

EFNS/PNS CIDP GUIDELINES

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

Joint Task Force of the EFNS and the PNS†

Abstract Background: Numerous sets of diagnostic criteria have sought to define chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and randomized trials and systematic reviews of treatment have been published. Objectives: The aim of this guideline was to prepare consensus guidelines on the definition, investigation, and treatment of CIDP. Methods: Disease experts and a representative of patients considered references retrieved from MEDLINE and Cochrane Systematic Reviews in May 2004 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 as follows: (1) intravenous immunoglobulin (IVIg) or corticosteroids should be considered in sensory and motor CIDP (level B recommendation); (2) IVIg should be considered as the initial treatment in pure motor CIDP (good practice point); (3) if IVIg and corticosteroids are ineffective, plasma exchange should be considered (level A recommendation); (4) 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); and (5) symptomatic treatment and multidisciplinary management should be considered (good practice point).

Key words: chronic inflammatory demyelinating polyradiculoneuropathy, definition, diagnosis, guidelines, treatment

Address correspondence to: Richard A. C. Hughes, Department of Clinical Neuroscience, King's College London School of Medicine, Guy's Hospital, London SE1 1UL, UK. E-mail: richard.a.hughes@kcl.ac.uk

*Anticipated date for updating this guideline: Not later than October 2008.

†Membership of Task Force: Richard A. C. Hughes (Chair), UK; Pierre Bouche, France; David R. Cornblath, USA; Eileen Evers, UK; Robert D. Hadden, UK; Angelika F. Hahn, Canada; Isabel Illa, Spain; Carol L. Koski, USA; Jean-Marc Léger, France; Eduardo Nobile-Orazio, Italy; John D. Pollard, Australia; Claudia Sommer, Germany; Peter Van den Bergh, Belgium; Pieter A. van Doorn, Netherlands; Ivo N. van Schaik, Netherlands.

Objectives

The aim of this guideline was to construct guidelines for the definition, diagnosis, and treatment of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) based on the available evidence and, where adequate evidence was not available, consensus.

Background

The first proposal for diagnostic clinical criteria for CIDP was published by Dyck *et al.* (1975; 1982) and included progressive course at 6 months, usually

slowed nerve conduction velocities (and occurrence of conduction block), spinal fluid albumino-cytological dissociation, and nerve biopsy demonstrating segmental demyelination and remyelination, subperineurial or endoneurial edema, and perivascular inflammation. Exclusion criteria were associated diseases, monoclonal gammopathy, and evidence of hereditary neuropathy. This descriptive proposal was the basis for a formalized set of criteria (Barohn *et al.*, 1989). Mandatory inclusion and exclusion criteria reduced the required disease progression time to 2 months. Major laboratory criteria consisted of nerve biopsy abnormalities, motor conduction slowing to <70% in two nerves, and spinal fluid protein >450 mg/L. Fulfillment of all criteria was necessary for a definite diagnosis. Fulfillment of only two or one laboratory criteria led to the diagnostic categories of probable and possible, respectively. Research criteria were proposed by the American Academy of Neurology (AAN) in 1991 (*Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force, 1991*). Fulfillment of clinical, physiological, pathological, and spinal fluid criteria led to three diagnostic categories (definite, probable, and possible). Fulfillment of pathological criteria was necessary for a definite diagnosis. Physiological criteria for primary demyelination were very detailed but restrictive when applied clinically because three of four nerve conduction parameters were required to be abnormal, even for the diagnosis of possible CIDP. By contrast, the criteria for partial motor conduction block and abnormal temporal dispersion were probably not restrictive enough, as suggested by American Association of Neuromuscular & Electrodiagnostic Medicine (AAEM) consensus criteria for the diagnosis of partial conduction block (Olney, 1999). Patients who meet AAN research criteria certainly have CIDP, but many patients who are diagnosed with CIDP by clinicians do not meet these criteria. In research studies of therapy of CIDP, several different sets of diagnostic criteria for CIDP have been created. These have been reviewed in an addendum to this article, which is available on the Peripheral Nerve Society (PNS) website (http://pns.ucsd.edu/CIDP_Guidelines_Supplement.pdf). For the present needs of the EFNS and PNS we offer the present diagnostic criteria to balance more evenly specificity (which needs to be higher in research than clinical practice) and sensitivity (which might miss treatable disease if set too high).

Since the first treatment trial of prednisone of Dyck *et al.* (1982), a small body of evidence from randomized trials has accumulated to allow some evidence-based statements about treatments. These trials have been the subject of Cochrane reviews on which we have based some of our recommendations.

Search Strategy

We searched MEDLINE from 1980 onwards to July 24, 2004 for articles on chronic inflammatory demyelinating polyradiculoneuropathy and 'diagnosis' or 'treatment' or 'guideline' but found that the personal databases of Task Force members were more useful. We also searched the Cochrane Library in September 2004.

Methods for Reaching Consensus

Pairs of Task Force members prepared draft statements about definition, diagnosis, and treatment, which were considered at a meeting at the EFNS congress in September 2004. Evidence was classified as class I–IV and recommendations as level A–C according to the scheme agreed for EFNS guidelines (Brainin *et al.*, 2004). When only class IV evidence was available but consensus could be reached, the Task Force offered advice as good practice points (Brainin *et al.*, 2004). The statements were revised and collated into a single document, which was then revised iteratively until consensus was reached.

Results

Diagnostic criteria for CIDP

New criteria are currently being developed for defining CIDP from first principles by a group led by C. L. Koski, but in the meantime, the Task Force was obliged to develop their own criteria based on consensus. Criteria for CIDP are closely linked to criteria for detection of peripheral nerve demyelination. At least 12 sets of electrodiagnostic criteria for primary demyelination have been published, not only to identify CIDP (for review, see Van den Bergh and Piéret, 2004). Nerve biopsy, usually sural sensory nerve biopsy, is considered useful for confirming the diagnosis, but it is a mandatory criterion for a definite diagnosis of CIDP only in the AAN criteria (*Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force, 1991*). The available evidence indicates that sural 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. Increased spinal fluid protein occurs in at least 90% of patients. Therefore, increased protein levels can be used as a supportive but not mandatory criterion for the diagnosis. Integration of magnetic resonance imaging (MRI) abnormalities of nerve roots, plexuses, and peripheral nerves in diagnostic criteria for CIDP may enhance both sensitivity and specificity and may therefore be useful as a supportive criterion for the diagnosis. Because most patients with CIDP respond to

steroids, plasma exchange (PE), or intravenous immunoglobulin (IVIg), a positive response to treatment may support the diagnosis and has been suggested as another diagnostic criterion (Latov, 2002). There is only class IV evidence concerning all these matters. Nevertheless, the Task Force agreed on good practice points to define clinical and electrophysiological diagnostic criteria for CIDP with or without concomitant diseases (Tables 1–6).

Investigation of CIDP

On the basis of 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 2. Minor electrodiagnostic features are greater abnormality of median than sural nerve sensory action potential, reduced sensory nerve conduction velocities, and F-wave chronodispersion. If electrodiagnostic criteria for definite CIDP are not met initially, repeat electrodiagnostic testing in more nerves or, at a later date, cerebrospinal fluid (CSF) examination, MRI of the spinal roots, brachial or lumbar plexus, and nerve biopsy should be considered (Table 6). The nerve for biopsy should be clinically and electrophysiologically affected and is usually the sural, but occasionally the superficial peroneal, superficial radial, or gracilis motor nerve. Sometimes, the choice of nerve may be

assisted by MRI. The minimal examination should include paraffin sections, immunohistochemistry, and semithin resin sections. Electron microscopy and teased fiber preparations are highly desirable. There are no specific appearances. Supportive features are endoneurial edema, macrophage-associated demyelination, demyelinated and to a lesser extent remyelinated nerve fibers, onion bulb formation, endoneurial mononuclear cell infiltration, and variation between fascicles. During the diagnostic workup, investigations to discover possible concomitant diseases should be considered (good practice points, Table 6).

Treatment of CIDP

Corticosteroids

In one unblinded randomized controlled trial (RCT) with 28 participants, prednisone was superior to no treatment (Dyck *et al.*, 1982; Mehndiratta and Hughes, 2001) (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 IVIg 2.0 g/kg (Hughes *et al.*, 2001; van Schaik *et al.*, 2004) (class II evidence). However, there are many observational studies reporting a beneficial effect from corticosteroids except in pure motor CIDP, in which they have sometimes appeared to have a harmful effect (Donaghy *et al.*, 1994). Consequently, a trial of corticosteroids should be considered in all patients with significant disability (level B 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 (Bromberg and Carter, 2004).

Table 1. 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 |
| One of the following, but otherwise as in typical CIDP (tendon reflexes may be normal in unaffected limbs) |
| Predominantly distal weakness (distal acquired demyelinating symmetric, DADS) |
| Pure motor or sensory presentations, including chronic sensory immune polyradiculoneuropathy affecting the central process of the primary sensory neuron (Sinnreich <i>et al.</i> , 2004) |
| Asymmetric presentations (multifocal acquired demyelinating sensory and motor, MADSAM, Lewis–Sumner syndrome) |
| Focal presentations (e.g., involvement of the brachial plexus or of one or more peripheral nerves in one upper limb) |
| Central nervous system involvement (may occur with otherwise typical or other forms of atypical CIDP) |
| (2) Exclusion criteria |
| Diphtheria, drug or toxin exposure likely to have caused the neuropathy |
| Hereditary demyelinating neuropathy, known or likely because of family history, foot deformity, mutilation of hands or feet, retinitis pigmentosa, ichthyosis, liability to pressure palsy |
| Presence of sphincter disturbance |
| Multifocal motor neuropathy |
| Antibodies to myelin-associated glycoprotein |

CIDP, chronic inflammatory demyelinating polyradiculoneuropathy.

Table 2. Electrodiagnostic criteria.

-
- (1) Definite: at least one of the following
 - (a) At least 50% prolongation of motor distal latency above the upper limit of normal values in two nerves, or
 - (b) At least 30% reduction of motor conduction velocity below the lower limit of normal values in two nerves, or
 - (c) At least 20% prolongation of F-wave latency above the upper limit of normal values in two nerves (>50% if amplitude of distal negative peak CMAP <80% of lower limit of normal values), or
 - (d) Absence of F-waves in two nerves if these nerves have amplitudes of distal negative peak CMAPs at least 20% of lower limit of normal values + at least one other demyelinating parameter* in at least one other nerve, or
 - (e) Partial motor conduction block: at least 50% amplitude reduction of the proximal negative peak CMAP relative to distal, if distal negative peak CMAP at least 20% of lower limit of normal values, in two nerves, or in one nerve + at least one other demyelinating parameter* in at least one other nerve, or
 - (f) Abnormal temporal dispersion (>30% duration increase between the proximal and distal negative peak CMAP) in at least two nerves, or
 - (g) Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) of at least 9 ms in at least one nerve + at least one other demyelinating parameter* in at least one other nerve
 - (2) Probable
 - At least 30% amplitude reduction of the proximal negative peak CMAP relative to distal, excluding the posterior tibial nerve, if distal negative peak CMAP at least 20% of lower limit of normal values, in two nerves, or in one nerve + at least one other demyelinating parameter* in at least one other nerve
 - (3) Possible
 - As in (1) but in only one nerve
-

CMAP, compound muscle action potential. 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. Temperatures should be maintained to at least 33°C at the palm and 30°C at the external malleolus (good practice points).

*Any nerve meeting any of the criteria (a–g).

Table 3. Supportive criteria.

-
1. Elevated cerebrospinal fluid protein with leukocyte count <10/mm³ (level A recommendation)
 2. Magnetic resonance imaging 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. Nerve biopsy showing unequivocal evidence of demyelination and/or remyelination in ≥5 fibers by electron microscopy or in >6 of 50 teased fibers
 4. Clinical improvement following immunomodulatory treatment (level A recommendation)
-

Table 4. CIDP in association with concomitant diseases.

One of the following is present:

- (a) Conditions in which, in some cases, the pathogenesis and pathology are thought to be the same as in CIDP
 - Diabetes mellitus
 - HIV infection
 - Chronic active hepatitis
 - IgG or IgA monoclonal gammopathy of undetermined significance
 - IgM monoclonal gammopathy without antibodies to myelin-associated glycoprotein
 - Systemic lupus erythematosus or other connective tissue disease
 - Sarcoidosis
 - Thyroid disease
 - (b) Conditions in which the pathogenesis and pathology may be different from CIDP
 - Borrelia burgdorferi* infection (Lyme disease)
 - IgM monoclonal gammopathy of undetermined significance with antibodies to myelin-associated glycoprotein*
 - POEMS syndrome
 - Osteosclerotic myeloma
 - Others (vasculitis, hematological and non-hematological malignancies, including Waldenström’s macroglobulinemia and Castleman’s disease)
-

CIDP, chronic inflammatory demyelinating polyradiculoneuropathy.

*Patients with antibodies to myelin-associated glycoprotein are considered to have a disease with a different mechanism and are excluded (Table 1).

Plasma exchange

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 (Dyck et al., 1986; Hahn et al., 1996a; Mehndiratta et al., 2004) (class I evidence). PE might be considered as an initial treatment (level A recommendation). However,

Table 5. 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 |

CIDP, chronic inflammatory demyelinating polyradiculoneuropathy.

because adverse events related to difficulty with venous access, use of citrate, and hemodynamic 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 113 participants showed that IVIg 2.0 g/kg

Table 6. Investigations to be considered.

| |
|--|
| To identify CIDP |
| Nerve conduction studies |
| Cerebrospinal fluid cells and protein |
| MRI spinal roots, brachial plexus, and lumbosacral plexus |
| Nerve biopsy |
| To detect concomitant diseases |
| Serum and urine paraprotein detection by immunofixation (repeating this should be considered in patients who are or become unresponsive to treatment) |
| Oral glucose tolerance test |
| Complete blood count |
| Renal function |
| Liver function |
| HIV antibody |
| Hepatitis B and C serology |
| <i>Borrelia burgdorferi</i> serology |
| C reactive protein |
| Antinuclear factor |
| Extractable nuclear antigen antibodies |
| Thyroid function |
| Angiotensin-converting enzyme |
| Chest radiograph |
| Skeletal survey (repeating this should be considered in patients who are or become unresponsive to treatment) |
| To detect hereditary neuropathy |
| Examination of parents and siblings |
| <i>PMP22</i> gene duplication or deletion (especially if slowing of conduction is uniform and no evidence of partial motor conduction block or abnormal temporal dispersion) |
| Gene mutations known to cause CMT1 or hereditary neuropathy with liability to pressure palsies |

CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CMT1, Charcot-Marie-Tooth disease type 1.

produces significant improvement in disability lasting 2–6 weeks (*van Doorn et al., 1990; Vermeulen et al., 1993; Hahn et al., 1996b; Mendell et al., 2001; van Schaik et al., 2004*) (class I evidence). Because the benefit from IVIg is short lived, treatment, which is expensive, needs to be repeated at intervals that need to be judged on an individual basis. Crossover trials have shown no significant short-term difference between IVIg and PE (*Dyck et al., 1994*) or between IVIg and prednisolone (*Hughes et al., 2001*), but the samples were too small to establish equivalence (both are class II evidence).

Immunosuppressive agents

No RCTs have been reported for any immunosuppressive agent except for azathioprine, which showed no benefit when added to prednisone in 14 patients (*Dyck et al., 1985; Hughes et al., 2004*). Immunosuppressive agents (Table 7) 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 (*Hughes et al., 2004*). More research is needed before any recommendation can be made. In the meantime, immunosuppressant treatment may be considered when the response to corticosteroids, IVIg, or PE is inadequate (good practice point).

Interferons

One crossover trial of interferon-β1a (IFN-β1a) for 12 weeks did not detect significant benefit (*Hadden et al., 1999*), but the trial only included 10 patients. In a more recent non-randomized open study of intramuscular IFN-β1a 30 μg weekly, seven of 20 patients treated showed clinical improvement, 10 patients remained stable, and three patients worsened (*Vallat et al., 2003*). An open study of IFN-α showed benefit in nine of 14 treatment-resistant patients (*Gorson et al., 1998*), and there have been other favorable smaller reports. In the absence of evidence, IFN treatment

Table 7. Immunosuppressant and immunomodulatory drugs that have been reported to be beneficial in CIDP [class IV evidence, see *Hughes et al. (2004)* for review].

| |
|-----------------------|
| Anti-CD20 (rituximab) |
| Azathioprine |
| Cyclophosphamide |
| Ciclosporin |
| Etanercept |
| Interferon-α |
| Interferon-β1a |
| Mycophenolate mofetil |

CIDP, chronic inflammatory demyelinating polyradiculoneuropathy.

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, which do not or only slightly interfere with activities of daily living, may be monitored without treatment. Urgent treatment with corticosteroids or IVIg should be considered for patients with moderate or severe disability, e.g., when hospitalization is required or ambulation is severely impaired. Common initial doses of corticosteroids are prednisolone or prednisone 1 mg/kg or 60 mg daily, but there is a wide variation in practice (*Bromberg and Carter, 2004*). The usual first dose of IVIg is 2.0 g/kg given as 0.4 g/kg on 5 consecutive days. Contraindications to corticosteroids will influence the choice toward 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.

Long-term management (good practice points)

No evidence-based guidelines can be given because none of the trials systematically assessed long-term management. Each patient requires assessment on an individual basis. 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 to a low maintenance level over 1 or 2 years and eventual withdrawal should be considered. For patients starting on IVIg, observation to discover the occurrence and duration of any response to the first course should be considered before embarking on further treatment. Between 15 and 30% of patients do not need further treatment. If patients respond to IVIg and then their condition worsens, further and ultimately repeated doses should be considered. Repeated doses may be given over 1 or 2 days. The amount per course needs to be titrated according to the individual response. Repeat courses may be needed every 2–6 weeks. If a patient becomes stable on a regime of intermittent IVIg, the dose per course should be reduced before the frequency of administration is lowered. If frequent high-dose IVIg is needed, the addition of corticosteroids or an immunosuppressive agent should be considered. Approximately 15% of patients fail to respond to any of these treatments. Some probably do not appear to respond because of severe secondary axonal degeneration which takes years to improve.

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 physiotherapy and the advice that should be offered concerning immunizations. International and national support groups offer information and support, and physicians may consider putting patients in touch with these organizations at <http://www.guillain-barre.com> or <http://www.gbs.org.uk> (good practice point).

Recommendations

Good practice points for defining diagnostic criteria for CIDP

- 1 Clinical: typical and atypical CIDP (Table 1);
- 2 Electrodiagnostic: definite, probable, and possible CIDP (Table 2);
- 3 Supportive: including CSF, MRI, nerve biopsy, and treatment response (Table 3);
- 4 CIDP in association with concomitant diseases (Table 4);
- 5 Categories: definite, probable, and possible CIDP with or without concomitant diseases (Table 5)

Good practice points for diagnostic tests

- 1 Electrodiagnostic tests are recommended in all patients (good practice point);
- 2 CSF, MRI, and nerve biopsy should be considered in selected patients (good practice point);
- 3 Concomitant diseases should be considered in all patients, but the choice of tests will depend on the clinical circumstances (Table 6).

Recommendations for treatment

For induction of treatment

- 1 IVIg or corticosteroids should be considered in sensory and motor CIDP in the presence of troublesome symptoms (level B recommendation). The presence of relative contraindications to either treatment should influence the choice (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).
- 4 If IVIg and corticosteroids are ineffective, PE should be considered (level A recommendation).

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 are high, combination treatments or adding an immunosuppressant or immunomodulatory drug may be considered (Table 7) (good practice point).
 - 3 Advice on foot care, exercise, diet, driving, and lifestyle management should be considered. Neuropathic pain should be treated with drugs according to EFNS guideline on treatment of neuropathic pain (*Attal N, 2005, in preparation*). 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 to those who would like it (good practice point).

Conflicts of Interest

The following authors have reported conflicts of interest: R. Hughes, personal none, departmental research grants or honoraria from Bayer, Biogen-Idec, Schering-Laboratoire Français du Biofractionnement (LFB), and Kedrion; D. Cornblath, personal honoraria from Aventis Behring and Baxter; A. Hahn, personal honoraria from Baxter, Bayer, and Biogen-Idec; C. Koski, personal honoraria from American Red Cross, Baxter, Bayer, and ZLB-Behring; 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 and Bayer. The other authors have nothing to declare.

References

- Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force (1991). Research criteria for the diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). *Neurology* 41:617–618.
- Barohn RJ, Kissel JT, Warmolts JR, Mendell JR (1989). Chronic inflammatory demyelinating polyradiculoneuropathy. Clinical characteristics, course, and recommendations for diagnostic criteria. *Arch Neurol* 46:878–884.
- Brainin M, Barnes M, Baron J-C, Gilhus NE, Hughes R, Selmaj K, Waldemar G (2004). Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations 2004. *Eur J Neurol* 11:577–581.
- Bromberg MB, Carter O (2004). Corticosteroid use in the treatment of neuromuscular disorders: empirical and evidence-based data. *Muscle Nerve* 30:20–37.
- Donaghy M, Mills KR, Boniface SJ, Simmons J, Wright I, Gregson N, Jacobs J (1994). Pure motor demyelinating neuropathy: deterioration after steroid treatment and improvement with intravenous immunoglobulin. *J Neurol Neurosurg Psychiatry* 57:778–783.
- Dyck PJ, Daube J, O'Brien P, Pineda A, Low PA, Windebank AJ, Swanson C (1986). Plasma exchange in chronic inflammatory demyelinating polyradiculoneuropathy. *N Engl J Med* 314:461–465.
- Dyck PJ, Lais AC, Ohta M, Bastron JA, Okazaki H, Groover RV (1975). Chronic inflammatory polyradiculoneuropathy. *Mayo Clin Proc* 50:621–651.
- Dyck PJ, Litchy WJ, Kratz KM, Suarez GA, Low PA, Pineda AA, Windebank AJ, Karnes JL, O'Brien PC (1994). A plasma exchange versus immune globulin infusion trial in chronic inflammatory demyelinating polyradiculoneuropathy. *Ann Neurol* 36:838–845.
- Dyck PJ, O'Brien PC, Oviatt KF, Dinapoli RP, Daube JR, Bartleson JD, Mokri B, Swift T, Low PA, Windebank AJ (1982). Prednisone improves chronic inflammatory demyelinating polyradiculoneuropathy more than no treatment. *Ann Neurol* 11:136–141.
- Dyck PJ, O'Brien P, Swanson C, Low P, Daube J (1985). Combined azathioprine and prednisone in chronic inflammatory demyelinating polyneuropathy. *Neurology* 35:1173–1176.
- Gorson KC, Ropper AH, Clark BD, Dew RB III, Simovic D, Allam G (1998). Treatment of chronic inflammatory demyelinating polyneuropathy with interferon-alpha 2a. *Neurology* 50:84–87.
- Hadden RD, Sharrack B, Bensa S, Soudain SE, Hughes RAC (1999). Randomized trial of interferon beta-1a in chronic inflammatory demyelinating polyradiculoneuropathy. *Neurology* 53:57–61.
- Hahn AF, Bolton CF, Pillay N, Chalk C, Benstead T, Brill V, Shumak K, Vandervoort MK, Feasby TE (1996a). Plasma-exchange therapy in chronic inflammatory demyelinating polyneuropathy (CIDP): a double-blind, sham-controlled, cross-over study. *Brain* 119:1055–1066.
- Hahn AF, Bolton CF, Zochodne D, Feasby TE (1996b). Intravenous immunoglobulin treatment (IVIg) in chronic inflammatory demyelinating polyneuropathy (CIDP): a double-blind placebo-controlled cross-over study. *Brain* 119:1067–1078.
- Hughes RAC, Bensa S, Willison HJ, Van den Bergh P, Comi G, Illa I, Nobile-Orazio E, van Doorn PA, Dalakas M, Bojar M, Swan AV, and the Inflammatory Neuropathy Cause and Treatment Group (2001). Randomized controlled trial of intravenous immunoglobulin versus oral prednisolone in chronic inflammatory demyelinating polyradiculoneuropathy. *Ann Neurol* 50:195–201.
- Hughes RAC, Swan AV, van Doorn PA (2004). Cytotoxic drugs and interferons for chronic inflammatory demyelinating polyradiculoneuropathy (Update). *Cochrane Database Syst Rev* 4:CD003280.
- Latov N (2002). Diagnosis of CIDP. *Neurology* 59:S2–S6.
- Mehdiratta MM, Hughes RAC (2001). Corticosteroids for chronic inflammatory demyelinating polyradiculoneuropathy. *Cochrane Database Syst Rev* 3:CD002062.

- Mehndiratta MM, Hughes RAC, Agarwal P (2004). Plasma exchange for chronic inflammatory demyelinating polyradiculoneuropathy (Cochrane Review). *Cochrane Database Syst Rev* 3:CD003906.
- Mendell JR, Barohn RJ, Freimer ML, Kissel JT, King W, Nagaraja HN, Rice R, Campbell WW, Donofrio PD, Jackson CE, Lewis RA, Shy M, Simpson DM, Parry GJ, Rivner MH, Thornton CA, Bromberg MB, Tandan R, Harati Y, Giuliani MJ (2001). Randomized controlled trial of IVIg in untreated chronic inflammatory demyelinating polyradiculoneuropathy. *Neurology* 56:445–449.
- Olney RK (1999). Guidelines in Electrodiagnostic Medicine: consensus criteria for the diagnosis of partial conduction block. *Muscle Nerve* 22:S225–S229.
- Sinnreich M, Klein CJ, Daube JR, Engelstad J, Spinner RJ, Dyck PJB (2004). Chronic immune sensory polyradiculoneuropathy: a possibly treatable sensory ataxia. *Neurology* 63:1662–1669.
- Vallat JM, Hahn AF, Leger JM, Cros DP, Magy L, Tabaraud F, Bouche P, Preux PM (2003). Interferon beta-1a as an investigational treatment for CIDP. *Neurology* 60:S23–S28.
- Van den Bergh PYK, Piéret F (2004). Electrodiagnostic criteria for acute and chronic inflammatory demyelinating polyradiculoneuropathy. *Muscle Nerve* 29:565–574.
- van Doorn PA, Brand A, Strengers PF, Meulstee J, Vermeulen M (1990). High-dose intravenous immunoglobulin treatment in chronic inflammatory demyelinating polyneuropathy: a double-blind, placebo-controlled, crossover study. *Neurology* 40:209–212.
- van Schaik IN, Winer JB, de Haan R, Vermeulen M (2004). Intravenous immunoglobulin for chronic inflammatory demyelinating polyneuropathy. *Cochrane Database Syst Rev* 2:CD001797.
- Vermeulen M, van Doorn PA, Brand A, Strengers PFW, Jennekens FGI, Busch HFM (1993). Intravenous immunoglobulin

treatment in patients with chronic inflammatory demyelinating polyneuropathy: a double blind, placebo controlled study. *J Neurol Neurosurg Psychiatry* 56:36–39.

Appendix: Guidelines

Aim of guidelines

This guideline has been produced by the Task Force members of the European Federation of Neurological Societies (EFNS) who are also members of the Peripheral Nerve Society (PNS). Additional non-European members of the Task Force were appointed on the recommendation of the Board of Directors of the PNS. The Task Force adopted the methods and classification scheme of the EFNS (see Appendix Tables 1 and 2). Where only class IV evidence existed, a consensus opinion was expressed as a good practice point (*Brainin et al., 2004*). "The aim of an EFNS neurological management guideline is to provide evidence-based guidance for clinical neurologists, other health care professionals and health care providers about important aspects of management of neurological disease. It provides the view of an expert task force appointed by the Scientific Committee of the EFNS. It represents a peer-reviewed statement of minimum desirable standards for the guidance of practice based on the best available evidence. It is not intended to have legally binding implications in individual cases" (*Brainin et al., 2004*). This guideline is not intended to have implications regarding reimbursement.

Appendix Table 1. Evidence classification scheme for a therapeutic intervention.

Class I: An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required:

- (a) randomization concealment;
- (b) primary outcome(s) is/are clearly defined;
- (c) exclusion/inclusion criteria are clearly defined;
- (d) adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias;
- (e) relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class II: Prospective matched-group cohort study in a representative population with masked outcome assessment that meets (a)–(e) above or a randomized controlled trial in a representative population that lacks one criteria (a–e)

Class III: All other controlled trials. (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion

Rating of recommendations

- Level A rating (established as effective, ineffective, or harmful) requires at least one convincing class I study or at least two consistent, convincing class II studies
- Level B rating (probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence
- Level C (possibly effective, ineffective, or harmful) rating requires at least two convincing class III studies

Appendix Table 2. Evidence classification scheme for a diagnostic measure.

Class I: A prospective study in a broad spectrum of persons with the suspected condition, using a 'gold standard' for case definition, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class II: A prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by gold standard) compared with a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class III: Evidence provided by a retrospective study where either persons with the established condition or controls are of a narrow spectrum, and where test is applied in a blinded evaluation

Class IV: Any design where test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls)

Rating of recommendations

- Level A rating (established as useful/predictive or not useful/predictive) requires at least one convincing class I study or at least two consistent, convincing class II studies
- Level B rating (established as probably useful/predictive or not useful/predictive) requires at least one convincing class II study or overwhelming class III evidence
- Level C rating (established as possibly useful/predictive or not useful/predictive) requires at least two convincing class III studies