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EFNS TASK FORCE ARTICLE

European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of multifocal motor neuropathy*

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Several diagnostic criteria for multifocal motor neuropathy have been proposed in recent years and a beneficial effect of intravenous immunoglobulin (IVIg) and various other immunomodulatory drugs has been suggested in several trials and uncontrolled studies. The objectives were to prepare consensus guidelines on the definition, investigation and treatment of multifocal motor neuropathy. Disease experts and a patient representative considered references retrieved from MEDLINE and the Cochrane Library in July 2004 and prepared statements which were agreed in an iterative fashion. The Task Force agreed good practice points to define clinical and electrophysiological diagnostic criteria for multifocal motor neuropathy and investigations to be considered. The principal recommendations and good practice points were: (i) IVIg (2 g/kg given over 2–5 days) should be considered as the first line treatment (level A recommendation) when disability is sufficiently severe to warrant treatment. (ii) Corticosteroids are not recommended (good practice point). (iii) If initial treatment with IVIg is effective, repeated IVIg treatment should be considered (level C recommendation). The frequency of IVIg maintenance therapy should be guided by the individual response (good practice point). Typical treatment regimens are 1 g/kg every 2–4 weeks or 2 g/kg every 4–8 weeks (good practice point). (iv) If IVIg is not or not sufficiently effective then immunosuppressive treatment may be considered. Cyclophosphamide, ciclosporin, azathioprine, interferon beta1a, or rituximab are possible agents (good practice point). (v) Toxicity makes cyclophosphamide a less desirable option (good practice point).

Objectives

To construct guidelines for the definition, diagnosis and treatment of multifocal motor neuropathy (MMN) based on the available evidence and, where adequate evidence was not available, consensus.

Background

Patients with a pure motor, asymmetric neuropathy with multifocal conduction blocks (CB) have been reported from 1986 onwards [1–3]. Pestronk *et al.* [4] first introduced the term multifocal motor neuropathy and highlighted the association with IgM anti-ganglioside GM1 antibodies and the response to immune modulating therapies. The diagnosis of MMN is based on clinical, laboratory and electrophysiological characteristics [5–8]. Several diagnostic criteria for this neuropathy have been proposed [9–11]. These criteria share the following clinical features: slowly progressive, asymmetric, predominantly distal weakness without objective loss of sensation in the distribution of two or more individual peripheral nerves, and absence of

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upper motor neuron signs. The hallmark of the disease is the presence of multifocal CB on electrophysiological testing outside the usual sites of nerve compression [5,12–15]. CB is a reduction in the amplitude or area (or both) of the compound muscle action potential (CMAP) obtained by proximal versus distal stimulation of motor nerves in the absence of or with only focal abnormal temporal dispersion [7,12,16]. The extent of reduction of the CMAP amplitude and/or area necessary for CB are still matters of debate. For this guideline we present clinical and electrophysiological diagnostic criteria based on published criteria and consensus agreed upon by the task force.

Multifocal motor neuropathy is a treatable disorder. A beneficial effect of various immunomodulatory drugs has been suggested in several uncontrolled studies [4,17–25], and were reviewed in a Cochrane systematic review [26]. Four trials have shown high dose intravenous immunoglobulin (IVIg) therapy to be effective in MMN and this treatment currently is considered the standard treatment for MMN [27–30]. These trials have also been reviewed in a Cochrane systematic review [31]. This small body of evidence allowed some evidence-based statements about treatment.

Search strategy

We searched MEDLINE from 1980 onwards on July 24 2004 for articles on ('multifocal motor neuropathy' 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 in September 2004. Evidence was classified as class I to IV and recommendations as level A to C according to the scheme agreed for European Federation of Neurological Societies guidelines (EFNS) [32]. When only class IV evidence was available but consensus could be reached the Task Force has offered advice as good practice points. The statements were revised and collated into a single document which was then revised iteratively until consensus was reached.

Results

Diagnostic criteria for MMN

The Task Force developed their own diagnostic criteria based on the published criteria [5–11]. The clinical criteria are listed in Table 1. The main clinical features are weakness without objective sensory loss, slowly progressive or stepwise progressive course, asymmetric involvement of two or more nerves, and absence of upper motor neuron signs. Additional clinical criteria have also been proposed: no more than seven of eight affected limb regions, predominance of weakness in the upper limbs, decreased or absent tendon reflexes, and age of onset between 20 and 65 [6]. These additional features were associated with a more frequent response to immunoglobulin therapy but it was unclear how they influenced diagnostic accuracy, and the absence of some of these features is not uncommon in patients with otherwise typical MMN [8]. The Task Force decided not to include an age limit in the criteria. The presence of CB in motor nerve fibres is the hallmark of the disease.

The first papers defined CB as a 20–30% amplitude or area reduction if the distal CMAP duration did not exceed 15% greater than normal. In one of the main papers concerning the diagnostic criteria of MMN grading of CB was defined as definite or probable and in the other as definite, probable and possible [9–11]. There is only class IV evidence concerning all these matters. Nevertheless the Task Force agreed good practice points to define clinical and electrophysiological diagnostic criteria for MMN (Tables 1 and 2).

Investigation of MMN

Based on consensus expert opinion, consideration of MMN should enter the differential diagnosis of any

Table 1 Clinical criteria for MMN

Core criteria (both must be present)
1. Slowly progressive or stepwise progressive, asymmetric limb weakness, or motor involvement having a motor nerve distribution in at least two nerves, for more than 1 month[a]
2. No objective sensory abnormalities except for minor vibration sense abnormalities in the lower limbs
Supportive clinical criteria
3. Predominant upper limb involvement[b]
4. Decreased or absent tendon reflexes in the affected limb[c]
5. Absence of cranial nerve involvement[d]
6. Cramps and fasciculations in the affected limb
Exclusion criteria
7. Upper motor neuron signs
8. Marked bulbar involvement
9. Sensory impairment more marked than minor vibration loss in the lower limbs
10. Diffuse symmetric weakness during the initial weeks
11. Laboratory: CSF protein >1 g/l

[a]Usually more than 6 months; [b]At onset, predominant lower limb involvement account for nearly 10% of the cases; [c]Slightly increased tendon reflexes, in particular in the affected arm have been reported and do not exclude the diagnosis of MMN provided criterion 7 is met; [d]12th nerve palsy has been reported.

Table 2 Electrophysiological criteria for conduction block[a]

1. Definite motor CB[a]: negative CMAP area reduction on proximal versus distal stimulation of at least 50% whatever the nerve segment length (median, ulnar and peroneal). Negative CMAP amplitude on stimulation of the distal part of the segment with motor CB must be $>20\%$ of the lower limit of normal and >1 mV (baseline negative peak) and an increase of proximal negative peak CMAP duration must be $\leqslant 30\%$
2. Probable motor CB[a]: negative CMAP area reduction of at least 30% over a long segment of an upper limb nerve with an increase of proximal negative peak CMAP duration $\leqslant 30\%$; or negative CMAP area reduction of at least 50% (same as definite) with an increase of proximal negative peak CMAP duration $>30\%$
3. Normal sensory nerve conduction in upper limb segments with CB and normal sensory nerve action potential amplitudes (see exclusion criteria)

[a]Evidence for conduction block must be found at sites distinct from common entrapment or compression syndromes.

patient with a slowly or stepwise progressive asymmetrical limb weakness without objective sensory abnormalities, upper motor neuron or bulbar signs or symptoms. MMN should be differentiated from motor neuron disease, entrapment neuropathies, hereditary neuropathy with liability to pressure palsy, Lewis–Sumner syndrome, and chronic inflammatory demyelinating polyneuropathy, in particular its purely motor variant [1,3,9,33–43].

Clinical examination and electrodiagnostic tests are mandatory and the features suggesting a diagnosis of MMN are listed under diagnostic criteria. A family history should be obtained. Other tests which can support the diagnosis MMN are CSF protein <1 g/l, anti-ganglioside GM1 antibodies [44–46] and increased signal intensity on T2-weighted MRI scans of the brachial plexus [6,9,22]. CSF, anti-ganglioside GM1 antibodies and MRI scans of the brachial plexus are not normally needed for patients fulfilling the clinical and electrodiagnostic criteria of MMN. Nerve biopsies are not routinely performed in MMN but can be useful in detecting an alternative cause [47,48]. Needle EMG, serum and urine paraprotein detection by immunofixation [49], thyroid function [50], creatine kinase [6,20], CSF cells and protein [6,51] are investigations which can be helpful to discover concomitant disease or exclude other possible causes. This list is not complete and additional investigations should be guided by the clinical findings.

Treatment of MMN

The treatment options for people with MMN are sparse. In contrast to the response in CIDP, MMN does usually not respond to steroids or plasma exchange, and patients may worsen when they receive these treatments [7,52–54].

The efficacy of intravenous immunoglobulin (IVIg) has been suggested by many open, uncontrolled studies. Four randomized controlled double-blind trials of IVIg for treating MMN have been done [27–30]. These four RCTs included a total of 45 patients with MMN and have been summarized in a Cochrane systematic review [31]. Intravenous immunoglobulin treatment is superior to placebo in inducing an improvement in muscle strength in patients with MMN (NNT 1.4, 95% CI 1.1–1.8)). As weakness is the only determinant of disability in patients with MMN, it is to be expected that in patients whose muscle strength improves after IVIg treatment, disability will improve as well. In a large retrospective study elevated anti-ganglioside GM1 antibodies and definite CB were significantly correlated with a favourable response to IVIg [6]. In approximately a third of patients prolonged remission (>12 months) was established with IVIg alone; approximately half of patients need repeated IVIg infusions and, of them, half need additional immunosuppressive treatment [25]. Effectiveness declines during prolonged treatment, even when dosage is increased, probably because of ongoing axonal degeneration [55,56]. However, in one retrospective study, treatment with higher than normal maintenance doses of IVIg (1.6–2.0 g/kg given over 4–5 days) promoted reinnervation, decreased the number of CBs and prevented axonal degeneration in 10 MMN patients for up to 12 years [57].

Uncontrolled studies suggest a beneficial effect of cyclophosphamide [4,17,18,20–22], interferon beta1a [23,24], and azathioprine [19,25]. There is conflicting evidence for rituximab [58,59]. Cyclophosphamide was not recommended by one group of experts because concern exists about its toxicity and lack of evidence of efficacy in MMN [10].

Recommendations and good practice points

Diagnostic criteria (good practice points)

1 Clinical: the two core criteria and all exclusion criteria should be met (Table 1)
2 Electrodiagnostic: definite or probable CB in at least two nerves (Table 2)
3 Supportive: anti-GM1 antibodies, MRI, CSF and treatment response (Table 3)
4 Categories: definite and probable MMN (Table 4)

Table 3 Supportive criteria

1. Elevated IgM anti-ganglioside GM1 antibodies (level A recommendation)
2. Magnetic resonance imaging showing gadolinium enhancement and/or hypertrophy of the brachial plexuses (good practice point)
3. Clinical improvement following IVIg treatment (good practice point)

Table 4 Diagnostic categories

Definite MMN
Clinical criteria 1, 2 and 7–11 and electrophysiological criteria 1 and 3 in one nerve
Probable MMN
Clinical criteria 1, 2 and 7–11 and electrophysiological criteria 2 and 3 in two nerves
Clinical criteria 1, 2 and 7–11, and electrophysiological criteria 2 and 3 in one nerve, and at least one supportive criteria 1–3 (Table 3)

Diagnostic tests (good practice points)

1 Clinical examination and electrodiagnostic tests should be considered in all patients

2 Anti-ganglioside GM1 antibody testing, MRI of the brachial plexus, and CSF examination should be considered in selected patients

3 Investigations to discover concomitant disease or exclude other possible causes should be considered but the choice of tests will depend on the individual circumstances

Treatment

1 IVIg (2 g/kg given over 2–5 days) should be considered as the first line treatment (level A recommendation) when disability is sufficiently severe to warrant treatment

2 Corticosteroides are not recommended (good practice point)

3 If an initial treatment with IVIg is effective, repeated IVIg treatment should be considered in selected patients (level C recommendation). The frequency of IVIg maintenance therapy should be guided by the response (good practice point). Typical treatment regimens are 1 g/kg every 2–4 weeks, or 2 g/kg every 1–2 months (good practice point)

4 If IVIg is not or not sufficiently effective then immunosuppressive treatment may be considered. Cyclophosphamide, ciclosporin, azathioprine, interferon beta1a, or rituximab are possible agents (good practice point)

5 Toxicity makes cyclophosphamide a less desirable option (good practice point)

Anticipated date for updating this guideline

Not later than October 2008.

Conflicts of interest

The following authors have reported conflicts of interest: RAC Hughes personal none, departmental research grants or honoraria from Bayer, Biogen-Idec, Schering-LFB and Kedrion, D Cornblath personal honoraria from Aventis Behring and Baxter, C Koski personal honoraria from American Red Cross, Baxter, Bayer, ZLB-Behring, JM Léger personal none, departmental research grants or honoraria from Biogen-Idec, Baxter, Laboratoire Français du Biofractionnement (LFB), Octapharma, E Nobile-Orazio personal honoraria from Kedrion, Grifols, Baxter, 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 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.

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Appendix: Guidelines

Aim of guidelines

This guideline has been produced by a Task Force of members of the European Federation Neurological Societies who are also members of the Peripheral Nerve Society. Additional non-European members of the Task Force were appointed on the recommendation of the Board of Directors of the Peripheral Nerve Society. The Task Force adopted the methods and classification scheme of the EFNS (see tables). Where only class IV evidence existed a consensus opinion was expressed as a good practice point (32). '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 pros pective 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 amongst 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

Appendix table 1. (continued)

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