Clinical Reasoning:

An 82-year-old man with worsening gait

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SECTION 1

An 82-year-old man with hypothyroidism presented with difficulty walking.

One year prior to presentation, he noticed that his legs occasionally “froze” when initiating walking. His gait progressively worsened over the year. He developed balance difficulty, tripping and falling twice without loss of consciousness. In the 4 months prior to presentation, he started using a cane, a rolling walker, then a wheelchair. He reported occasional

neck and left leg cramps. He denied bowel or bladder symptoms.

The patient was previously healthy, playing competitive sports at the national level into his late 70s. His only medication was levothyroxine.

Question for consideration:

1. What examination findings would help to localize the etiology of his abnormal gait?

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SECTION 2

The neurologic basis of gait spans the entire neuraxis, requiring assessment of sensory (visual, vestibular, proprioceptive), motor, and higher-order control (frontal lobes, basal ganglia, brainstem, cerebellum) systems.

Our patient's mental status, cranial nerve, strength, sensory, and reflex examinations were normal. There was no tremor, hypomimia, scanning speech, hypophonia, or bradykinesia. He had mild resistance to passive movement in his left leg, without spasticity, rigidity, or contracture. There was right

arm dysdiadochokinesia and right leg dysmetria, but no left-sided or truncal ataxia. He could bicycle his legs in bed and march in place while sitting, but could not stand without assistance. Once standing, he could not begin to walk unless an object was placed on the ground for him to step over. Once he began walking, he continued slowly with small steps, but no further freezing.

Question for consideration:

1. What is the localization and differential diagnosis based on the patient's history and examination?

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SECTION 3

Our patient's history and examination were notable for subacute development of freezing of gait and cerebellar ataxia.

Freezing of gait is characterized by sudden, brief periods of difficulty initiating or continuing locomotion, with inability to lift the foot from the floor despite normal leg strength. It can occasionally be overcome with visual cues and is thought to be caused by deficits in functional networks involving the frontal lobes, basal ganglia, brainstem, and dorsomedial cerebellar locomotor region.¹

Freezing of gait is associated with parkinsonism. It can occur in idiopathic Parkinson disease (PD), atypical parkinsonian syndromes such as multiple system atrophy (MSA, which may also be associated with cerebellar ataxia), progressive supranuclear palsy (PSP), and corticobasal syndrome (CBS), as well as secondary parkinsonism (e.g., due to vascular disease or normal pressure hydrocephalus [NPH]). Our patient's symptoms progressed more rapidly than is typical for these disorders, and he lacked key features of these diagnoses, such as tremor or bradykinesia (PD), autonomic abnormalities such as orthostatic hypotension (MSA), cortical findings such as alien limb phenomenon, speech or motor apraxia, or cortical sensory loss (CBS), or cognitive or bladder

impairment (NPH). Although he did not have supranuclear vertical gaze palsy or impaired vertical saccades to suggest classic PSP, the pure akinesia with gait freezing variant of PSP can present with isolated freezing of gait.

Subacute cerebellar ataxia can be immune-mediated (associated with anti-Yo, Hu, Tr, Ri, Ma2, GAD65, calcium and potassium channel antibodies²; Hashimoto encephalopathy), neoplastic, toxic (e.g., alcohol, antiepileptics, heavy metals), infectious (e.g., progressive multifocal leukoencephalopathy due to JC virus), prion diseases (such as Gerstmann-Sträussler-Scheinker), or metabolic (e.g., vitamin E deficiency, hepatocerebral degeneration). Of these conditions, cerebellar ataxia and parkinsonian symptoms (such as the freezing of gait seen in our patient) can co-occur in GAD65 autoimmunity, hepatocerebral degeneration, and prion disease. Parkinsonian symptoms and ataxia can also co-occur in spinocerebellar ataxia types 2, 3, 6, 8, and 17,³ though these inherited diseases tend to present at a younger age than in our patient, who also had no family history of neurologic disease.

Question for consideration:

1. What diagnostic studies should be performed to narrow the differential diagnosis?

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SECTION 4

Our patient's serum complete blood count, comprehensive metabolic panel, liver function tests, antinuclear antibody, thyroid function tests, antithyroid peroxidase, vitamin E, and vitamin B₁₂ were normal. Brain MRI was normal, as was brain PET (performed to look for metabolic signatures of neurodegeneration) and dopamine transporter SPECT. Dopamine transporter SPECT measures dopamine uptake in the basal ganglia and is abnormal in neurodegenerative parkinsonian disorders such as PD, MSA, CBS, and PSP, but cannot distinguish among them.

To evaluate for autoimmune or paraneoplastic cerebellar degeneration, the patient had CSF studies sent along with serum and CSF antineuronal antibodies and underwent PET/CT of the body to

evaluate for underlying malignancy. His basic CSF measures and PET/CT were normal. However, CSF electrophoresis revealed a monoclonal (M) spike in the absence of a similar pattern on serum electrophoresis, indicating intrathecal antibody production.

One month after presentation, while antibody studies were pending, the patient developed painful left leg cramps, fixed left ankle dorsiflexion, and pronounced neck stiffness. EMG of the left leg demonstrated continuous motor unit activity in the left medial gastrocnemius, peroneus longus, and vastus medialis.

Question for consideration:

1. What is the patient's diagnosis?

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SECTION 5

Our patient's worsening axial and limb stiffness and EMG are suggestive of stiff-person syndrome (SPS). Patients with SPS classically present with symmetric, board-like stiffness of axial and limb musculature, as well as painful muscle spasms that can be precipitated by startle. However, limited and asymmetric forms of SPS, such as stiff-limb or stiff-trunk syndrome, also exist. EMG in patients with SPS demonstrates the electrophysiologic correlate of muscle spasm: continuous motor activity of opposing muscle groups. Laboratory testing often reveals elevated anti-GAD65 antibodies. Our patient's GAD65 antibody returned positive at 113 nmol/L in the serum (normal <0.02 nmol/L) and 16.4 nmol/L in the CSF.

Notably, GAD65 antibodies are not only associated with SPS, but can also be associated with

cerebellar ataxia. Individuals with GAD65-associated cerebellar ataxia can also have multifocal neurologic symptoms, including brainstem dysfunction, parkinsonism, or other movement disorders. Roughly 25% of GAD65 antibody-positive individuals with these multifocal extrapyramidal symptoms also have limited SPS.⁴

Taken together, our patient's cerebellar ataxia, parkinsonian freezing of gait, neck and left leg stiffness, and elevated anti-GAD65 titer suggest a diagnosis of limited SPS (stiff-limb syndrome) in the context of multifocal GAD65 autoimmune neurologic disease.

Question for consideration:

1. How would you treat the patient?

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SECTION 6

Treatment of SPS involves immunomodulatory and symptomatic therapy.

Immunomodulation is more effective when initiated early⁵ and should be considered before antibody tests return if SPS is highly suspected. Monthly IV immunoglobulin (IVIg) is standard of care for SPS,⁶ though azathioprine, mycophenolate, or methotrexate have been used as IVIg-sparing maintenance therapies. Rituximab and cyclophosphamide have been used for refractory cases.⁵

Symptomatic treatment of SPS includes baclofen, tizanidine, and diazepam. High doses of diazepam may be required for symptomatic relief in SPS, ranging from 5 to 360 mg/d in classic SPS (median 40 mg/day) and 2 to 90 mg/d in limited SPS (median 17.5 mg/day).⁷

Patients with GAD65-positive SPS typically have chronic symptoms and thus require long-term treatment.⁷ Withdrawal of treatment and clinical monitoring after 5 years without symptom progression or relapse can be considered.⁵

Our patient was started on monthly IVIg and diazepam 2 mg TID. Within a week, he had remarkable improvement in fluidity and speed of gait and no longer needed a walker. After several months of treatment, he could enter a car and step into a bathtub independently.

DISCUSSION GAD65 is an isoform of glutamic acid decarboxylase that converts glutamate to the inhibitory neurotransmitter GABA. Neurologic disease associated with GAD65 antibodies is remarkably diverse, and is thought to arise from immune-mediated dysfunction of GABAergic transmission in affected structures throughout the neuraxis⁵ (table).

Antibodies to GAD65 are common. They are present in 8% of the general population⁸ and are frequently present in individuals with type I diabetes, thyroid disease, and pernicious anemia. They are rarely associated with neurologic disease: SPS is the most common GAD65 antibody-associated neurologic disease, and prevalence is estimated at 1:1,250,000.⁹

It is important to note that when GAD65 antibodies are associated with neurologic disease, serum titers are markedly high—often above 100 nmol/L (reference <0.02 nmol/L). Antibodies are often also present in the CSF.⁴ In contrast, individuals with non-neurologic autoimmune disorders such as diabetes mellitus type 1 or thyroiditis usually have titers less than 20 nmol/L,¹⁰ and antibody-positive individuals without autoimmune disease tend to have titers in the low-positive range (0.03–2 nmol/L).⁸

GAD65 antibody-positive SPS is not usually associated with an underlying neoplasm. However, because a small percentage of cases are associated with malignancy, patients warrant an age-appropriate malignancy screening.⁵ In addition, GAD65 antibody-positive individuals with SPS should be screened for the co-occurrence of other antibodies associated with SPS (including antiampiphysin, glycine receptor, GABA-A receptor, and dipeptidyl-peptidase-like protein 6⁵). The presence of antiampiphysin should raise concern for paraneoplastic disease. In our patient, antiampiphysin antibody testing was negative.

Our patient's case demonstrates that GAD65 antibody-associated neurologic disease can evolve over time and mimic neurodegenerative disease. It is therefore important to consider GAD65 autoimmunity in patients with atypical presentations of cerebellar ataxia, SPS, or parkinsonism, because early

Table Spectrum of neurologic phenotypes associated with elevated glutamic acid decarboxylase antibodies

Localization	Clinical syndrome
Cortical	Limbic encephalitis
	Autoimmune temporal lobe epilepsy
	Psychiatric disturbance without seizures
Cerebellar, brainstem, extrapyramidal	Cerebellar ataxia ± downbeat nystagmus
	Parkinsonism, dystonia, chorea
	Opsoclonus-myoclonus syndrome
Spinal cord	Stiff-person syndrome spectrum disorders
	Classic stiff-person syndrome
	Limited stiff-person syndrome (stiff-limb syndrome or stiff-trunk syndrome)
	Progressive encephalomyelitis with rigidity and myoclonus
Peripheral	Myelopathy
	Large fiber neuropathy
	Autonomic neuropathy

treatment with immunomodulatory and symptomatic therapy can greatly improve GAD65-associated neurologic symptoms.

AUTHOR CONTRIBUTIONS

Dr. Chew drafted the initial manuscript, revised the manuscript, and was involved in the clinical care of the patient. Dr. Vodopivec revised the manuscript and was involved in the clinical care of the patient. Dr. Berkowitz revised the manuscript and was involved in the clinical care of the patient.

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DISCLOSURE

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