

EFNS/PNS PDN GUIDELINE

European Federation of Neurological Societies/Peripheral Nerve Society Guideline* on management of paraproteinemic demyelinating neuropathies. Report of a Joint Task Force of the European Federation of Neurological Societies and the Peripheral Nerve Society – first revision

Joint Task Force of the EFNS and the PNS[†]

Abstract The aim of this guideline is to update the 2006 EFNS/PNS guideline on management of patients with a demyelinating neuropathy and a paraprotein (paraproteinemic demyelinating neuropathy [PDN]) by review of evidence and expert consensus. In the absence of adequate evidence, the panel agreed on good practice points: (1) patients with PDN should be investigated for a malignant plasma cell dyscrasia; (2) a monoclonal gammopathy of undetermined significance is more likely to be causing the neuropathy if it is immunoglobulin (Ig)M, anti-neural antibodies are present, and the clinical phenotype is chronic distal sensory neuropathy; (3) patients with IgM PDN usually have predominantly distal sensory impairment, prolonged distal motor latencies, and often anti-myelin-associated glycoprotein antibodies; (4) IgM PDN may respond to immunomodulatory therapies. Their potential benefit should be balanced against possible side effects and the usually slow disease progression; (5) IgG and IgA PDN may be indistinguishable from chronic inflammatory demyelinating polyradiculoneuropathy; and (6) Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, and Skin changes syndrome is a multi-system malignant PDN.

Key words: demyelinating, guidelines, MAG, monoclonal gammopathy, neuropathy, paraprotein, POEMS, treatment

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Objectives

Our objective was to construct clinically useful guidelines for the diagnosis, investigation, and treatment of patients with both a demyelinating neuropathy and a paraprotein (paraproteinemic demyelinating neuropathy [PDN]), based on the available evidence and, where evidence was not available, consensus. This is the first revision of the original 2006 guideline (*Joint Task Force of the EFNS and the PNS, 2006*).

Background

The neuropathies associated with paraproteins are complex and 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 (Yeung *et al.*, 1991; Ropper and Gorson, 1998). In the absence of an agreed diagnostic classification, specific diagnostic criteria are available for only a few of these disorders, and treatment trials are therefore difficult to interpret.

Both demyelinating and axonal neuropathies may be associated with paraproteins, but this guideline concentrates on the demyelinating neuropathies. 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 as the same disease or as different diseases. Paraproteinemic axonal neuropathies are mentioned briefly in the section on Other Neuropathy Syndromes Associated with Paraproteinemia. As both paraproteins and neuropathies are common, it often remains uncertain whether the paraprotein is causing the neuropathy or is coincidental.

Search Strategy

We searched MEDLINE and the Cochrane Library on May 1, 2009 for articles on ('paraprotein(a)emic demyelinating neuropathy' AND ['diagnosis' OR 'treatment' OR 'guideline']) and used the personal databases of Task Force members.

Methods for Reaching Consensus

Evidence was classified as Class I–IV and recommendations as Level A–C (Brainin *et al.*, 2004). When only Class IV evidence was available but consensus could be reached, the Task Force has offered advice as good practice points. The original 2006 guideline (Joint Task Force of the EFNS and the PNS, 2006) 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. There is no consensus as to which should take precedence in classification. This guideline distinguishes 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 a different response to treatment. Nevertheless, there is a significant overlap between the clinical and electrophysiological features of the neuropathy with different types of paraprotein.

Investigation and Classification of the Paraprotein

Background

While some paraproteins (monoclonal gammopathy, monoclonal Ig) 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 (Vrethem *et al.*, 1993; Keren, 1999). Heavy (IgM, IgG, or IgA) and light chain (kappa or lambda) classes should be identified. A paraprotein indicates an underlying clonal B-cell expansion, usually in bone marrow, which may be malignant (and may itself require treatment) or a monoclonal gammopathy of undetermined significance (MGUS) (Table 1) (International Myeloma Working Group, 2003).

Most bone lesions causing neuropathy are sclerotic or mixed lytic–sclerotic, most commonly in the vertebral bones or pelvis. Although there is limited evidence on imaging of sclerotic lesions, skeletal survey (or computed tomography [CT]), magnetic resonance imaging (MRI), and positron emission tomography (PET)/CT are complementary imaging modalities and more than one may be needed if the index of suspicion is high (Dimopoulos *et al.*, 2009).

Table 1. Classification of hematological conditions with a paraprotein.

I. Malignant monoclonal gammopathies
1. Multiple myeloma (<i>overt, asymptomatic [smoldering], non-secretory, or osteosclerotic</i>)
2. Plasmacytoma (<i>solitary, extramedullary, multiple solitary</i>)
3. Malignant lymphoproliferative disease: <ol style="list-style-type: none"> Waldenström's macroglobulinemia Malignant lymphoma Chronic lymphocytic leukemia
4. Heavy chain disease
5. Primary amyloidosis (AL) (<i>with or without myeloma</i>)
II. Monoclonal gammopathy of undetermined significance

Table 2. Investigation of a paraprotein.

The following should be considered in patients with a paraprotein:

1. Serum immunofixation electrophoresis
2. Physical examination for peripheral lymphadenopathy, hepatosplenomegaly, macroglossia, and signs of POEMS syndrome (see section on the Other Neuropathy Syndromes Associated with Paraproteinemia)
3. 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
4. Total IgG, IgA, and IgM concentrations
5. Serum free light chains
6. Random urine collection for the detection of Bence-Jones protein (free light chains), and, if positive, 24-h urine collection for protein quantification
7. Radiographic X-ray skeletal survey (including skull, pelvis, spine, ribs, and long bones) to look for lytic or sclerotic lesions. Part or all of this may be replaced by CT, which is more sensitive but involves greater radiation exposure except where low-dose whole body CT is available. If the index of suspicion is high, CT and/or MRI of the spine, pelvis, or whole body, and perhaps whole body FDG-PET/CT, may be considered
8. Ultrasound or CT of chest, abdomen, and pelvis (to detect lymphadenopathy, hepatosplenomegaly, or malignancy)
9. Serum VEGF levels if POEMS syndrome suspected
10. Consultation with a hematologist and consideration of bone marrow examination

CT, computed tomography; FDG, F18-fluorodeoxyglucose; Ig, immunoglobulin; MRI, magnetic resonance imaging; PET, positron emission tomography; POEMS, Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy and Skin changes; VEGF, vascular endothelial growth factor.

Recommended investigations

Table 2 suggests investigations to be considered in patients with a paraprotein. SIFE should be performed in patients with a known paraprotein to define the heavy and light chain types, in patients with acquired demyelinating neuropathies, and in patients in whom a paraprotein is suspected but not detected by SPEP.

Definition of MGUS

The definition of IgM MGUS is different from that for IgG and IgA MGUS (Table 3). Patients with IgM MGUS have alternatively been classified as either 'IgM-related disorders' if they have clinical features attributable to the paraprotein (such as neuropathy), or 'asymptomatic IgM monoclonal gammopathy' if not (Owen *et al.*, 2003).

Typical Syndromes of PDN

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 (*Joint Task Force of the EFNS and the PNS, 2010*). If there are subtle features of demyelination not meeting these criteria, further investigations should be considered to clarify the possible pathogenic link between the paraprotein and the neuropathy (see section on the Cerebrospinal Fluid and Nerve Biopsy).

IgM paraproteinemic demyelinating neuropathy *Clinical phenotype*

Most patients with IgM PDN have predominantly distal, chronic (duration over 6 months), slowly progressive, symmetric, predominantly sensory impairment, with ataxia, relatively mild or no weakness, and often tremor (Class IV evidence) (Yeung *et al.*, 1991; Maisonobe *et al.*, 1996; Chassande *et al.*, 1998; Simovic *et al.*, 1998; Capasso *et al.*, 2002; Magy *et al.*, 2003). This phenotype is most strongly associated with IgM anti-MAG antibodies. 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 few patients with IgM PDN have proximal weakness more typical of IgG/IgA PDN, and some CIDP patients have distal weakness without a paraprotein (Katz *et al.*, 2000).

Electrophysiology

Patients with IgM PDN may meet the definite electrophysiological criteria for CIDP (*Joint Task Force of the EFNS and the PNS, 2010*). They may also have additional specific electrophysiological features in one or more nerves which help to distinguish from CIDP, typically uniform symmetrical, and predominantly distal reduced conduction velocity (terminal latency index <0.25) without conduction block (Table 4, adapted

Table 3. Definition of MGUS.

1. *IgM MGUS* is defined by the presence of both of the following:
 - a. No lymphoplasmacytic infiltration on bone marrow biopsy, or equivocal infiltration with negative phenotypic studies
 - b. No signs or symptoms suggesting tumor infiltration (e.g., constitutional symptoms, hyperviscosity syndrome, organomegaly)
2. *IgG or IgA MGUS* is defined by the presence of all of the following:
 - a. Serum monoclonal component ≤ 30 g/l
 - b. Bence-Jones proteinuria ≤ 1 g/24 h
 - c. No lytic or sclerotic lesions in bone
 - d. No anemia, hypercalcemia, or chronic renal insufficiency
 - e. Bone marrow plasma cell infiltration <10%

MGUS, monoclonal gammopathy of undetermined significance.

Table 4. Electrophysiological features associated with IgM PDN.

1. Uniform symmetrical reduction of conduction velocities; more severe sensory than motor involvement
2. Disproportionately prolonged DML. This may be quantified as terminal latency index (defined as distal distance/[motor conduction velocity × DML]; i.e., 'distal velocity'/'intermediate segment velocity') ≤ 0.25
3. Absent sural potential (i.e., less likely to have the 'abnormal median, normal sural' sensory action potential pattern)
4. Partial motor conduction block (i.e., proximal/distal CMAP amplitude ratio < 0.5) and marked distal CMAP dispersion are very rare

CMAP, compound muscle action potential; DML, distal motor latency; PDN, paraproteinemic demyelinating neuropathy.

from Kaku *et al.*, 1994; Notermans *et al.*, 2000; Capasso *et al.*, 2002).

Antibodies to MAG and other neural antigens

Almost 50% of patients with IgM PDN have high titers of anti-MAG IgM antibodies (Nobile-Orazio *et al.*, 1994), more commonly associated with kappa than lambda light chains, and this is the best defined syndrome of PDN (Van den Berg *et al.*, 1996). Weakly positive anti-MAG antibodies are less specific and may occur in the absence of neuropathy.

Testing for antibodies to MAG should be considered in all patients with IgM PDN (Nobile-Orazio *et al.*, 2008). If negative, then testing for IgM antibodies against other neural antigens, including gangliosides GQ1b, GM1, GD1a and GD1b, and SGPG, 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.

IgG or IgA paraproteinemic demyelinating neuropathy

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 (Joint Task Force of the EFNS and the PNS, 2010). They usually have more rapid progression than IgM PDN (Simovic *et al.*, 1998; Di Troia *et al.*, 1999; Magy *et al.*, 2003). However, a minority of patients with IgG or IgA PDN has the clinical and electrophysiological phenotype typical of IgM PDN.

In patients with IgG or IgA paraprotein, no specific antibody has been consistently associated with demyelinating neuropathy, and therefore there is no need to test for serum antibodies to known neural epitopes in routine practice.

Other Neuropathy Syndromes Associated with Paraproteinemia

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

POEMS syndrome

POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy and Skin changes) syndrome usually has an underlying osteosclerotic myeloma, with IgA or IgG lambda paraprotein, or is sometimes associated with Castleman disease. POEMS neuropathy has clinical features similar to severe CIDP. Many patients are initially thought to have CIDP or ordinary PDN, until POEMS is suggested by the presence of systemic features. Major diagnostic criteria are polyneuropathy, monoclonal plasma cell proliferative disorder (almost always lambda), and sclerotic bone lesions or Castleman disease or raised vascular endothelial growth factor (VEGF) levels (Dispenzieri, 2007). Minor diagnostic criteria are organomegaly (hepatosplenomegaly or lymphadenopathy); extravascular volume overload (edema, pleural effusion, or ascites); endocrinopathy; skin changes (hypertrichosis, hyperpigmentation, plethora, acrocyanosis, flushing, dermal glomeruloid hemangiomas, and white nails); papilledema; or thrombocytosis/polycythemia (Dispenzieri, 2007).

There is no specific diagnostic test for POEMS, so if it is suspected then the diagnostic criteria should be sought by detailed clinical examination and appropriate investigations (Table 2). Serum or plasma VEGF levels are usually markedly raised in POEMS, and are normal or only slightly raised in CIDP or PDN (Watanabe *et al.*, 1998), so are a useful supportive diagnostic test. Nerve biopsy may show uncompacted myelin lamellae (Vital *et al.*, 2003).

Electrophysiology often shows a mixed demyelinating and axonal picture (Kelly, 1983). Features that may help to distinguish POEMS from CIDP include reduced motor nerve conduction velocities more marked in intermediate than distal nerve segments (increased terminal latency index 0.35–0.6, the opposite of IgM PDN); rarity of conduction block; and severe length-dependent axonal loss (Sung *et al.*, 2002; Min *et al.*, 2005).

Waldenström's macroglobulinemia

Waldenström's macroglobulinemia 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 (Owen, 2003). The associated neuropathy is clinically heterogeneous, but patients with indolent or asymptomatic Waldenström's macroglobulinemia may have anti-MAG reactivity and clinical features of IgM anti-MAG neuropathy (Baldini et al., 1994).

CANOMAD syndrome

The syndrome of Chronic Ataxic Neuropathy with Ophthalmoplegia, IgM Monoclonal gammopathy, cold Agglutinins, and Disialoganglioside (IgM anti-ganglioside GD1b/GQ1b) antibodies (CANOMAD) is a rare neuropathy similar to chronic Fisher syndrome, with mixed demyelinating and axonal electrophysiology (Willison et al., 2001).

Other neuropathies with a paraprotein

Axonal neuropathy is often present in patients with MGUS, but the pathogenesis and causal relationships vary, and this will not be considered further in these guidelines.

A few patients with cryoglobulinemia (Vital et al., 2000) or primary (AL) amyloidosis (Vital et al., 2004) 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 nerve or other tissues. Chronic axonal polyneuropathy with IgG MGUS, without symptoms or signs of amyloidosis, is usually indistinguishable from chronic idiopathic axonal polyneuropathy.

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 drug-induced insults, and cord or root compression due to vertebral collapse from lytic lesions (Kelly et al., 1981). Subacute weakness similar to Guillain-Barré syndrome may be caused by extensive infiltration of nerves or roots by lymphoma or leukemia (Diaz-Arrastia et al., 1992).

Multi focal motor neuropathy is occasionally associated with an IgM MGUS, which does not seem to affect the behavior of the disease (Nobile-Orazio et al., 2005).

Is the Paraprotein Causing the Neuropathy?

A causal relationship of the paraprotein to the neuropathy is more likely with an IgM than an IgG or IgA MGUS. There is still no expert consensus as

Table 5. Causal relationship between paraprotein and demyelinating neuropathy.

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1. **Highly probable** if IgM paraprotein (MGUS or Waldenström's) and:
 - a. High titers of IgM 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 titers of IgM antibodies to other neural antigens (GM1, GD1a, GD1b, GM2, sulfatide, etc.), and slowly progressive predominantly distal symmetrical sensory neuropathy, or
 - b. IgG or IgA paraprotein and nerve biopsy evidence (as in 1b 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 2b
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CANOMAD, Chronic Ataxic Neuropathy with Ophthalmoplegia, IgM Monoclonal gammopathy, cold Agglutinins, and Disialoganglioside; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; Ig, immunoglobulin; MAG, myelin-associated glycoprotein; MGUS, monoclonal gammopathy of undetermined significance.

to whether IgG or IgA PDN may merely be CIDP with a coincidental paraprotein. The only published criteria of causality were in a study in which all patients had predominantly distal sensory neuropathy, demyelinating physiology, and MGUS (IgM or IgG) (Notermans et al., 2000). We extensively modified these criteria, and propose factors which suggest whether or not the paraprotein is likely to be causing the neuropathy (Table 5).

Cerebrospinal Fluid and Nerve Biopsy

Cerebrospinal fluid (CSF) examination and nerve biopsy may be helpful in selected circumstances (Table 6, Good Practice Points), but are usually not necessary if there is clearly demyelinating physiology with MGUS. The CSF protein is elevated in 75%–86% of patients with PDN (Notermans et al., 2000; Capasso et al., 2002). The presence of widely spaced myelin outer lamellae on electron microscopy is highly sensitive and specific for anti-MAG neuropathy. Ig deposits may be identified on nerve structures (Vallat et al., 2000).

Table 6. 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 cryoglobulinemia)
 - 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 Ig 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

CSF, cerebrospinal fluid; Ig, immunoglobulin; MAG, myelin-associated glycoprotein; PDN, paraproteinemic demyelinating neuropathy.

Treatment of Paraproteinemic Demyelinating Neuropathies

Monitoring of hematological disease

Patients with MGUS or asymptomatic Waldenström's macroglobulinemia may not need treatment, unless required specifically because of neuropathy or other IgM-related conditions (Kyle *et al.*, 2003). Whether they have a neuropathy or not, they should have regular hematological 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 Ig concentrations, erythrocyte sedimentation rate, 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 macroglobulinemia, or every 3 months if there is a higher risk of malignant transformation (Cesana *et al.*, 2002; Morra *et al.*, 2004) (Good Practice Point).

Treatment of IgM PDN

The 2006 Cochrane Review of anti-MAG paraproteinemic neuropathy concluded that there was inadequate evidence to recommend any particular immunotherapy (Lunn and Nobile-Orazio, 2006). The same conclusion may be extended to IgM PDN without anti-MAG antibodies. Based on the 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 or cytotoxic agents, or interferon-alpha). Only seven controlled studies on a total of 145 patients have been performed (Lunn and Nobile-Orazio, 2006), two new studies being added since our first guidelines (Niermeijer *et al.*, 2007; Dalakas *et al.*, 2009).

Plasma exchange

In a review of uncontrolled studies or case reports (Nobile-Orazio *et al.*, 2000), PE 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 PE with chlorambucil was no more effective than chlorambucil alone (Oksenhendler *et al.*, 1995) (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 (Dyck *et al.*, 1991) (Class II). In this study anti-MAG reactivity was not examined.

Corticosteroids

In a review of uncontrolled studies or case reports (Nobile-Orazio *et al.*, 2000), approximately half of the patients responded to corticosteroids given in association with other therapies, but corticosteroids were seldom effective alone (Class IV).

Intravenous immunoglobulin

In one randomized double-blind placebo-controlled trial only 2 of 11 patients improved with IVIg, not significantly better than placebo (Dalakas *et al.*, 1996) (Class II). A multi-center 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 (Comi *et al.*, 2002) (Class II). Ten of 22 patients improved with IVIg and 4 improved with placebo. The short duration of follow-up leaves it unclear whether this was clinically useful. Regular long-term IVIg was not tested. In an open study, 20 participants were randomized to IVIg or interferon-alpha and only 1 of 10 treated with IVIg improved (Mariette *et al.*, 1997) (Class II).

Interferon-alpha

In an open comparative trial against IVIg, 8 of 10 patients with PDN and anti-MAG IgM improved

with *interferon-alpha* (Mariette *et al.*, 1997) but the improvement was restricted to sensory symptoms. However, no benefit was shown by the same authors in a randomized placebo-controlled study on 24 patients with PDN and anti-MAG IgM (Mariette *et al.*, 2000) (Class II).

Immunosuppressive therapies

In a review of uncontrolled studies or case reports (Nobile-Orazio *et al.*, 2000; Lunn and Nobile-Orazio, 2006), chlorambucil was effective in one-third of patients when used alone and in a slightly higher proportion in combination with other therapies (Class IV).

A randomized controlled trial (RCT) of pulsed oral cyclophosphamide (500 mg daily for 4 days repeated every month for 6 months) with prednisolone (60 mg daily for 5 days) took 8 years to recruit 35 patients, 17 with anti-MAG antibodies (Niermeijer *et al.*, 2007). There was no significant difference in the primary outcome measure, the Rivermead Mobility Index (33% improved vs. 21% with placebo), although significant improvements were seen in secondary outcomes including Medical Research Council (MRC) score up to 2 years of follow-up, and sensory, ataxia, quality of life, hematological and neurophysiological outcomes (Class I evidence). It is unclear whether the risk of malignant transformation after cyclophosphamide (9% in 5 years in this trial) significantly exceeded the background risk. Cyclophosphamide was effective in 40%–100% of patients in two open trials using cyclic high-dose oral or intravenous cyclophosphamide with corticosteroids (Notermans *et al.*, 1996) or PE (Blume *et al.*, 1995) (Class IV), but was rarely effective when used alone.

In an open study, 5 of 16 patients treated with fludarabine improved with outcomes sustained for at least a year (Class III) (Niermeijer *et al.*, 2006), complementing previous anecdotal reports (Sherman *et al.*, 1994; Wilson *et al.*, 1999).

There are anecdotal reports on the efficacy of cladribine (Ghosh *et al.*, 2002), and high-dose chemotherapy followed by autologous bone marrow transplantation (Rudnicki *et al.*, 1998) in IgM PDN. These studies were limited to very small numbers and need to be confirmed in larger series.

Rituximab

Rituximab, the humanized monoclonal antibody against the CD20 antigen, has shown some benefit in several open studies. The usual dose is 375 mg/m² intravenously every week for 4 weeks, with further doses after a longer interval if necessary. In one open prospective study, over four-fifths of 21 patients with neuropathy with IgM antibodies to

neural antigens (including 7 with PDN and anti-MAG IgM) improved in strength, compared with none of 13 untreated patients (Pestronk *et al.*, 2003) (Class III). No response to rituximab was observed in another two patients (Rojas-Garcia *et al.*, 2003). In an open phase II study of nine patients with chronic polyneuropathy with IgM monoclonal gammopathy and anti-MAG antibodies treated with rituximab, two patients had clinically useful improvement (≥ 10 points on the Neuropathy Impairment Score), four had marginal improvement (2–5 points), two remained stable, and one worsened (Class IV) (Renaud *et al.*, 2003). Eight (62%) of 13 patients with PDN and anti-MAG IgM improved in the Inflammatory Neuropathy Cause And Treatment (INCAT) sensory and MRC scores and seven (54%) also in the INCAT disability score (Benedetti *et al.*, 2007). After a single course of rituximab, improvement lasted 2 years in 8 of 10 patients and 3 years in 6 (Benedetti *et al.*, 2008). Another open study of 17 patients with IgM PDN showed improved disability in two and improved sensory sum score in nine (Niermeijer *et al.*, 2009). In non-randomized comparisons, this Dutch group found similar benefits and fewer adverse effects from rituximab compared with cyclophosphamide/prednisolone or fludarabine (Niermeijer *et al.*, 2009).

In the only published placebo-controlled RCT, 13 of 26 patients with anti-MAG antibodies were randomized to receive rituximab (Dalakas *et al.*, 2009). The primary outcome measure using the intention-to-treat population of 26 subjects was not significant (Class II). In *post hoc*, non-pre-specified analysis, in which one subject was removed from the treated group, there appeared to be a significant difference between treated and untreated subjects. This method of analysis raises questions about the conclusion of the published article.

We await the results of another RCT now in progress (RiMAG).

Good practice points for treatment of IgM PDN

- In patients without significant disability or hematological reason for treatment, there is no evidence that immunosuppressive or immunomodulatory treatment is beneficial. Patients may be offered symptomatic treatment for tremor and paresthesiae, and reassurance that symptoms are unlikely to worsen significantly for years.
- In patients with significant chronic or progressive disability, immunosuppressive or immunomodulatory treatment may be considered, although none are of proven efficacy, and there is no consensus on which treatment to use first. IVIg or PE may be considered, especially in patients with rapid worsening

or clinically similar to typical CIDP, although any benefit may be only short term and repeated treatments may be required. In attempts to achieve longer-term benefit (or in patients unresponsive to IVIg or PE), clinicians have used rituximab, cyclophosphamide with prednisolone, fludarabine, and chlorambucil. All remain unproven and all have risks which must be balanced against any possible benefits.

- More research on pathogenesis and treatment is needed.

Treatment of IgG and IgA PDN

In a review of uncontrolled studies on small series of patients with an IgG or IgA MGUS, 80% of those with CIDP-like neuropathy responded to the same immunotherapies used for CIDP (corticosteroids, PE, and IVIg) compared with 20% of those with axonal neuropathy (*Nobile-Orazio et al., 2002*) (Class IV). The only RCT, on 39 patients with neuropathy associated with MGUS including 18 with IgG or IgA MGUS and 21 with IgM (*Dyck et al., 1991*), showed PE was efficacious compared with sham exchange only in patients with IgG or IgA MGUS (Class II) (*Allen et al., 2007*). 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.

Treatment of POEMS syndrome

This is a malignant condition which should be managed in consultation with a hemato-oncologist. The 2008 Cochrane Review concluded "Despite the absence of evidence from randomized trials, the review authors consider it clinically logical that the foundation of treatment is radiation for patients with a solitary osteosclerotic lesion... and high-dose melphalan with autologous peripheral blood stem cell transplantation for patients under 65 years with diffuse disease as demonstrated by multiple bone lesions or documented clonal plasma cells in iliac crest biopsy. Lenalidomide/thalidomide, anti-VEGF monoclonal antibody (bevacizumab), and conventional chemotherapy with melphalan or cyclophosphamide may also be treatment options" (*Kuwabara et al., 2008*).

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 macroglobulinemia. It is beyond the scope of this guideline to discuss the treatment of these conditions in general.

Conflicts of Interest

The following authors have reported conflicts of interest as follows: D. R. Cornblath: personal honoraria from Merck, Pfizer, Mitsubishi Pharma, Sangamo, Sanofi-Aventis, Bristol-Myers Squibb, Eisai, Octapharma, Sun Pharma, Acorda, DP Clinical, Exelixis, Geron, Johnson & Johnson, Genzyme, Cebix, Abbott, CSL Behring, Bionevia, Schwarz Biosciences, Avigen, FoldRx, GlaxoSmithKline; R. D. M. Hadden: personal honoraria from Janssen-Cilag and Baxter Healthcare; A. F. Hahn: departmental research grants and personal honoraria from Bayer, Baxter, Biogen-Idec, Talecris; I. Illa: departmental research grant from Grifols; C. L. Koski: personal honoraria from American Red Cross, Baxter, Bayer, ZLB-Behring; J.-M. Léger: departmental research grants or honoraria from Biogen-Idec, Baxter, Laboratoire Français du Biofractionnement (LFB), Octapharma; M. P. T. Lunn: commissioned to give opinions on IVIg and PE usage by UK Department of Health and received honoraria from Baxter Pharmaceuticals and LFB; E. Nobile-Orazio: personal from Kedrion, Grifols, Baxter, LFB (and commissioned by Kedrion and Baxter to give expert opinions to the Italian Ministry of Health on IVIg in dysimmune neuropathies); J. D. Pollard: departmental research grants from Biogen-Idec, Schering; C. L. Sommer: personal honoraria from Biogen-Idec and Baxter International Inc.; P. A. van Doorn: departmental research grants or honoraria from Baxter and Bayer; and I. N. van Schaik: unrestricted departmental research grant from Sanquin blood supply foundation. The other authors have nothing to declare.

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