Clinical Reasoning:

Reversible gait ataxia

From wheelchair to independent mobility

Tarig Mohammed Abkur,
MRCPI
Peter Bede, MD, PhD

Correspondence to
T.M. Abkur:
tarig1982@hotmail.com

SECTION 1

A 65-year-old right-handed man presented with a 7-year history of progressive gait impairment and unsteadiness. He was only able to ambulate at home with a frame for very short distances and started using a wheelchair outside his home to prevent falls 4 years prior to presentation. The patient had no autonomic, dermatologic, or rheumatologic symptoms, unintentional weight loss, or night sweats. He was an ex-smoker, with a 20-pack-year history of smoking, and did not consume alcohol. There was no family history of neurologic conditions.

The patient has a history of ischemic heart disease and takes aspirin 75 mg, atorvastatin 40 mg, and bisoprolol 1.25 mg for secondary prevention.

Neurologic examination revealed reduced vibration sense in both lower limbs up to the patient's hips and joint position sense was severely impaired in all 4 limbs. He had a positive Romberg sign. A patchy distribution of sensory loss for pain and temperature was detected over the trunk and proximal lower limbs. Pseudoathetosis, slow involuntary writhing finger movements were observed when the patient stretched out his arms, which became more prominent with eye closure. Tone and power were normal throughout, but deep tendon reflexes were only present with reinforcement and plantar responses were flexor.

Questions for consideration:

1. What differential diagnoses would you consider?
2. What investigations would you perform?

[GO TO SECTION 2](#)

From the Department of Neurology (T.M.A., P.B.), Beaumont Hospital, Dublin; and Quantitative Neuroimaging Group (P.B.), Academic Unit of Neurology, Trinity College Dublin, Ireland.

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Figure 1 A review of the anatomical localization of sensory ataxias

Parietal cortex

- PCA, AD
- Stroke

Thalamus

- Stroke, APS, PRES

Internal arcuate fibres
(Sensory decussation)

Dorsal root ganglion

- Paraneoplastic
- Autoimmune
- HIV, HCV, HTLV
- Pyridoxine intoxication
- Chemotherapeutic agents

Peripheral sensory nerves

- Diabetes mellitus
- CIDP, AIDP, MFS
- Vitamin E deficiency
- Paraproteinemia
- Celiac disease
- Paraneoplastic syndromes

Medial lemniscus

- Multiple sclerosis

Dorsal columns

- Vitamin B12 deficiency
- Tabes dorsalis
- Copper deficiency
- Myelopathy
- HIV, HCV
- Demyelination

Sensory nerve roots

- Chronic immune sensory radiculopathy (CISP)

AD = Alzheimer disease; AIDP = acute inflammatory demyelinating polyneuropathy; APS = antiphospholipid antibody syndrome; CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; HCV = hepatitis C virus; HTLV = human T-cell lymphotropic virus; MFS = Miller Fisher syndrome; PCA = posterior cortical atrophy; PRES = posterior reversible encephalopathy syndrome.

SECTION 2

The patient presented with progressive gait ataxia. The first step in localization is to distinguish between cerebellar, sensory, and vestibular ataxia. Our patient had no nystagmus, finger-nose dysmetria with the eyes open, dysdiadochokinesis, or dysarthria to indicate cerebellar disease. The patient had no hearing impairment, tinnitus, or prior use of ototoxic antibiotics. The head-impulse test was negative, i.e., rapid turning of the head to either side while the patient was fixing his gaze on a target did not provoke a corrective saccade, making a primary vestibular pathology unlikely.

Ataxias due to mixed pathology are relatively common, such as chronic alcohol abuse, celiac disease, vitamin B₁₂ and E deficiency, Friedreich ataxia, Refsum disease, cerebellar ataxia neuropathy and bilateral vestibular areflexia, ataxia telangiectasia, and paraneoplastic syndromes. Other mixed ataxia syndromes include ataxia with ocular apraxia, spinocerebellar ataxias 2, 3, 4, and 25, and polymerase- γ (*POLG*) mutations such as sensory ataxic neuropathy dysarthria and ophthalmoparesis. Accordingly, a meticulous

clinical examination, detailed family history, and neurophysiologic studies are needed to accurately categorize ataxia. The marked impairment in joint position and vibration sense in our patient was suggestive of a sensory ataxia either mediated by peripheral neuropathy, dorsal root ganglionopathy, posterior column myelopathy, medial lemniscus lesion, or thalamic or parietal cortex pathology. Figure 1 summarizes the anatomic localization of sensory ataxias. There was no evidence of overt parietal lobe involvement; no apraxia, neglect, or features of Gerstmann syndrome were detected. Preserved reflexes would typically indicate a central pathology, i.e., spinal cord involvement, but do not rule out a peripheral etiology. The sensory deficits were not limited to proprioception and vibration; therefore it was suspected that the pathology is not merely dorsal column mediated. The constellation of gait ataxia and patchy, proximal, and asymmetric sensory loss in a non-length-dependent pattern was felt to be atypical for peripheral neuropathy.

Question for consideration:

1. What investigations would you perform?

GO TO SECTION 3

Figure 2 MRI of the spine

(A) Sagittal view shows marked cord atrophy. (B) Axial view at the level of T3 reveals dorsal column hyperintensity.

SECTION 3

Routine blood tests including full blood count, fasting glucose, renal profile, electrolytes, liver function tests, C-reactive protein, serum protein electrophoresis, serum angiotensin-converting enzyme, and erythrocyte sedimentation rate were normal. Comprehensive autoimmune screening was negative for antinuclear antibodies, antineutrophil cytoplasmic antibodies, rheumatoid factor, anti-double-stranded DNA, anti-phospholipid antibodies, cryoglobulins, anti-Ro/SSA and La/SSB antibodies, antiganglioside antibodies, myelin oligodendrocyte glycoprotein antibodies, and

aquaporin-4 antibodies. Anti-tissue transglutaminase and anti-gliadin were also negative. Serologic tests for syphilis (venereal disease research laboratory), viral hepatitis B and C, human T-cell lymphotropic virus, varicella-zoster virus, and HIV serology were negative as well as the paraneoplastic antibody screen for anti-Hu, anti-Yo, anti-Ri, anti Ma/Ta, CRMP5, and amphiphysin. Copper, zinc, vitamin E, vitamin B₁₂, methylmalonic acid, vitamin B₆, and phytanic acid levels were normal.

MRI of the brain was normal with no evidence of cerebellar atrophy or parietal, thalamic, or brainstem abnormalities. MRI of the spinal cord showed marked cord atrophy along its entire length with increased T2 signal intensity in the dorsal columns (figure 2). Spinal imaging showed no evidence of nerve root enhancement or cauda equina enlargement. CSF analysis revealed no pleocytosis and normal protein and glucose and was negative for oligoclonal bands. Spinal fluid cytologic examination and flow cytometry were unremarkable.

Nerve conduction studies revealed normal motor potentials and late responses, with no signs of denervation; however, the sensory amplitudes were absent, with the exception of bilateral symmetric, very small radial sensory responses bilaterally. Sural nerve biopsy was performed to exclude the remote possibility of vasculitis. This showed axonal loss with no evidence of active inflammation, vasculitis, or malignant infiltration.

Questions for consideration:

1. What is the final diagnosis?
2. Would you consider other tests?

GO TO SECTION 4

SECTION 4

The patient presented with a progressive, asymmetric, multifocal sensory disturbance in a non-length-dependent pattern, with preserved motor function resulting in severe proprioceptive deficits and considerable gait impairment. Based on the integration of the clinical, radiologic, and neurophysiologic findings, dorsal ganglionopathy (DG) was considered the most likely diagnosis. One of the key differential diagnoses was chronic immune sensory polyradiculopathy (CISP), but based on the absence of root enhancement and inflammatory markers in the CSF, CISP was considered less likely.

In view of the strong association between DG and occult malignancy, repeated anti-HU antibody screening, CT thorax, abdomen, and pelvis, and whole-body PET scans were performed, which showed no evidence of malignancy. The link between DG and Sjögren syndrome is also well-recognized; therefore, a lip biopsy was performed, which showed no features of sicca syndrome. As idiopathic DG is thought to have an autoimmune pathophysiology,¹ the patient received 5 days of IV methylprednisolone followed by PO prednisolone. Steroids were then gradually tapered to a maintenance dose and mycophenolate was also commenced. In addition, a course of IV immunoglobulin (IVIg) was given, but no clinical improvement was noted. Subsequently, the patient underwent plasma exchange with dramatic effect; the patient started independently mobilizing with a stick from previously being wheelchair-bound. The dramatic response to plasmapheresis was somewhat unexpected given the absence of inflammatory markers in the CSF, the absence of enhancement on MRI, and the strikingly longstanding disability. We also note that the patient underwent extensive physical therapy and occupational therapy in conjunction with his immunotherapy.

DISCUSSION DG or sensory neuronopathies comprise a specific subgroup of peripheral neuropathies. Selective degeneration of dorsal root ganglia leads to degeneration of peripheral axons and central sensory projections in the dorsal column.²

The etiologic spectrum of this condition includes paraneoplastic syndromes, inflammatory processes, e.g., Sjögren syndrome, systemic lupus erythematosus, viral infections, vitamin B₆ toxicity, and platinum-based chemotherapeutic agents. Therefore, early diagnosis is important, as DG may herald an occult malignancy or an underlying autoimmune condition. Despite extensive investigations, the cause remains unclear in up to 50% of patients.³

DG is characterized by early-onset ataxia and patchy asymmetric sensory disturbance. Motor function is not affected and reflexes are usually

depressed.⁴ Nystagmus has also been described, likely reflecting impaired proprioceptive input from the extraocular muscles or vestibular system.³ Dorsal root ganglion biopsy is the only definitive method to demonstrate the pathology; however, this is not routinely performed because of the invasive nature of the procedure.⁵ Neurophysiologic studies demonstrate reduced or absent sensory nerve action potentials with normal or slightly reduced sensory conduction velocities and normal motor conduction velocities.⁶ MRI of the spinal cord is useful, as it may demonstrate dorsal column hyperintensities and diffuse cord atrophy. This is thought to be the consequence of centripetal Wallerian degeneration from the dorsal root ganglionopathy.⁷

Management of dorsal root ganglionopathies is determined by the underlying cause. No randomized, controlled trials exist to guide therapy in patients with Sjögren-associated DG. A variety of treatments have been tried with some success, including plasma exchange,⁸ IVIg, rituximab, corticosteroids, azathioprine, and cyclophosphamide. As mentioned above, it is crucial to screen for an underlying malignancy. Repeated radiographic studies (thoracic/abdominal/pelvic CT, FDG-PET) and anti-HU antibody screening are recommended every 6 months up to 4 years from the diagnosis.⁹

CISP is an important differential that also responds to immunotherapy, but it is typically associated with root enhancement on MRI and raised CSF inflammatory markers.

As demonstrated, ataxia syndromes require a systematic anatomical approach and careful integration of clinical, radiologic, and neurophysiologic clues. This case illustrates that some ataxia syndromes may be curable despite longstanding disability and that the aggressive management of a suspected autoimmune process may lead to dramatic improvement.¹⁰

AUTHOR CONTRIBUTIONS

T.M.A. and P.B. drafted the article, reviewed the literature, participated in the clinical care of the patient, and approved the final submission.

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DISCLOSURE

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