RESIDENT & FELLOW SECTION

Section Editor
Mitchell S.V. Elkind, MD, MS

Clinical Reasoning: An 85-year-old man with paresthesias and an unsteady gait

Aaron L. Berkowitz, MD, PhD
Ruchira M. Jha, MD
Joshua P. Klein, MD, PhD
Anthony A. Amato, MD

Correspondence to Dr. Berkowitz: aberkowitz3@partners.org

SECTION 1

An 85-year-old man developed tingling in his feet, followed 1 week later by a similar sensation in both hands. He reported difficulty buttoning his shirt and unsteadiness when walking. There was no ascent of his symptoms proximal to the wrists and ankles. He denied pain, orthostasis, and bowel or bladder symptoms. He had had no prior similar symptoms, preceding illnesses, or recent changes in his health or medications. He had received the influenza vaccine 1 week prior to symptom onset.

His medical history included congestive heart failure and idiopathic pulmonary fibrosis for which he took low-dose prednisone. There was no history of illicit drug use, excessive alcohol consumption, toxic exposures, or family history of neurologic disorders.

On examination, he had no cranial nerve deficits and full strength. He had preserved light touch, temperature, and pinprick sensation, but symmetrically diminished vibration sense and proprioception to the level of both wrists and ankles. Reflexes were absent bilaterally in his upper and lower extremities. On pronator drift testing, his arms drifted upward, and his fingers made small involuntary movements. On finger-nose testing the patient had difficulty reaching and maintaining contact with a target, which worsened with eyes closed. He had no Romberg sign, but had mild gait instability.

Questions for consideration:

1. What is the localization of his deficits?
2. What further evaluation should be undertaken?

GO TO SECTION 2

From the Department of Neurology, Brigham and Women's Hospital, Boston, MA.
Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

SECTION 2

The patient's gait unsteadiness, upward drift of the arms with pseudoathetosis of the fingers (subtle movements suggestive of a proprioceptive deficit), and worsening of finger-nose testing with eyes closed suggest a sensory ataxia. Sensory ataxia, diminished vibration sense, decreased proprioception, and areflexia localize to the posterior columns, large fibers of peripheral nerves, or intervening dorsal root ganglia or nerve roots; the bilaterality, symmetry, and areflexia make a supratentorial etiology improbable.

The differential diagnosis for disease processes causing peripheral neuropathy, ganglionopathy, polyradiculopathy, or posterior column dysfunction includes infections, nutritional deficiencies, endocrine dysfunction, inflammatory/autoimmune conditions, malignancy, paraneoplastic processes, toxic exposures, medications, and hereditary conditions (table).

Before referral to a neurologist, the patient had undergone laboratory evaluation for etiologies of peripheral neuropathy, revealing normal vitamin B12, thyroid-stimulating hormone, hemoglobin A1C, serum and urine protein electrophoresis, and liver enzymes. Given the rapidly evolving nature of his symptoms and absent reflexes, he was admitted due to concern for possible Guillain-Barré syndrome (GBS). CSF analysis to assess for inflammation or infection revealed normal glucose (60 mg/dL), mildly elevated protein (64.2 mg/dL), and no red or white blood cells. EMG and nerve conduction studies (NCS) were performed to distinguish between axonal and demyelinating etiologies of presumed polyneuropathy. NCS demonstrated reduced amplitudes of sensory nerve action potentials (SNAPs) in the sural (left 3.3 μV, right 0.60 μV; normal >5 μV), superficial peroneal (left 3.7 μV, right 3.3 μV; normal >5 μV), median (left 6.0 μV, right 6.1 μV; normal >30 μV), and ulnar nerves (left not recordable, right 5.2 μV; normal >10 μV); slightly reduced amplitudes of combined motor action potentials (CMAPs) of bilateral median (left 4.5 mV, right 2.5 mV; normal >5 mV), left ulnar (3.4 mV; normal >5 mV), and bilateral peroneal nerves (left 1.7 mV, right 1.9 mV; normal >2 mV); and normal nerve conduction velocities (NCV), distal latencies, and F waves. EMG was normal in bilateral tibialis anterior, left first dorsal interosseous, and left extensor digitorum brevis muscles.

Questions for consideration:

1. How can the NCS be interpreted?
2. What features are suggestive of GBS or one of its variants, and which aspects would be inconsistent with a diagnosis of GBS?

GO TO SECTION 3

Table Causes of peripheral neuropathy, ganglionopathy, radiculopathy, or posterior column disease

	Peripheral neuropathy	Ganglionopathy	Radiculopathy	Posterior column dysfunction
Infectious				
Syphilis			X	X
HIV	X	X	X	X
Hepatitis B (polyarteritis nodosa)	X			
Hepatitis C (cryoglobulinemia)	X			
Leprosy	X			
Lyme	X		X	
HSV			X	
CMV	X		X	
EBV	X	X		
VZV		X	X	
HTLV-1	X	X		
Diphtheria	X			
Nutritional				
Vitamin B_{12} deficiency	X			X

Continued

Table Continued

	Peripheral neuropathy	Ganglionopathy	Radiculopathy	Posterior column dysfunction
Vitamin E deficiency	X	X		X
Copper deficiency	X			X
Endocrine				
Diabetes	X		X	
Thyroid dysfunction	X			
Inflammatory/autoimmune				
AIDP/CIDP	X		X	
Sjögren syndrome	X	X		
Sarcoidosis	X		X	
Vasculitis	X			
Amyloid	X		X	
Anti-MAG	X			
Neoplastic/paraneoplastic				
Multiple myeloma	X			
Waldenstrom macroglobulinema	X			
Lymphoma	X		X	
POEMS	X			
Anti-Hu		X		
Anti-CRMP-5		X		
Toxic				
Alcohol	X			
Heavy metals (lead, arsenic, thallium, mercury)	X			
Nitrous oxide	X			
Organophosphates	X			
Ciguatera toxin	X			
Medication-related				
Chemotherapies including vincristine, taxols, bortezomib, suramin	X			
Platinum-based chemotherapy including cisplatin, carboplatin		X		
Isoniazid (due to B_6 deficiency)	X			
Amiodarone	X			
Chloroquine/hydroxychloroquine	X			
Pyridoxine (vitamin B_6) excess	X	X		
Hereditary				
Charcot-Marie-Tooth	X			
Friedreich ataxia	X			X
Hereditary sensory and autonomic neuropathy	X	X		
Porphyria	X			

Abbreviations: AIDP = acute inflammatory demyelinating polyradiculoneuropathy; CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; CMV = cytomegalovirus; CRMP-5 = collapsin response mediator protein 5; EBV = Epstein-Barr virus; HSV = herpes simplex virus; HTLV = human T-cell lymphotrophic virus; POEMS = polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes; VZV = varicella-zoster virus.

SECTION 3

Reduced SNAP and CMAP amplitudes with preserved NCV and distal latencies in multiple nerves suggest a disease process affecting sensory and motor axons. Distal paresthesias and areflexia can be seen in GBS; however, lack of weakness several weeks into the illness would be atypical for the classic form of the disease. Subtypes of GBS can be broadly divided into acute inflammatory demyelinating polyradiculoneuropathies (AIDP) and axonal forms (acute motor axonal neuropathy and acute motor and sensory axonal neuropathy). AIDP variants include Miller Fisher syndrome (ophthalmoplegia, ataxia, areflexia), paraparetic, pure sensory, pure motor, pandysautonomic, cervico-brachial-pharyngeal, oculopharyngeal, and ophthalmoplegic forms[1,2]; these variants of AIDP share decreased tendon reflexes, electrographic features of demyelination, and cytoalbuminologic dissociation in the CSF, despite the diversity of other aspects of their clinical phenotypes.[1] This patient did not fit into any of the above categories given the lack of weakness or bulbar symptoms and NCS lacking features of demyelination with preserved F waves. He underwent extensive but unrevealing evaluation for possible autoimmune, infectious, or paraneoplastic processes (serum antinuclear antibodies, SS-A [Ro], and SS-B [La]; rapid plasma reagin and HIV; anti-Hu, anti-GQ1B, and anti-GM1 autoantibodies; and CT of the chest, abdomen, and pelvis). Although the etiology of his illness was unclear, intravenous immunoglobulin (IVIg) 0.4 g/kg/day was administered for 5 days. His symptoms remained stable and he was discharged for rehabilitation.

He initially noted improvement in his gait and only minimal persistent numbness of his hands and feet. One month later, however, his gait acutely worsened over several days, such that he was too unsteady to walk or stand unassisted. He had a Romberg sign, swayed from side to side when standing, and had a magnetic gait. His sensory, motor, and reflex examinations were otherwise unchanged from his initial examination.

Questions for consideration:

1. What is the differential diagnosis at this point?
2. What further evaluation should be undertaken?

GO TO SECTION 4

SECTION 4

The differential diagnosis of the patient's progressive sensory symptoms includes chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and ganglionopathy. Like AIDP, CIDP has many variants, including sensorimotor (e.g., classic, Lewis-Sumner syndrome/multifocal acquired demyelinating sensory and motor neuropathy) and solely sensory (e.g., chronic sensory demyelinating neuropathy, distal acquired demyelinating symmetric neuropathy).[3,4] Demyelination is a characteristic electrodiagnostic feature of CIDP; however, the nerve conduction studies in our patient showed normal NCV. Ganglionopathy presents with sensory ataxia and deficits in proprioception and vibration sense with reduced SNAPs (subclinical reduced CMAPs may also be seen),[5] all seen in our patient.

EMG/NCS were repeated and demonstrated relatively unchanged SNAPs and CMAPs compared to his prior NCS. Since worsening axonal neuropathy or ganglionopathy would have been expected to result in further decrement in his SNAPs, his clinical progression in the setting of stable electrodiagnostic studies suggested a more proximal lesion at the level of the nerve roots or posterior columns.

Question for consideration:

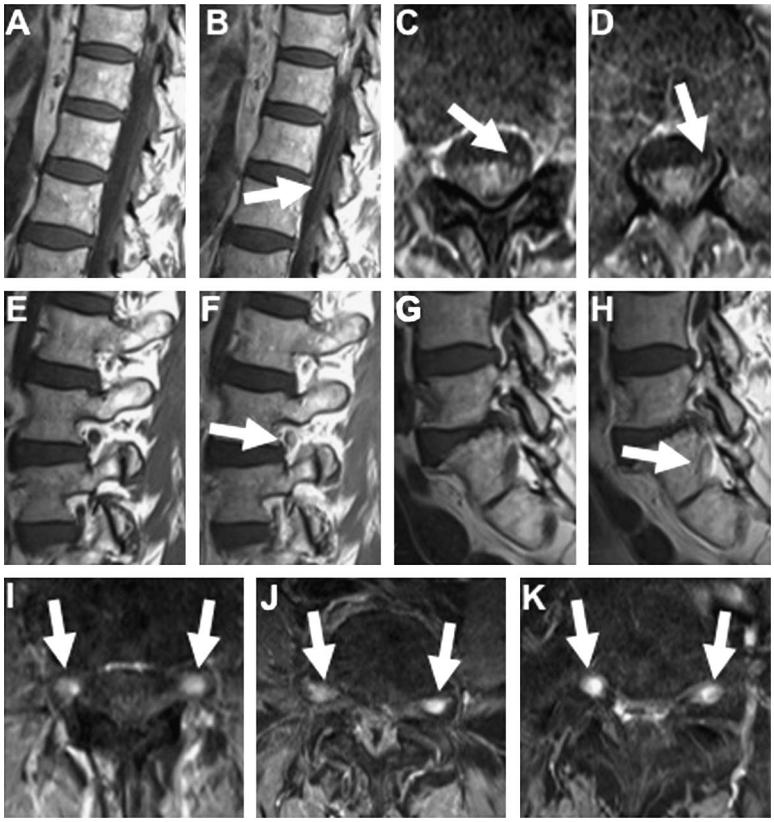
1. What diagnostic studies can aid in distinguishing between posterior column disease, radiculopathy, ganglionopathy, and peripheral neuropathy?

GO TO SECTION 5

SECTION 5

Somatosensory evoked potentials (SSEPs) measure the response to peripheral nerve stimulation at several levels along the somatosensory pathway: dorsal root ganglia (Erb's point above the clavicle for the upper extremity; over the lumbar spine for the lower extremity), nuclei cuneatus and gracilis (electrode placed over the second cervical vertebra; records N13 potential), and somatosensory cortex (recorded over the contralateral scalp; records N19-P22 potentials).[6,7] In this patient, SSEPs revealed no reproducible waveforms at any site. Given the presence of SNAPs on routine NCS, the absence of SSEPs suggests block of conduction more proximally (e.g., at the level of proximal nerve roots or posterior columns). MRI of the spine with gadolinium was performed, demonstrating enhancement of numerous lumbosacral nerve roots and dorsal root ganglia with a normal-appearing spinal cord (figure). Nerve biopsy was proposed, but deferred by the patient and his family. This constellation of clinical, electrodiagnostic, and imaging features is suggestive of chronic immune sensory polyradiculopathy (CISP).

Figure MRI of the patient's lumbosacral spine



Sagittal T1-weighted MRI with fat saturation before (A) and after (B) IV administration of gadolinium contrast shows abnormal enhancement of a left-sided nerve root at the T12-L1 vertebral level (B, arrow), also seen on axial postcontrast images (C, D, arrows). Multiple other nerve roots of the cauda equina demonstrated abnormal contrast enhancement though none were enlarged or clumped. Sagittal precontrast (E, G) and postcontrast (F, H) images of the intervertebral foramina show abnormal enhancement of right-sided dorsal root ganglia at L2-L3 (F, arrow) and L4-L5 (H, arrow). Axial postcontrast images show abnormal enhancement of the bilateral dorsal root ganglia at L2-L3 (I, arrows), L4-L5 (J, arrows), and L5-S1 (K, arrows).

DISCUSSION CISP was described in a case series of 15 patients with sensory ataxia, proprioceptive deficits, gait ataxia, paresthesias, and absent reflexes, but full strength; normal SNAPs; normal MRI of the brain and spinal cord with enlargement or enhancement of lumbar nerve roots; abnormal SSEPs suggestive of a lesion at the level of the nerve root; elevated CSF protein; and biopsy-proven inflammatory hypertrophic changes of sensory nerve rootlets.[8] The clinical, laboratory, electrophysiologic, radiologic, and pathologic features of CISP suggest dorsal root inflammation as the underlying etiology. Our patient's SNAPs and CMAPs were reduced, suggesting some degree of ganglionopathy or axonal neuropathy. The asymmetry of SNAP and CMAP amplitude reduction suggests that concurrent idiopathic sensorimotor polyneuropathy or age-related changes alone would not entirely explain these findings. Since his disease progressed dramatically in the presence of unchanged SNAPs and CMAPs, and his MRI showed no dorsal column enhancement (which is often seen in advanced ganglionopathy), but rather nerve root and dorsal root ganglion enhancement, his predominant underlying pathophysiology was believed to be sensory polyradiculopathy, albeit with some component of ganglioneuropathy.

Patients with CISP may respond to IVIg or high-dose steroids, returning to normal ambulation with reversal of sensory abnormalities.[8] Our patient was treated with another course of 5 days of IVIg followed by 1 g/kg over 2 days monthly for 4 months and prednisone 60 mg daily. His neurologic status did not improve with therapy, suggesting that he had developed irreversible damage to his proximal nerve segments. He died several months later from complications of his underlying cardiopulmonary disease.

AUTHOR CONTRIBUTIONS

A. Berkowitz drafted the initial manuscript, revised the manuscript, and was involved in the clinical care of the patient. R. Jha drafted the initial manuscript, revised the manuscript, and was involved in the clinical care of the patient. J. Klein revised the manuscript, interpreted the neuroradiology, and created the figure. A. Amato revised the manuscript and was involved in the clinical care of the patient.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

A. Berkowitz reports no disclosures relevant to the manuscript. R. Jha and J. Klein report no disclosures. A. Amato has served as a medical consultant for MedImmune, Amgen, and Biogen. Go to Neurology.org for full disclosures.

REFERENCES

1. Ropper AH. The Guillain-Barré syndrome. N Engl J Med 1992;326:1130–1136.
2. Hughes RA, Cornblath DR. Guillain-Barré syndrome. Lancet 2005;366:1653–1666.
3. Lewis RA. Chronic inflammatory demyelinating polyneuropathy. Neurol Clin 2007;25:71–87.
4. Vallat JM, Sommer C, Magy L. Chronic inflammatory demyelinating polyradiculoneuropathy: diagnostic and therapeutic challenges for a treatable condition. Lancet Neurol 2010;9:402–412.
5. Sheikh SL, Amato AA. The dorsal root ganglion under attack: the acquired sensory ganglionopathies. Pract Neurol 2010;10:326–334.
6. Chiappa KH, Ropper AH. Evoked potentials in clinical medicine (second of two parts). N Engl J Med 1992;306:1205–1211.
7. Yiannikas C, Vucic S. Utility of somatosensory evoked potentials in chronic acquired demyelinating neuropathy. Muscle Nerve 2008;38:1447–1454.
8. Sinnreich M, Klein CJ, Daube JR, et al. Chronic immune sensory polyradiculopathy: a possibly treatable sensory ataxia. Neurology 2004;63:1662–1669.