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REVIEW ARTICLE

Neuropathy and paraproteins: review of a complex association

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Coexistence of neuropathy and monoclonal gammopathy represents a common but complex problem in clinical practice. This association is here reviewed considering latest available literature. The association is not infrequent, and various possible syndromes need to be distinguished. However, coincidental co-occurrence also needs to be recognized. The monoclonal gammopathy may be a 'monoclonal gammopathy of uncertain significance' (MGUS) or occur in a context of malignancy such as multiple myeloma or Waldenström's macroglobulinaemia. IgM paraproteins can bind to myelin-associated glycoprotein (MAG) in peripheral nerve. In this case, the paraprotein is directly linked to the neuropathy, causing a specific phenotype. One randomized controlled trial of this ('Anti-MAG') neuropathy showed possible moderate effect of rituximab on disability. Results of another trial are awaited. IgM/G/A paraproteins can be associated with a polyneuropathy indistinguishable from chronic inflammatory demyelinating polyneuropathy. Axonal neuropathies may coexist with IgM/G/A MGUS. There is insufficient evidence about causality or effective treatment in such cases. Pain/dysautonomia with an axonal neuropathy and serum paraprotein raises the possibility of amyloidosis. Specific haematological treatment is required for malignant disorders, although caution is required with neurotoxic agents. Polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes syndrome and chronic ataxic neuropathy with ophthalmoplegia, M-protein, cold agglutinins and disialosyl antibodies represent rare separate entities for which evidence-based treatment options are still lacking. The association of monoclonal gammopathy and neuropathy requires the appropriate neurological/haematological investigations for a precise diagnosis. Causality is only established in few cases. Adequate management ideally requires joint neurological/haematological input for diagnosis, monitoring and treatment.

Introduction

Prevalence of neuropathy rises with age, reaching up to 8% of subjects > 60 years [1]. Monoclonal proteins are also increasingly frequent with age, attaining 3% in patients > 70 years [2] and 10% in those > 80 years [3]. Although a serum protein electrophoresis (SPE) is routinely performed in all subjects with neuropathy, immunoelectrophoresis or immunofixation, more sensitive to detect lower levels of monoclonal protein, is advisable in the case of normal SPE in patients with neuropathy, particularly of the demyelinating type [4].

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Although coincidental association cannot be excluded in a significant proportion of cases, there are a number of entities where a direct link exists and needs to be recognized. In this review, the principal neurological diagnoses resulting from the association will be examined. The main current hypotheses and knowledge regarding causality will be discussed, and the relevance of these in relation to diagnosis and management also reviewed.

A paraprotein consists of a monoclonal gammopathy comprising two same class and subclass heavy polypeptide chains and two same type light polypeptide chains. Monoclonal gammopathies are produced by a clone of plasma cells in the bone marrow. The proliferative process can be low grade as in 'monoclonal gammopathy of undetermined significance' ('MGUS') or, alternatively, malignant as in multiple myeloma (MM) or Waldenström's macroglobulinaemia (WM)

[5]. Associated neuropathies can occur in various clinical, electrophysiological and pathological forms. The presence of a paraprotein itself raises a number of possible haematological diagnoses. The most common is MGUS, diagnosed in the absence of malignancy. MGUS accounts for two-thirds of paraproteins [6]. MGUS is characterized by a level of monoclonal protein < 30 g/l, $< 10\%$ of plasma cells in the bone marrow, no or only low-level monoclonal protein in the urine, absence of anaemia/ hypercalcaemia/ bone lesions/renal failure and stability of the monoclonal protein. A MGUS may transform into a malignant process. The annual risk is of about 1% per year [6]. As a result, indefinite follow-up of patients with annual serum protein electrophoresis and levels is recommended. An association between a MGUS and neuropathy is suggested by the high prevalence of the association. This is estimated at about 5% for IgG paraproteins, 10–15% for IgA paraproteins and 30–50% for IgM bands [7]. Concurrently, 5–10% of patients investigated for a neuropathy may have a paraprotein [7]. The prevalence is variable and dependent on patient selection, vigour with which a monoclonal band is sought and diagnostic methods utilized to ascertain the presence of neuropathy. Malignant haematological disease with monoclonal proteins may also be accompanied by a neuropathy. Examples are WM, B-cell lymphomas and MM. In each case, the neuropathy subtype may again be variable.

Table 1 Recommended investigations for patients with neuropathy and monoclonal gammopathy

Neurological
Full General Examination + Detailed objective clinical functional neuromuscular assessment at baseline, to be repeated at regular intervals
Detailed electrophysiology with determination of DML/MNCV/ TLI, assessment for CB/TD
Cerebrospinal Fluid study: cellularity/cytospin/protein level
In selected cases: serum VEGF level
In selected cases: MR imaging of nerve roots/brachial plexus, as for CIDP[38]
In selected cases: nerve histology
Haematological
Full Examination for hepatomegaly/splenomegaly/lymphadenopathy/macroglossia
Full blood count/renal function/liver function tests/calcaemia/C-reactive protein/ESR
Serum Immunofixation if required
Serum free light chains/Cryoglobulins
Bence-Jones proteinuria and if positive 24-h collection
Skeletal Survey
Bone marrow examination
In selected cases: whole body CT scan/PET scan

DML, distal motor latency; MNCV, motor nerve conduction velocity; TLI, terminal latency index; CB, conduction block; TD, temporal dispersion; VEGF, vascular endothelial growth factor; CIDP, chronic inflammatory demyelinating polyneuropathy; ESR, erythrocyte sedimentation rate.

Clinical syndromes associating neuropathy and serum paraprotein

There are a number of separate clinical syndromes with different neuropathy subtypes that may be associated with a serum paraprotein. These have different clinical and electrophysiological phenotypes, probably very differing underlying pathophysiological mechanisms, with occasionally proven or more frequently, uncertain, causal link. Management strategies are diverse. Investigations recommended in the presence of the association are summarized in Table 1.

IgM MGUS with anti-MAG antibody activity ('Anti-MAG neuropathy')

This is a phenotypically characteristic neuropathy, described as 'distal acquired demyelinating symmetric' ('DADS') sensory and motor neuropathy. It is predominantly distal, usually very slowly progressive, with the prominence of sensory involvement/sensory ataxia, little or no weakness and frequent tremor [8].

This neuropathy is associated with auto-antibodies to myelin-associated glycoprotein (MAG), which is a constituent of normal peripheral nerve myelin. MAG has a molecular weight of 110 kDa and contains 30% of carbohydrate. The IgM monoclonal protein binds to MAG in 50% of patients with IgM MGUS[9], and the binding requires the carbohydrate moiety [10]. This results in characteristic changes in peripheral nerve myelin, consisting of widening of myelin lamellae (Fig. 1.) [10]. Although more frequent in the setting of an IgM MGUS, anti-MAG neuropathy can also occur with concurrent WM or a B-cell lymphoma [11].

Anti-MAG neuropathy usually has a benign course, with little functional deterioration over time [8]. However, the neuropathy may evolve more rapidly throughout its course or at certain stages.

The diagnosis of anti-MAG neuropathy relies on the identification of an IgM paraprotein on SPE/immunofixation, as well as the presence of high-titre ($\geq$ 1:6400) enzyme-linked immunosorbent assay (ELISA) against the peripheral MAG [11]. Alternatively, antibodies may be directed against sulphated glucuronyl paragloboside (SGPG) and sulphated glucuronyl lactosaminyl paragloboside (SGLPG) [12].

Electrophysiologically, anti-MAG neuropathies demonstrate generally diffusely absent/markedly

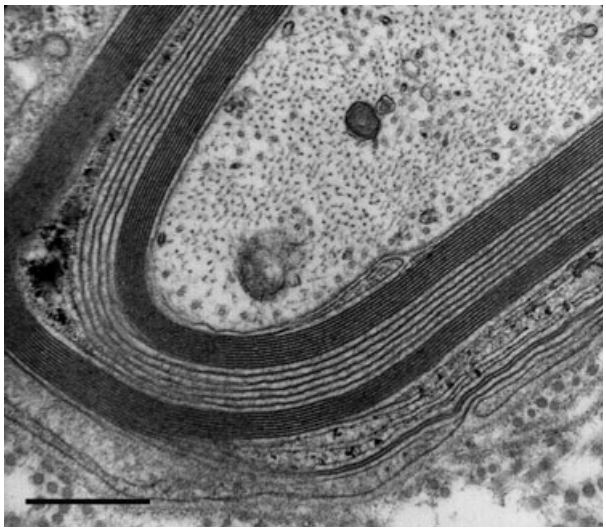

Figure 1 Anti-MAG neuropathy with IgM kappa paraprotein. Electron Microscopy of sural nerve specimen, showing widely spaced myelin involving central lamellae (Bar = 0.5 μm).

reduced sensory action potentials. Motor nerve conduction velocities are significantly slowed, but the degree of distal slowing, and hence prolongation of the distal motor latency, is much greater. This may be quantified by the 'terminal latency index' (distal distance/{forearm motor conduction velocity × distal motor latency}), which is highly specific of anti-MAG neuropathy when < 0.26 in a patient with demyelinating neuropathy without conduction block (Fig. 2) [11,13]. Cerebrospinal fluid protein is raised in about over 80% of cases, but cellularity is normal. Histologically, electron microscopy demonstrates the presence of widely spaced myelin lamellae, highly sensitive for anti-MAG neuropathy [14].

Treatment of anti-MAG neuropathy should focus on any eventual need for specific haematological therapy, if the patient has WM, rather than an IgM MGUS. However, caution is required if potentially neurotoxic drugs such as vincristine are considered. In patients with an IgM MGUS, treatment should be considered for the neuropathy exclusively if functionally relevant. Decision to attempt treatment should be made on a case-by-case basis, depending on severity and rate of objective functional decline. Several agents have been utilized, with reports of moderate functional benefit, from retrospective analyses. Plasma exchanges were shown temporarily effective in about 50% of patients in a review of uncontrolled studies [15]. This was not confirmed by a prospective analysis that included a majority, but not exclusively, anti-MAG-positive cases, and which showed that plasma exchanges in combination with chlorambucil was no more effective than chlorambucil alone [16]. Similarly, steroids in combination with other immunosuppressants, but not alone, were effective in half of the patients studied [15].

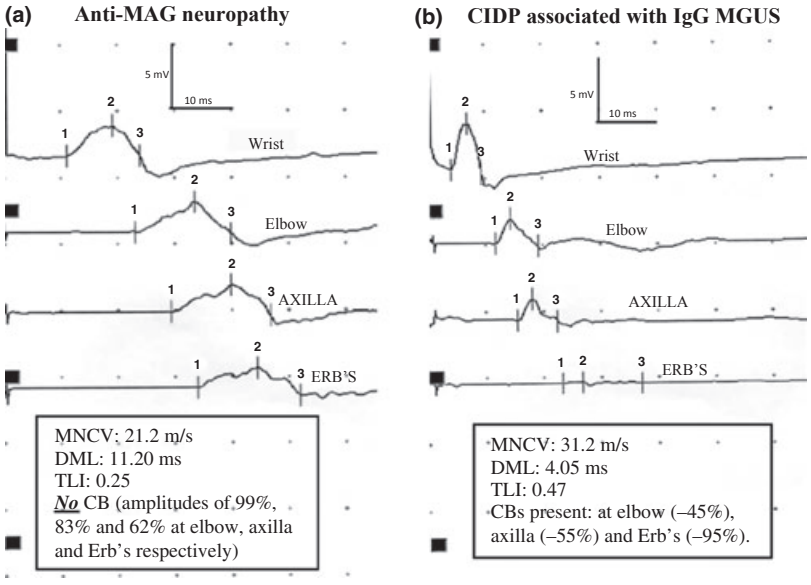

Figure 2 Left Median Nerve electrophysiological recordings at wrist, elbow, axilla and Erb's point in two patients: (a) with anti-MAG neuropathy (b) with chronic inflammatory demyelinating polyneuropathy (CIDP) associated with IgG monoclonal gammopathy of uncertain significance (MGUS). MNCV, motor nerve conduction velocity; CB, conduction block; DML, distal motor latency; TLI, terminal latency index.

Intravenous immunoglobulins may have a limited effect, uncertain from a functional perspective, in a low percentage of patients, as shown in a small double-blind RCT (randomized controlled trial) that however included patients without anti-MAG activity [17] and another open-labelled study [18]. A further multicentre RCT showed significant improvement with IVIg at four weeks versus placebo [19]. Interferon-alpha showed improved sensory function in an open study [18], although an RCT did not confirm this [20]. There are uncontrolled studies and anecdotal small reports of efficacy of chlorambucil, cyclophosphamide, fludarabine, cladribine or autologous bone marrow transplant [11]. A Cochrane review in 2006 found that none of the above-mentioned treatments showed efficacy in reducing disability/functional impairment except for IVIg that was safe and may produce some short-term benefit [21]. The latest agent tried in an RCT has been rituximab [22]. Rituximab is a genetically engineered chimeric murine/human monoclonal antibody directed against CD20, a protein found on the surface of normal and malignant pre-B and mature B cells, until their differentiation into plasma cells. Small pilot studies had previously suggested the efficacy of this agent in anti-MAG neuropathy [23]. In this RCT, 13 subjects were treated with 4 weekly infusions of 375 mg/m^2 of rituximab and compared with 13 subjects treated with placebo. The primary outcome measure was the Inflammatory Neuropathy Cause and Treatment (INCAT) disability score. In intention-to-treat analysis, the results failed to reach significance ($P = 0.094$). However, on excluding one patient who had a normal INCAT disability score at entry and who could therefore not have improved, the analysis reached significance ($P = 0.036$). The 10-m walk time improved in over two-thirds of patients ($P = 0.042$). Rituximab caused B-cell depletion for over 6 months, 34% reduction in IgM levels and 50% reduction in anti-MAG antibody titres. This study suggested sustained benefits after over 12 months. Follow-up data from other groups suggested similar sustained efficacy [24]. Importantly, rituximab was well tolerated. A further, larger (26 patients treated with rituximab and 28 with placebo) French/Swiss RCT of rituximab ('RiMAG Study') has been completed, but results are not yet published [25]. At this time, given the findings of the only published RCT and despite its statistical analysis providing a positive result in a controversial way, rituximab may remain an option to consider, especially in rapidly deteriorating patients. The decision to treat may be more justified haematologically than neurologically, in case of WM, for example.

IgM/G/A MGUS with associated neuropathy resembling chronic inflammatory demyelinating polyneuropathy (CIDP)

A typical clinical and electrophysiological presentation of a CIDP may accompany the presence of an IgM, IgG or IgA MGUS [11]. Such patients usually have symmetrical proximal and distal weakness of the four limbs, sensory involvement and areflexia. CIDP is a relapsing or progressive sensori-motor disorder involving the peripheral nerves. It has an auto-immune basis and progresses by definition over more than 2 months. There are rarer atypical forms of CIDP, [26] which may also be associated with a MGUS. Electrophysiologically, the findings are that of motor nerve demyelination combined in various electrodiagnostic criteria [27]. Demyelination affects intermediate as opposed to distal segments (which are more involved in anti-MAG neuropathy), and conduction blocks are frequent (Fig. 2). Raised CSF protein is found in about 70% of cases, and nerve histology may show features of macrophage-mediated demyelination. The treatment of CIDP-like neuropathy associated with MGUS is that of idiopathic CIDP. Steroids, intravenous immunoglobulins and plasma exchanges represent the three main therapeutic options. About 80% of patients respond to one of these treatments [28]. There is currently no evidence from RCTs for immunosuppressive therapies. Treatment is not always essential, as a proportion of patients stabilize without continuing therapy [29,30]. This association is probably coincidental, although anti-MAG negative IgM MGUS-associated demyelinating neuropathy may represent a separate entity, as some consider IgM MGUS as more likely to be causative of the neuropathy than IgG or IgA MGUS, irrespective of the presence of additional features [11].

IgM/G/A MGUS with associated axonal neuropathy

MGUS may be associated with a sensory or sensori-motor axonal neuropathy, involving distal extremities in a length-dependent fashion. The link between the two is in that case elusive [31]. Clinically, the usual initial presentation is one of distal lower limb sensory symptoms and signs, with motor weakness at a later stage. Electrophysiologically, axonal degeneration is observed. Typically, CSF protein is normal and nerve histology shows non-inflammatory axonal loss. Progression is slow and often does not require any treatment, although some patients may benefit from anti-neuropathic pain agents.

Cyoglobulinaemia and neuropathy

Cryoglobulins are proteins that precipitate when cooled and dissolve when heated. Type I is monoclonal. Type

II is mixed, with two or more immunoglobulins, one of which is monoclonal. Type III is polyclonal without monoclonal protein. Mixed cryoglobulinaemia that causes multi-organ, including neuropathic involvement, is the most frequent subtype to result in neuropathy. It is often associated with chronic hepatitis C infection that is considered to be its trigger [32]. The neuropathy is multifocal and axonal and has been described as due to a necrotising vasculitis [33]. Treatment is that of the hepatitis infection. Plasma exchanges may be helpful in severe cases [34]. Cryoglobulinaemia is otherwise not known to be associated with monoclonal gammopathy and haematological disease requiring specific therapy.

Amyloidosis

The coexistence of a MGUS with an axonal neuropathy should raise the possibility of amyloidosis. Index of suspicion should be high in case of red flag signs such as pain, weight loss, macroglossia, organomegaly (hepatomegaly and/or splenomegaly) or cardiomyopathy [35]. Amyloidosis refers to the extracellular accumulation of fibrils composed of low molecular weight subunits of a variety of proteins [35]. Primary (AL) amyloidosis is due to the deposition of protein derived from immunoglobulin light-chain fragments. It can coexist with MM in 10% of cases. Twenty per cent of patients with systemic light-chain AL present with a neuropathy [36]. Eighty per cent demonstrate a monoclonal protein [37]. This is most frequently IgG than IgA or IgM. Lambda light chains predominate over kappa light chains. The neuropathy itself is mostly symptomatic in the distal lower limbs, predominantly sensory, of the small fibre and painful type [35]. Autonomic dysfunction is frequent. Diagnosis rests on the demonstration of amyloid in tissue using Congo Red stain producing apple-green birefringence with polarizing light [35]. The liver may be the most sensitive tissue to biopsy, followed by peripheral nerve or abdominal fat or the rectum [35]. Nerve biopsy is positive in most cases with a clinically symptomatic sensory neuropathy. Endoneurial amyloid deposits are identified in the majority of cases on routine paraffin-embedded fragments but are sometimes only visible at ultrastructural examination [38]. Serum amyloid P component scanning consisting of scintigraphy with radioisotope-labelled SAP can identify distribution of amyloid and total body burden of fibrillar deposits [39]. However, SAP scanning is unable to detect amyloid in peripheral nerve tissue. Of note, the presence of a MGUS does not necessarily imply a definite diagnosis of primary (AL) [40], rather than genetic amyloidosis, a low grade MGUS being detected in about 25% of genetic cases. The prognosis of AL amyloidosis is poor with a median of less than 18 months from onset [41]. Treatment with melphalan and prednisolone may prolong survival [42]. Autologous peripheral stem cell transplant may also be effective in combination with melphalan [43]. It is imperative that patients with confirmed amyloidosis are referred to specialist tertiary centres for adequate management.

CANOMAD: 'chronic ataxic neuropathy with ophthalmoplegia, M-protein, cold agglutinins and disialosyl (anti-ganglioside anti-GD1b and anti-GQ1b) antibodies'

This is a very rare phenotype associated with an IgM MGUS. It possibly corresponds to a chronic form of Miller Fisher syndrome, itself a variant of Guillain-Barré Syndrome. Ataxia is profound, severely impairing function, but motor strength remains relatively spared [44]. Electrophysiology and histology show either/both demyelinating and axonal features. A partial response to intravenous immunoglobulins has been described in some cases [44]. One recent case was described as responsive to rituximab [45].

POEMS ('polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes') syndrome

POEMS is a separate rare entity. The acronym refers to polyneuropathy, organomegaly, endocrinopathy, the presence of M-protein and skin changes, although some of these elements may be lacking. Recognized associated features are sclerotic bone lesions, Castleman's disease, papilloedema and ascites [46]. Other names for the syndrome include 'osteosclerotic myeloma' or 'Crow-Fukase Syndrome'. Neuropathy is the main feature of this syndrome and often precedes the diagnosis of osteosclerotic myeloma. Positive sensory symptoms and slowly progressive, predominantly distal weakness occur [47].The electrophysiological picture is axono-demyelinating, with predominantly intermediate nerve segment conduction slowing and rare conduction block/dispersion [48]. Typically, the monoclonal protein is IgG or IgA and the light chain is almost exclusively lambda. The paraprotein level is usually low, of < 2 g/l in 90% of patients [46]. The level of vascular endothelial growth factor (VEGF), which may a driving factor in the disorder, is diagnostically useful [49]. Nerve histology reveals appearances of uncompacted myelin lamellae, which although not specific, favour the diagnosis in the right context [50]. The prognosis of POEMS syndrome is poor, with a median survival of 12–33 months. From the therapeutic perspective, there are no data from RCTs. Various options have been attempted, including high-dose melphalan,

radiotherapy of osteosclerotic lesions and autologous peripheral blood stem cell transplant that has become the treatment of choice, particularly in younger patients. Other potential avenues are lenalidomide, thalidomide, anti-VEGF monoclonal antibody and cyclophosphamide [51]. In the rare cases where a solitary plastocytoma is detected, its removal may be effective [52].

Neuropathy and lymphoma

A monoclonal gammopathy is present in over 50% of cases in the presence of this association [53]. Neuropathies occur most frequently by direct nerve infiltration, but are also thought to result from paraneoplastic, metabolic, infectious mechanisms or toxic effects of therapy [54]. Neuropathy often reveals the lymphoma. Demyelinating forms may have a more favourable prognosis, with greatest therapeutic efficacy reported chemotherapy/immunomodulation [53]. Isolated radiculopathy suggests proximal infiltration usually associated with aggressive B-cell lymphoma with poor prognosis, while axonal multiple mononeuropathies suggest distal infiltration, of better outcome [53].

Conclusion

The association of neuropathy and serum paraprotein represents a common but complex, heterogeneous entity, with multiple possible neurological, but also concurrent, haematological diagnoses. Detailed further investigations are required to establish an accurate diagnosis and formulate a management plan.

Causality may be only accepted or highly likely for anti-MAG-positive cases, amyloidosis and CANOMAD, but is uncertain in POEMS syndrome [50,55]. Otherwise, for other associations, a definite link is unconfirmed and this should be remembered and acknowledged at the time of therapeutic decision-making to avoid consideration of irrelevant and inappropriate therapies.

In case of established malignant haematological disease requiring treatment, this should take priority over the treatment of the neuropathy, although the latter may also be desirable. The same agent may treat both aspects in presence, and rituximab may represent such an example in WM associated with an anti-MAG neuropathy. When haematological therapy is not required, the neuropathy should only be treated if this is functionally relevant. There is no justification, for example, to use unconfirmed treatments to treat a CIDP associated with MGUS using chemotherapeutic methods, in the absence of haematological malignancy, given the availability of safer immunomodulatory agents.

In the presence of the association of neuropathy and paraprotein, detailed investigations are required to establish an accurate diagnosis (Table 1.). In practice, a multidisciplinary approach appears highly recommended, with joint subspecialist neurological and haematological input being the most adequate way to diagnose, investigate, monitor, appropriately advise and manage this challenging group of patients.

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Disclosure of conflict of interest

The author declares no financial or other conflict of interests.

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