CASE REPORT

Waldenstrom-associated anti-MAG paraprotein polyneuropathy with neurogenic tremor

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SUMMARY

A 71-year-old female patient presented with a 14-year history of slowly progressive distal limb numbness, paraesthesia and reduced vibration perception, ataxic gait and intentional tremor. Examination revealed with a length-dependent sensory neuropathy. Nerve conduction studies showed a chronic sensorimotor inflammatory demyelinating polyneuropathy. Intravenous immunoglobulin treatment (on two occasions) proved ineffective. Serum electrophoresis showed increased monoclonal IgM with kappa light chains. Anti-myelin-associated glycoprotein (MAG) levels were extremely elevated, >70 000 BTU. Bone marrow biopsy revealed 15%–20% small B cells and positive MYD88 mutation, indicative of Waldenstrom macroglobulinaemia.
A diagnosis of Waldenstrom-associated anti-MAG paraprotein neuropathy with intentional (neurogenic) tremor was made. Repeat nerve conduction study showed a severe sensory demyelinating neuropathy with no axonal lesion. Treatment with rituximab was given for 1 month with minimal improvement. Repeat anti-MAG levels dropped to 53 670 BTU, with minimal clinical improvement.

BACKGROUND

- It highlights the importance of recognising that intention tremor is not always cerebellar, and that resting tremor is not always Parkinson disease; both types can be caused by a paraprotein neuropathy (mainly IgM), which entails a completely different treatment and prognosis.
- It highlights the link between intentional tremor and anti-myelin-associated glycoprotein positivity; it reviews the relatively unknown clinical entity: peripheral (neurogenic) tremor.
- It emphasises the need to pursue further investigations—such as bone marrow biopsy—in patients with peripheral neuropathies and monoclonal gammopathies.
- The value of nerve conduction study in these cases is crucial. It is important to recognise the different neurophysiological phenotypes most frequently seen in paraprotein neuropathies.
- It emphasises the value of follow-up electrophoresis in such patients; a sharp monoclonal (paraprotein) rise can be indicative of malignant transformation; the sooner it is discovered, the sooner treatment can start.

CASE PRESENTATION

A 71-year-old left-handed female patient with a history of hypothyroidism noticed roughly 14 years ago (2004) that her handwriting was becoming illegible. Concurrently, she noticed bilateral painful paraesthesia and numbness in both hands (more marked on left side), and on the lateral aspect of her left foot up to the ankle. There was also a constant sharp pain in her left heel, sometimes felt as a 'sharp grip'. Occasionally, she felt 'patchy' numbness along the left quadriceps. Approximately 1 year later, she started presenting left-sided intentional tremor with very mild right-sided tremor. During the following years, these symptoms slowly progressed.

Five years after onset (2009), a subtle pill-rolling tremor in the left hand was detected leading to a diagnosis of Parkinson disease. A CT and MRI were both normal. Treatment with co-beneldopa was started but discontinued after 1 year due to no improvement. She was then given propranolol, primidone, gabapentin and clonazepam, with no improvement. Four years ago (2014), she began noticing that her balance was deteriorating, also finding it very difficult to move about in dark environments and repetitively tripping over. The sensory symptoms continued, and the tremor intensified. She was seen in our neurology department for the first time in 2015. Examination showed positive Romberg test with high-stepping sensory ataxia, normal strength with the exception of a very mild reduced left-handed grip. A length-dependent pattern of sensory loss and areflexia was noticed in all four limbs. Pinprick sensation was normal from the mid-shin bilaterally; however, there was a loss of vibration perception up to the hip joint. A marked postural and intentional tremor was noticeable in both hands, mainly on the left side, with no obvious resting tremor. A nerve conduction study (2015) revealed prolonged distal median and ulnar latencies, bilateral ulnar and median nerve conduction block, prolonged F wave, almost undetectable upper and lower limb motor conductions, absent sural nerve sensory action potentials, undetectable sensory responses in all four limbs and occasional polyphasic units in the right tibialis anterior. These findings were compatible with a sensorimotor chronic inflammatory demyelinating polyneuropathy. Protein electrophoresis showed increased IgM (15.0 g/L) with normal free kappa light chain (13.4 mg/L) and low free lambda chain. ESR was slightly elevated and anti-myelin-associated glycoprotein (MAG) antibodies were very elevated (table 1). All other blood investigations include liver

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Table 1 Serum electrophoresis, serum-free light chain assay, immunofixation, anti-MAG levels and ESR

	2015	6 August 2018	22 August 2018	24 September 2018	November 2018	Normal values
Serum electrophoresis						
IgG	4.5	17.5	14.1	8.4	7.2	6.0 – 16.0 g/L
IgA	0.52	0.43	0.55	0.38	0.31	0.8 – 4.00 g/L
IgM	**15.0**	**20.3**	**20.5**	**20.5**	**19.4**	0.50 – 2.00 g/L
Total paraprotein	10.6	21.0	16.8	16.8	13.8	< 0.0 g/L
Gamma protein 1	10.6	21.0	16.8		13.8	< 0.0 g/L
Serum-free light chain assay						
Free kappa	13.4	**21.4**				3.3 – 19.4 mg/L
Free lambda	2.2	8.5				5.7 – 26.3 mg/L
Kappa/lambda ratio	6.09	2.52				0.26 – 1.65
Immunofixation	IgM kappa paraprotein (gamma)	IgM kappa paraprotein (gamma)	IgM kappa paraprotein (gamma)	IgM kappa paraprotein (gamma)	IgM kappa paraprotein (gamma)	
Anti-MAG	**70 000+**	**64 874**		**70 000+**	**53 670**	
ESR	**49**	**206**				0–30 mm/hour

Bolded values represent abnormal values.
ESR, erythrocyte sedimentation rate; MAG, myelin associated glycoprotein.

and renal function tests, calcium, vitamin B_{12} and folate, rheumatoid factor, ANA and ANCA (table 3). All tumour markers were negative; CT chest–abdomen–pelvis did not show signs of malignancy; X-ray skeletal survey did not show lytic lesions and the MRI head and spinal cord were all normal. There was no lymphadenopathy, splenomegaly or weight loss. This led to a diagnosis of IgM-monoclonal gammopathy with anti-MAG sensorimotor demyelinating neuropathy. Two courses of intravenous immunoglobulin (IVIg) (30 g/day) were administered with no improvement.

From 2015 until the beginning of 2018, the patient remained stable. However, in March 2018, she noticed an increase in the intensity of her tremor (videos 1 and 2), of distal limb pain and of ataxia; she had fallen twice in less than a month. Repeat blood investigations showed that erythrocyte sedimentation rate (ESR) levels had tripled, the anti-MAG levels remained very high and the serum protein electrophoresis showed a sharp rise in IgM levels, free kappa light chain, which had been normal 3 years ago (table 1). Further examination did not reveal weight loss, loss of appetite, night sweats or recent infection. No B symptoms, lymphadenopathy or splenomegaly were noted. One month later, a follow-up protein electrophoresis showed a very similar result. Soon after, a bone marrow aspirate was performed, showing maturing trilineage haematopoiesis and 24% mature lymphoid cells; flow cytometry showed 5% monoclonal B cells and 1% monoclonal plasma cells favouring a diagnosis of lymphoplasmacytic lymphoma (Waldenstrom macroglobulinaemia). Trephine sampling showed 15%–20% small B cells and 5%–10% plasma cells. Genetic analysis of bone marrow sample revealed MYD88 L265P mutation [c.794T>C], confirming the diagnosis of Waldenstrom macroglobulinaemia. Cerebrospinal fluid was negative for oligoclonal bands and demonstrated few lymphomononuclear cells and no excess of lymphoid cells or neoplastic cells; CSF protein was 0.71 g/L and glucose 3.0 mmol/L. A diagnosis of Waldenstrom-associated anti-MAG paraprotein neuropathy with neurogenic tremor was established. A repeat nerve conduction showed a sensory demyelinating pattern without axonal involvement. This result did not differ much from the first study. A left sural nerve biopsy revealed loss of sensory fibres associated with severe demyelination. Rituximab was started (four weekly infusions of 375 mg/m^2 throughout the month of October). Her Overall Neuropathy Limitation Scale (ONLS) was 6 before treatment was started. Fifteen days after starting rituximab, her lactate dehydrogenase, calcium, and renal function were normal and her haemoglobin remained low (table 2).

Following the treatment (1 month), the ONLS was reduced to 4 and the repeat serum protein electrophoresis (November 2018) showed only a marginal improvement (table 1). Although her limb pain slightly improved, her tremor

Video 1 Intentional tremor

Video 2 Intentional tremor

Table 2 EPT versus neurogenic tremor

EPT	Neurogenic tremor
► Low amplitude	► Large amplitude
► High frequency (8–12 Hz)	► Low frequency
► Symmetric	► Asymmetric (>worse on neuropathy side)
► Postural	► Postural, intentional or even resting
► Suppression of EMG burst pattern	► More distal than proximal
	► Less affected by inertial weighting than EPT

EMG, electromyography; EPT, enhanced physiological tremor.

remained unchanged. The post-rituximab anti-MAG level was 53 670 BTU. A neurosurgical opinion was requested for deep brain stimulation; however, the patient was not keen on surgical intervention.

INVESTIGATIONS

Nerve conduction studies and protein electrophoresis were both crucial in this case. The former determines the presence of a peripheral neuropathy and also determines whether there it is an axonal or a demyelinating lesion. The latter is useful to determine the presence of monoclonal gammopathy (paraprotein) and types of light chains. Anti-MAG measurements are important when presented with a patient with both peripheral demyelinating neuropathy and intentional tremor. CT chest, abdomen and pelvis, paraneoplastic antibodies and tumour markers were useful to rule out malignancies. The bone marrow biopsy was the most important investigation in this case: it proved the presence of Waldenstrom macroglobulinaemia. Other important investigations include complete blood count, ESR, liver function renal function tests, calcium levels and vitamin B_{12} levels. MRI of spinal cord and brain is also useful to rule out structural lesions.

DIFFERENTIAL DIAGNOSIS

The combination of a chronic progressive length-dependent, large-fibre sensorimotor polyradiculoneuropathy associated with a paraprotein (especially IgM) suggests an acquired pathology, warranting a nerve conduction study and in most cases, a bone marrow biopsy to rule out an underlying lymphoproliferative disease or plasma cell disorder. It can be difficult to *clinically* distinguish between axonal and demyelinating disease; however, the presence of symmetrical and distal numbness for light touch and vibration (length-dependent) associated with generalised areflexia is usually suggestive of large-fibre demyelination, rather than of axonopathy. In this case, four paraproteinaemic neuropathies were considered in the differential diagnosis. Two of them—IgM monoclonal gammopathy of uncertain significance (MGUS) and Waldenstrom macroglobulinaemia—are associated with kappa light chain. The former causes length-dependent large-fibre demyelinating neuropathy with ataxia, while the later causes length-dependent large-fibre sensory demyelinating or axonal neuropathy (occasionally mononeuritis multiplex). The other two—light chain amyloidosis (AL) amyloid and POEMS (polyneuropathy, organomegaly, endocrinopathy, protein M and skin changes)—are linked to lambda light chain. The former causes Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) and the later a sensorimotor small fibre autonomic axonal polyneuropathy. POEMS and AL amyloid were excluded on the basis that this patient had kappa light chain and not lambda and that there was no autonomic dysfunction, endocrinopathy, hepatosplenomegaly or skin changes. Therefore, it was either IgM MGUS or Waldenstrom macroglobulinaemia. Anti-MAG can be associated with both, so it should not be considered a distinguishing feature; however, its presence—especially in high quantities— usually is linked to the pathogenesis of the neuropathy and to its severity. Furthermore, anti-MAG should be tested in patients with both peripheral polyneuropathy and intentional (neurogenic) tremor. The first nerve conduction study (2015) demonstrated a chronic sensorimotor inflammatory demyelinating polyneuropathy, which favoured the diagnosis. The bone marrow biopsy was crucial in finally establishing the presence of Waldenstrom macroglobulinaemia.

TREATMENT

Initially, before identifying a clear aetiology, the patient was treated only for symptom relieve, mainly for intentional tremor and limb pain with propranolol, primidone, clonazepam, gabapentin and co-benelopa. No improvement was noted. Once a neuropathy was identified and anti-MAG was positive, then IVIg was administered in two occasions, with minimal improvement. Following the bone marrow biopsy, a trial with rituximab (four weekly infusions of 375 mg/m^2, throughout the month of October) was administered. Her pre-rituximab ONLS was 6. ONLS 60 days post-rituximab was 4.

OUTCOME AND FOLLOW-UP

The patient continues to be followed up in the neurology, haematology and oncology departments, with a plan to repeat protein electrophoresis every 6–8 months. No further nerve conduction study has been arranged.

DISCUSSION

A monoclonal gammopathy results from a plasma-cell or B-cell expansion in the bone marrow, leading to the increase of one

Table 3 General blood investigations

	22 August 2018	24 September 2018	15 October 2018	November 2018
White blood count (x10^9/L)	5.1	8.3	7.0	7.3
Haemoglobin (g/L)	113.0 (11.3 g/dL)	111 (11.1 g/dL)	117.0 (11.7 g/dL)	111.0 (11.1 g/dL)
Platelets (x10^9/L)	254	241	310	309
Globulins (g/L)		55	42	43
Calcium (mmol/L)	2.43	2.62	2.45	2.46
Urea (mmol/L)	5.7	6.3	4.8	5.0
Creatine (µmol/L)	72	73	72	74
Anti-Hu/Ri, La, RNP, Ro, SCL-70, Sm CA19.9, CEA, AFP and CA125		Negative		
Lactate dehydrogenase 125–220 U/L			171	

AFP, Alpha Feto Protein; CA125, Cancer Antigen 125; CA19.9, Cancer Antigen 19.9; CEA, Carcinoembyronic Antigen; RNP, Ribonucleoprotein; SCL, anti-exosome.

specific immunoglobulin (antibody), that is, a paraprotein, which in turn, can develop into an MGUS, multiple myeloma, Waldenstrom macroglobulinaemia, POEMS syndrome or AL.

MGUS occurs in up to 1%–2% of normal people over the age of 50 years and its incidence increases with age, reaching 6% above the age of 90 years.[1] It is diagnosed if: (A) <3 g/dL of monoclonal protein in serum, (B) no signs of renal insufficiency, osteolytic or osteosclerotic lesions, anaemia or hypercalcaemia and (C) if there is stable amount of the monoclonal protein in follow-up examinations. Apart from carrying a risk for developing lymphoproliferative disorders and a lifelong risk of multiple myeloma[2] (at a rate of 1% per year[3]), it can also lead to end organ damage such as membranoproliferative glomerulonephritis and/or peripheral neuropathy. Depending on which immunoglobulin predominates, the clinical problems can vary as can the types and risks of neoplastic development.

Approximately 60% of patients with IgM monoclonal gammopathy[4 5] may develop a sensorimotor polyneuropathy (vs 30% in IgG and 10% in IgA[6]), in particular, if the M-protein binds to peripheral nerve antigens,[7 8] mainly to MAG, which can act as a self-antigen.[9] Antibodies against MAG (directed against HNK-1 carbohydrate epitope on MAG, which is also present on other peripheral nerve glycoconjugates such as sulfate-3-glucoronyl paraganglioside [SGPG][10] ; the majority of patients with positive anti-MAG also have positive anti-SGPG,[11] which seems to be more specific than MAG[12]) can be detected by Western blot[13] and ELISA[14] (the later more sensitive than the former[15] ; however, with anti-MAG levels between 1000 and 100 000 BTU, the specificity of ELISA is reduced due to cross-reactivity with GM1 and disialosyl gangliosides[12]) in ∼60%–70%[16] of patients with IgM monoclonal gammopathy and polyneuropathy.

In this patient, the IgM monoclonal gammopathy coupled with very elevated levels of anti-MAG provided the first direct clues that could potentially explain the 14-year history of sensory neuropathy and intentional tremor (table 1)

Up until recently, it was though that IgM anti-MAG neuropathy was a clinically homogeneous entity, however this is now known not to be the case. Magy *et al*[17] described three main patterns of peripheral nervous system involvement: (A) a sensory ataxic neuropathy (most common), (B) an almost purely subjective sensory (sometimes painful) neuropathy and (C) a sensory and motor neuropathy with variable degrees of weakness. Most commonly, patients present a predominantly distal, chronic, symmetric sensory neuropathy and ataxia.[18 19] Areflexia in lower limbs is very common, then it becomes generalised. Upper limb tremor is common, while head, chin and voice tremor do not occur.[20] It is usually a marked postural tremor and is more intense on the side in which the neuropathy is more marked. This patient had bilateral—although much more marked on the left side (the side the neuropathy was more manifest)—postural tremor with no resting tremor.

By 1997, there had been several studies investigating the characteristics and prevalence of tremor in patients with CIDP and Charcot-Marie-Tooth[21 22] (this patient was negative for PMP22 and 17q12); however, there still was not a clear understanding of the tremor seen in patients with other acquired neuropathies, such as IgM anti-MAG. The cause of this tremor is still elusive; Said *et al*[23] feel that it is simply an enhanced physiological tremor caused by weakness and alteration of the stretch reflex, yet others claim that it is directly secondary to the neuropathy, that is, a neurogenic tremor. One explanation for the latter, proposed by Bain *et al* (1996)[20] is that non-uniform segmental demyelination of the large diameter sensory neurons causes distortion in the afferent sensory input to the thalamus. This then leads the cerebellum to misinterpret these inputs and the limb position error that results participate in an abnormal feedback loop. Dalakas *et al* (1984)[24] found that the tremor had no relationship with either weakness nor with proprioceptive loss. In 1990, Elble and Koller[25] summarised 25 years of sometimes contradictory research regarding paraprotein-associated tremor and concluded that the tremor can be essential, Parkinsonian and cerebellar, occurring both at rest and/or with action. Pedersen *et al*[26] demonstrated that tremor in anti-MAG neuropathy is of higher amplitude, lower frequency, irregular and often asymmetric (more marked on the most affected side of the neuropathy). They concluded that these findings are more characteristic of neurogenic tremor and not of exaggerate physiological tremor (table 2). Schwingenschuh *et al*[27] demonstrate evidence that tremor in patients with inflammatory neuropathy is associated with cerebellar dysfunction. More so, they demonstrate that the central compensation needed to account for delays caused by the peripheral neuropathy depend on plastic changes within the cerebellum and connections that link and mediate between sensory and motor systems.

In 2015, the nerve conduction revealed changes compatible with a sensorimotor chronic inflammatory demyelinating polyneuropathy and the serum protein electrophoresis showed an increased IgM (15.0 g/L) with normal kappa light chain (13.5 μg/L) and the ESR was mildly elevated (49 mm/hour). There was no lymphadenopathy, splenomegaly, weight loss, hypercalcaemia or sclerotic bone lesions. No further investigations were done, and she was kept under close surveillance. At this stage, the two risk factors she had—IgM isotype and elevated ESR—indicated that she had a 37% risk of developing a lymphoproliferative disorder.

In August 2018, there was a spike in IgM (20.3 g/L) and kappa light chain (21.4 mg/L) levels; there was also a sharp rise in ESR (from 49 to 206 mm/hour). It is very likely that this sudden and noticeable increase signified the development of Waldenstrom macroglobulinaemia. Interestingly, immediately before and throughout this period, her tremor, ataxia and painful limb paraesthesia were worsening. At this stage, before doing the bone marrow, there were three important risk factors (IgM isotype, IgM >20 g/L and ESR >40 mm/hour), which increased the risk of a malignancy to roughly 58%.[28] Klein *et al*[29] showed that a cut-off of IgM >1830 mg/dL (18.3 g/L) and haemoglobin levels <12.6 g/dL can achieve 71% of sensitivity and 88% specificity for predicting Waldenstrom macroglobulinaemia cases *independent* of nerve conduction studies. In August 2018, the patient had IgM 20.3 g/L and haemoglobin of 11.3 g/dL (table 3).

The bone marrow analysis demonstrated 15%–20% small B cells, 5%–10% plasma cells and positive mutation of MYD88 L265P, which is altered in 91% of patients with Waldenstrom macroglobulinaemia.[30] A repeat nerve conduction study showed a very marked sensory demyelinating pattern without axonal involvement, not much different from the initial study.

Some polyneuropathies in Waldenstrom macroglobulinaemia may be related to specific antigenic targets of the monoclonal serum IgM, including anti-MAG.[31 32] According to a review by Levine *et al*,[33] patients with Waldenstrom-associated anti-MAG present mainly sensory loss, with distal and symmetric loss of large and small fibres. Strength is preserved, pinprick and vibration perception are reduced; however, proprioception is preserved. Klein *et al*[29] found in a retrospective analysis, that in 73% of bone marrow-confirmed Waldenstrom macroglobulinaemia cases, there was predominantly axonal features in the nerve conduction study, whereas 62% of IgM MGUS patients had demyelinating features. This patient

presented loss of vibration and pinprick perception in both lower limbs.

Cerebrospinal fluid analysis is useful in patients with borderline demyelination or axonal electrophysiological results or atypical phenotype. The CSF protein can be elevated up to 250 mg/dL. Interestingly, the IgM may also infiltrate the CSF via dorsal root ganglia that lacks a blood–CSF barrier.[34] A sural nerve biopsy might also prove beneficial in anti-MAG neuropathy. It is most useful when considering amyloidosis, vasculitis (cryoglobulinaemia), malignant lymphoproliferative infiltration of nerves and IgM neuropathy with negative anti-MAG antibodies.[35] Biopsy typically shows diminished number of myelinated axons with elective loss of large myelinated fibres. Widening of myelin lamellae (WML) is typically seen on electron microscopy in patients with distal acquired demyelinating phenotype.[36] WML is considered as a specific feature of IgM anti-MAG neuropathy.

With regards to treatment, it has been shown that IgM anti-MAG neuropathy usually responds poorly to most conventional immunomodulatory therapies.[37] A Cochrane Review by Lunn and Nobile-Orazio[38] identified only five studies, [39 40 41 42 43], including a total of 97. Of these studies, only Comi *et al*[43] (22 patients) fulfilled the predefined inclusion criteria. It was concluded that none of these interventions had provided beneficial effects for the treatment of anti-MAG neuropathies. In 2009, Dalakas *et al*[44] published the results of using rituximab in such patients: there was depletion of B cells lasting for more than 6–8 months and resulted in reduction of IgM by 34% and the MAG titres by 50%. In most patients, the improvement began after 3 months (it was clear by month 6 and lasted for up to a year or longer). More recently, Svahn *et al*[35] have suggested beneficial use of rituximab in the early phase of anti-MAG neuropathy. Overall, at this current juncture, there is inadequate reliable evidence from trials of immunotherapies in anti-MAG paraproteinaemic neuropathy to form an evidence base supporting any particular immunotherapy treatment. A Cochrane Review by Lunn and Nobile-Orazio[45] includes the results of Légers *et al*[46] RCT, which included 52 patients with anti-MAG IgM gammopathy, a demyelinating neuropathy and either MGUS or low-grade non-Hodgkin B-cell lymphoma; it concluded that rituximab is ineffective in improving inflammatory neuropathy cause and treatment sensory score in patients with IgM anti-MAG demyelinating neuropathy. Campagnolo *et al*[47] conclude that the clinical feature and response (if present) to rituximab therapy (generally months later) does not change irrespective of the underlying haematological disease (IgM MGUS or Waldenstrom's macroglobulinaemia).

There is a growing role of deep brain stimulation for neurogenic tremor. As Bain *et al*[20] explain the most likely rationale is that by stimulating the thalamus, the cerebellar circuitry is affected (which has been implicated in tremor generation). If the cerebellum receives disorganised sensory input (due to peripheral nerve demyelination), resulting in tremor, it is then reasonable to conclude that the tremor may improve by activating the thalamus. The Vim is a key relay structure within the spino-cerebellar-thalamo-cortico-spinal loops, being involved in the non-parkinsonian tremor.[48] Ramirez-Zamora and Okun[49] report suppression of refractory neurogenic tremor following thalamic deep brain stimulation (DBS). Ruzicka *et al*[50] reported a 50% benefit in the disability and tremor scores in a patient with IgM paraproteinaemic neuropathy, who received unilateral Vim DBS. Blomstedt *et al*[51] report a 70% improvement of neurogenic tremor achieved at 12 months in a patient treated with unilateral posterior subthalamic area DBS. At the moment, there is limited evidence to determine the long-term efficacy of DBS in neurogenic tremor and the procedure is still considered investigational.

Learning points

- Anti-myelin associated glycoprotein (MAG) positivity must be considered in patients with demyelinating (or axonal) neuropathy with intentional tremor.
- Intentional tremor is not always indicative of a cerebellar pathology, it can also be present as a 'neurogenic' tremor in anti-MAG peripheral polyneuropathies.
- IgM monoclonal gammopathy associated with axonopathy favours Waldenstrom macroglobulinaemia; more so, if there is anaemia (<12.6 g/dL) and elevated IgM concentration (>18.3 g/L). In such cases, a bone marrow biopsy is required to rule out lymphoproliferative disorders. The presence of demyelination should not preclude a bone marrow biopsy.
- Rituximab is a good treatment option for patients with anti-MAG neuropathy.
- Deep brain stimulation can be considered for refractory neurogenic tremor in anti-MAG neuropathies.

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