

European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society — First Revision

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Background: Consensus guidelines on the definition, investigation, and treatment of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) have been previously published in *European Journal of Neurology* and *Journal of the Peripheral Nervous System*.

Objectives: To revise these guidelines.

Methods: Disease experts, including a representative of patients, considered references retrieved from MEDLINE and Cochrane Systematic Reviews published between August 2004 and July 2009 and prepared statements that were agreed in an iterative fashion.

Recommendations: The Task Force agreed on Good Practice Points to define clinical and electrophysiological diagnostic criteria for CIDP with or without concomitant diseases and investigations to be considered. The principal treatment recommendations were: (i) intravenous immunoglobulin (IVIg) (Recommendation Level A) or corticosteroids (Recommendation Level C) should be considered in sensory and motor CIDP; (ii) IVIg should be considered as the initial treatment in pure motor CIDP (Good Practice Point); (iii) if IVIg and corticosteroids are ineffective, plasma exchange (PE) should be considered (Recommendation Level A); (iv) if the response is inadequate or the maintenance doses of the initial treatment are high, combination treatments or adding an immunosuppressant or immunomodulatory drug should be considered (Good Practice Point); (v) symptomatic treatment and multidisciplinary management should be considered (Good Practice Point).

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Objectives

The aim is to update the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) guideline on management of CIDP (2005), based on newly available evidence and, where adequate evidence was not available, consensus.

Background

Several different sets of diagnostic criteria for CIDP have been created but sensitivity and specificity vary [1]. Patients who meet American Academy of Neurology (AAN) research criteria [2] certainly have CIDP, but many patients who are diagnosed with CIDP by clinicians do not meet these criteria. The EFNS/PNS consensus guideline [3] was designed to offer diagnostic criteria to balance more evenly specificity, which needs to be higher in research than clinical practice, and sensitivity which might miss disease if set too high.

Since the first treatment trial of prednisone in CIDP by Dyck *et al.* [4], a small but growing body of evidence from randomized trials has accumulated to allow evidence-based statements about treatments. These trials have been the subject of Cochrane reviews on which our recommendations are based.

Search strategy

We searched MEDLINE and the Cochrane Library from August 2004 onwards to July 2009 for articles on CIDP and ‘diagnosis’ or ‘treatment’ or ‘guideline’.

Methods for reaching consensus

Task Force members prepared draft statements about definition, diagnosis, and treatment. Evidence and recommendations were classified according to the scheme agreed for EFNS guidelines [5]. When only class IV evidence was available but consensus could be reached, the Task Force offered advice as good practice points [5]. The statements were revised and collated into a single document, which was then revised iteratively until consensus was reached.

Results

Diagnostic criteria for CIDP

In almost all diagnostic criterion sets for CIDP, the diagnosis rests upon a combination of clinical, electrodiagnostic and laboratory features with exclusions to eliminate other disorders that may appear as CIDP. In practice, criteria for CIDP have been most closely linked to criteria for detection of peripheral nerve demyelination. At least 12 sets of electrodiagnostic criteria for primary demyelination have been published to identify CIDP (for review, see [1]). The EFNS/PNS criteria [3], which include clinical and electrodiagnostic criteria, proposed new electrodiagnostic criteria which have been successfully used in subsequent clinical trials [6]. Additionally, Rajabally *et al.* [7] applied the EFNS/

PNS criteria to 151 patients with CIDP from four European centres and reported 81% sensitivity and 96% specificity.

Koski *et al.* [8] recently derived another set of diagnostic criteria. Experts reviewed the case notes including longitudinal follow-up of patients diagnosed with CIDP excluding those with paraproteins and genetic neuropathy, chronic acquired demyelinating polyneuropathy including those with paraproteins, and other chronic neuropathies. Using classification and regression tree analysis, two sets of criteria were developed: one which included electrodiagnostic criteria (recordable compound muscle action potential in $\geq 75\%$ 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 ≥ 1 limb). The diagnostic criteria were validated and shown to distinguish CIDP from Lewis–Sumner syndrome, multifocal motor neuropathy, and other chronic neuropathy types. The authors reported 83% sensitivity and 97% specificity. Although the Koski and coworkers criteria have the advantage of diagnosing CIDP when electrodiagnostic criteria are not fulfilled, all prior criteria sets included electrodiagnostic criteria. Thus, the task force was uncertain whether to adopt these criteria at this time.

Whilst the majority of those with CIDP have a chronic onset of a progressive or relapsing phase of over 8 weeks, there are patients eventually diagnosed with CIDP who have an acute onset resembling Guillain–Barré syndrome (GBS). This may occur in up to 16% of all patients with CIDP. ‘Acute-onset CIDP’ in a patient initially diagnosed as GBS is likely if deterioration continues > 2 months from onset or if ≥ 3 treatment-related fluctuations occur [9]. ‘Acute-onset CIDP’ should be suspected in patients with GBS with prominent sensory symptoms and signs at presentation [10]. Different clinical presentations have been associated with CIDP with pure motor or sensory impairment or with distal, multifocal or focal distributions. The task force considered these as atypical CIDP. Both typical and atypical CIDP are rarely associated with multifocal central nervous system demyelination, resembling multiple sclerosis [11,12].

Based on case reports, numerous diseases have been associated with CIDP. These include diabetes mellitus, IgG or IgA monoclonal gammopathy of undetermined significance, IgM monoclonal gammopathy without antibodies to myelin-associated glycoprotein, HIV infection, chronic active hepatitis, systemic lupus erythematosus or other connective tissue diseases, sarcoidosis, thyroid disease, inflammatory bowel disease

[13], membranous glomerulonephritis [14], bone marrow or solid organ transplantation [15]. There is insufficient evidence to consider CIDP associated with these diseases different from idiopathic CIDP.

Recommended strategy for investigation to confirm the diagnosis of CIDP

Based on consensus expert opinion, CIDP should be considered in any patient with a progressive symmetrical or asymmetrical polyradiculoneuropathy in whom the clinical course is relapsing and remitting or progresses for more than 2 months, especially if there are positive sensory symptoms, proximal weakness, areflexia without wasting, or preferential loss of vibration or joint position sense. Electrodiagnostic tests are mandatory and the major features suggesting a diagnosis of CIDP are listed in Table 1. The sensitivity of electrodiagnostic criteria for motor nerves may be improved by examining more than four nerves, by including proximal stimulation in the upper limbs [17,18] and by examining sensory nerves [19,20]. Somatosensory evoked potentials can be useful to demonstrate abnormal proximal sensory conduction, particularly in sensory CIDP [21,22] (Good Practice Point). If electrodiagnostic criteria for definite CIDP are not met initially, repeat study at a later date should be considered. Cerebrospinal fluid (CSF) examination, gadolinium-enhanced MRI of spinal roots, brachial or lumbar plexus, and trial of

immunotherapy with objective assessment of endpoints [23] may assist the diagnosis. Nerve biopsy can provide supportive evidence for the diagnosis of CIDP, but positive findings are not specific and negative findings do not exclude the diagnosis. The nerve selected for biopsy should be clinically and electrophysiologically affected and is usually the sural, but occasionally the superficial peroneal, superficial radial, or gracilis motor nerve. 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. There is only class IV evidence concerning all these matters. Investigations to discover possible concomitant diseases should also be considered (Good Practice Points, Table 2).

Treatment of CIDP

Corticosteroids

In one unblinded randomized controlled trial (RCT) with 28 participants, prednisone was superior to no treatment [4,24] (Class II evidence). Six weeks of oral prednisolone starting at 60 mg daily produced benefit that was not significantly different from that produced by a single course of intravenous immunoglobulin (IVIg) 2.0 g/kg [25,26] (Class II evidence). In addition, many observational studies report a beneficial effect

Table 1 Electrodiagnostic criteria

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- (1) Definite: at least one of the following
- (a) Motor distal latency prolongation $\geq 50\%$ above ULN in two nerves (excluding median neuropathy at the wrist from carpal tunnel syndrome), or
 - (b) Reduction of motor conduction velocity $\geq 30\%$ below LLN in two nerves, or
 - (c) Prolongation of F-wave latency $\geq 30\%$ above ULN in two nerves ($\geq 50\%$ if amplitude of distal negative peak CMAP $< 80\%$ of LLN values), or
 - (d) Absence of F-waves in two nerves if these nerves have distal negative peak CMAP amplitudes $\geq 20\%$ of LLN + ≥ 1 other demyelinating parameter^a in ≥ 1 other nerve, or
 - (e) Partial motor conduction block: $\geq 50\%$ amplitude reduction of the proximal negative peak CMAP relative to distal, if distal negative peak CMAP $\geq 20\%$ of LLN, in two nerves, or in one nerve + ≥ 1 other demyelinating parameter^a in ≥ 1 other nerve, or
 - (f) Abnormal temporal dispersion ($> 30\%$ duration increase between the proximal and distal negative peak CMAP) in ≥ 2 nerves, or
 - (g) Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) increase in ≥ 1 nerve (median ≥ 6.6 ms, ulnar ≥ 6.7 ms, peroneal ≥ 7.6 ms, tibial ≥ 8.8 ms)^b + ≥ 1 other demyelinating parameter^a in ≥ 1 other nerve
- (2) Probable
 $\geq 30\%$ amplitude reduction of the proximal negative peak CMAP relative to distal, excluding the posterior tibial nerve, if distal negative peak CMAP $\geq 20\%$ of LLN, in two nerves, or in one nerve + ≥ 1 other demyelinating parameter^a in ≥ 1 other nerve
- (3) Possible
 As in (1) but in only one nerve
-

To apply these criteria, the median, ulnar (stimulated below the elbow), peroneal (stimulated below the fibular head), and tibial nerves on one side are tested. If criteria are not fulfilled, the same nerves are tested at the other side, and/or the ulnar and median nerves are stimulated bilaterally at the axilla and at Erb's point. Motor conduction block is not considered in the ulnar nerve across the elbow and at least 50% amplitude reduction between Erb's point and the wrist is required for probable conduction block. Temperatures should be maintained to at least 33°C at the palm and 30°C at the external malleolus (good practice points).

CMAP, compound muscle action potential; ULN, upper limit of normal values; LLN, lower limit of normal values.

^aAny nerve meeting any of the criteria (a–g).

^bIsosé S. *et al.*, in press [16].

Table 2 Investigations to be considered

To diagnose chronic inflammatory demyelinating polyradiculoneuropathy
Electrodiagnostic studies including sensory and motor nerve conduction studies, which may be repeated, performed bilaterally, or use proximal stimulation for motor nerves
CSF examination including cells and protein
MRI spinal roots, brachial plexus, and lumbosacral plexus
Nerve biopsy
To detect concomitant diseases
(a) Recommended studies
^a Serum and urine paraprotein detection by immunofixation
Fasting blood glucose
Complete blood count
Renal function
Liver function
Antinuclear factor
Thyroid function
(b) Studies to be performed if clinically indicated
^a Skeletal survey
Oral glucose tolerance test
Borrelia burgdorferi serology
C reactive protein
Extractable nuclear antigen antibodies
Chest radiograph
Angiotensin-converting enzyme
HIV antibody
To detect hereditary neuropathy
Examination of parents and siblings
Appropriate gene testing (especially PMP22 duplication and connexin 32 mutations)
Nerve biopsy

^aRepeating these should be considered in patients who are or become unresponsive to treatment.

from corticosteroids except in pure motor CIDP, where they can be harmful [27,28]. Consequently, a trial of corticosteroids may be considered in all patients with significant disability (level C recommendation). There is no evidence and no consensus about whether to use daily or alternate day prednisolone or prednisone or intermittent high-dose monthly intravenous or oral regimens. The generally accepted dosage for prednisolone is 60 mg/day (1–1.5 mg/kg in children) as induction with maintenance therapy slowly tapering over months to years [29].

Plasma exchange (PE)

Two small double-blind RCTs with altogether 47 participants showed that PE provides significant short-term benefit in about two-thirds of patients but rapid deterioration may occur afterwards [30–32] (Class I evidence). PE might be considered as an initial treatment as neurological disability may improve rapidly (Recommendation Level A). For stabilization of CIDP, PE needs to be combined with other treatments. Because adverse events related to difficulty with venous access, use of citrate and haemodynamic changes are

not uncommon, either corticosteroids or IVIg should be considered first (Good Practice Point).

Intravenous immunoglobulin

Meta-analysis of four double blind RCTs with altogether 235 participants showed that IVIg 2.0 g/kg produces significant improvement in disability lasting 2–6 weeks [26,33–37] (Class I evidence, Recommendation Level A). A recent international study of 117 patients from 33 countries showed that the efficacy of IVIg (2.0 g/kg baseline loading dose divided over 2–4 days followed by maintenance infusions of 1.0 g/kg over 1–2 days every 3 weeks) was maintained over 24 weeks and possibly over 48 weeks with greater improvement of disability and less relapses when compared to placebo [38]. Because the benefit from IVIg is short lived, treatment needs to be repeated at intervals and doses that need to be judged on an individual basis [29]. Crossover trials have shown no significant short-term difference between IVIg and PE [39] or between IVIg and prednisolone [25], but the samples were too small to establish equivalence (both Class II evidence).

Immunosuppressive agents

Randomized controlled trials have been reported only for azathioprine and methotrexate. Azathioprine (2 mg/kg) showed no benefit when added to prednisone in 14 patients for 9 months [40,41], but the trial was probably too short and the dose too low to be able to show a benefit. No significant benefit was observed when methotrexate 15 mg daily for 24 weeks was compared with placebo in 62 patients treated with IVIg or corticosteroids [6]. Immunosuppressive agents (Table 3) are often used together with corticosteroids to reduce the need for IVIg or PE or to treat patients who have not responded to any of these treatments, but there is only class IV evidence on which to base this practice [29,41]. More research is needed before any recommendation can be made. In the meantime, immunosuppressant treatment may be considered when

Table 3 Immunosuppressant and immunomodulatory drugs that have been reported to be beneficial in chronic inflammatory demyelinating polyradiculoneuropathy (Class IV evidence [29,41])

Alemtuzemab
Azathioprine
Cyclophosphamide
Ciclosporin
Etanercept
Interferon- α
Interferon- β 1a
Mycophenolate mofetil
Methotrexate
Rituximab
Stem cell transplantation (haematopoietic)

the response to corticosteroids, IVIg or PE is inadequate (Good Practice Point).

Interferons

One crossover trial of interferon beta 1a for 12 weeks did not detect significant benefit [42], but the trial only included 10 patients. In a more recent non-randomized open study of intramuscular interferon- β 1a 30 mcg weekly 7 of 20 patients treated showed clinical improvement, 10 remained stable and three worsened [43]. An open study of interferon- α showed benefit in nine of 14 treatment-resistant patients [44] and there have been other favourable smaller reports. In the absence of evidence, interferon treatment may be considered when the response to corticosteroids, IVIg or PE is inadequate (Good Practice Point).

Initial management (Good Practice Points)

Patients with very mild symptoms that do not or only slightly interfere with activities of daily living may be monitored without treatment. Treatment with corticosteroids or IVIg should be offered to patients with moderate or severe disability. PE is similarly effective but may be less tolerated. IVIg is often the first choice as improvement can be fast. The usual first dose of IVIg is 2.0 g/kg given as 2 g/kg over 2–5 consecutive days. Contraindications to corticosteroids will influence the choice towards IVIg and vice versa. For pure motor CIDP, IVIg treatment should be the first choice and if corticosteroids are used, patients should be monitored closely for deterioration.

Therapy of patients with CIPD requires individualized assessment of the treatment response. For patients starting on corticosteroids, a course of up to 12 weeks

on their starting dose should be considered before deciding whether there is no treatment response. If there is a response, tapering the dose slowly to a low maintenance level over 1 or 2 years and eventual withdrawal should be considered. Patients starting on IVIg should be closely monitored to objectify occurrence and duration of response to the first course before embarking on further treatment. Between 15% and 30% of patients require only a single course of IVIg.

Long-term management (Good Practice Points)

No evidence-based guideline can be given as none of the trials systematically assessed long-term management. IVIg given in doses of 1 g/kg over 1–2 days every 3 weeks has been shown to be efficacious over 24 (and possibly 48) weeks with improvement of grip strength, disability and health-related quality of life [38,45], but the appropriate dose needs to be individualized (usually 0.4–1.2 g/kg every 2–6 weeks) [29]. If a patient becomes stable on a regimen of intermittent IVIg, the dose (or, perhaps, frequency) of IVIg should be reduced periodically to establish the need for ongoing therapy because patients may need less IVIg than they receive or in fact none at all. In a recent international study, the IVIg dose could be reduced by over 20% without deterioration in almost half of the patients [6]. If frequent high-dose IVIg is required, addition of corticosteroids or an immunosuppressive agent should be considered, but there is not sufficient evidence to recommend a particular drug. Patients benefiting from long-term IVIg treatment who become refractory to IVIg may respond again after a short course of PE [46]. Approximately 15% of patients fail to respond to any of the proposed treatments.

Table 4 Clinical diagnostic criteria

(1) Inclusion criteria

(a) Typical CIDP

Chronically progressive, stepwise, or recurrent symmetric proximal and distal weakness and sensory dysfunction of all extremities, developing over at least 2 months; cranial nerves may be affected; and

Absent or reduced tendon reflexes in all extremities

(b) Atypical CIDP (still considered CIDP but with different features)

One of the following, but otherwise as in (a) (tendon reflexes may be normal in unaffected limbs):

Predominantly distal (distal acquired demyelinating symmetric, DADS) or

Asymmetric [multifocal acquired demyelinating sensory and motor neuropathy (MADSAM), Lewis–Sumner syndrome] or

Focal (e.g., involvement of the brachial or lumbosacral plexus or of one or more peripheral nerves in one upper or lower limb)

Pure motor or

Pure sensory (including chronic immune sensory polyradiculopathy affecting the central process of the primary sensory neuron)

(2) Exclusion criteria

Borrelia burgdorferi infection (Lyme disease), diphtheria, drug or toxin exposure probably to have caused the neuropathy

Hereditary demyelinating neuropathy

Prominent sphincter disturbance

Diagnosis of multifocal motor neuropathy

IgM monoclonal gammopathy with high titre antibodies to myelin-associated glycoprotein

Other causes for a demyelinating neuropathy including POEMS syndrome, osteosclerotic myeloma, diabetic and non-diabetic lumbosacral radiculoplexus neuropathy. PNS lymphoma and amyloidosis may occasionally have demyelinating features

Table 5 Supportive criteria

1. Elevated CSF protein with leukocyte count $< 10/\text{mm}^3$ (level A recommendation)
2. MRI showing gadolinium enhancement and/or hypertrophy of the cauda equina, lumbosacral or cervical nerve roots, or the brachial or lumbosacral plexuses (level C recommendation)
3. Abnormal sensory electrophysiology in at least one nerve (good practice points):
 - a. Normal sural with abnormal median (excluding median neuropathy at the wrist from carpal tunnel syndrome) or radial sensory nerve action potential (SNAP) amplitudes; or
 - b. Conduction velocity $< 80\%$ of lower limit of normal ($< 70\%$ if SNAP amplitude $< 80\%$ of lower limit of normal); or
 - c. Delayed somatosensory evoked potentials without central nervous system disease
4. Objective clinical improvement following immunomodulatory treatment (level A recommendation)
5. Nerve biopsy showing unequivocal evidence of demyelination and/or remyelination by electron microscopy or teased fibre analysis (good practice point)

General treatment

There is a dearth of evidence concerning general aspects of treatment for symptoms of CIDP such as pain and fatigue. There is also a lack of research into the value of exercise and occupational and physical therapy in the management of CIDP. Evidence is limited concerning immunizations. International and national support groups offer information and support to patients (<http://www.gbs-cidp.org>) (Good Practice Point).

Recommendations

Good Practice Points for defining diagnostic criteria for CIDP:

1. Clinical: typical and atypical CIDP (Table 4)
2. Electrodiagnostic: definite, probable and possible CIDP (Table 1)
3. Supportive: including CSF, MRI, nerve biopsy and treatment response (Table 5)
4. Categories: definite, probable, and possible CIDP (Table 6)

Recommendations for treatment

For induction of treatment

1. IVIg (level A recommendation) or corticosteroids (level C recommendation) should be considered in sensory and motor CIDP in the presence of disabling

Table 6 Diagnostic categories

Definite CIDP
Clinical criteria 1 (a or b) and 2 with electrodiagnostic criterion 1; or
Probable CIDP + at least one supportive criterion; or
Possible CIDP + at least two supportive criteria
Probable CIDP
Clinical criteria 1 (a or b) and 2 with electrodiagnostic criterion 2; or
Possible CIDP + at least one supportive criterion
Possible CIDP
Clinical criteria 1 (a or b) and 2 with electrodiagnostic criterion 3
CIDP (definite, probable, possible) associated with concomitant diseases.

symptoms. PE is similarly effective (level A recommendation) but may be less tolerated. The presence of relative contraindications to any of these treatments should influence the choice (good practice point). The advantages and disadvantages should be explained to the patient who should be involved in the decision making (Good Practice Point).

2. The advantages and disadvantages should be explained to the patient who should be involved in the decision making (Good Practice Point).
3. In pure motor CIDP, IVIg should be considered as the initial treatment (Good Practice Point).

For maintenance treatment

1. If the first-line treatment is effective, continuation should be considered until the maximum benefit has been achieved and then the dose reduced to find the lowest effective maintenance dose (Good Practice Point).
2. If the response is inadequate or the maintenance doses of the initial treatment (IVIg, steroids, or PE) result in adverse effects, the other first-line treatment alternatives should be tried before considering combination treatments or adding an immunosuppressant or immunomodulatory drug may be considered, but there is no sufficient evidence to recommend any particular drug (Table 3) (Good Practice Point).
3. Advice about foot care, exercise, diet, driving and life style management should be considered. Neuropathic pain should be treated with drugs according to the EFNS guideline on treatment of neuropathic pain [47]. Depending on the needs of the patient, orthoses, physiotherapy, occupational therapy, psychological support and referral to a rehabilitation specialist should be considered (Good Practice Points).
4. Information about patient support groups should be offered (Good Practice Point).

Conflicts of interest

The following authors have reported conflicts of interest: D. Cornblath, personal honoraria from Merck,

Pfizer, Mitsubishi Pharma, Sangamo, Bristol-Myers Squibb, Eisai, Octapharma, Sun Pharma, Acorda, DP Clinical, Geron, Exelixis, Johnson&Johnson, Genzyme, Cebix, Abbott, CSL Behring, Pfizer, Schwartz Biosciences, Avigen, FoldRx; R.D.M. Hadden, personal honoraria from Janssen-Cilag and Talecris; A. Hahn, personal honoraria from Baxter, Bayer, and Biogen-Idec, Talecris; I. Illa, personal none, departmental research grant from Grifols; C. Koski, personal honoraria from Baxter, CSL and Talecris; J. M. Léger, personal none, departmental research grants or honoraria from Biogen-Idec, Baxter, LFB, Octapharma; E. Nobile-Orazio, personal honoraria from Kedrion, Grifols, Baxter, and LFB (and he has been commissioned by Kedrion and Baxter to give expert opinions to the Italian Ministry of Health on the use of IVIg in dysimmune neuropathies); J. Pollard, personal none, departmental research grants from Biogen-Idec, Schering; P. van Doorn, personal none, departmental research grants or honoraria from Baxter, Talecris, and Bayer. The other authors have nothing to declare.

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