Chronic inflammatory demyelinating polyradiculoneuropathy: diagnostic and therapeutic challenges for a treatable condition

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Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a chronic neuropathy of supposed immune origin. Understanding of its pathophysiology has recently improved, although its causes remain unclear. The classic presentation of CIDP includes sensory and motor symptoms in the distal and proximal segments of the four limbs with areflexia, evolving over more than 8 weeks. Raised protein concentrations in CSF and heterogeneous slowing of nerve conduction are typical of the condition. In addition to this usual phenotype, distribution of symptoms, disease course, and disability can be heterogeneous, leading to underdiagnosis of the disorder. Diagnosis is sometimes challenging and can require use of imaging and nerve biopsy. Steroids and intravenous immunoglobulin are effective, and plasma exchange can be helpful as rescue therapy. The usefulness of immunosuppressants needs to be established. The identification of specific diagnostic markers and new therapeutic strategies with conventional or targeted immunotherapy are needed to improve the outlook for patients with CIDP.

Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a clinically heterogeneous, grossly symmetric, sensory and motor neuropathy evolving as a monophasic, relapsing, or progressive disorder. It develops over more than 8 weeks, distinguishing the condition from Guillain-Barré syndrome (GBS), which has an acute onset. CIDP is thought to have an immune basis, its hallmark being inflammatory-mediated demyelination. According to Burns, Eichhorst described the first case of chronic and recurrent polynейritis in 1890, and a few similar cases were reported during the following decades. During the 1950s, the concept of steroid-responsive chronic or relapsing polynейritis emerged. Along with experimental studies, this notion pointed to an immune mechanism. Later, investigators showed that reduced conduction velocities and conduction block resulted from segmental demyelination, which was considered typical of CIDP and related disorders. For years, various terms were used to describe the condition and in 1982, Dyck and co-workers used the term chronic inflammatory demyelinating polyradiculoneuropathy, which summarises its clinicopathological features.

Clinical trials have subsequently proven the efficacy of immunotherapy in patients with CIDP, and, to aid recognition of these patients, the American Academy of Neurology (AAN) proposed research diagnostic criteria. During the following years these criteria seemed insufficiently sensitive for clinical practice, so new sets were proposed by several experts. In 2008, the French CIDP Study Group provided recommendations on diagnostic strategies for typical and atypical cases to help to improve diagnosis of this neuropathy.

Although most patients with CIDP are recognised, since we still do not have definitive diagnostic tests, diagnosis can sometimes be challenging. Moreover, the prevalence of CIDP, which varies roughly between one and seven in 100 000 across studies, is probably underestimated, partly because of an absence of recognition of possible or probable cases. In view of its clinical variability, the diagnosis of CIDP should be envisaged during investigation of almost any multifocal or generalised neuropathy of unknown cause. This consideration is important because the condition is treatable. Recent advances have been made in CIDP and other immune-mediated neuropathies. In this Review, we discuss these advances, with particular emphasis on pathophysiological data, modern work-up methods, and therapeutic management.

Epidemiology

Few studies have examined the epidemiology of CIDP, but its prevalence is probably underestimated because of difficulty in diagnosis of so-called atypical cases. At present, only six published studies exist showing variable results for prevalence: between one in 100 000 in southeast UK and 7·7 in 100 000 in northern Norway. Such discrepancies could be linked to several factors, including genetic predisposition, use of different electrophysiological criteria, under-reporting of patients in remission, and omission of patients with an associated paraproteinemia or a multifocal neuropathy. In all studies, CIDP was observed to be most frequent in adult men, as was reported in a Japanese population with an annual incidence of 0·48 per 100 000.

Pathophysiology

CIDP is regarded as an autoimmune disease involving cellular and humoral immunity. However, by contrast with GBS, a single triggering antigen has not yet been found, except in rare cases of CIDP associated with melanoma, in which tumour cells share carbohydrate epitopes with Schwann cells. In an immune response to a specific antigen, a local clonal expansion of T cells reactive to this antigen would be expected. In CIDP, such a clonal proliferation could not be shown, although immunohistochemistry revealed increased numbers of
purified IgG from patients with CIDP induced conduction significance remains unclear. Intraneural injection of interleukin 2,21,22 suggesting T-cell activation. Migration of activated T cells into peripheral nerves depends on interaction between their surface molecules and adhesion molecules on endothelial cells. An increase in adhesion molecules, matrix metalloproteinases, and chemokines in CSF and nerves of CIDP patients has been shown.23–26 Along with a reduced amount of the tight-junction proteins claudin 5 and ZO-1 in sural nerve biopsy specimens from patients with CIDP,27 this finding suggests damage to the blood–nerve barrier. Once the T cells have breached this barrier, they are reactivated inside the endoneurium, as suggested by Schwann-cell expression of the adhesion and T-cell stimulatory molecule CD58 in nerve samples from patients with CIDP.28 Furthermore, patients with CIDP were shown to have decreased FAS function and thus a reduced rate of T-cell apoptosis.29 Suppressor T-cell function might also be defective, as in a recent study in which the number and suppressive function of circulating T-regulatory cells were reduced in 15 patients with CIDP.30

Genetic factors implicated in control of early T-cell activation are probably important in CIDP; investigators have shown a significant association with a homozygous genotype for a low repeat number of tandem GA in the SH2D2A genotype for a low repeat number of tandem GA in the SH2D2A gene coding for the T-cell-specific adapter protein.31 This genotype could result in defective control and elimination of autoreactive T cells. The potential role of co-stimulatory molecules such as B7-1 (CD80)32 and BB-133 has been suggested by their expression in biopsy samples from some patients with CIDP. Diabetic mice deficient in B7-2 develop a spontaneous autoimmune neuropathy.34 Another co-stimulatory molecule, the inducible co-stimulator (ICOS), was localised in T cells and its ligand, ICOS-L, on macrophages in nerves from patients with CIDP and GBS.35 Macrophages in CIDP are active as antigen-presenting cells and as destructors of myelin, as exemplified by the presence of active myelin breakdown by macrophages and macrophage clustering around endoneurial vessels in nerve samples from patients with CIDP.36,37 Macrophages invading the endoneurium were shown to express proinflammatory cytokines and cyclo-oxygenase 2.38

Although a contribution of autoantibodies to the pathogenesis of CIDP was suggested in the early 1980s,39 antibodies to myelin proteins and gangliosides were identified only in subsets of patients,40–42 and their significance remains unclear. Intraneural injection of purified IgG from patients with CIDP induced conduction block and demyelination in rat nerves.43 Myelin protein zero (MPZ) has been deemed the antigen responsible for this effect,43 a view that is supported by experimental induction of neuropathy by MPZ-reactive T cells.44 Peripheral myelin protein 2 (PMP2) might also be a good candidate.44 The therapeutic benefits of plasma exchange (PE) have been evoked as an argument for a role of autoantibodies in CIDP, but improvement might additionally be caused by elimination of other inflammatory mediators such as nitric oxide, cytokines, and complement factors. These mediators have been suggested as factors contributing to demyelination and determining axonal loss in CIDP.39 The role of proinflammatory cytokines is supported by studies that showed raised serum concentrations of TNFα in a CIDP patient with severe disability and subacute progression.45 B cells from patients with CIDP have been shown to have reduced expression of FCGR2B, an inhibitory receptor that prevents B cells from entering the germinative centre and becoming IgG-positive plasma cells. After patients were effectively treated with intravenous immunoglobulin (IVIg), FCGR2B expression was upregulated on monocytes and B cells.46 Furthermore, relatively more patients with CIDP than controls were positive for the rare 386C/120A FCGR2B promoter polymorphism, which results in reduced promoter activity.

Clinical presentation and course

The classic form and variants

After the first description by Dyck and co-workers,1 the clinical pattern of CIDP was defined by several features: (i) selective involvement of the peripheral nervous system; (ii) involvement of proximal as well as distal limb structures; (iii) involvement of both motor and sensory fibres (although in some cases motor or sensory fibres only might be affected); and (iv) a recurrent, continuously worsening, or fluctuating course. The classic pattern of limb involvement in CIDP is then a sensory and motor diffuse polyneuropathy with generalised areflexia, and proximal involvement evolving over more than 2 months. Cranial nerves are occasionally affected, with a particular tropism for the VIIth pair, but ophthalmoplegia or bulbar weakness can be present.47–49 The disease course is usually separated into monophasic, progressive, and relapsing forms, although a strict definition of the relapsing form has seldom been used in the literature.

Several variants have been described on the basis of distribution of symptoms and signs (table).50–55 Although controversies have emerged as to whether some of these syndromes are distinct clinical entities,56,57 the common pathogenic mechanism of inflammatory demyelination clearly shows that they belong to the spectrum of CIDP.58,59 Moreover, identification of patients with these variants is crucial because they respond to immunomodulatory therapy as well as patients with the classic phenotype.

CIDP can be associated with various conditions, including hepatitis C, inflammatory bowel disease, lymphoma, monoclonal gammopathy of undetermined significance (MGUS), HIV/AIDS infection, organ transplant, and connective tissue disorders. Similarly, investigators have reported that CIDP was more frequent in patients with diabetes mellitus than it was in the


**Table: Main clinical variants of CIDP based on pattern of symptoms and signs**

<table>
<thead>
<tr>
<th>Type of CIDP</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Pure motor form(^{49,50})</td>
<td>Symmetrical and selective involvement of motor fibres, nerve conduction studies show frequent conduction blocks; the condition seems to be more responsive to IVIg than it is to steroids.</td>
</tr>
<tr>
<td>Sensory CIDP or chronic sensory demyelinating neuropathy(^{51,52})</td>
<td>Numbness in the extremities is a frequent presenting symptom; ataxia can be prominent; despite pure sensory symptoms, nerve conduction studies show motor abnormalities typical of CIDP; significant weakness can appear at follow-up.</td>
</tr>
<tr>
<td>Minimal forms(^{53,54})</td>
<td>Strength is usually normal; symptoms consist of distal numbness or tingling or fatigue; worsening can occur in the long term.</td>
</tr>
<tr>
<td>Multifocal form;(^{55}) Lewis-Summer syndrome,(^{56}) multifocal acquired demyelinating sensory and motor neuropathy(^{57,58})</td>
<td>Clinical presentation is that of a multifocal neuropathy; conduction block is found in affected nerves; by contrast with multifocal motor neuropathy, sensory involvement is manifest and response to steroids is usually good.</td>
</tr>
<tr>
<td>Distal form; distal acquired demyelinating symmetric neuropathy(^{59,60})</td>
<td>Proximal weakness is absent; when no monoclonal protein is found, response to therapy seems similar to that of typical CIDP.</td>
</tr>
<tr>
<td>Chronic immune sensory polyradiculopathy(^{61})</td>
<td>Clinical picture consists of sensory ataxia and large fibre sensory loss; nerve conduction studies are normal, although somatosensory evoked potentials suggest sensory root involvement; histological pattern of rootlet biopsy is similar to that of CIDP.</td>
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IVIg=intravenous immunoglobulin. CIDP=chronic inflammatory demyelinating polyradiculoneuropathy.

Review, we should emphasise that nerve conduction involvement of the central pathways in some patients, suggesting that CIDP might involve the central as well as the peripheral nervous system.\(^{67,68}\) This finding seems to differ from that of a population of patients in whom there is an association between a CIDP-like disorder and a multiple sclerosis-like condition, in which clinical involvement of the peripheral as well as the central nervous system is obvious.\(^{69}\) Finally, CIDP has been reported in patients with Charcot-Marie-Tooth disease,\(^{70}\) suggesting that superimposed inflammatory mechanisms might occur in hereditary neuropathies and contribute to disability.\(^{71}\)

Childhood CIDP has been extensively reported, allowing a precise picture to be drawn of the presentation, response to treatment, and prognosis.\(^{72,75}\) Overall, children with CIDP have a more rapid onset, greater disability at the peak of the disease, and a more frequent relapsing course than do adults, but respond better to treatment and have a more favourable long-term outcome.

**Clinical course**

By consensus, the minimum duration of symptoms until patients with CIDP reach their nadir is 2 months, mainly to distinguish the condition from GBS, which evolves over less than 4 weeks.\(^{7,8}\) Oh and colleagues\(^{8}\) defined patients who fall between the two time windows as having subacute inflammatory demyelinating polyneuropathy (SIDP). Most of these patients improve fully with treatment and do not relapse at follow-up. They seem to have an antecedent infection more frequently than do patients with CIDP. Overall, their clinical presentation appears similar to that of monophasic CIDP, with an excellent response to steroids and a shortened course, so SIDP seems to bridge the gap between GBS and CIDP.

In some cases, CIDP can start acutely with a GBS-like presentation.\(^{7,8}\) Distinguishing true GBS from acutely starting CIDP is challenging and has major therapeutic implications. Indeed, although patients with CIDP reach their nadir in more than 8 weeks, some are referred early in the course of their disease, and are treated before 4 weeks, the theoretical limit for GBS diagnosis.\(^{79}\) Conversely, some patients with CIDP reach their maximum deficit in less than 4 weeks and are treated as patients with GBS, but relapse during the plateau phase of the disease.\(^{79}\) In these cases, a second course of IVIg is usually administered because treatment-related fluctuation is supposed. Early relapse occurring less than 9 weeks after onset seems to be more common in patients with GBS than it is in patients with acute-onset CIDP.\(^{80}\)

Moreover, prominent sensory signs can predict conversion to CIDP, although involvement of the autonomic nervous system, facial weakness, a preceding infectious illness, and the need for mechanical ventilation are more common in GBS.\(^{81}\)

After the initiation phase, the course of CIDP can be highly variable. Three types of disease course have been described: (i) a monophasic course in which patients progress to their nadir then fully recover with treatment and usually do not relapse; (ii) a relapsing–remitting course in which patients have complete remissions between relapses; and (iii) a chronic progressive course in which patients progressively deteriorate until treatment is given. The relative proportion of each of these disease courses varies greatly between series, mainly because of variation in definition of relapsing and monophasic forms.\(^{78,79,82,83}\) Overall, 20–35% of patients with CIDP have the relapsing form, whereas 7–50% have monophasic illness.

**Diagnostic tests**

**Nerve conduction studies**

Although technical issues are beyond the scope of this Review, we should emphasise that nerve conduction
studies should be undertaken with extreme caution by trained practitioners, and that exploration of proximal segments of nerves can be particularly useful in a disease with multifocal demyelinating lesions such as CIDP.** Nerve conduction findings are a key part of diagnostic investigation for patients with suspected CIDP. Indeed, slowing of nerve conduction is usually due to nerve demyelination, either diffuse or segmental, and is highly suggestive of CIDP in the appropriate clinical situation.1 Following the work of Albers and Kelly,** consensus electrophysiological research criteria for CIDP were elaborated in the early 1990s.7 Several variables were considered: (i) slowing of motor nerve conduction velocities; (ii) lengthening of distal motor latencies; (iii) prolonged minimal F wave latencies; and (iv) partial conduction block. The severity of slowing in individual nerves and the number of nerves in which abnormalities had to be found were carefully chosen to be specific enough for research purposes, but several investigators have judged the sensitivity of these criteria to be insufficient for clinical practice.5,6,7 Therefore, several sets of electrophysiological criteria for CIDP have been proposed to improve detection of patients with this treatable disorder.6,8,10 Thaisethawatkul and colleagues8 showed that dispersion of distal motor action potentials was another useful criterion, and others, including a panel of experts from the European Federation of Neurological Societies (EFNS) and the Peripheral Nerve Society (PNS), have proposed that this measure be included in electrophysiological criteria for CIDP. 8,9,10 The EFNS/PNS criteria seem to provide the best chance of identification of patients with CIDP.9

Whether axonal forms of CIDP exist has been a matter of debate.52 Axonal involvement in this primary demyelinating neuropathy is obvious in many cases and is closely linked to disability.53 Uncini and co-workers54 described five patients with a condition they called steroid-responsive axonal polynuropathy, suggesting that it was an axonal variant of CIDP.55 However, whether the inflammatory process directly involves axons, the condition being the chronic counterpart of acute motor sensory axonal neuropathy, is far from proven from this study.55 Indeed, patients who do not meet neurophysiological criteria for a primary demyelinating neuropathy might have evidence of inflammatory demyelination on nerve biopsy.7

**Other laboratory investigations**

Many patients with CIDP have raised CSF protein with leucocyte counts lower than ten cells per μL, which is indicative of root inflammation, and this disease criterion was in the past regarded as mandatory.1 However, as has long been recognised, protein content can be normal in at least 10% of patients, and the criterion is now considered supportive.57 When leucocyte count is raised in the CSF, Lyme borreliosis, HIV/AIDS infection, lymphoma, or sarcoidosis should be considered. Since root involvement is not accessible to conventional nerve conduction studies, somatosensory evoked potentials have been investigated in patients with chronic demyelinating neuropathies.59 This technique might be especially useful when assessing for proximal involvement of sensory nerves in patients with normal sural sensory potentials. Similarly, breakdown of the blood–nerve barrier at the root level could cause contrast enhancement on MRI.60 Moreover, root hypertrophy can be shown by MRI at the lumbar or cervical level in patients with CIDP and can occasionally cause clinical findings that are attributable to lumbar or cervical stenosis.61,62 Because inflammation can be widespread along nerves in CIDP, contrast enhancement and hypertrophy are sometimes shown by conventional MRI at the plexus level.63,64 Besides conventional MRI sequences, diffusion neurography, which is a modified diffusion-weighted MRI technique, might be a promising method to identify abnormalities in nerves of patients with CIDP.65

**Pathology**

CIDP is caused by a multifocal inflammatory and demyelinating process involving the spinal roots, plexuses, and nerve trunks in a diffuse manner. Although the general view is that CIDP mainly affects large myelinated fibres, small fibres are not unaffected, as shown by nerve and skin biopsy findings.66,67 The chronic proximal demyelinating lesions frequently induce distal axon degeneration with dropout of large myelinated fibres. Such an axonal pattern, which is sometimes prominent, will induce electrophysiological anomalies so that some patients might be regarded as having chronic idiopathic axonal polynuropathy rather than CIDP. In such cases, nerve biopsy might be of value for diagnosis of CIDP.

The EFNS/PNS CIDP guidelines7 state that the nerve chosen for biopsy should be one that is clinically and

Panel: Pathological features of chronic inflammatory demyelinating polyradiculoneuropathy

**Mandatory criteria**

- Nerve biopsy showing unequivocal evidence of demyelination and remyelination
- Demyelination by either electron microscopy (>5 fibres) or teased fibre studies (>12% of teased fibres, minimum of four internodes each, showing demyelination or remyelination)

**Supportive criteria**

- Subperineurial or endoneurial oedema
- Mononuclear cell infiltration
- Onion-bulb formation
- Prominent variation in degree of demyelination between fascicles

**Exclusionary criteria**

- Vasculitis, neurofilamentous swollen axons, amyloid deposits, or intracytoplasmic inclusions in Schwann cells or macrophages indicating adrenoleukodystrophy, metachromatic leukodystrophy, globoid cell leukodystrophy, or other evidence of specific pathological changes
electrophysiologically affected (usually the sural nerve, but occasionally the superficial peroneal or the superficial radial nerves). Sometimes, the choice of nerve can be assisted by MRI. Minimum examination should include paraffin sections and semithin resin sections. When available, immunohistochemistry, electron microscopy, and teased fibre preparations are of value. The pathological criteria of the AAN are most widely used (panel), although they are not wholly specific for CIDP. When a nerve biopsy is done, the final diagnosis will result from a synthesis of the clinical, electrophysiological, and histological data made by the clinician in charge of the patient.

On paraffin sections, mononuclear cell infiltrates can be seen as scattered cells, often surrounding vessels. These infiltrates can be seen in the endoneurium (figure 1), as well as in the perineurium and the epineurium by optic microscopy, but are sometimes more clearly seen by ultrastructural examination. However, the presence of these small clusters of inflammatory cells is uncommon in nerve biopsy samples from patients with CIDP and is not mandatory for the diagnosis. Immunopathological studies can reveal the presence of T cells and macrophages; macrophages suggest diagnosis of CIDP when they are present as small perivascular clusters in the endoneurium. On paraffin sections, mononuclear cell infiltrates can be seen as scattered cells, often surrounding vessels. These infiltrates can be seen in the endoneurium (figure 1), as well as in the perineurium and the epineurium by optic microscopy, but are sometimes more clearly seen by ultrastructural examination. However, the presence of these small clusters of inflammatory cells is uncommon in nerve biopsy samples from patients with CIDP and is not mandatory for the diagnosis. Immunopathological studies can reveal the presence of T cells and macrophages; macrophages suggest diagnosis of CIDP when they are present as small perivascular clusters in the endoneurium.56

Demyelination and remyelination are pathological hallmarks of CIDP. Segmental demyelination is best seen on teased fibre preparations; on electron microscopic examination, macrophages can sometimes be observed to penetrate a Schwann-cell cytoplasm (figure 2) and cause dissociation of the myelin sheath. Remyelinating lesions that are clearly shown by electron microscopy are characterised by overly thin myelin sheaths in proportion to axon diameter, along with onion-bulb proliferations. In CIDP, these Schwann-cell formations are usually small and frequently difficult to see on semithin sections; they often surround bare or thinly myelinated axons. Sprouts of regeneration showing abortive attempts at repair can be seen; these clusters can be numerous in patients with long disease courses, but they are less frequent in patients with short disease courses and whose lesions are characterised by an inflammatory process with active demyelination.

The value of nerve biopsy in diagnosis of patients with supposed CIDP has been debated. However, most agree that biopsy should be done in patients with atypical clinical or neurophysiological findings, and could be considered in patients with poor response to treatment to rule out alternative diagnoses (figure 3).

**Differential diagnosis**

CIDP can be associated with some general disorders (paraproteinaemia, diabetes, thyroid dysfunction, neoplasm), probably as a result of a dysimmune process, but the association with MGUS is the most common. Indeed, some patients with CIDP have a concomitant IgG MGUS. There is no evidence from published work and our personal experience that these patients should be considered and treated differently from those without monoclonal gammopathy. In some cases of malignant gammopathies, a direct link to the neuropathy needs to be eliminated by nerve biopsy because the monoclonal component or malignant cells can sometimes infiltrate the nervous parenchyma. If the monoclonal paraprotein is an IgM, the distinction between an anti-myelin associated glycoprotein (MAG) neuropathy and CIDP is based on an anti-MAG assay. Most patients with anti-MAG neuropathy are of middle or old age and have a pure sensory ataxic or painful neuropathy, with nerve conduction studies usually showing a disproportionate lengthening of terminal latencies and a severe decrease in motor and sensory responses in the lower limbs. Although CIDP and anti-MAG neuropathy are regarded as distinct entities, there might be some overlap at the clinical, neurophysiological, and neuropathological levels; response...
to immunotherapy, however, is usually poor in patients with anti-MAG neuropathy.109 Diagnosis of the multifocal form of CIDP can be challenging, and misdiagnosis with multiple entrapment neuropathy or multifocal motor neuropathy with conduction block is common because of the frequent upper-limb predominance of the three conditions. Similarly, conduction block because of partial nerve ischaemia might erroneously suggest segmental demyelination in patients with multiple mononeuropathy due to necrotising vasculitis.110

Another challenging issue is the polyneuropathy of POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes), which is very similar to CIDP.111 It does not usually respond to conventional immunotherapy, but rather necessitates radiation therapy for solitary lesions or high-dose chemotherapy.112 Since the polyneuropathy of POEMS syndrome is usually rapidly disabling, its diagnosis can be a matter of urgency. Nerve biopsy can show specific lesions,113 but the presence of a lambda light chain along with sclerotic bone lesions is usually sufficient to make the diagnosis. Moreover, high serum concentrations of vascular endothelial growth factor are a very useful and specific diagnostic measure for this condition.114 At any age, but chiefly if patients have a predominantly distal weakness or poor response to treatment, a hereditary neuropathy such as Refsum’s disease, Charcot-Marie-Tooth disease, or transthyretin amyloid neuropathy115 should be ruled out.

Finally, the first diagnosis in some patients with CIDP will be chronic idiopathic axonal neuropathy or cryptogenic sensory polyneuropathy, and the disease will be allowed to progress without intervention despite the availability of effective therapy. After some time, any chronic demyelinating neuropathy will induce axonal loss. Patients who do not meet electrophysiological criteria for CIDP might benefit from extensive tests including nerve biopsy to look for possible CIDP, especially young patients and those with an aggressive course or prominent motor involvement, since they could benefit from immunotherapy.116

Treatment

Treatment options

Steroids have been widely used in CIDP since a single randomised controlled trial showed the efficacy of prednisone. Since then, the usefulness of steroids in CIDP has been confirmed121,122 and a controlled study showed that a 6-week course of 60 mg daily oral prednisolone with rapid tapering is as effective as one course of IVIg at 2–0 g/kg. Therefore, recent consensus guidelines concluded that “a trial of steroids should be considered in all patients with CIDP and significant disability”. Continuous oral steroid therapy is the commonest regimen used, but some have proposed pulsed high-dose treatment with dexamethasone123 or oral methylprednisolone.119 Steroid treatment seems to be beneficial in 60–70% of patients with CIDP,120 and long-term treatment needs to be individually tailored according to disease course, with careful attention paid to potential side-effects.

Efficacy of IVIg in CIDP has been shown in four randomised placebo-controlled trials121–124 and is as effective as PE125 and steroids.1 Benefit of a course of 2 g/kg IVIg over 2–5 days is usually limited in time, so repeated infusions at regular intervals are usually necessary to prevent relapse.126 Recent results have confirmed the long-term efficacy and safety of repeated infusions of IVIg.127 Again, optimum frequency and dose of IVIg infusion must be individually adjusted because need varies between patients and disease course can be subject to spontaneous remission or plateau phases. Two randomised trials have shown the efficacy of PE in patients with CIDP.128,129 Most patients can improve with this treatment (ten courses of PE over 4 weeks) in the short term, but relapse occurs usually shortly (1–2 weeks) after discontinuation.130 Therefore, PE is regarded as a second-line short-term option in patients with CIDP. Moreover, adverse effects and venous access problems seriously hamper long-term use.131

About 60–80% of patients are able to improve under any of the treatments we describe.132 Along with the

Figure 3: Proposed diagnostic strategy for CIDP

CIDP=chronic inflammatory demyelinating polyradiculoneuropathy. CMAP=compound muscle action potential. POEMS=polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes. SNAP=sensory nerve action potential. "Consider anti-MAG neuropathy if predominantly distal conduction slowing, or hereditary neuropathy if uniform slowing or multiple entrapments. "If leucocyte count is higher than 10 cells per μL, consider Lyme neuroborreliosis, HIV/AIDS infection, or lymphoma. If bone pain, lambda light chain, oedema, or skin changes are present, consider POEMS syndrome; if enlarged lymph nodes or weight loss is present, consider lymphoma.

Nerve conduction studies

EFNS/PNS electrodiagnostic criteria present* EFNS/PNS electrodiagnostic criteria absent

CSF examination shows raised protein concentrations (supportive)?

Progressive or relapsing sensory and motor neuropathy evolving over more than 2 months

CIDP

If at least one criterion present, consider:
  • Root or plexus MRI
  • Somatosensory evoked potentials
  • Nerve biopsy

The following criteria might support a diagnosis of CIDP:
  Clinical:
  • Young age
  • Relapsing course
  • Cranial nerve involvement
  • Proximal weakness
  • Upper-limb predominance
  • Diffuse areflexia

Electrodiagnostic:
  • Weakness and normal CMAPs
  • Slowed sensory conduction
  • Low median/normal sural SNAP
  • Normal SNAPs with sensory loss

Biological:
  • High CSF protein concentrations

necessity of finding a way to decrease the need for steroids or IVIg, this incomplete responsiveness prompted the search for alternative treatments for refractory and treatment-dependent patients. Immunosuppressant drugs are widely used, although evidence is weak for the efficacy of any of these treatments in CIDP. Azathioprine at fairly low doses did not show any effect in one randomised trial. Cyclophosphamide at high doses with or without stem-cell rescue might be effective in refractory patients, albeit with potentially serious side-effects. Similarly, the benefit of mycophenolate mofetil still needs to be established. Recent results did not support use of methotrexate to reduce doses of steroids or IVIg in patients with CIDP. Finally, interesting results have been obtained with conventional doses (3–5 mg/kg per day) of ciclosporin in uncontrolled studies of severe refractory CIDP. Other drugs, such as interferon beta, etanercept, or rituximab, need to be assessed in randomised trials to confirm their potential efficacy in CIDP.

Treatment choice
Choice of treatment will depend on several variables, and in particular initial disease severity, age, general health status, and potential contraindications to steroids or IVIg (figure 4). No consensus guidelines exist for which treatment to use in an individual patient, except in patients with pure motor CIDP, who should be treated with IVIg because deterioration can occur with steroids. If patients have mild symptoms, waiting to see whether deterioration occurs can be reasonable. In these cases, patients should be seen regularly, and repeated neurophysiological examination can help to decide when to start treatment. If there is no contraindication to steroids and disability is significant, starting with 1 mg/kg bodyweight or 60 mg daily prednisone for at least 4 weeks is advisable, followed by progressive tapering over months. Other patients can be treated with at least one course of 2 g/kg bodyweight IVIg over 5 days. Around 15–30% of patients will not relapse after this first course, and for patients who need additional treatment, dose and intervals between courses should be individually tailored to achieve the most cost-effective regimen. If a patient does not respond to one of these first-line therapies, switching to the other is advisable. PE or a combination of steroids and IVIg can be started if neither of these treatments proves effective. Refractory cases might need intensive immunosuppression, as has been proposed by some investigators. Long-term maintenance therapy will require careful attention because of side-effects of treatments on the one hand, and because of the risk of relapse and axonal loss on the other. No randomised trial has shown the usefulness of any immunosuppressant or targeted therapy as steroid or IVIg-sparing treatment in CIDP.

Figure 4: Proposed algorithm for CIDP treatment
At any step, if treatment fails, consider the following diagnoses: POEMS syndrome, lymphoma, amyloidosis, or sarcoidosis. If the patient still worsens under treatment or needs constant treatment maintenance, consider adding an immunosuppressant. CIDP=chronic inflammatory demyelinating polyradiculoneuropathy. EMG=electromyography. IVIg=intravenous immunoglobulin. NCS=nerve conduction studies. PE=plasma exchange. POEMS=polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes. *Almost no impairment and disability, no effect on daily life, no axon loss. †Mild to moderate impairment and disability, no serious effect on daily life (the patient can work or has near normal social life). ‡Moderate to severe impairment or disability, clear effect on daily life, active axon loss.
Long-term prognosis

Available data suggest that the long-term prognosis of CIDP is highly dependent on age at onset, clinical form of the disease, and initial response to treatment. Young patients with a rapid (subacute) onset or a monophasic course are more likely to respond to treatment and recover completely. The effect of age of onset seems especially important in elderly people, for whom full recovery after treatment is less frequent than for juvenile patients or adults aged younger than 64 years. Among the clinical variables, proximal weakness has been linked to a higher remission rate and good in patients with CIDP, especially in those with a monophasic or relapsing course. Similarly, two concordant studies have shown that a distal pattern of nerve demyelination is correlated with a good response to treatment and an improved prognosis. Overall, studies suggest that long-term outcome is usually good in patients with CIDP, especially in those with a monophasic or relapsing course. Moreover, although this variable has not been systematically assessed, experience shows that time from onset to treatment might be a key issue determining the prognosis of CIDP.

Conclusions

CIDP is a potentially disabling immune-mediated neuropathy. Its diagnosis is important because the condition is responsive to several disease-modifying therapies such as steroids, IVlg, PE, and immunosuppressants. In view of recent studies suggesting that prevalence of CIDP has been largely underestimated, we think investigation in a patient suspected of having CIDP should use all available methods, including nerve biopsy. The strategy for diagnosis of CIDP has been reviewed elsewhere and should chiefly be based on clinical presentation and electrodiagnostic evaluation (figure 3). Ultimately, a trial of steroids or IVlg seems reasonable if sufficient evidence suggests the diagnosis is at least probable. Future research is needed to identify disease markers to improve diagnosis and to develop new therapeutic strategies based on available and emerging therapies.

Conflicts of interest

LM has received honoraria, consultancies, or speaker’s fees from Bayer Schering Pharma, Biogen Idec, CSL Behring, LFB, Menarini, Merck Serono, Pfizer, and Sanofi-Aventis. CS has received honoraria for serving on the scientific advisory board of Pfizer and Lilly Pharma and for educational talks from Boehringer Ingelheim, Genzyme, Pfizer, and Schwarz-Pharma. JMV has no conflicts of interest.

References

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