkul et al. [80]. These electrophysiological criteria have been reproduced in the first revision of the EFNS/PNS CIDP
Epidemiology

Studies on the prevalence and incidence of CIDP are scarce and difficult to interpret because of different diagnostic criteria. Using the AAN criteria [110], Lunn et al. [122] reported a prevalence of 1.0/100,000 in South-East England. Using the same criteria, McLeod et al. [123] and Chio et al. [124] found a prevalence rate of 1.9/100,000 in New South Wales, Australia, and 3.58/100,000 in Northern Italy (Piemonte and Valle d’O斯塔) with incidence rates of 0.15 and 0.36/100,000, respectively. Using diagnostic criteria by Albers and Kelly [125], which are more liberal than the AAN criteria, Mygland and Monstad [126] reported a much higher prevalence of 7.7/100,000 in a relatively small Norwegian community. The most comprehensive study was performed in Leicestershire and Rutland, UK [127]. Whereas prevalence and incidence rates of 1.97 and 0.35/100,000 were observed when using the AAN diagnostic criteria, much higher figures were noted when the EFNS/PNS diagnostic criteria [7] were applied (4.77 and 0.70/100,000 respectively). The importance of the sensitivity of diagnostic criteria also is demonstrated by Mahdi-Rogers et al. [128], reporting a prevalence rate of 2.8/100,000 in South-East London when using EFNS/PNS diagnostic criteria, which is almost 3x the rate observed by Lunn et al. [122] in the same geographic area when using the AAN criteria. Mahdi-Rogers et al. [128] and Rajabally et al. [127] found that, respectively, 11 and 15.7% pure sensory CIDP, 22 and 15.2% Lewis-Sumner syndrome, and 6.0 and 6.5% DADS CIDP. Prevalence is higher in males and increases with age.

Pathophysiology of chronic inflammatory demyelinating polyradiculoneuropathy

The clinical similarity of CIDP to GBS, its histologic resemblance to experimental autoimmune neuritis and its response to immunosuppressive therapy, all suggest an autoimmune pathogenesis. Pathophysiological mechanisms implicated in CIDP are believed to involve both humoral and cellular immunity [129]. No pathogenic antibody or definite triggering antigen has been so far identified in CIDP. Immunohistochemical studies have shown the presence of increased T-cells with γδ-receptors in peripheral nerve of CIDP patients [130], who otherwise have been found to have increased concentrations of TNF and interleukin 2, indicating T-cell activation [131,132]. The predominant attack in CIDP comes from macrophages which actively contribute to the demyelinating process. Cytokines from activated T-cells ultimately result in this macrophage-induced peripheral nerve demyelination [133]. Dysfunction of T-cells with immunoregulatory faculties may sustain a localized inflammatory process an in turn, contribute to disease progression. Increased serum, CSF and nerve concentrations of adhesion molecules, chemokines and matrix metalloproteinases may result in facilitating

Guideline except for the single cut-off value for distal CMAP dispersion, which was replaced by a cut-off value for each of the four routinely studied motor nerves as determined by Iosse et al. [7,81] (Table I). High diagnostic sensitivity and specificity and high negative and positive predictive values of the EFNS/PNS criteria were demonstrated in a population of CIDP patients by Tackenberg et al. [120]. In 2009, Koski et al. [121] published a set of diagnostic criteria, based on data derived from patients diagnosed with CIDP by consensus of a group of experts, excluding those with Lewis-Sumner syndrome, paraproteins, and genetic neuropathy. Using classification and regression tree analysis, two sets of criteria were developed: one which included electrophysiological criteria based on the AAN criteria [110] (recordable CMAP in at least 75% of nerves and either abnormal distal latency or abnormal motor conduction velocity or abnormal F-wave latency in > 50% of studied nerves) and one which relied on clinical criteria alone (symmetric onset or examination, weakness of four limbs, and proximal weakness in at least one limb). This is the only criteria set so far published, which allows to establish the diagnosis of CIDP on either clinical or electrophysiological criteria. The authors reported 83% sensitivity and 97% specificity on validation studies. The multicentre study by Rajabally et al. [119], however, found a sensitivity level of only 63% with 99.3% specificity for these criteria, whereas sensitivity and specificity levels of 81.3 and 96.2%, respectively, were reached for the EFNS/PNS criteria [7]. One of the explanations for the lower sensitivity of the Koski et al. [121] criteria is that atypical CIDP cases may be missed.

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<td>Basic EFNS/PNS chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) guideline electrophysiological criteria</td>
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<td>Motor conduction parameter</td>
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<td>Conduction velocity slowing</td>
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<td>Distal latency prolongation</td>
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<td>Temporal dispersion</td>
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<td>Distal CMAP duration prolongation</td>
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Abnormality of one out of six conduction parameters in two motor nerves is sufficient for the electrophysiological diagnosis of primary demyelination.

*These limiting values were derived from data obtained with a bandpass of 20 Hz–10 kHz, whereas all others were derived with a 2 Hz–10 kHz bandpass. Adapted from references [7,114].
permeability across the blood-nerve barrier for lymphoid cell migration [134,135]. Activation of migrant T-cells in the endoneurium together with probable suppressor T-cell activity then results [136,137], with the implication of genetic factors which are also likely to play a role in the T-cell mediated attack by possible impaired control and regulation of autoreactive T-cells [138]. Humoral factors play also a likely significant role in the pathophysiology of CIDP as is suggested by the disease transfer from patients to experimental animals through serum [139] and by the favourable effects of plasma exchange (PE) in the disorder. The latter may also be due however to elimination of other inflammatory mediators such as nitric oxide, cytokine and complement factors [25]. In addition, and in keeping with a humoral component, complement-fixing immunoglobulin deposits have been found on nerve biopsy specimens of CIDP patients [140] and antibodies to various myelin proteins such as MPZ [141], P2 [142], or neurofascin [143] have been described in CIDP patient sera but not in that of controls. Despite the many recent advances in knowledge summarized above, substantial uncertainties nevertheless persist and more research is needed to clarify and fully understand the precise pathophysiological mechanisms implicated in CIDP, which may itself represent a heterogeneous entity as could be suggested by its variable clinical and electrophysiological phenotype.

Treatment

IVIG has been shown to be effective in CIDP in a number of different studies. Five placebo-controlled trials [144–149] provided the evidence for their efficacy in the disorder. In addition, IVIG has also been found as effective as PE [150] and as steroids [113]. More recently, an Italian multicentre study actually demonstrated better efficacy and tolerability of IVIG given at the dose of 2 g/kg over 4 days in comparison to intravenous steroids (60 mg of prednisolone daily tapered over 6 weeks) and IVIG (single course of 2 g/kg) [113]. This led to the consensus expert opinion formulated in the EFNS/PNS guideline on CIDP management [7] where steroid therapy was considered as advisable as IVIG in functionally impaired patients. There is now potential debate about this given that the results of the recent above-mentioned multicentre Italian trial clearly favoured IVIG over steroids [151]. However, both this trial and the long-term follow-up of patients from the PREDICT study [155], which compared pulse oral high-dose dexamethasone to continuous oral prednisolone, demonstrated a high proportion of remission after corticosteroids [156]. In the case of the Italian study, remission was shown to be more likely with steroids than with IVIG. This leads on to the important question of what initial treatment should be considered for CIDP. These recent data indicate that given the more likely short-term response, IVIG probably represent the ideal therapy when patients are severely disabled and need to be rapidly improved. However, in milder disease, and when there are no contraindications, the first-line agent should probably be steroids, given the higher likelihood of long-term remission than with IVIG. These recent data may equally suggest that the combination of IVIG and steroids would have the potential of offering additional benefit, allowing theoretically rapid improvement with also, a greater chance of remission [157]. Only future trials using this combination may confirm this in future. Steroids should be preferably given in high-dose pulse rather than continuous form, as equally efficacious but less likely to cause some unpleasant side-effects namely sleeplessness and Cushing face [155].

The effect of PE in CIDP was demonstrated by 2 randomized controlled trials [158,159]. PE appears efficacious for short lengths of time as relapses are reported 1 to 2 weeks after discontinuation. Furthermore, venous access and a less favourable side-effect profile than that of IVIG mean that PE should be considered only, as far as possible, as a second-line temporary measure in the treatment of IVIG- and steroid-unresponsive CIDP.

Up to 80% of patients respond to one the three first-line therapies, i.e. IVIG, steroids or PE, alone or in combination [160]. However, there are refractory cases for which other treatments may need to be considered, mainly in severely affected individuals. Unfortunately, although frequently used in practice, to date no immunosuppressant therapy has been
**Figure 2**

Therapeutic algorithm for management of CIDP based on current evidence

- **Non-functionally impairing CIDP**
  - Monitor without treatment
    - No change
    - Deterioration of function
      - Steroids: Pulsed oral Dexamethasone or IV Methylprednisolone or Oral Methylprednisolone
      - IVIg 2g/kg for 3 courses at 3-4 week intervals
      - Monitor progress
        - Adequate functional improvement
          - Continuously monitor to assess need for maintaining treatment (dose/frequency) required
            - Adequate functional improvement
              - Consider alternate therapy, i.e., replace steroids by IVIg or IVIg by steroids
                - No or inadequate functional improvement
                  - No further treatment
        - No or inadequate functional improvement
          - No or inadequate functional improvement
            - Trial of Plasma Exchange
              - Adequate functional improvement
              - No or inadequate functional improvement

- **CIDP with mild functional deficit**
  - No contraindication to steroids
    - If no significant disability and stable:
      - No further treatment

- **CIDP with severe functional deficit**
  - Contraindication to steroids
    - If severe disability or progressing:
      - Consider cautious use of immunosuppressants (NO current existing evidence):
        - e.g. Cyclophosphamide in severe cases
        - Azathioprine, Methotrexate, Rituximab in less severely affected patients
      - Consider combination of PE and steroid/IVIg therapy
        - Adequate functional improvement
        - No or inadequate functional improvement

If no significant disability and stable: No further treatment

If severe disability or progressing: Consider cautious use of immunosuppressants (NO current existing evidence):
- e.g. Cyclophosphamide in severe cases
- Azathioprine, Methotrexate, Rituximab in less severely affected patients

Consider combination of PE and steroid/IVIg therapy
- Adequate functional improvement
- No or inadequate functional improvement
shown to be unequivocally useful in CIDP directly or to allow reduction of steroid or IVIG therapy [161,162]. Only three agents have been tested in randomized trials: azathioprine, interferon beta 1a and methotrexate. Importantly, although no evidence for benefit can be ascertained for any of the 3, none of the trials performed were large enough to rule out a small or moderate benefit. Although anecdotal reports have demonstrated benefit of various agents such as cyclophosphamide [163] and ciclosporin [164], there is no trial evidence to use these potentially highly toxic drugs. The same applies for potentially less toxic agents such as mycophenolate [165] or rituximab [166]. Autologous peripheral blood stem cell transplant has also been described as a potentially efficacious therapy [167] although serious adverse effects such as sepsis make this an unlikely recommended avenue for future research.

A subcategorization of CIDP has recently been suggested in terms of long-term outcome by an expert panel. This resulted in a grading system described by the authors as the “CIDP Disease Activity Status”, or “CDAS” [168]. In an analysis of 106 patients, nearly a third were found to be cured or in remission, and in such cases, not requiring further treatment. This is an important point as long-term CIDP therapy is expensive and can result in potential serious adverse effects, hence the importance of well establishing the activity status in any case, so as to adapt therapy individually in the most appropriate way. In figure 2, we suggest a therapeutic algorithm that may be used in view of recent knowledge in the field, to optimize treatment of CIDP in different patients, depending on the clinical situation, risk of side-effects and response.

Disclosure of interest: the authors declare that they have no conflicts of interest concerning this article.


Chronic inflammatory demyelinating polyradiculoneuropathy


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