

Clinical Reasoning: A 57-year-old woman with progressive ataxia and falls

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Section 1

A 57-year-old woman presented with progressive ataxia and falls. She was in her usual state of health until she developed sudden onset of progressive imbalance for a month. She then presented to an emergency department. Examination revealed significant vibration sensation impairment and proprioceptive loss, with normal pinprick and temperature sensation; sensory ataxia with pseudoathetosis in the hands; no finger to nose incoordination; normal rapid alternating movements of upper extremities; heel to shin incoordination; diminished deep tendon reflexes; wide-based gait; and positive Romberg test. She did not have cognitive impairment, nystagmus, dysarthria, weakness, muscle atrophy, or fasciculations.

Questions for consideration:

1. What is the localization for the patient's presentation? How can you differentiate between cerebellar and sensory ataxia?
2. What are the differential diagnoses at this stage?

GO TO SECTION 2

Section 2

The patient presented with subacute progressive sensory ataxia with no significant weakness. The marked proprioceptive loss is an explanation for the ataxia. Absence of nystagmus, dysarthria, and upper extremities incoordination made a cerebellar lesion less likely. Diminished deep tendon reflexes suggest a peripheral nervous system lesion. These findings are suggestive of subacute sensory large fiber involvement with no apparent motor fiber involvement. The sensory disorder could result from lesions of posterior column in the spinal cord, the dorsal root ganglions, or large sensory fibers in the peripheral nerves. This could happen due to various disorders: metabolic disorders like

vitamin B₁₂ or E deficiency; Sjögren syndrome (autoimmune disorder usually with dry eyes and dry mouth); infections like HIV, syphilis, and herpes simplex virus (HSV); paraneoplastic disorders; pure sensory inflammatory demyelinating polyradiculopathy; paraproteinemias like monoclonal gammopathy of undetermined significance (MGUS); and toxicity from cisplatin and analogs or excess vitamin B₆ (unlikely as the patient was not taking those medications).

Question for consideration:

1. What investigations can narrow the differential diagnoses?

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Section 3

Extensive investigations showed no evidence of an immunologic, infectious, or metabolic disorder. CSF showed 5 white blood cells, normal glucose, and slightly elevated protein 0.67 g/L (normal <0.45 g/L); cytology showed no malignant cells.

Nerve conduction studies (table) revealed findings in keeping with a possible demyelinating polyneuropathy or

polyradiculoneuropathy involving motor and sensory fibers according to European Federation of Neurologic Societies criteria as right peroneal motor study recording at extensor digitorum brevis showed distal latency prolongation more than 50% above upper limit of normal values and a reduction in conduction velocity more than 30% below the lower limit of normal values. There was focal slowing in the right ulnar nerve at the level of the elbow, possibly due to compression. Needle EMG showed low-grade fibrillation potentials in right first dorsal interosseous and irritability in gastrocnemius.

Table Nerve conduction studies

Nerve and site	Latency, ms	Amplitude, mV or μ V	Segment	Distance, mm	Conduction velocity, m/s
Motor nerve conduction					
R peroneal					
Ankle	10.4	0.2	EDB-ankle	85	
Fibula (head)	21.7	0.2	Ankle-fibula (head)	305	27
Popliteal fossa	23.6	0.2	Ankle-popliteal fossa	392	30
R peroneal					
Fibula (head)	3.1	7.7	Tibialis anterior-fibula (head)	105	
Popliteal fossa	6.0	8.0	Fibula (head)-popliteal fossa	102	35
R tibial					
Ankle	6.1	6.8	Abductor hallucis-ankle	85	
Popliteal fossa	13.9	3.9	Ankle-popliteal fossa	355	46
R ulnar					
Wrist	5.0	10.2	ADM-wrist	65	
Below elbow	8.4	8.7	Wrist-below elbow	202	59
Above elbow	12.3	7.0	Wrist-above elbow	318	44
R median					
Wrist	12.6	4.0	APB-wrist	70	
Elbow	18.1	3.8	Wrist-elbow	216	39
F-waves					
R tibial	63.0			1,083	
R ulnar	38.3			642	
Sensory nerve conduction					
R sural					
Mid-calf	NR	NR	Ankle-mid-calf	140	
R superficial peroneal					
Ankle	NR	NR	Lower leg-ankle	140	
R ulnar					
Wrist	4.9	4.9	Fifth-wrist	110	
Elbow	12.6	1.4	Wrist-elbow	345	46

Abbreviations: ADM = abductor digiti minimi; APB = abductor pollicis brevis; EDB = extensor digitorum brevis.

There was evidence of mild to moderate old axon loss, with reinnervation in upper and lower limb muscles.

An acquired polyneuropathy with diffuse, patchy demyelination and minor axonal involvement was diagnosed. CT of the chest, abdomen, and pelvis showed no evidence

of malignancy, and paraneoplastic antibody panel was negative.

Questions for consideration:

1. What treatment options would you consider?
2. What are your expectations?

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Section 4

The previous investigations showed mild inflammation in the CSF and patchy demyelinating lesions in the electrodiagnostic study. These findings could be consistent with inflammatory demyelinating polyneuropathy. A course of IV immunoglobulin (IVIg) 400 mg/kg daily for 5 days was given (ideally there should be improvement in patient condition or at least no worsening). Plasma exchange is another option that was not used in this case.

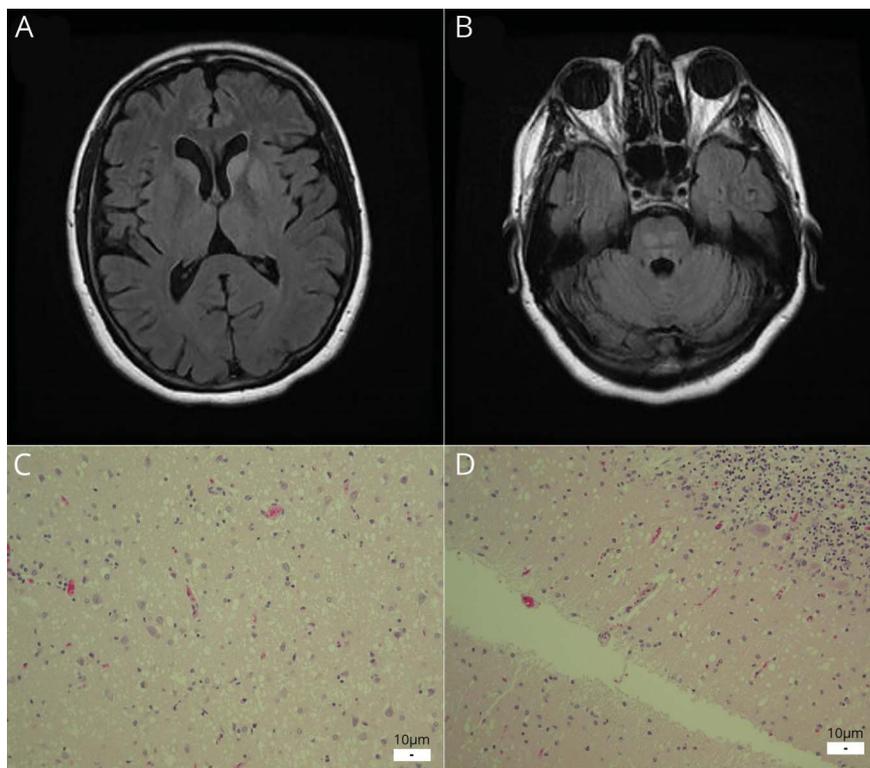
IVIg course produced no improvement and the patient continued to decline. Two months later, she started to

have cognitive impairment; short-term memory became severely impaired with time. Worsening ataxia in the limbs was noted. She became bedridden. MRI brain (figure, A and B) showed T2/fluid-attenuated inversion recovery hyperintensity in the caudate and putamen, with reverse hot cross bun sign in the pons, which may be seen with toxic/metabolic disturbances or Creutzfeldt-Jakob disease (CJD).

Question for consideration:

1. How would you confirm your diagnosis?

Figure MRI brain and brain histopathology



(A) T2 fluid-attenuated inversion recovery (FLAIR) image of the brain shows hyperintensities in the medial thalamus and basal ganglia. (B) T2 FLAIR image of the brain shows reverse hot cross bun in pons. (C) Cingulate gyrus. Spongiform appearance with empty vacuoles between neurons, and no inflammatory cells. (D) Cerebellum. Similar changes in the cerebellar cortex, especially in the molecular layer shown here.

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Section 5

EEG was normal, despite the patient's cognitive decline. A second CSF study showed endpoint quaking-induced conversion was positive for disease-associated isoforms of the prion protein. ELISA protein assay for 14-3-3 gamma was 71,791 AU/mL (threshold >20,000 AU/mL), and microtubule-associated protein tau was 6,589 pg/mL (threshold >976 pg/mL). This was considered positive for sporadic CJD.

The patient continued to deteriorate and died 5 months after symptom onset.

The brain at autopsy weighed 1,172 grams. Grossly, the lateral ventricles showed mild symmetric enlargement. There was focal congestion in the right superomedial frontal white matter. The cerebellar hemispheres were atrophic. Microscopic examination revealed widespread spongiosis (figure, C and D). In cortical sections, the cingulate gyrus showed significant disease, with moderate changes in the frontal cortex and milder changes involving the temporal, parietal, and occipital cortices. There was marked involvement of the anterior and posterior hippocampus and caudate nucleus, with mild to moderate changes in the amygdala and thalamus. The midbrain, pons, and medulla showed patchy spongiosis. The cerebellum showed extensive involvement with associated severe foliar atrophy. No peripheral nerve tissue was available for examination.

Discussion

Human prion diseases, including CJD, are transmissible diseases that predominantly involve the CNS. Some patients with CJD show subclinical signs of peripheral nerve involvement, such as areflexia, ataxia, length-dependent sensory disturbance, and amyotrophy, later in the disease.¹⁻⁵ Electrophysiologic and histologic studies have been reported to show the presence of demyelinating or axonal neuropathy, or loss of anterior horn cells in the spinal cord.¹⁻⁶

Demyelinating polyneuropathy is a rare consequence of CJD; few patients have been described in the literature.³⁻⁵ Early involvement of the peripheral nervous system (PNS) is more unexpected in sporadic CJD than in infectious forms of the disease that involve a peripheral route of contamination. Neuropathologic information on the PNS is rare in CJD. An extensive accumulation of PrP^{Sc} in the dorsal root ganglia and autonomic ganglia has been reported.⁷ However, Antoine et al.³ performed a pathologic analysis of the PNS in a patient with sporadic CJD presenting with demyelinating polyneuropathy that did not show PrP^{Sc} accumulation.

This is a case of sporadic CJD in which a rapidly progressive demyelinating sensorimotor neuropathy was the initial presentation. Initially, various disorders need consideration:

metabolic disorders like vitamin B₁₂ or E deficiency; Sjögren syndrome (autoimmune disorder usually with dry eyes and dry mouth); infections like HIV, syphilis, and HSV; paraneoplastic disorders; pure sensory inflammatory demyelinating polyradiculopathy; paraproteinemias like MGUS; and toxicity from cisplatin and analogs or excess vitamin B₆. As soon as a patient develops CNS symptoms, the approach will change to include disorders that could affect central and peripheral nervous systems. Although CJD is a rare cause of central and peripheral nervous system involvement, it should be in the differential diagnosis, as this case demonstrated.

Previously published reports of PNS involvement in CJD described patients with advanced CJD; rarely was polyneuropathy the initial manifestation. Neufeld et al.¹ reported 2 familial cases with a codon 200 mutation of the *PrP* gene. The first patient had an 18-month history of CJD and was found to have axonal polyneuropathy without demyelination; the second patient had triphasic wave on EEG and later was found to have evidence of severe demyelination on electrodiagnostic testing. Niewiadomska et al.² studied nerve conduction and EMG changes in 16 patients with definite CJD: 3 patients had amyotrophy or absent deep tendon reflexes and electrophysiologic features of PNS involvement were demonstrated in 14 patients (motor neuropathy, axonal or demyelinating neuropathy). Antoine et al.³ reported a case of familial CJD with early dementia, cerebellar signs, and polyneuropathy. Esiri et al.⁴ describe a patient with a 3-month history of CJD, with early cerebellar signs and painful neuropathy. Sadeh et al.⁵ reported a case with a 20-month history of CJD who developed late signs of polyneuropathy. Kovacs et al.⁸ reported a case of demyelinating peripheral neuropathy and amyotrophy, presenting simultaneously with symptoms of CJD. Dorien et al.⁹ reported a genetic CJD case presenting with a chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)-like picture. Baiardi et al.¹⁰ demonstrated in 303 patients with sporadic CJD that about 40% of them had symptoms and signs suggestive of PNS involvement and occurred at disease onset in 9.3%. Extensive investigations suggested a pattern characterized by prominent signs of axonal damage with secondary demyelination. There is no consensus as to how CJD causes polyneuropathy, but this finding has been associated with some subtypes of the disease.

This case suggests that sporadic CJD is a neurologically widespread disease of the nervous system that may be revealed by the early appearance of demyelinating peripheral neuropathy. CJD should be in the differential diagnosis of patients who present with a CIDP picture, especially if there is rapid disease progression and no response to immunotherapy and if there are additional symptoms suggesting CNS involvement.

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Disclosure

The author reports no disclosures relevant to the manuscript. Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures.

Appendix Author

Name	Location	Contribution
Adnan Badahdah, MD, FRCPC	Dalhousie University, Halifax; University of Jeddah	Data collection, drafting and revision of manuscript

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