

# Clinical Reasoning: A 75-year-old woman with visual disturbances and unilateral ataxia



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## SECTION 1

A 75-year-old woman presented in July 2007 with 2 months of oscillopsia when looking downward and horizontal diplopia during rapid rightward gaze. She reported 3 weeks of progressive clumsiness of the right limbs, weakness of the right leg, and an unsteady gait. She denied cognitive dysfunction, headache, bulbar or sensory symptoms, muscle stiffness/spasms, antecedent infection, fever, or other systemic complaints.

Nine years earlier, the patient had experienced an episode of diplopia and unsteadiness which resolved spontaneously after 3 months. Her neurologic examination in 1998 had revealed downbeat nystagmus, a right internuclear ophthalmoparesis (INO), and gait ataxia. Brain MRI and stroke evaluation had been negative. Type I diabetes mellitus was diagnosed several months after this initial episode.

In the 1980s, a low vitamin B<sub>12</sub> level (value unknown) was thought to have been an incidental finding; levels >500 ng/L have been maintained with a B<sub>12</sub> supplement. There was also a history of well-controlled hypertension. A grandparent had type I diabetes, but no relatives had neurologic disorders. She rarely consumed alcohol and never used tobacco or recreational drugs.

General medical examination had normal results, including the absence of vitiligo. Mental status exam-

ination was unremarkable with clear speech. Fundoscopic, pupillary, visual field, and monocular acuity examinations were unremarkable. Near card straight-ahead binocular acuity was 20/20, but only 20/50 in lateral downgaze due to oscillopsia. The eye movement abnormalities were saccadic pursuit, gaze-evoked nystagmus, downbeating nystagmus maximal on lateral downgaze, and saccadic slowing but full range of the left adducting eye (i.e., left INO) (see videos 1, 2a, and 2b on the *Neurology*<sup>®</sup> Web site at [www.neurology.org](http://www.neurology.org)). Convergence was normal. There was no rigidity or stiffness of limb or axial muscles. There was 4+/5 right leg weakness (hip/knee flexors, toe extensors), with hyperreflexia, downgoing plantar responses, and normal sensation. There was right-sided dysmetria, dysdiadochokinesia, loss of check, and exaggerated rebound. The patient could sit upright unsupported but required assistance to ambulate due to weakness and ataxia.

Steady progression lasted 4 months, with deficits persisting without improvement. Hashimoto thyroiditis was diagnosed several months after the second episode began.

### Question for consideration:

1. How would you localize the lesions?

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

## SECTION 2

The INO localizes to the medial longitudinal fasciculus. The hemiataxia and leg weakness may localize to the pontocerebellar and corticospinal tracts, respectively. While downbeat nystagmus, often seen in conjunction with saccadic pursuit and gaze-evoked nystagmus, traditionally localizes to the flocculus-paraflocculus, it is hypothesized to also occur with pontomedullary paramedian tract lesions.<sup>1</sup> Thus, a single left pontine lesion may account for the patient's findings.

Brain MRI was unremarkable at presentation (with head/neck magnetic resonance angiography) and unchanged at 1 month, 8 months, and 2 years (no restricted diffusion, abnormal enhancement, or atrophy).

Our patient had a subacute, apparently recurrent, sporadic ataxia.

### Questions for consideration:

1. What is the differential diagnosis of a sporadic ataxia with or without brainstem features?
2. Which entities typically cause recurrent attacks?
3. What tests should be performed?

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### SECTION 3

Unilateral brainstem dysfunction is rare in neurodegeneration and toxic-metabolic conditions, but not uncommon in mass lesions and infectious/postinfectious syndromes and typical, particularly with INO, of demyelinating disease and stroke. The sporadic ataxias may also be split (imperfectly) into 2 groups according to their tendency to recur: 1) disorders that are either progressive or typically monophasic (but may recur) and 2) a smaller group that includes inherently recurrent conditions and recurrent stroke. Group 1 includes neurodegeneration (e.g., spinocerebellar ataxia, late-onset Friedreich ataxia, olivopontocerebellar atrophy, cerebellar-type multisystem atrophy); brainstem abscess/tumor (e.g., glioma, lymphoma); toxic-metabolic (e.g., alcohol, lithium, amiodarone, anticonvulsants, hypothyroidism, vitamin E deficiency, thiamine deficiency [includes INO, but corticospinal tracts spared]); infection (e.g., progressive multifocal leukoencephalopathy and JC virus cerebellar granule cell neuronopathy, viral brainstem encephalitis [e.g., herpes simplex virus (HSV) 1 and 2, varicella zoster virus (VZV), cytomegalovirus (CMV) (primarily immunocompromised host), Epstein-Barr virus (EBV)], *Listeria* rhombencephalitis, Lyme encephalomyelitis); prion (e.g., Creutzfeldt-Jakob disease); paraneoplastic cerebellar degeneration; progressive/monophasic forms of demyelinating disease; and immune disorders (e.g., postinfectious cerebellitis, gluten sensitivity, Bickerstaff brainstem encephalitis [BBE]). Viral encephalitis can present as a unilateral brainstem syndrome, possibly recurrent, but typically with systemic symptoms (e.g., fever, headache) and progression over days to weeks. While BBE may present with hemiataxia and ophthalmoplegia, there must be an altered sensorium, long tract signs (sometimes asymmetric), or an abnormal MRI; serum immunoglobulin G (IgG) anti-GQ1b antibodies are elevated in roughly two-thirds of cases. As long tract signs were absent during our patient's first attack, a BBE-forme fruste can be considered. Arguments against BBE include the lack of antecedent infection, progression beyond 4 weeks, and absence of recovery. IgG anti-GQ1b titers should be measured in the acute phase, as titers decline over time.

The recurrent ataxias include the episodic ataxias, relapsing multiple sclerosis, and strokes. Episodic ataxia 2 is characterized by episodes ranging from

minutes to weeks but usually hours (vs seconds to minutes in type 1), with a typical age at onset from 5 to 15 years. Allelic to episodic ataxia 2, spinocerebellar ataxia 6 occasionally presents with episodic ataxia. A paramedian basilar artery branch occlusion could cause the patient's signs, but would not explain the steadily progressive course. Multiple sclerosis is an unlikely diagnosis given the patient's advanced age and normal MRI.

No improvement occurred after administration of IV thiamine. Vitamins B<sub>12</sub> (911 ng/L) and E, thyroid function tests, Lyme titer, and celiac and paraneoplastic panels (including amphiphysin) were normal or negative. CSF revealed 6 leukocytes/mm<sup>3</sup> (5 lymphocytes, 1 monocyte), 335 erythrocytes/mm<sup>3</sup>, glucose 118 mg/dL (serum 268), protein 75 mg/dL, and normal/negative Lyme serology/PCR, cryptococcal antigen, VDRL, *Tropheryma whipplei* PCR, anti-Hu/Yo/Ri, cytology, and flow cytometry. CSF for HSV (acutely) and VZV/CMV/EBV PCR and HSV/VZV CSF:serum antibody ratios would have been of interest. An intensive malignancy search (body CT, mammogram, breast MRI, FDG-PET) was negative. AntiGAD<sub>65</sub>-antibody (antiGAD-Ab) levels were elevated (>30 U/mL [normal ≤1], Quest Diagnostics, and 46.6 nmol/L [normal ≤0.02], Mayo Medical Laboratories). Thyroperoxidase/thyroglobulin, pancreatic islet cell, and gastric parietal cell/intrinsic factor antibody levels were also elevated.

We hypothesized a glutamic acid decarboxylase (GAD) brainstem syndrome, probably recurrent, associated with polyendocrinopathy. Our patient's ataxia cannot be attributed to pernicious anemia (myelopathy/myeloneuropathy) or thyroid antibodies (Hashimoto ataxia generally applies to the cognitively impaired patient). Repeat lumbar puncture (for antiGAD-Abs, oligoclonal bands, IgG index) was declined. Human leukocyte antigen typing was not performed. Nerve conduction studies and needle EMG were normal, without continuous motor unit activity at rest. Serum anti-IgG GQ1b antibody titers were not measured acutely, but were normal 2.5 years later.

#### Questions for consideration:

1. What are antiGAD-Abs?
2. What are the neurologic associations?

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## SECTION 4

GAD catalyzes the synthesis of  $\gamma$ -aminobutyric acid (GABA), the primary CNS inhibitory neurotransmitter. Low-titer serum antiGAD-Abs (<20 nmol/L) are found in newly diagnosed type I diabetes (80%) vs normal controls (1%), whereas high titers (>20 nmol/L) are associated with polyendocrinopathy or rare neurologic disorders.<sup>2,3</sup> Our patient's titer (46.6 nmol/L) was modestly elevated; much higher median titers have been reported (1,429 nmol/L<sup>2</sup>). The relationship between titers and clinical characteristics, and whether antiGAD-Abs are directly pathogenic, require further study.

The most well-recognized neurologic associations are stiff-person syndrome (SPS), with >80% affected having high titers, and cerebellar ataxia.<sup>4</sup> SPS is characterized by fluctuating axial and limb muscle stiffness with superimposed episodic painful spasms. Similarities between GAD-associated SPS and cerebellar ataxia include female predominance; associated type I diabetes and polyglandular autoimmunity; asymmetric presentations (e.g., stiff-limb syndrome); and potential for immunotherapy responsiveness.<sup>4-7</sup> A paraneoplastic variant of SPS with amphiphysin antibodies occurs primarily in older women with breast cancer. HLA-DRB1\*0301 and DQB1\*0201 are susceptibility alleles for SPS.<sup>8</sup> In patients with unexpectedly high-titer antiGAD-Abs, neurologic characteristics were typically multifocal, most commonly with cerebellar ataxia and brainstem manifestations. The clinical course was usually subacute but could be insidious, and only rarely relapsing. MRI was frequently normal.<sup>2</sup> Other manifestations are seizures, periodic alternating nystagmus, idiopathic limbic encephalitis, and paraneoplastic syndromes.<sup>2,4,9</sup>

The CSF in GAD-associated disorders is typically acellular, with a normal to modestly elevated protein; CSF-specific oligoclonal bands and increased IgG index are common.<sup>2,4</sup> Intrathecal antiGAD-Ab synthesis is often elevated, confirming that GAD autoimmunity is neurologically related.<sup>5</sup>

Potential diagnostic clues for a GAD-associated ataxia include the following:

1. Acute/subacute onset or quick progression (although insidious onset/progression is not uncommon), late onset, relapses, prominent asymmetry/unilaterality, and stiff-person phenomenon
2. Type I diabetes
3. Associated autoimmune conditions/marker
4. Strong family history of autoimmunity
5. CSF oligoclonal bands and elevated IgG index

Treatment options are primarily immunotherapies or enhancers of GABAergic neurotransmission. While response to immunotherapy is often limited, significant improvement may occur.<sup>10</sup> In our patient, IV methylprednisolone (1 g/day for 5 days) and IV immunoglobulin (0.4 g/kg/day for 5 days) were ineffective and poorly tolerated; mycophenolate mofetil and azathioprine were poorly tolerated. Side effects limited the use of GABA-enhancers baclofen/tiagabine and glutamate-antagonist memantine, which were empirically employed to treat the oscillopsia associated with downbeat nystagmus. While treatment effects on antiGAD-Ab levels were not studied, titers remained >30.0 U/mL 2.5 years later.

Our patient with a relapsing unilateral brainstem syndrome after 9 years was found to have elevated antiGAD-Abs and polyendocrinopathy. The evidence supporting an antiGAD-Ab-related syndrome would have been significantly enhanced by demonstrating elevated CSF antiGAD-Abs. The striking asymmetry sometimes observed in GAD-ataxia remains unexplained. Less likely diagnostic possibilities include recurrent demyelination, stroke, Bickerstaff or viral brainstem encephalitis, or that the episodes were unrelated to each other.

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## DISCLOSURE

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