

# Clinical Reasoning: A 79-year-old man with polyneuropathy and dysautonomia

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## SECTION 1

A 79-year-old man was referred to the neuromuscular clinic for evaluation of severe polyneuropathy. Four years ago, he noted bilateral lower extremity numbness below the knee, particularly in his shins. At the time he also had a right transcarpal ligament release at an outside institution for a diagnosis of carpal tunnel syndrome. This procedure did not provide any relief of his right-hand numbness. He also had numbness in his left hand. One year ago, he began tripping over his feet due to ankle weakness, resulting in falls on several occasions. Concurrently, he complained of burning in the hands more than in the feet, and treatment with gabapentin and a topical Lidoderm patch was started. Six months ago, he started having bilateral hand weakness with trouble opening jars or manipulating buttons. At the same time, he developed near-syncope and was found to have orthostatic hypotension, and treatment with midodrine was started.

A Foley catheter was placed 1 year ago because of urinary retention and bilateral hydronephrosis,

attributed at the time to benign prostatic hypertrophy. He also noted erectile dysfunction and constipation for a few years. The patient reported an involuntary 25-pound weight loss in the last year.

His medical history included bilateral cataract surgery at 75 years but was otherwise negative. He denied any family history of neuropathy. He was a heavy smoker but did not drink or use illicit drugs. There were no toxic exposures. His general examination showed a drop of 20 mm Hg in his systolic blood pressure when standing without an increase in pulse rate. His mental status and cranial nerves were normal. His intrinsic hand muscles were atrophic. He had bilateral mild proximal and severe distal weakness in his arms and legs. He had loss of sensation to pinprick up to the knees and midforearms bilaterally and vibratory sensation loss in his toes and fingertips. His reflexes were absent except for those for the biceps and brachioradialis, which were diminished.

## Question for consideration:

1. What is the differential diagnosis at this stage?

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*Disclosure:* Author disclosures are provided at the end of the article.

## SECTION 2

This patient had chronic sensorimotor polyneuropathy with pronounced autonomic symptoms. His dysautonomia included constipation, erectile dysfunction, orthostatic hypotension, and urinary retention. His weight loss could be related to a systemic condition that resulted in neuropathy or could be part of the dysautonomia, which may cause early satiety from reduced gastric emptying. Most polyneuropathies have some involvement of the autonomic system, but when autonomic signs are prominent as in this patient, the differential diagnosis is narrower.<sup>1</sup> The differential diagnosis of chronic polyneuropathy with prominent dysautonomia can be divided into acquired vs hereditary. Acquired etiologies include metabolic causes such as diabetes mellitus, toxic causes such as chemotherapy or other medication or heavy metal toxicity, infectious causes such as HIV and Chagas disease, autoimmune conditions such as Sjögren syndrome or rheumatoid arthritis, paraneoplastic disease such as anti-Hu–associated polyneuropathy, and amyloid neuropathy due to multiple

myeloma or light-chain (AL) amyloidosis. Some of these etiologies can be ruled out by history. For example, this patient denied any toxic exposures and did not have risk factors or clinical findings suggestive of infectious disorders. Anti-Hu neuropathy is primarily a sensory neuropathy and does not result in motor weakness. Screening for other etiologies such as metabolic and autoimmune disease is necessary because neuropathy may be the only manifestation of the disease.

Inherited autonomic neuropathies include familial amyloid polyneuropathy (FAP) and the hereditary sensory autonomic neuropathies (HSANs). HSANs are unlikely in this patient because of his age. FAP still needs to be considered; although the patient's parents are asymptomatic, there may be genetic anticipation.

### Question for consideration:

1. What tests should be ordered to narrow the differential diagnosis?

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### SECTION 3

At this time EMG and nerve conduction studies (NCS) should be performed to define the underlying

pathology (demyelinating vs axonal) and the extent and distribution of the neuropathy (generalized vs multifocal). In addition, the patient should be screened for acquired causes.

In this patient, the EMG and NCS showed a severe, mixed, but predominately axonal sensorimotor polyneuropathy that has resulted in prominent motor axon loss in distal limb muscles (table). His laboratory workup included complete blood count, comprehensive metabolic panel, hemoglobin A1c, Lyme disease titer, anti-hepatitis C antibodies, HIV testing, antinuclear antibodies, rheumatoid factor, erythrocyte sedimentation rate, C-reactive protein, vitamin B12 level, anti-Ro and anti-La antibodies, immunofixation of serum (IFE), quantitative immunoglobulins in the blood and urine, and cryoglobulins. Test results were all unremarkable. A chest X-ray and skeletal survey were also done to rule out myeloma, and results were negative.

**Table** Motor nerve conduction studies showing diffuse reduction in amplitude and velocity<sup>a</sup>

Motor NCS	Recording site	Latency	Amplitude, mV	Velocity, m/s
R median: wrist	APB	7.65 <sup>b</sup>	0.6 <sup>b</sup>	
Elbow	APB	16.25	0.7 <sup>b</sup>	30.2 <sup>b</sup>
R ulnar: wrist	ADM	5.45 <sup>b</sup>	2.6 <sup>b</sup>	
Below the elbow	ADM	10.60	2.3 <sup>b</sup>	33.0 <sup>b</sup>
Above the elbow	ADM	14.80	2.5 <sup>b</sup>	28.6 <sup>b</sup>
R tibial: ankle	AH	NR <sup>b</sup>	NR <sup>b</sup>	NR <sup>b</sup>
Popliteal fossa	AH	NR <sup>b</sup>	NR <sup>b</sup>	NR <sup>b</sup>
R common peroneal: fibular head	TA	3.30	4.5 <sup>b</sup>	
Knee	TA	6.15	2.7	45.6

Abbreviations: ADM = abductor digiti minimi; AH = abductor hallucis; APB = abductor pollicis brevis; NCS = nerve conduction studies; NR = not recordable; TA = tibialis anterior.

<sup>a</sup> Sensory NCS in the limbs were NR.

<sup>b</sup> Abnormal values.

#### Question for consideration:

1. What is the next step in this patient's workup?

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#### SECTION 4

The most likely diagnosis is polyneuropathy associated with transthyretin (TTR) amyloidosis, AL amyloidosis, or amyloidosis due to multiple myeloma. In these 3 diagnoses, autonomic neuropathy tends to occur relatively early in the course of the disease and results in sexual impotence in men, gastrointestinal motility problems, and bladder retention. In addition, carpal tunnel syndrome is frequently seen in amyloidosis. However, the normal IFE, renal function, and quantitative immu-

noglobulin level favor TTR amyloid neuropathy. Other causes of hereditary amyloid neuropathy are ruled out because of the clinical features. For instance, gelsolin amyloidosis typically manifests with lattice corneal dystrophy, often by age 20–30 years, followed a decade later by progressive cranial neuropathies, which was not the case in our patient.

#### Question for consideration:

1. What test can be ordered to diagnose TTR amyloidosis?

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## SECTION 5

A tissue biopsy can be obtained to prove the diagnosis but one can also test for a *TTR* gene mutation. Classically, a subcutaneous fat aspiration (FA) has been used successfully to diagnose systemic amyloidosis. The procedure is easy to perform and is a safe and less invasive alternative to a nerve biopsy, but the sensitivity of 72% is relatively low.<sup>2</sup> Moreover, it has been shown that in patients with isolated polyneuropathy due to amyloidosis who do not have autonomic symptoms, the yield of FA is null, as none of the 143 such patients in one study had positive FA results.<sup>3</sup> Hence, the gold standard for diagnosing amyloid neuropathy is sural nerve and muscle biopsy. However, in this patient, genetic testing should be done first for diagnosis of a potential *TTR* mutation. If results of genetic testing are negative, one can then proceed with a sural nerve and muscle biopsy.

In this patient, the genetic testing showed a DNA sequence alteration (Val30Met) in the first *TTR* allele, which confirmed the diagnosis of TTR amyloidosis.

**DISCUSSION** In this patient, the presence of prominent dysautonomia and the chronicity of the symptoms narrowed the diagnosis. After acquired causes of chronic polyneuropathy and autonomic neuropathy were ruled out, the most likely diagnosis was amyloid polyneuropathy. The clinical presentation, normal IFE, and normal renal function suggested TTR amyloidosis, which was proven by genetic testing.

TTR amyloidosis is the most common form of autosomal dominant hereditary systemic amyloidosis.<sup>4</sup> Our patient denied any familial history but later revealed that his brother also had the *TTR* mutation and died of complications of liver transplantation. His parents may have died before developing severe symptoms, or genetic anticipation may have occurred. FA is a reasonable test when patients have systemic amyloidosis, but readers should be aware that the sensitivity of this test is relatively low, and in the setting of isolated polyneuropathy, one should biopsy the sural nerve and muscle directly.<sup>3</sup>

Autonomic neuropathy in FAP typically occurs early in the course of the disease and results in sexual impotence in men, gastrointestinal motility problems, and bladder retention as in our patient. Carpal tunnel syndrome is often an early feature and may be the only clinical manifestation.<sup>5</sup> The recurrent laryngeal nerve may be involved, manifesting as vocal hoarseness.<sup>6</sup> The “scalloped pupil” deformity, which is due to amyloid deposition in the ciliary nerve is pathognomonic for FAP.<sup>5</sup> Vitreous opacities are more common, seen in 20% of those with *TTR* mutations and may be the first manifestation of FAP.<sup>6</sup> Restrictive cardiomyopathy is an important cause of morbidity and mortality in pa-

tients with TTR amyloidosis. It should be noted that not all amyloid disorders are associated with a peripheral neuropathy. For example, peripheral neuropathy is not seen in reactive (secondary) amyloidosis or in most of the inherited amyloidoses characterized by renal, hepatic, or cardiac deposition. Furthermore, there are nonneuropathic forms of familial TTR amyloidosis.<sup>7</sup> Further testing in patients with TTR amyloidosis includes echocardiogram, EKG, gadolinium-enhanced MRI of the brain and spinal cord to evaluate CNS amyloidosis, and ophthalmologic evaluation.

The only effective treatment for patients with the *TTR* mutation is liver transplantation. This procedure is typically reserved for patients with polyneuropathy restricted to the lower extremities or with autonomic neuropathy alone. These patients should be younger than 60 years, should have disease duration of less than 5 years, and should not have significant cardiac or renal dysfunction.<sup>8</sup> Without treatment, the disease is progressive and unremitting, resulting in death in 10 years after the onset of symptoms. With liver transplantation, the estimated survival rate at 5 years is 60%.<sup>9</sup>

## DISCLOSURE

Dr. Karam serves on the editorial board of the *Neurology*<sup>®</sup> Resident & Fellow Section. Dr. Scelsa has served on scientific advisory boards for Avanir Pharmaceuticals and GlaxoSmithKline; receives publishing royalties for *Peripheral Neuropathies in Clinical Practice* (Oxford University Press, 2010); receives research support from the NIH; and has served as an expert witness in a medicolegal case.

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