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Investigation and management of IgM and Waldenström-associated peripheral neuropathies: recommendations from the IWWM-8 consensus panel

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Summary

Paraproteinaemic neuropathies are a heterogeneous group of disorders most frequently associated with IgM monoclonal gammopathies including Waldenström macroglobulinaemia (WM). Their consequences are significant for affected patients, and their management challenging for their physicians. The variability in clinical presentation and time course hamper classification and management. The indications for invasive investigations such as cerebrospinal fluid analysis, nerve conduction tests and sensory nerve biopsies are unclear, and the optimum way to measure clinical response to treatment unknown. When to intervene and and how to treat, also present challenges to physicians. As part of its latest deliberations at the International Workshops on WM (IWWM) in London, UK (August 2014), the IWWM8 panel have proposed a consensus approach to the diagnosis and management of peripheral neuropathies associated with IgM monoclonal gammopathies, including WM. Importantly, a consensus regarding the use of clinical outcome measures and recommended models of care for this group of patients is discussed, as well as appropriate treatment interventions.

Keywords: IgM, paraproteinaemic neuropathy, Waldenstrom macroglobulinaemia.

IgM paraprotein-associated neuropathies are a heterogeneous group of disorders whose exact prevalence is unknown. Their consequences are significant and challenging for patients and physicians alike with no consensus regarding clinical evaluation and optimal baseline assessment.

The International Workshops on Waldenström Macroglobulinaemia (IWWM) have proposed criteria for diagnosis and therapy (Owen *et al*, 2003), response (Owen *et al*, 2013), and treatment (Dimopoulos *et al*, 2014) in WM patients. As part of its latest consensus deliberations (IWWM8, London 2014), the panel reviewed the management of peripheral neuropathies associated with IgM monoclonal gammopathies, including WM.

The prevalence of peripheral neuropathy (PN) in persons with monoclonal gammopathies of undetermined significance (MGUS) is approximately 5% in IgG, 15% in IgA and possibly up to 30–50% in IgM MGUS (Nobile-Orazio *et al*, 1984; Gosselin *et al*, 1991; Yeung *et al*, 1991; Kissel & Mendell, 1996), although this high prevalence rate probably reflects patient selection bias in specialist settings and sensitive identification of sub-clinical cases (Dispenzieri & Kyle, 2005). Monoclonal gammopathies are common, with a prevalence of 1% of the general population aged 50 years and increasing to 8–9% by the age of 90 years (Kyle *et al*, 2006). PN affects 2·4% of the general population, increasing to 8·0% with advancing age (Martyn & Hughes, 1997). A frequent challenge when two such conditions coexist is to relate a causative role of the MGUS versus coincidental association.

High quality evidence links at least 50% of demyelinating neuropathies to a causal IgM paraprotein, including antibody transfer models (Tatum, 1993; Willison *et al*, 1993), high titre IgM antibodies with a neural target antigen [e.g. myelin associated glycoprotein (MAG)], site-specific binding studies by light and immunoelectron microscopy, a unique pathological substrate (widely spaced myelin) and a response to treatment to reduce paraprotein levels. Other antibody

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targets have been proposed and identified in a small number of cases (for example the gangliosides GM1 and GD1b and sulphatide), and more are postulated.

The presence of a neuropathy alone is not a justification for treatment, but steady progression with accumulating disability should prompt action. There is little evidence to recommend specific therapies (Rajabally, 2011); outcomes of clinical trials are hampered by few appropriate participants for trial inclusion, their heterogeneity and use of ordinal multi-item composite outcome measures that lack reliability, validity and responsiveness (DeVellis, 2006; Merkies *et al*, 2012).

Diagnostic evaluation

General work-up

We first present the broad concepts of diagnostic evaluation, before discussing specifics relating to each diagnosis below.

Neurological evaluation of a PN accompanied by a paraprotein is best achieved with parallel investigation into the nature of the IgM monoclonal gammopathy (Table I). In this document, the use of the terms IgM MGUS, asymptomatic WM and symptomatic WM are based on the clinicopathological definition of WM according to the consensus panel recommendations from the Second IWWM (Owen *et al*, 2003). A history and examination delineates the important clinical features of the PN and are key to subsequent management (Table II). It is important to identify alternative causes of neuropathy, such as diabetes, nutritional deficiencies and alcohol, connective tissue disease, drugs (the majority are axonal, rather than demyelinating) or pre-existent hereditary neuropathy. The nature of the symptoms, speed of onset, clinical course, rate of change and effect on functional abilities, involvement of motor, sensory or autonomic systems helps to hone in on a differential diagnosis. The conclusions from these investigations, based on discussion between a haematologist and neurologist, will help to establish whether the PN is related to the monoclonal gammopathy and whether there is a need for treatment.

Nerve conduction tests and electromyography

Electrical tests, including nerve conduction studies (NCS) and electromyography (EMG), are an extension of the clinical examination and characterise the nature, pattern and extent of nerve damage. Evidence for demyelination and/or axonal damage should be determined by standard criteria (American Academy of Neurology AIDS Task Force 1991). Features indicative of axonal and demyelinating neuropathy are shown in Table III.

Electrophysiological features associated with IgM-associated PN include symmetrical reduction of conduction velocities; more severe sensory than motor involvement; disproportionately prolonged distal motor latency (DML) and absent sural potentials. Partial motor conduction block and marked distal compound muscle action potential dispersion are rare (Force, 2006). Specific features of the different paraprotein-associated neuropathies are delineated below in each section.

It is important to provide a question or have a discussion with the neurophysiologist when requesting NCS so that the examination can be tailored for maximal yield. The presence of some (but not all) cardiac pacemakers

Table I. Work up for monoclonal gammopathy.

History	Examination	Investigations
Assessment of wellbeing and performance status	Lymphadenopathy	Full blood count
Fatigue	Hepatosplenomegaly	Renal function
Weight loss	Macroglossia	Liver function
Fevers	Postural hypotension	Bone chemistry
Infections		B_2microglobulin
Symptoms of hyperviscosity		Lactate dehydrogenase
Clinical manifestations of cryoglobulinemia such as purpura, digital ischaemia, arthralgia, fever, Raynaud phenomenon		NT-proBNP
		Cryoglobulin testing
Clinical manifestations of AL amyloidosis, such as unexplained cardiac failure, gut dysmotility, purpura		Serum free light chains
		SPEP
		Immunofixation
		HIV serology
		Hepatitis B and C serology
		Urinalysis including UPEP
		Bone marrow cytology, biopsy (with Congo red stain if suspicion of amyloid) and *MYD88* L265P detection
		CT chest, abdomen, pelvis

CT, computed tomography; HIV, human immunodeficiency virus; NT-proBNP, N-terminal pro b-type natriuretic peptide; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis.

Table II. Work up of the peripheral neuropathy.

History	Examination	Investigations
Duration of symptoms	Full examination of peripheral and central nervous system	Serum B12 and folate HbA1C
Clinical course (relapsing/remitting/monophasic)	Wasting	Anti-MAG antibodies
Rate of progression	Fasciculation	Anti-ganglioside antibodies (GQ1b, GM1, GD1a, GD1b, SGPG)
Sensory/motor predominance		VEGF if POEMS is suspected
Topographic distribution (symmetry/distal/ proximal/ multifocal/cranial nerve involvement)		Enzyme immunoassay or Indirect immunofluorescence assay for suspected Lyme disease Appropriate neuroimaging to rule out infiltration if suspected
Ataxia		Nerve conduction studies/electromyography
Falls		CSF examination for protein including immunofixation
Postural dizziness		CSF examination for cells including cytology, immunophenotyping and molecular studies Nerve biopsy if indicated

CSF, cerebrospinal fluid; MAG, myelin associated glycoprotein; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes; VEGF, vascular endothelial growth factor.

Table III. Typical nerve conduction study abnormalities seen with axonal loss or demyelination.

	Axonal loss	Demyelination
Sensory responses	Small or absent	Small or absent
Distal motor latency	Normal or slightly prolonged	Prolonged
CMAP amplitude	Small	Normal (reduced if conduction block or temporal dispersion)
Conduction block/temporal dispersion	Not present (responses may disperse slightly)	Present
Motor conduction velocity	Normal or slightly reduced	Notably reduced
F waves minimum latency	Normal or slightly prolonged	Significantly prolonged

CMAP, compound muscle action potential.

may contraindicate NCS, as life-threatening events can be triggered by an external voltage applied in close proximity to an implantable cardioverter/defibrillator device. Clarification by the patient's cardiologist will be useful in this case. Anticoagulants are associated with a risk of intramuscular haematoma with EMG needling; anticoagulants might need to be suspended prior to an examination.

Recommendations

- **Neurophysiological testing is recommended where a neuropathy is identified on clinical examination to clarify the nature of the neuropathy and expand or curtail investigation.**
- **Specific clinical questions should be included in the request for neurophysiological studies to allow for appropriate modifications by the neurophysiologist during testing.**
- **The results of neurophysiological testing should be assessed in conjunction with the clinical picture and the haematological context (MGUS, asymptomatic, symptomatic WM) in order for meaningful and practical conclusions to be drawn.**
- **Appropriate steps should be taken to minimise the risk to the patient on anticoagulants or with a pacemaker or implantable defibrillator.**

Cerebrospinal fluid (CSF) examination

CSF protein (normal range usually 0·15–0·45 g/l) is significantly elevated (>1·0 g/l) in up to 80% of demyelinating paraproteinaemic neuropathies (Notermans *et al*, 2000). In these cases, the mechanism is most likely to be antibody-mediated attack. In cases, of painful patchy nerve dysfunction or progressive involvement of nerve roots suggestive of infiltration, where an asymmetrical or mononeuritis multiplex pattern is seen, infiltration of the peripheral nerves rather than a humoral mechanism is likely. If neurolymphomatosis (invasion of peripheral nerves by lymphoma) is suspected, and biopsy of possibly affected nerves is often not feasible, a lumbar puncture for CSF examination combined with appropriate imaging [positron emission tomography/computed tomography and/or gadolinium-enhanced magnetic resonance imaging] may help to confirm the diagnosis (Shaikh *et al*, 2015).

If the clinical examination is in keeping with central nervous system (CNS) disease, evidence for malignancy should

be sought by immunocytology, flow cytometry, molecular studies and immunofixation of the CSF or vitreous fluid. Using polymerase chain reaction analysis of CSF or vitreous fluid, *IGH* rearrangement studies to amplify the CDR-3 region of the *IGH* (Hegde *et al*, 2005) a neoplastic proliferation of lymphocytes, with a unique variable/diversity/joining (VDJ) arrangement will result in a single sharp band on agarose gel. Detection of *MYD88* L265P in CSF has been shown to be helpful in the confirmation of CNS involvement by WM (Bing-Neel syndrome) (Poulain *et al*, 2014; Frustaci *et al*, 2016). A single large volume (10 ml) CSF sample will have a 50% chance of identifying pathological cells; three serial 10 ml samples increases the pick-up rate to about 90% (Glantz *et al*, 1998).

A false-positive CSF result may occur if a CSF sample is contaminated by peripheral blood lymphocytes due to active systemic lymphoma. The presence of numerous red blood cells in the CSF provides a clue to this possibility. It is important to interpret the cytology results in the context of the protein studies to clarify the likelihood of blood contamination.

Recommendations

- **In cases of demyelinating neuropathy, although not mandatory, examination of the CSF supports the diagnosis if the protein is raised and other biochemical constituents are normal, or if immunofixation is positive.**
- **When the clinical work-up is inconclusive, and a malignant meningitis or invasion of the CNS is suspected, (repeated) examination of the CSF is indicated for examination of cellular constituents.**
- **If cellular material is identified, then cytological examination, immunophenotyping and molecular studies are indicated to characterize the cellular population.**

Nerve biopsy

The indications for nerve biopsy are limited. Sensory nerve biopsies are associated with a permanent sensory deficit and a 10–20% risk of post-biopsy pain.

However, if a comprehensive clinical work up fails to identify the cause of a progressive and debilitating PN, and amyloidosis, vasculitis or direct nervous system invasion is suspected, a sensory nerve biopsy is recommended, in a centre with appropriate surgical and analytical experience. In suspected amyloidosis, alternative sites, such as bone marrow, abdominal fat or rectum, should be explored first. Where histological evidence for amyloid has been found in other tissues and the clinical and neurophysiological characteristics of the PN are compatible with amyloidosis, a nerve biopsy is not required.

Congo red staining identifies amyloid, which can be further sub-classified by immunohistochemistry (Thomas & King, 1974) or mass spectrometry (Klein *et al*, 2011) to identify immunoglobulin light chain or familial types, e.g., transthyretin. In case of suspected lymphomatous infiltration of peripheral nerves, immunohistochemical staining for monoclonal B cell surface markers is mandatory, although the diagnostic yield is often low due to the small sample size.

Recommendations

- **The indications for nerve biopsy are limited.**
- **Where a comprehensive systemic work up has failed to identify a cause and there remains a suspicion of amyloid, vasculitis or direct cellular invasion, in atypical cases unresponsive to treatment, or progressive, debilitating conditions, a sensory nerve biopsy may be indicated.**
- **The risk-benefit ratio of carrying out the biopsy needs to be carefully weighed; if the procedure is likely to alter the course of management, it should be performed.**
- **The need for a nerve biopsy should be ratified by a neurologist with a specialist interest in PN and carried out at a centre with relevant expertise.**

Skin biopsies

Full thickness skin biopsy samples may be useful for histological confirmation of a small fibre neuropathy. The procedural risks are low, and complications are rare. However, epidermal nerve fibre density is abnormally decreased in only two-thirds of patients with small fibre neuropathy (Periquet *et al*, 1999). Dermal fibre analysis is evolving in usefulness for demonstrating IgM deposits on myelinated nerve fibres (Lauria *et al*, 2006), but this remains in development.

Recommendations

- **Skin biopsy is not routinely recommended. A normal skin biopsy does not rule out a small fibre neuropathy and the test rarely provides information that alters the management of the patient.**

Imaging

MRI should be performed *prior* to a diagnostic lumbar puncture (LP) for CSF analysis, as false-positive leptomeningeal enhancement may result from LP-related meningeal irritation.

Targeted MR sequences with or without gadolinium enhancement are indicated in cases of suspected neural compression, leptomeningeal or radicular infiltration (Keraliya *et al*, 2015) or where peripheral nervous system and CNS features are present. Focal neurological signs of motor, sensory or higher function are indicative of possible brain involvement visualised as parenchymal lesions on MRI images, the so called Bing-Neel syndrome (Castillo *et al*, 2016). Progressive root or cranial nerve involvement,

radicular pain or symptoms of meningism are indicative of meningeal involvement and may be identified by leptomeningeal, subependymal or dural enhancement, or cranial nerve enlargement and enhancement. Spinal MRI can reveal enhancing intradural soft tissue, thickening and enhancement of nerve roots and leptomeninges (Haldorsen *et al*, 2011). Lymphomatous infiltration of individual nerves, spinal roots, cranial nerves or plexi is characterised by nodular or diffuse thickening of nerves, which usually enhance with contrast (Grisariu *et al*, 2010). Ultrasound scanning can identify focal and more extensive thickened nerves in the distal limbs, but has no other differentiating ability.

Recommendations

- **MRI of the neuraxis should be performed prior to lumbar puncture to avoid false positive meningeal enhancement.**
- **Prior discussion of likely sites of involvement with an experienced neuroradiologist will ensure that the correct sequences of the correct anatomical area are performed with appropriate Gadolinium enhancement.**
- **MRI, CT and ultrasound have little ability to differentiate the nature of individual nerve lesions but can target diagnostic biopsies.**

Clinical phenotypes and their treatment

The paraprotein-associated neuropathies fall into a number of identifiable clinical groups, in which the paraprotein is considered causal. Where a causal association is suspected, the following statements can act as a useful guide and are adapted from European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of paraproteinemic demyelinating neuropathies (Force, 2006):

- In the presence of an IgM MGUS or WM and high titres of anti-MAG antibodies, a causal relationship between the paraprotein and a demyelinating PN is highly probable (high quality evidence).
- An IgM paraprotein with high titres of IgM antibodies to other neural antigens (such as GD1a, GD1b, GM2) and a slowly progressive predominantly distal neuropathy may be causally associated (low quality evidence).
- An IgM paraprotein with a high titre of anti-GM1 associated with a multifocal motor neuropathy is likely to be causally linked (moderate quality evidence).
- An IgM paraprotein with a high titre of antibodies against disialyated gangliosides (GQ1b, GT1a, GT1b, GD1b, GD2 and GD3) and a neuropathy with ophthalmoplegia and ataxia (chronic ataxic neuropathy ophthalmoplegia IgM paraprotein cold agglutinins disialosyl antibodies, CANOMAD) are probably associated (high quality evidence).

A causal antibody relationship is *less likely* in IgM MGUS cases in the following situations:

- The neuropathy is axonal.
- Time to peak of PN less than 6 months; most antibody-targeted paraprotein-associated neuropathies are slowly progressive. Consider amyloidosis, vasculitis or other incidental causes.
- A neuropathy with a relapsing and remitting course (spontaneous or to prednisolone/intravenous immunoglobulin (IVIG) treatment) is more suggestive of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP))
- There is cranial nerve involvement. Other than CANOMAD, this is more likely to be due to meningeal involvement (cellular infiltration), amyloid (light chain infiltration), vasculitis, CIDP or infection.
- Non-symmetrical distribution (consider vasculitis, infiltration, diabetes, pressure palsies such as carpal tunnel syndrome)
- History of infection 10 days to 6 weeks preceding the onset (consider Guillain-Barré syndrome, polio and other viral neuroinvasive diseases, human immunodeficiency virus, diphtheria, Lyme disease, leprosy).
- A lambda light chain is present and systemic symptomatology suggestive of possible POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal plasma cell disorder, Skin changes) syndrome are identified.

In the following section, the most common clinical entities will be addressed. A schematic decision tree is shown in Fig 1, which assists in clarifying the pathways to particular IgM-associated diagnoses, and highlights alternative entities.

IgM MGUS-associated PN without antibodies (Distal acquired demyelinating sensorimotor neuropathy) PN

The typical clinical phenotype of antibody-negative PN seen in the setting of IgM MGUS is a distal, chronic (>6 months), symmetrical, painless neuropathy with a predominance of sensory symptoms, accompanied by imbalance or ataxia, tremor and mild or minimal weakness with demyelination on electrophysiological studies (Smith, 1994; Nobile-Orazio *et al*, 2000). This phenotype is so characteristic, that the acronym DADS (Distal, Acquired, Demyelinating, Sensory-neuropathy) has been coined to capture its features. While the DADS phenotype may be seen in association with anti-MAG antibodies (Katz *et al*, 2000) (see below), some patients may have more prominent ataxia and others show proximal weakness reminiscent of CIDP (Katz *et al*, 2000).

Antibody targets for the paraprotein are seldom found but the uniform clinical picture is well recognised and the link is presumed, probably constituting one of the "IgM-related disorders" within the criteria proposed by Owen *et al* (2003).

Rapid progression, a mixed axonal and demyelinating or an axonal predominant PN should raise the possibility of primary (AL) amyloidosis, especially if neuropathic pain or autonomic dysfunction are present (Vital *et al*, 2004) or cryoglobulinaemia (Gemignani *et al*, 2005) if appropriate features are present.

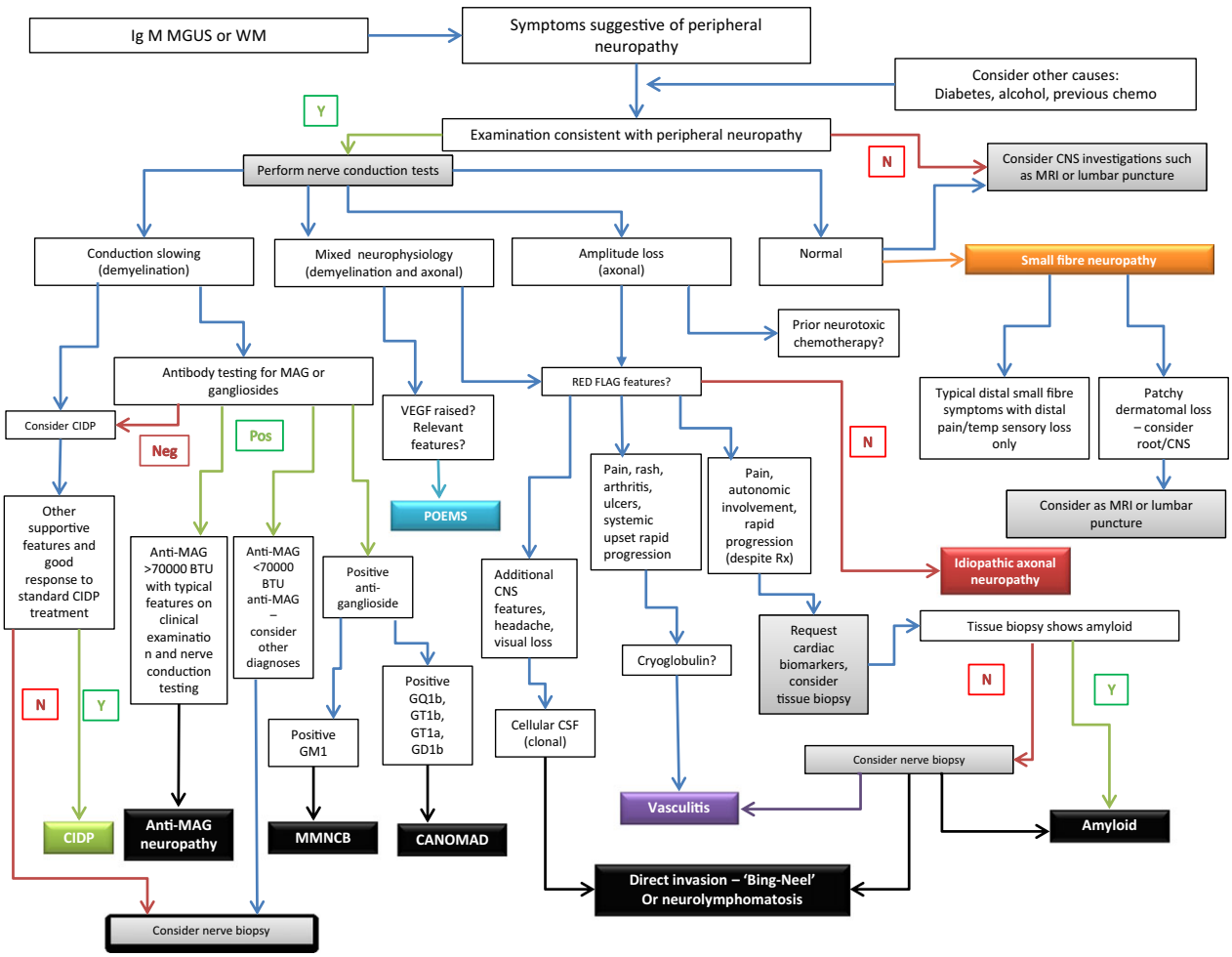

Fig 1. Schematic decision tree for the evaluation of IgM-associated peripheral neuropathies. Boxes in black denote IgM-related diagnoses. Other colours denote relevant differential diagnoses. BTU, Bühlmann units; CANOMAD, chronic ataxic neuropathy with ophthalmoplegia, M-protein, cold agglutinins and disialosyl ganglioside antibodies; CIDP, chronic inflammatory demyelinating polyneuropathy; CNS, central nervous system; CSF, cerebrospinal fluid; IgM, immunoglobulin M; MAG, myelin associated glycoprotein; MGUS, monoclonal gammopathy of undetermined significance; MMNCB, multifocal motor neuropathy with conduction block; MRI, magnetic resonance imaging; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes;Rx, radiotherapy; WM, waldenström macroglobulinaemia.

A number of studies of anti-MAG-negative IgM-associated PN have been reported. Response to immunomodulation including IVIG, corticosteroids, plasma exchange, or a combination is inferior in IgM-PN/DADS than idiopathic CIDP (Simmons *et al*, 1993a; Larue *et al*, 2011). Although short-term improvement is seen, no long term benefit has been shown for IVIG in IgM MGUS-associated PN (Dalakas, 1996; Comi *et al*, 2002).

Although these approaches have not been tested prospectively, in patients with rapid worsening neuropathy, a trial of IVIG, steroids or plasma exchange may prevent irreversible disability. Other agents, including chlorambucil and interferon-alpha, have not been pursued beyond early studies because of toxicity and limited or no benefit in trials (Oksenhendler *et al*, 1995; Mariette *et al*, 2000).

Recommendations

- **In patients without significant disability or haematological reason for treatment, there is no indication for immunosuppressive or immunomodulatory treatment, but ongoing surveillance is recommended to detect change.**
- **In patients with significant or progressive disability associated with a demyelinating non-MAG associated IgM MGUS with a co-existent neuropathy, immunosuppressive or immunomodulatory treatment may be considered.**
- **In treated patients who are unresponsive to IVIG, steroids or plasma exchange, rituximab, in combination with alkylators, purine analogues or steroids should be considered.**

- **Symptomatic treatment for tremor (propranolol, clonazepam, topiramate, gabapentin, barbiturates, botulinum toxin) and paraesthesia (gabapentinoids, tricyclic or newer antidepressant drugs) should be considered. Such patients should remain under review to identify evidence for clinical evolution.**

Anti-MAG antibody-associated PN

Up to 50% of patients with IgM-associated demyelinating PN have anti-MAG antibodies, more commonly IgMκ than λ (Nobile-Orazio *et al*, 1994) in the setting of IgM MGUS or WM (Baldini *et al*, 1994). Men are more often affected than women and experience unsteadiness, tremor or distal weakness. The typical age of onset is in the 7th decade and the course of the disease is insidious. In up to 50% patients, significant disability develops 10–15 years following the diagnosis (Nobile-Orazio *et al*, 2000).

All patients with IgM-associated demyelinating PN should be tested for anti-MAG antibodies. A clinically significant result is 'strongly positive' [for example >70 000 Bühlmann units (BTU)]. 'Weakly positive' (1000–7000 BTU) or 'positive' (7000–70 000 BTU) anti-MAG antibodies are less specific for typical anti-MAG neuropathy and may occur in the absence of a PN or alongside an incidental neuropathy. Low titres of anti-MAG IgM (1:200 or less) have been detected in 17 of 101 control patients without IgM M-proteins (Nobile-Orazio *et al*, 1989).

If the anti-MAG assay is negative in the presence of an IgM-associated PN, testing for IgM antibodies against other neural targets, including the gangliosides GM1, GD1a, GD1b, GT1b, GM2 and GM3 and the paragloboside, sulphate-3-glucuronyl para-globoside (SGPG), should be undertaken. Positive results may be supportive of a link between the paraprotein and the PN. If these antibodies are present, the probability of an association is increased but not proven. GM1 antibodies may be causally associated with a multifocal motor neuropathy, as can IgM GD1b antibodies. IgM disialosyl antibodies associate with CANOMAD (see below). Thirty to 40% of IgM-related demyelinating neuropathies still have no identifiable antibody.

The electrophysiological features associated with anti-MAG IgM demyelinating PN are readily recognisable with slowing of the main trunk velocity but disproportionate prolongation of the DML. Conduction block and abnormal temporal dispersion, more typically seen in CIDP, are very rare in this setting (Notermans *et al*, 2000).

A Cochrane Review summarises the evidence for treatments of IgM anti-MAG neuropathy (Lunn & Nobile-Orazio, 2012). IVIG may have some limited benefit in the short term (timescale of weeks), but this is of little clinical use. Corticosteroids alone are not effective (Nobile-Orazio *et al*, 2000), but may be beneficial in combination with other agents, such as cyclophosphamide (Niermeijer *et al*, 2007). The purine analogues have demonstrated a modest improvement in some studies (Ghosh *et al*, 2002; Niermeijer *et al*, 2006), and although tolerance of these agents was reported as good, the studies were small. For occasional patients with rapidly worsening neuropathy, especially with signs of motor disability, combinations of active agents or even high dose therapy have been attempted.

There are several non-randomised studies of rituximab in anti-MAG-associated PN, many reporting positive benefit in small groups of patients (Renaud *et al*, 2003, 2006; Briani *et al*, 2011; Zara *et al*, 2011; Hospital *et al*, 2013). Five published studies reported a worsening of the PN following rituximab (Broglio & Lauria, 2005; Gironi *et al*, 2006; Stork *et al*, 2013; Sala *et al*, 2014; Weiss & Becker, 2014). In the largest report (10 patients) of deterioration (Sala *et al*, 2014), worsening was acute and severe, and occurred during the treatment period, possibly related to an IgM flare. All the patients improved after initial deterioration but at final evaluation only one improved compared to baseline, five worsened and four stabilized.

Two randomised controlled trials of rituximab have been negative in their primary outcome measures, but the trials were both underpowered and the primary outcome measures inadequate (Dalakas *et al*, 2009; Leger *et al*, 2013). However, secondary outcome measures including patient impression of change were positive and a Cochrane Systematic review containing a meta-analysis highlights significant therapeutic benefit (Lunn & Nobile-Orazio, 2016).

Factors predictive of a response to rituximab in anti-MAG neuropathy remain to be elucidated. Short disease duration (less than 2 years), active progression at time of treatment and preservation of nerve density in biopsies might predict response (Treon *et al*, 2010). Anti-MAG titres and levels of IgM paraprotein are not related to the severity of neuropathy or predictive of response to treatment. It has been suggested that a significant drop in antibody titres might be necessary to achieve a response but the depth of optimal haematological remission is not known (Benedetti *et al*, 2007). Complete elimination of the clonal IgM is neither practical nor possible with current treatments.

Stability rather than improvement is the most likely outcome of treatment although rare dramatic improvements are reported.

Recommendation

- **There is moderate quality evidence that rituximab is of benefit in the treatment of anti-MAG demyelinating neuropathy. The standard dose of 375 mg/m^2 administered weekly for 4 weeks is recommended.**
- **In patients with significant or progressive disability associated with a demyelinating anti- MAG associated IgM MGUS with co-existent neuropathy, immunosuppressive or immunomodulatory treatment may be**

considered as an alternative to rituximab depending on availability, comorbidity and patient preference.
- **Measurably progressive disease causing disability is an indication to consider definitive treatment given earlier (<2 years from onset where possible) rather than later.**
- **Anti-MAG titres and levels of IgM paraprotein are neither related to the severity of neuropathy nor predictive of response to treatment.**

WM-associated PN

Symptoms of PN are present in about 20% of patients with WM at diagnosis, and up to 50% are affected at some time in the course of their disease (Levine *et al*, 2006), most often a distal chronic symmetrical predominantly sensory polyneuropathy. Nerve conduction studies show evidence of demyelination with prolonged DML and reduced conduction velocities in the cases associated with MAG antibodies. There are many exceptions with axonal neuropathies or mixed axonal and demyelinating neuropathies seen, especially when anti-MAG assay is negative (Viala *et al*, 2012).

When significant titres of anti-MAG antibodies (for example 'strongly positive' or >70 000 BTU) are present, they are probably pathogenic in the WM setting. If atypical clinical or electrophysiological features are present, other pathologies, including amyloidosis, cryoglobulinaemia, vasculitis or direct tumoural invasion of peripheral nerves, may be instrumental and appropriate investigations carried out as above.

Where neurotoxic therapy has been used, chemotherapy-induced PN, which is almost always axonal with rare exceptions, may be present and will need to be distinguished from WM-associated PN, based on the temporal pattern, character and electrophysiology.

The criteria for the initiation of therapy in symptomatic WM are well established (Dimopoulos *et al*, 2014) and include PN due to WM.

There are no trial data specifically assessing the efficacy of treatment options in WM-associated PN. Treon *et al* (2010) reported on the incidence, characteristics and treatment outcome of 199 disease-related PN identified in 900 WM patients. Among 122 PN patients evaluated for neuropathic antibodies, 24·5%, 1·64% and 0·81% were positive for MAG, GM1 and sulfatide antibodies, respectively (Treon *et al*, 2010). Thirteen of 61 (21·3%) patients examined for amyloid were confirmed positive. One hundred and fifty-one PN patients received chemotherapy comprising an alkylator, purine analogue or rituximab; or rituximab/purine analogue combination, cyclophosphamide, thalidomide or bortezomib. Of these, 71 (47%) had improvement and 8 (5·3%) had complete resolution of PN following therapy. Symptomatic improvement was more likely with non-amyloid related PN, in patients who achieved a major haematological response, those who received therapy within 24 months of the onset and those who received rituximab combination vs. any monotherapy vs. rituximab alone.

It is important to be aware that a paradoxical increase in IgM levels following rituximab ('flare') occurs in 30–70% of patients immediately after completing the rituximab course (Treon *et al*, 2004) and may be associated with a worsening of existing PN (Noronha *et al*, 2006), although this has been reported to be temporary. This phenomenon may be severe and resemble an acute inflammatory demyelinating neuropathy requiring appropriate management. Appropriate precautions should be taken in patients considered at high risk of a flare (IgM > 40 g/l), such as deferring rituximab until cycle 2 of combination chemotherapy or performing prior plasma exchange.

Avoidance of neurotoxic agents is important, although the speed of response to proteasome inhibitor-containing therapy may outweigh the risk of worsening the PN. Alternative dosing strategies, such as weekly dosed bortezomib, or second-generation agents like carfilzomib or ixazomib show promise in this regard (Alsina *et al*, 2012; Treon *et al*, 2014). Vinca alkaloids have no place in WM patients because they are associated with increased neuropathy rates without increasing response rate (Ioakimidis *et al*, 2009). Ibrutinib has shown symptomatic improvement in WM-associated PN that progressed after rituximab and could also be considered in WM patients with symptomatic IgM-related PN (Treon *et al*, 2015a). Plasmapheresis (Cortese *et al*, 2011), corticosteroids and IVIG are of little or no value (Treon *et al*, 2010) in the treatment of WM-associated neuropathies.

WM-related CNS manifestations, including Bing–Neel Syndrome (Castillo *et al*, 2016) and myelopathy are not within the scope of this review and are covered in a separate article (Minnema *et al*, 2016).

Recommendations

- **Patients with slowly progressing WM and/or PN do not require immediate therapy.**
- **Where treatment is required, treatments such as rituximab alone, dexamethasone, cyclophosphamide and rituximab (DRC), bendamustine-rituximab (BR), carfilzomib, rituximab, dexamethasone (CARD) or purine analogue combinations are possible options.**
- **When indicated, treatment of appropriate intensity to remit both the systemic disease and the neurological component is required.**
- **Ibrutinib, where available, could be considered in the setting of intolerance of chemotherapy-based therapies or if previous therapies have failed.**
- **Appropriate precautions should be taken in patients considered at high risk of a flare (IgM > 40 g/l), such as deferring rituximab until cycle 2 of combination chemotherapy or performing prior plasma exchange.**
- **Avoidance of neurotoxic agents is important; the vinca alkaloids have no place in the management of WM, particularly those with PN.**

- **Plasmapheresis, corticosteroids and IVIG are of little or no value in the treatment of WM-associated neuropathies.**

CANOMAD

Chronic ataxic neuropathy with ophthalmoplegia, M-protein, cold agglutinins and disialosyl ganglioside (IgM Anti-GD1b/GT1b/GQ1b) antibodies (CANOMAD) is a rare chronic neuropathy that presents as a chronic peripheral sensory ataxia, ophthalmoplegia and sometimes other cranial nerve involvement (Willison *et al*, 2001). NCS show a mixed picture of axonal loss and demyelinating features, including very low or absent sensory action potentials and degrees of slow motor conduction velocities. It is important to exclude alternative, infiltrative causes of cranial nerve abnormalities.

Clinical improvement has been noted following IVIG and Rituximab (Loscher *et al*, 2013).

Recommendations

There are no specific recommendations; each case must be treated on its own merit following discussion between haematologist and neurologist.

AL amyloidosis

AL amyloidosis should always be considered as a possible cause of a paraproteinaemic neuropathy. PN is reported as a symptomatic clinical feature in up to 20% of patients with AL amyloidosis, and evidence for a subclinical PN is found in 35% of patients (Rajkumar *et al*, 1998; Matsuda *et al*, 2011). In the IgM amyloidosis series by Sachchithanantham et al, combining an abnormal NT-proBNP and troponin T with liver involvement and the presence of neuropathy provided a useful risk model: the median overall survival of patients with zero, one, or two+ abnormal factors was 90, 33, and 16 months, respectively (Sachchithanantham et al, 2016). Common presentations include a progressive, painful small fibre predominant length-dependent PN which typically starts in the feet, accompanied by an autonomic neuropathy in about 65% of cases (Rajkumar *et al*, 1998). Amyloid causes direct nerve damage through the presumed action of fibrils in the endoneurium and the endoneurial vessels. Amyloid can also cause nerve damage by other mechanisms for example entrapment neuropathies including carpal tunnel syndrome, and neural or radicular infiltration resulting in multifocal mononeuropathies, lumbosacral or brachial radiculopathies and cranial neuropathies in the absence of a polyneuropathy (Rajkumar *et al*, 1998; Matsuda *et al*, 2011).

Amyloid is most often a systemic disease with other organ involvement and this is a strong pointer to an amyloid PN. Other features should be actively sought, such as cardiac insufficiency and arrhythmia, renal impairment with proteinuria, autonomic neuropathy, gastrointestinal bleeding, macroglossia and bleeding diatheses. Early recognition is important to curtail irreversible organ damage and reduce mortality. Notwithstanding pre-existing co-morbidities, screening for AL amyloidosis can be performed using two biomarkers, serum N-terminal pro b-type natriuretic peptide (NT-proBNP) and urinary albumin, that detect early amyloidosis in 97% of patients (Merlini *et al*, 2013).

Nerve conduction studies show a symmetrical, axonal sensorimotor neuropathy but occasionally patchy presentations or slowing (reported as 'demyelination') are found. A definitive diagnosis requires the demonstration of amyloid in a tissue. The most accessible and innocuous site is periumbilical abdominal fat that shows Congo red positive deposits in 80% of patients (Fernandez de Larrea *et al*, 2015). When combined with similar analysis of bone marrow, the sensitivity reaches 90% or more. In the rare patients in whom both biopsies are negative, a nerve biopsy might be considered. The sensitivity of nerve biopsy for detecting amyloid varies from 30% to 100% (Simmons *et al*, 1993b), depending upon the size and site of the biopsy and the expertise of the pathologist.

Urgent measures to suppress the clone responsible for the production of the amyloid protein are essential. Agents that produce a brisk response are preferred, including bendamustine and rituximab, followed by high does therapy and an autologous stem cell transplant in eligible patients (Sachchithanantham *et al*, 2016). The latter can result in a 53% 10-year survival for those achieving a complete response (Sanchorawala & Seldin, 2007). Best outcomes are likely to be achieved in centres that specialise in this condition.

For transplant ineligible patients (75–80% cases), bendamustine-, purine analogue- or bortezomib-based combinations are effective. There is some rationale and anecdotal experience of the benefit of maintenance rituximab as a way to deepen the light chain response in treatment of amyloidosis in the WM (but not MGUS) setting (Wechalekar, personal communication). When used, bortezomib needs to be administered with particular caution due to its neurotoxic potential, which can be reduced by subcutaneous administration and weekly scheduling. There is anecdotal evidence for the effect of carfilzomib in this setting tempered by concern about possible cardiotoxicity (Atrash *et al*, 2015).

Recommendations

- **Treatment of AL amyloidosis should be risk-adapted and response-tailored; neurotoxic agents should be used with caution.**
- **Rapidly-acting induction regimens followed by dose therapy and autologous stem cell transplantation in first response is the treatment of choice in suitable patients and should be carried out in centres with appropriate expertise.**
- **Appropriate treatments include purine analogue, bendamustine or bortezomib in combination with rituximab.**

Small fibre neuropathy

Typical small fibre neuropathy presents with length dependent burning pain beginning in the feet and may spread more proximally in a length dependent fashion. Symptoms are worse at night where they can disturb sleep, resulting in fatigue and increased daytime pain.

Similar small fibre symptoms, presenting as patchy dermatomal sensory disturbance subsequently coalescing are due to small fibre involvement of the sensory ganglia of lesser-understood pathology.

The diagnosis of a small fibre neuropathy is made on the basis of the history; the only clinical sign is a length-dependent sensory alteration to pinprick or temperature. This may be patchy with ganglion involvement. Investigations to prove small fibre involvement are quantitative sensory tests and skin biopsies stained for epidermal nerve fibres (distal small fibre neuropathy), which can be quantified in microscopy.

Treatment is symptomatic with gabapentinoids, tricyclic or newer antidepressants (Hoeijmakers *et al*, 2012; Themistocleous *et al*, 2014).

Recommendations

- **Evidence-based justification for treating a WM or MGUS-associated small fibre neuropathy is completely lacking.**
- **Treatment is usually symptomatic with tricyclic antidepressants, newer selective serotonin reuptake inhibitor/serotonin norepinephrine reuptake inhibitor drugs, opioids and gabapentinoids (very low quality evidence).**

Treatment response and clinical outcome measures

Clinical response in the setting of treated IgM and WM-associated neuropathies is a multifaceted process, taking account of the haematological response as per IWWM7 criteria (Owen *et al*, 2013) as well as the neurological response. The rate and degree of neurological response depends on the pre-treatment status of the patient (Galassi & Tondelli, 2016). Patients with significant axonal damage may have limited neurological recovery (Kawagashira *et al*, 2015).

Historically, outcome measures have focused on assessment of impairment based on muscle strength and sensory testing and disability, using classical test theory derived scales.

The Medical Research Council (MRC) sum score and the Neuropathy Impairment Score (NIS) sums the scores in muscles to represent the overall strength of a patient (Dyck *et al*, 2003). Sensory scores, including the Inflammatory Neuropathy Cause and Treatment (INCAT) sensory sum score (ISS) and Neuropathy Impairment Sensory score (NIS_{sens}) are similarly used to capture the sensory status of a patient (Dyck *et al*, 2005) but these measures require detailed and consistent neurological assessment and may not show meaningful changes over time.

Disability measures have been developed for inflammatory neuropathies, and the overall neuropathy limitations score or ONLS (van Nes *et al*, 2008) is a standard measure for US Food and Drug Administration (FDA) licensing requirements. Disability measures more accurately reflect meaningful change in a patient's condition.

Rasch Theory-built scales linearly reflect patient function over the whole range of abilities and are designed and validated for individual diseases. They comprise a simple questionnaire that can be easily completed by the patient in the waiting room. The Inflammatory Rasch-Built Overall Disability Scale (I-RODS), designed as part of the PN Outcome Measurement Standardisation (PeriNomS) study (Merkies *et al*, 2003; Vanhoutte *et al*, 2012; Draak *et al*, 2014) is a valid disability scale for inflammatory neuropathies which captures meaningful changes over time.

Recommendations

- **The I-RODS more often captures clinically meaningful changes over time, with a greater magnitude of change, compared with the INCAT-ONLS disability scale and its use is therefore suggested in future trials involving patients with inflammatory neuropathies.**

Models of care

The clinical entities that comprise IgM-associated PNs are managed in a variety of clinical settings by haematologists, oncologists and neurologists. In order to achieve successful outcomes for these patients, joint working across disciplines offers a favourable approach that should overcome the barriers of working in isolation and and increases the likelihood of performing appropriate diagnostics and offering optimum therapeutic and supportive input.

Physical and occupational therapists play a vital role in helping to improve and maintain functions that may be limited by PN including exercise intervention to help improve strength (Streckmann *et al*, 2014), balance and coordination activities which can help decrease the risk of falling (Riva *et al*, 2014). Tailored home exercise is acceptable to individuals with inflammatory neuropathies and is associated with significant improvements in activity limitation, fatigue, quality of life and mood (White *et al*, 2015). Patient education can focus on improving safety, preventing injury and finding alternative ways to perform certain tasks.

Provision of appropriate and well-fitting orthotic supports, can improve the efficiency of movement as well as harvesting energy from gait (Alam *et al*, 2014).

Recommendations

- **A suggested model of care is a combined neurological and haematological clinic, in which patients are seen jointly**

by a specialist neurologist and haematologist and a decision can be made about the sequence of investigations, interventions and the formulation of a treatment plan.

- **Appropriate and timely referral to physical, occupational and orthotic professionals is recommended in order to maximise safety and function.**

Future perspectives

A number of biological agents are currently under investigation in WM that may prove particularly suited to the treatment of patients with paraproteinaemic neuropathies, given their non-neurotoxic side effect profiles.

The next generation proteasome inhibitor, carfilzomib, has been assessed in combination with rituximab and dexamethasone (Treon *et al*, 2014), showing an overall response rate (ORR) of 87% and a low risk of neurotoxicity. Trials with ixazomib are ongoing. Everolimus, an oral mTOR inhibitor (Treon *et al*, 2013) (ORR 72% in the upfront setting) has some grade ≥2 adverse events which do not include PN. Other effective agents that have favourable side effect profiles in this setting include the Bruton tyrosine kinase inhibitors ibrutinib (Treon *et al*, 2015b), acalabrutinib (Wu *et al*, 2016), and BG-3111 (Tam *et al*, 2015) and IMO-8400 (Thomas *et al*, 2015), an oligonucleotide specifically designed to inhibit Toll-like receptor signalling pathways, for which MYD88 is a key linker protein. Daratumumab, a human antibody to CD38, has also shown encouraging responses (Phipps *et al*, 2015) and may be particularly suited to those instances when the clinical features are a consequence of the M protein, such as hyperviscosity and neuropathy.

Conclusions

There is much to be done to improve outcomes for patients with IgM and WM-associated peripheral neuropathies. Starting with early recognition of the problem, appropriate causal attribution achieved through sensitive diagnostics that are not overly invasive, timely therapeutic intervention with effective and non-neurotoxic therapies, achievement of an appropriate degree of clonal reduction for optimum clinical outcomes and the use of reproducible and readily applicable tools to measure outcomes. Clinical trials of emerging therapies are urgently needed in this clinical setting.

Author Contributions

The entire authorship made up the Consensus Panel, which reviewed this subject and devised the strategy for the paper. SD, MJK, MPL wrote the paper, JJC, MD, EK, EL, VL, GM, SPT and JMV contributed to various sections of the paper and reviewed the completed document.

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