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EFNS TASK FORCE ARTICLE

European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of paraproteinaemic demyelinating neuropathies: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society*

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Background. Paraprotein-associated neuropathies have heterogeneous clinical, neurophysiological, neuropathological and haematological features. *Objectives*. To prepare evidence-based and consensus guidelines on the clinical management of patients with both a demyelinating neuropathy and a paraprotein (paraproteinaemic demyelinating neuropathy, PDN). *Methods*. Search of MEDLINE and the Cochrane library, review of evidence and consensus agreement of an expert panel. *Recommendations*. In the absence of adequate data, evidence based recommendations were not possible but the panel agreed the following good practice points: (1) Patients with PDN should be investigated for a malignant plasma cell dyscrasia. (2) The paraprotein is more likely to be causing the neuropathy if the paraprotein is immunoglobulin (Ig)M, antibodies are present in serum or on biopsy, or the clinical phenotype is chronic distal sensory neuropathy. (3) Patients with IgM PDN usually have predominantly distal and sensory impairment, with prolonged distal motor latencies, and often anti-myelin associated glycoprotein antibodies. (4) IgM PDN sometimes responds to immune therapies. Their potential benefit should be balanced against their possible side-effects and the usually slow disease progression. (5) IgG and IgA PDN may be indistinguishable from chronic inflammatory demyelinating polyradiculoneuropathy, clinically, electrophysiologically, and in response to treatment. (6) For POEMS syndrome, local irradiation or resection of an isolated plasmacytoma, or melphalan with or without corticosteroids, should be considered, with haemato-oncology advice.

Objectives

To construct clinically useful guidelines for the diagnosis, investigation and treatment of patients with both a demyelinating neuropathy and a paraprotein (paraproteinaemic demyelinating neuropathy, PDN), based on the available evidence and, where evidence was not available, consensus.

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Background

The neuropathies associated with paraproteins (monoclonal gammopathy, monoclonal immunoglobulin) are difficult to classify, because of heterogeneity in the clinical and electrophysiological features of the neuropathy, the class, immunoreactivity, and pathogenicity of the paraprotein, and the malignancy of the underlying plasma cell dyscrasia [1–3]. In the absence of an agreed diagnostic classification, it is not yet possible to provide specific diagnostic criteria, and treatment trials are more difficult to interpret.

Many patients with PDN have a neuropathy that is indistinguishable from chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and there is no consensus as to whether these should be considered the same or different diseases. We aim to be as inclusive as possible, but have chosen to concentrate in this guideline on demyelinating neuropathies. Axonal neuropathies with a paraprotein are not part of the scope of these guidelines but are mentioned briefly in *other neuropathies with a paraprotein* (page 5). As both paraproteins and neuropathies are common, it may be uncertain whether the paraprotein is causing the neuropathy or coincidental.

Search strategy

We searched MEDLINE from 1980 onwards on July 24, 2004 for articles on ['paraprotein(a)emic demyelinating neuropathy' AND ('diagnosis' OR 'treatment' OR 'guideline')] and used the personal databases of Task Force members. We searched the Cochrane Library in September 2004.

Methods for reaching consensus

Pairs of task force members prepared draft statements about classification, investigation and treatment which were considered at a meeting in September 2004. Evidence was classified as class I–IV and recommendations as level A–C [4]. 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 collated into a single document, which was revised iteratively until unanimous consensus was reached.

Results

Any diagnostic classification of PDN must take account of the dimensions of clinical phenotype, immunoglobulin (Ig) class, presence of malignancy, antibodies to myelin associated glycoprotein (MAG), electrophysiological phenotype, and causal relationship of the paraprotein to the neuropathy (Table 1). There is no consensus in the literature as to which should take precedence in classification. Here we distinguish IgM from IgG and IgA PDN, because IgM PDN tends to have a typical clinical phenotype, pathogenic antibodies, a causal relationship between paraprotein and neuropathy, and the evidence about treatment is different. Nevertheless, there is significant overlap between the clinical and electrophysiological features of the neuropathy with different types of paraprotein. The website gives a table summarizing some of the published evidence on investigation of PDN (Appendix S1).

Table 1 Dimensions in classification of paraproteinaemic neuropathy

Clinical phenotype
Immunoglobulin class
Monoclonal gammopathy of undetermined significance or malignant plasma cell dyscrasia
Presence of antibodies to myelin associated glycoprotein
Electrophysiology
Likelihood that paraprotein is causing the neuropathy

Investigation and classification of the paraprotein

Background

Whilst some paraproteins are detected by standard serum protein electrophoresis (SPEP), both serum immunoelectrophoresis (SIEP) and serum immunofixation electrophoresis (SIFE) are more sensitive techniques which detect lower paraprotein concentrations [5,6]. Heavy (IgM, IgG or IgA) and light chain (kappa or lambda) classes should be identified. A paraprotein indicates an underlying disease of plasma cells in bone marrow, which may be malignant (and may itself require treatment) or a monoclonal gammopathy of uncertain significance (MGUS, Table 2 [7]). For detection of myeloma bone lesions, X-ray skeletal survey has similar sensitivity to Tc99m sesta-2-methoxy-isobutyl-isonitrile (MIBI), and both are superior to conventional radionuclide scintigraphy [8–10], although these studies did not distinguish osteolytic from osteosclerotic myeloma.

Recommended investigations

Table 3 suggests investigations to be considered in all patients with a paraprotein. SIFE should be performed

Table 2 Classification of haematological conditions with a paraprotein

(1) Malignant monoclonal gammopathies
(a) Multiple myeloma [*overt*, *asymptomatic* (*smouldering*), *non-secretory*, *or osteosclerotic*]
(b) Plasmacytoma (*solitary*, *extramedullary*, *multiple solitary*)
(c) Malignant lymphoproliferative disease:
(i) Waldenström's macroglobulinaemia
(ii) Malignant lymphoma
(iii) Chronic lymphocytic leukaemia
(d) Heavy chain disease
(e) Primary amyloidosis (AL) *(with or without myeloma)*
(2) Monoclonal gammopathy of undetermined significance

Table 3 Investigation of a paraprotein

The following should be considered in all patients with a paraprotein
(a) Serum immunofixation electrophoresis
(b) Physical examination for peripheral lymphadenopathy, hepatosplenomegaly, macroglossia and signs of POEMS syndrome (see Other neuropathy syndromes associated with paraproteinaemia)
(c) Full blood count, renal and liver function, calcium, phosphate, erythrocyte sedimentation rate, C-reactive protein, uric acid, beta 2-microglobulin, lactate dehydrogenase, rheumatoid factor and serum cryoglobulins
(d) Total immunoglobulin (Ig)G, IgA and IgM concentrations
(e) Random urine collection for the detection of Bence–Jones protein (free light chains), and, if positive, 24 h urine collection for protein quantification
(f) Radiographic X-ray skeletal survey [including skull, pelvis, spine, ribs and long bones (shoulder to wrist and hip to ankle)] to look for lytic or sclerotic lesions. If this is negative, then a Tc99m sestaMIBI (2-methoxy-isobutyl-isonitrile) scan if high degree of suspicion of myeloma (IgA lambda and IgG lambda paraproteins are more frequently associated with osteosclerotic myeloma)
(g) Ultrasound or computed tomography of abdomen and chest (to detect lymphadenopathy and hepatosplenomegaly)
(h) Consultation with a haematologist and bone marrow examination (morphology, immunophenotype and biopsy)

Table 4 Definition of monoclonal gammopathy of undetermined significance (MGUS)

(1) IgM–MGUS is defined by the presence of all of the following:
(a) No lymphoplasmacytic infiltration on bone marrow biopsy, or equivocal infiltration with negative phenotypic studies
(b) No signs or symptoms suggesting tumour infiltration (e.g. constitutional symptoms, hyperviscosity syndrome and organomegaly)
(c) No evolution to malignant lymphoproliferative disease requiring treatment within 12 months from first detection of paraprotein
(2) IgG or IgA–MGUS is defined by the presence of all of the following:
(a) Monoclonal component ≤30 g/l
(b) Bence-Jones proteinuria ≤1 g/24 h
(c) No lytic lesions in bone
(d) No anaemia, hypercalcaemia, or chronic renal insufficiency
(e) Bone marrow plasma cell infiltration <10%
(f) No evolution to myeloma or other lymphoproliferative disease within 12 months after first detection of paraprotein

in all cases of known paraprotein to define the heavy and light chain type, in all acquired demyelinating neuropathies, and if a paraprotein is suspected but not detected by standard SPEP.

Definition of MGUS

The definition of MGUS is different for IgM from IgG and IgA (Table 4). Patients with IgM MGUS have alternatively been classified as 'IgM-related disorders' if they have clinical features attributable to the paraprotein (such as neuropathy), or as 'asymptomatic IgM monoclonal gammopathy' [11].

Good prognostic features suggesting a low risk of malignant transformation are:

(i) *IgM MGUS:* normal full blood count (in particular, haemoglobin > 12.5 g/dl, lymphocytes $<4 \times 10^9$/l), absent (or only a small amount of) Bence–Jones protein in the urine, erythrocyte sedimentation rate (ESR) < 40 mm/h, monoclonal protein < 30 g/l [12].

(ii) *IgG/IgA MGUS:* absent (or only small amount of) Bence–Jones protein in the urine, no reduction of polyclonal serum immunoglobulin concentrations, ESR < 40 mm/h, <5% bone marrow plasma cell infiltration, monoclonal protein <20 g/l [13, 14].

Typical syndromes of paraproteinaemic demyelinating neuropathy

The most common types of PDN are those with demyelinating neuropathy and MGUS without non-neurological symptoms. The neuropathy is defined as demyelinating if it satisfies electrophysiological criteria for CIDP [15]. If there are subtle features of demyelination not meeting these criteria, further investigations should be considered to confirm evidence of immune-mediated demyelination (see Cerebrospinal fluid and nerve biopsy).

IgM PDN

Clinical phenotype. Most patients with IgM PDN have the 'distal acquired demyelinating symmetrical' (DADS) clinical phenotype of predominantly distal, chronic (duration over 6 months), slowly progressive, symmetric, predominantly sensory impairment, with ataxia and relatively mild or no weakness, and often tremor (class IV evidence) [1,16–20]. The DADS phenotype is most strongly associated with IgM anti-MAG antibodies, and some patients have more prominent ataxia with impairment predominantly of vibration and joint position sense. However, the clinical features do not correlate exactly with the paraprotein type: a

Table 5 Electrophysiological features associated with the distal acquired demyelinating symmetric (DADS) clinical phenotype

(a) Uniform symmetrical reduction of conduction velocities; more severe sensory than motor involvement
(b) Disproportionately prolonged distal motor latency (DML). This may be quantified by low-terminal latency index (TLI). TLI is defined as distal velocity/intermediate velocity = distal distance/(motor conduction velocity × DML). TLI ≤0.25 is suggestive of the DADS phenotype
(c) Severe involvement of peroneal nerves
(d) Absent sural potential (i.e. less likely to have the 'abnormal median, normal sural' sensory action potential pattern)
(e) Partial motor conduction block (i.e. proximal/distal compound muscle action potential amplitude ratio < 0.5) is very rare

minority of patients with IgM PDN have proximal weakness with the phenotype more typical of IgG/IgA PDN, and some DADS patients do not have a paraprotein so that they are classified as a variant of CIDP [21].

Electrophysiology. Patients with the DADS clinical phenotype usually meet the definite electrophysiological criteria proposed for CIDP. They may also have additional specific electrophysiological features indicating uniform symmetrical and predominantly distal reduced conduction velocity, usually without conduction block (Table 5, adapted from [17, 22, 23)].

Antibodies to myelin-associated glycoprotein and other neural antigens. Almost 50% of patients with IgM PDN have high titres of anti-MAG IgM antibodies [24], more commonly associated with kappa than lambda light chains, and this is the best defined syndrome of PDN [25]. Testing of antibodies to neural antigens should be considered in patients with IgM PDN (Table 6).

IgG or IgA PDN

Patients with IgG or IgA PDN usually have both proximal and distal weakness, with motor and sensory impairment, indistinguishable clinically and electrophysiologically from typical CIDP. They usually have more rapid progression than DADS [19,20,26]. However, a minority of patients with IgG or IgA PDN have the DADS clinical phenotype and associated electrophysiological features. In patients with IgG or IgA paraprotein, no specific antibody has been consistently associated with demyelinating neuropathy, and therefore there is no need for antibody testing.

Other neuropathy syndromes associated with paraproteinaemia

This section briefly mentions other types of neuropathy associated with a paraprotein, including those with haematological malignancy, systemic symptoms or axonal electrophysiology, although these are not part of the main guidelines and not discussed in detail.

POEMS

Polyneuropathy, organomegaly, endocrinopathy, m-band and skin changes (POEMS) syndrome usually has an underlying osteosclerotic myeloma, with IgA or IgG lambda paraprotein, but is sometimes associated with Castleman's disease. POEMS neuropathy has similar clinical features to CIDP. Many patients are initially thought to have CIDP or ordinary PDN, until POEMS is suggested by the presence of systemic features such as sclerotic bone lesions, hepatosplenomegaly, lymphadenopathy, endocrinopathy, papilloedema, skin changes (hypertrichosis, hyperpigmentation, diffuse skin thickening, finger clubbing, dermal haemangiomas, and white nail beds) and oedema [27].

Electrophysiology often shows a mixed demyelinating and axonal picture [28]. Features that help to distinguish POEMS from CIDP include: reduced motor nerve conduction velocities more marked in intermediate than distal nerve segments (terminal latency index 0.35–0.5, the opposite of the DADS phenotype); rarity of conduction block; and compound muscle action potential amplitudes smaller in lower than upper limbs [29].

Table 6 Antibodies against neural antigens in patients with IgM PDN

(A) In patients with IgM PDN, testing for antibodies to myelin associated glycoprotein (MAG) should be considered. These antibodies may be considered to be:
(i) definite if Western Blot against human MAG positive at a titre of 1/6400 or more
(ii) probable if enzyme-linked immunosorbent assay (ELISA) against sulphated glucuronyl paragloboside (SGPG) or human MAG positive at high titre (usually 1/6400 or more, but depends on the laboratory and system used)
(iii) possible if presence of complement fixing antibodies to peripheral nerve homogenate, or IgM binding to myelin detected by indirect immunohistochemistry or immunofluorescence of nerve sections (these methods are not specific and may also be positive in patients with high-titre anti-sulphatide IgM), or lower titres by (i) or (ii).
(B) In patients with IgM PDN without anti-MAG antibodies, testing for IgM antibodies against other neural antigens, including gangliosides GQ1b, GM1, GD1a and GD1b, SGPG and sulphatide, may be considered. The presence of these antibodies increases the probability of, but does not prove, a pathogenetic link between the paraprotein and the neuropathy. Their diagnostic relevance is not defined
(C) In suspected CANOMAD, testing for anti-ganglioside antibodies should be considered (preferably by thin-layer chromatography, but anti-GQ1b ELISA may be adequate)

There is no specific diagnostic test for POEMS, but if it is suspected then the following investigations should be considered: endocrine blood tests (thyroid, follicle stimulating hormone, luteinizing hormone, glucose, prolactin, and morning cortisol); ultrasound or computed tomography of abdomen and chest (organomegaly and lymphadenopathy); skin biopsy (may show distinctive glomeruloid haemangiomas in the dermis [30]); serum vascular endothelial growth factor [31]; and nerve biopsy (may show uncompacted myelin lamellae [32]).

Waldenström's macroglobulinaemia

Waldenström's macroglobulinaemia is defined by the presence of an IgM (usually kappa) paraprotein (irrespective of concentration) and a bone marrow biopsy showing infiltration by lymphoplasmacytic lymphoma with a predominantly intertrabecular pattern, supported by appropriate immunophenotypic studies [11]. The associated-neuropathy is clinically heterogeneous, but sometimes associated with anti-MAG reactivity and clinical features of IgM anti-MAG neuropathy [33].

CANOMAD

The syndrome of Chronic Ataxic Neuropathy with Ophthalmoplegia, IgM Monoclonal gammopathy, cold Agglutinins and Disialoganglioside (IgM anti-GD1b/GQ1b) antibodies (CANOMAD) is a rare neuropathy similar to chronic Fisher syndrome, with mixed demyelinating and axonal electrophysiology [34].

Other neuropathies with a paraprotein

Axonal neuropathy is often present in patients with MGUS, but the pathogenesis and causal relationship vary and it will not be considered further in these guidelines. A few patients with cryoglobulinaemia [35] or primary (AL) amyloidosis [36] have demyelinating neuropathy, although far more have axonal neuropathy. AL-amyloidosis should be suspected in the presence of prominent neuropathic pain or dysautonomia, and may be demonstrated by biopsy of rectum, bone marrow, kidney or nerve, or fat aspirate.

In patients with lytic multiple myeloma (usually associated with IgA or IgG kappa or lambda paraprotein) neuropathy may be caused by heterogeneous mechanisms, including amyloidosis, metabolic and toxic insults, and cord or root compression due to vertebral collapse from lytic lesions [37]. Subacute weakness similar to Guillain-Barré syndrome may be caused by extensive infiltration of nerves or roots by lymphoma or leukaemia [38].

Is the paraprotein causing the neuropathy?

A causal relationship is more likely with an IgM than an IgG or IgA paraprotein [15]. Our Task Force has classified CIDP with a paraprotein separately from CIDP without a paraprotein, but there is still no consensus amongst experts as to whether IgG or IgA PDN may merely be CIDP with a co-incidental paraprotein. Malignant paraproteins may also cause a neuropathy, but the mechanism is incompletely understood. The only published criteria of causality were in a study in which all patients had the DADS phenotype, demyelinating physiology and MGUS (IgM or IgG) [23]. We extensively modified these criteria, and propose factors which suggest whether or not the paraprotein is likely to be causing the neuropathy (Table 7).

Cerebrospinal fluid and nerve biopsy

Cerebrospinal fluid (CSF) examination and nerve biopsy may be helpful in selected circumstances (Table 8, good practice points), but are not usually

Table 7 Causal relationship between paraprotein and demyelinating neuropathy

(1) Highly probable if IgM paraprotein [monoclonal gammopathy of uncertain significance (MGUS) or Waldenström's] and:
- (a) high titres of anti-MAG or anti-GQ1b antibodies; or
- (b) nerve biopsy shows IgM or complement deposits on myelin, or widely-spaced myelin on electron microscopy.

(2) Probable if either:
- (a) IgM paraprotein (MGUS or Waldenström's) with high titres of IgM antibodies to other neural antigens (GM1, GD1a, GD1b, GM2, sulphatide, etc.), and slowly progressive predominantly distal symmetrical sensory neuropathy; or
- (b) IgG or IgA paraprotein and nerve biopsy evidence (as in 1(b) but with IgG or IgA deposits).

(3) Less likely when any of the following are present in a patient with MGUS and without anti-MAG antibodies (diagnosis may be described as 'CIDP with coincidental paraprotein'):
- (a) time to peak of neuropathy <6 months;
- (b) relapsing/remitting or monophasic course;
- (c) Cranial nerves involved (except CANOMAD);
- (d) asymmetry;
- (e) history of preceding infection;
- (f) Abnormal median with normal sural sensory action potential;
- (g) IgG or IgA paraprotein without biopsy features in 2(b);

Table 8 Cerebrospinal fluid (CSF) examination and nerve biopsy

(1) CSF examination is most likely to be helpful in the following situations
(a) In patients with borderline demyelinating or axonal electrophysiology or atypical phenotype, where the presence of raised CSF protein would help to suggest that the neuropathy is immune-mediated
(b) The presence of malignant cells would confirm lymphoproliferative infiltration
(2) Nerve biopsy (usually sural nerve) is most likely to be helpful when the following conditions are being considered:
(a) amyloidosis
(b) vasculitis (e.g. due to cryoglobulinaemia)
(c) malignant lymphoproliferative infiltration of nerves or
(d) IgM PDN with negative anti-MAG antibodies, or IgG or IgA PDN with a chronic progressive course, where the discovery of widely-spaced myelin on electron microscopy or deposits of immunoglobulin and/or complement bound to myelin would support a causal relationship between paraprotein and neuropathy
However, clinical decisions on treatment are often made without a biopsy

necessary if there is clearly demyelinating physiology with MGUS. The CSF protein is elevated in 75–86% of patients with PDN [17, 23]. The presence of widely spaced myelin outer lamellae on electron microscopy is highly sensitive and specific for anti-MAG neuropathy. Immunoglobulin deposits may be identified on nerve structures [39, 40].

Treatment of paraproteinaemic demyelinating neuropathies

Monitoring of haematological disease

Patients with MGUS or asymptomatic Waldenström's macroglobulinaemia do not need treatment, unless required specifically because of neuropathy or other IgM-related conditions, according to a consensus panel guideline [41]. Whether they have a neuropathy or not, they should have regular haematological evaluation for early detection of malignant transformation, which occurs at approximately 1.3% per year. The following should be measured: paraprotein concentration, Bence Jones protein in the urine, serum immunoglobulin concentrations, ESR, creatinine, calcium, beta 2-microglobulin and full blood count, at a frequency of once a year for MGUS, every 6 months for asymptomatic Waldenström's macroglobulinaemia, or every 3 months if there is a higher risk of malignant transformation [12–14] (Good Practice Point).

IgM PDN

A recent Cochrane review of anti-MAG paraproteinaemic neuropathy concluded that there is so far inadequate reliable evidence to recommend any particular immunotherapy [42]. The same conclusion may be extended to IgM paraprotein-associated neuropathy without anti-MAG antibodies. Based on evidence regarding the pathogenicity of anti-MAG antibodies, therapy has been directed at reducing circulating IgM or anti-MAG antibodies by removal (plasma exchange, PE), inhibition (intravenous immunoglobulin, IVIg) or reduction of synthesis (corticosteroids, immunosuppressive, cytotoxic agents or interferon alpha). Only five controlled studies on a total of 97 patients have been performed [42].

Plasma exchange. In a review of uncontrolled studies or case reports [43], plasma exchange was temporarily effective in approximately half of the patients both alone and in combination with other therapies (class IV evidence). However, this was not confirmed in two controlled studies. In one, a randomized comparative open trial on 44 patients with neuropathy associated with IgM monoclonal gammopathy, 33 of whom had anti-MAG IgM, the combination of plasma exchange with chlorambucil was no more effective than chlorambucil alone [44] (class III). In a double-blind sham-controlled trial on 39 patients with neuropathy (axonal and demyelinating) associated with all classes of MGUS, PE was significantly effective overall, and in subgroups with IgG and IgA, but not in the 21 patients with IgM MGUS [45] (class II). In this study, anti-MAG reactivity was not examined.

Corticosteroids. In a review of uncontrolled studies or case reports [43], approximately half of the patients responded to corticosteroids given in association with other therapies, but corticosteroids were seldom effective alone (class IV).

High-dose intravenous immunoglobulin. Intravenous immunoglobulin was effective in two of 11 patients in a randomized double-blind placebo-controlled trial [46] (class II). A multicentre double-blind cross-over trial of 22 patients with PDN with IgM MGUS, half of whom had anti-MAG IgM, showed significant improvement at 4 weeks with IVIg compared with placebo [47] (class II). The short duration of follow-up leaves it unclear as to whether this was clinically useful. In an open study, 20 participants were randomized to IVIg or interferon-alpha and only one of 10 treated with IVIg improved [48] (class II).

Interferon-alpha. In the open comparative trial against IVIg, eight of 10 patients with PDN and anti-MAG IgM improved with interferon-alpha [48], but the improvement was restricted to sensory symptoms (class II). These results were not confirmed by the same authors in a randomized placebo-controlled study on 24 patients with PDN and anti-MAG IgM [49] (class II).

Immunosuppressive therapies. In a review of uncontrolled studies or case reports [42, 43], *chlorambucil* was effective in one-third of patients when used alone and in a slightly higher proportion in combination with other therapies (class IV). *Cyclophosphamide* was rarely effective when used alone, but was effective in 40–100% of patients in two open trials using cyclic high-dose oral or intravenous cyclophosphamide together with corticosteroids [50] or plasma exchange [51] (class IV).

There are recent anecdotal reports on the efficacy of *fludarabine* [52,53], *cladribine* [54] and *high-dose chemotherapy followed by autologous bone marrow transplantation* [55] in IgM PDN. These studies were limited to very small numbers and need to be confirmed in larger series.

Rituximab. The humanized monoclonal antibody (Rituximab) against the CD20 antigen was tested in several recent open pilot trials. In an open prospective study, over 80% of 21 patients with neuropathy with IgM antibodies to neural antigens (including seven with PDN and anti-MAG IgM) improved in strength after 1 and 2 years, compared with none of 13 untreated patients [56] (class III). The average improvement in strength was 13% at 1 year and 23% at 2 years. However, it was not reported how many patients with anti-MAG antibodies improved, or whether Rituximab improved the sensory ataxia, the most frequently disabling feature. No response to Rituximab was observed in two patients, including one with an IgM monoclonal gammopathy-associated chronic motor neuropathy with anti-ganglioside IgM antibodies [57]. Six of nine patients with chronic polyneuropathy with IgM monoclonal gammopathy and anti-MAG IgM treated with Rituximab in an open phase II study had detectable improvement (defined as ≥2 points improvement in the Neuropathy Impairment Score), two remained stable and one worsened [58]. However, only two patients had clinically useful improvement (≥10 points), and four had marginal improvement (five or less) (class IV).

Good practice points for treatment of IgM PDN:

(i) In patients without significant disability, consideration should be given to withholding immunosuppressive or immunomodulatory treatment, providing symptomatic treatment for tremor and paraesthesiae, and giving reassurance that symptoms are unlikely to worsen significantly for several years.

(ii) In patients with significant disability or rapid worsening, IVIg or PE should be considered as initial treatment, although their efficacy is unproven.

(iii) In patients with moderate or severe disability, immunosuppressive treatment should be considered, although its long-term efficacy remains unproven. Preliminary reports suggest that Rituximab may be a promising therapy.

(iv) More research is needed.

IgG and IgA PDN

In a review of uncontrolled studies on small series of patients, 80% of those with CIDP-like neuropathy responded to the same immunotherapies used for CIDP (corticosteroids, plasma exchange and IVIg) as compared with 20% of those with axonal neuropathy [59] (class IV). The only randomized controlled trials, on 39 patients with neuropathy associated with MGUS including 18 with IgG or IgA MGUS and 21 with IgM [45], showed plasma exchange was efficacious compared with sham exchange in patients with IgG or IgA MGUS only (class II). No distinction between demyelinating and axonal forms of neuropathy was made in terms of response to therapy.

Good practice point for treatment of IgG and IgA PDN. In patients with a CIDP-like neuropathy, the detection of IgG or IgA MGUS does not justify a different therapeutic approach from CIDP without a paraprotein.

POEMS

There are no controlled trials on the treatment of neuropathy in POEMS. Patients with a solitary plasmacytoma may benefit from local radiation or surgical excision. In a recent retrospective study on 99 patients with POEMS (including a review of previous studies) [27], 74% of patients had some response to therapy (class IV). *Local radiation*, performed only in patients with a localized or dominant plasmacytoma, was effective in 58% of 70 patients (54% improved and 4% stabilized) (class IV). A combination of *melphalan and corticosteroids* was effective in 56% of 48 patients (44% improved and 12% stabilized) whilst *corticosteroids alone* were effective in 22% of 41 patients (class IV). Plasma exchange, azathioprine and ciclosporin were only effective when used in combination with corticosteroids. There is no evidence that plasma exchange, IVIg, or other immunosuppressive agents are effective when used alone. Tamoxifen, interferon-alpha, alkylating agents and trans-retinoic acid have been used but the evidence is insufficient. Autologous peripheral blood stem cell transplantation induced neurological improvement or stabilization in 14 of 16 patients but has significant morbidity [60].

Good practice points for treatment of POEMS:

(i) Patients should be managed in consultation with a haemato-oncologist.

(ii) Local radiation or surgery should be considered as the initial treatment for isolated plasmacytoma.

(iii) Melphalan (with or without corticosteroids) should be considered for patients with multiple or no detectable bone lesions.

Other syndromes

In the neuropathy associated with multiple myeloma, there are no controlled trials and little evidence of response to any treatment in anecdotal reports. There are no controlled treatment trials in the neuropathy associated with Waldenström's macroglobulinaemia.

Supplementary material

The following material is available online at : www.blackwell-synergy.com

Appendix S1 Published evidence on investigation of paraproteinaemic demyelinating neuropathy (PDN).

Anticipated date for updating this guideline

Not later than October 2008.

Conflicts of interest

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