Clinical Reasoning: A 67-Year-Old Woman With Progressive Tingling Sensations and Imbalance

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Section 1

A 67-year-old woman presented with 4 months of progressive numbness, tingling, and weakness in her hands and feet symmetrically with gait imbalance. Symptoms started in her upper and lower extremities at approximately the same time. She denied skin changes, tremors, weight loss, autonomic symptoms, or other systemic symptoms. She did not have a family history of a neuromuscular disorder. Her initial neurologic examination was notable for proximal and distal weakness (Medical Research Council [MRC] scale shoulder abduction 4+/5; elbow flexion, elbow extension, wrist flexion, wrist extension finger extension, finger flexion 4/5; finger abduction 4+/5; hip flexion 4−/5; knee extension 4+/5; and knee flexion, dorsiflexion, plantarflexion, toe extension, toe flexion 5/5 bilaterally). Sensation to pinprick, vibration, and temperature were decreased in the distal hands and feet below the levels of the wrists and ankles, respectively. Proprioception was impaired at the toes but intact at the ankles. Her reflexes were 1 in the upper extremities and absent in the lower extremities. She did not have pes cavus.

Questions for Consideration:

1. What are possible localizations of this presentation on the neuromuscular axis?
2. What is the best next diagnostic step?

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Section 2

The combination of weakness, sensory changes, and hyporeflexia localizes to the nerve roots, plexuses, and/or peripheral nerves. The symmetric upper and lower extremity involvement suggests a systemic process, narrowing localization to a peripheral neuropathy. The simultaneous involvement of the upper and lower extremities suggests a non–length-dependent pattern. The next best diagnostic step is to characterize the patient's neuropathy with nerve conduction studies (NCS). These studies were performed, and the results are summarized in Table.

Question for Consideration:

1. What is the interpretation of the NCS?

Table Nerve Conduction Studies

Nerve/Sites	Rec. Site	Dist (cm)	Peak (ms)	Amp. (μV)	Vel. (m/s)	Temp. (°C)
Sensory nerve conduction studies						
R median						
Wrist	Digit 2	15		NR		32.6
Palm	Digit 2	8		NR		32.4
R ulnar						
Wrist	Digit 5	12	3.9	*3.6	39.1	31.9
R radial						
Forearm	Snuff box	10	2.2	54.6	60.0	32.2
L median						
Wrist	Digit 2	15	4.5	*8.3	48.8	33.1
Palm	Digit 2	8	2.4	*8.4	49.5	32.9
L ulnar						
Wrist	Digit 5	12	4.8	*10.7	32.0	32.1
L radial						
Forearm	Snuff box	10	2.3	50.2	58.2	32.2
L sural						
Posterior leg	Lat Mall	12	3.5	11.0	41.9	30.4
L superficial peroneal						
Lateral leg	Ankle	12	3.5	10.3	41.9	29.9

Nerve/Sites	Rec. Site	Dist. (cm)	Lat. (ms)	Amp. (mV)	Area (mVms)	Dur. (ms)	Vel. (m/s)	Temp. (°C)
Motor nerve conduction studies								
R median—APB								
Wrist	APB	6	*9.8	5.2	20.0	7.8		32.4
Elbow		23	15.7	4.6	20.7	7.7	39.4	32.4
R ulnar—ADM								
Wrist	ADM	6	*5.3	7.5	24.9	7.9		31.2
Below ulnar groove		20.5	9.9	5.5	19.5	8.0	44.2	31.1
Above ulnar groove		10	12.4	4.0	18.5	8.9	39.2	31.1
Median stimulation at elbow			13.0	1.2	3.3	5.6		31
R ulnar—FDI								
Wrist	FDI		7.4	8.5	23.0	5.4		32.9

Continued

Table Nerve Conduction Studies *(continued)*

Nerve/Sites	Rec. Site	Dist. (cm)	Lat. (ms)	Amp. (mV)	Area (mVms)	Dur. (ms)	Vel. (m/s)	Temp. (°C)
Below ulnar groove		20.5	11.8	4.9	14.2	5.4	47.4	32.4
Above ulnar groove		10	14.2	3.4	11.7	7.0	40.9	32.1
Median stimulation at elbow			12.5	1.8	5.0	5.2		31.5
L median—APB								
Wrist	APB	6	*7.1	10.6	33.4	6.6		32.1
Elbow		22.5	12.0	10.0	34.5	7.3	46.0	32.1
L ulnar—ADM								
Wrist	ADM	6	*4.7	6.2	24.0	7.6		31.6
Below ulnar groove		19.5	8.7	6.2	22.5	7.6	48.6	31.5
Above ulnar groove		10	10.9	5.7	21.1	7.8	44.7	31.3
L ulnar—FDI								
Wrist	FDI		6.9	7.0	19.7	5.9		32.4
Below ulnar groove		19.5	11.1	5.8	17.5	5.8	46.8	32.2
Above ulnar groove		10	13.0	4.8	16.0	6.2	51.9	32
Median stim at elbow	FDI		14.3	1.7	4.8	5.7		32
L peroneal—EDB								
Ankle	EDB	9	*10.9	*1.5	6.1	6.9		29.4
Below fibular head		28	18.1	*1.5	4.1	6.3	39.0	29.3
Above fibular head		10	20.4	*1.5	4.9	7.0	43.6	29.2
L tibial—FHB								
Medial malleolus	FHB	11	*9.0	*2.3	6.2	6.5		28.8
Popliteal fossa		41	19.2	*2.6	7.3	7.0	40.0	28.8

F wave latencies

Nerve	Fmin (ms)	Fmax (ms)	Max–min (ms)
R median—APB	*42.29	*45.42	3.13
R ulnar—ADM	*39.48	*42.97	3.49
L median—APB	*37.08	*39.74	2.66
L ulnar—ADM	*36.09	*38.44	2.34
L tibial—FHB	*79.48	*84.27	4.79

Abbreviation: ADM = abductor digiti minimi; APB = abductor pollicis brevis; EDB = extensor digitorum brevis, FHB = flexor hallucis brevis; NR = no response.
Findings include bilateral Martin-Gruber anastomoses, a normal anatomic variant.
*Abnormal.

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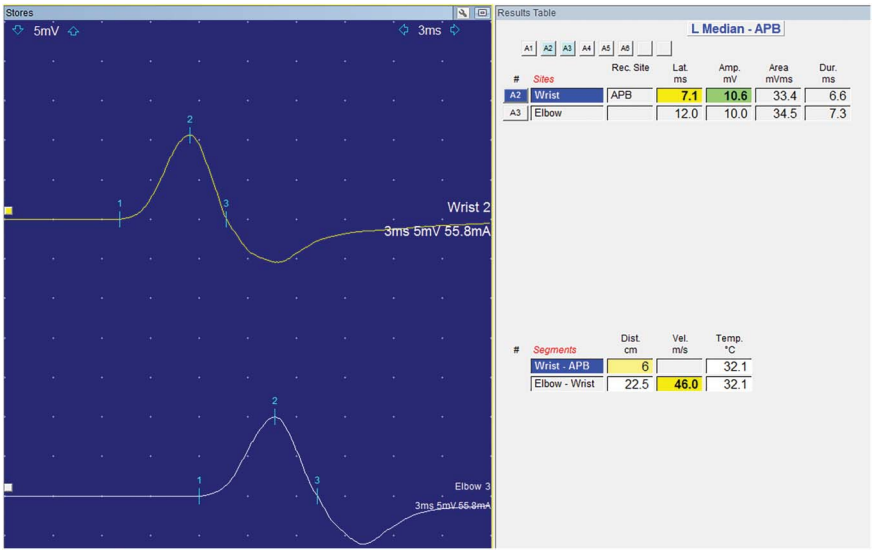
Section 3

NCS showed decreased sensory nerve action potential (SNAP) amplitudes in the upper extremities, whereas lower extremity SNAPs were normal, as can be seen in non–length-dependent or "sural-sparing" neuropathies. This pattern of SNAP abnormalities is highly specific for demyelinating neuropathies and helps differentiate them from axonal neuropathies.[1] Compound muscle action potentials (CMAPs) had mildly slowed conduction velocities with markedly prolonged distal latencies (Figure) without conduction block or marked temporal dispersion. F-wave latencies were uniformly prolonged. These findings suggest a generalized, non–length-dependent, sensorimotor, and demyelinating polyneuropathy.

Questions for Consideration:

1. What is the differential diagnosis for sensory and motor demyelinating neuropathy?
2. What are the best next steps in evaluation?

Figure Nerve Conduction Studies Demonstrating Left Median Compound Muscle Action Potential Recording at the Abductor Pollicis Brevis, With Markedly Prolonged Distal Latency Out of Proportion to Mildly Slowed Conduction Velocity



Abbreviations: APB = abductor pollicis brevis; L = left.

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Section 4

The differential diagnosis for subacute or chronic sensory and motor demyelinating neuropathy includes chronic inflammatory demyelinating polyneuropathy (CIDP) and its variants; paraproteinemic neuropathy, such as anti–myelin-associated glycoprotein (MAG) neuropathy, POEMS syndrome (organomegaly, endocrinopathy, monoclonal protein, and skin changes), GALOP syndrome (gait disorder, autoantibody to a neural antigen, late-age onset, and polyneuropathy), and CANOMAD syndrome (chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins, and disialosyl antibodies); inherited polyneuropathies, such as the demyelinating subtype of Charcot-Marie-Tooth (CMT) disease; and neuropathy secondary to medication exposures, such as tumor necrosis factor inhibitors and amiodarone.[2,3] Clinical history may help differentiate between these, for example, systemic symptoms suggestive of a plasma cell dyscrasia (PCD) underlying a paraproteinemic neuropathy or medication exposures, neither of which applied to this patient. The degree of demyelinating changes on NCS may also be helpful, in our case showing less severe demyelinating changes as would be expected in CMT disease.

The best next step is to evaluate for reversible causes of demyelinating neuropathy. Serum electrophoresis and immunofixation (IFE) are essential for evaluating a monoclonal gammopathy as cause for a paraproteinemic neuropathy. Anti-MAG antibodies and vascular endothelial growth factor should also be considered, the former especially if NCS demonstrate CMAPs with markedly prolonged distal motor latencies and the latter if features of POEMS are present.[4] Antibodies against gangliosides should also be considered. CSF studies are helpful for detecting albuminocytologic dissociation, although this finding may be seen in multiple diagnoses. In this case, SPEP/IFE and anti-MAG antibodies were sent, the former showing a restricted band in IgM and the corresponding kappa region. Anti-MAG antibodies were positive at >1:102,400 (normal <1:1,600). CSF protein was elevated at 119 mg/dL (normal 15–45 mg/dL).

The patient was given a diagnosis of anti-MAG neuropathy and initiated on treatment with rituximab, with a plan for 375 mg/m^2 weekly for 4 weeks and maintenance dosing every 2–3 months for 6–24 months pending her clinical course. She also underwent bone marrow and fat pad biopsies to evaluate for a hematologic malignancy, which were negative.

After receiving 2 weekly doses of rituximab, the patient experienced progressive weakness leading to difficulty with ambulation. On neurologic examination, her upper extremity strength was similar but her lower extremity strength had declined (MRC scale hip flexion 3/5; knee flexion 4+/5; knee extension 4/5; and dorsiflexion, plantarflexion, toe extension, and toe flexion 5/5 bilaterally). Sensory examination was unchanged from initial evaluation, but she was now areflexic.

Question for Consideration:

1. What treatment may be considered?

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Section 5

Acute worsening of symptoms of anti-MAG has been described,[5] and paradoxical worsening with rituximab has also been reported.[6] Our patient underwent plasmapheresis (PLEX) with reversal of her acute worsening over days. After discharge, she was continued on rituximab therapy. She experienced progressive improvement in her weakness and function over the following months.

Discussion

Anti-MAG neuropathy is a paraproteinemic neuropathy in which monoclonal Immunoglobulin M (IgM) targets MAG, leading to IgM and complement deposition on myelin sheath and splitting of myelin lamellae.[7] Its exact prevalence is difficult to quantify, given the high prevalence of monoclonal gammopathy of undetermined significance (MGUS) in the general population estimated at 3%–4% in adults over age 50[2] and the limited specificity of anti-MAG antibodies, which is found in approximately 50% of cases of IgM MGUS, most of which do not have a clinical diagnosis of anti-MAG neuropathy. In a large series of 202 patients ultimately diagnosed with anti-MAG neuropathy, 68% presented initially with MGUS, while 15% presented initially with neuropathy.[8] The phenotype is a distal acquired demyelinating symmetrical neuropathy characterized by sensory abnormalities and marked ataxia with gait unsteadiness, although motor weakness is common in severe cases.[3] Our patient had an unusual presentation—while her distal sensory symptoms and gait imbalance were classic, she also had marked proximal weakness, which is more common with a traditional CIDP phenotype.

Anti-MAG neuropathy is diagnosed by a combination of consistent clinical features, electrodiagnostic studies demonstrating demyelinating neuropathy, and the presence of anti-MAG antibodies. Of note, a small subset of patients with positive antibodies do not have monoclonal gammopathy such that a normal SPEP/IFE should not deter from antibody testing if clinical suspicion is high.[9] Early studies describe an electrodiagnostic profile of anti-MAG neuropathy with disproportionate slowing of conduction in the distal segments of motor nerves such that prolonged distal latencies are out of proportion to slowed conduction velocities, but this feature is nonspecific.[10] More recent research describes that this finding is most commonly seen at the median nerve (specifically with terminal latency index <0.25), but this too is nonspecific and may be seen in other IgM neuropathies without MAG reactivity.[11]

Treatment for anti-MAG neuropathy differs from that of CIDP. Rituximab is prescribed as first-line therapy targeting antibody production. A large placebo-controlled trial evaluating rituximab for the treatment of anti-MAG neuropathy found improvement in several secondary outcomes including the inflammatory neuropathy cause and treatment (INCAT) disability scale but failed to meet the primary outcome of change in INCAT sensory score.[12] It is believed that rituximab may be particularly helpful early in the disease course[7] and that response to treatment is greater in patients with slower evolution of symptoms and those with proximal weakness of the lower limbs. Response to treatment does not correlate with electrodiagnostic data.[13] It was also believed not to correlate with anti-MAG titers, but a recent retrospective study found that a sustained reduction of greater than 50% compared with pretreatment titers may correlate with therapeutic response.[14] Our patient experienced deterioration after 2 doses of rituximab. Small case series have suggested the benefit of PLEX in such cases, with the rationale of slowing disease activity through removal of monoclonal IgM from the circulation.[4] Despite treatment, nearly half of patients suffer long-term disability.[15]

There are important nuances in the management of patients with paraproteinemic neuropathy, among these the potential for MGUS to progress to overt hematologic malignancies. IgM MGUS carries risk of progression to Waldenstrom macroglobulinemia, immunoglobulin A (IgA) and IgG MGUS to multiple myeloma, light-chain MGUS to light-chain type of multiple myeloma, and all forms to amyloid light chain (AL) amyloidosis.[2] As such, the management of paraproteinemic neuropathy may require the expertise of hematology colleagues to guide the screening for an underlying hematologic malignancy. Our patient underwent serial serologic testing for kappa and lambda light chains and bone marrow aspiration to evaluate for an underlying hematologic malignancy, which has thus far been negative.

Our case illustrates the need for a thorough workup to identify the cause of a subacute motor and sensory demyelinating neuropathy, particularly to differentiate between CIDP and less common diagnoses including PCD-associated peripheral neuropathy, given the differences in treatment and the importance of a timely diagnosis of a malignancy. Anti-MAG may be managed with the combined expertise of a neurologist and hematologist.

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Appendix *(continued)*

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