Investigation and Management of Immunoglobulin M– and Waldenström-Associated Peripheral Neuropathies

Oliver Tomkins, BMBS, MRCP[a], Veronique Leblond, MD, PhD[b], Michael P. Lunn, FRCP, PhD[c], Karine Viala, MD[d], Damien Roos-Weil, MD, PhD[b], Shirley D'Sa, FRCP, FRCPath, MD(Res)[a,*]

KEYWORDS

• IgM neuropathy • Paraproteinemic neuropathy • Anti-MAG • CANOMAD

KEY POINTS

- Immunoglobulin M (IgM)-associated peripheral neuropathies are a heterogeneous group of disorders, which together represent most of the cases of paraproteinemic neuropathy.
- Anti-myelin-associated glycoprotein neuropathy constitutes half of the IgM-related cases, and antibody-negative IgM demyelinating neuropathy, multifocal motor neuropathy with conduction block, light chain amyloid neuropathy, cryoglobulinemic neuropathy, and CANOMAD syndrome form most of the remainder.
- Patients with a progressive disability could be treated with rituximab-based therapy, with or without additional chemotherapy.

INTRODUCTION

The immunoglobulin M (IgM)-associated peripheral neuropathies (PNs) are a heterogeneous group of disorders that can result in significant disability, and together they represent most of the cases of paraproteinemic neuropathy.[1] IgM-PNs are associated with a monoclonal gammopathy of undetermined significance (MGUS)—in this

[a] Department of Haematology, Centre for Waldenströms Macroglobulinaemia and Related Conditions, University College London Hospitals NHS Foundation Trust, 250 Euston Road, London NW1 2PG, UK; [b] Department of Haematology, Sorbonne University and Pitié Salpêtrière Hospital, 47-83 Bd de l'Hôpital, Paris 75013, France; [c] National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK; [d] Department of Clinical Neurophysiology, Sorbonne University and Pitié Salpêtrière Hospital, 47-83 Bd de l'Hôpital, Paris 75013, France
* Corresponding author.
E-mail address: s.dsa@nhs.net
Twitter: @tomkinsoliver (O.T.)

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context, perhaps better termed monoclonal gammopathy of neurological significance—or Waldenström macroglobulinemia (WM).[2,3] More rarely, IgM-PN occurs with other chronic B-cell disorders secreting IgM.

The pathophysiologic mechanisms through which the underlying clonal disorder causes neuropathy are manifold and include (1) autoantibody activity of the IgM directed to different antigenic components of the peripheral nerves, (2) the physicochemical properties of the circulating IgM resulting in cryoglobulinemic vasculitis, (3) the deposition of amyloid causing direct neural insult, and (4) neoplastic infiltration of peripheral nerves, known as neurolymphomatosis. The various mechanisms determine different clinically distinct presentations. Appropriate investigations may help clinicians identify the neuropathy mechanism to adapt the therapeutic strategy to the patient.

Given the significant background rates of both neuropathies and paraproteinemia, their coexistence in an individual patient does not immediately infer causality. However, an IgM paraprotein is of unique immunogenicity and is often significant. At the heart of the diagnostic approach lies the collaborative work and experience of the hematologist and neurologist in the clinic.

INCIDENCE AND PREVALENCE

IgM paraproteins and neuropathies are common in an older population where the median age of onset of paraproteinemic neuropathy is 59 years.[4] The population prevalence of monoclonal gammopathy is estimated to be 3.2% in persons older than 50 years, increasing steadily with age. IgG paraproteins account for the majority; IgM paraprotein comprises 16.9% of the overall total.[5] MGUS exceeds WM as the underlying diagnosis by at least 3:1,[6] probably because MGUS is more common. The prevalence of disease-related IgM-PN in patients with WM is 13% to 22%.[7,8] For IgM MGUS, estimates of an associated IgM-PN are 15% to 31%, but the latter is likely to be an overestimate.[9] A recent analysis with a 20% prevalence of PN in patients with IgM monoclonal gammopathies identified that a quarter of the "IgM-PN" cases had other causes, resulting in an IgM-PN prevalence of 15%.[6] Thus, neuropathies associated with IgM paraproteins are frequently encountered, but a causal link is not always present, and other causes of neuropathy or disability should be sought.

PROGNOSIS

Most patients remain functionally able and independent even after many years, and most will not come to require treatment.[10] However, some will progress, and the varying neuropathologies have differing clinical consequences (eg, progressive autonomic failure alongside sensory and motor deficits in light chain (AL) amyloid result in specific disabilities). Some will need mobility aids, analgesia, and cardiovascular support.

SPECIFIC IMMUNOGLOBULIN M AUTOANTIBODY REACTIVITY

Immunoglobulin M Anti-myelin-Associated Glycoprotein Paraproteinemic Peripheral Neuropathy

The clinical phenotype of anti-MAG neuropathy is classic and easily recognisable. Patients are typically men and in their seventh decade (median 62.6 years).[11] Patients present with progressive, symmetric distal sensory loss in the feet associated with early unsteadiness and frequently a complex tremor. The tremor is postural and has both cerebellar and peripheral features, with a side-to-side finger tremor and some jerkiness, potentially disabling.[12] Anti-MAG PN is usually painless, and positive

sensory symptoms include “tightness” or “aching.” As a result of the sensory loss, patients walk with a broad-based gait with foot misplacement and experience unsteadiness predominantly in the dark. Motor weakness is a late feature and predominantly involves the distal legs.

On examination, sensory neuropathy with reduced or absent reflexes is found. Defining features are a tremor of the upper limbs, little or no wasting of muscles, and a typical sensory loss. Pinprick is reduced distally in the lower limbs, joint position sense is minimally impaired, but vibration sensation is often reduced to the hips or even the costal margin.[13]

Typical nerve conduction study (NCS) findings demonstrate a patchy demyelinating neuropathy, with very prolonged distal motor latencies compared with the slowing of the main motor trunk, resulting in a terminal latency index of less than 0.25 in some but not necessarily all tested nerves.[11,14]

Anti-MAG activity is part of the innate antibody repertoire. Disease-relevant IgM anti-MAG activity can be detected in the serum using one of several techniques, usually enzyme-linked immunosorbent assay–based. Anti-MAG antibodies cross-react with sulfoglucuronyl paragloboside and sulfoglucuronosyl lactosaminyl paragloboside, gangliosides that all display the common carbohydrate HNK-1 epitope.[1,15,16] Although there are various ways that these antibodies are reported, anti-MAG activity is much more likely to be relevant when the levels of activity are reported as “strongly positive” (Buhlmann titer units > 70,000).[17–19] Finding an anti-MAG antibody does not mandate a diagnosis of an anti-MAG neuropathy; the clinical and electrophysiologic picture must also be consistent, with the antibody result considered confirmatory. A nerve biopsy is usually not performed, as the clinical and electrophysiologic features associated with an anti-MAG antibody are usually diagnostic. When performed, widely spaced myelin (widening of the intraperiod line on electron microscopy) is pathognomic.[15,20]

The natural history is most usually indolent and slowly progressive, with favourable long-term outcomes even without treatment in some. Disability rates at 5 years from diagnosis have been quoted at 16%, increasing to 22% to -24% at 10 years and 50% at 15 years.[4,10] Half of patients do not require treatment. The mere presence of anti-MAG neuropathy is not an indication for treatment, whereas measurably progressive patient disability is.[2] More data regarding the treatment of anti-MAG neuropathy are needed. Therapy is best considered stabilizing, as clinical improvement is less common and typically limited.[2] A Cochrane meta-analysis concluded that there is an insufficient evidence base to support specific treatments[21] and that intravenous immunoglobulin (IVIg) had a statistically, but probably not clinically, significant short-term effect with rapidly waning efficacy. Meta-analysis of 2 rituximab studies demonstrated a benefit not found in the underpowered individual studies. The placebo-controlled RiMAG[22] study (375 mg/m^2 weekly for 4 weeks) found no significant difference in sensory scores but significant improvement in disability scales at 12 months. Self-assessment by patients found that 26% experienced improvement and 52% stabilization following rituximab. With placebo, figures were 3% and 36%, respectively. A second study found a significant improvement in the time to walk 10 meters in patients randomized to rituximab over placebo.[23]

Transient worsening with rituximab has been reported, attributed to IgM flares in the setting of WM.[24] Despite the paucity of evidence, rituximab is recommended for progressive anti-MAG neuropathy, especially when associated with MGUS.[2] A short disease duration (<2 years and probably <5 years) and active progression at treatment time favourably predict response to therapy.[7]

In severe and rapid progressive anti-MAG neuropathy, adding chemotherapy to rituximab can be an option leading to a shorter response time. In a retrospective study in

64 patients, improvement at 1 year of the modified Rankin score rates were 46% and 18% in the immunochemotherapy group and rituximab group of patients, respectively, with a median time to response of 8 and 13 months ($p = 0.023$).[25] The Bruton tyrosine kinase (BTK) inhibitor ibrutinib also has some early promising reports, with several patients exhibiting PN stabilization or improvement; this includes subjective reports in 13 patients and objective reports in 3 patients with the $MYD88^{L265P}$ mutation, most previously treated with rituximab.[26–28]

Neuropathies with Immunoglobulin M Activity Directed to Other Peripheral Nerve Epitopes

Gangliosides are present on the surface of many cells but are elaborated on nervous system cells with more than 100 classes detected. They present a somewhat carbohydrate antigenic target, as the glycoprotein MAG mentioned earlier, and likewise can be targeted by IgM antibodies.

Multifocal Motor Neuropathy with Conduction Block

IgM paraprotein with autoantibody activity against ganglioside GM1 is associated with a progressive motor phenotype with distal, asymmetric upper limb weakness, a characteristic distinct from other IgM-PN. Sometimes there is combined anti-GD1b activity with high laboratory titers implicating the paraprotein component. Neurophysiology demonstrates a demyelinating neuropathy characterized by multiple conduction blocks and normal sensory action potentials. In multifocal motor neuropathy with conduction block (MMNCB), individual nerves can be identified with a mononeuritis multiplex presentation.[29]

Anti-GM1 IgM is seen in 40% of all cases of MMNCB. GM1 serves an important function in maintaining motor nerve function. Although anti-GM1 antibodies are identifiable in healthy individuals, in the presence of a suspected immune motor neuropathy, a high-titer anti-GM1 IgM is 85% specific.[30] IVIg has an established role in managing nonparaproteinemic MMNCB, and multiple randomized controlled trials have demonstrated a clear benefit.[31] A Cochrane meta-analysis concluded a 76% improvement in muscle strength with IVIg versus 4% in placebo.[32] Most patients depend on maintenance IVIg to maintain muscle strength. Although there is an improvement with evidence of remyelination and reinnervation, there is still progressive axonal loss over time.[33] If IVIg is ineffective, suppression of the IgM clone is worthwhile, although unsupported by evidence.

CANOMAD Syndrome

This is an acronym for the very rare condition of chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins, and disialosyl antibodies. Patients are typically in their seventh decade of life (median age 62 years) and 80% are men.[34] IgM targets disialosyl epitopes on gangliosides, GD1b/GD3/GT1b/GC1b.[34,35] Half of the cases have antidisialosyl IgM that reacts to all 4 epitopes.[34] These gangliosides predominate in the dorsal root ganglia and oculomotor nerves, resulting in a clinical presentation with chronic ataxic neuropathy and ophthalmoplegia. The acronym can be restrictive, as not all features are always present; ophthalmoplegia is present in only half of the cases and cold agglutinins in a third.[34] CANDA, chronic ataxic neuropathy with disialosyl antibodies, has been suggested as an alternative.[36] A recent study identified that the main clinical features were sensory symptoms with ataxia and paraesthesia (100%), motor weakness (42%), ophthalmoplegia (42%), and bulbar symptoms (12%). Cold agglutinins were identified in 13 (30%) patients. Electrophysiologic studies showed a predominant demyelinating pattern with low or absent

sensory action potentials and slow motor conduction velocities. An axonal pattern is rare.[34] Excluding infiltrative causes in patients with ophthalmoplegia and other cranial nerve palsies is imperative.

CANOMAD syndrome is responsive to IVIg in 40% to 60%[34,37] and therapeutic plasmapheresis in 50% of cases,[34] in retrospective analyses. Improvement with rituximab-based therapy has an efficacy of 53%, used in patients refractory to IVIg. It can be readministered efficaciously in patients who progress after a period of improvement or stability, although no randomized evidence exists.[34]

Physicochemical properties of the immunoglobulin M

Cryoglobulinemic vasculitis. Monoclonal IgM can be associated with type I and type II cryoglobulinemia. IgM monoclonal type I cryoglobulin deposits result in vascular occlusion, whereas type II results in small and medium vasculitis. There is a greater proportion of peripheral neuropathy in type II.[38,39] Patients with cryoglobulinemic vasculitis present with painful distal sensory neuropathy with burning, shooting pains, and deep aching; however, it can present with asymmetrical presentations or multifocal mononeuropathy. Systemic clues are livedo reticularis and lower limb ulceration, with multiple small and "punched out" ulcers. Renal involvement and polyarthralgia are rarer. PN is the most frequent symptom after skin purpura.[38,40–42]

Neurophysiology demonstrates an axonal length-dependent sensorimotor neuropathy, often with an asymmetrical component. A nerve biopsy is required in cases of isolated cryoglobulinemia without cutaneous or renal features. The most affected sensory nerve, typically the sural or superficial peroneal, can be identified neurophysiologically. Typical findings are of large fiber degeneration without evidence of regeneration, and alongside are common features of vasculitis with inflammatory infiltrates around the vessels. Intravascular cryoglobulin deposition in vasa nervorum is described.[43]

Mild symptoms may abate with cold prevention, but in cases of rapidly progressive neuropathies plasma exchange may temporize critical symptoms. Definitive treatment should be directed at the underlying clone. High-dose corticosteroids and rituximab are first-line treatments. After rituximab failure, alkylating agents in combination with rituximab and other treatments can be used.[44]

Light chain amyloid neuropathy. IgM-associated AL amyloidosis accounts for 5% to 7% of all amyloidosis. In IgM-related AL amyloidosis, direct axonal nerve damage occurs through amyloid fibril deposition in endoneurium and endoneurial vessels, resulting in neuropathy. It represents 6% of cases of IgM-PN.[6,8] Neuropathy is the presenting feature in 15% of all AL amyloid cases and 28% of IgM-related AL amyloid.[45,46] Compared with non-IgM amyloidosis, the proportion of lambda light chain is small with a relatively low free light chain level. Patients have rapidly progressive length-dependent painful PN with paraesthesia, burning, and allodynia. Asymmetric distribution is seen in 50%.[47] Cranial nerve involvement and a mononeuritis multiplex have been described.[48] The neurophysiology shows progressive axonal neuropathy. Initially, there is a small fiber neuropathy resulting in autonomic dysfunction,[49,50] but with time there is large fiber involvement. Small fiber neuropathies are distal, symmetrical, purely sensory, and painful. The pain is characteristically burning and very prominent at night, often disturbing sleep. No signs are found on examination, as the tendon reflexes and joint position, vibration, and sometimes pinprick sensation are preserved. Standard neurophysiology testing is also normal, but thermal thresholding (quantitative sensory testing) or Sudoscan can demonstrate abnormalities.[51] Other findings consistent with AL amyloidosis should be sought, for example, orthostatic hypotension, erectile dysfunction, diarrhoea, proteinuria, and cardiac involvement.[6,47]

Incidental MGUS can occur with non-AL amyloidosis causes, most commonly hereditary transthyretin amyloidosis.[47] The diagnosis of amyloidosis is histological. Attempts should initially focus on least invasive biopsies, such as abdominal fat aspiration, a rectal biopsy, and/or trephine biopsy, with Congo red staining. A nerve biopsy may be necessary when the index of suspicion remains high.[2,47] Where biopsy is inconclusive or not feasible, a radiolabelled serum amyloid-P scan with a 90% sensitivity is used when available. Although unable to demonstrate nervous deposition, it can confirm the presence of visceral amyloid deposits to be biopsied.[52]Any biopsy confirming the presence of amyloid deposition should be sent for typing to determine the precursor protein and accurately diagnose the amyloidosis subtype before initiating treatment.

Therapy for IgM-related AL amyloidosis is urgently directed at the underlying clone to suppress amyloid production. In the context of an IgM-related disorder, there is no therapeutic consensus, but it typically involves bendamustine and rituximab therapy followed by high-dose therapy and autologous stem cell rescue if fit.[53] Proteasome inhibitor–containing therapy should be used with caution in cases of neuropathy.[54]

Peripheral neurolymphomatosis in Waldenström macroglobulinemia. Cases caused by lymphoplasmacytic lymphoma (LPL) with IgM paraprotein are described.[55–57] LPL is a rare entity, and neuropathy can affect a combination of peripheral nerves, nerve roots, plexus, or cranial nerves. Invasion of the peripheral nervous system by LPL should come within the definition of Bing-Neel syndrome. Invasion can present with almost any of the aforementioned symptoms or signs; mono- or multiple neuropathies, confluent motor and sensory distal neuropathies, or proximal and distal weakness of a polyradiculoneuropathy reminiscent of chronic inflammatory demyelinating polyneuropathy (CIDP) can all be presenting features. Neuropathic pain is frequent. Cases progress over weeks and can be aggressive and disabling. Electrophysiology shows axonal neuropathy, sometimes with electrical "pseudoblock," which can also be confluent or patchy. Cerebrospinal fluid (CSF) can occasionally yield a diagnosis but frequently shows elevated protein, with or without pleocytosis. Cytological examination, immunophenotyping, and molecular studies, including polymerase chain reaction (PCR) for immunoglobulin heavy-chain variable-region (IgVH) rearrangements and *MYD88* mutations, are required to search for clonal cells. PET/computed tomography (CT) scans can sometimes identify affected nerves and may correlate with high-field MRI neurography images, with a higher diagnostic yield than with either modality alone. A nerve biopsy may be required, with a reported sensitivity of 30% to 100%.[55,58]

Other neuropathies

Chronic inflammatory demyelinating polyneuropathy. This type of neuropathy has been mentioned in several series but with few clinical details.[59,60] The prevalence of monoclonal gammopathy is 18% in idiopathic chronic inflammatory demyelinating polyneuropathy.[61] A demyelinating polyneuropathy in patients without anti-MAG antibodies may suggest a CIDP; despite the absence of an antibody, there is likely to be a causal link between IgM and neuropathy. The clinical picture of patients with demyelinating polyneuropathy is varied, with pure sensory, sensorimotor, or pure motor symptoms. A demyelinating neuropathy was the primary feature in three-quarters of the patients; early axonal loss during the neuropathy often leads to the suspicion of an associated hemopathy. Three main treatments are currently used: corticosteroids and IVIg as first-choice treatments and plasma exchange as an alternative.[37] In refractory or CIDP first-line–dependant patients, rituximab showed a 75% response rate and is effective in patients with an associated hematological disease.[62] The addition of alkylators, purine analogues, or steroids can be considered in refractory cases.[2]

Axonal neuropathies unrelated to the immunoglobulin M gammopathy. Patients with monoclonal IgM gammopathy may present with neuropathy due to another cause, such as diabetes, alcohol, or age. In the general population, in those older than 65 years, there is a prevalence of mild axonal slowly evolutive sensory neuropathy of 25%. In a prospective study, Levine and colleagues[60] found mild axonal sensory neuropathy to be the most frequent type of neuropathy in WM.

APPROACH TO DIAGNOSIS

The clinical history and examination are paramount to investigating a patient with suspected IgM-PN. Alternative causes of neuropathy should be considered, including hereditary neuropathies. Salient points in the clinical history, physical examination, and baseline investigations are outlined in **Table 1**. The Inflammatory Rasch-Built Overall Disability Scale (I-RODS) is the recommended disability assessment scale for inflammatory neuropathies, able to capture temporal changes in function.[63]

Table 1
Approach to diagnosis

History	Examination	Initial Investigations
Rate of progression	Peripheral nervous system	NCS and EMG
Clinical course—monophasic, relapsing and remitting, or progressing	Cranial nerve examination	B12 and folate, MMA, B9
Ataxia, falls	Fundoscopy	HbA1c
Motor vs sensory symptoms	Wasting	HIV antibody, hepatitis B core antibody, hepatitis B surface antigen, hepatitis C antibody, ± lyme serology
Tremor	Fasciculation	C3, C4 complement levels, ANA, and dsDNA
Atypical symptoms, including pain	Hepatosplenomegaly	Anti-MAG
Infective trigger	Macroglossia	Antiganglioside antibodies GQ1b, GM1, CD1a, GD1b, SGPG
Alcohol and drug exposure	Lying and standing blood pressure	+/− VEGF
Effect on functional abilities		Urine protein:creatinine ratio
Autonomic symptoms		Cryoglobulin testing (warmed tubes)
		NT-proBNP, troponin T
		+/TTR sequencing
		ECG
		Bone marrow aspirate morphology, immunophenotyping, MYD88L265P, trephine biopsy including Congo red staining
		CSF for cell count, protein, IgM, PCR for IgVH rearrangement and MYD88 mutations, immunophenotyping

Nerve Conduction Tests

Neurophysiologic examination, such as NCS and electromyography, is undertaken when PN is identified or suspected on clinical grounds; this determines the predominant targets of damage (conduction slowing and axonal), the pattern (sensory, motor, or sensorimotor and patchy or length dependent), and the extent of nerve damage.[2] Distinguishing between conduction slowing (demyelinating) and axonal neuropathy is essential to suggesting a pathomechanism, investigation, and eventual diagnosis of the neuropathy (**Figs. 1–3**).

Serological Testing

All patients with neuropathy and an IgM paraprotein should undergo testing for anti-MAG antibodies and a panel of antiganglioside antibodies, including anti-GM1 and the disialosyl gangliosides GD1b, GD3, GT1b, and GQ1b. A search for cryoglobulins with appropriate warmed tubes and transport chain, C3, C4 complement levels, ANA and dsDNA, glucose, free-light chain measurement, B12 and B9 vitamins, hepatitis and Lyme serologies and probably TTR sequencing should be considered in many. Cryoglobulinemia tests must be repeated before concluding their negativity.

Cerebrospinal Fluid Analysis

CSF analysis is indicated if there is clinical concern regarding direct lymphomatous central nervous system infiltration (Bing-Neel syndrome) or peripheral neurolymphomatosis. Traditional CSF analysis of total protein, glucose, and bacterial culture is inadequate in many patients. CSF proteins can be measured, including albumin, IgG, IgM, and beta-2 microglobulin, which is useful in determining CSF involvement. The CSF should also undergo a cellular count from a large sample and cytology. Immunophenotyping by flow cytometry and molecular studies, including PCR for IgVH rearrangement and *MYD88* ^{L265P} mutation in WM patients, are key investigations on CSF. Large-volume CSF (at least 5–10 mLs) and rapid examination (within hours) increase the diagnostic yield.[2] Immunophenotyping on a typical small-volume sample taken during a lumbar puncture or a long delay before the sample is processed leads to false-negative results.

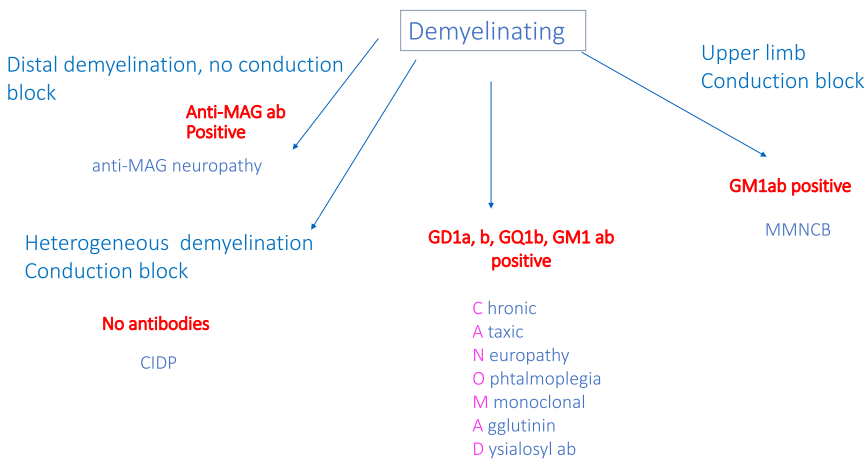

Fig. 1. Diagnostic algorithms of IgM-related neuropathy according to neurophysiological pattern. CIDP, chronic inflamatory demyelinating neuropathy; MMNCB, multifocal motor neuropathy with conduction block.

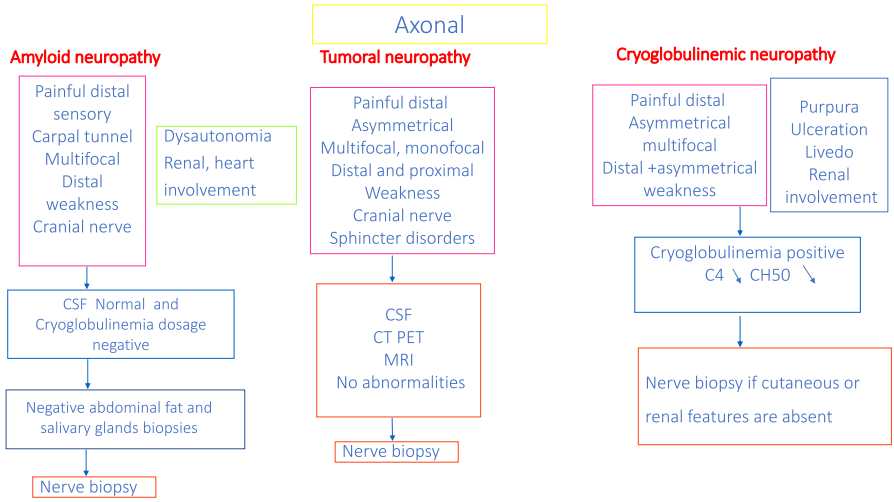

Fig. 2. Diagnostic algorithms of IgM-related neuropathy according to neurophysiological pattern.

Imaging

MRI must be performed before a lumbar puncture to avoid postprocedural spurious leptomeningeal enhancement, which could be misinterpreted as infiltrative disease. Targeted imaging should be obtained where there is suspicion of neural compression, leptomeningeal, or direct proximal radicular neural infiltration. The cauda equina has the best diagnostic yield. Imaging can assist in decisions regarding the optimal site of nerve biopsy but not the differential nature of nerve lesions.[2] Neurolymphomatosis is suggested if there is thickening and enhancement of individual nerves.[2,58] PET/CT scan has a higher diagnostic sensitivity than MRI alone for neurolymphomatosis and should be undertaken.[58,64]

Bone Marrow Aspirate and Trephine Biopsy

Most of the IgM-associated PN is caused by IgM MGUS.[65] Low-level MYD88-mutated small B-cell clones, identifiable only on flow cytometry on a bone marrow aspirate sample, have been identified in patients with an IgM-associated PN.[66] Indeed, the incidence of $MYD88^{L265P}$ may be higher in those with IgM paraproteins affected by neuropathy.[67] Compared with other patients with WM, those with PN have been found to have lower serum IgM and lower bone marrow disease burden,[7] perhaps a product of earlier diagnosis in the context of immune-mediated clinical symptoms prompting diagnostic evaluation. Bone marrow evaluation should be undertaken to demonstrate the nature of the underlying clonal disorder (immunophenotyping, PCR for $MYD88^{L265P}$), including evidence of these small clones, and has utility in suspected cases of AL amyloidosis, where a positive Congo red stain can prevent a sural nerve biopsy.

Nerve Biopsy

The role of nerve biopsy has diminished in recent years, as noninvasive diagnostic tests (such as anti-MAG antibody testing and CSF immunophenotyping) have facilitated nonbiopsy diagnosis. Nerve biopsy should be used in selected cases as a targeted diagnostic tool for neurolymphomatosis, amyloid, and vasculitis, synthetized

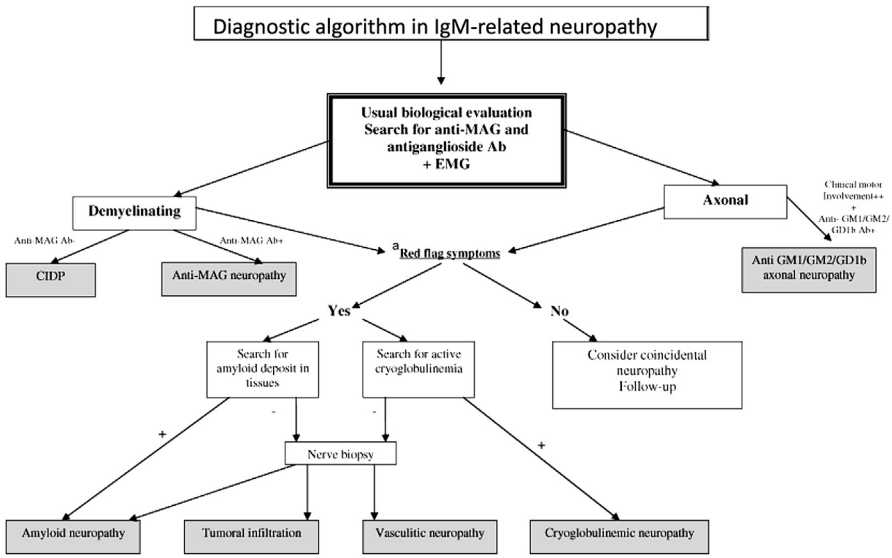

Fig. 3. Suggested strategy for diagnosing neuropathy in patients with Waldenström macroglobulinemia. [a]Red flag features are pain, multifocal topography, rapidly evolving course, cranial nerve involvement, dysautonomia, weight loss, cutaneous signs, heart/kidney/lung involvement, and abnormal serum-free light-chain concentration and ratio. Ab, antibodies; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; EMG, electromyography; MAG, myelin-associated glycoprotein. Usual biological evaluation including serum protein electrophoresis and immunofixation, free light chain in the serum, blood cell count, sedimentation rate, complement (hemolytic 50, C3, and C4 levels), rheumatoid factor, search for cryoglobulinemia, serum glucose, urea, and vitamin B12, Lyme, hepatitis, and HIV serologies. (*Adapted from* Viala K et al, 2012.)

in **Table 2**, guided by an experienced neurologist and hematologist and performed at a centre with expertise in peripheral nerve harvest and analysis.[2,68] Long-term sequelae, including pain and paraesthesia, are possible but infrequent, and thus the risks and benefits should be balanced.[2] Evidence of amyloid deposition should first be sought in other tissues, such as fat pad aspirate or trephine biopsy.

In cases of lymphocytic histological infiltration, immunophenotyping and molecular studies should be attempted to distinguish clonal from inflammatory infiltrate. Congo red staining for amyloid and kappa/lambda light chain immunostains can assist in clarifying pathology. Some stains and studies require an unfixed frozen nerve sample that must be determined before the biopsy, to be snap-frozen and not fixed.

TREATMENT SUMMARY

The presence of neuropathy alone is not an immediate indication for treatment, given the slowly progressive nature of the IgM-PN. To balance the risks and benefits of immunosuppressive treatments, a period of close monitoring is typically warranted initially, with documented progression prompting treatment.[2] Most of the clinical evidence is for anti-MAG PN, although even here, it is scant. Low-level MYD88-mutated small B-cell clones seem to be associated with treatment responsiveness to single-agent rituximab,[66] and a similar approach is taken to patients with underlying IgM MGUS. Patients with WM associated with a progressing IgM-PN are typically treated with

Table 2
Specific features of the individual immunoglobulin M peripheral neuropathies

Condition	Clinical	Electrophysiology	Antibody	Nerve Biopsy
Anti-MAG	• Slowly progressive distal sensory • Painless paraesthesia • Ataxia • Prominent tremor • Motor only in late	• Markedly prolonged distal latency index	MAG	Widened myelin lamellae
Multifocal motor neuropathy with conduction block	• Motor only • Distal, asymmetric upper limb weakness	Motor nerve conduction block as noncompressible sites	GM1/GD1b	May be normal
CANOMAD syndrome	• Distal sensory • Chronic ataxic neuropathy • Ophthalmoplegia +/− Bulbar palsies	Demyelinating pattern with very low or absent sensory action potentials and slow motor conduction velocities	GD1b/GD3/GT1b/GC1b	Demyelinating, axonal, and mixed features
Cryoglobulinemic vasculitis	• Painful distal sensory neuropathy with burning, shooting pains, and deep aching +/− Skin purpura +/− Renal involvement	Axonal length–dependent sensorimotor neuropathy often with an asymmetrical component	Negative	Large fiber degeneration, no regeneration, vasculitis, cryoglobulin deposition
AL amyloid	• Rapidly progressing sensorimotor • Painful, burning, allodynia • Autonomic symptoms	• May be normal Axonal sensorimotor neuropathy +/− median nerve entrapment • Abnormal thermal thresholds	Negative	Amyloid deposition on Congo red staining
Peripheral neurolymphomatosis	Mono- or multiple neuropathies, confluent motor and sensory distal neuropathies, or proximal and distal weakness of a polyradiculoneuropathy	Axonal neuropathy, sometimes with electrical "pseudoblock"	None	Lymphomatous infiltration

rituximab alone, dexamethasone-cyclophosphamide-rituximab, or bendamustine-rituximab. BTK inhibitors can also be considered according to local reimbursement arrangements.

SUMMARY

The IgM-PNs are a heterogeneous group of disorders capable of causing progressive patient disability. Although effective interventions can be used in patients with progressive symptoms, high-quality evidence is lacking, and disability may be irreversible. The collective experience of the peripheral nerve neurologist and hematologist in the clinic lies at the heart of early detection and timely intervention, alongside access to orthotics, specialist therapy services, and neuropathic adjuncts.

CLINICS CARE POINTS

- IgM is uniquely immunogenic but given the significant background rates of neuropathies and paraproteinaemia, their coexistence in an individual patient does not immediately infer causality.
- The various pathophysiologic mechanisms through which the underlying clonal disorder causes neuropathy determines different clinically distinct presentations.
- I-RODS is the recommended disability assessment scale for inflammatory neuropathies.
- Anti-MAG neuropathy represents half of the cases, with a classic clinical phenotype of progressive, symmetric distal sensory loss in the feet associated with early unsteadiness and frequently a complex tremor.
- The presence of neuropathy alone is not an immediate indication for treatment, given the slowly progressive nature of the IgM-peripheral neuropathies. To balance the risks and benefits of immunosuppressive treatments, a period of close monitoring is typically warranted initially, with documented progression prompting treatment.

DISCLOSURE

O. Tomkins, K. Viala, and D.R. Weil declare no conflicts of interests related to this publication. V. Leblond has received honoraria from Astra Zeneca, Abbvie, BeiGene, Janssen, Amgen Lilly, and MSD and is a consultant for Janssen, BeiGene, and Lilly. M.P. Lunn is PI for trials with Novartis and UCB Pharma; PI on Investigator led Optic, Perinoms, and IMAGiNe studies; DSMB for Octapharma trial and Investigator led IoC trial; has received honoraria from CSL Behring, Grifols, Novartis, UCB Pharma, and AstraZeneca pharmaceuticals; and ad hoc travel support grants from CSL Behring. S. D'Sa has received honoraria from BeiGene, Janssen, and Sanofi; was a consultant/advisor for Janssen, BeiGene, and Sanofi; received research funding from Janssen; and received travel and accommodations reimbursement from Janssen, BeiGene, and Sanofi.

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